

## Green and Sustainable Solvents in Chemical Processes

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**ABSTRACT:** Sustainable solvents are a topic of growing interest in both the research community and the chemical industry due to a growing awareness of the impact of solvents on pollution, energy usage, and contributions to air quality and climate change. Solvent losses represent a major portion of organic pollution, and solvent removal represents a large proportion of process energy consumption. To counter these issues, a range of greener or more sustainable solvents have been proposed and developed over the past three decades. Much of the focus has been on the environmental credentials of the solvent itself, although how a substance is deployed is as important to sustainability as what it is made from. In this Review, we consider several aspects of the most prominent sustainable organic solvents in use today, ionic liquids, deep eutectic solvents, supercritical fluids, switchable solvents, liquid polymers, and renewable solvents. We examine not only the performance of each class of solvent within the context of the reactions or extractions for which it is employed, but also give consideration to the wider context of the process and system within which the solvent is deployed. A wide range of technical, economic, and environmental factors are considered, giving a more complete picture of the current status of sustainable solvent research and development.



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## 1. INTRODUCTION

In 2015, the UN outlined a new sustainability focused development plan under the title “Transforming Our World: The 2030 Agenda for Sustainable Development”.<sup>1</sup> The plan is composed of 17 sustainable development goals (SDGs) that address a wide range of issues, many of which recognize the need for green and sustainable chemistry and engineering. This ambitious project highlights the role of sustainable imperatives as drivers for chemical research, which provide new challenges, opportunities, and importantly, direction. Sustainability has

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previously been described by Cséfalvay et al.: “Resources including energy should be used at a rate at which they can be replaced naturally and the generation of waste cannot be faster than the rate of their remediation.”<sup>2</sup> The concept of sustainable chemistry is well established.<sup>3,4</sup>

Large quantities of organic solvents, relative to reagents, are usually essential for chemical reactions to proceed. In addition, many extractions, purifications, and cleaning processes also depend on solvents, with large excesses necessary to achieve sufficient product purity. The annual industrial-scale production of organic solvents has been estimated at almost 20 million MT (metric tons).<sup>5</sup> The excessive consumption of nonrenewable, toxic solvents is environmentally detrimental and an outstanding example of unsustainable practices. Nonetheless, solvents are essential for many chemical processes, and solvation provides several major advantages, such as selectivity control, safety (for example, as a heat sink or containment of any toxic reagents), and improved handling.<sup>6</sup> Reichardt and Welton have published a detailed description of the role of solvents and their effects in organic chemical reactions.<sup>7</sup>

The fine chemical and pharmaceutical industries have previously been identified as significant sources of chemical waste.<sup>8</sup> This is largely due to the production of complex molecules, which require large quantities of solvent during synthesis and purification. For example, the raw materials needed to prepare active pharmaceutical ingredients (APIs) can be up to 85% solvent by mass.<sup>9</sup> Furthermore, solvent requirements do not decrease for many drug manufacturing processes as they pass from early stage development to commercial processes.<sup>10</sup> Efforts to address these issues are a central part of sustainable development, and many industrial processes are now being scrutinized for solvent consumption.<sup>11–13</sup> However, in terms of absolute volume, large-scale sectors such as the oil refining industry ( $10^6$ – $10^8$  tonnes product, E-factor <0.1) and bulk chemicals industry ( $10^4$ – $10^6$  tonnes product, E-factor <1–5) produce more waste than the fine chemical or pharmaceutical sectors (product tonnage  $10$ – $10^3$ , E-factor 25–100).<sup>14,15</sup> Hence, regardless of material or process efficiency, significant progress can be made by moving toward more sustainable solvent alternatives.

In recent years, environmental directives and legislation have sought to reduce solvent emissions (such as the Clean Air Act of 1990 and the European Union Solvents Emission Directive 1999/13/EC) or regulate the usage of potentially harmful or environmentally damaging chemical substances (Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)).<sup>16</sup> However, many existing chemical processes still depend on harmful, toxic solvents, and some developing countries are increasing their consumption (e.g., dichloromethane<sup>17</sup>) because of low prices and availability. Until recently, such economic factors have been neglected from sustainability assessments. Welton has since amended the sustainable chemistry statement to include: “A sustainable chemical product should be supplied at a price that enables it to be accessed by its users while at the same time being commercially viable for its producers.”<sup>18</sup> However, Horváth et al. argue that sustainability is an intrinsic property of a molecule or process and that social and economic factors are compromises, resulting in “suitable developments” rather than sustainable developments.<sup>19</sup> For the purpose of this Review, we will attempt to consider all aspects of sustainable chemical processes, including economic factors as an indicator of market viability.

A number of alternative chemical procedures have been proposed to help reduce the amount of toxic, harmful organic solvents in use. Mechanochemistry can be used to eliminate the usage of solvents altogether;<sup>20–22</sup> however, these processes are limited by slow reaction rates, high capital costs, and low energy efficiencies. Replacing harmful organic solvents with less harmful organic solvents (e.g., chloroform with ethanol) can offer simple solutions; however, such substitutions can be synthetically restricting and may be economically unfeasible.

This Review aims to describe an overview of chemical processes employing neoteric solvents that are proposed as sustainable alternatives. The following sections cover a wide range of neoteric solvents with very different properties, each suited to particular applications or processes. Moreover, the chosen solvents are at various stages of development, meaning that the challenges facing each solvent are significantly different. We aim to place an emphasis on the environmental and economic impacts of implementing developed neoteric solvents as the technical aspects have been covered elsewhere.<sup>9,23,24</sup> However, the technical aspects of more recent neoteric solvents are considered in a sustainable context. Examples of sustainable solvent processes include, but are not limited to, solvents derived from renewable sources such as biomass, solvents designed to facilitate product isolation and reaction workups, solvents that may be tuned to improve reaction outcomes, and solvents that possess little to no environmental risk.

### 1.1. Green Chemistry and Sustainability

The objective of green chemistry is to reduce the usage and production of hazardous substances for chemical processes, while reducing energy consumption and moving toward renewable sources. In an effort to guide researchers toward this goal, Anastas and Werner published the 12 principles of green chemistry in 1998.<sup>25</sup> Today, green chemistry is considered a tool for introducing sustainable concepts at the fundamental level and therefore aimed toward inventing new products, routes, and processes, rather than improving existing ones.<sup>26,27</sup> Many published articles claim to provide green alternatives to existing processes,<sup>28</sup> often by stating how their research complies with one or more of the green principles. Winterton argues that such strategies are in fact “green herrings”, and consideration must be given to the larger context, particularly in terms of scalability, economics, and regulatory constraints.<sup>29</sup> This viewpoint is in accordance with sustainable chemistry, which takes a more holistic approach to the development of chemical technologies. A multidisciplinary approach is therefore an integral part of green and sustainable chemistry at the development stage, due to the inherent interconnections of sustainability.<sup>30–33</sup>

### 1.2. Sustainability and Solvents

Many organic solvents are harmful, toxic, and environmentally damaging. Therefore, their use poses risks to both human health and the environment. Understanding solvent properties is a necessary part of sustainable development, and many solvents have therefore been ranked by their environmental, safety, and health (ESH) characteristics.<sup>34</sup> These rankings are the core principle of solvent selection guides, most of which are published by pharmaceutical companies such as GSK,<sup>35</sup> AstraZeneca,<sup>36</sup> Pfizer,<sup>37</sup> and Sanofi,<sup>38</sup> and specialty groups such as the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCI-PR)<sup>36</sup> and Innovative Medicines Initiative (IMI)-CHEM21.<sup>39</sup> The aim is to help researchers choose solvents that have low ESH impacts, discouraging the use of

Table 1. A Selection of Common Green Chemistry Metrics, Their Descriptions, and Some Comments<sup>a</sup>

metric	description	comment	examples
atom economy (AE)	molecular weight of the product divided by the sum of molecular weights of all substances involved in the reaction	introduced by Trost in 1991; <sup>44</sup> equations for linear, branched, and convergent syntheses can be used for process atom economy	organic synthesis <sup>45</sup>
carbon efficiency (CE)	percentage of carbon from reagents that remain in the final product	ideal for the organic synthesis of large carbon frameworks; it is a simple calculation originally designed by GlaxoSmithKline scientists <sup>46,47</sup>	Fischer–Tropsch Synfuel <sup>48</sup> biomass pretreatments <sup>49</sup> analyte analysis <sup>50</sup>
EcoScale <sup>42</sup>	based off a 100-point system that then takes into account price, safety, setup, temperature and time, workup, and purification of the reaction	designed for organic chemistry to give a quick overall assessment of a reaction; can be used for analytical procedures	
effective mass yield (EMY) <sup>47</sup>	looks at the mass of the product as compared to the mass of hazardous and toxic reagents, ignoring “benign” compounds such as water	“benign” is not clearly defined nor are the levels of acceptable toxicology	organic synthesis <sup>51</sup> biocatalysis <sup>52</sup>
environmental factor (E-factor) <sup>47</sup>	the mass ratio of the waste to the desired product	introduced by Sheldon in 1992; <sup>53</sup> multiplying by an unfriendliness quotient (Q) gives the environmental quotient <sup>54</sup>	organic synthesis <sup>15</sup> bulk chemical synthesis <sup>54</sup> pharmaceutical <sup>14</sup>
process mass intensity (PMI)	ratio of the total mass used in the process to the mass of the product <sup>55</sup>	considers the reagents, solvents, and stoichiometry for the synthesis of product and can be linked with E-factor calculations; however, the impact of the waste produced from the process is not accounted for	pharmaceutical <sup>56</sup> organic synthesis <sup>57</sup>
reaction mass efficiency (RME)	an inverse of E-factor that allows the user to identify the parts of the process that are impacting the score the most	can be useful to look at for an industrial process because it allows for identification of a specific part of a process that is contributing the most negatively/positively to the process; a useful tool to help reduce waste	engineering process design <sup>58</sup> pharmaceutical <sup>59</sup>
material recovery parameter (MRP) <sup>60</sup>	a parameter that takes into account the recovery and recycling of products used during the reaction including purification and workup <sup>61</sup>	if all solvents, catalysts, and nonproduct reagents are recovered, then $MRP = 1$ <sup>61</sup>	pharmaceutical <sup>59</sup>

<sup>a</sup>The reader is directed to the references provided for further details regarding each metric. Atom Economy (AE):  $AE = \frac{\text{mass of atoms in desired product}}{\text{mass of atoms in reactants}}$ ; Carbon Efficiency (CE):

$CE = \frac{\text{number of carbon atoms in the product}}{\text{number of carbon atoms in reagents}}$ ; Ecoscale: Complex, no general equation available; Effective Mass Yield (EMY):  $EMY = \frac{\text{mass of desired product}}{\text{mass of non-benign reagents}}$ ; E-factor:  $E\text{-factor} = \frac{\text{mass of produced waste}}{\text{mass of desired product}}$ ; Process Mass

Intensity (PMI):  $PMI = \frac{\text{mass of used raw material}}{\text{mass of desired product}}$ ; Reaction mass efficiency (RME):  $RME = \frac{\text{mass of desired product}}{\text{mass of reactants}}$ .

toxic, harmful solvents that are common to laboratories. Overall, most solvent selection guides come to similar conclusions, although there are minor deviations. Some have even been expanded to include renewable and neoteric solvents.<sup>13,39</sup> The ranking of solvents and the production of selection guides is now an important strategy that is being used to produce immediate results for sustainable development. However, most do not contain information regarding the performance of solvents, so one solvent that has better ESH properties may sacrifice another sustainable facet of the chemical process, that is, process economics. Nonetheless, determining the ESH properties of established and neoteric solvents should be a key step toward a sustainable solvent future.

Through a series of industrial examples, Welton summarized the ways in which solvents may make chemical processes more sustainable.<sup>18</sup> The solvent may (i) have dual roles, for example, as a reagent, (ii) lead to higher quality products, (iii) reduce the number of synthetic steps, (iv) reduce byproduct formation, and (v) improve product separation.

Industrial chemical processes mainly employ classical organic solvents; hence, this list arises from careful solvent selection and consideration of the role of the solvent in the entire process. Neoteric solvents are slowly being integrated into industrial processes. This is because they provide advantages over organic, or aqueous, solvents, typically by improving product separation. Examples of neoteric solvents include ionic liquids (ILs), deep eutectic solvents (DES), liquid polymers, supercritical carbon dioxide (scCO<sub>2</sub>), gas expanded solvents (GXLs), and switchable solvents, all of which will be discussed in this Review. There are many barriers that need to be addressed before neoteric solvents are adopted by the chemical industry, such as price, availability, purity, regulations, disposal procedures, recycling procedures, and costs. However, if an existing solvent can be replaced by a neoteric solvent, it does not mean that it should be. In accordance with sustainability, the entire life cycle of a chemical process and the solvents, auxiliaries, reagents, products, and subsequent isolation and purifications must be considered and compared. It is entirely possible that using a small amount of an easily separated “traditional” organic solvent could provide a more sustainable process than a neoteric solvent.

In 2010, Jessop conducted a brief survey of academic researchers and asked the question: “...what class of solvent will be responsible for the greatest reduction in environmental damage?”<sup>40</sup> The answers were in favor of CO<sub>2</sub>, water, and careful selection of organic solvents, whereas the proportion of papers published in the journal *Green Chemistry* that year were mainly focused on ionic liquids. This disagreement prompted Jessop to ask whether scientists are studying the right solvents. In response, he outlined four grand challenges for solvent research, the aim being to encourage diversity in green solvents and stimulate researchers to consider the environmental impact of large-scale applications. The challenges were (1) to ensure green solvents may replace any nongreen solvent, (2) find and use methods of assessing the total environmental impact of solvents, (3) find polar aprotic solvents that are easier to remove than existing solvents, and (4) to eliminate energy intensive distillations.

### 1.3. Evaluating Chemical Processes

Measuring reaction efficiencies in yield can be a good indication of process economics; however, it does not provide enough

information to advance sustainable practices.<sup>41</sup> Fortunately, a broad range of green chemistry metrics (GCMs) are now available for researchers to compare synthetic routes and methodologies in terms of sustainability; see Table 1. The simplicity of GCMs encourages researchers to consider sustainable chemistry at the development stage, especially with regards to waste prevention. However, upstream and downstream processes are not accounted for by most GCMs, and these can ultimately determine the success of a sustainable process. Some specialized GCMs and screening methods have attempted to integrate economic and environmental factors at the development stage;<sup>42,43</sup> however, as more details are added, the assessments become increasingly complicated and costly. Furthermore, nonoptimized lab-scale reactions may produce poor ratings when assessed by GCMs. A more comprehensive approach is required for sustainable chemistry development; nevertheless, GCMs have become useful tools for quickly assessing laboratory-scale processes relative to each other.

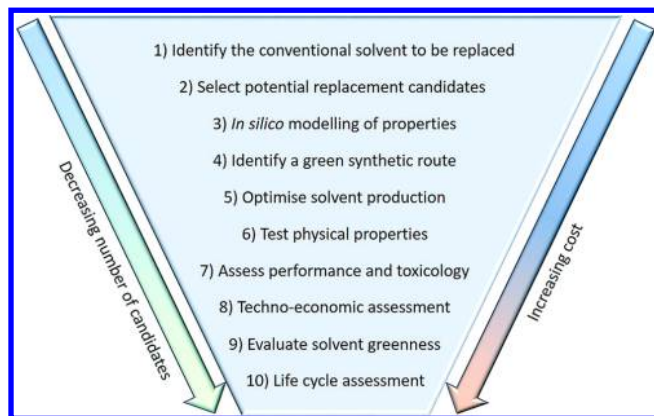
The environmental impact, mass flow, and energy flow of a chemical process may be evaluated through a life cycle assessment (LCA). This approach uses data acquired from secondary sources, such as databases, literature references, and simulations, and considers the entire life of the products and raw materials, that is, cradle-to-grave. However, there is an inherent uncertainty to LCAs, especially when considering emerging technologies that do not have sufficient data to enable a reliable evaluation. LCAs are also complex and require considerable time and resources, which often deters researchers from utilizing them. Some simplified LCAs do exist that aim to solve these problems, such as streamlined LCAs or fast life cycle assessment of synthetic chemistry (FLASC).<sup>62</sup> Simplified analyses can also be undertaken by narrowing the boundaries of an LCA, for example, the gate-to-gate or cradle-to-gate approaches.<sup>63</sup> This allows the assessment of chemical processes under development as exact data for the use phase of a full LCA are only available after the chemical becomes available on the market. In terms of solvents, LCAs, or simplified LCAs, can help identify the balance between production, application, and disposal, while accounting for environmental impact.<sup>64</sup>

Different assessment methods consider different system boundaries and require different data inputs. Therefore, the characteristics of each method should be clearly described to understand what environmental problems are addressed. Hellweg et al. have explored the environmental impacts of 13 organic solvents using ESH, LCA, and persistence and spatial range (PSR) analysis to demonstrate how these techniques may be complementary.<sup>65</sup> Interestingly, the results indicated that chlorinated solvents are problematic, but for different reasons. The high chronic toxicity gave high ESH scores, while the high persistency gave high PSR scores. Although the LCA results incorporate such factors, the large amount of sodium hydroxide required for flue gas cleaning for end-of-life treatment was further identified as an environmental “hotspot” for chlorinated solvents. The cradle-to-grave approach of LCA can therefore help to understand associated problems outside of the use phase. The simplicity of ESH assessments makes them ideal for screening at the development stage as they can be applied to numerous alternative processes with ease (e.g., when changing solvents). PSR analysis calculates the transport, environmental partitioning, and degradation of chemical in the environment. For volatile solvents, transport occurs in the air, and the air residence time determines the potential of long-range transport. These types of assessments, whether simplified or not, are



crucial for the development of sustainable solvents. However, determining the environmental impacts of new solvents can be difficult as the data required for assessment may not exist.<sup>66</sup>

Jin et al. have developed a 10-step method, which encompasses a hierarchy of assessments and tests designed to help identify replacements of organic and guide the development of new biobased solvents (Figure 1).<sup>67</sup> Initial steps of the



**Figure 1.** The 10-step method as suggested by Jin et al. for screening new biobased solvents. Reproduced with permission from ref 69. Copyright 2017 Faraday Discussions.

model utilize Kamlet–Abboud–Taft (KAT) solvatochromic parameters and Hansen solubility parameters to compare solvent properties. These models can be used to identify solvent types missing from the current biobased solvent library, similar to the method demonstrated by Jessop.<sup>68</sup> The model then becomes an aid in the screening of new solvents. Intermediate steps involve the careful optimization of synthetic pathways, making use of green chemistry principles. Consideration of solvent physical properties is next, and simple toxicological testing such as the Ames test is used for early screening. The authors state that model development, such as quantitative structure activity relationship (QSAR), may be unnecessarily time-consuming and must be further confirmed experimentally. Final steps make use of more expensive, more time-consuming LCA studies. This framework can be used for the selection of new solvent candidates with most of the required properties to qualify as a green solvent and to potentially meet any required regulations. Workflows such as this are important for organizing investigations and ensuring solvent development is streamlined and efficient.

While it is clear that the motivations behind sustainable solvent research are aimed toward reducing environmental impact, its methods can sometimes be at odds with this goal. Researchers also rarely consider the scale of manufacturing processes. As noted by Sheldon, this can lead to unfortunate conclusions about the impact of green chemistry.<sup>70</sup> For solvents, it is clear that the volume of solvent used in a process will scale its impact, and while solvent recycling is an important aim, it is not always possible or even desirable. Many large-scale applications involving solvents (bulk chemical synthesis) require “disposal” solvents (such as toluene), which can be incinerated after use. This not only avoids expensive solvent cleanup procedures, it also provides necessary process heat, albeit at the cost of increased emissions. Only a full accounting of process options, including solvent disposal,

can reveal whether a novel alternative actually makes the process better.

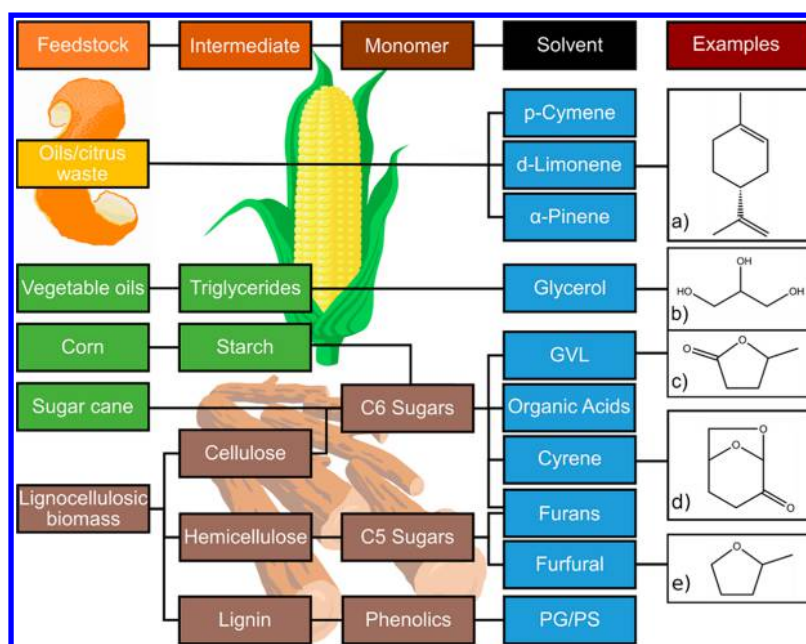
#### 1.4. Economic Considerations

The impact of solvent cost on process competitiveness is a major concern. There are a number of efficiency considerations that govern the viability of using a solvent in a given application. These include both application-specific technical factors (such as performance) and process-specific economic factors (such as solvent cost).<sup>71–73</sup> While a majority of academic and scientific investigations have focused on the performance criteria (yield, for example), industrial uptake is normally dictated by the economic viability of using the solvent inside the process, along with more general considerations such as availability, scale, and disposal methods, as well as corrosion, thermal stability, or toxicity concerns. A common example is the high viscosity of ionic liquids, liquid polymers, and deep eutectic solvents, which can limit transport in applications involving multiphase processing (especially gas/liquid transport as in catalysis).<sup>74–76</sup>

Economic considerations are of high import if neoteric solvent-based technologies are to graduate from academic curiosities to widespread commercial reality. While there are sustainability considerations to take into account when a solvent is proposed for use, the attending energy costs regarding solvent recovery are likewise of key economic importance. Only a full process technoeconomic model or life cycle assessment can identify these key issues.<sup>77</sup> Technoeconomic analysis can be used to estimate the cost of bulk-scale production of chemicals, including solvents even as complex as ionic liquids. However, researchers can still make informed estimates about the cost of solvents from general considerations of solvent origin and method of production.

The chemical industry is now considering renewable sources and the valorization of wastes as the primary source of sustainable solvents.<sup>78</sup> Additionally, process design has moved beyond cradle-to-grave, and now considers efficiency and a circular economy, that is, cradle-to-cradle.<sup>78</sup> The evolution from a traditional linear economy to a circular economy is necessary for sustainable production to advance. Recovery and regeneration of resources should be a design element in all future chemical processes. Recirculation therefore needs to be considered during process design, as recovery and reuse minimizes impact on ecology and health. Clark et al. have described the innovations in technology that are helping to make a circular economy possible.<sup>79</sup> One solvent-related example is the improvements in the textile industry, where the recycling of dimethyl sulfoxide can be used for dye stability, reducing solvent waste by 99%.

Sherwood et al. have investigated the challenges inherent in characterizing biobased products and solvents, as well as assessing the sustainability and life cycle impacts of that product, or solvent, once it is in consumer hands.<sup>80</sup> Policy changes as well as consumer pressures are setting standards and driving the development of these processes. These global challenges offer a unique opportunity for innovation and development. The circular economy is estimated to save over \$340 billion in material costs by recycling resources and a continued \$520 billion savings annually with implementation of green economy processes within the EU.<sup>81</sup> The market for biobased products is expected to grow from \$203.3 billion in 2015 to \$487 billion by 2024.<sup>82</sup> The overall market share of white biotechnology chemicals in 2050 as a percentage of the



**Figure 2.** A number of sustainable solvents can be derived from plant biomass. While plant sugars and oils require less processing, lignocellulosic biomass can produce a broader range of solvents. Structural examples show (a) d-limonene, (b) glycerol, (c)  $\gamma$ -valerolactone, (d) cyrene, and (e) 2-MeTHF.

total market share for organic chemicals is predicted to range from 7% (unfavorable conditions) to 17.5% (medium) to 38% (favorable conditions), dependent on the price of oil, feedstock costs, market growth, and subsidies.<sup>83</sup>

Future sustainable solvents will undoubtedly have diverse chemical compositions and a broad range of physicochemical properties. However, they should all ideally have one common feature, renewability. Efforts to produce new biobased solvents from renewable sources are providing researchers with a variety of solvents, some direct replacements for nonrenewable solvents and some with novel structures and unique properties and chemistries. The next generation of renewable solvents will originate from a range of renewable sources, each with advantages and disadvantages of their own.

## 2. RENEWABLE SOLVENTS

### 2.1. Introduction

Plant biomass is currently considered the primary source of renewable chemicals for the chemical industry. Crops such as corn and sugar cane, grasses like *Miscanthus*, agricultural residues, and agroforestry products including timber are all considered potential feedstocks for the generation of renewable fuels and solvents. The sustainability of biomass production is complex and highly dependent on the implementation of sustainable land-management practices.<sup>84–86</sup> However, an increase in the cultivation of crops and trees for biomass may also have secondary benefits such as increased tree cover, leading to improved air quality and higher soil carbon sequestration and increased income for farmers. The biomass-economy offers a potential win–win situation for the climate and agricultural economy if implemented correctly.

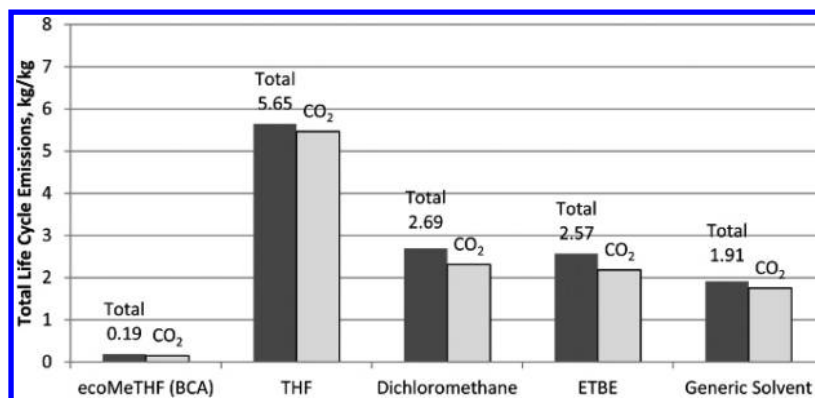
First generation biofuels such as bioethanol are generated from the fermentation of sugar or starch from crops such as corn or sugar cane. As of 2010, production of bioethanol exceeded 22 billion gallons/year.<sup>87</sup> Bioethanol is applied as an additive in fuel, but could quickly provide a route to renewable

ethanol, an important industrial solvent with low toxicity. However, the food versus fuel debate means that first generation biofuel production remains contentious.<sup>88</sup> Second generation biofuel production, using agricultural residues, grasses, and agroforestry products (lignocellulosic biomass), provides a renewable feedstock without competing directly with food, but processing of lignocellulosic biomass is more intensive (in both energy and cost).

### 2.2. Integrated Biorefinery

From an industrial perspective, the biorefinery concept faces many challenges. These include feedstock diversity (composition differs from species-to-species, geographical locations, and environmental factors), biomass supply and transport, issues with land usage, and, importantly, economic viability.<sup>89,90</sup> The “integrated biorefinery” concept is an attempt to recognize the need for flexibility and economic potential. An integrated biorefinery couples fuel production with a range of value-added products, such as platform chemicals, materials, and polymers. Flexible, robust, and low energy conversion processes are therefore required to transform a range of biomass materials into target molecules. However, the technical feasibility of chemical production alone may be insufficient to ensure economic viability.<sup>30</sup>

Several biofuels can also be used as renewable solvents (e.g., bioethanol), and a variety of other renewable solvents may also be derived from biomass.<sup>91</sup> For bioderived solvents to be economically sustainable, they should be supplied at competitive prices and industry-scale volumes; economic considerations can therefore help shape technical aspects of solvent design. Clark et al. have reviewed options for converting biomass to hydrocarbons, similar to current feedstock molecules, to exploit pre-existing manufacturing infrastructure.<sup>5</sup> This approach takes advantage of low market barriers and avoids start-up costs and investments that new chemical processes require. However, if oil prices remain low, competing with conventional feedstocks may not be a viable approach.



**Figure 3.** Total and CO<sub>2</sub> life cycle emission for 2-MeTHF (ecoMeTHF), THF, DCM, ethyl *tert*-butyl ether (ETBE), and a generic solvent (classical organic solvent). Reproduced with permission from ref 111. Copyright 2012 Wiley-VCH.

