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Diformylxylose as a new polar aprotic solvent produced from renewable biomass†

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Demand for sustainable polar aprotic solvents is increasing due to their unique solubilizing properties and the toxicity of conventional analogs, which are facing pressure from extensive safety legislation. Polar aprotic solvents are particularly difficult to produce renewably because polar molecules that lack hydroxyl groups are rarely found in abundance in the natural world. Here, we explore the use of diformylxylose (DFX), a xylose-derived molecule that can be produced in a single step from lignocellulosic biomass, as a novel polar aprotic bio-based solvent. We notably demonstrate that diformylxylose shows a similar performance to conventional polar aprotic solvents (DMF, NMP, DMSO) in alkylation, cross-coupling (Heck), and hydrogenation reactions. We also demonstrate its straightforward production from commercial xylose and show that it is non-mutagenic, according to the Ames test. Renewable DFX appears to be a greener alternative to common polar aprotic solvents that are considered problematic for industry.

Introduction

In recent decades, the gradual depletion of fossil resources, increase in global energy consumption, and the environmental issues associated with the extraction and consumption of hydrocarbons have encouraged the development of new chemicals and materials produced from renewable biological sources (biomass, food waste, *etc.*). One area of interest to the chemical and pharmaceutical industry is the development of bio-based solvents that could compete with existing petroleum-derived solvents. In principle, bio-based solvents will have reduced net carbon dioxide emissions in the atmosphere during their life cycle and thus cause less damage to the environment.[1]

The development of viable replacements for polar aprotic solvents has recently been identified as a key priority for green chemistry research according to ACS Green Chemistry Institute® Pharmaceutical Roundtable.[2] They possess unique characteristics such as high polarity and low reactivity, which makes them excellent media for the production of active pharmaceutical ingredients. However, many commonly used polar aprotic solvents are extremely hazardous, mutagenic, and negatively impact the environment,[3,4] which provokes regulatory response. For instance, the European Union REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation has restricted the industrial use of *N*-methylpyrrolidinone (NMP), and listed *N*,*N*-dimethylacetamide (DMAc) and *N*,*N*-dimethylformamide (DMF) as substances of very high concern due to their severe reproductive toxicity.[5] Moreover, solvent sustainability is often a determining factor in the environmental performance of processes because large solvent quantities are usually required to run said processes. Consequently, environmental regulatory agencies of different countries strongly encourage the development of innovative and safe reaction media, preferably from renewable sources.[3]

Direct production of polar aprotic compounds from renewable feedstock is challenging. The majority of molecules that can be extracted from biological sources are protic (*e.g.*, carbohydrates, carboxylic acids, lignin, alcohols, *etc.*). Therefore, multi-step processes, sometimes involving metals and high pressure are often required to convert protic molecules to aprotic ones.[6,7] This significantly increases the production cost of solvents and strongly limits their widespread use. Some examples of bio-based polar aprotic solvents that have seen limited applications at an industrial scale, notably due to a higher production cost compared to petroleum based alternatives, are γ-valerolactone (GVL), dimethylisosorbide.[4] Another commercially available "green" aprotic solvent with moderate polarity—cyclopentyl methyl ether (CPME)—is currently produced by petrochemical means as its production from bio-based substrates cannot compete with fossil counterpart.[8]

Apart from the cost, several properties (*e.g.* boiling/melting points, viscosity, stability, flammability, *etc.*) are also impor-

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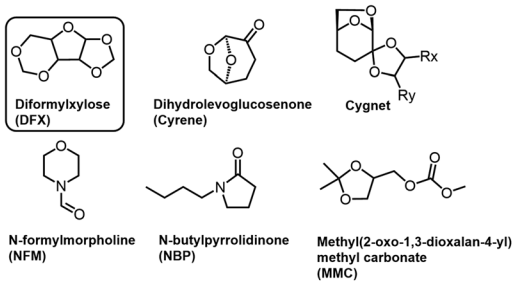
tant factors for a solvent's implementation in industry and routine laboratory use. For example, the well-known green solvent 2-Me-THF is still considered "problematic" by industry due to its high flammability.[9] The use of cyclic carbonates (ethylene and propylene carbonates), GVL, or Cyrene is limited by poor stability in the presence of strong reactants (acids, bases, oxidizers, reducers). The recently reported Cygnet (Cyrene derivative)[10] and *N*-formylmorpholine are solids at room temperature and have high boiling points (>230 °C), which complicates their recovery and handling. This also applies to Methyl(2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC), which also appears to be mutagenic, according to preliminary tests.[11] A novel potential replacement for DMF and NMP—*N*-butylpyrrolidinone (NBP)—is more acutely toxic (LD50 rat oral, 300–2000 mg kg^{-1}) than NMP (~4000 mg kg^{-1}), quite expensive and not well-studied yet (Scheme 1).[12]

Overall, developing a solvent that can be produced inexpensively from renewable sources, and has attractive physical–chemical properties combined with non-toxic and environmentally friendly nature, is a very challenging task. In this context, acetal-stabilized xylose, or diformylxylose (DFX), could be an interesting candidate for use as a polar aprotic solvent. In particular, DFX can be produced directly from biomass at over 95% yield (on a xylan basis) or from xylose using inexpensive mineral acids as catalysts in common glassware under mild conditions in a single step.[13–15] In this work, we exploit DFX's ease of production and explore its properties when used as a bio-based polar aprotic solvent in alkylation, hydrogenation, and cross-coupling reactions.



Scheme 1 Diformylxylose and other novel polar aprotic solvents.

