Solvent Selection in Transfer Hydrogenation and Suzuki Cross-coupling

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Abstract Solvent selection plays a key role in facilitating sustainable chemical processes. The use of green solvents, which facilitate both substrate and catalyst dissolution, increase reaction activity and selectivity, and enable easy separation of the product and recycling of the catalyst, is desirable. But the question of which green solvent to use must consider solvent production processes and whether the solvent can be recycled and re-used. In this study, selected solvents were ranked according to sustainability. Each solvent was evaluated not only for its production process and its physical properties, but also for its performance in reaction (including in terms of product separation) for two representative reactions—transfer hydrogenation of unsaturated organic compounds, where the solvent is also a reactant, and Suzuki cross-coupling of halobenzene and phenylboronic acid. Based on solvent life-cycle and physical characteristics ethylene glycol was found to be the most sustainable solvent for the transfer hydrogenation reaction and glycerol was found to be the most sustainable solvent for the Suzuki cross-coupling reaction.

Keywords Green Chemistry, Green Solvent, Sustainable Solvent, Catalysis, Glycerol, Transfer Hydrogenation, Suzuki Cross Coupling

In general, for a given process, several different solvents, each with its own advantages and disadvantages, are usually suitable^[5,6]. The selection of a solvent for a reaction medium is traditionally based on solvent performance in the reaction. However, solvent characteristics such as its chemical, physical and biological properties may not only affect operational conditions, they could also dictate product separation and catalyst recovery procedures. In addition, the evaluation of a solvent must also consider its local environmental impact—i.e., the extent to which its use leads to water, air, or land contamination—and its toxicity. The latter refers to any harmful or adverse biological effects that result from exposure to the solvent. Equally important in evaluating a solvent's potential environmental impact is the issue of its global effect, or whether use of the solvent leads to global warming and ozone depletion. Finally, solvent cost, which comprises its preparation, recycling and disposal, is also important.

Ranking the environmental impact of solvents or chemical reactions is complicated as there are multiple factors to consider and the data available is incomplete. However, several metrics and methods were developed over the years to calculate the sustainability or greenness of commonly used organic solvents^[7] and to evaluate the environmental performance of organic reactions^[8,9]. In addition, some examples of life-cycle assessment (LCA) of organic reactions, which considers cumulative environmental impacts from all life cycle stages, i.e. from “cradle-to-grave”, were also reported^[10, 11]. However, the use of life-cycle assessment for process selection and development is a novel area of research, and though the importance of including the environmental aspects from the beginning of process design is recognized, the application of life-cycle for the process design is still limited and usually used to compare between different reaction pathways in terms of cumulative mass and energy demand and greenhouse gas emissions.

During the last three decades, the search for green reaction mediums with low environmental impacts has also expanded. Currently, the five main solvent systems considered to be “green” are water^[12], ionic liquids (ILs)^[13], fluorous solvents^[14], supercritical fluids^[15], and glycerol-based

1. Introduction

Environmental, health and safety considerations, inherent in many technical, political and economic decision-making processes, have likewise driven the chemical industry to find new, more environmentally friendly methods, e.g., green chemistry, to achieve more efficient resource utilization and to reduce or even eliminate the discharge of deleterious waste to the environment^[1,2]. As organic solvents are used daily in numerous industrial processes as reaction media, in separation procedures, and as diluters, the quest for green solvents that will have minimal impacts on the environment is of the utmost concern^[3,4].

solvents [16-18]. The greenness of each solvent is mainly derived from its physicochemical properties, such as its volatility and stability, and from its recyclability and reusability. In addition, solvent greenness depends on whether the solvent supports improved reaction activity and/or selectivity and whether it allows catalyst recycling. Yet from the environmental perspective, beyond solvent performance in the reaction step, the selection of a reaction solvent should also consider its whole life-cycle, which includes the material and energy utilized and the chemicals emitted during its production, use, and disposal [19, 20], (Fig. 1a [21]), i.e., the solvent's sustainability. Furthermore, the sustainability of a chemical process is derived from the total energy and materials consumed and chemicals discharged not only during the chemical process, but also during the reaction work-up steps, e.g., product separation, catalyst recycling, and re-use of chemicals (Fig. 1b [21]). Thus, the effect of solvent selection on the sustainability of a chemical process should include solvent production, the effects of solvent use on reaction conditions and performance, the heating technique, and the processes of product separation and catalyst recycling.