Alternatively, the chemical composition of biomass can be exploited to design new solvents, taking advantage of more efficient chemical transformations. These “bioprivileged molecules” may also offer distinct advantages over current solvents, and these could provide bioderived solvents with a competitive edge.<sup>92</sup> Examples of bioderived solvents and their intermediates and feedstocks are shown in Figure 2.

### 2.3. Constraints

Production volume is an important factor for future renewable solvents. Horvath et al. have reported a new set of metrics for evaluating the sustainability of carbon-based chemicals.<sup>19</sup> On the basis of ethanol equivalent (EE),<sup>2</sup> the metrics were used to establish a sustainability indicator (SUS<sub>ind</sub>) for ethylene, propylene, toluene, *p*-xylene, styrene, and ethylene oxide as if they were made from bioethanol via known processes (e.g., by first dehydrating bioethanol to ethylene). The authors found that 151.93 MT of bioethanol was needed to produce the quantities of all six chemicals consumed in the U.S. during 2008. For a mass yield of 30%, this equates to 515 MT of corn, which is 1.67 times larger than the 2008 U.S. corn production. This equates to 53 million hectares of farmable land, or 40.2% of the total available at the time. All six chemicals were therefore not producible via this process at the time; it was suggested that a 10-fold increase in bioethanol production could have resulted in sustainable production. This analysis illustrates the problems facing renewable production, particularly industrial-scale volumes.

Paggiola et al. investigated whether limonene (Figure 2a) derived from citrus waste can replace toxic solvents such as toluene in the cleaning sector.<sup>93,94</sup> Here, the authors calculated worldwide citrus peel waste at 65 million MT per annum, potentially providing up to 500 000 MT of limonene, a figure significantly lower than the global toluene consumption at 14.79 million MT. It is theoretically possible for large citrus producing countries (e.g., Brazil, Spain, India, South Africa, and the U.S.) to completely replace fossil fuel-derived toluene in their industrial cleaning sectors with limonene derived from citrus peels. However, the authors point out that their investigation makes many assumptions and has inherent complexity and uncertainty due to economic and technological factors.

In addition, terpenes such as  $\beta$ -pinene,  $\alpha$ -pinene, *p*-cymene, and d-limonene have recently been identified as high risk solvents for environmental emissions.<sup>95</sup> Their moderate inhalation toxicities and high photochemical ozone creation potentials (POCPs) are made worse by their environmental

partitioning into air. New ESH information can impact the adoption of solvents in the chemical industry. For example, stringent regulations for the long-established solvent trichloroethylene have been imposed by the European commission due to its classification as a category 1B carcinogen.<sup>96</sup> Importantly, when a product or chemical is bioderived, it does not mean that it is automatically sustainable with a low health or environmental impact. For example, the aprotic bioderived solvent, methyl(2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (MMC), is cleanly synthesized from glycerol in two steps, and is a promising replacement for solvents such as dichloromethane, acetone, and ethyl acetate.<sup>69</sup> However, MMC was found to be a mutagen and possible carcinogen, and consequently MCC was not developed further as a green solvent. Ultimately, bioderived solvents will have to conform to the same regulations as fossil-fuel derived solvents.

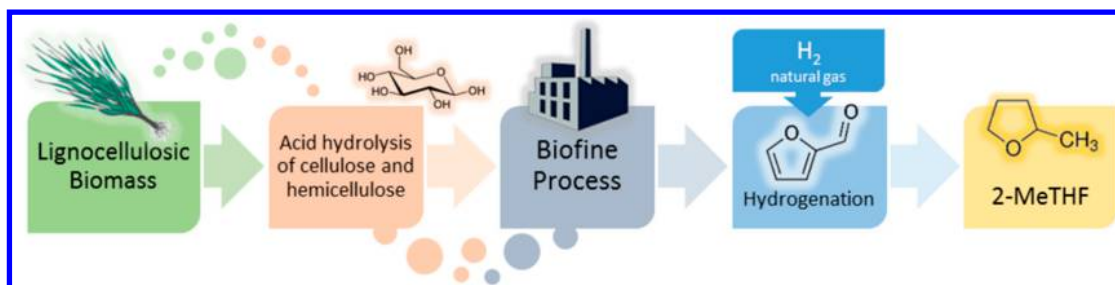
Fiorentino et al. have reviewed other constraints facing the transition to a renewable chemical economy, with an emphasis on technology versus environmental feasibility.<sup>97</sup> The following sections will detail three other solvents that may be obtained from cellulose biopolymers: one established and two at the development stage. 2-Methyltetrahydrofuran (2-MeTHF) will be used to highlight issues facing established renewable solvents, while  $\gamma$ -valerolactone and dihydrolevoglucosenone (Cyrene) will describe progress related to development stage solvents.

### 2.4. Solvents Derived from Cellulose and Starch

As the major components of biomass, starch and cellulose are readily available from renewable sources. Both biopolymers are composed of glucose units joined by glycosidic bonds, with starch containing  $\alpha$ -1,4 connections and cellulose containing  $\beta$ -1,4 connections.<sup>98,99</sup> The hydrolysis of starch and cellulose may be achieved chemically or enzymatically to produce glucose.<sup>100–104</sup> Subsequent chemical transformations of glucose can provide a wide range of value-added chemical products, many of which may be used as solvents for chemical processes. Careful consideration is needed when selecting an appropriate bioderived solvent as many contain reactive heterocycles or functional groups. The properties of the most popular bioderived solvents, such as d-limonene, 2-MeTHF, and  $\gamma$ -valerolactone, have been extensively investigated.<sup>94,105–107</sup>

**2.4.1. 2-MeTHF.** 2-Methyl tetrahydrofuran (2-MeTHF, Figure 2e) was originally intended as a biofuel; however, it is now being used as a renewable alternative to THF.<sup>105</sup> 2-MeTHF has a lower water miscibility, higher stability, and lower volatility than THF (2-MeTHF has a melting point of





**Figure 4.** Conversion of biomass into 2-MeTHF using the Biofine process. Reproduced with permission from ref 106. Copyright 2015 Elsevier.

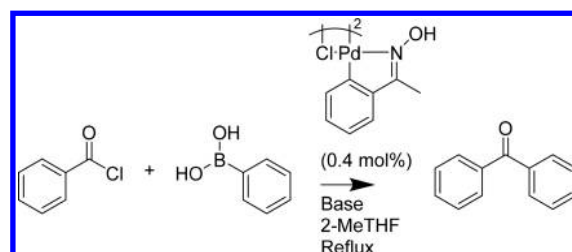
−136 °C and a boiling point of 80.2 °C as compared to THF, which has a melting point of −108.4 °C and boiling point of 66 °C). Initial studies have shown 2-MeTHF to have lower toxicity, and it has been approved for use in pharmaceutical chemical processes.<sup>108</sup> It can be synthesized from xylose and glucose, both of which are derived from biomass via other feedstock intermediates such as levulinic acid and furfural.<sup>105,109</sup>

Acidic pathways from levulinic acid, through an intermediate of  $\gamma$ -valerolactone (GVL), can produce 2-MeTHF. This pathway gives the potential for a dual high value stream of 2-MeTHF and GVL.<sup>105</sup>

Ashcroft et al. conducted a survey of solvent usage in publications from the journal *Organic Process Research & Development* between 1997 and 2012.<sup>110</sup> They found that the use of chloroform and *n*-hexane has steadily decreased since 2001; however, the use of dichloromethane (DCM) and many other solvents of concern has remained consistent. In terms of renewable solvents, the only increase was found for 2-methyltetrahydrofuran (2-MeTHF), which was present in 14.3% of publications from 2009 to 2012. The production of 2-MeTHF from furfural, which may be derived from many agricultural wastes, has been calculated to reduce solvent emissions by 97% relative to nonrenewable THF production (Figure 3).<sup>111</sup> Despite being derived from renewable sources, the CHEM21 selection guide still ranks 2-MeTHF as problematic due to its high flammability.<sup>39</sup>

Khoo et al. performed a detailed LCA for the production of bioderived 2-MeTHF from three biomass sources (corn stover, sugar cane bagasse, and rice straw).<sup>112,113</sup> The life cycle assessment investigated the environmental implications, such as land usage emissions (such as eutrophication) and global warming potential (from CO<sub>2</sub>, methane, and NO<sub>x</sub> emissions), and the total energy of production (per kilogram of 2-MeTHF). The synthetic route involved the conversion of sugars to levulinic acid and subsequent hydrogenation to form 2-MeTHF (see Figure 4). The LCA results showed that the energy usage and environmental damage caused by crop production far outweighed that of biomass processing. These results demonstrate how solvent (and fuel or chemical) sustainability is also dependent on feedstock cultivation. The energy consumption for the processing of 2-MeTHF was calculated to be ~0.2 MJ/kg.

Mondal and Bora describe the synthesis of aromatic ketones using a Suzuki–Miyaura reaction with an oxime-palladacycle catalyst in bioderived 2-MeTHF solvent (Figure 5).<sup>114</sup> A maximum yield of 98% was achieved at 80 °C, with 1 mol % Pd, after 4 h. 2-MeTHF performed better than acetone, toluene, DMF (2,5-dimethylfuran), THF (tetrahydrofuran), acetonitrile, dichloromethane, PEG-400, isopropanol, and a 3:1 mix of 2-MeTHF and water. A yield of 97% was achieved after optimization. Isolation of the product was also demonstrated



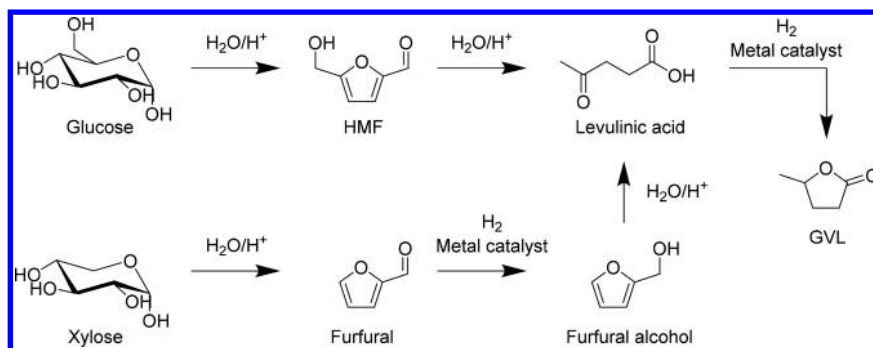
**Figure 5.** Suzuki–Miyaura coupling of benzoyl chloride and phenylboronic acid with a palladium catalyst in 2-MeTHF. Reproduced with permission from ref 114. Copyright 2013 Wiley-VCH.

to be relatively simple as 2-MeTHF is partially miscible with water. After quenching with water, the 2-MeTHF phase was separated and evaporated without the need for additional organic solvents. The authors reported an atom economy of 64.2%, and an E-factor of 39.3, which is in line with fine chemical production. The advantages and disadvantages of 2-MeTHF in chemical reactions have been thoroughly reviewed elsewhere.<sup>105,115</sup>

**2.4.2.  $\gamma$ -Valerolactone (GVL).**  $\gamma$ -Valerolactone (GVL, Figures 2c and 6) has become a popular bioderived platform chemical, which may also be used as a renewable fuel or solvent. GVL can be produced from cellulose via the production of hydroxymethylfurfural to levulinic acid, or via furfural from hemicellulose.<sup>106,116</sup> The production of LA has been demonstrated at a pilot scale, and GVL can be obtained with high yields within 1–2 steps.<sup>106</sup> Omoruyi et al. have reviewed the current progress and challenges facing the conversion of LA to GVL by homogeneous catalysis.<sup>117</sup> Unfortunately, hydrogenation of LA to GVL requires H<sub>2</sub> and a metal catalyst. Currently, commercial H<sub>2</sub> is produced from hydrocarbons via steam reforming. The cost and sustainability of GVL is therefore linked to H<sub>2</sub> production. However, the current drive toward a sustainable hydrogen economy may provide a solution,<sup>118–120</sup> further expanding the list of 100% renewable solvents available in the future. Alonso et al. have reviewed GVL as a platform chemical including a discussion of GVL as a solvent.<sup>106</sup>

GVL is stable and does not decompose at room temperature; it is a colorless water-soluble liquid, with a boiling point of 207–208 °C and a melting point of −31 °C.<sup>121–124</sup> Unfortunately, GVL has a high vapor pressure, exceeding 10 Pa.<sup>106</sup> There are also concerns that, unless mineral acids are eliminated from the pretreatment process, industrial grade GVL will likely contain mineral acid as a contaminant. Small amounts of acid have been found to catalyze the ring opening of GVL to 4-hydroxyvaleric acid (4-HVA), which may act as a chelate for metals used as catalysts, leading to metal leaching. At high temperatures (100 °C), GVL was also found to react with water

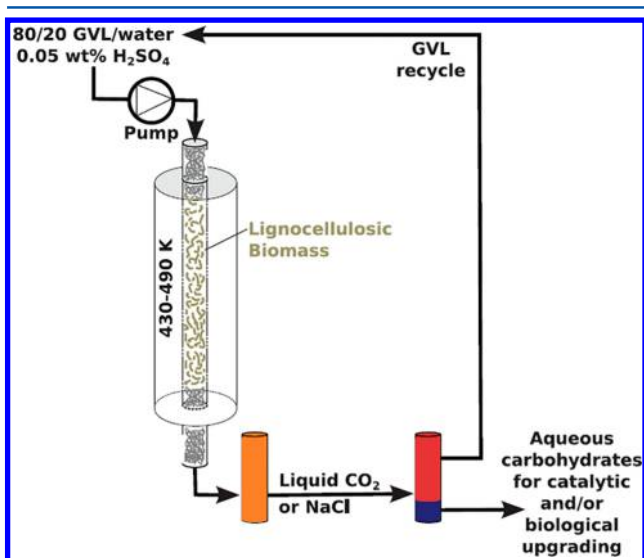




**Figure 6.** GVL can be synthesized from cellulose or hemicellulose from the monosaccharides glucose and xylose via levulinic acid.

to form 4-HVA, which may limit the application of GVL in high temperature reactions.<sup>125</sup>

GVL is an attractive solvent for biomass pretreatment. The cost of the enzymes used for the saccharification of cellulose is often considerable as compared to that of biomass-derived chemicals.<sup>127</sup> Eliminating enzymes could reduce the costs considerably. Luterbacher et al. have reported the production of sugars (glucose and xylose) from lignocellulosic biomass without enzymes in GVL solvent.<sup>126</sup> High yields were obtained using corn stover, hardwoods, and softwoods. Furthermore, fewer sugar degradation products and solid wastes were produced due to the low acid concentrations used. The separation of carbohydrates could also be achieved by using aqueous sodium chloride, or  $\text{CO}_2$  and GVL recycling was demonstrated (Figure 7). The depolymerization of lignin was



**Figure 7.** GVL can be used to extract carbohydrates from lignocellulosic biomass. Liquid  $\text{CO}_2$  and NaCl are used to extract the products and GVL can be recycled. Reproduced with permission from ref 126. Copyright 2016 American Association for the Advancement of Science.

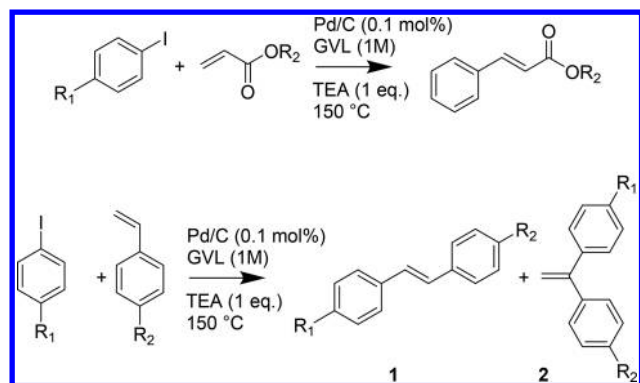
integrated into this process. However, THF had to be used as a solvent, due to its higher stability and resistance to hydrogenation.<sup>128</sup> Depolymerization of lignin also required  $\text{H}_2$  and a Ru catalyst, which may be of too high energy and a resource intensive process to carry out at a large industrial scale. The generation of solvents from lignin has also been investigated using metal catalysts to produce alkyl-substituted phenolics such as propyl guaiacol (PG) and propyl syringol (PS).<sup>128</sup>

These lignin-derived solvents can also be used to pretreat biomass, enabling a “closed-loop” biorefinery that sustains its own process needs by supplying solvent.<sup>129</sup> It should be noted, however, that many solvents derived from biomass may also be as problematic in terms of toxicity.<sup>130</sup> Propyl guaiacol (PG), for example, is toxic and an irritant.

Currently, GVL has limited applications at an industrial scale due to high production costs. Han has performed a techno-economic analysis of the generation of GVL from lignocellulosic biomass using lignin-derived propyl guaiacol as a solvent.<sup>131</sup> The analysis suggested that the process was economically competitive with current commercial processes. Purchasing of corn stover (\$84.1/t) accounted for 41% of the total annual cost. When byproduct sales and surplus electricity, generated from burning residual lignin, were also factored in, the minimum selling price for GVL was calculated to be \$3081/t (which is comparable to high-end dipolar aprotic solvents such as dimethylformamide). Han found that an effective heat exchanger system was required to reduce heating costs and that efficient catalyst and solvent recycling systems were essential.<sup>132</sup>

Strappaveccia et al. identified GVL as a sustainable alternative to toxic dipolar aprotic solvents such as acetonitrile, dimethylformamide (DMF), or *N,N*-dimethylacetamide (DMA) in cross-coupling reactions.<sup>133</sup> They used GVL for the Heck–Mizoroki coupling reactions of iodobenzene with acrylic esters and iodobenzene with styrenes containing different substituents using charcoal-supported palladium catalysts. Leaching of the metal catalysts as well as purity of the products from the Heck–Mizoroki coupling reaction were investigated, and E-factors were provided. Strappaveccia et al. reported high yields (>80%) for the coupling of iodobenzene with acrylic esters/acids and iodobenzenes with styrenes; see Figure 8.

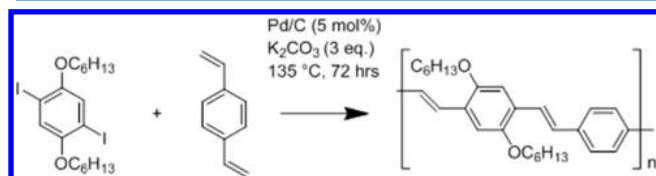
The reported E-factors (between 14 and 27) varied with the substituents but were comparable to E-factors commonly seen in fine chemical production  $5 \rightarrow 50$  and pharmaceuticals  $25 \rightarrow 100$  kg waste/kg product.<sup>134</sup> Palladium leaching was also tested and compared to other solvents for the reaction of iodobenzene and methyl acrylate. GVL reduced residual Pd in the product (7.7 ppm at 150 °C) as compared to products produced using *N*-methyl-2-pyrrolidone (NMP = 835 ppm) and dimethylformamide (DMF = 50 ppm), although Pd in the solvent was not reported. GVL could accomplish 100% conversion; however, this required a longer reaction time of 2 h at 130 °C as compared to 30 min with DMF and NMP. Palladium content in GVL was found to be highly dependent on temperature, with reactions performed at higher temperatures having lower palladium contamination. At 130 °C and 2 h, a palladium



**Figure 8.** Coupling of iodobenzene with acrylic esters (top) and iodobenzene with styrenes (bottom) to yield stilbenes using Pd/C catalysts in GVL.

content of 8.96 ppm was recorded as compared to 835 ppm in NMP at 150 °C and 50 ppm in DMF at 150 °C.

The synthesis of poly(*p*-phenylene)vinylene (PPV) (5C) was then demonstrated using GVL as a solvent (Figure 9). The



**Figure 9.** Production of PPV with GVL or NMP solvents. Pd leaching was 6 ppm for GVL or 860 ppm for NMP.

process was performed at 135 °C for 72 h and resulted in a lower number average molecular weight and a lower weight average molecular weight polymer ( $M_n = 8.14$  kDa and  $M_w = 16.27$  kDa as compared to NMP, which gave a  $M_n = 16.43$  kDa and  $M_w = 36.98$  kDa) at a similar yield (72% vs 70% with NMP). The leaching of the catalyst was also measured. GVL produced PPV contained 6 ppm of Pd, while NMP had 860 ppm. The PPV produced had a photovoltaic and transistor device performance comparable to those produced from conventional solvents.<sup>133</sup> Overall, GVL appears to be a promising renewable solvents. However, GVL is also a useful platform molecule to fuels and other value-added chemicals.<sup>121,135</sup> Future applications of GVL as a solvent therefore depend on the development of those areas.

**2.4.3. Cyrene.** Sherwood et al. have shown that dihydrolevoglucosenone (Cyrene, Figure 2d) can be produced

from cellulose in a two-step process, thereby ensuring a low environmental footprint.<sup>136</sup> Moreover, cellulose was converted to levoglucosenone (LGO), which was subsequently hydrogenated to Cyrene in a solvent-free process, with >90% yield. Like GVL, Cyrene has been proposed as a replacement for toxic polar aprotic solvents such as NMP. The authors therefore compared the Kamlet–Abboud–Taft and Hansen solubility parameters of Cyrene against a range of solvents, including NMP, cyclohexanone, DMF, dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), and sulfolane (Table 2). Dispersion, polar, and hydrogen-bonding interactions for Cyrene were reported to be 18.8, 10.6, and 6.9 MPa, respectively, making it most similar to DMSO (18.4 MPa) from a dispersion perspective, to DMAc (11.5 MPa) from a polar interaction perspective, and to NMP (7.2 MPa) with regards to hydrogen-bonding interactions.<sup>136</sup>

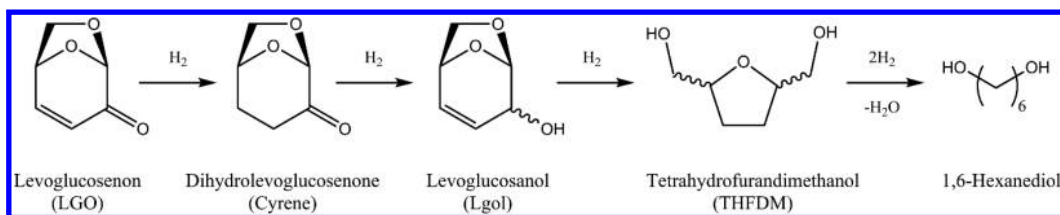
Levoglucosenone (LGO) can be further hydrogenated to levoglucosanol (Lgol) (Figure 10).<sup>137</sup> Hydrogenolysis of Lgol gives tetrahydrofuran dimethanol (THFDM), which is also a potential renewable solvent. Other products are also accessible from THFDM, for example, HMF; however, HMF may be obtained in a single step from cellulose.<sup>138</sup> He et al. have provided a techno-economic analysis for the production of LGO using a THF and water mixture.<sup>139</sup> The conversion reactor and separator would contribute the most to the capital expenditure's base cost when considering the process. Overall the production of LGO is estimated to be less than \$3.00 per kg, with the feedstock being the major contributor to the cost. This makes the production of Cyrene feasible for commercial production, and once again in line with high-end organic solvents such as DMF.

Cyrene has the potential to replace many reactions that require nonrenewable dipolar aprotic solvents. Reactions conducted in solvents such as DMF, NMP, and DMAc may be replaced with Cyrene, for example, organic chemistry or MOF synthesis.<sup>140,141</sup> In 2017, Mistry et al. used Cyrene for the synthesis of urea compounds (from isocyanates and amines), which have applications in the pharmaceutical industry for a number of different drugs.<sup>142</sup> Solvent removal was easier, and the molar efficiencies were improved relative to other production methods. Salavagione et al. found the viscosity of Cyrene also provides near-perfect conditions for graphene dispersion, improving graphene exfoliation when compared to NMP.<sup>143</sup> Wilson et al. have also used Cyrene as a solvent for Sonogashira Pd cross-coupling.<sup>144</sup> The pH sensitivity of Cyrene was identified as a potential limitation, although increasing the reaction temperature could compensate for this problem. Acidic

**Table 2.** A Comparison of Kamlet–Abboud–Taft Parameters and Hansen Solubility Parameters for Cyrene and Six Solvents That It Can Potentially Replace<sup>a</sup>

	Cyrene	NMP	cyclohexanone	DMF	DMAc	DMSO	sulfolane
$E_T^N$	0.333	0.355	0.281	0.386	0.377	0.444	0.41
$\alpha$	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$\beta$	0.61	0.75	0.58	0.71	0.73	0.74	0.30
$\pi^*$	0.93	0.90	0.71	0.88	0.85	1.00	0.96
$\delta_D/\text{Mpa}^{0.5}$	18.8 <sup>b</sup>	18.0	17.8	17.4	16.8	18.4	20.3
$\delta_P/\text{Mpa}^{0.5}$	10.6 <sup>b</sup>	12.3	6.3	13.7	11.5	16.4	18.2
$\delta_H/\text{Mpa}^{0.5}$	6.9 <sup>b</sup>	7.2	5.1	11.3	10.2	10.2	10.9
BP/°C	203	202	155	153	165	189	282
$\rho/\text{g mL}^{-1}$	1.25	1.030	0.95	0.9400	0.94	1.10	1.26

<sup>a</sup>Reproduced with permission from ref 136. Copyright 2014 The Royal Society of Chemistry. <sup>b</sup>Calculated with HSPiP software.



**Figure 10.** LGO serves as a platform chemical for the production of solvents and other useful renewable compounds. Hydrogenation of LGO produces Cyrene, which can be isolated for use as a solvent. Further hydrogenation of Cyrene produces Lgol, as a chiral precursor. Reproduced with permission from ref 137. Copyright 2017 The Royal Society of Chemistry.

or basic solutions are therefore not advised for Cyrene, as well as strong oxidizing and reducing agents. Implementation of Cyrene as a renewable solvent therefore requires further technical investigations to ensure solvent degradation is avoided. Although Cyrene can be made in a two-step process from cellulose, its stability may limit potential applications. However, Cyrene may be an ideal replacement for certain toxic chemicals, provided the conditions of the chemical processes operate under mild conditions.

Overall, the highlighted renewable cellulose-derived solvents represent three stages of progression. 2-MeTHF has a structure similar to that of THF; however, its properties are slightly different, and in some respects this has led to an improvement in applications (e.g., water miscibility). The issues facing 2-MeTHF are now concerned with industrial adoption; however, given its similarity to THF, this is unlikely to be problematic. Furthermore, increasing concerns with nonrenewable fossil fuel-derived chemicals have popularized renewable solvents and compelled researchers to consider their use. As easily accessible solvents, 2-MeTHF and limonene have led this transition.

GVL and Cyrene are becoming increasingly popular as alternative renewable solvents. GVL is more established in the research community and has been applied to a broad variety of applications, while Cyrene is relatively new and its investigated applications are currently limited. However, both solvents offer advantages of their own. The simplicity of Cyrene synthesis offers great hope for simplified process implementation, but questions around stability under harsh or long-term process conditions may limit it to a few niche applications. In contrast, GVL shows a robust nature, but the production cost may be higher. The production of both GVL and Cyrene requires the use of  $H_2$ , which is at present derived from nonrenewable sources, and represents a hidden energy consumption and cost. Remarkably, both of these leading renewable solvents have estimated production costs of ca. \$3/kg, which would put them in the range of very expensive, but widely used, organic solvents such as DMF or DMSO. This offers both an expectation that these solvents can be produced at scale and a clear outline of the present limitations for their use (and therefore the next set of development challenges).

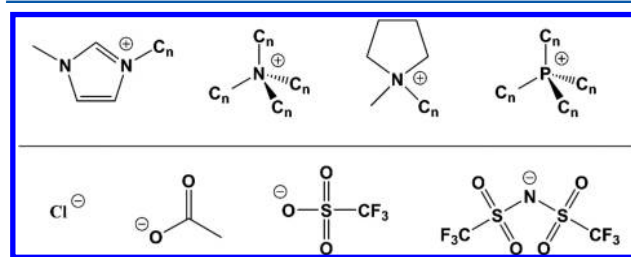
Renewability is not the only requirement for future sustainable solvents. There are a wide range of alternative solvents currently under development, and most have unique features or properties that are exploited in some way. However, one property that seems advantageous in the laboratory may be technically, economically, or environmentally detrimental at industrial scale. Sustainable development now places an emphasis on considering the origins and impacts of solvents (and all chemicals) throughout their lifetimes. This realization has been best documented for ionic liquids, which has led

researchers to consider the future of their applications at industrial scale.