Results and discussion

Physical properties of diformylxylose

The most relevant solvent properties were measured for DFX and compared with other solvents (Table 1). The boiling point of DFX was measured as 237 °C, which is close to the value for ethylene carbonate. This high boiling point can increase the complexity and energy requirements of its recycling, but it also lowers the risk of human exposure and the environmental impact (specifically aquatic toxicity) due to its low volatility.[16,17] DFX has a high melting point as well (48 °C), which puts it on a par with other solvents that are solids at room temperature (*e.g.*, ethylene carbonate, *N*-formylmorpholine, cygnet, sulfolane). The density of DFX as was experimentally determined as 1.35 g mL^{-1} at 50 °C, which is close to the density of sulfolane, cyrene, and some chlorinated solvents at 25 °C. DFX has poor solubility in water, similar to 2-MeTHF, which allows it to be easily recovered from water and also allows it to be used in applications that require water-immiscible solvents.[16]

Solvation properties of diformylxylose

Solvation properties such as polarity, hydrogen bonding ability, and van der Waals (dispersion) forces play a significant role in controlling reaction kinetics, extraction ability, product selectivities, and consequently, the efficiency of using the solvent. There are computation tools available to predict these properties for novel solvent candidates and compare them to those of conventional analogs that need replacing. Moreover, such tools allow for modelling the molecular geometry of the new solvents to see how they will interact with surrounding solutes, *e.g.* which regions of the molecule will be predominantly involved in those interactions. This knowledge can explain observed effects and could inform ways of further modifying the solvent structure to achieve effective solvation.

Table 1 Physical and solvation properties of DFX compared to selected solvents

	Physical properties				Kamlet–Taft Parameters			Hansen solubility parameters, $MPa^{\frac{1}{2}}$			
Solvents	Boiling point, °C	Melting poing,°C	Density, g ml^{-1} (at 25 °C)	Solubility in water, g per 100 g (at 25 °C)	α	β	π^*	δD	δP	δH	Ref.
Diformylxylose	237	48	1.35	13	0.00	0.82	0.92	17.9	9.0	7.60	This work
DMSO	189	19	0.89	∞	0.00	0.74	1.00	18.4	16.4	10.2	23
Ethylene carbonate	238	35	1.32	26	0.00	0.32	0.99	18.0	21.7	5.10	44
Sulfolane	282	27.5	1.26	∞	0.00	0.39	0.98	17.8	17.4	8.70	32
Cyrene	155	<−20	1.25	∞	0.00	0.61	0.93	18.9	12.7	7.10	32
NMP	202	−24	1.25	∞	0.00	0.75	0.90	18.0	12.3	7.20	23
GVL	207	−31	1.05	∞	0.00	0.60	0.83	15.5	4.70	6.60	24
N-Butylpyrrolidinone	241	<−75	0.96	∞	0.00	0.92	0.77	17.4	6.70	5.20	12
1,4-Dioxane	101	11.8	1.03	∞	0.00	0.37	0.55	17.3	4.30	8.40	23
2-Me-THF	80	−136	0.85	14	0.00	0.58	0.53	16.9	5.00	4.30	24

***In silico* COSMO-RS modelling.** To investigate chemical nature of DFX, the molecule was first modelled using the COSMO-RS Software, which is widely used for property estimation and solvent screening.[18,19] The charge density found on the surface of DFX was calculated to produce a 3D representation (Fig. 1A), which was then used to plot the corresponding sigma-profile (Fig. 1B). The Sigma profile of DFX covers the range from +0.017 e A^{-2} to −0.01 e A^{-2}, which corresponds to normal σ values for stable organic molecules.[20] COSMO-RS theory considers σ regions outside of +0.01 e A^{-2} and −0.01 e A^{-2} as strongly polar with molecules having the potential to form hydrogen bonds, while the region between ±0.01 e A^{-2} is considered nonpolar (no charge). The profile for DFX shows a peak outside of this region (Fig. 1B) indicating its ability to accept hydrogen bonds. A lot of DFX's non-polar hydrocarbon bonds are visually reflected in the σ-profile as a peak around −0.007 e A^{-2}. The fact that both peaks are sufficiently spaced from zero reflects the polar nature of the molecule, which is very similar to the sigma-profile of some polar aprotic solvents such as DMSO, DMF, and acetone.[21] This suggests that DFX could be a reasonable substitution for those solvents in chemical reactions. This generated COSMO-RS data can also be used to estimate the thermodynamic properties, relative solvation energies, predict equilibria, and explain results obtained in model reactions.

Solvatochromic (Kamlet–Abboud–Taft) parameters. Computationally predicted properties of DFX were confirmed experimentally using the Kamlet–Abboud–Taft solvatochromic parameters.[22–24] These parameters represent a reliable set of solvent polarity indicators that can quantitatively describe three principle chemical properties of a solvent: polarity/polarizability (π^*), hydrogen-bond donating ability or acidity (α), hydrogen-bond accepting ability or basicity (β). The determination of the Kamlet–Abboud–Taft parameters relies on solvatochromic phenomena observed when the absorption spectrum of a chemical substance (dye) changes in different solvents depending on their polarity and hydrogen-bonding ability (Fig. 1C and D). The solvatochromism of DFX (Table 1) demonstrated that this molecule was quite polar since its value of π^* (0.92) was in the range of conventional highly polar aprotic solvents (*e.g.* DMSO, NMP). DFX's hydrogen bond accepting ability (β) was also very high, which is likely due to the presence of 5 oxygen atoms in its structure, which can each donate an electron pair. The parameter α was assumed to be 0.00 as is the case for other polar aprotic solvents that cannot act as hydrogen bond donors. Based on the resulting Kamlet–Abboud–Taft parameters, we established a two-dimensional solvent map to compare DFX with other existing solvents in a parametric space (Fig. 2). Solvents, which are close to one another on the solvent map, are likely to have similar solvent properties. DFX occupies a unique space above conventional polar aprotic solvents, due to its high basicity. This area of the solvent map is not yet populated by any known bio-based solvents or green solvents, which suggests that DFX is a promising candidate for the replacement of some of the highly toxic polar aprotic solvents such as NMP, DMF, DMAc, *etc.* and might also have unique applications due to its high hydrogen bond accepting ability.