In this study, several solvents were rated, each according to its sustainability impact over the course of its entire life-cycle, from solvent production process through reaction performance to product separation. Several commonly used

solvents were studied in two representative reactions, the transfer-hydrogenation of either nitrobenzene or benzaldehyde (Fig. 2a and b, respectively) and the palladium catalyzed Suzuki cross-coupling of halobenzenes with phenylboronic acid (Fig. 2c).

Figure 2. Reactions used in the study: (a) transfer hydrogenation of benzaldehyde; (b) transfer hydrogenation of nitrobenzene; (c) Suzuki cross-coupling of halobenzene with phenylboronic acid.

Figure 1. Schematic life-cycle diagram of (a) solvent (b) reaction medium [21].

Table 1. Solvent characteristics for representative reactions [22]

Solvent	T _{NBP} (°C)	P° -20 °C (mmHg)	LD ₅₀ (mg/Kg)	FR ^a	HR ^a	R ^a	Properties Ranking
Transfer hydrogenation reaction							
Glycerol	290.0	7.95*10 ⁻⁴	12,600	1	2	0	1
1,2-Propanediol	187.6	1.27	20,000	1	2	0	1
1,3-Propanediol	214.0	0.08	15,000	1	2	0	1
Ethylene glycol	197.3	0.06	4,700	1	2	0	2
1-Propanol	97.5	15.00	1,870	3	2	0	3
2-Propanol	82.5	31.50	5,054	3	1	0	2
1-Pentanol	138	1.50	200	3	3	0	4
Suzuki cross-coupling							
Glycerol	290.0	7.95*10 ⁻⁴	12,600	1	2	0	1
BminBF ₄	-	-	300-500	1	1	0	2
Triacetin	259.0	2.90*10 ⁻³	1100	1	1	1	1
Water	100	17.41	91000	0	0	0	0

[a] Fire rating (FR), Hazard rating (HR) and reactivity (R): 0—lowest, 1—slight, 2—moderate, 3—high, 4—extreme

2. Methodology

The methodology used to rank the sustainability of the solvents was as follows: (i) first, a set of solvents was chosen for each reaction based on a literature review and on the availability of reaction date; (ii) each solvent was ranked in terms of environmental impact in several steps based on their general properties, solvent production process, and performance in the corresponding reaction and in product separation by extraction. In each step, solvents were ranked from 0-4 corresponding to most (0) to least (4) sustainable; (iii) the final step entailed a total sustainability ranking based on all the previous ranking steps.

2.1. Solvent Properties

Because solvent selection is a key step in green chemistry, the first stage in the investigation was the selection of potential solvents for the two representative reactions (Fig. 2). As the solvent in the catalytic transfer hydrogenation of unsaturated organic compounds is also simultaneously used as hydrogen donor, several short chain alcohols were proposed, together with diols (ethylene glycol and propandiol) and glycerol, as solvents. Representative solvent characteristics, including normal boiling point, vapor pressure, and median lethal dose (LD₅₀, which represents solvent toxicity), as well as flammability rating (FR), hazard rating (HR) and reactivity (R), are listed in Table 1 [22].

The same characteristics were also compared for four representative green solvents—water, glycerol, glycerol triacetate (triacetin) and 1-butyl-3-methyl tetrafluoroborate, BmimBF₄, as a representative ionic liquid—which were used in the Suzuki cross-coupling of halobenzenes and phenylboronic acid (Fig. 2c, Table 1). These green solvents were selected based on available reaction performance data, which will be used in the third step of the study.