### 3. IONIC LIQUIDS (ILs)

#### 3.1. Introduction

Ionic liquids (ILs) are salts that are molten at, or close to, room temperature.<sup>145,146</sup> They are composed of discrete anions and cations (Figure 11) and have extremely high enthalpies of

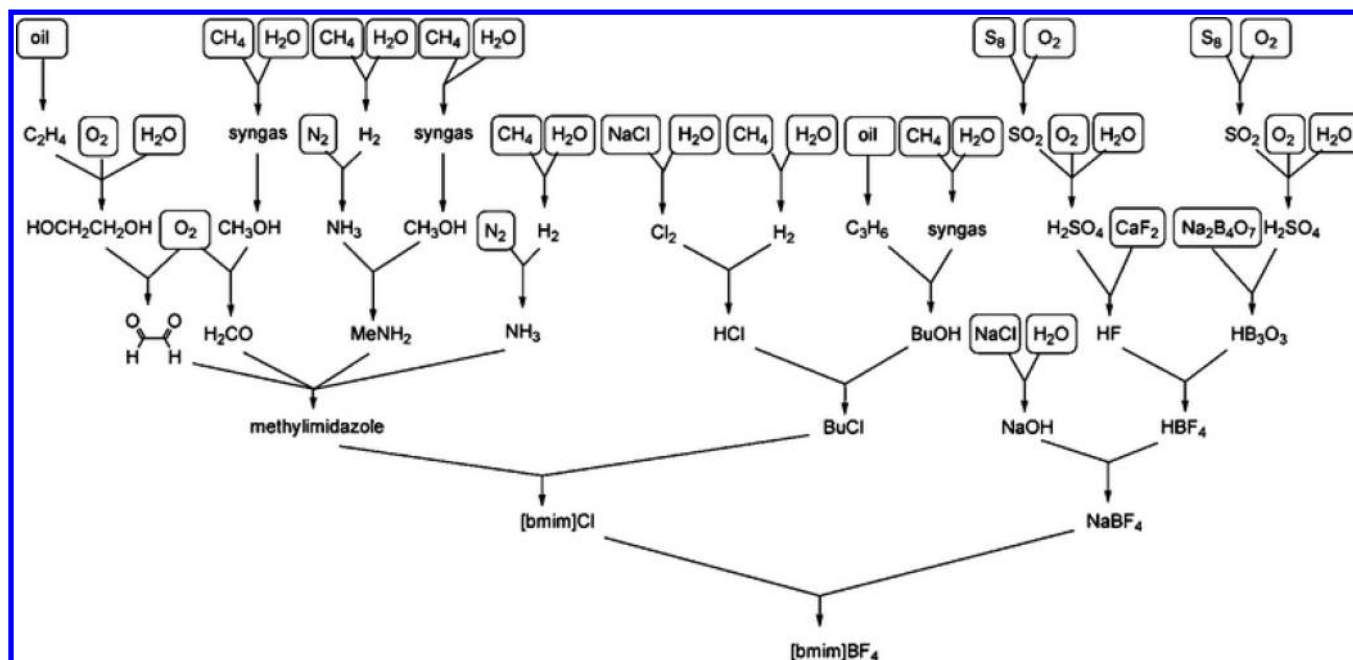


**Figure 11.** Common aprotic cations (top) and some anions (bottom), which may be paired in any combination.

vaporization ( $\Delta_{\text{vap}}H$ ), making them effectively nonvolatile.<sup>147</sup> Moreover, ionic liquids have high chemical and thermal stabilities and remarkable solvating power; hence, they were popularized as green solvents.<sup>148–150</sup> Changing anion–cation combinations of ionic liquids also changes their physicochemical properties, although this cannot be achieved in situ as with other tunable solvents. Concerns over the extensive manufacturing procedures of ionic liquids were highlighted early on.<sup>66,77,151</sup> The problem has been best represented by the life cycle tree of the common ionic liquid  $[C_4C_1\text{Im}][\text{BF}_4]$  (Figure 12), which shows the large number of steps required to produce the ionic liquid from its origins. This includes nonrenewable crude oil and natural gas sources, and a range of toxic, harmful intermediates. Furthermore, LCA has determined that replacing organic solvents with ionic liquids simply shifts the use of volatile solvents and pollutants to the ionic liquid production stage.<sup>77</sup> Hence, assessing a chemical process without considering the production of the starting materials, auxiliaries, and solvents can provide misleading information.

Aprotic ionic liquids are traditionally made by nucleophilic substitution ( $S_N2$ ) reactions of amines or phosphines with alkylhalides or alkylsulfates. Their preparations are generally slow (depending on reagents) and require inert conditions and solvent-demanding purifications (i.e., recrystallization), if reasonable purity is desired. Alternatives to conventional heating, such as sonochemical, mechanochemical, or microwave-assisted procedures, have been demonstrated to allow solvent-free preparations by avoiding viscosity related issues (i.e., diffusion and heat transfer).<sup>152–154</sup> Substituting starting





**Figure 12.** Life cycle tree for  $[\text{C}_4\text{C}_1\text{Im}][\text{BF}_4]$  ( $[\text{BMIm}][\text{BF}_4]$ ) as reported by Jessop. Reproduced with permission from ref 68. Copyright 2016 Royal Society of Chemistry.

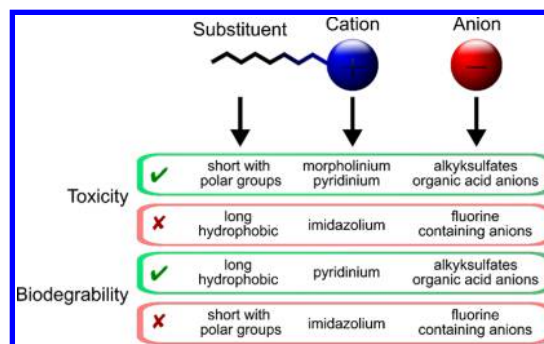
materials can also give halide-free ionic liquids (halides are common contaminants post ion-metathesis) or afford ionic liquids with properties that improve their separation and purifications.<sup>155,156</sup> Ionic liquids have even been prepared using other neoteric solvents. For example, Zhou et al. described the preparation of 1-butyl-3-methylimidazolium chloride ( $[\text{C}_4\text{C}_1\text{Im}]\text{Cl}$ ) in supercritical  $\text{CO}_2$ .<sup>157</sup>

### 3.2. Environmental Impacts

The high chemical stability and low volatility of ionic liquids ensure that emissions from ionic liquids are of low environmental concern. However, this means that they may also be stable and persistent environmental pollutants. This issue has been known for some time (especially regarding aquatic environments), and Chatel et al. have likened ionic liquids to poly chlorinated biphenyls (PCBs), because they have several similar properties.<sup>158,159</sup> High levels of PCB emissions from widespread use and poor disposal practices have had devastating ecological impacts throughout the globe. Chatel et al. therefore highlighted the need for a deeper understanding of the biodegradation of ionic liquids and suggested that LCA studies should focus on toxicological and environmental risks.

Stolte et al.<sup>160</sup> have emphasized that clear guidelines are required for such investigations and that generalized approaches are inadequate.<sup>161–163</sup> For example,  $\text{EC}_{50}$  (the half maximal effective concentration) has been deemed insufficient for understanding ionic liquid toxicity. More sophisticated subcellular investigations are ideally required (e.g., in vitro assays)<sup>164,165</sup> to understand ionic liquid toxicities and facilitate their future designs. Stolte et al.<sup>160</sup> suggest the direct investigations of endocrine disruption; mutagenicity, carcinogenicity, and teratogenicity; long-term and chronic toxicity; chemosensitizing potential; bioaccumulation; and persistency.

Cvjetko Bubalo et al. have recommended some guidelines for producing “greener” ionic liquids (see Figure 13).<sup>166</sup> However, generalized suggestions can misinform researchers and lead to investments in potentially harmful substances. For example,



**Figure 13.** Suggestions presented by Cvjetko Bubalo et al. for the synthesis of less toxic and more biodegradable ionic liquids. However, these results may be misleading as toxicity is organism-specific. This illustrates the difficulties encountered when trying to design broad guidelines. Adapted with permission from ref 166. Copyright 2014 Elsevier.

Cvjetko Bubalo et al. suggest the use of pyridinium ionic liquids as less toxic alternatives.<sup>166</sup> Yet the toxicities of pyridinium salts toward *Vibrio fischeri* (*V. fischeri*) are higher than most other ionic liquids, including imidazolium salts.<sup>167,168</sup> Quantitative structure activity/property relationship (QSAR/QSPR) models can provide structural rationalizations for observed ecotoxicity trends.<sup>169</sup> These models can even help to predict the ecotoxicity of new ionic liquids. However, assessing every ionic liquid (there are said to be  $10^{18}$  possible structures) against every organism is an impossible task.

Perales et al. have demonstrated the difficulty in predicting ecotoxicity by examining two solvents with similar physico-chemical properties but very different structures.<sup>170</sup> The toxicities of the well-known ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ( $[\text{C}_4\text{C}_1\text{Im}][\text{PF}_6]$ ) and the relatively unknown 3-bis(2,2,2-trifluoroethoxy)propan-2-ol (BTFIP) were determined for three bioindicators: bacteria, crustaceans, and fishes, representing three trophic levels. BTFIP is a glycerol derivative and has been used as a solvent for

enantioselective catalysis;<sup>171,172</sup> hence, it has been labeled as a (partly) bioderived neoteric solvent. The authors found that BTFIP was nontoxic toward *V. fischeri* and *D. magna*, while [C<sub>4</sub>C<sub>1</sub>Im][PF<sub>6</sub>] was nontoxic toward *V. fischeri* but moderately toxic toward *D. magna* (see Table 3). Both BTFIP and

**Table 3.** EC<sub>50</sub> (mg/L) Results and Standard Deviations (SD) Reported by Perales et al. for *V. fischeri*, *D. magna*, and *D. rerio* Tests with BTFIP and [BMIM][PF<sub>6</sub>]<sup>a</sup>

ionic liquid	<i>V. fischeri</i>		<i>D. magna</i>		<i>D. rerio</i>	
	EC <sub>50</sub>	SD	EC <sub>50</sub>	SD	EC <sub>50</sub>	SD
BTFIP	1597	2.375	477	6.978	353	0.773
[C <sub>4</sub> C <sub>1</sub> Im][PF <sub>6</sub> ]	1473	3.293	31	4.538	550	6.348

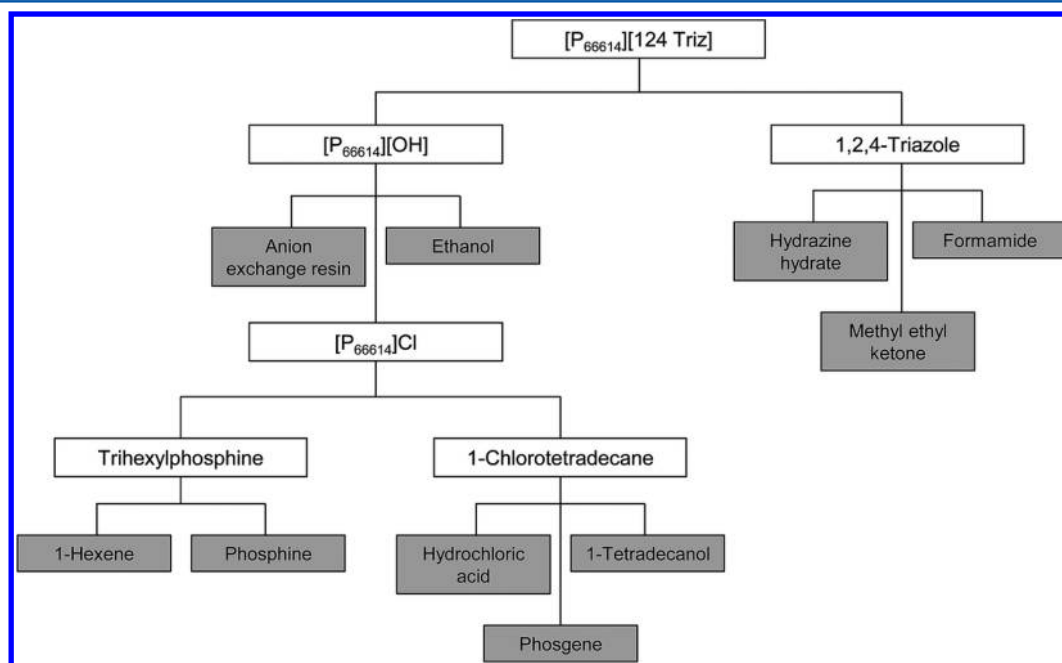
<sup>a</sup>Reproduced with permission from ref 170. Copyright 2016 Elsevier.

[C<sub>4</sub>C<sub>1</sub>Im][PF<sub>6</sub>] were moderately toxic toward *D. rerio*; however, BTFIP caused erratic and abnormal behavior in *D. rerio* at concentrations above 2000 mg/L. These results suggested that BTFIP could be more harmful than indicated for aquatic environments and challenge the authors' predictions that BTFIP would be a safer alternative to [C<sub>4</sub>C<sub>1</sub>Im][PF<sub>6</sub>]. This study highlights the limitations of EC<sub>50</sub> data, and thus further investigations are required for understanding solvent toxicity. Reid et al. have compared the microbial toxicity of 12 aprotic and 12 analogous protic ionic liquids against eight bacterial and 12 fungal strains. Gram-positive bacteria were more sensitive to both types of IL, and fungal strains were the most resilient. In the bacterial study, there was no consensus as to which type of IL was more toxic; however, cation functional groups were found to be the most important predictor of toxicity, with more lipophilic cations being the most toxic.<sup>173</sup> Costa et al. have thoroughly reviewed ionic liquid (eco)toxicity and (bio)degradability and highlighted the need for under-

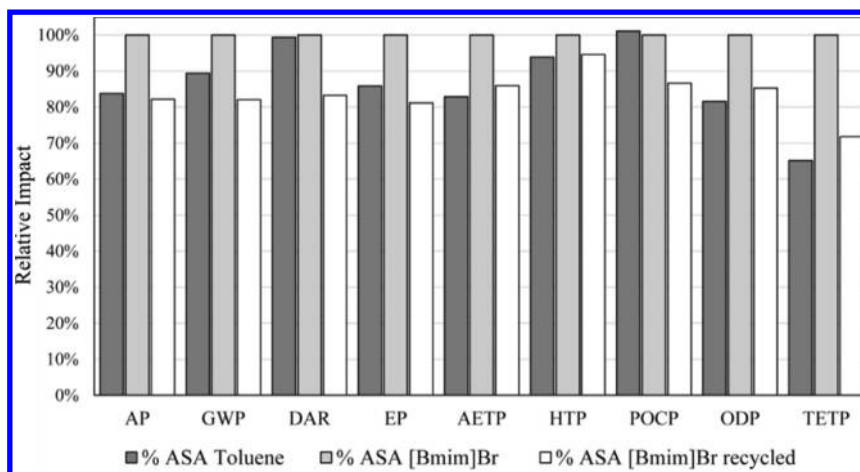
standing bioaccumulation and persistence in soil as well as their metabolic pathways.<sup>174</sup>

As different microorganisms have different metabolic pathways, determining all potential ionic liquid metabolites is challenging.<sup>175</sup> However, metabolites possess environmental behaviors and toxicity profiles different from those of parent ionic liquids. Understanding the metabolic pathways of ionic liquids is therefore important for ensuring environmental sustainability. In terms of biodegradability, some ionic liquids are more biodegradable than others. For example, cholinium ionic liquids with amino acid anions are readily degradable with mineralization levels of 62–87%.<sup>176</sup> Biodegradation of recalcitrant cations (e.g., imidazolium) can be enhanced by incorporating readily biodegradable moieties, such as organic acids<sup>177,178</sup> or amino acids.<sup>179</sup>

Mehrkeš et al. have investigated the ecological impacts of ionic liquids on aquatic systems when directly released into waste waters, to represent industrial-scale emissions from solvent recovery (0.04% to 0.08% IL release fraction).<sup>180</sup> The authors compared their findings to the aquatic impacts of upstream production of the ionic liquids, that is, cradle-to-gate assessments. The results revealed that the production of all ionic liquids ([C<sub>4</sub>C<sub>1</sub>Im]Cl, [C<sub>4</sub>C<sub>1</sub>Im]Br, [C<sub>4</sub>C<sub>1</sub>Im][BF<sub>4</sub>], [C<sub>4</sub>C<sub>1</sub>Im][PF<sub>6</sub>], and [C<sub>4</sub>Py]Cl) had ecotoxicity impacts 1 order of magnitude higher than their direct release. Furthermore, on average, 83% of production ecotoxicity resulted from hazardous materials, as opposed to energy related emissions. Disproportionately high contributions from bromobenzene (from bromobutane production, for [C<sub>4</sub>C<sub>1</sub>Im]Br) and chloramine (from pyridine production, for [C<sub>4</sub>Py]Cl) were identified. Environmental impacts could be significantly reduced by avoiding these hotspots or by employing alternative preparations. The authors therefore stressed the importance of assessing precursor materials for the design of more environmentally sustainable ionic liquids.



**Figure 14.** Life cycle tree for the production of [P<sub>66614</sub>][124Triz] (the shaded boxes indicate the compounds for which data are available in LCA databases; data for the compounds shown in clear boxes are not available). Reproduced with permission from ref 181. Copyright 2016 The Royal Society of Chemistry.



**Figure 15.** Relative life cycle impacts of ASA production using toluene,  $[C_4C_1Im]Br$  ( $[Bmim]Br$ ), and recycled  $[C_4C_1Im]Br$ , with  $[C_4C_1Im]Br$  referenced to 100%. Terms on the x axis refer to impact categories using the CML characterization method: acidification potential (AP), global warming potential (GWP), depletion of abiotic resources (DAR), eutrophication potential (EP), aquatic ecotoxicity potential (AEP), human toxicity potential (HTP), photochemical ozone creation potential (POCP), ozone layer depletion potential (ODP), and terrestrial ecotoxicity (TETP). Reproduced with permission from ref 182. Copyright 2016 Elsevier.

Unfortunately, ionic liquid assessments often have to make assumptions regarding materials properties as data are not available. For example, Cuéllar-Franca et al. have performed cradle-to-gate assessments of trihexyltetradecylphosphonium 1,2,4-triazolide ( $[P_{66614}][124Triz]$ ) and monoethanolamine (MEA) to determine whether phosphonium ionic liquids are viable alternatives to MEA for  $CO_2$  capture.<sup>181</sup> Figure 14 shows the life cycle tree for  $[P_{66614}][124Triz]$  as presented by the authors, with available data shown as gray boxes and unavailable data shown as white boxes. Despite the absence of data for several key intermediates, the ionic liquid was assessed using lab-scale information, and the results were supported by sensitivity and uncertainty analyses. The raw materials were identified as environmental hotspots, which resulted in significantly higher environmental impacts for  $[P_{66614}][124Triz]$  in 10 out of 11 categories. However, the human toxicity potential for MEA was 18 times higher than that for  $[P_{66614}][124Triz]$ .

Alviz et al. compared the environmental impact of replacing toluene with  $[C_4C_1Im]Br$  for the preparation of acetylsalicylic acid (ASA).<sup>182</sup> Cradle-to-gate assessments showed that for the preparation of 1 kg of ASA, toluene production contributed 7% to the total environmental impact, while  $[C_4C_1Im]Br$  contributed 20%. Again, this was due to the lengthy preparation of the ionic liquid; in this case, hydrogen bromide and 1-butanol were identified as key contributors. The authors also investigated ionic liquid recycling and assessed the environmental impact of a 89–98% ionic liquid recovery rate (suggested by nanofiltration) for the same process (Figure 15). The impacts were reduced in all categories, as would be expected. The authors therefore emphasized that recovery and recycling of ionic liquids is crucial for reducing their environmental impacts, as well as process economics.

Researchers have started to explore alternative ionic liquid preparation methods, the aim being less toxic ionic liquids, with low environmental impacts. Fortunately, ionic liquids are extremely versatile and may be designed with properties in mind.<sup>183</sup> Biodegradable and bioderived are now common labels found in numerous ionic liquid publications.<sup>184–188</sup> Many of these labels may be deserved; however, the challenge remains, to produce the next generation of ionic liquids while

maintaining economic viability. If ionic liquids cannot be produced at low cost, their large-scale industrial applications will remain limited.<sup>189</sup>

### 3.3. Economic Viability of Ionic Liquids

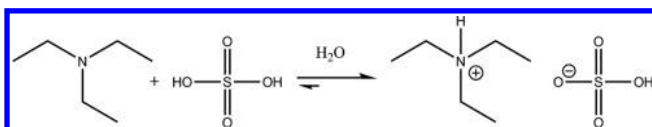
Although ionic liquid recycling can have positive influences on the environmental impacts of ionic liquids, the economics of solvent recycling must be addressed. Baral et al. assessed the techno-economics of an ionic liquid pretreatment process utilizing 1-ethyl-3-methylimidazolium acetate ( $[C_2C_1Im][OAc]$ ) for a 113 million L/year cellulosic biorefinery.<sup>190</sup> The recovery process was identified as the most energy-intensive step due to purification of the ionic liquid, which consumed ~88% of the total recovery energy. Furthermore, even with 80% IL recovery, the high IL cost (\$2.5/kg) made ionic liquid makeup the major contributor to the operational costs. The authors suggested that improvements in IL recovery are therefore more important than reducing IL prices.

A range of ionic liquid recycling methods have been proposed to date; however, most require large amounts of energy or produce lots of waste. The efficient recycling of ionic liquids is a major challenge and a significant barrier for their industrial adoption.<sup>191</sup> However, it is important to note that, while IL cost is important, the use of the solvent inside a process is equally of concern. Solvent recycling can reduce cost, but there is no 100% recyclable solvent, nor would one be desirable. Solvent purge is an important means of removing inert impurities from a process, and while all solvents can be recycled (distillation or extraction), the utility of such an approach can be called into question for some applications. For example, many pharmaceutical production processes require ultralow levels of impurities to meet regulations, and so solvent recycling is not possible. However, for most applications, IL cleanup and reuse is crucial, so process considerations (use of other solvents for purification) and solvent properties (stability) need to be known.<sup>192</sup>

Regardless of recycling, aprotic ionic liquids require lengthy preparations from expensive starting materials. Furthermore, salt metathesis leads to low atom economies and the production of salt wastewaters, which require further costly treatment before disposal.<sup>193</sup> Alternatively, protic ionic liquids

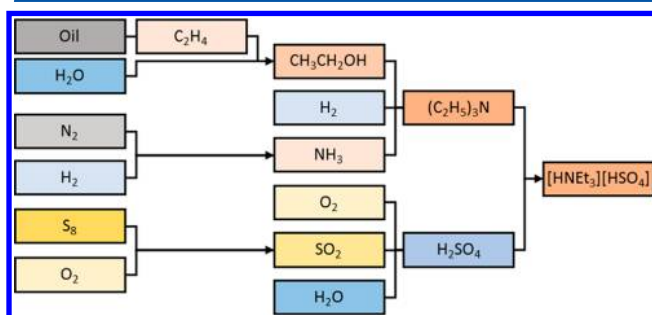


can be prepared by atom-economic acid–base neutralizations, for example,  $[\text{N}_{2220}][\text{HSO}_4]$  prepared from triethylamine and sulfuric acid (Figure 16), without further purification. In



**Figure 16.** A one-step preparation of  $[\text{N}_{2220}][\text{HSO}_4]$ , often referred to as [TEA][HSO<sub>4</sub>], by acid–base neutralization of triethylamine and sulfuric acid in water.

addition, many protic ionic liquids have short life cycle trees as they employ simple acids and bases (Figure 17). As such, protic ionic liquids can be made extremely low-cost.



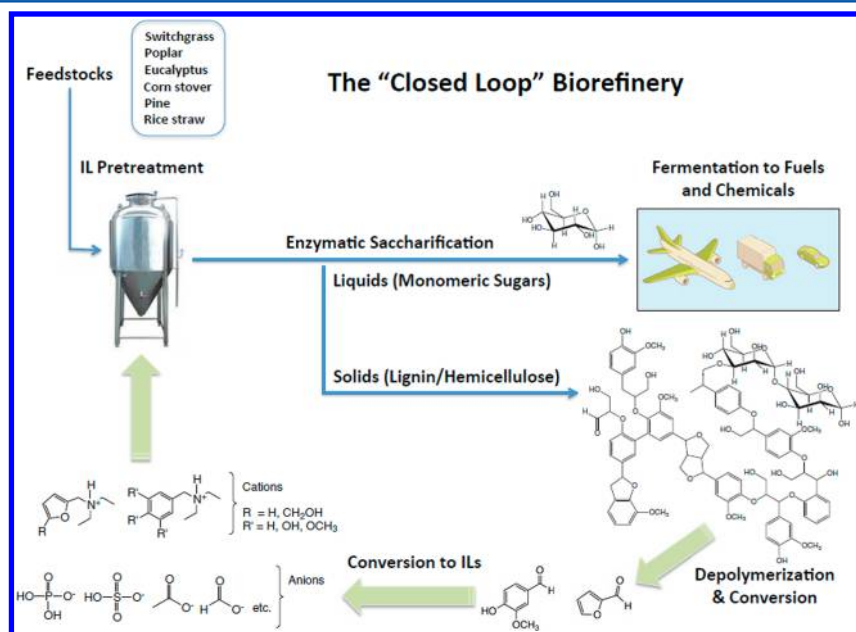
**Figure 17.** Life cycle tree for  $[\text{N}_{2220}][\text{HSO}_4]$ , adapted with permission from ref 72. Copyright 2014 The Royal Society of Chemistry.

As a simple set of criteria dedicated specifically to ionic liquid production, it is noteworthy that the function of the ionic liquid will play the first role in solvent selection. As a crude example, a highly acidic ionic liquid is not a viable solvent for use in base-catalyzed synthesis. However, even once a specific ion type is identified, there are some general assessments that can be made to identify whether a solvent is likely to be of high cost. The

first of these involves the number of synthetic steps required for solvent synthesis, as has been exemplified for both cost and sustainability (waste).<sup>68,72</sup> As a rough guide, the cost of a solvent could be assumed to double with each step away from a precursor. This also points to the complexity of the solvent; ILs employing aprotic (fully alkylated) cations normally require an extra step (ion metathesis) and will therefore be much more expensive than ILs with protic cations. The choice of amine precursor also matters; the cation switch from  $[\text{N}_{2220}][\text{HSO}_4]$  to  $[\text{HC}_{1\text{im}}][\text{HSO}_4]$  increased the (2014) cost of the IL from \$1.24/kg to \$2.96–\$5.88/kg, an increase of 2.5–5 times.<sup>72</sup> This is exclusively due to the cost of methylimidazole (a specialty chemical made in multiple steps from ammonia) versus triethylamine (a bulk chemical made in one step from ammonia).<sup>194</sup> Likewise, longer-chain alkyl tails will increase cost, as will more functionalization of either side-chain or ring carbons.

While anion choice is a more obvious technical performance consideration, there are still simple ways of identifying cost issues. Highly fluorinated anions such as  $[\text{OTf}]^-$  or  $[\text{NTf}_2]^-$  are difficult to synthesize, and the cost of either precursor salts or conjugate acids can indicate the complexity of synthesis rather than simple availability or demand. Further, the relative size of the ions is an often overlooked cause of high cost, as the larger ion occupies a larger proportion of the salt and therefore dominates cost. Also, Jessop suggested that the number of synthetic steps in a solvent will be a dominant factor on the environmental impact of the solvent, as more synthetic steps yield more waste and larger energy usage.<sup>68</sup> This will also apply to cost analysis. It is no accident that the cost of production should be linked to the size of the synthesis tree, as more synthetic steps will increase solvent cost alongside waste production and energy usage.

The low cost of  $[\text{N}_{2220}][\text{HSO}_4]$  (\$1.24/kg) compares favorably with the selling price of common organic solvents such as acetone (\$1.32/kg) or ethyl acetate (\$1.39/kg), and is midway between higher-end organic solvents, such as



**Figure 18.** Closed-loop lignocellulose biorefinery as proposed by Socha et al. Reproduced with permission from ref 195. Copyright 2014 United States National Academy of Sciences.

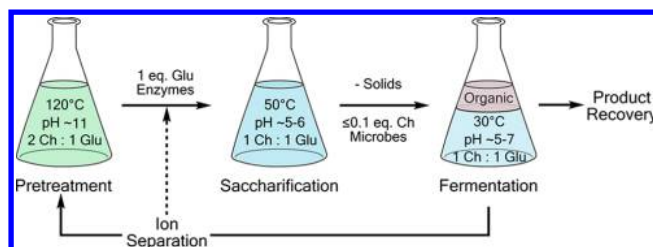
acetonitrile (\$1.54/kg) and low-cost solvents such as toluene (\$1.03/kg). However, it is important to note that low cost of starting materials will not alone ensure a low-cost IL, as the number of synthetic steps, the complexity of those transformations, and the degree of substitution will also play a role. Heteroatoms such as phosphorus will also ensure higher cost cations, as phosphine production is far more expensive (and far more dangerous) than amine synthesis.