In addition to the Kamlet–Abboud–Taft parameters, we measured Nile red dye absorbance in DFX. The Nile Red absorbance is a measure of both polarity and acidity together, but is not dependent on polarizability (unlike the π^* parameter, which always incorporates both polarity and polarizability). In the case of polar aprotic solvents, the acidity is 0, so the value is dictated by polarity only. We found the wavelength of maximum absorbance of Nile red in DFX to be 543 nm and the E_{NR} (kcal mol^{-1}) = 52.68 (Fig. S1†). The value for DFX lies between that of sulfolane (545 nm) and DMF (541 nm),[25] which are two well-known aprotic solvents with high polarity.

Hansen solubility parameters. The Hansen solubility parameters (HSP) are often used as another metric to characterise the solvation profile of solvents in terms of their dispersion forces (δD), polar dipole–dipole interactions (δP), and specific interactions such as hydrogen bonding (δH).[26] Together these three parameters are used to construct a 3D coordinate space called "Hansen space", containing all solvents as separate data points. Based on the Hansen Solubility Parameters (Table 1), we calculated the distance between DFX and other solvents in the Hansen space. The closest matching solvents were dimethyl isosorbide, dichloromethane, cyclohexanone, 1,4-dioxane, 1,3-dioxolane, isophorone, NMP, and THF (Table S4†).

Despite the close HSP match between DFX and dichloromethane, other approaches didn't show such similarity. In contrast to the Kamlet–Abboud–Taft approach, the Hansen model doesn't distinguish between hydrogen bond donating and accepting ability. Also, the latter differentiates between dispersion forces and polarity, which are combined into the term π^* in the Kamlet–Abboud–Taft model. These differences in assumptions in each model might explain some contrasts in solvent similarity predictions. The COSMO-RS approach

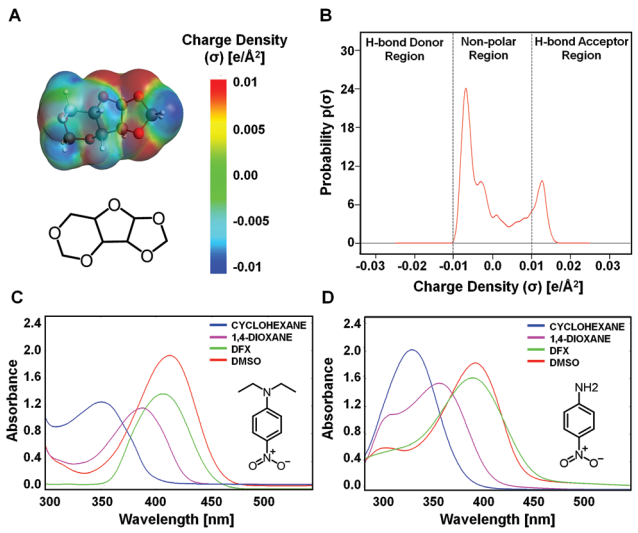


Fig. 1 (A) Sigma-surface of DFX and (B) Sigma-profile of DFX modelled with COSMO-RS. (C) Absorption spectra of *N*,*N*-diethyl-4-nitroaniline and (D) 4-nitroaniline in different solvents.

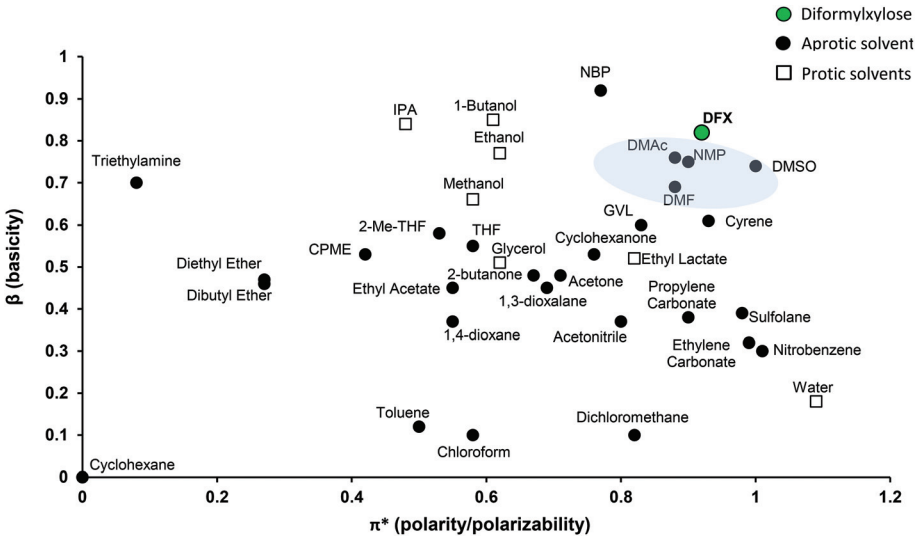


Fig. 2 Solvent map based on Kamlet–Abboud–Taft parameters β and π^* comparing DFX (green marker) to other solvents, including traditional highly polar aprotic solvents (highlighted within the blue oval).

also demonstrated no significant similarity between DFX and chlorinated solvents, which occupy the same region as ethers in the Hansen space. In other works, COSMO-RS calculations have shown that the hydrogen bonding of chlorinated solvents is acidic in character,[27] while for oxygenated solvents (including DFX) it is basic (*i.e.* electron donating). Nevertheless, all approaches help to identify potential substitution targets and suitable applications for DFX.