From the environmental and operational points of view, all polyols are preferable solvents to simple alcohol in the transfer hydrogenation reaction due to the high boiling points and the low volatilities, flammabilities, toxicities and hazard ratings of the former (Table 1). In addition, although increasing the organic chain of the alcohol (as represented by comparing 1-pentanol and 1-propanol) decreases solvent volatility, it simultaneously increases its toxicity and potential health impact. Moreover, a comparison of the four polyols shows that ethylene glycol is the most toxic, as expressed by its lowest LD₅₀, while glycerol has the highest boiling point and lowest volatility.

For the Suzuki cross-coupling reaction, water was ranked as the most sustainable solvent while glycerol and triacetin were ranked afterward and received rankings of one, while BmimBF₄, which is much more toxic, received a ranking of two.

2.2. Solvent Production

In addition to a solvent's fundamental properties, which determine its potential environmental and health impacts when used, because its production process involves the use of materials and energy, it should also be considered in any sustainability analysis (Fig. 1, Table 2).

The alcohol solvents that were selected for use in the transfer hydrogenation reactions can be produced via different routes, and therefore, to facilitate the comparison, the following commercial processes were selected [23]: hydroformylation of ethylene or butene followed by hydrogenation of the formed aldehydes to produce 1-propanol or 1-pentanol, correspondingly; direct or indirect hydration of propene to produce 2-propanol; acid catalyzed hydration and ring opening of ethylene oxide to ethylene glycol and direct hydrolysis of propylene oxide to produce 1,2-propanediol; hydrolysis of acrolein to 3-hydroxypropanal followed by hydrogenation to produce 1,3-propanediol; and transesterification of oil (jatropha oil) for the production of glycerol [24].

Several reaction and process parameters were considered for the sustainability comparison of the various solvent production processes (Table 2): (1) **Renewability origin** – whether the solvent originates from a renewable source; (2) **Atom economy** – describes the theoretical conversion efficiency of a chemical process in terms of atoms that are involved in the production of the desired product; (3) **Reaction yield** – the ratio of the desired product formed to the total amount that could have been produced if conversion of the limiting reactant was 100% and no side reactions

occurred; (4) **E-factor** – the ratio of the mass of waste per unit of desired product; (5) **Reaction temperature range** – indicates the energy consumption during the process.

For transfer hydrogenation in alcohols, while glycerol originates from a renewable source and all other alcohols are manufactured mainly from petroleum based molecules and glycerol's production conditions are relatively low, glycerol production is the less efficient reaction with respect to its atom economy, E-factor and reaction yield (Table 2). Thus, based on these parameters, its solvent production step should render glycerol the less sustainable solvent among all the selected alcohols (solvents ranking based on this date is presented in Table 2 in brackets). Yet determining the sustainability of glycerol in terms of its production as a solvent is more complex. Glycerol is a by-product of the simple and efficient transesterification of oils and fats in the production of fatty acid derivatives for cosmetics and biofuel, i.e., biodiesel. Moreover, the synthesis of glycerol by glycerolysis of oil leads to the production of fatty acid derivatives that, as unwanted molecules and waste of glycerolysis, contribute to the calculations of atom economy and E-factor, but they are actually the desired molecules. Thus, the atom economy of glycerol synthesis by transesterification can be considered as 100% and the E-factor is much lower. Based on this characterization, therefore, glycerol was ranked as the most sustainable solvent among all alcohols in terms of its solvent production step.