### 3.4. Renewable Ionic Liquids

The wide range of biobased ionic liquids described to date has been summarized by Hulsbosch et al., who examined their application as solvents in lignocellulose processing.<sup>187</sup> Ionic liquids produced from the byproducts of a lignocellulose biorefinery can enable a “closed-loop” biorefinery that sustains its own needs for process solvents. This concept was presented by Socha et al. who reported the production of ionic liquids from lignin and hemicellulose, two lignocellulose pretreatment byproducts (see Figure 18).<sup>195</sup> In the case of biomass pretreatment, imidazolium-based ionic liquids have been shown to be effective at fractionating and separating lignocellulosic components.<sup>98,196,197</sup> However, imidazolium ionic liquids are not (currently) prepared from renewable sources, and so researchers are now looking to alternative cations that are able to achieve comparable performance. Ideally, a closed-loop biorefinery would also exploit waste valorization to produce high-value chemicals, alongside liquid fuels from enzymatic saccharification and subsequent fermentation. Ionic liquids have also been introduced as media for the conversion of lignocellulose into platform chemicals, membranes, and other materials.<sup>198</sup>

Choline, (2-hydroxyethyl)trimethylammonium, is a quaternary ammonium cation that is prevalent in biology. Choline salts are essential nutrients found in many foods, and they are therefore considered to be renewable, biocompatible, and biodegradable (although at present choline is produced from petrochemical sources). A variety of choline ionic liquids ([Cho][A]) have been prepared and used as versatile solvents and catalysts for a wide range of chemical processes.<sup>199</sup> Biomass processing using choline ionic liquids shows great potential, especially when combined with amino acid anions.<sup>200–202</sup>

Liszka et al. have proposed a one-pot conversion of biomass to biofuels with choline ionic liquids.<sup>203</sup> The authors showed that dicarboxylic acids can produce ionic liquids that are pH-switchable to potentially enable pretreatment, saccharification, and fermentation (PSF) in a single medium. A 1:1 ratio of choline to glutamate or succinate gives basic ionic liquids (i.e., [Cho]<sub>2</sub>[A]) that facilitate pretreatment, while a 2:1 ratio gives acidic ionic liquids (i.e., [Cho][A]) that are compatible with commercial cellulases (for saccharification) and *E. coli* (for fermentation). The pH decrease was achieved by the addition of one equivalent of glutamic or succinic acid, and electro-dialysis (ED) was suggested as a method of removing it to reform the dianionic salt (Figure 19). Lab-scale experiments gave a 91% conversion of switchgrass to fermentable sugars in dilute (10–25 wt %) IL-solutions. The subsequent fermentation in the presence of the ionic liquids was also demonstrated, albeit after a 2-fold solvent dilution. A techno-economic analysis of the process suggested that the minimum selling price (MSP) could range from \$3.6 to \$4.0 gal<sup>−1</sup>, \$1 gal<sup>−1</sup> lower than a traditional water-wash step.<sup>204</sup> Unfortunately, the authors make several assumptions, for example, high IL recovery (>99.9 wt %, without demonstrating a functioning



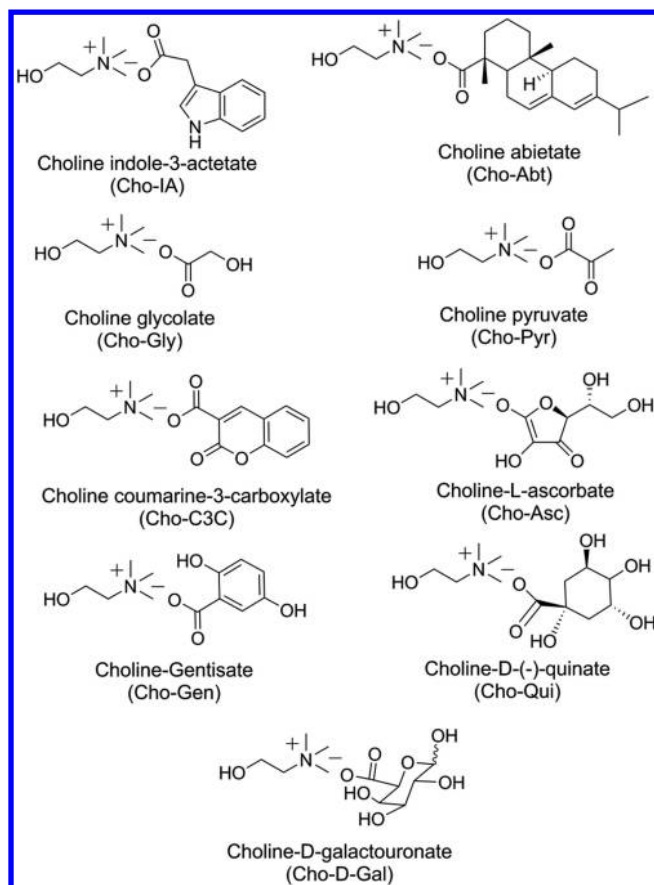
**Figure 19.** One-pot process for the conversion of lignocellulosic biomass to biofuels using aqueous DCA-IL solutions, as proposed by Liszka et al. Reproduced with permission from ref 203. Copyright 2016 The Royal Society of Chemistry.

process) and an extremely low estimation for the IL price (\$1 gal<sup>−1</sup>). Therefore, while the complete process may be technically unfeasible, the flexibility of ionic liquids for multistep processes is demonstrated. Other examples of switchable solvents will be discussed later in this Review to demonstrate the power of solvents with in situ tunable physicochemical properties.

Other one-pot biomass conversions using choline ionic liquids have also been suggested. Xu et al. demonstrated that dilute choline ionic liquids (10 wt %) can enable a high-solid feeding strategy to continuously provide a concentrated glucose stream for ethanol production.<sup>205</sup> The authors calculate an 85% reduction in wastewater and 40% reduction in annual operating costs (AOC) when compared to a corn stover water-washing process. Reducing the number of unit operations for a chemical process can have significant impacts on the waste production and cost. In this case, combined pretreatment and enzymatic hydrolysis can avoid the washing step necessary after a dilute acid pretreatment.

Mondal et al. have demonstrated the use of cholinium ionic liquids with bioactive natural acid anions (see Figure 20) for the purification of immunoglobulin G (IgG), an antibody with a variety of biomedical applications.<sup>206</sup> Six of the biocompatible ionic liquids (Cho-IA, Cho-Qui, Cho-Asc, Cho-Gly, Cho-Pyr, and Cho-D-Gal) were found to form aqueous biphasic systems (ABS) with polypropylene glycol (PPG 400) and were therefore further investigated. Quantitative extraction of pure IgG in the IL-rich phase was observed for all ionic liquids, except for (Cho-IA). Degradation or denaturing of IgG was not observed after ABS extractions, and the best ABS led to a 58% increase in IgG purity (against its purity in the original serum). Typical IgG purification processes require clarification, concentration, and chromatographic polishing.<sup>207</sup> Hence, cost-effective extraction techniques such as this have great potential to improve the sustainability of protein purifications, particularly in terms of energy and waste reduction. Other types of ABS will be discussed later in this Review.

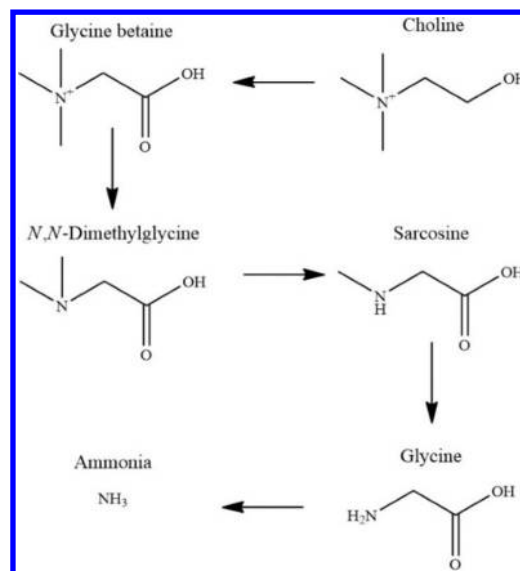
Choline ionic liquids are often said to be bioderived as choline chloride can be obtained from biological sources. However, choline chloride is currently made from ethylene oxide, trimethylamine, and hydrochloric acid in a gas-phase process.<sup>199</sup> The E-factor for this process is therefore very low as no waste is produced. Bioethylene oxide can be produced from bioethanol (by ethanol dehydration to ethylene, then oxidation to ethylene oxide), and the production of choline chloride from bioethylene oxide would provide a partly bioderived salt. Furthermore, many bioderived cholinium ionic liquids are synthesized via acid–base chemistry of choline hydroxide and organic acids.<sup>208</sup> Choline hydroxide can be made from the



**Figure 20.** Biomass-derived biocompatible ionic liquids used for extraction of IgG antibodies, as reported by Mondal et al. Reproduced with permission from ref 206. Copyright 2016 The Royal Society of Chemistry.

chloride salt by ion exchange; however, large-scale ion exchange processes have high operating costs and generate excessive waste streams through operation and regeneration. Therefore, before choline chloride and its derivatives are employed in large-scale chemical processes, LCA and techno-economic investigations into their production are necessary. Additionally, Morandeira et al. have shown that complete removal of choline from waste effluents is difficult to achieve, despite the claimed biodegradable nature of the ionic liquids.<sup>209</sup> Only one halophilic bacterium could metabolize the cation, and the proposed degradation pathway is shown in Figure 21.

Ionic liquids represent a family of chemicals with massive molecular diversity. This has driven the development of solvents with exceptional performance and high solvation power. However, the major issues preventing the adoption of ionic liquids industrially are still largely unresolved. Synthetic routes are often too complex and costly, and toxic or nonrenewable reagents are often required. Those with simpler synthetic routes may face issues such as high acidity and may cause corrosion. Ensuring recyclability and reusability will be critical for successful implementation as well as routes of disposal. Unknown or high toxicity is often a major criticism of ionic liquids. Techniques or guidelines used to predict toxicity should be used with caution, and a formula for the design of nontoxic ILs remains elusive. Toxicity and environmental biodegradability may be more complex with ionic liquids than other solvents, as the fate of both anion and cation will have to be considered. That said, renewable and bioderived ILs show



**Figure 21.** Biodegradation pathway of choline with a halophilic bacterium, as proposed by Morandeira et al. Reproduced with permission from ref 209. Copyright 2017 American Chemical Society.

much promise as solvents in the biorefinery and a number of strategies have been identified, which can increase biodegradability.

Ionic liquids provide researchers with a highly tunable reaction medium. Their chemical diversity is so broad that categorizing ionic liquids and making general statements regarding their properties can be misleading. Their popularity is a result of their unique features, which offer unusual advantages for an extremely diverse range of applications. This diversity has also enabled the development of nontoxic, biodegradable ionic liquids with limited environmental impacts. However, ionic liquids may remain confined to niche, small-scale applications if they cannot be produced for a low cost.

The economic viability of ionic liquids depends on balancing performance with production costs. Some low-cost ionic liquids have already been described and demonstrated to improve a range of chemical processes.<sup>71,73</sup> Environmental sustainability is often an afterthought during the design of these ionic liquids, and toxic, nonrenewable precursors are usually employed. However, simple preparation procedures and short synthesis trees are inherent to low-cost ionic liquids, which may compensate for any toxic materials used.

The dynamics of exchanging economic and environmental features are only understandable by LCAs and similar detailed assessments. Ionic liquid designs are therefore not only dependent on technical, economic, and environmental factors, but they ultimately depend on the assessment tools used to understand their suitability/sustainability. This is true for all tunable media and an important consideration for their future. Therefore, to exploit the full potential of extremely versatile solvents such as ionic liquids, powerful and thorough assessment tools are not only required, but they must be used in the correct way.

## 4. DEEP EUTECTIC SOLVENTS (DES)

### 4.1. Introduction

Deep eutectic solvents (DES) are formed from mixtures of Brønsted or Lewis acids and bases. The melting points of DES are lower than the individual components, and they are often



prepared by mixing two solid reagents to form a liquid product. Different types of DES have been described, and most contain hydrogen-bond acceptors (HBAs) such as choline chloride and hydrogen-bond donors (HBDs) such as urea. Alternatively, they may also contain metal salts or hydrated metal salts; full explanations can be found in dedicated reviews.<sup>210,211</sup> DES are excellent solvents for a variety of chemical processes, for example, extractions, catalysis, organic synthesis, and electro-deposition.<sup>212–214</sup>

DES can be made from components that have renewable sources, and DES composed entirely of plant metabolites (such as ammonium salts, sugars, and organic acids) are labeled natural deep eutectic solvents (NADES).<sup>215–217</sup> Paiva et al. have reviewed the history and development of DES and NADES and emphasized their potential as “next generation solvents”.<sup>218</sup> Usually, DES are prepared by simply heating and mixing two or more components without additional purification steps. Sometimes solvents such as water are used to facilitate mixing of the two components; these can then be removed under vacuum.<sup>219</sup> DES have been suggested as superior green solvents to ionic liquids, which require lengthy, air-sensitive preparations in comparison.

Crawford et al. have also demonstrated the power of mechanochemical synthesis for DES preparation.<sup>220</sup> An optimized twin screw extrusion (TSE) process was shown to produce Reline 200 (choline chloride:urea, 1:2) at 6.54 kg h<sup>−1</sup> using a screw speed of 50 rpm and a barrel temperature of 65 °C. The authors calculated the space time yield (STY) of this process to be 3 250 000 kg m<sup>−3</sup> day<sup>−1</sup>, which is 4 orders of magnitude higher than a Reline 200 batch synthesis (500 kg m<sup>−3</sup> day<sup>−1</sup>). Furthermore, the short residence time in the barrel was shown to enable the production of high-purity DES synthesized from thermally sensitive components, such as D-fructose (see Figure 22). TSE has also been used for the



**Figure 22.** Choline chloride DES prepared using TSE (left) as compared to conventional heating (right). Reproduced with permission from ref 220. Copyright 2016 The Royal Society of Chemistry.

preparation of metal organic frameworks (MOFs) and organic compounds and is becoming a popular solvent-free synthetic method.<sup>221,222</sup> It is especially suited to DES as it enables the rapid production of high-purity product and avoids thermal decomposition and problems with handling.

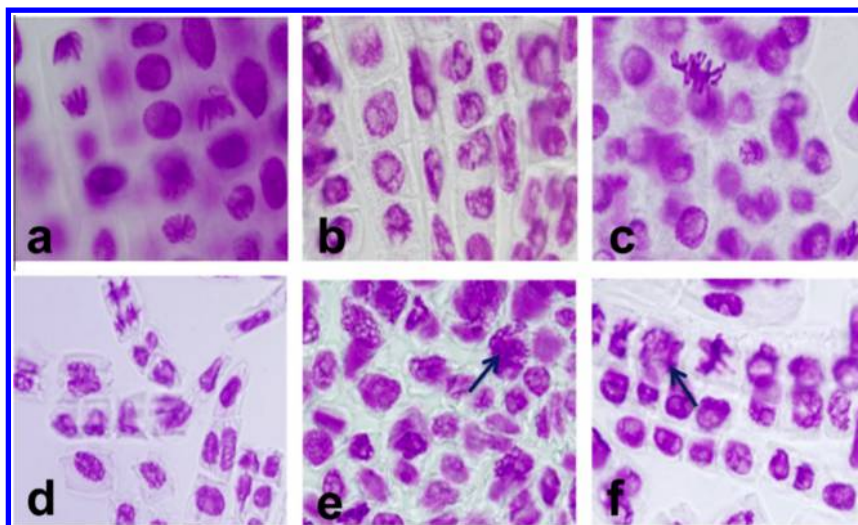
Like ionic liquids, DES have been proposed as alternative solvents that can improve the sustainability of many chemical processes.<sup>223–225</sup> The wide range of bioderived components found in DES and the popularization of NADES have vastly improved the reputation of deep eutectics as environmentally friendly solvents. Furthermore, the biocompatibility of NADES has enabled the development of many biotechnology and bioengineering applications.<sup>214</sup> Key renewable components of

DES include glycerol, sugars, and natural acids.<sup>226–229</sup> Glycerol is a major byproduct of biodiesel production (10 kg of glycerol is generated per 100 kg of biodiesel), soap, and fatty acid manufacturing via the hydrolysis of triglycerides.<sup>136,230</sup> However, as a byproduct, crude glycerol requires further purification if it is intended to be used as a solvent. The best method of purifying glycerol is currently vacuum distillation (bp = 290 °C at 760 mmHg), which is costly and energy intensive.<sup>231</sup> Hence, progress in glycerol purification is needed if glycerol is to be adopted by the chemical industry as a reaction medium. Al Omar et al. have demonstrated that glycerol is a versatile HBD by synthesizing six glycerol-based DES systems (70 DES) with a range of phosphonium and ammonium salts.<sup>226</sup>

Glycerol is highly viscous and may therefore be problematic for many chemical processes.<sup>232</sup> Abbott et al. have shown that choline chloride:glycerol DES have lower viscosities than pure glycerol or other DES, such as glycerol:diol mixtures.<sup>229</sup> Viscosity is often a problem for many neoteric solvents (e.g., ionic liquids and liquid polymers), and high viscosities have detrimental effects on mass transfer, reaction rates, and handling. Cosolvents are often used to reduce viscosity; however, polar protic solvents can disrupt the hydrogen-bonding networks of DES. Dai et al. examined the hydrogen bonding and viscosity of NADES diluted with water.<sup>233</sup> The authors found that hydrogen bonding between the HBD and HBA was gradually weakened until 50% (v/v) when it was completely disrupted. However, small quantities of water could greatly reduce viscosity, suggesting that cosolvents are viable options for viscosity reduction. Guajardo et al. have subsequently demonstrated that nonviscous DES/water mixtures can significantly enhance the enzymatic esterification of benzoic acid and glycerol to  $\alpha$ -monobenzoate glycerol ( $\alpha$ -MBG).<sup>234</sup> The employed lipase successfully functioned as a synthetic biocatalyst in the solvent mixture and performed best in a choline chloride/glycerol mixture with 8% (v/v) water. Viscosity issues of DES have also been addressed by Germani et al.<sup>235</sup> The authors prepared DES consisting of several linear and cyclic *N*-oxides as hydrogen-bond acceptors and phenylacetic acid as hydrogen-bond donor. These DES have low freezing points (20, −21, −27, and −34 °C) and very low viscosities, in the range of 175–412 centistokes at 25 °C, which is much lower than most other common and used DES in literature (e.g., choline chloride/urea with 600 centistokes at 25 °C). The polarities have been assessed by UV–vis measurements with solvatochromic dyes and are similar to those of methanol and [bmim][PF<sub>6</sub>] in two cases, and in general comparable to common organic solvents. These properties promote a use of these DES as solvents even at room temperature. However, the authors claim that the prepared DES are “green”, which was actually not assessed by any metrics. In fact, this claim is based on the fact that the substrates are eco-compatible (due to the biodegradability of the *N*-oxides and the natural occurrence of phenylacetic acid), but attention must be paid as the properties of a DES can be different from the properties of the single components.

#### 4.2. Toxicity of DES

DES should not automatically be assumed to be nontoxic if they are prepared from naturally occurring compounds. Hayyan et al. have investigated the toxicity and cytotoxicity of four choline chloride-based DES (with glycerine, ethylene glycol, triethylene glycol, and urea as HBDs).<sup>236</sup> The authors found



**Figure 23.** Impact on the cells from the root tip of *A. sativum* (a) with deionized water, (b) choline chloride, (c) ethylene glycol, (d) choline acetate and glycerol, (e) choline acetate and urea, and (f) choline chloride and acetamide. Cellular (nuclear) disruption is visible. Reproduced with permission from ref 237. Copyright 2015 Elsevier.

that all DES were nontoxic; however, the cytotoxicity of each DES was significantly higher than their respective individual components. Wen et al. suggested a systematic approach in assessing both the toxicity and the biodegradability of DES.<sup>237</sup> Using various organisms, toxicity was tested on bacteria, hydras, and garlic (*A. sativum*, see Figure 23), and the biodegradability was determined by the closed bottle test.

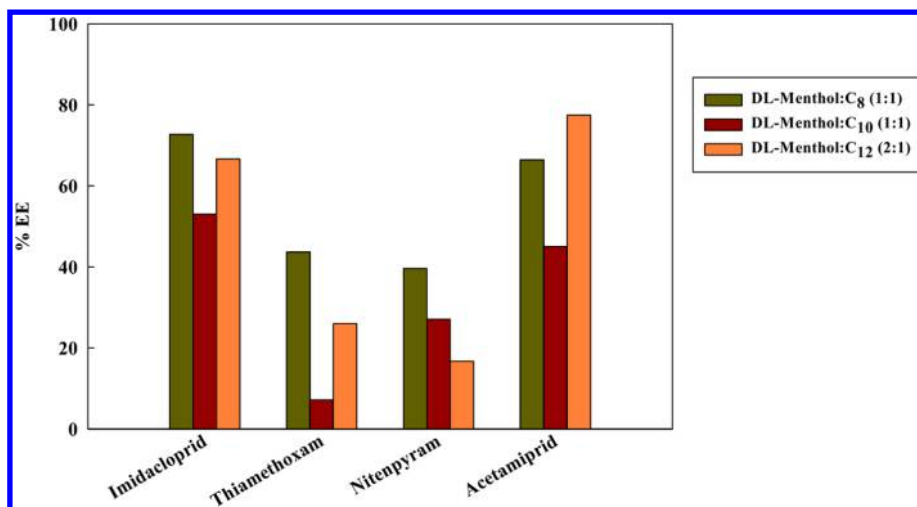
The results demonstrate that increased concentrations of choline chloride and choline acetate-based DES can negatively impact the cellular membranes of organisms even though most of the starting materials are categorized as nontoxic (see Figure 23). The same trend was observed when the antibacterial activity was investigated: the corresponding  $EC_{50}$  values for *E. coli* range from 58–532 mM, whereas the single components of the DES all showed  $EC_{50}$  values well above 800 mM. In addition, it was found that only the minority of the investigated DES can be considered as biodegradable, as only 3 out of 8 DES showed a biodegradability of 60% or higher, which is the general threshold for such determinations. The cytotoxicity of DES can be higher as well as lower as compared to their individual components. For example, a series of phosphonium-based DES has been found to exhibit significantly higher cytotoxicity than their components,<sup>238</sup> whereas the trend is inverted for a series of ammonium-based DES.<sup>239</sup>

Other studies conducted using cholinium-based DES have compared their toxicity and biodegradability to those of ionic liquids. de Moraes et al. compared the toxicity profiles of DES consisting of cholinium chloride with organic acids (acetic, citric, lactic, and glycolic acid) as HBDs to those of comparable ionic liquids (cholinium glycolate, cholinium acetate, cholinium dihydrogen citrate, and cholinium lactate).<sup>240</sup> Although it has often been assumed that DES solvents would be less toxic than their IL counterparts, evidence from these studies confirms the opposite. The authors suggest that rather than disrupting cellular membrane function, DES enter the cytoplasm and disrupt the pH. Juneidi et al. examined the toxicity and biodegradability of various types of DES.<sup>241</sup> Type I DES were composed of organic salts and metal salt, type II of organic salt and hydrate metal salt, and type III of organic salts and hydrogen-bond donor (HBD: ethylene glycol, glycerol, urea, and malonic acid) as well as zinc chloride and zinc nitrate

hexahydrate. Toxicity tests of pure DES as well as dilute DES were conducted on *Aspergillus niger* and *Cyprinus carpio*. The tests demonstrated that  $LC_{50}$  was greatly dependent on the concentration as well as the individual components of the DES. Their impacts on the living systems also varied, suggesting that not all DES disrupt living systems in the same fashion. Toxicity tests on fungi revealed that the DES tested were more toxic than their components.

NADES have received some attention as cytotoxicity tests suggest that they are less toxic than DES. Hayyan et al. used choline chloride along with five metabolites as hydrogen-bond donors: glucose, fructose, sucrose, glycerol, and malonic acid.<sup>242</sup> Utilizing COSMO-RS software to model mechanisms in which these NADES could potentially interact with the phospholipid bilayers of cell membranes, it was determined that careful selection is necessary despite the “benign” starting materials of the NADES. For example, organic acid HBD increased the cytotoxicity of the NADES. Computer modeling could be an effective and efficient method for initial exploration into the “best” NADES or DES for a given application. In another study,<sup>243</sup> the same authors discovered that the above-mentioned NADES show  $EC_{50}$  values in the range of 98–516 mM (depending on the cell line) and exhibit lower cytotoxicity than the DES *N,N*-diethyl ethanolammonium chloride:triethylene glycol ( $EC_{50}$  values in the range of 34–20 mM, depending on the cell line). Nevertheless, this trend was reversed in vivo: here, two of the tested NADES showed  $LD_{50}$  values of 1.24 and 1.84 g/mL, whereas the value for the DES was found to be 4.46 g/mL. Furthermore, they found that the NADES exhibit a lower cytotoxicity as compared to their individual components ( $EC_{50}$  values in the range of 35–49 mM), which raises the question if NADES are synthesized within the cells to counteract the cytotoxicity of their chief components.

Most of the studies demonstrated the high antibacterial or antifungal properties of DES and NADES, which can be an advantage for certain chemical processes, especially in the biotech industry.<sup>214,238,244</sup> The toxicity may be used as an advantage in understanding cellular metabolic pathways as well as a potential anticancer agent.<sup>243,245</sup> These solvents have low vapor pressures, good thermal stabilities, and broad applica-



**Figure 24.** Extraction efficiencies (EE) of three DES (consisting of DL-menthol and octanoic, decanoic, and dodecanoic acid, respectively) in the extraction of four neonicotinoids. Reproduced with permission from ref 252. Copyright 2017 Elsevier.

tions, which make them extremely attractive as replacements to traditional organic solvents. However, concerns arise particularly for soil and water contamination at the point of disposal.

#### 4.3. Applications of DES

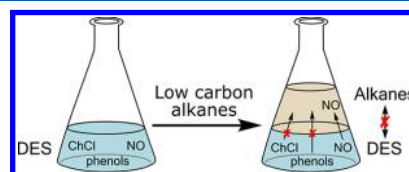
Besides electrochemical processes, the most common applications of DES are extractions and separations.<sup>246,247</sup> Jiang et al. used DES composed of choline-like HBAs with butyl, octyl, dodecyl, and phenyl groups with FeCl<sub>3</sub> for fuel desulfurization.<sup>248</sup> The best DES [C<sub>12</sub>DMEA]Cl/FeCl<sub>3</sub> was found to extract up to 52.9% of sulfur; however, this increased to 99.3% after five sequential extractions. Importantly, this investigation claims to utilize biodegradable DES, as choline chloride is biodegradable, without considering the effects of structural modification or incorporation of FeCl<sub>3</sub>. Furthermore, Sintra et al. have found that the same DES are moderately toxic toward *V. fischeri* and that longer alkyl chains significantly increase the toxicity of the DES.<sup>249</sup> The assumed biodegradability of the choline derivative is therefore misleading and an example of a “green herring”.

Osch et al. have used hydrophobic DES composed of decanoic acid and quaternary ammonium salts for biphasic extractions.<sup>250</sup> Longer alkyl chains increased hydrophobicity as well as extraction efficiency. NADES from choline, betaine, and proline have been utilized for the extraction of bioactive compounds. Duan et al. found that extraction ability correlates to physicochemical properties of the compound being extracted (pH, viscosity, polarity, H-bonding) and that NADES may be a safer method of extraction as compared to potentially toxic organic solvents.<sup>251</sup> Florindo et al. employed hydrophobic DES for the extraction of four neonicotinoids from aqueous solutions.<sup>252</sup> Both HBD and HBA of the DES were hydrophobic, and the DES were water stable. The highest extraction efficiencies were obtained using DES consisting of DL-menthol as the HBA and different saturated fatty acids (octanoic, decanoic, and dodecanoic acid) as HBDs; the results are shown in Figure 24. It can be observed that the extraction efficiency follows the inverse order of their water solubility, but there is no clear trend between the extraction efficiency and the hydrophobicity of the DES. Furthermore, the authors employed different hydrophobic imidazolium-based ionic liquids to compare the extraction efficiencies, and they found that the ionic liquids always perform better than the best-

working DES. Sometimes, the differences were not significant, but especially in the case of Thiamethoxam, all ILs had roughly the 2-fold extraction efficiency (80%) of the best-working DES (40%). The recyclability of the DES was also tested, but the extraction efficiencies dropped by at least one-half after four cycles.