Performance of diformylxylose in model reactions

Alkylation (Menshutkin) reaction. Alkylation reactions are among the most frequent transformations performed in medicinal chemistry and the pharmaceutical industry.[28,29] Among Alkylations, the Menshutkin reaction has been extensively studied as a model reaction for revealing solvent effects on chemical reactivity because its rate is quite sensitive to solvent polarity.[30,31] Here, the reaction was performed between 1-bromodecane and 1,2-dimethylimidazole, which is analogous to the system used by Sherwood, *et al.* to assess Cyrene as a solvent.[32] The rate of the reaction was studied in DFX and 9 other solvents (Fig. 3) in order to cover a range of polarities and obtain strong correlations. The Kamlet–Abboud–Taft parameters of the solvents (α, β, π^*) were used to correlate the measured kinetic rate constants with solvent properties using a Linear Solvation Energy Relationship (LSER).[22] This model implements multiple regression analysis based on solvent-dependent physicochemical properties. The resulting LSER regression gave the following expression (eqn (1)) for our case study:

$$\ln k = -8.46\text{–}0.05\alpha - 0.14\beta + 2.16\pi * (R^2 = 0.98)(1) \qquad (1)$$

From this regression, the π^* parameter (polarity/polarizability) had the greatest positive effect on the reaction rate, while two other parameters (α, β) had a mostly negligible effect. As a result, we observed a near linear correlation

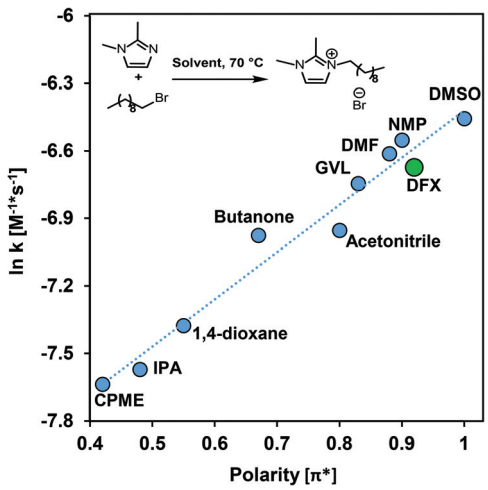


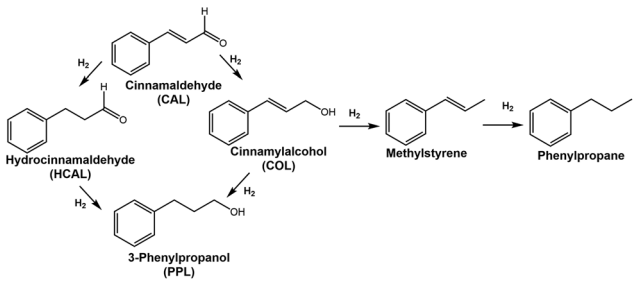
Fig. 3 Solvent effects on the model Menshutkin reaction as shown by the relationship between solvent polarity and the natural logarithm of the rate of reaction constant.

between the natural log of the rate constants and polarity/polarizability of the solvents (Fig. 3).

This correlation with polarity is consistent with the proposed mechanism of the Menshutkin reaction, where solvent polarity facilitates a charge separation at the transition state *via* favourable solute–solvent interactions, accelerating the whole process.[33,34] This makes solvents like DMSO the best medium for accelerating heteroatom alkylations. However, typical high polarity solvents such as DMSO, DMF, NMP are toxic and associated with many environmental and sustainability concerns. In this regard, DFX could be one of the best alternatives for this type of reaction, outperforming some other polar aprotic solvents, including recently proposed "green" alternatives such as GVL[35] or CPME.[8]

Hydrogenation reactions. Hydrogenation of cinnamaldehyde (CAL) is an industrially relevant reaction as it produces useful intermediates for pharmaceuticals and fragrances.[36] Usually, hydrocinnamaldehyde (HCAL) and cinnamylalcohol (COL) are formed through two parallel reactions, while 3-phenylpropanol (PPL) is formed by consecutive hydrogenation of both HCA and CAL (Scheme 2). Propyl benzene and a trace of β-methylstyrene can also be formed during this reaction.[37] Furthermore, hydrogenation of CAL over a heterogeneous catalyst is an example of a triphasic system with interfaces between a liquid and solid (catalyst) and between a liquid and a gas (hydrogen gas), which makes it an interesting case study for investigating solvent effects.