Table 2. Solvent production process for representative reactions [23]

Solvent	Renewable origin	Atom economy (%)	Yield (%)	E-Factor ^[a]	Production Temperature (°C)	Production Ranking
Transfer hydrogenation reaction						
Glycerol [19]	Yes	30	84	5.58	60	(4) 0
1,2-Propanediol	No	100	100	3.89	100-125	(3) 4
1,3-Propanediol	No	100	45	1.22	100-150	(3) 4
Ethylene glycol	No	100	90	1.42	50-70	(1) 2
1-Propanol	No	61	99	0	90-150	(0) 1
2-Propanol	No	100	70	1.07	270-300	(2) 3
1-Pentanol	No	100	90	0.10	100-200	(0) 1
Suzuki cross-coupling						
Glycerol [19]	Yes	30 (100)	84	5.58	60	(0)
BminBF ₄ [21]	No	75	90	1.97	70-80	2
Triacetin [20]	Yes	86	100	2.22	100	1
Water	Yes	-	-	-	-	0

[a] (g waste)/(g solvent)

Comparing the characteristics of all other alcohols showed that while the production yields of 1-pentanol and 1-propanol are high and their E-factors are relatively low, the productions of the three diols are associated with the discharge of relatively high amount of waste (Table 2). Furthermore, the reaction conditions in the synthesis of ethylene glycol are much lower than that of propane diols, and thus its rank is higher, while 2-propanol production required relatively high temperature and resulted in lower yield than the two primary alcohols, and thus its ranking was higher.

Finally, glycerol was ranked together with water, whose production process cannot be compared, as the most sustainable solvents in terms of solvent production process for the Suzuki cross-coupling reaction. Triacetone^[25] and BminBF₄^[26] were ranked as less sustainable in terms of their production process parameters.

2.3. Solvent Reaction Performance and Product Separation

The next step of the study was to rank solvent sustainabilities in the reaction step. For the transfer hydrogenation reaction, this was done by averaging the reaction conversion of the two selected reactants, benzaldehyde and nitrobenzene (Fig. 2a and b) (Table 3)^[27-29]. As illustrated in Table 3, it was found that the three tested diols and 2-propanol showed the highest yields while glycerol, which bears three hydroxyl groups, was less active. This finding may be attributed to the higher polarity of glycerol, which leads to the lower miscibility of the relatively non-polar substrates in glycerol, and to its high viscosity, which may affect mass and heat transfer. It is also worth mentioning that 2-propanol, which is commonly used as the donor solvent in transfer hydrogenation, received a high ranking due to the higher conversions of both substrates in 2-propanol compared to in either 1-propanol or in

1-pentanol. This result may be explained by the secondary alcohol's oxidation potential, which was higher than those of the primary alcohols.

As product separation and catalyst and solvent recycling also determine the sustainability of a reaction process, these parameters were also considered for the transfer hydrogenation reaction. In the case of the simple alcohols like 1-propanol, separation of the product is usually done by solvent evaporation under reduced pressure and washing of the catalyst. In contrast, using polyols as donor solvents allowed product separation by extraction with polyol-immiscible solvents such as ethers or dichloromethane, and although it required the addition of an extraction solvent, which is also toxic, it also allowed catalyst recycling and solvent re-use. Thus, extractions of neat aniline, the product of the transfer hydrogenation of nitrobenzene (Fig. 2b), from the four tested polyols were performed with petroleum ether as the representative extraction solvent followed by extraction solvent evaporation under reduced pressure. The extraction yields of aniline are illustrated in Table 3. Though the differences between the four tested solvents were small, extraction of aniline from glycerol was slightly higher.

Solvent effect on reaction performance was also evaluated for the Suzuki cross-coupling reaction of halobenzenes with phenylboronic acid (Fig. 2c, Table 4). The dates of experiments recounted in the literature under relatively similar reaction conditions were collected^[18,30-32], but it was difficult to find a reaction date for the Suzuki cross-coupling of a simple halobenzene, like iodobenzene in water, when simple palladium salt was used as the catalyst and thus bromotoluene was used as a reactant^[32]. The results in Table 4 show that the reactions in water and BminBF₄ were much faster but at higher temperatures and that with the exception of the reaction in triacetone, all the reactions reached almost full conversion.

Table 3. Transfer hydrogenation in alcoholic solvents.