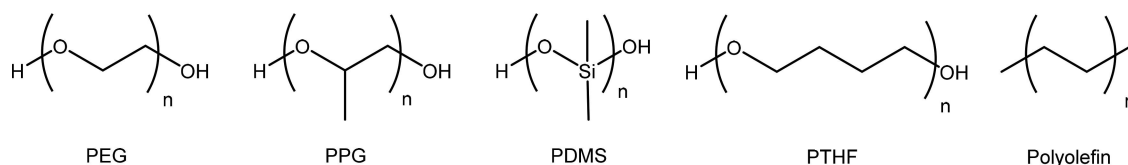
Alternative reaction methods, such as ultrasound or microwave reactions, have also been investigated by Bubalo et al. to extract phenolics from grapes skins with DES.<sup>253</sup> Choline chloride was mixed with glycerol, oxalic acid, malic acid, sorbose, and proline with malic acid to produce the DES. Grape skin flavonoids were extracted with the choline chloride:oxalic acid DES producing the highest extraction yields. Extraction via ultrasound was found to provide results superior to microwave and chemical extraction. Other studies into the use of microwaves and ultrasound have also found acidic DES to be more effective than organic solvent extractions.<sup>254</sup> Although results on microwave-assisted reactions have looked promising, Chen et al. in their extraction of hydrophobic and hydrophilic compounds from red sage discovered that the recovery of DES was difficult.<sup>255</sup>

The use of DES is not without challenges. As with ILs, oil extractions cause small amounts of oil to be retained in the DES.<sup>256</sup> Organic solvents combined with DES can combat this problem. Ji et al. suggest the addition of a small amount of alkanes such as *n*-hexane, cyclohexane, and *n*-nonane. Extraction of this oil can be achieved at 92.2% in approximately 15 min, and no temperature dependency is observed. Extraction of toluene, benzene, *o*-xylene, *m*-xylene, and *p*-xylene was examined via the process scheme shown in Figure 25. However, the use of low carbon alkanes to remove oil from DES is not ideal for sustainability.



**Figure 25.** Scheme of extraction of neutral oils (NO) from quaternary ammonium salts and phenolic compounds by the addition of low-carbon alkenes such as *n*-hexane, cyclohexane, and *n*-nonane.





**Figure 26.** Chemical structures of some liquid polymers used as solvents: (left to right) polyethylene glycol (PEG), polypropylene glycol (PPG), poly(dimethylsiloxane) (PDMS), poly(tetrahydrofuran) (PTHF), and a polyolefin.

Other concerns have also been investigated in the use of DES for electrochemical applications. Haerens et al. found that toxic materials, for example, dioxanes, chloroform, and DCM, were formed by electrochemical decomposition of choline chloride and glycerol.<sup>257</sup> Investigation to improve the longevity of DES during electrolysis highlights another challenge, and perhaps a closed-loop process may prevent some decomposition while anode optimization may increase the life span of the solvents. These are issues in common with IL-based electrochemical reductions; in both cases, there needs to either be a sacrificial reducing agent or else the solvent will act as one.

To reduce the use of VOCs, DES/NADES have been explored as a potential solvent replacement for some organic syntheses. Studies have been published on the use of DES in common organic reactions such as aldol, cycloaddition, and catalysts for reactions.<sup>258–261</sup> Recent advances in organic synthesis are listed below. In 2016, Marset et al. successfully synthesized tetrahydroisoquinolines using choline chloride:ethylene glycol in the presence of a copper catalyst and found that the reaction only proceeds in the presence of the DES.<sup>262</sup> The yield of product was directly correlated with the conductivity of the DES. Recycling of the DES up to 10 times demonstrated no ill effect to yield. Vidal et al. demonstrated organolithium reactions in air were possible with the use of DES.<sup>263</sup> This process improves sustainability by eliminating the need for toxic organic solvents and oxygen-free atmosphere. However, there are times when DES do not work as well as traditional organic solvents as demonstrated on the Suzuki–Miyaura, Sonogashira, or Heck couplings by Marset et al. Although yields may be lower compared to the case of conventional solvents, recycling up to five times has shown consistent yields. In addition, prophosphine catalysts with pyridinium appendages can lead to improved catalytic activity and retention of catalyst in the DES.

## 5. LIQUID POLYMERS

Polyethylene glycol (PEG) and the structurally similar polypropylene glycol (PPG) are the most extensively studied liquid polymers (LP) and are the focus of this section (Figure 26). Other, more hydrophobic LPs, such as poly(dimethylsiloxane) (PDMS)<sup>264</sup> and poly(tetrahydrofuran) (PTHF),<sup>265</sup> remain relatively unexplored in comparison. Polyolefins can act as a low volatility replacement for hexane,<sup>266</sup> but are highly flammable and are extremely slow to biodegrade. These LPs are not discussed here.

Liquid polymers have the inherent advantage of negligible volatility. The ESH properties of PEG and PPG are already well described as they are ubiquitous in both chemistry and biology, with commercial applications ranging from personal care products to food additives.<sup>267</sup> PPG displays an unusual inverse temperature-solubility relationship in water.<sup>265</sup> High  $M_w$  PPG (such as PPG-2000) exhibits extremely low solubility in water, which has limited its applicability in aqueous systems.<sup>265</sup> PEG is readily biodegradable and several strains of soil bacteria can

degrade it;<sup>268–270</sup> however, PPG has a slightly lower biodegradability, and both polymers become less biodegradable as their molecular weights increase. The regulatory and technological restrictions for the introduction of PEG and PPG as industrial solvents are likely to be low. However, liquid polymers are yet to be used commercially as a replacement for conventional solvents.

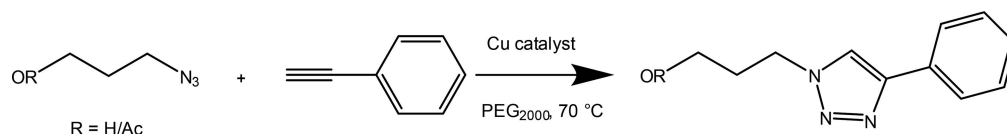
### 5.1. Polyethylene Glycol (PEG) and Polypropylene Glycol (PPG) Properties

Below 600 Da, PEG can be used as a solvent in its pure form. Above 800 Da, PEG becomes a low melting point waxy solid that requires elevated temperatures or cosolvents (commonly water) to be used as reaction media.<sup>271</sup> PEGs are highly soluble in water due to the hydration of the ether groups and terminal hydroxyl group. Lower  $M_w$  PEG is more soluble due to an effective increase in the density of terminal OH groups. PEG effectively lowers the polarity of aqueous solutions facilitating the dissolution of a greater range of organic substrates, increasing the range of reactions than can be carried out in aqueous solutions. It is also soluble in a range of organic solvents, but insoluble in nonpolar organic solvents such as hexane and  $\text{scCO}_2$ .

PEG is produced primarily from ethylene glycol, a byproduct of the petrochemical industry.<sup>272</sup> Sustainable sources of ethylene glycol are of great interest; the global market for ethylene glycol is estimated to be \$20 billion/year with around 15 million tonnes/year being produced.<sup>273</sup> Sustainable ethylene glycol can be produced directly from sugars or lignocellulosic biomass or via modified *E. coli*;<sup>272</sup> algal PEG may also be achievable.<sup>274</sup> Production of ethylene glycol from sugars such as cellulose, xylitol, and sorbitol is atom economical and sustainable, retaining the hydroxyl groups of the sugars.<sup>275</sup> PEG derived from agricultural products such as sugar cane waste is already commercially available.

### 5.2. Separations and Extractions Using PEG

Aqueous biphasic systems (ABS) formed by mixing PEG with water and a salt (usually phosphate, citrate, or sulfate) have been used extensively for the separation and purification of proteins and biomolecules for over 50 years, due to the biocompatibility of PEG and the limited solubility of proteins in organic solvents. The high water content protects proteins from denaturation.<sup>276</sup> Aqueous solutions of PEG form two immiscible phases that separate when the concentration of PEG or a solute, for example, a polymer, sugar, or a salt, is adjusted. Modifications to the biphasic behavior of PEG can be achieved simply, for example, by adjusting the PEG concentration or PEG  $M_w$ . Phase behavior can also be modified through modification of the PEG end groups.<sup>277</sup> Ionic liquid–PEG mixtures are particularly promising for ABS. The introduction of an IL can afford greater control over the phase behavior and the polarity difference between the two phases. Thermo responsive ABS based on simple and low-cost protic-ILs and less polar PPG combine simplicity with efficient



**Figure 27.** Copper-catalyzed azide–alkyne cycloaddition was carried out in PEG<sub>2000</sub> to produce a variety of triazol compounds.

protein partitioning, with phase separation occurring when the temperature is raised from 25 to 45 °C. Proteins partition with the more polar hydrated IL phase.<sup>278</sup> These mixed ABS systems afford greater control for separations and are easily scalable; however, the greater complexity of a biphasic system means that adoption by industry is slow.

The biocompatibility of these polymers mean that PEG and PPG are also utilized for solvents for biocatalysis using enzymes or whole cells.<sup>279</sup> A nonaqueous phase can improve efficiency of bioreactors by removing toxic or inhibitory solutes from the aqueous phase. PEG increases the range of soluble substrates and has been shown to improve the stability of enzymes. PEGylation, the covalent attachment of PEG chains to macro or biomolecules, has also been used to improve the solubility or activity of enzymes; advances in these fields are covered elsewhere.<sup>280</sup>

### 5.3. Organic Synthesis in PEG

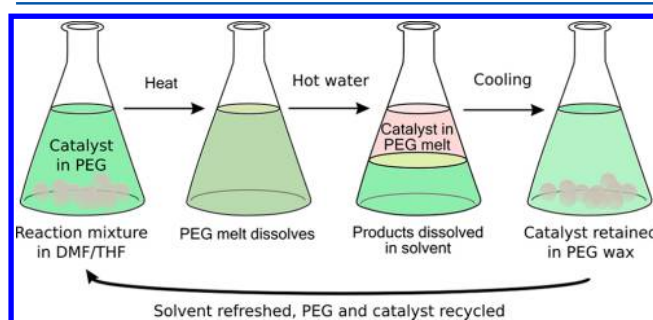
PEG has been used as a substitute for conventional solvents in organic synthesis. It is reported to be stable to acid and basic conditions,<sup>267</sup> and PEG degradation is rarely reported. PEG increases the range of substrates available for aqueous phase reactions. In many cases, it may be superior to conventional solvents in carbon–carbon bond-forming reactions such as Suzuki, Heck, Stille, and Sonogashira coupling reactions. Progress in this area has been reviewed extensively.<sup>281</sup> However, PEG is also used as an “alternative reaction media”, utilizing the biphasic nature demonstrated in ABS systems for more advanced reaction engineering.

Aqueous biphasic reactive extractions (ABREs) provide an alternative to organic–aqueous biphasic chemical processes. Reactions carried out in ABREs can be engineered to control the partitioning of reactants, catalysts, and products. ABREs can also be used to provide a reaction driving force, and ultimately this can provide greater product yields and product selectivity.<sup>267</sup> A third phase, in the form of a light organic phase, is present when reactants have low solubility in the PEG phase.<sup>267</sup> PEG acts as a phase-transfer-catalyst (PTC),<sup>282</sup> shuttling aqueous phase reactants into the organic phase. A discussion of the progress made in PEG-ABS is reviewed elsewhere.<sup>267</sup> The complexity of ABRE may hinder the immediate introduction of these systems into industrial-scale processes, and a greater understanding of the mechanism of phase separation may be necessary.

Product separation, particularly removing lipophilic products from the PEG phase, can be problematic. In some cases, vacuum distillation can be used; otherwise, separation of products may require PEG-insoluble solvents such as diethyl ether or hexane. This means that the use of toxic and volatile solvents is reduced but not eliminated. Alternatively, extraction from the PEG phase can be achieved if the product is soluble in scCO<sub>2</sub>, eliminating the need for organic solvents altogether.<sup>265</sup> Clean product separation and purification is essential for ensuring the sustainability of industrial processes, along with the recovery and regeneration of a clean solvent.

PEG is an effective chelator of metals and salts, and has been used as a cheaper, less toxic alternative to crown ethers or PTC, albeit at the cost of selectivity.<sup>283,284</sup> As a solvent in organic reactions, the ability to chelate catalysts is advantageous. Azide–alkyne cycloaddition was carried out using a variety of Cu catalysts to produce triazoles from lipophilic and hydrophilic substrates in PEG-2000 (Figure 27).<sup>285</sup> Chelation of the catalytic copper by PEG was investigated by electron paramagnetic resonance spectroscopy. PEG protected the Cu from atmospheric oxidation, allowing the reaction to proceed without an inert atmosphere. Cu was retained in the PEG once the solvent was recycled, reducing the concentration of metal in the product. The PEG–Cu solvent could be recycled six times without loss in activity, although Cu was gradually accumulated in the PEG phase. Ultrafiltration could be used to remove water-soluble cycloadduct, the lipophilic products were removed with dichloromethane, and diethyl ether was used to precipitate the PEG.

One of the most promising applications of PEG in organic chemistry is for catalyst recovery. Thermomorphic biphasic solutions (Figure 28) carried out using PEG (polyWax<sub>400</sub>) in



**Figure 28.** A thermomorphic biphasic system composed of a polar phase (DMF/THF) and an immiscible PEG phase was used to carry out cross-coupling reactions upon heating. The Pd catalyst could be isolated and recycled in the PEG phase upon cooling.

place of hexane were shown to reduce the leaching of a colloidal Pd catalyst by an order of magnitude (99.88% recovery), especially when coupled with polymeric ligands.<sup>286</sup> The leaching of PEG into the second phase (DMF) was also found to be reduced in comparison to hexane. Where expensive catalysts cannot be avoided, and contamination of the product with catalyst has to be minimized, PEG systems have demonstrated effective and clean partitioning.

Reducing the number of synthetic steps can reduce the cost of a process considerably. PEG has been demonstrated as an effective solvent for many cross-coupling reactions. Ruthenium-catalyzed direct C–H bond functionalization has been used in the olefination of Weinreb amides to form C–C, C–O, and C–N bonds in a single, atom-economical step (Figure 29).<sup>287</sup> Isoquinolinones, isocoumarins, and *N*-methyl isoquinolinones were synthesized in a one-pot synthesis from aromatic amides and acids, using PEG as the reaction medium. The synthesis of the isoquinoline proceeded with a yield of 93% in PEG 400,

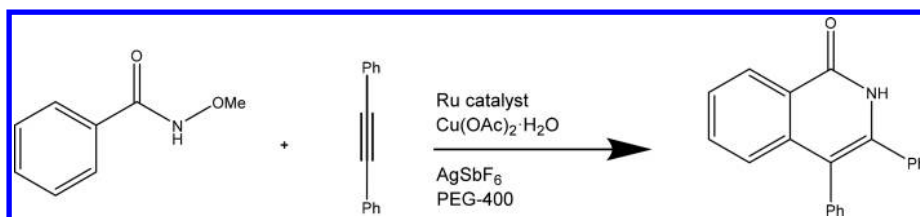


Figure 29. Synthesis of an isoquinolinone using a ruthenium catalyst in PEG-400.

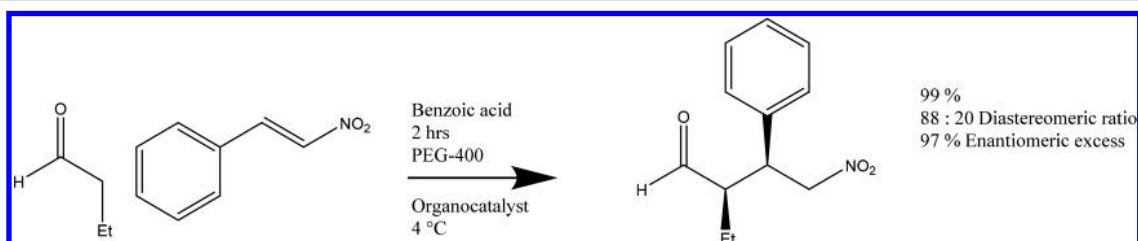


Figure 30. Asymmetric Michael addition of butyraldehyde to *trans*- $\beta$ -nitrostyrene using a hydrophobic organocatalyst in PEG gave high enantiomeric selectivity. Reproduced with permission from ref 289. Copyright 2014 The Royal Society of Chemistry.

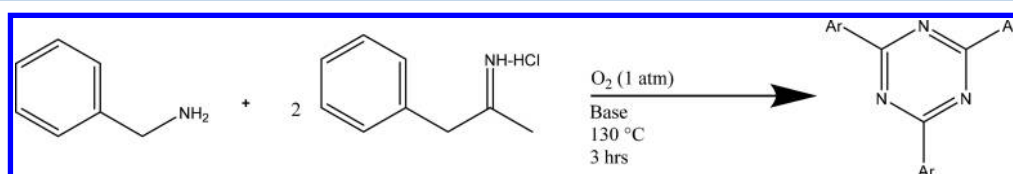


Figure 31. Catalyst-free synthesis of 1,3,5-triazines in PEG-600 using  $O_2$ .

superior to both PEG-200 (61%) and other high  $M_w$  PEGs (37%), but the addition of water was found to considerably reduce the yield in this case. The product was synthesized successfully at a gram scale and quickly extracted using diethyl ether; the recovered PEG-catalyst system could be recycled up to four times without considerable loss in product yield. It was not clear if the loss in yield was due to a loss of catalyst during the workup.

Michael addition can be carried out successfully in aqueous solutions; however, PEG provides effective catalyst removal.  $RuCl_2(p\text{-cymene})_2/Cu[OAc]_2$  was used to carry out the tandem oxidative alkenylation/oxa-Michael addition reaction of benzoic acids with alkenes to form phthalides,<sup>288</sup> an important motif in a number of bioactive molecules. The PEG phase was used to recover the catalyst, which was recycled six times with no loss in yield (93–96%) or decrease in reaction rate. No decomposition of PEG was reported. The recovery and reuse of expensive catalysts will be a key determinant of the affordability of an industrial-scale process.

Enantiomeric selectivity is important for producing high value molecules such as drug molecules. The Michael addition of butyraldehyde to *trans*- $\beta$ -nitrostyrenes using an organocatalyst was carried out successfully in EtOH, water, toluene, and glycerol; however, shorter reaction times and increases in yield, diastereoselectivity, and enantioselectivity were found when PEG-400 was used as the reaction medium. The Michael addition of aldehydes to nitroolefins was also studied (Figure 30),<sup>289</sup> and the high yield and selectivity of PEG-400 were suggested to be the result of the formation of a host–guest complex with nitrostyrene, facilitating nucleophilic addition. However, this complex was not confirmed experimentally. Recyclability was demonstrated over five cycles, and yields of 99–89% were achieved.

Transition metal-free organic syntheses eradicate the need for expensive catalysts or toxic reagents, simplifying the workup, recycling, and disposal procedures of chemical processes. Catalyst-free synthesis of 1,3,5-triazines from benzylamines and *N*-substituted benzylamines by aerobic oxidation has been carried out in PEG-600 without the need for a Ru phosphine catalyst (Figure 31).<sup>290</sup> At 100 °C, the reaction did not proceed in water, ethanol, or glycerol; however, a yield of 70% was achieved after switching the solvent to PEG-600. The optimized reaction gave a yield of 95%, and PEG was recycled three times without any loss in product, although some PEG was lost during the process.

Multiple component reactions (MCRs)<sup>291</sup> form a single product from three or more starting materials. MCRs have been carried out in a range of unconventional solvents including PEG, water, ILs, and bioderived solvents. Combined with smart synthetic strategies such as click chemistry,<sup>292</sup> MCRs have the potential to streamline organic synthesis substantially. The one-pot synthesis of thiazoloquinoline scaffolds is an excellent example of MCRs in PEG solvents. High yields of 92% and short reaction times of 2 h were achieved in 10% v/v PEG-400/water, whereas a range of both protic and aprotic polar solvents gave very low yields. Products could be recrystallized from the reaction media using MeOH–DCM. The fundamentals of MCR in PEG–water mixtures are not completely understood; however, increased solubility of reagents and the hydrogen-bonding properties of water are thought to play a significant role. Catalyst-free MCRs have also been demonstrated for the synthesis of selenopyridines using ultrasound.<sup>293</sup> Selenopyridines were synthesized from aldehydes, malononitrile, and benzeneselenol in a multicomponent reaction, involving the creation of four new bonds. It was suggested that PEG activated the aldehyde and malononitrile to form an intermediate, playing an active role in the catalytic cycle.



#### 5.4. Synthesis of Nanomaterials and Polymers

PEG has also been reported as an effective solvent for the synthesis of functional organic materials, nanorods, and nanoparticles.<sup>294</sup> Silver nanoparticles were synthesized using PEG as a reducing agent and as a solvent, and the PEG  $M_w$  was shown to alter the size of the developing nanoparticles.<sup>295</sup> Lower  $M_w$  PEGs encouraged the formation of spherical agglomerates, and as the  $M_w$  increased, the nanoparticles became more porous and their absorbance blue-shifted. PEG solvents were also found to prevent aggregation by stabilized particles with  $-OH$  end groups, so smaller  $M_w$  values were better for stabilization as they contain more hydroxyl functional groups. Nanoparticles have also been synthesized directly from PEG from a simple thermal treatment, and have been used for biological imaging applications.<sup>296</sup>

Polymerization reactions can be carried out in PEG, with the solvent displaying remarkable stability. Atom transfer radical polymerization (ATRP) allows for the synthesis of low PDI polymers; however, this requires the use of a transition metal catalyst. Building on previous work using Cu catalysts in PEG, many groups have reported using an iron catalyst with PEG as the solvent and ligand for the polymerization of methyl methacrylate (MMA).<sup>297,298</sup> Low polydispersity PMMA was achieved with low  $M_w$  PEG due to the stabilizing effect of the terminal hydroxyl groups. Polymerization proceeded with much better control and much higher yields (PEG<sub>600</sub> = 84.0% yield) than in DMF (43.6%), MeCN (8.6%), and DMSO (28.2%). This may be due to a difference in polymerization kinetics. Catalyst leaching into the polymer is also reduced when PEG is used.

PEG has been used for free radical polymerization and was found to accelerate polymerization rates and suppress diffusion-controlled bimolecular termination.<sup>299</sup> Solutions of PEG have also been used in the synthesis of diblock copolymers, which undergo polymerization-induced self-assembly (PISA), something that has also been carried out in volatile organic solvents, alkanes, mineral oils,  $scCO_2$ , and ionic liquids. However, it has been found that the enhanced viscosity of PEG allowed for a greater rate of reaction and more control over polymerization.<sup>300</sup> Polymer concentrations reached 50%, and the rate was found to be faster with lower  $M_w$  PEG. These polymers then self-assembled into a number of vesicles of different morphologies.

As a solvent, PEG has been explored extensively in the literature. This is attributed to the low cost of PEG, abundant use in industry, and established low-toxicity. The applicability of PEG to a wide range of processes and reactions has been demonstrated, although comparisons with other solvents, especially other liquid polymers, are rare. Nonvolatile solvents reduce the risk of environmental exposure, but this does come at a cost of higher viscosity. PEG recycling has been demonstrated, but catalyst and side-products may accumulate over time, and this may enhance the rate of PEG degradation. Regenerating PEG may be challenging as the solvent can no longer be distilled, and chemical regeneration of spent polymers is a technical challenge.<sup>301</sup>

In aqueous PEG, biphasic systems may not only be limited to biological separations in the future. Industrial processes may take advantage of ABRE once they are characterized in greater detail, and the advantages of this approach may be demonstrated at larger scales. Separation of lipophilic products from the PEG phase is difficult, however, and toxic organic solvents are often needed to extract products from the liquid

polymer phase. Indeed, in the case of PEG, ILs, and DES, the nonvolatile, highly polar, and highly viscous nature of the solvents normally leads to the use of organic solvents for (nonvolatile) product extraction, potentially defeating the purpose of avoiding those solvents in the first place.

The ability of PEG to chelate metals to enhance catalytic activity or to stabilize and separate catalysts is particularly useful. Reducing leaching of metal and organic catalysts into products may drastically reduce washing steps, which can contribute to high solvent usage. PEG has also been shown to enhance the stereoselectivity of reactions and reduce the polydispersity of polymerizations as compared to conventional solvents. Given the benefits of liquid polymers, further assessments are needed to frame their performance relative to other neoteric solvents. There are currently no examples of green metric assessments for liquid polymers, to the best of our knowledge.

The full diversity of liquid polymers has not been explored, and there is vast potential for manipulation of these systems. There has been limited studies on modified PEG, such as the direct incorporation of catalysts.<sup>302</sup> Copolymers, or liquid polymers with more complex architecture, have not been investigated as solvents at all, but could provide a means for more interesting phase behavior. However, more complex systems may be more difficult to implement at larger scales, and the trade-off between simplicity and efficiency must be considered carefully.

PEG has properties that may make it more attractive than other neoteric solvents, especially as the toxicology profiles are well-defined. However, the polarity of PEG is below that of many ionic liquids and deep eutectic solvents, and so liquid polymers may find a role complementary to other sustainable solvents in the future. Solvents with tunable physicochemical properties are not bound by limitations such as this. The ability to change solvent properties by altering pressures, temperatures, or introducing external triggers can overcome the separation problems that restrict ILs, DES, and liquid polymers. In addition, tunable solvents generally have lower viscosities, which further enhance their performance in extractions and separations processes.

#### 6. CO<sub>2</sub> TUNABLE SOLVENTS

Purifications and extractions need either large excesses of solvents, large amounts of energy, i.e., distillations, or both. Whatever the separation requirements, increases in capital and operational costs are inevitable if further workup procedures are necessary. Furthermore, large amounts of volatile solvents drastically increase the environmental impacts of chemical processes. Many new methodologies have been proposed as a means of avoiding intermediate purifications, for example, pot economy via telescope or cascade reactions.<sup>303</sup> Unfortunately, these processes are often limited by unwanted side reactions, byproduct accumulation, and solvents. Therefore, whether wasteful or energetically demanding, solutions to separations can drastically improve the economic and environmental impacts of large-scale processes. Although most neoteric solvents are intended to facilitate separations through some tunable mechanism, that is, changing the counterions in ionic liquids, in situ tunability may be achieved in other ways.<sup>8</sup> For example, supercritical carbon dioxide ( $scCO_2$ ), switchable solvents, and gas expanded liquids (GXLs) all take advantage of the properties of  $CO_2$ , which is nontoxic, nonflammable, cheap, and readily available.<sup>304–306</sup> Solvent tunability may be

achieved through altering gas pressures, temperatures, or the amount of CO<sub>2</sub> in the system. The properties of CO<sub>2</sub> also allow tunability through different mechanisms, broadening their scope by enabling either continuous tunability or abrupt changes in physical properties, that is, switching.<sup>307,308</sup> Furthermore, CO<sub>2</sub> tunable solvents can access a wide range of solvent properties;<sup>309,310</sup> the importance of this was highlighted by Jessop and discussed at the beginning of this Review.<sup>68</sup> Altering solvent properties in situ has been demonstrated as a powerful approach to lowering the energy demands of separation.<sup>311</sup> The scope and sustainability of CO<sub>2</sub> tunable solvents are discussed below.

### 6.1. Supercritical CO<sub>2</sub> (scCO<sub>2</sub>)

Supercritical fluids (SCFs) are well-established alternative solvents in both industry and academia.<sup>304,305,312</sup> A wide range of substances have readily accessible critical points; however, this Review will focus on supercritical carbon dioxide (scCO<sub>2</sub>;  $T_c = 31\text{ }^\circ\text{C}$ ,  $p_c = 72.8\text{ atm}$ ) due to safety and renewability. Typically, SCFs exhibit liquid-like, relatively high densities and concurrently low viscosities and high diffusivities similar to the gas state. High diffusivities offer a potential for increased reaction rates, and the high solubility of gases makes them suitable media for reactions involving gaseous substrates. For scCO<sub>2</sub>, organic cosolvents are usually required to increase the solubility of solid reagents and products, as the polarity of pure scCO<sub>2</sub> is very low.<sup>313</sup> Computational studies suggest that the formation of hydrogen bonds between solutes and cosolvents plays an important role in the solvation process.<sup>314,315</sup> Furthermore, additives known as “CO<sub>2</sub>-philes” have been developed, which can increase the solubility of insoluble materials by acting as chelating agents or ligands. CO<sub>2</sub>-philes are fluorocarbons, siloxanes, and polyether-carbonate copolymers, but they can also be based on natural materials such as sugars and proteins.

**6.1.1. Extractions.** Supercritical CO<sub>2</sub> has been used extensively as an extraction solvent in the food, beverage, flavor, and cosmetic industries,<sup>316,317</sup> most famously for the decaffeination of coffee, which is carried out without subsidy. However, its use requires high capital installation and running costs. For example, Pinelo et al.<sup>318</sup> compared the scCO<sub>2</sub> extraction of grape pomace with ethanol extraction and found that the former yields extracts with significantly higher concentrations of phenolic compounds (~400 ppm as compared to ~200 ppm for ethanol extraction); nevertheless, it should be noted that 8% ethanol was used as a cosolvent in the scCO<sub>2</sub> extraction. In another study,<sup>319</sup> scCO<sub>2</sub> extraction of *Rumex acetosa* roots was highly selective for the phenolic compounds emodin and *trans*-resveratrol, but, in contrast to ethanol extraction and Soxhlet extraction with four different organic solvents, resulted in lower extraction yields. The scCO<sub>2</sub> extraction of the phenolic compound thymol from thyme was also performed,<sup>320</sup> and the results were compared to pressurized organic solvent extraction at 100 atm. Thymol concentration in the scCO<sub>2</sub> extract was 310 mg/g, which was found to be more than 3-fold higher than the highest thymol concentration in the extracts obtained by pressurized liquid extraction (89.6 mg/g).