To this effect, the hydrogenation of CAL was examined in a series of organic solvents at 70 °C over Pd/C catalyst (Fig. 4). Several past studies have demonstrated that the associated reaction rate was dependent on the solvent used, with alcohols showing the highest rates.[37–39] Our results were consistent with the literature as we observed 81% and 90% CAL conversion in isopropanol (IPA) and methanol (MeOH), respectively. However, similarly high conversions were also achieved in nonpolar aprotic solvents (dibutyl and diethyl ethers (DEE), and cyclohexane). Li Yan, *et al*. reported conversion of CAL over Pd/C in DEE that was about two-fold lower than in DMF and about three-fold lower than in THF.[40] This inconsistency can be a result of the differences in the metal loadings (1 *vs.* 5 wt%), and/or the temperatures (70 *vs.* 50 °C). Ethers with medium polarity (1,4-dioxane and THF) also facilitated the reaction, while conventional polar aprotic solvents (DMSO, DMF) led to the slowest kinetics. DFX was in line with the trend for other polar aprotic solvents, making it a suitable solvent for this reaction if a cheap non-volatile bio-based solvent is required. Increasing catalyst loading to 10 wt% and letting the reaction proceed for 24 h led to 90% conversion in DFX (Fig. 4, Fig. S5†). Overall, the observed order of CAL conversion over Pd/C at 70 °C was the following: nonpolar aprotic ≥ protic > medium polar aprotic > highly polar aprotic.



Scheme 2 Cinnamaldehyde hydrogenation network.

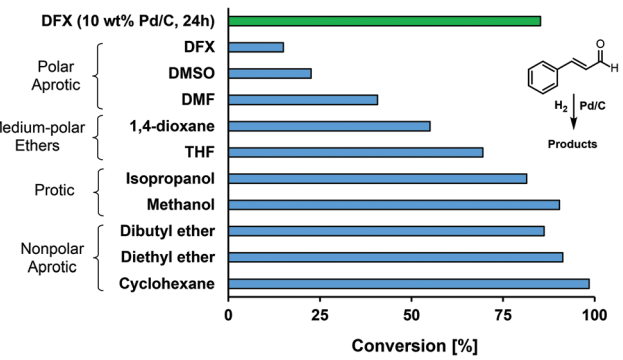


Fig. 4 Conversion of cinnamaldehyde under hydrogenation conditions in various solvents over 1 wt% Pd/C catalyst at 70 °C, after 30 min (or otherwise indicated).

In order to explain these results, we again attempted to correlate the Hansen Solubility Parameters of all studied solvents to conversion values in these solvents. Surprisingly, the conversion appeared to increase when all three terms (solvent polarity, dispersion, and hydrogen-bonding ability) decreased for all aprotic solvents (Fig. S3†). This could be explained by the fact that any properties of the solvent that facilitate interaction with the solvent and catalyst could increase competitive adsorption of the solvent and decrease rates. Past results have shown that competitive adsorption can occur due to coordination between the solvent and metal surface, which blocks hydrogenation active sites.[38]Hence, any solvent having exclusive electron pairs (high β) can be expected to interact with the catalyst to some extent, which is the case for DFX, DMSO, and DMF. Dispersion interactions between the surface and solvent, although weak, can also affect conversion. Therefore, more "inert" solvents such as cyclohexane (almost 100% conversion) provide the best option for this reaction in the chosen conditions as they do not adsorb on the catalysts as much as others. Simultaneously, they don't strongly interact with the substrate, which, in principle, should limit the reaction, but this effect might be negligible due to the high temperature that is used. Interestingly, protic solvents methanol and IPA did not follow this trend. However, previous research suggests that protic solvents promote hydrogenation through hydrogen bonding with the substrates and products, which would overcome the inhibition imposed by competitive adsorption.[41]

Another factor that influences this heterogeneous reaction is the solubility of the gaseous reactant, H_2. Total conversion had an almost linear relationship (R^2 = 0.98) with the solubility of H_2 in polar aprotic solvents (Fig. S4†). The rate of this reaction has previously been shown to be proportional to a square root of hydrogen concentration,[42] which means that solubility of hydrogen in the solvent plays a vital role and explains the resulting trends.

In terms of selectivity, HCAL was the main product obtained in all the tested solvents including DFX, where a selectivity of more than 60% was always obtained (Table S6†). These results are consistent with other studies.[37,40] Hydrogenation in IPA and MeOH led to the formation of acetals, which is an undesirable feature of alcoholic solvents and limits their use for this reaction despite the high conversion observed in these solvents.

Importantly, DFX remained stable under hydrogenation conditions (40 bar of H_2, 70 °C, 24 h), suggesting that this

solvent could be used in reactions requiring high pressure of H_2, elevated temperature, and/or long reaction time, which is a very desirable property for biomass-derived solvents.

Cross-coupling (Heck) reaction. The Heck or Mizoroki–Heck reaction is a palladium-catalysed cross-coupling reaction that is frequently used in the pharmaceutical industry.[43] The reaction is notably used for preparation of substituted alkenes from aryl halides. To further benchmark DFX as a solvent, we used the case study of methyl acrylate and iodobenzene reacting at 363 K with $Pd(OAc)_2$ as a catalyst in both DFX and other solvents to compare their relative performance. This reaction is a common system that has been used in prior studies to test novel solvents, such as *N*-butylpyrrolidinone as a substitute for NMP solvent,[12] as well as other green solvents such as cyclic carbonates[44] or GVL.[45]