Solvent	Nitrobenzene conversion ^[a] (%)	Benzaldehyde Conversion ^[b] (%)	Aniline extraction yield ^[c] (%)	Reaction Ranking
Glycerol	47.2	19.1	92	3
1,2-Propanediol	88.9	36.9	85	0
1,3-Propanediol	88.5	35.9	84	0
Ethylene glycol	88.2	36.7	81	0
1-Propanol	38.4	11.9	-	3
2-Propanol	76.5	32.0	-	0
1-Pentanol	-	18.2	-	4

[a] Reaction conditions: 5 g solvent, 1 g nitrobenzene, 0.2 g NaOH, 0.1 g Raney nickel, 100 °C, 24 h.

[b] Reaction conditions: 4 g solvent, 2.2 mmol benzaldehyde, Ru(p-cumene)Cl₂-dimer -S/C=100, 270 °C, 5 h.

[c] Extraction conditions: 5 g glycerol, 1 g nitrobenzene, 5×5 mL petroleum ether, room temperature

Table 4. Palladium catalyzed Suzuki cross-coupling in various green solvents

Solvent	Catalyst (%mol)	Substrate (mmol)	Base (mmol)	T (°C)	t (min)	Yield (%)	Reaction Ranking
Glycerol [25]	Pd(OAc) ₂ (2)	IB (0.5)	NaCO ₃ (0.6)	80	60	95	0
BminBF ₄ [26]	Pd(PPh ₃) ₄ (1.2)	IB (2.5)	NaCO ₃ (5)	110	10	95	0
Triacetin [13]	Pd(OAc) ₂ (2)	IB (0.5)	NaCO ₃ (0.6)	80	150	70	1
Water [27]	Pd(OAc) ₂ (0.4)	4-BT (1)	NaCO ₃ (3)+ TBAB (1)	150	5	96	0

2.4. Total Sustainability Ranking

As previously mentioned, the total sustainability of each reaction in a cretin solvent should consider many aspects and measures, yet the relative weight of each parameter is very difficult to determine. It is clear that reaction yield is one of the most important factors, and that it also dictates the reaction condition and the separation procedures, and thus the E-factor. However, in an overall perspective the solvent production procedure should also be considered as well as its hazard and flammability rating.

The sustainability ranking of all solvents in the transfer hydrogenation in alcohols is illustrated in Fig. 3. The ranking for glycerol in the solvent production step used that which took into account that glycerol is a by-product of the transesterification of oils in the production of valuable fatty acid derivatives (i.e., 100% atom economy and low E-factor). It was found that for transfer hydrogenation in alcohol that act both as solvent and hydrogen donor, there is no single solvent which is superior over the other. Glycerol's renewable origin and preferable properties as well as to it being a by-product in the production of fatty acid derivatives makes it attractive solvent, however the catalytic performance in glycerol is lower. On the other hand, all three diols have promising characteristics and allowed high products yields, yet their production process is associated with relatively high amount of waste. Finally, based on the various aspects that were studied, it seems that ethylene glycol is the most sustainable solvent for the reaction, while the traditionally used short alcohols were less attractive in terms of sustainability.

Figure 3. Sustainability ranking for transfer hydrogenation reaction

For the Suzuki cross-coupling reaction, BminBF₄ was found to be the less sustainable solvent due to its non-sustainable production process and high toxicity. Triacetin, a green solvent produced from a renewable source, was found to perform very low in the reaction step, which significantly decreased its total sustainability ranking. Thus, the total sustainability ranking for the Suzuki cross-coupling of halobenzene and phenylboronic acid (Fig. 2c) was found to be water = glycerol > triacetin > BminBF₄.

3. Conclusions

In this study selected solvents that were used as reaction mediums in two representative reactions—transfer hydrogenation of unsaturated organic compounds and Suzuki cross-coupling of halobenzene and phenylboronic acid—were each assigned a sustainability ranking based on the solvent's fundamental properties, production process, and how it performed in the reaction and in product separation. Based on solvent life-cycle and physical characteristics ethylene glycol was found to be the most sustainable solvent for the transfer hydrogenation reaction and glycerol was found to be the most sustainable solvent for the Suzuki cross-coupling reaction.

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