Liu et al. showed that the extract of *emblica* fruit demonstrated high antimicrobial activity when scCO<sub>2</sub> with methanol as cosolvent was used as extraction solvent.<sup>321</sup> This activity was attributed to the volatile compounds in the extract, whose main components were the hydrocarbons  $\beta$ -bourbonene

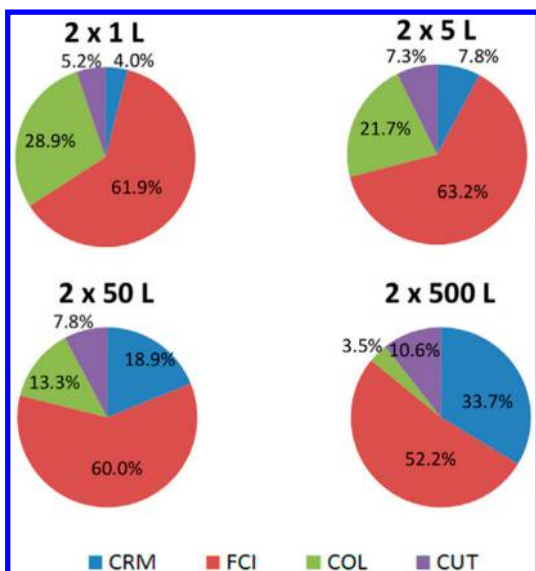
and tetracosane. Contrarily, the extract did not show any or only low antimicrobial activity when organic solvent extraction using methanol was performed. Extraction of an antitumor diterpenoid from the fern *Pteris semipinnata*<sup>322</sup> was highly selective and efficient with scCO<sub>2</sub>: the extraction yield of 0.504 g/kg dry herb material was 3-fold higher as compared to the case of organic solvent extraction, and the purity of 5.148 g/kg dried extract was even 9-fold higher. Response surface methodology (RSM) has been recently used to rationally optimize the extraction conditions by correlating process variables like extraction time, temperature, pressure, and amount of cosolvents to the extraction yields of the desired products.<sup>323,324</sup> Ultrasound-assisted scCO<sub>2</sub> extraction has also found recent attention, for example, in the extraction of capsaicinoids from pepper.<sup>325</sup> The application of ultrasound accelerated the extraction rate as well as the extraction yield. The extraction of cobalt from spent Li ion batteries was also performed using scCO<sub>2</sub> as the solvent, resulting in higher extraction yields and a drastically reduced extraction time as compared to the conventional process.<sup>326</sup>

The spectrum of compounds that have been extracted by scCO<sub>2</sub> is very large and includes, but is not limited to, lipids, oils, terpenes, terpenoids, carotenoids, caffeine, phytochemicals, glycosides, and vitamins.<sup>317</sup> Generally, it is important to note that in scCO<sub>2</sub> extraction, usually multiple components are extracted together.<sup>327</sup> The composition of the extracts depends, in addition to substrate vapor pressure, upon operation conditions such as temperature, pressure, fluid flow rate, extraction time, and cosolvent, and on the solvent-to-feed ratio.

The industrial application of scCO<sub>2</sub> extraction has been excellently reviewed by Brunner<sup>327</sup> and encompasses the production of sesame oil, the cleaning of rice, extraction of soybeans, cork treatment, and treatment of spent rubber tires.

The economic viability of a scCO<sub>2</sub> extraction is process-specific and can therefore not be generalized. For example, Vigano et al. recently showed that upscaling a multistep process for the extraction of phytonutrients from passion fruit bagasse using mainly scCO<sub>2</sub> has a crucial effect on its economics.<sup>328</sup> Performing economic simulations for plants with two extraction vessels of increasing volumes (1–500 L), they found a tremendous decrease of the cost of manufacturing from 220.51 USD/kg of extract to 26.33 USD/kg of extract. Considering several economic factors such as cost of raw materials (CRM), fixed capital investment (FCI), cost of operational labor (COL), and cost of utilities (CUT), they found different trends in the contributions of these factors to the cost of manufacturing. As evident from Figure 32, the contribution of CRM increases, whereas the contribution of COL clearly decreases with increasing plant dimensions. This results in the clear decrease of the cost of manufacturing, and considering a selling price of 230.00 USD/kg of extract, the authors claim the economical applicability of this process in a large production scale.

Aguiar et al. examined the use of supercritical CO<sub>2</sub> for the extraction of oleoresin from malagueta peppers.<sup>329</sup> Capsicum oleoresin has a variety of applications in both the pharmaceutical and the food industries. The SuperPro Designer 8.5 software was used to simulate the economics of the extraction. The cost of equipment was estimated from work compiled by Rocha-Urbe et al.<sup>330</sup> looking at three different sized extraction vessels: 0.05, 0.3, and a 0.5 m<sup>3</sup>. The total cost of manufacturing (COM) was calculated according to the following equation, which has also been used elsewhere:<sup>331</sup>



**Figure 32.** Influence of the plant dimensions on the different contributions of the economic factors on the cost of manufacturing. CRM, cost of raw materials; FCI, fixed capital investment; COL, cost of operational labor; CUT, cost of utilities. Reproduced with permission from ref 328. Copyright 2017 Elsevier.

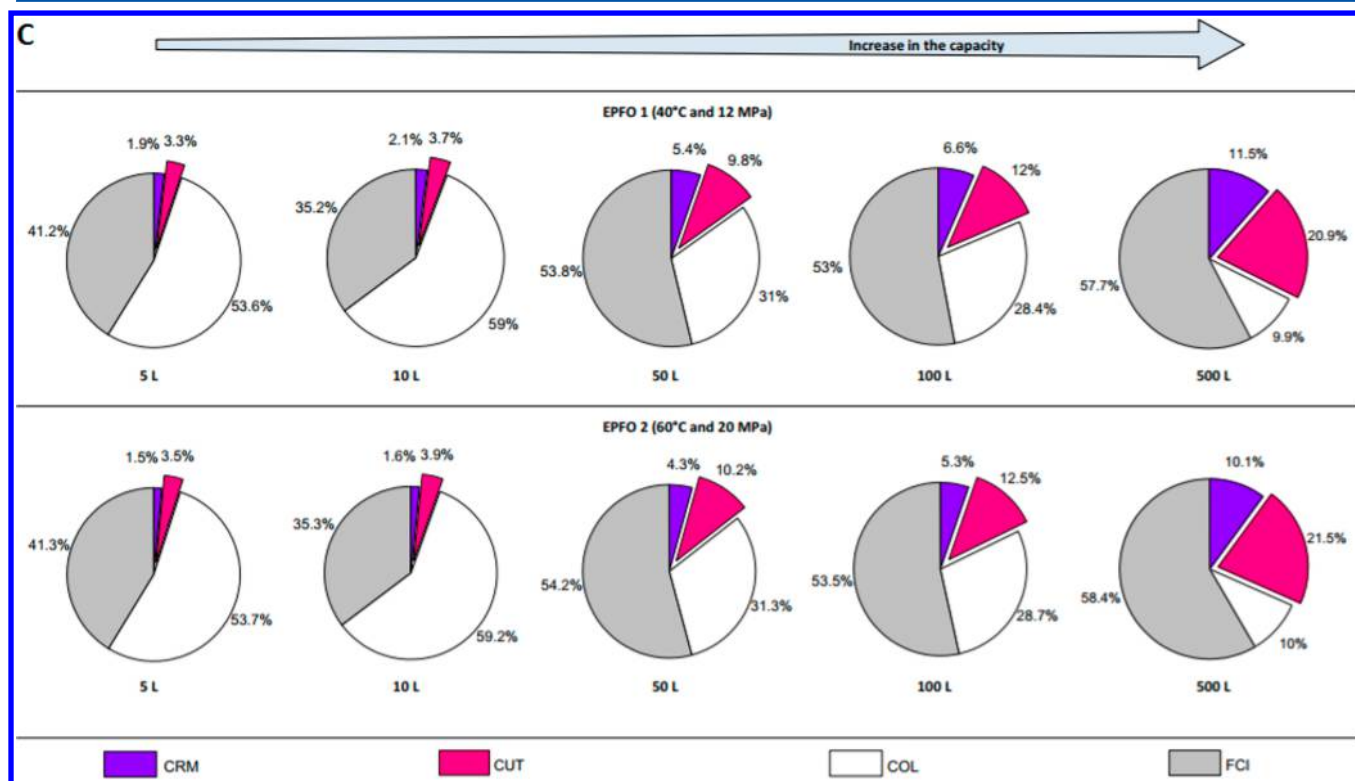
$$\text{COM} = 0.304 \times \text{FCI} + 2.73 \times \text{COL} + 1.23 \times (\text{CUT} + \text{CWT} + \text{CRM})$$

FCI represents the fixed capital of investment or physical assets such as the cost of the buildings and machinery necessary for the process. COL is the cost of operational labor (any nonautomated labor), CUT is the cost of utilities or energy

used, and CWT is the cost of waste treatment (which in this case was set at zero as the residues are nontoxic and no additional treatment is required prior to disposal). CRM is the cost of the raw materials, which includes preprocessing such as cleaning or milling. The cost of the raw material used was \$2.50 per kg, and the extraction yield was based on previous scale-up data gained by Martinez and Silva.<sup>332</sup>

The most economic results of the simulation are obtained using two 0.5 m<sup>3</sup> vessels and an extraction time of 4 h, which results in a COM of \$125.41 per kg of extract. The largest expenditure is the CRM representing almost 63% of the total cost, which includes the preprocessing step with a capital expenditure of 29% of the total costs. The return on investment as well as capital recovery period are dependent on market conditions, mainly the price of the pepper as well as the selling price of the oleoresin.

Zabot et al. utilized supercritical CO<sub>2</sub> as antisolvent for the precipitation of quercetin extracts from onion peels following a pressurized liquid extraction;<sup>333</sup> this process is called extraction and particle formation online (EPFO). Quercetin is a flavonoid known for its anti-inflammatory properties. It is found in various foodstuffs and commonly used in the pharmaceutical industry. The use of supercritical CO<sub>2</sub> allowed for the control of particle size of the precipitated quercetin-rich extracts. An economic evaluation was conducted with the simulation software SuperPro Designer 9.0. Four conditions of varying microparticle yields, concentrations of quercetin, and extraction temperature and pressure were considered, and vessels ranging from 5 to 500 L in size were simulated. COM was calculated with the same equation previous listed. There was no cost associated with obtaining the onion peels, and the costliest portion of the acquisition of the raw materials was the



**Figure 33.** Detailed comparison of each cost contribution for microparticle production at 40 °C and 12 MPa, and 60 °C and 20 MPa, respectively. Reproduced with permission from ref 333. Copyright 2017 Elsevier.



transporting and preparation. Pressure as well as temperature impacted the particle yield, and the highest concentration of quercetin was obtained at 40 °C and 12 MPa. Larger reacting vessels lowered the overall COM; however, this also increased the FCI (see also Figure 33). In addition, there was a direct relationship between the extraction pressure and COM, while temperature was inversely related.

Production costs range from \$45.50 to \$475.46 per kg with return on investment consistently available in productions with greater than 50-L capacities. FCI is the main contributor to cost in this case with the cost of labor being the second major expense.

Kurniawansyah et al. used similar economic parameters to investigate the feasibility of supercritical CO<sub>2</sub> as an antisolvent to produce *para*-coumaric acid (PCA) and hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD).<sup>334</sup> Their process utilizes atomization devices to dispense the solution into a pressurized chamber with CO<sub>2</sub> as the antisolvent (known as the ARISE process, the Atomized Rapid Injection Solvent Extraction process). This process, like the one mentioned by Zabot et al., allows for the control of the precipitated particle size. Increased batch sizes also improved product recovery. The economic analysis is similar, providing additional support that up-scaling and industrialization of supercritical processes are feasible.

In all examples, proper design and economic modeling is needed to ensure that all critical variables and expenses are accounted for. Initial capital can be a challenge. However, return on investment depending on market conditions is rapid, usually within a few years. Depending on the process, involved raw materials rather than physical assets may be the major expense. However, if the additional value generated by the process is very high, this expense may be mitigated by demand.

The economics of an extraction process can also depend on the state of the spent material at the end of the process. For example, the scCO<sub>2</sub> extraction of soybeans<sup>327</sup> has been shown to be very economical because of that reason: Although the cost of the extraction process is twice as high as compared to hexane extraction (12 cents/L of oil vs 6 cents/L of oil), the scCO<sub>2</sub> process may be the better economic alternative. The reason is that the spent material (i.e., the extracted soybeans) is not contaminated by treatment with CO<sub>2</sub> and can be used, as a consequence, for the production of human food. Contrarily, hexane extraction contaminates the spent material, rendering the usage for human food production impossible. As the removed oil is only 20% of the feed, the fate of the spent material has a large impact on the economics. This highlights one of the most noteworthy advantages of scCO<sub>2</sub> over all other solvents (organic, neoteric, and water); pure scCO<sub>2</sub> solvent can be completely removed from products, leaving no toxic solvent residue or contaminated liquid solvent for regeneration or disposal.

The effect of energy integration on process economics as well as environmental impact for the extraction of essential oil from oregano and rosemary were recently assessed by Moncada et al.<sup>335</sup> scCO<sub>2</sub> extraction was compared to organic solvent extraction as well as water distillation. Energy integration led to a decrease of the production cost in all technologies. In the case of oregano, the lowest production cost was achieved using scCO<sub>2</sub> extraction (6.71 USD/kg). However, in the case of rosemary, water distillation was the most profitable method (6.57 USD/kg), and the use of scCO<sub>2</sub> resulted in a production cost of 6.95 USD/kg. This demonstrates the dependence of the economic viability of a process on the feedstock. The

assessment of the environmental impact shows, not surprisingly, that the environmentally most harmful technology is by far the extraction using the organic solvent hexane, whereas the environmental impacts of scCO<sub>2</sub> extraction and water distillation are very similar. Interestingly, for both oregano and rosemary, the technology with the lowest carbon footprint due to fossil energy requirements is scCO<sub>2</sub> extraction at full energy integration. Therefore, energy integration is a promising strategy to reduce the environmental impacts of scCO<sub>2</sub> extraction processes.

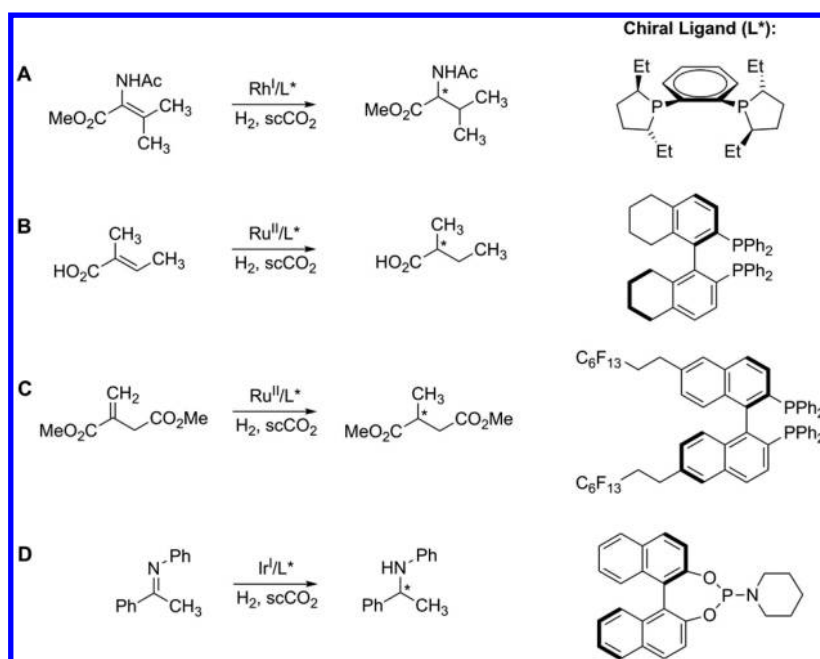
Parjikelaei et al. investigated the recovery of astaxanthin from shrimp waste using scCO<sub>2</sub>, organic solvents, and sunflower oil and assessed the applicability of these processes to shrimp feed production.<sup>336</sup> The extraction efficiency was best using the organic solvent mixture (hexane and isopropanol) with a yield of 26.4 kg/year, but the applicability of this nongreen process in feed production is limited. scCO<sub>2</sub> extraction resulted in the lowest extraction yield (12.8 kg/year), but the extraction was the most selective as it yielded a pure astaxanthin extract. Nevertheless, the applicability for shrimp feed production turned out to be prohibitive, as the production cost is 10–80 times higher than the cost of the feed when synthetic astaxanthin is used.

Todd et al. compared three strategies for the extraction of bioactives from grape marc (extraction with scCO<sub>2</sub>, subcritical water, and organic solvent).<sup>337</sup> In their technoeconomic analysis, they found the scCO<sub>2</sub> process to be the less advantageous for several reasons. First, the cost of manufacture is clearly higher for this process as compared to the subcritical water and the organic solvent process (123.40 NZD/kg vs 89.60 NZD/kg and 87.0 NZD/kg respectively). Second, the potential environmental impact, including greenhouse emissions, of this process is also higher when compared to the other processes. However, this process was not energy-integrated, and in the light of the results from Moncada et al. discussed above, an energy-integrated scCO<sub>2</sub> extraction process might be suitable to significantly reduce the cost of manufacturing as well as the carbon footprint.

These last examples show that the assessment of economic viability as well as sustainability of such processes is indeed a multivariate problem and that many different factors have to be taken into consideration. Therefore, it seems almost impossible to provide general guidelines for process design. It rather seems to be inevitable to consider each process separately.

**6.1.2. Chemical Synthesis.** Because of the good miscibility of gases with CO<sub>2</sub>, hydrogenation reactions in scCO<sub>2</sub> have been extensively studied. One example of a hydrogenation in scCO<sub>2</sub> used CO<sub>2</sub> itself as the substrate,<sup>338</sup> which was reduced to methanol and formic acid. Jessop et al. used a ruthenium(II)-phosphine complex to produce formic acid, which was significantly more active in scCO<sub>2</sub> as compared to tetrahydrofuran at the same reaction conditions (205 atm, 50 °C). Whereas the remarkable turnover frequency of 1400/h was observed for the former case, a turnover frequency of only 80/h was observed for the latter case. This method has also been extended to the production of esters and amides, by using the corresponding alcohols and amines as additional substrates.<sup>339,340</sup>

The hydrogenation of alkenes in scCO<sub>2</sub> has also been investigated. For example, Yilmaz et al. studied the hydrogenation of styrene, 1-octene, and cyclohexene in scCO<sub>2</sub> and compared the results to these reactions in the classical organic solvents toluene, hexane, and methanol.<sup>341</sup> They observed that



**Figure 34.** Examples for the stereoselective hydrogenation of olefins (A–C) and an imine (D) in  $\text{scCO}_2$ .

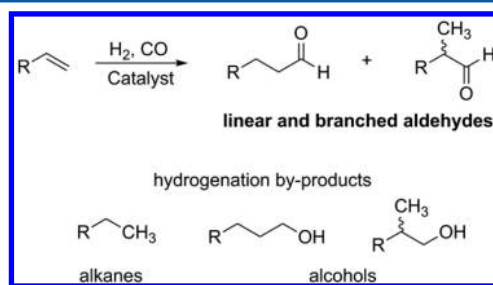
the reaction rates are sometimes higher in  $\text{scCO}_2$  (turnover frequency (TOF) up to  $372 \text{ h}^{-1}$ , highest TOF for organic solvent  $81 \text{ h}^{-1}$ ), but the conversions are similar. Additionally, significant side-product formation by double bond isomerization was found when 1-octene was used as a substrate in both the classical organic solvents and the  $\text{scCO}_2$ . Furthermore, catalyst poisoning by CO was found (due to the reverse water–gas shift reaction). These results indicate that the use of  $\text{scCO}_2$  is not a beneficial alternative for these reactions.

The stereoselective hydrogenation of prochiral olefins in  $\text{scCO}_2$  is an effective approach to obtaining optically pure organic compounds. Common catalytic systems consist of chiral phosphine and phosphite ligands, often derived from 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), with ruthenium and rhodium as metals; see Figure 34.

For example, the rhodium-catalyzed hydrogenation of enamides with a DuPHOS ligand (Figure 34A) yields significantly higher enantiomeric excesses (ee) when conducted in  $\text{scCO}_2$  (up to 88%) as compared to organic solvents (highest ee: 70% in hexane).<sup>342</sup> The same trend was observed for the hydrogenation of tiglic acid employing a ruthenium catalyst bearing a BINAP-derived catalyst (Figure 34B).<sup>343</sup> The corresponding saturated acid was obtained with 89% ee with  $\text{scCO}_2$  as the solvent (a fluorinated alcohol was added as cosolvent), whereas an ee of 82% and a higher reaction rate were reached with methanol as the solvent. There are also studies showing that organic solvents can yield better enantioselectivities than  $\text{scCO}_2$ . For example, the hydrogenation of dimethyl itaconate with a ruthenium catalyst and a fluorinated BINAP-derived ligand could be performed with only 73% ee in  $\text{scCO}_2$ , but with 95% ee in methanol (Figure 34C).<sup>344</sup> The production of chiral amines from imines<sup>345</sup> (Figure 34D) can also be facilitated in  $\text{scCO}_2$  with better enantioselectivities and reaction rates as compared to organic solvents (up to 90% ee for  $\text{scCO}_2$  and up to 87% ee for dichloromethane; full conversion in 50 min for the former and after 19 h for the latter solvent). Analogously, chiral alcohols can be produced from the respective ketones.<sup>346</sup> Current

research is focusing on hydrogenations using metal catalysts<sup>347,348</sup> with a  $\text{CeO}_2$  support, for example, for the highly selective hydrogenation of cinnamaldehyde or to produce *n*-butanol as a biofuel from ethanol via a dehydrogenation–aldol condensation–hydrogenation sequence. Higher conversions in comparison to other solvents are found and attributed to the ability of  $\text{CO}_2$  to reoxidize the Ce without affecting the actual metal catalyst.

Another reaction type that has been extensively investigated using  $\text{scCO}_2$  as the solvent are hydroformylations, which facilitate the production of aldehydes from alkenes via reaction with syngas, a mixture of carbon monoxide and hydrogen. Figure 35 shows the general reaction scheme of these reactions,



**Figure 35.** General reaction scheme for hydroformylation reactions, showing products and byproducts.

displaying the two typically obtained regioisomers and hydrogenation byproducts. Again, the high solubility of the gaseous reactants in  $\text{scCO}_2$  is exploited.

The first hydroformylation in  $\text{scCO}_2$  was conducted by Rathke et al.<sup>349</sup> who used a cobalt catalyst to hydroformylate propene in the presence of hydrogen and carbon monoxide at 56 atm and  $80^\circ\text{C}$ . The linear aldehyde, which is usually the desired regioisomer, was obtained with a relative yield of 88%, and no formation of byproducts was observed. A similar selectivity was found in benzene at 80 atm and  $80^\circ\text{C}$ , and the linear aldehyde was obtained with a relative yield of 83%. The

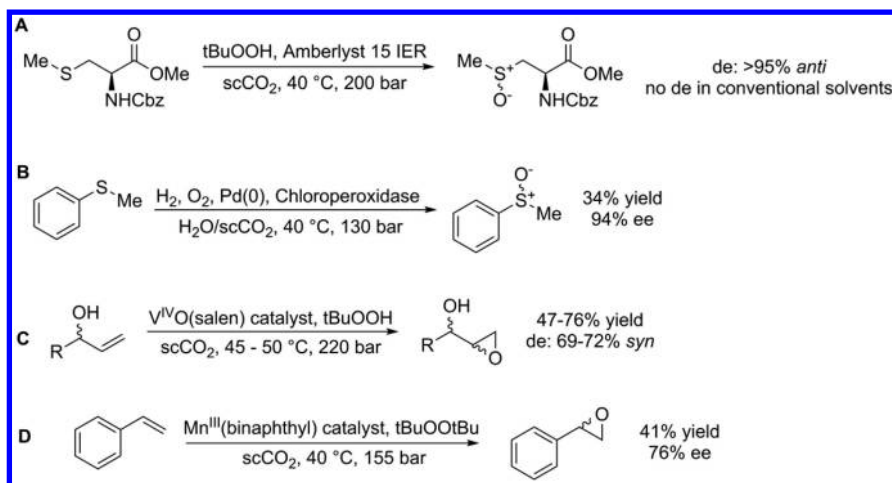


Figure 36. Stereoselective oxidations in  $\text{scCO}_2$ .

reaction rates were also very similar in both solvents. Koch et al. performed rhodium-catalyzed hydroformylations of olefins with terminal and internal double bonds in quantitative yields at a temperature range of 40–65 °C.<sup>350</sup> They found that changes in temperature and pressure generally had similar effects on reaction rates and selectivities as compared to conventional organic solvents. Depending on the catalyst, higher reaction rates and regioselectivities were also found when  $\text{scCO}_2$  was used as the solvent. Remarkably, no olefin isomerization was observed, which usually occurs in traditional organic solvents.

More recently, methods for the hydroformylation of disubstituted alkenes have been developed.<sup>351</sup> Higher TOFs were reached for the conversion of 1,2-disubstituted alkenes like cyclohexene and 2-octene (up to 6600  $\text{h}^{-1}$ ) than for 1,1-disubstituted alkenes, for example,  $\alpha$ -methyl styrene and methyl methacrylate (up to 340  $\text{h}^{-1}$ ). The use of a bulky phosphite ligand in the rhodium-catalyzed reactions even yielded an unprecedentedly high TOF for the conversion of styrene, that is, 27 000  $\text{h}^{-1}$ . In the same study, macromonomers based on styrene and methyl methacrylate could also be effectively hydroformylated. The use of  $\text{scCO}_2$  as a solvent enabled the efficient separation of the catalyst and impurities from the macromonomer phase.

Hydroformylation of alkenes in  $\text{scCO}_2$  using heterogeneous catalysts has also been investigated.<sup>352</sup> The catalyst was synthesized by the incorporation of rhodium nanoparticles in a hyper-cross-linked polystyrene matrix. Hydroformylation of styrene was more efficient in  $\text{scCO}_2$  (conditions: 65 °C and 250 atm), in terms of conversion and regioselectivity (100% and  $n/i = 91/9$ ), than in toluene (72% conversion and  $n/i = 70/30$ ). Furthermore, recycling experiments in  $\text{scCO}_2$  showed quantitative conversion over six cycles, with consistent regioselectivities. In the seventh cycle, the conversion dropped by one-half, which was attributed to catalyst leaching. The  $n/i$  ratio was, in contrast, almost unaffected. Despite the advantages of  $\text{scCO}_2$  in hydroformylation, other alternative solvents (e.g., gas-expanded liquids) have given superior results, especially when the energy cost for pressurization is taken into consideration.

Oxidations with molecular oxygen as the oxidant have also been performed in  $\text{scCO}_2$  because of the high gas solubility in the medium and impossibility of solvent oxidation or combustion. Chapman et al. established a continuous-flow process for the oxidation of primary and secondary alcohols to

the respective ketones, aldehydes, and carboxylic acids.<sup>353</sup>

Running conditions were 100 bar and 130 °C, and a Pt and Bi catalyst on aluminum oxide was used. A maximum yield of 75% was observed for the oxidation of 2-octanol. Yields of other secondary alcohols were often considerably lower (almost always below 50%, sometimes only 10%), and in multiple cases the reaction did not proceed at all, for unknown reasons. Subtle control of the reaction conditions prevented overoxidation of the aldehyde to the carboxylic acid when 1-octanol was used as a substrate. Other catalysts that have been used encompass Pd nanoparticles,<sup>354</sup> a fluorinated silica glass doped with a perruthenate,<sup>355</sup> and polyoxometalates.<sup>356</sup> Jiang and co-workers performed Wacker oxidation reactions of terminal olefins in  $\text{scCO}_2$ <sup>357</sup> and showed that the selectivities toward the desired methylketones increased in comparison to methanol as the solvent, but the conversion of the substrates significantly decreased. Small amounts of methanol and ethanol were used as cosolvents, which led to an acceleration of the reactions.