From the results of solvent screening, the initial rate of reaction to give methyl cinnamate was found to be proportional to the polarity of the solvent expressed as π^* (Fig. 5). Hydrogen bond-accepting ability (β) was not statistically significant. The comparative kinetic study[46] showed that the rate-determining step of the catalytic cycle in the Heck reaction was the dissolution of palladium aggregates, which explained the observed trends. Polar solvents have a strong influence on the solubilization and stabilization of palladium.[47] Notably, DMF was found to be an outlier of the otherwise linear relationship, demonstrating the fastest kinetics, which was consistent with previous studies.[12,44,48] This is probably due to the well-known coordination behaviour of DMF, which can effectively stabilize palladium particles in solution phase. Moreover, the formyl proton of DMF can participate in hydrogen bonding between DMF molecules, thus enhancing interactions between the solvent and solutes, while other polar aprotic solvents do not have this feature.[49] Another coordinating amide solvent, NMP, also favoured the reaction. However, both DMF and NMP are reprotoxic and banned (at least partially) from industrial use, so their high reactivity is not substantial enough to justify their use. DFX has the right solvation properties to promote this reaction even if it led to slightly slower kinetics compared to solvents with similar polarity. These slower kinetics could be related to the absence of any π bonding in the structure of DFX, which has been thought to stabilize the formation of the adduct between the catalyst and reactant by coordinating with the emergent palladium-carbon bond.[44,50]

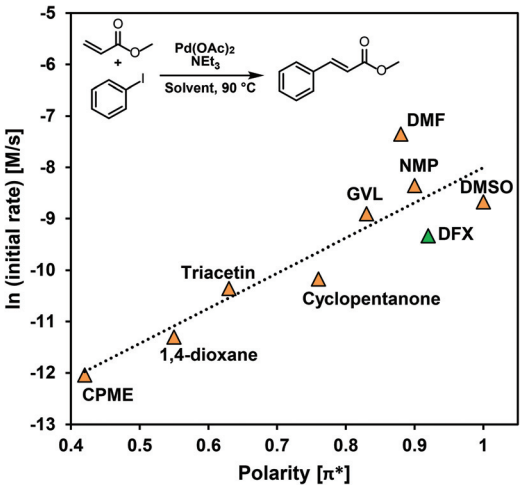


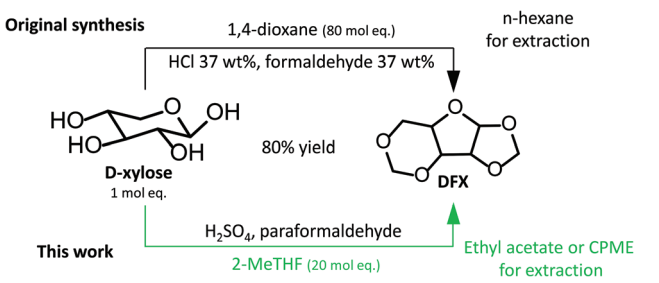
Fig. 5 Solvent effects on the model Heck reaction as shown by the relationship between solvent polarity and the natural logarithm of the initial rate of reaction.

Toxicological assessment

New compounds introduced in industrial applications and other human activities are always subject to toxicological assessment. Such assessments are even more essential for the development of new solvents as they will be used in relatively big quantities within a process. Because of the large quantities used compared to the product, these solvents can find their way into many everyday products, which can in turn expose the public.[51] Full toxicity testing is beyond the scope of this early proof-of-concept work but some predictive tools and simple screening tests can be used. Specifically, a toxicological assessment of DFX was performed using the Ames test – a worldwide standard for testing new compounds to quickly determine if they are potentially mutagenic and carcinogenic.[52] According to the test, DFX was unable to cause mutations both directly or indirectly (Fig. S7†), which indicates that it is a promising molecule in terms of health and safety, although other extensive *in vitro* and *in vivo* tests would be necessary to provide a robust assessment.

Diformylxylose production

Diformylxylose can be produced during formaldehyde-assisted processing of biomass at a yield close to 95–99% of native xylan.[14] We also reported that it can be directly synthesized from D-xylose in the presence of a 37 wt% aqueous solution of formaldehyde and 37 wt% aqueous solution of HCl using 1,4-dioxane as a solvent.[15] In this work, we propose a novel synthetic route for the direct production of DFX from D-xylose using safer, more environmentally friendly chemicals (bio-based 2-Me-THF instead of 1,4-dioxane, solid paraformaldehyde instead of aqueous solution of formaldehyde, ethyl acetate and CPME instead of *n*-hexane, (Scheme 3). This new



Scheme 3 Original and new synthetic approach for the synthesis of DFX from D-xylose.

synthetic route also reduced the required quantity of solvent without sacrificing any yield.

First, we eliminated water from the synthesis by substituting the HCl (37 wt% aqueous solution) with H_2SO_4 (98–99 wt%) and the formaldehyde (37 wt% aqueous solution, formalin) with paraformaldehyde. These modifications allowed us to use a green solvent – 2-Me-THF (which is not miscible with water) – in the reaction instead of 1,4-dioxane, a carcinogen linked to organ toxicity and an environmental contaminant.[54,55] Moreover, significantly less solvent can now be used (3-times less by volume) to achieve the same yield (75–80%) (Fig. S8†). Interestingly, the yield of furfural produced during dehydration of xylose under acidic conditions was almost negligible in this new synthesis. We hypothesize that this is because the 2-Me-THF didn't promote the dehydration as much as 1,4-dioxane as it has been shown that polar aprotic solvents significantly affect the kinetics of this acid-catalysed reaction by changing the stabilization of the acidic proton relative to the protonated transition states.[56]

Second, ethyl acetate or CPME can be used as extraction solvents instead of *n*-hexane (a known neurotoxin). Obviously, as a formaldehyde-releasing agent, paraformaldehyde is also a potential carcinogen.[57] However, based on available toxicological information, it is still a safer alternative. For example, its lethal concentration by inhalation (LC50, 4 h exposure) in rats is 1070 mg L^{-1}, while for formalin, the LC50 is 0.578 mg L^{-1}. Also, for oral median lethal dose (LD50) the corresponding values are 800 mg kg^{-1} for paraformaldehyde and 500 mg kg^{-1} for formaldehyde 37 wt%.[58,59]

Diformylxylose stability

The stability of DFX under harsh conditions (in the presence of strong acids, bases, or high pressure) was explored to identify potential limitations of its use.