Stereoselective oxidations have also been performed in  $\text{scCO}_2$ , and in some cases, no stereoselectivities were observed in conventional solvents. For example, Oakes et al. performed diastereoselective sulfur oxidations of sulfur-containing amino acids in  $\text{scCO}_2$  with *tert*-butyl hydroperoxide as the oxidant.<sup>358</sup> Whereas no stereoselectivity was observed in the conventional solvents toluene and dichloromethane, a diastereomeric excess (de) of more than 95% was achieved in the best case, when Cbz-protected (S)-methyl cysteine methyl ester was used as the substrate (Figure 36A). It is important to note that the de significantly depended on the pressure, with the best result at 200 bar (the temperature was kept constant at 40 °C); however, no satisfying explanation for the different outcomes (conventional solvents vs  $\text{scCO}_2$ ) was provided. Karmee et al. performed a biocatalytic enantioselective sulfur oxidation in a  $\text{scCO}_2$ /water biphasic system by using thioanisole as the substrate, in situ generated hydrogen peroxide as the oxidant, and a chloroperoxidase as the catalyst (Figure 36B). The sulfoxide could be produced with ee values up to 94%; however, the yield did not exceed 60%. Dia- and enantioselective epoxidations have also been described in  $\text{scCO}_2$ . For example, different allylic alcohols were oxidized at 45–50 °C and 220 bar using a vanadyl salen oxo catalyst,<sup>359</sup> and the results were comparable to those obtained in conventional solvents (up to 76% yield and 69–72% de, Figure 36C). Erdem et al. performed the enantioselective



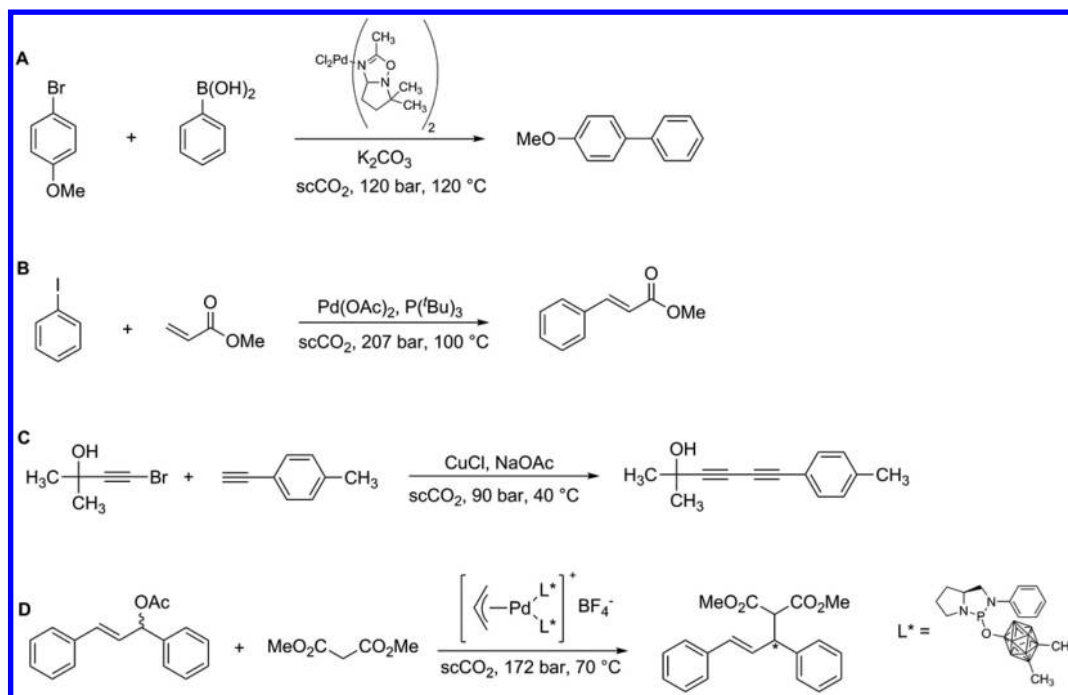


Figure 37. Cross-coupling reactions in  $\text{scCO}_2$ .

epoxidation of styrene using chiral Mn-catalysts in  $\text{scCO}_2$  (40 °C and 155 bar) and DCM<sup>360</sup> and found similar conversions in both solvents, but the enantioselectivities were better in  $\text{scCO}_2$  (Figure 36D). The ee values ranged from 41% to 76% in the case of  $\text{scCO}_2$  and from 24% to 74% in DCM.

Transition-metal-catalyzed cross-couplings in  $\text{scCO}_2$  have also been extensively studied,<sup>361</sup> due to their versatility to form C–C bonds and thus build up complex molecules. Initial problems concerned the poor solubility of reagents, catalysts, and the usually employed inorganic bases in this solvent. These problems have been addressed using fluorinated ligands and ligands containing carbosilane dendromers as well as polydimethylsiloxanes. Furthermore, the inorganic bases can be substituted by organic bases, and, as always, the addition of small amounts of cosolvent can increase solubility of the reactants. Whereas there are several examples where cross-coupling reactions yield better results when performed in  $\text{scCO}_2$  instead of traditional organic solvents, it must be noted that often superior results are reached when water is used as the solvent. Figure 37 shows some examples of these reactions in  $\text{scCO}_2$ .

Figure 37A shows the Suzuki coupling reaction of 1-bromo-4-methoxybenzene and phenylboronic acid, catalyzed by an oxadiazoline Pd(II) complex, conducted in  $\text{scCO}_2$  by Fernandes et al.<sup>362</sup> A quantitative yield was observed after 1 h with a low catalyst loading of 0.025 mol %. In contrast to that, the use of conventional solvents (methanol, toluene, and tetrahydrofuran) under ceteris paribus conditions resulted in moderate yields (67% and 72%), and, in the THF case, only traces of the biphenyl product were observed.

Early et al. also showed that Heck reactions can be performed in  $\text{scCO}_2$  with good yields.<sup>363</sup> Figure 37B shows the reaction of iodobenzene with methyl acrylate catalyzed by a palladium phosphine catalyst. A yield of 77% was reached with a catalyst loading of 5 mol %, and a quantitative yield was obtained when 10 mol % catalyst was used. Additionally, the authors showed that Heck reactions as well as Suzuki reactions

with polymer-tethered substrates can also be performed, and the yields are in the same range as those for the free substrates. Cross-coupling reactions of bromoalkynols and terminal alkynes in  $\text{scCO}_2$  have also been described. Figure 37C<sup>364</sup> shows such a reaction; CuCl was used as the catalyst, and, after optimization of the reaction conditions, which included the addition of methanol as a cosolvent, the corresponding diyne was produced with a yield of 93%. The reaction was extended to a large spectrum of substrates, and, in general, an increase of the alkyl chain length of the bromoalkynol resulted in a decrease of yield. Furthermore, if a bromoalkyne was used as a substrate, that is, there was no hydroxyl group present, no yield was observed at all; the authors did not suggest a reason though. Figure 5D<sup>365</sup> shows the first example of a Tsuji–Trost alkylation reaction in  $\text{scCO}_2$ , which could be performed with moderate conversion (60%) and good ee (81%). The outcome could be eventually improved by using another ligand (100% conversion and 90% ee). More recently, biphasic  $\text{scCO}_2$ /ionic liquid systems were employed to perform Suzuki couplings of aryl halides with arylboronic acids.<sup>366</sup> The employed ionic liquid [hmim][NTf<sub>2</sub>] and the Pd catalyst could easily be recycled, and the yield of biphenyl in the model reaction remained almost constant during six cycles (initial yield, 92%; final yield, 89%).

Other currently studied reactions include C–H bond functionalizations and Huisgen cycloadditions (“click reactions”). For example, light alkanes have been functionalized by reaction with ethyl diazoacetate in the presence of a copper catalyst to yield the corresponding ethyl esters.<sup>367</sup> A huge variety of triazoles were synthesized in  $\text{scCO}_2$  employing click chemistry by Zhang et al.<sup>368</sup> The reaction in this medium was suitable to produce small molecular triazoles as well as polymers containing triazole moieties.

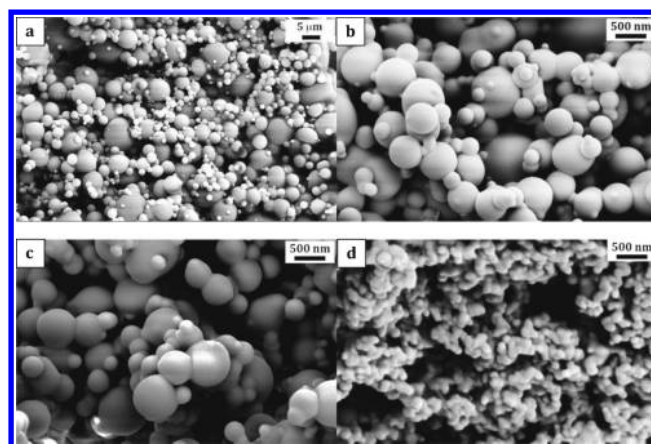
The biocatalytic esterification of carboxylic acids using immobilized enzymes has also recently gained some attention.<sup>369,370</sup> For example, using this methodology, Badgujar et al. produced a variety of levulinic acid esters in moderate to

quantitative yields using  $\text{scCO}_2$  as the solvent.<sup>369</sup> In contrast, switching to the organic solvent butanone resulted in poor to moderate yields (best yield: 52%). Immobilization of the biocatalyst CAL-B enabled its effective reusability. After the fifth cycle, however, the yield has dropped from quantitative to 70%, which is attributed to continuous deactivation of the enzyme by both substrates. Importantly, the authors conducted a green metrics analysis of the process, and for the optimized procedure, an E-factor of 1.142, a carbon efficiency of 82.5, a mass intensity of 2.14, and a mass productivity of 73.49 were reported. On the basis of these data, the authors claim the process to be very sustainable. Unfortunately, a green metrics analysis was not conducted for the organic solvent case; however, on the basis of the moderate yields, it can be assumed that these values would be worse than in the  $\text{scCO}_2$  case.

**6.1.3. Materials Processing.** The synthesis and processing of polymers in  $\text{scCO}_2$  have been widely studied and recently reviewed. Step and chain growth polymerizations have been conducted to produce a large variety of polymers, for example, polyesters, polycarbonates, polyamides, polyurethanes, poly(ethylene terephthalates), and polyureas. The chain growth polymerizations can be divided into homogeneous, precipitation, dispersion, suspension, and emulsion polymerizations, and due to inertia of radical species to  $\text{CO}_2$ , radical polymerizations are the most commonly reported in this solvent. Current research is focused on the synthesis of  $\text{CO}_2$ -philic surfactants,<sup>371</sup> which are necessary for emulsion polymerizations, for example, by employing vinyl trifluorobutyrate as the monomer instead of vinyl acetate. Furthermore,  $\text{scCO}_2$  has been currently used to process porous organic polymers<sup>372</sup> to enhance their total pore volume and specific surface area, as a drying medium for aerogel formation,<sup>373</sup> and for unidirectional foaming of PLA/graphene oxide foams.<sup>374</sup>

Synthesis and processing of bulk materials, aerogels, thin films, coatings, particle suspensions, powders, and nanoparticles can also be conducted in  $\text{scCO}_2$ , and materials that have been processed in this solvent have often superior properties due to the very effective wetting of surfaces, facilitated by the fact that  $\text{CO}_2$  has no surface tension. This way, chemical reactions can easily happen on substrate surfaces, resulting in materials with higher surface areas and better defined nanostructures. For the formation of micro- and nanoparticles, rapid expansion of supercritical solutions (RESS) and supercritical antisolvent (SAS) precipitation are common techniques that are frequently applied and well implemented. Recently, De Marco et al. investigated the control of particle size of polyvinylpyrrolidone particles in an SAS precipitation process using solvent mixtures (Figure 38).<sup>375</sup> The solvents differed in their dissolving power toward the substrate, and with increasing percentage of the “worse” solvent, the particle size as well as particle size distribution consistently shrunk: the use of pure ethanol resulted in the formation of well-separated, spherical micro-particles (Figure 38a), whereas the use of ethanol/acetone mixtures resulted in the formation of submicro and nano-particles (Figure 38b–d).

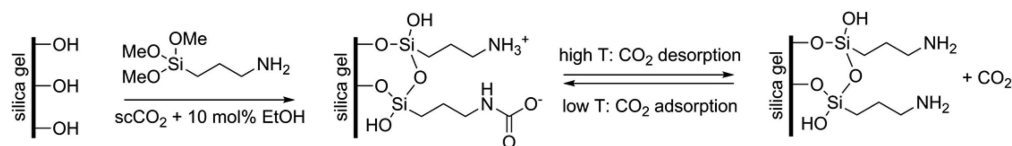
In another recent study, Zhao et al.<sup>376</sup> used  $\text{scCO}_2$  to disperse Pd nanoparticles on graphene and were thus able to produce a highly effective electrocatalyst for the oxidation of formic acid and methanol for application in fuel cells. Similarly, this technique was used for Pt deposition on carbon nanotubes for catalytic  $\text{CO}_2$  reduction, with formic acid and methane as the main products.<sup>377</sup>



**Figure 38.** FESEM images of polyvinylpyrrolidone precipitated at 40 °C and 10 MPa by SAS from different acetone/ethanol mixtures percentages (w/w): (a) 0/100, (b) 30/70, (c) 50/50, and (d) 70/30. Reproduced with permission from ref 375. Copyright 2015 Elsevier.

A  $\text{scCO}_2$ -based process to produce functionalized silica gel has recently been developed for the application in carbon capture (Figure 39).<sup>378</sup> This process is superior to the conventional one, which uses toluene as a solvent for several reasons that reach beyond simple solvent replacement. First, capillary forces in the (liquid) toluene have been shown to damage the porous structure of the gel. Second, the functionalization is faster due to the superior transport properties of  $\text{scCO}_2$ . Furthermore, the  $\text{CO}_2$  can react with trace amounts of water to form carbonates and bicarbonates, which catalyze the hydrolysis and condensation of the aminopropyltrimethoxysilane precursor.  $\text{CO}_2$  adsorption capacities of the synthesized materials were determined and range from 0.7–1.5 mmol/g at atmospheric pressure to 8–12 mmol/g at 4.0 MPa, which is a promising result for the application of these materials in carbon capture technology.

Many industrial chemical processes produce wastewaters that need to be treated before they are returned to the environment. Although a range of sustainable wastewater treatments are available,<sup>379,380</sup> preventing wastewater remains the best option in terms of sustainability. Large quantities of effluent are produced by aqueous textile dyeing. For example, around 100–150 L of water is needed to dye 1 kg of wool fiber.<sup>381</sup> Furthermore, the aqueous effluents contain residual dyes, salts, acids, persistent organics, surfactants, and heavy metals,<sup>382</sup> many of which are poorly biodegradable and toxic to aquatic life. Previous efforts have therefore been directed toward replacing water with alternative solvents to help eliminate the production of wastewater and avoid costly treatments. The water-free dyeing of natural and synthetic textiles has since been demonstrated in  $\text{scCO}_2$  using nonpolar reactive dyes,<sup>383–385</sup> with high dye fixation. Textile rinsing is subsequently not needed, and so no water is used during the entire process. A range of commercial and synthesized hydrophobic disperse reactive dyes have been shown to give good coloration behaviors and characteristics in  $\text{scCO}_2$  dyeing.<sup>386</sup> Industrial-scale  $\text{scCO}_2$  textile dyeing has therefore become an established alternative to aqueous dyeing<sup>387,388</sup> because of the low viscosity and high diffusivity of  $\text{scCO}_2$ , which shortens processing times and energy consumption. By simultaneously reducing chemical requirements and waste production,  $\text{scCO}_2$  textile dyeing can lead to as much as 50% lower operational costs.<sup>389</sup> Textile dyeing represents an area



**Figure 39.** Functionalization of silica gel with 3-aminopropyltrimethoxysilane in  $\text{scCO}_2$  for carbon capture technology.

where solvent replacement can have a dramatic impact on the sustainability of a chemical process. While the balance between capital expenses and operational advantages might not always be as apparent,  $\text{scCO}_2$ -based processes are increasing in popularity because of such examples.

The application of  $\text{scCO}_2$  in leather processing has recently been reviewed, setting a special focus on the economic viability.<sup>390</sup> Although the applicability of  $\text{scCO}_2$  on degreasing, fibers separation, deliming, chrome and vegetable tanning, retanning, faltiquoring, dyeing, and finishing has been demonstrated, there is no report available on the cost of  $\text{scCO}_2$  on leather applications. Therefore, in this Review, the process economics were approximated on the basis of the cost analysis for food and aroma  $\text{scCO}_2$  extraction combined with leather application, which might be inaccurate to some extent, but should be sufficient for a preliminary assessment.

Leather processing with  $\text{scCO}_2$  offers several general as well as process-specific advantages as compared to conventional methods. For example, additionally to the fundamentally reduced pollution due to the replacement of organic solvents and nonbiodegradable surfactants,  $\text{scCO}_2$  extraction keeps the fat components intact, facilitating their reuse. Also, chromium-containing wastewater in the chrome tanning process can be reduced by 95%. Comparing this process with the conventional one in an economic point of view, an economic gain of 0.041 USD per kilogram hide is predicted by the authors, according to savings in chemicals and wastewater treatment. Besides the waste treatment costs, also the operational labor and raw material costs are very low, which also contributes to very low production costs as compared to other industrial fields employing  $\text{scCO}_2$ . These advantages can by far outperform the generally higher fixed investment for the high-pressure equipment. The authors conclude that  $\text{scCO}_2$  application in leather processing therefore can be economically very viable, especially when large-scale application is considered.

Recently, Peng et al. conducted a life cycle assessment of a  $\text{scCO}_2$ -based cleaning process to assess its potential environmental superiority over traditional processes in remanufacturing cleaning.<sup>391</sup> Analysis of the impact indicators, such as global warming potential, water eutrophication potential, production of respiratory inorganics, acidification potential, and Chinese resource depletion potential, shows that the  $\text{scCO}_2$ -based process is superior to the established high temperature decomposition, especially with respect to the two last mentioned indicators. Importantly, the environmental impact clearly depended on the power grid that supplied the electricity used for the process, as electricity was found to be the main environmental load contributor for the  $\text{scCO}_2$ -based process. Thus, using cleaner energy sources and optimizing the cleaning time are key aspects in assuaging environmental issues. As can be seen from this study, life cycle assessments are usually multivariate problems and very complex, as many different factors have to be considered. Actually, the authors state that this assessment is not exhaustive as it lacks the evaluation of other problems, for example, noise pollution, which is clearly

another environmental impact. Furthermore, this assessment is, obviously, conducted for a very specific case and does not reflect the general situation. Nevertheless, it can be a reference for later case studies.

In summary, the ready availability as well as benign solvent properties of  $\text{CO}_2$  relating to environmental impact and very often also to the outcome of a chemical process offer great potential as a sustainable and promising alternative to conventional solvents. The limited solvating power can efficiently be overcome using cosolvents and additives (and is often beneficial for solvent removal), although this may negate some of the aforementioned advantages. Nevertheless, the required high operating pressures resulting in potential operational safety risks, which also result in a relatively high energy demand of  $\text{scCO}_2$ -based processes, pose a challenge to the feasibility for commercial operation of  $\text{scCO}_2$ -based processes.

## 6.2. $\text{CO}_2$ Expanded Liquids (CXLs)

$\text{CO}_2$  can dissolve in organic solvents, leading to the volumetric expansion of the liquid phase. Different solvents expand by different amounts, and so  $\text{CO}_2$  expanded liquids (CXLs) have been divided into classes I, II, and III (explanations have been given elsewhere).<sup>392</sup> The solvents discussed here are class II CXL as the organic solvents are capable of dissolving large quantities of  $\text{CO}_2$ . CXLs have properties intermediate of SCFs and organic solvents, and their physicochemical properties can be controlled by altering the pressure, temperature, or amount of gas in the system. Hence, these solvents have a high degree of in situ tunability.

**6.2.1. Chemical Reactions.** A wide range of chemical reactions have been performed in CXLs, most utilizing gaseous reagents and metal catalysts, for example, hydrogenations, oxidations, and hydroformylations.<sup>393,394</sup> As compared to traditional liquid-phase processes, expanded liquids offer higher diffusivity, lower viscosity, and increased safety due to the nonflammable medium (inerted by the  $\text{CO}_2$  atmosphere). Furthermore, the solubility of gases is enhanced to give superior reaction rates, and product and catalyst separation can be easily achieved by tuning the solvent.

The rhodium-catalyzed hydroformylation of 1-octene to nonanal has been demonstrated in  $\text{CO}_2$  expanded acetone.<sup>395</sup> The high solubility of syngas and the improved transport properties of the medium increased the TOF of the catalyst and enhanced the selectivity to the linear aldehyde product (from 70% to 94%). Importantly, this process showed that the quantity of organic solvent could be reduced by 50%.<sup>396</sup> Furthermore, the CXL medium required mild operating conditions relative to other industrial and SCF-based processes (see Table 4). To further elaborate the benefits of CXL hydroformylations, Fang et al. performed a gate-to-gate economic and environmental impact analysis for a Rh-catalyzed hydroformylation (E-factor 0.34).<sup>397</sup> The authors showed that waste production was one-half that of the industrial Co-catalyzed Exxon process (E-factor 0.66). Unfortunately, the authors also showed that near quantitative recovery (>99.8%)



**Table 4. Comparison of Different 1-Octene Hydroformylation Processes<sup>a</sup>**

process (catalyst)	BASF (Co)	Shell (Co)	SCF-IL (Rh)	SCF (Rh)	CXL (Rh)
substrate	1-octene	1-octene	1-octene	1-octene	1-octene
<i>P</i> (MPa)	30	8	20	12.5	3.8
<i>T</i> (°C)	150	200	100	100	60
TOF (h <sup>-1</sup> )	35	20	517	259	316
<i>S<sub>n</sub></i> -aldehyde (%)	50	80	75	75	89

<sup>a</sup>Reproduced with permission from ref 396. Copyright 2006 Wiley-VCH.

of the Rh catalyst was needed for a favorable comparison to the Exxon process. A 99% catalyst recovery rate was calculated to quadruple the makeup costs, adversely affecting the economics of the hydroformylation.

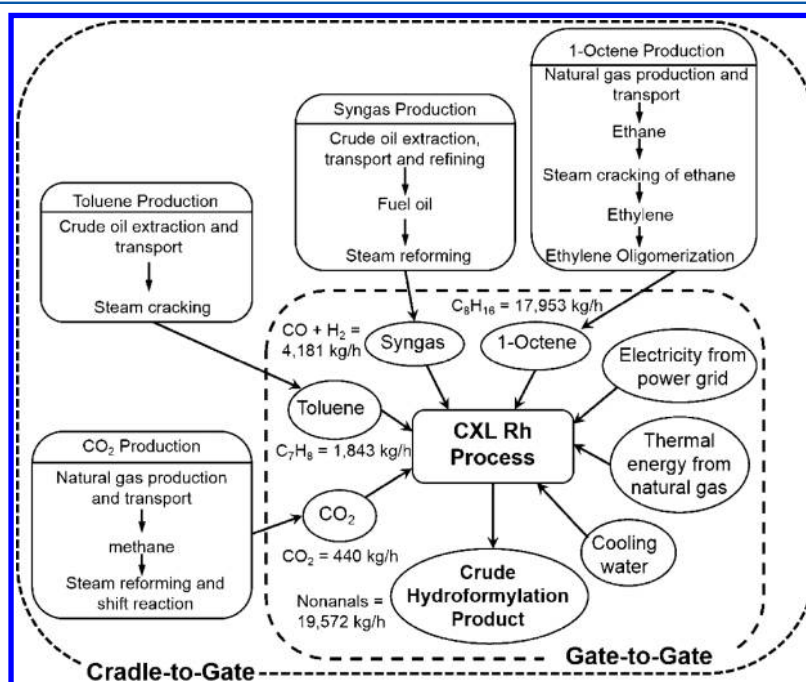
To avoid catalyst recovery problems, Xie et al.<sup>398</sup> investigated the environmental and economic impacts of 1-octene hydroformylation in CO<sub>2</sub> expanded toluene with rhodium immobilized on JanaPhos, a polymer-supported Biphephos derived ligand earlier developed by Jana et al.<sup>399</sup> The process was conducted at 50 °C and 3.2 MPa CO<sub>2</sub> with 0.6 MPa Syngas in combination with a nanofiltration membrane. The Rh/JanaPhos was retained in the membrane reactor, and catalyst loss in the effluent stream was found to be 0.2 wt % per hour. However, even at these low rates, the catalyst makeup cost was calculated to be 5-fold greater than the analogous Co catalyzed process, due to the extremely high Rh metal prices. Nevertheless, the total capital investment (TCI) for the CXL-based process was calculated to be significantly lower than the Co-catalyzed process as the lengthy Co catalyst regeneration steps could be avoided.

By comparing cradle-to-gate and gate-to-gate analyses (Figure 40), Xie et al. also predicted that the largest environmental impacts originate from sources outside of the

process plant, that is, raw material manufacturing. Therefore, for the CXL-based process to be environmentally comparable to the conventional process, the quantity of toluene must be reduced to less than 50 wt %. Although possible, toluene was necessary for dissolution of the JanaPhos ligand and could not be reduced below 33 wt %. Other investigations have shown that the quantity of organic solvent may be significantly reduced while retaining the benefits of the CXL medium.<sup>400</sup> Smaller quantities of organic solvent are ideal as environmental impacts are minimized; however, eventually solubility issues or slow reaction rates may negate these benefits. Bioderived solvents can be expanded by CO<sub>2</sub>, which may help to establish renewable-tunable solvent systems independent from non-renewable solvents.<sup>400,401</sup> However, as previously mentioned, renewability and environmental effects are independent properties.

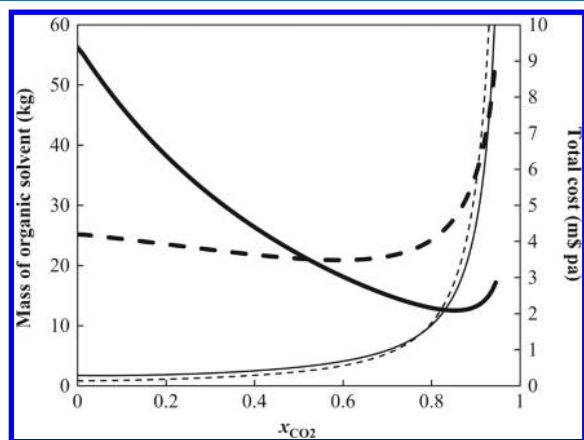
Although chemical processes themselves can be successfully compared by gate-to-gate analyses, raw materials manufacturing, equipment costs, and disposal procedures cannot be ignored under sustainable practices. The boundaries of LCAs must therefore be clearly defined for reliable conclusions to be drawn from assessments. For example, the production and disposal of solvents can be detrimental to environmental sustainability, yet beneficial to economic sustainability if high caloric solvents are incinerated for process heat. These considerations are especially pertinent for CXLs as solvents as specialized equipment and elevated pressures are balanced against enhanced performance and energy efficient separations.

Sioukrou et al. have modeled the economics of the Diels–Alder reaction between anthracene and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in CO<sub>2</sub>-expanded acetonitrile, acetone, and methanol.<sup>402</sup> For methanol, the cost was considerably higher than that of other CXLs due to the slow reaction rate and low solubility of anthracene. Pure acetone produced the lowest costs; however, an economic benefit was noted for low concentrations of CO<sub>2</sub> (4–7 mol %) in acetonitrile and



**Figure 40.** Boundaries for the LCA of the rhodium-catalyzed 1-octene hydroformylation by Xie et al. Reproduced with permission from ref 398. Copyright 2014 American Chemical Society.

methanol. Importantly, the authors investigated the trade-off between economic and environmental performance by considering process costs, organic solvent requirements, and CO<sub>2</sub> content (see Figure 41). The authors considered 10–15



**Figure 41.** Calculated mass of organic solvent (thick curves) and process costs (thin curves) as a function of CO<sub>2</sub> mole fraction for acetonitrile (solid) and acetone (dashed). Reproduced with permission from ref 402. Copyright 2014 Elsevier.

mol % of CO<sub>2</sub> to be a reasonable trade off point. A reduction in the organic solvent was also found to incur a large increase in energy consumption and process costs as the capital and operating costs of the compressor were identified as the largest contributors to overall process costs.

CXLs-based systems employing multiple phases can also be used to enhance catalyst recycling. For example, organic-aqueous tunable solvents (OATS) were developed to utilize CO<sub>2</sub> as a phase-switching agent capable of changing the polarity of an organic solvent enough to induce immiscibility with water. While these were first reported for the recovery of biocatalyst such as enzymes in biphasic systems of dimethyl ether and water,<sup>403</sup> subsequent examples included the use of multiphasic CO<sub>2</sub>–organic–water systems<sup>404</sup> for the recycling of biocatalysts<sup>405,406</sup> or chemocatalysts<sup>407</sup> using ca. 10 bar of CO<sub>2</sub> as a means of altering the polarity of miscible organic–aqueous systems enough to induce phase change. This enables the recovery of expensive organometallic complexes (or nanoparticles<sup>408</sup>) at high rates, provided the catalyst complex is preferentially soluble in water.<sup>311</sup> By this method, reactions can be run homogeneously in organic/aqueous mixed solvents in the absence of CO<sub>2</sub>, and then small amounts of CO<sub>2</sub> can be added postreaction to induce a phase split, with the products entering the organic phase and the catalyst the aqueous phase, leading to facile catalyst recycling and concomitant product recovery.<sup>404</sup> OATS was intended as a more environmentally benign version of the fluorine-organic tunable catalyst recycling systems using CO<sub>2</sub> as the use of the suspect fluorinated solvent was eliminated and the pressure reduced. Other CO<sub>2</sub> triggered switchable systems will be discussed in section 6.3 of this Review.