Carbohydrate-based molecules are typically converted into small molecules and insoluble humins in the presence of acid.[53] We evaluated the stability of pure DFX under harsh acidic conditions (0.8 M HCl). The results demonstrated that at a temperature range between 70 to 95 °C, more than 80% of DFX could be recovered (Fig. S9A†). The 20% of loss was most likely caused by typical sugar degradation to products such as furfural, carboxylic acids, and humins. Interestingly, when adding formaldehyde, around 90% of DFX remained stable likely due to a shift in equilibrium towards the reprotection of xylose (Fig. S9B†). For comparison, at the same conditions (95 °C or 70 °C, 0.8 M HCl), another novel commercially available carbohydrate-derived solvent such as Cyrene had undergone extensive degradation, as it formed a dark solidified slurry after 15 min of reaction. In this regard, DFX is relatively stable under acidic conditions, but we still advise against the use of strong acids when using DFX.

To assess DFX's stability under basic conditions, we tested a series of organic and inorganic bases at 1.4 M concentration of the base of interest at 80 °C and 110 °C for a maximum of 48 h (Table S8†). As a result, we identified that inorganic bases such as K_2CO_3, NaOH, $CsCO_3$ led to degradation (maximum 21% after 48 h) and the formation of a dark solution. Triethylamine caused less than 5% of degradation, but also led to the formation of a dark solution. In this case, it is likely that impurities existing in DFX (which was 95% pure) also contributed to the colour change. The presence of pyridine or KOAc, which are relatively weak bases didn't lead to any significant effect on DFX stability. Importantly, the control solution of pure DFX didn't undergo any degradation after 48 h at 110 °C, which demonstrated the high thermal stability of DFX.

Finally, under hydrogenation conditions DFX remained stable at 40 bar of H_2, 70 °C, 24 h and 40 bar of H_2, 250 °C, 3 h.

Experimental

Determination of the Kamlet–Abboud–Taft solvatochromic parameters

The Kamlet–Abboud–Taft parameters π^* and β were determined based on the shift in absorption spectrum of two dyes *N*,*N*-diethyl-4-nitroaniline (DENA), and 4-nitroaniline (NA), respectively. The dyes were dissolved in different solvents at three concentrations typically ranging from 10^{-3} to 10^{-4} M. The UV-vis spectra of the samples were then measured at 23 °C and 65 °C (for DFX) on a UV-visible scanning spectrophotometer UV-3100PC (VWR) at scan step 0.5 nm and a scan range 190–1000 nm.

Each of the Kamlet–Abboud–Taft parameters was scaled to two reference solvents, one set to a value of 1(DMSO) and the other to a value of 0 (cyclohexane).[24] The Kamlet–Abboud–Taft values were calculated using the following eqn (2)–(4):

$$\pi* = \frac{\nu_{\text{DENA (solvent)}} - \nu_{\text{DENA(cyclohexane)}}}{\nu_{\text{DENA(DMSO)}} - \nu_{\text{DENA(cyclohexane)}}} \quad (2)$$

$$\beta = \frac{\left(\Delta\nu_{\text{solvent}} - \Delta\nu_{\text{cyclohexane}}\right) \times 0.76}{\Delta\nu_{\text{DMSO}} - \Delta\nu_{\text{cyclohexane}}} \quad (3)$$

$$\Delta\nu = \nu_{\text{DENA}} - \nu_{\text{NA}} \quad (4)$$

where ν is the experimental wavenumber at the maximum wavelength of the probe. At least three independent samples were prepared to determine the solvatochromic parameters and associated standard deviation, which was lower than 2% in all measurements (Tables S2 and S3†).

Computational predictions

COSMO-RS. Amsterdam Density Functional (ADF) Software was used to preoptimize the geometry of DFX with a UFF (Universal Force Field), and then to fully optimize with standard "COSMO-RS Compound Preset Settings". COSMO-RS software was then used to generate a charge density map, and the corresponding sigma-surface and sigma-profile.

Hansen solubility parameters. Hansen Solubility Parameters HSP (δ_d, δ_p, δ_h), for DFX were predicted using the HSPiP software 5.3.02 using the Yamamoto-Molecular Break (Y-MB) method.

Model reactions

Heteroatom alkylation (Menshutkin reaction). 1,2-Dimethylimidazole (0.320 g, 3.33 mmol), 1-bromodecane (0.65 ml, 3.13 mmol), and the chosen solvent (3 ml) were combined in a 10 mL vial and stirred at 70 °C. Several aliquots were removed from the mixture at regular intervals, diluted and analysed by the gas chromatography with flame-ionization detection (GC-FID) (Agilent Technologies, model no. 7890B) equipped with an HP-5 column. The reaction was monitored by measuring the gradual decrease of 1-bromodecane peak and calculating conversion. The rate constant was calculated as a slope of the linear plot of 1/[1-bromodecane concentration]$_t$ *versus* time (Fig. S2†), which holds under 2nd order reaction kinetics.

Hydrogenation of cinnamaldehyde. The hydrogenation of cinnamaldehyde was performed in a 25 mL stainless steel Parr reactor. The reactor was loaded with cinnamaldehyde (CAL, 0.665 g, 5 mmol, 1.00 equiv.), Pd/C (1 wt%, 30 mg), and solvent (10 mL) and then sealed and pressurized with H_2 (40 bar). The reactor was heated up to 70 °C with stirring (600 rpm) and held at that temperature for the specified reaction time. The composition of the reaction mixture was analysed by GC-FID and GC-MS (gas chromatography-mass spectrometry). The conversion was calculated by dividing the moles of CAL consumed by the initial moles of CAL loaded into the reactor; the selectivity to a product was calculated by dividing the moles of the product produced by the sum of the moles of all products that were produced. The overall mass balance was ≥90% for all solvents.

Cross-coupling (Heck) reaction. Iodobenzene (0.69 mL, 6.00 mmol, 1.00 equiv.), methyl acrylate (0.54 mL, 6.00 mmol, 1.00 equiv.), triethylamine (0.84 mL, 6.00 mmol, 1.00 equiv.), and the solvent (5 mL) were combined in a 15 mL vial. The vial was then heated to 90 °C with stirring and $Pd(OAc)_2$ (0.1 mol%) was added. The reaction was sampled at designated intervals until the reaction exceeded 15% conversion as determined by GC-FID. The initial rate was calculated extrapolating the slope from the plot of methyl acrylate concentration *versus* time (Fig. S6†).

Toxicological testing

An AMES-384 ISO test kit by EBPI Inc. (Canada) with two *Salmonella typhimurium* bacterial strains (*TA100* with base-pair mutation hisG46 and *TA98* with frameshift mutation hisD3052) was used to perform preliminary toxicological screening of DFX. S9 liver homogenate from Aroclor 1254 Sprague-Dawley rats was used in a number of experiments as a source of mammal metabolic enzymes to expand the detection capabilities of the assay. For the test, DFX was dissolved in sterile water (100 mg mL^{-1}) and filtered through a 0.22 μm membrane filter. The maximum concentration of DFX in the exposure well was 80 mg per exposure well. Serial dilution of the sample was performed with a dilution factor of 2 (the minimum tested concentration was 2.5 mg per exposure well). 4-Nitroquinoline-*N*-oxide was used as a positive control for the TA100 strain. 2-Nitrofluorene was used as a positive control for the TA98 strain. 2-Aminoanthracene was used as a positive control when a rat liver fraction S9 was added to the TA100 or TA98 strains. For the negative controls, the same quantity of sterile water was added to the wells as was added in the case of the DFX assay. A more detailed experimental procedure is provided in the SI. Statistical analysis of the results included calculation of the baseline (the average response of negative control data and standard deviation), positive criteria for considering the testing compound as a mutagen (must be ≥2× baseline), and standard error of the mean. All calculations were conducted using an Excel spreadsheet provided by EBPI Inc.

Synthesis of diformylxylose

D-Xylose (15 g, 0.1 mol, 1.0 equiv.) and paraformaldehyde (15 g, equivalent to 0.50 mol formaldehyde, 5.0 equiv.) were added to 2-Me-THF (200 mL) in a 500 mL round bottom flask. Then, H_2SO_4 (98 wt%, 20 mL, 0.37 mol, 3.7 equiv.) was added dropwise with stirring to avoid the localized concentration of acid, which can degrade the sugar. The mixture was then heated to 80 °C for 20 min with stirring. The resulting solution was cooled to room temperature (~23–25 °C), neutralized with potassium bicarbonate, filtered, and concentrated *in vacuo* using a rotary evaporator with a bath temperature of 45 °C. The residue was extracted three times with 100 ml of ethyl acetate (or 50 ml of cyclopentyl methyl ether) and 100 ml of water in a separatory funnel. The resulting solution was distilled at 80 °C, under reduced pressure (0.02 mbar) to obtain a light yellow solid. The solid was then recrystallized in ethanol and dried in a vacuum desiccator, yielding the DFX as a white crystalline solid (≥98% pure by ^{1}H-NMR and GC-FID).

The yield of diformylxylose was optimized (Fig. S8†) by using high-performance liquid chromatography (Agilent Infinity 1260 equipped with refractive index detector, UV-Vis detector and an Aminex HPX-87H column at 60 °C using 5 mM H_2SO_4 in water at a flow rate of 0.6 mL min^{-1} as the mobile phase).

Conclusions

DFX appears to be a promising bio-based alternative to traditional polar aprotic solvents as determined by its evaluation in several model reactions. These results are noteworthy given that the molecule does not contain any nitrogen or sulphur heteroatoms, which are typically found in both conventional and bio-based aprotic solvents. Those heteroatoms are known to lead to environmental damage, and their absence is potentially beneficial.[3] The non-mutagenic and non-volatile nature of DFX indicates that this solvent could be safe for human health, which would make it truly "green". Furthermore, as it can be produced directly from lignocellulosic biomass, its production is likely to be both sustainable and economically feasible.

The primary disadvantages of DFX as a solvent are its high boiling and melting points, which may limit its use for certain industrial applications. Given the promise of the solvent's structure, our future work will aim to adjust its properties by introducing novel functionalities into the tricyclic acetal functionalized xylose core. Indeed, a variety of solvents with tuned properties could be formed by making derivatives of diformylxylose *via* modification of the aldehyde backbone that is used during biomass processing. In this way, diformylxylose modification could spur the development of a whole family of bio-based solvents.

Conflicts of interest

JSL is part owner of Bloom Biorenewables Ltd, a start-up company that is commercializing the aldehyde functionalization chemistry of biomass-derived molecules.

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