**6.2.2. Extractions.** CXLs have also been identified as promising solvents for biomass-based extractions as their low viscosities and high diffusivities facilitate penetration of cell walls and enhance extraction rates. In addition, CXL extractions can be operated at lower temperatures, allowing temperature-sensitive medium-to-high polarity compounds to be extracted without thermal decomposition.<sup>409</sup> Many examples of bioactive

compound<sup>410–412</sup> and microalgae<sup>413–415</sup> lipids extractions have been reported, with most improving upon existing solvent-based processes.

Wang et al. performed LCAs for microalgae oil extraction using CO<sub>2</sub> expanded methanol and ethanol.<sup>416</sup> The boundaries of the assessment excluded drying of the algae as this dehydration step consumes significant amounts of energy.<sup>417</sup> Final landfill disposal and equipment costs were also excluded from the analysis. When compared against a range of organic solvent mixtures and scCO<sub>2</sub>, the results were relatively simple and easily predicted. The organic solvent-based extractions were found to have the highest environmental impacts due to solvent production and their poor ESH properties. The environmental impact of the scCO<sub>2</sub>-based process was significantly lower because of the high recovery rate of the microalgae oil (>95%), low operating temperature (40 °C), and the absence of organic solvent. However, the high pressure needed for the scCO<sub>2</sub> solvent (148 atm) required significantly more electrical energy, and the cost of producing microalgae was therefore higher than any other process. The CXL-based processes had the lowest environmental impacts due to high extraction efficiencies, short extraction times, and low operating pressures (60–70 atm). Because equipment costs were excluded from the analysis, a detailed economic assessment could not be made.

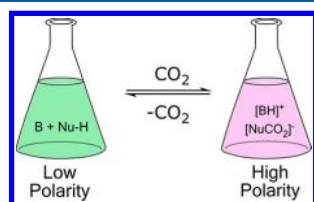
The economics of gas-expanded and supercritical solvents are essential aspects of their sustainability assessments, although performance remains the primary criterion driving solvent selection. The high capital and operating costs of scCO<sub>2</sub> and CXLs-based processes are balanced against the advantages they offer separations and extractions. Also, the tunability of solvent properties in these systems can offer benefits in selectivity (in both reactions and extractions), while key opportunities in catalyst recycling and higher gas solubility may offer unique platforms for CO<sub>2</sub>-based processing systems that cannot be realized with traditional organic solvents.<sup>407</sup> The essentially benign nature of CO<sub>2</sub> is also a major incentive to find opportunities to use this medium.

### 6.3. Switchable Solvents

The properties of switchable materials are changed when they are exposed to triggers such as gases, heat, or light.<sup>418–421</sup> Although each trigger has its own advantages, their foremost requirements include safe usage, low costs, little to no waste, with a readily reversible mechanism. As a chemical switch, CO<sub>2</sub> fulfills these criteria and also eliminates the need for conductive and transparent reaction systems. There are many types of CO<sub>2</sub> switchable materials, for example, polymers, catalysts, gels, acids, particles, and surfactants.<sup>420,422,423</sup> Switchable solvents have become one of the more popular applications for CO<sub>2</sub> responsive switches.<sup>23</sup> Their contribution to sustainable solvent development has primarily focused on low energy methods for separations and post reaction workup procedures. In addition, the ability to reversibly switch from one type of solvent to another has been shown to facilitate recycling of the solvent medium and improve product and catalyst recovery.<sup>424,425</sup> CO<sub>2</sub> switchable solvents are usually used at atmospheric pressures (1 bar) and can be divided into different categories, including switchable polarity solvents (SPSs), switchable hydrophobicity solvents (SHSs), and switchable water (SW). Both SPSs and SHSs undergo polarity switches upon CO<sub>2</sub> addition, while switchable water undergoes a change in ionic strength. Similar systems used for CO<sub>2</sub> capture have been termed CO<sub>2</sub>-binding

organic liquids (CO<sub>2</sub>BOLs) or biphasic amine solvents.<sup>426–429</sup> As with other “designer solvents” such as ionic liquids, the properties of switchable solvents may be changed by incorporating functional groups into their structures. Existing examples include ethers,<sup>430</sup> alcohols,<sup>431</sup> esters,<sup>432</sup> alkylsilyl and alkoxysilyl groups,<sup>433</sup> and even amino acid esters<sup>434</sup> that impart chirality to the switchable solvent itself. Of course, increasing complexity generally means expensive preparations that prevent future large-scale applications. For this reason, the majority of switchable solvent research is undertaken using simple amines, amidines, or guanidine. This Review will present a summary of each CO<sub>2</sub> switchable solvent class and address their potential as sustainable solvents. Other notable solvent switching mechanisms, such as the switchable volatility of piperylene sulfone<sup>435,436</sup> or the mixing of thermomorphic solvent systems,<sup>437,438</sup> will not be discussed here.

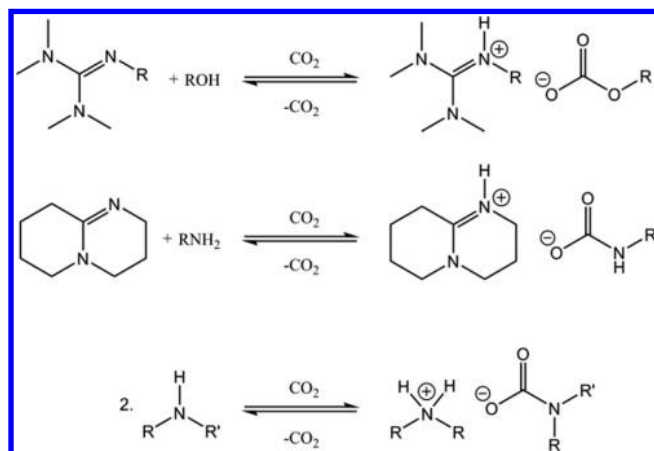
**6.3.1. Switchable Polarity Solvents (SPSs).** When CO<sub>2</sub> is bubbled through a SPSs, the molecular liquid of low polarity is switched to an ionic liquid of higher polarity, Figure 42.<sup>439</sup> The



**Figure 42.** Switchable polarity solvents experience a reversible change in polarity when exposed to CO<sub>2</sub>.

molecular liquids are often composed of equimolar mixtures of nucleophilic solvents, such as alcohols or amines, and an organic base, such as amines, amidines, or guanidines.<sup>440,441</sup> Carbon dioxide gas is chemically bound by the nucleophilic groups, leading to the formation of ammonium carbonate or carbamate salts. In the case of one-component switchable solvents, the same molecule acts as both the nucleophile and the base;<sup>433,442</sup> see Figure 43. CO<sub>2</sub> switchable solvents are reverted to molecular liquids by heating, bubbling with an inert gas, or sonication.

The organic bases of switchable solvents can react with water to give bicarbonate salts.<sup>443</sup> For this reason, alcohol-containing SPSs tend to be water sensitive, as the solid bicarbonate



**Figure 43.** Selected examples of switchable polarity solvents. Guanidine/alcohol (top), amidine/amine (middle), and secondary amine (bottom) examples are shown.

products are not readily returned to their neutral form. In addition, the formation of bicarbonate is thermodynamically more favorable than the formation of carbamate salts. Separations and chemical reactions in alcohol-containing SPSs therefore require dry conditions for the best performance. Organic reactions that produce water as a byproduct may need to be dried before the solvent is switched,<sup>444</sup> adding further processing steps to the work up procedure.<sup>445</sup> SPSs with amine nucleophiles tend to be more water stable as carbamate formation occurs much faster than bicarbonate formation.

Many organic reactions have been performed in SPSs, for example, polymerizations, Michael additions, and Heck reactions.<sup>445</sup> However, switchable functional groups are not always chemically innocent, and careful consideration is needed when choosing reactants or reagents. Simple one-component systems do not require equimolar quantities of alcohol (see Figure 43) but still contain potentially reactive amine functionalities. Additionally, one-component systems require 2 equiv of amine for 1 equiv of CO<sub>2</sub> to give one anion–cation pair. Larger quantities of one-component SPS may therefore be needed, depending on the chemical process.

The polarity switch expressed by an SPS can be beneficial for extractions and separations, as the change from low polarity to high polarity, or vice versa, can lead to precipitation or phase separation of a dissolved solute. SPSs have therefore been used for a variety of applications, such as the separation of soybean oil from soybeans,<sup>446</sup> heavy metal extractions,<sup>447</sup> and the pretreatment of lignocellulose.<sup>448,449</sup> Soudham et al. have shown that pretreatment using SPSs can be effective for a wide range of lignocellulosic materials.<sup>450</sup> The authors demonstrated that CO<sub>2</sub> triggered DBU/monoethanolamine (MEA) can perform as well as classical ionic liquids for delignification experiments. However, SO<sub>2</sub> triggered DBU/MEA was found to provide a superior pretreatment, especially for woody substrates. A cheap and effective pretreatment solvent can significantly accelerate the subsequent enzymatic hydrolysis of cellulose. Unfortunately, purification experiments with sodium lignosulfonate (SLS) have found difficulty in recovering dissolved lignin from DBU/MEA switchable solvents. For example, DBU/MEA switchable solvents retained up to 44 wt % of the original SLS, which could not be removed by the addition of any antisolvent.<sup>451</sup>

Interestingly, Phan et al. observed the transesterification of soybean oil during extractions of soybean flakes with a DBU/EtOH SPS at 70 °C.<sup>446</sup> The transesterification products of triglycerides and ethanol are fatty acid ethyl esters (FAEEs), which are used as biodiesel fuels. The process was optimized by Xue et al., who found that a 97.9% yield could be achieved in 2 h at 70 °C with a 12:1 ethanol to soybean oil ratio and a 2:1 DBU to soybean oil ratio.<sup>452</sup> The activation energy (*E*<sub>a</sub>) of the process was found to be 16.8 kJ mol<sup>−1</sup>, which is significantly lower than other base-catalyzed transesterification reactions that range from 33.6 to 84.0 kJ mol<sup>−1</sup>.

Cao et al. also showed that SPS can be used for the catalytic production of glycerol and fatty acid methyl esters (FAMEs), another popular form of biodiesel.<sup>453</sup> The authors examined a range of strong bases as catalysts for transesterification and found DBU to provide the highest yields. For a DBU/MeOH ratio of 1:1, complete separation of the glycerol and FAME products was achieved upon CO<sub>2</sub> bubbling, with a yield of 95.2% by decanting the product phase. Relative to DBU, a large molar excess of methanol was required to achieve reasonable methanolysis yields. For example, a DBU:MeOH ratio of 1:3

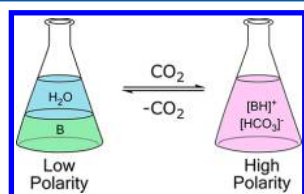


provided only 19.4% of FAMES, while a 1:6 ratio provided a yield of 95.2% after only 20 min. Unfortunately, glycerol was found to remain in the SPS phase and could only be separated from DBU with a saturated  $\text{NaCl(aq)}/\text{CHCl}_3$  extraction.

Bao et al. have also examined the intersolubilities of FAMES (from *Jatropha curcas* L. oil), methanol, glycerol, and DBU.<sup>454</sup> The FAME rich product layer and the SPS layer were analyzed with various DBU amounts (1–15%) and at various temperatures (25–60 °C). They found that higher quantities of DBU result in significantly lower purity FAMES, while higher temperatures have little impact. The quantity of glycerol found in the FAME product layer ranged from 2.02% to 20.90%, while the quantity of DBU ranged from 39.43% to 68.53%, which is significantly higher than previous observations.<sup>453</sup>

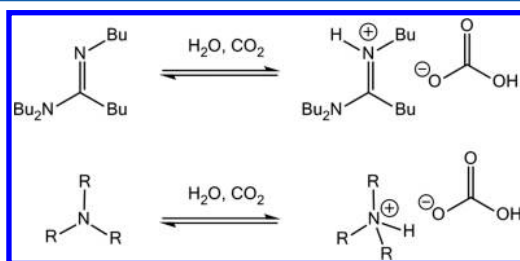
The purity requirements for biodiesel are very high, and many other processes are being explored for the cheap production of high-quality biodiesel fuels.<sup>455–457</sup> The ability of SPS to extract triglycerides from raw materials while simultaneously catalyzing their transesterification to biofuels is stimulating. In combination with low energy separations of the fatty acid esters from glycerol and catalysts, SPS may play a significant role in future biodiesel production. However, with the additional requirements of further workup procedures, such as washing and solvent distillations, the advantages of SPS are significantly diminished.

**6.3.2. Switchable Hydrophobicity Solvents (SHSs).** In the absence of  $\text{CO}_2$  SHSs are biphasic systems composed of a hydrophobic amine and an aqueous layer.<sup>458</sup> Upon exposure to 1 bar of  $\text{CO}_2$ , the organic base is protonated by the weakly acidic solution of carbonic acid and dissolved hydrated  $\text{CO}_2$  to give a single phase; see Figure 44. As with SPSs, this reaction



**Figure 44.** Switchable hydrophilicity solvents experience a change in polarity that allows the miscibility with water to be switched.

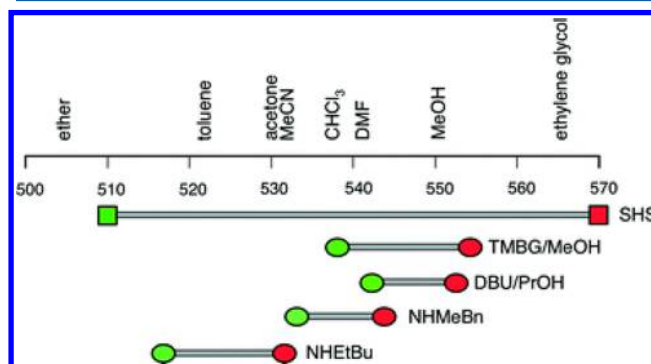
may be reversed by heating, sonicating, or bubbling with an inert gas to remove  $\text{CO}_2$  from the system. Ideally an SHS has a low water solubility in the absence of  $\text{CO}_2$  and a high water solubility in the presence of  $\text{CO}_2$ . Common SHS functional groups include alkylated amidines or secondary and tertiary amines that act as bases to deprotonate carbonic acid or hydrated  $\text{CO}_2$ ; see Figure 45. Although some hydrophobic



**Figure 45.** Example amidine (top) and tertiary amine (bottom) switchable hydrophilicity solvents (SHS).

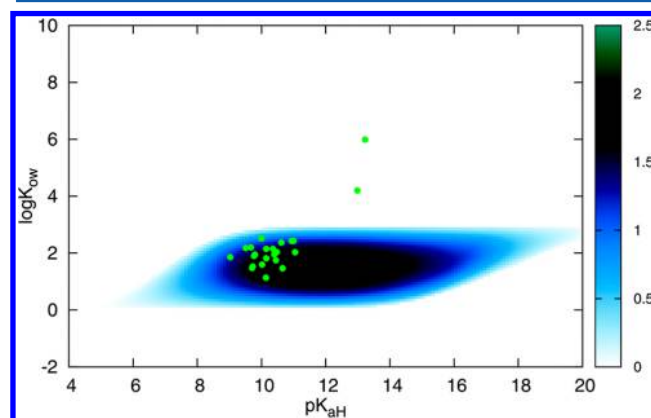
guanidines are readily converted to water-soluble bicarbonates, their high basicities mean that the release of  $\text{CO}_2$  requires too much energy for applications as SHSs.<sup>431</sup>

The polarity switches exhibited by SHSs are significantly larger than those for SPSs. For example, the amidine shown in Figure 45 has an absorbance of  $\lambda_{\text{max}} = 510$  nm with Nile red dye; however, when  $\text{CO}_2$  is introduced, the resulting solution has an absorbance of  $\lambda_{\text{max}} = 570$  nm.<sup>458</sup> This polarity switch is shown relative to a range of traditional solvents and SPSs in Figure 46.



**Figure 46.** Maximum wavelengths for solvents, measured with the Nile red dye. Switchable solvent polarities under air (green) and 0.1 MPa  $\text{CO}_2$  (red) are shown. A range of SPS (○) and one SHS (□) are also shown relative to traditional solvents (top). Reproduced with permission from ref 458. Copyright 2010 The Royal Chemical Society.

Durelle et al. have attempted to mathematically describe the  $\text{CO}_2$  triggered switching of two- and three-component mixtures, with the aim of optimizing processes on the basis of both intrinsic and extrinsic parameters.<sup>459</sup> The authors showed that the distribution coefficients of the SHS before and after  $\text{CO}_2$  exposure could be used to calculate a mapping parameter,  $\Omega$ , for three-component liquid systems, that is, to describe processes such as soybean oil extraction<sup>458</sup> and subsequent separations. Figure 47 shows a graphical representation of  $\Omega$ , which shows the  $\log K_{\text{OW}}$  and  $\text{pK}_{\text{aH}}$  regions of viable SHS (shaded) and existing SHS (green dots). The two green dots outside of the viable region represent



**Figure 47.** A graphical representation of the mapping parameter ( $\Omega$ ) for three-component systems, showing the shaded region of viable SHS and confirmed SHS (green dots). The two green dots outside of the shaded region represent amidine SHS. Reproduced with permission from ref 459. Copyright 2014 The Royal Society of Chemistry.

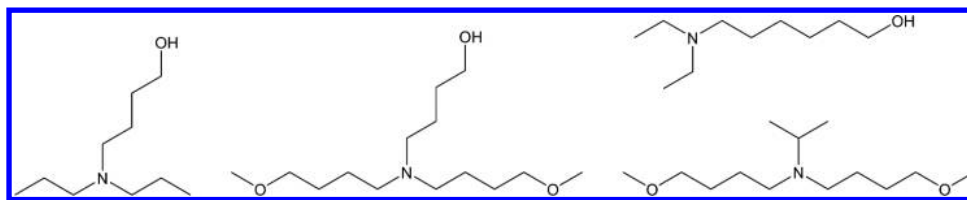


Figure 48. Tertiary amines identified by in silico screening as performed by Vanderveen et al. using predicted performance and EHS properties.

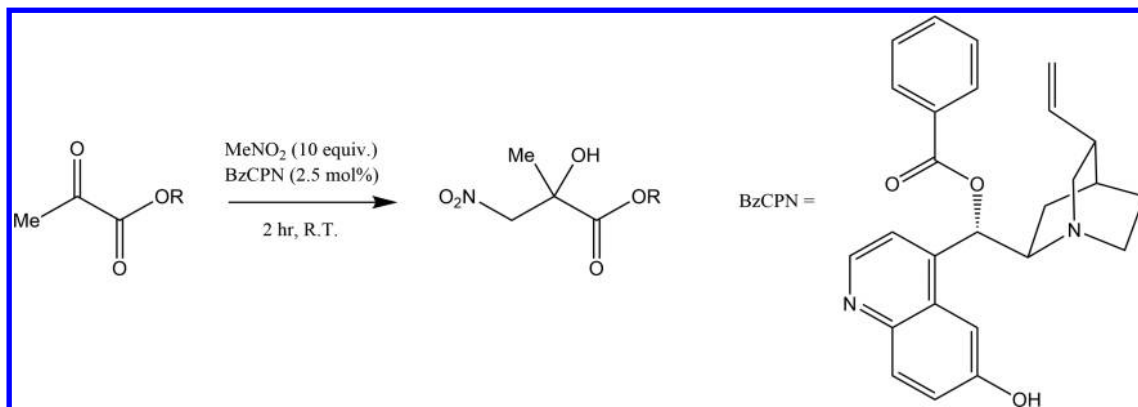


Figure 49. Enantioselective coupling of nitromethane and alkyl pyruvates (R = Me, Et) with benzoyl cupreine.

amidine SHS; hence, while amidines may function as SHS, they are not an ideal choice for extraction processes due to their high  $\log K_{ow}$  values. In addition, amidines that display SHS behavior are currently expensive to prepare and are therefore unsuitable for large-scale solvent applications.

Secondary amines contain available N–H bonds, and therefore carbamate salts may form under  $\text{CO}_2$  exposure, depending on the alkyl chain substituents.<sup>460</sup> Because carbamate salts require higher temperatures and longer times to reform the nonpolar organic phase, the energy requirements of these switchable solvent are significantly increased.<sup>461</sup> Branching of one of the alkyl substituents has been shown to prevent carbamate formation for secondary amines, while also providing lower energy requirements for  $\text{CO}_2$  removal.<sup>431</sup> For this reason, research in  $\text{CO}_2$  triggered switchable solvents has gradually moved toward secondary amines with one sterically hindered substituent and tertiary amines.

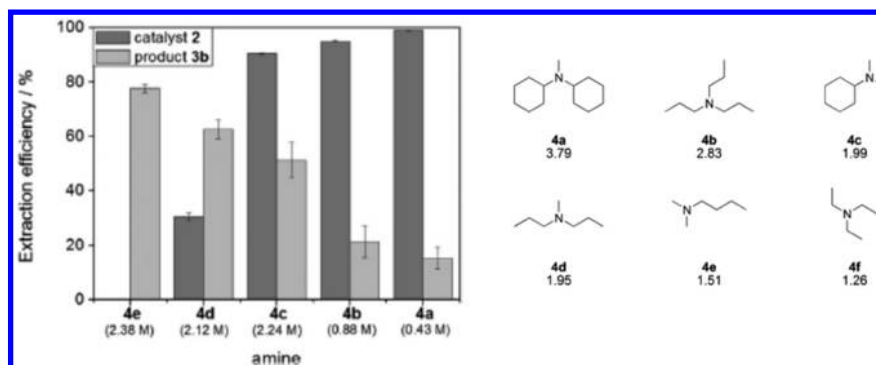
The Jessop group has shown that most amines with  $\text{p}K_{aH}$  values from 9.5 to 11 and  $\log K_{ow}$  values from 1.2 to 2.5 will act as SHSs with 1:1 water mixtures, under 1 bar of  $\text{CO}_2$ .<sup>431</sup> Amines with  $\text{p}K_{aH}$  values lower than 9.5 do not readily deprotonate carbonated water, while amines with higher  $\text{p}K_{aH}$  values do not display reversible behavior under mild conditions. Likewise, amines with  $\log K_{ow}$  values below 1.2 will mix with water and not form a biphasic system, while amines with higher  $\log K_{ow}$  values do not mix with water regardless of the  $\text{CO}_2$  pressure. Amines with  $\text{p}K_{aH}$  values below 9.5 or  $\log K_{ow}$  values above 2.5 can be forced to display SHS behavior by increasing the water to amine volume ratio or increasing the pressure of  $\text{CO}_2$ , that is, from 1 to 10 bar.<sup>462</sup> These amines will readily revert back to their water immiscible states and therefore possess desirable properties for  $\text{CO}_2$  switchable solvents. However, amines with high  $\log K_{ow}$  values should be avoided due to bioaccumulation risks and the potential difficulty in separating liquid organic products from the solvent.

Vanderveen et al. have demonstrated a virtual screening approach to identify tertiary amines that act as SHS with consideration to environmental impact, health, and safety

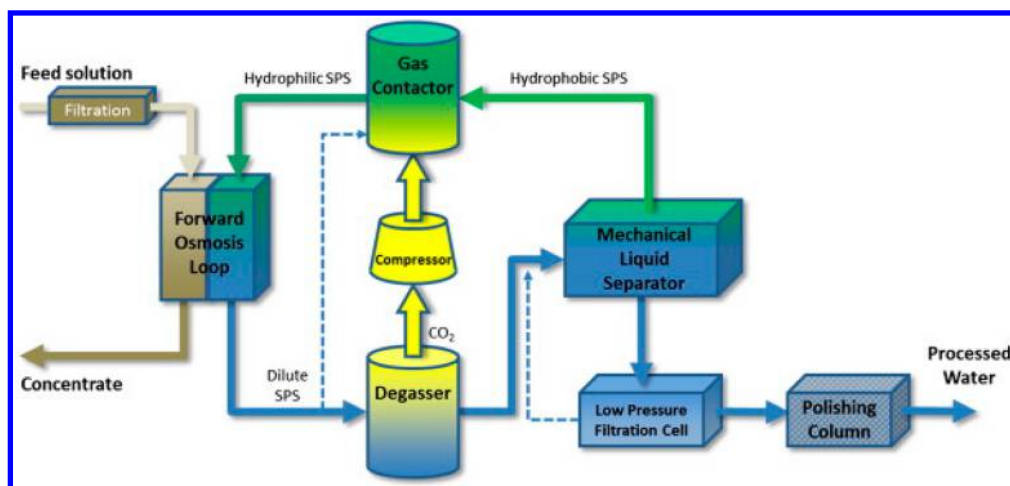
(EHS).<sup>463</sup> Amines were first identified by generating a library of molecular structures and predicting both their performance properties ( $\log K_{ow}$ ,  $\text{p}K_{aH}$ , and melting point) and their EHS properties (oral  $\text{LD}_{50}$ ,  $\text{LC}_{50}$ , bioaccumulation factor, flash point, vapor pressure, and boiling point). Parameter restrictions were used to filter out the generated structures to provide amines with the best characteristics for a SHS. The resulting tertiary amines were then further narrowed in terms of synthetic feasibility, and finally four amines were chosen and synthesized; see Figure 48. Amines 1–3 were found to exhibit the reversible  $\text{CO}_2$  triggered switches of SHS with 1 equiv of water; however, amine 4 was found to be water-soluble in the absence of  $\text{CO}_2$ . The authors acknowledge the difficulty in predicting water solubility and the synthetic viability of all generated structures; however, such virtual screening methods provide high throughput screening of potential SHSs.

When considering the performance and EHS of an SHS, it is difficult to identify and recommend one solvent over another. For example, secondary amino ester SHSs have lower toxicity, volatility, flammability, and eutrophication potentials than other SHSs. However, experiments have shown significant levels of ester hydrolysis during  $\text{CO}_2$  removal, severely limiting the recyclability of the SHS.<sup>431</sup> Other SHS studies of tertiary amines have produced generalized rules. For instance, Wilson et al. found that a C:N ratio between 6 and 12 is necessary for the amine to act as an SHS.<sup>464</sup>

Großeheilmann et al. have also investigated SHS for improved product separation and catalyst recycling for the enantioselective Henry reaction, Figure 49.<sup>424</sup> The hydrophilic  $\beta$ -nitroalcohol products are key intermediates in the preparation of aziridines and  $\beta$ -lactams. Importantly, the process is catalyzed by a hydrophobic organocatalyst, benzoyl cupreine (BzCPN),<sup>465</sup> meaning that SHS provides an excellent opportunity for catalyst/product separation. The initial solvent and parameter screening for the Henry reaction showed that an EtOAc solvent, 2.5% catalyst loading, and a 2 h reaction time provided the best yield (90%), with a high ee (90%).



**Figure 50.** Extraction efficiency of an organocatalyst and product from the Henry reaction in EtOAc using carbonated amine/water solutions. Reproduced with permission from ref 424. Copyright 2016 Wiley-VCH.



**Figure 51.** Switchable solvent forward osmosis process proposed by Wendt et al. Reproduced with permission from ref 472. Copyright 2015 Elsevier.

A range of tertiary amines were examined as SHS, and factors such as the amine/water ratio, the CO<sub>2</sub> bubbling times (i.e., the time required to obtain a single amine/water phase) and pH of the resulting ionic phase were considered. Figure 50 shows the extraction efficiency of the bicarbonate SHS toward the product and organocatalyst. The authors noted that low pH SHS amines, such as *N*-methylcyclohexylammonium hydrogen carbonate (pH = 6.7 at 0.43 M), result in protonation of the organocatalyst and hence a high extraction efficiency. The only SHS found to selectively extract either the product or the catalyst was carbonated *N,N*-dimethylbutylammonium hydrogen carbonate (pH = 8.0 at 2.38 M), which was found to remove 49% of the  $\beta$ -nitroalcohol product at a 2:1 ratio (SHS amine/water), 78% at a 1:1 ratio, and 84% at a 1:2 ratio.

The authors also investigated the racemization of the enriched enantiomeric product upon exposure to CO<sub>2</sub> removal conditions. Traditional methods such as sonication, heating, and gas dispersion (with argon) were noted to result in either significant solvent mass loss or a low ee. Instead, a falling-film microreactor (FFMR) was used as an alternative method of CO<sub>2</sub> removal. Under these conditions, racemisation of the 89% ee product was not observed, as opposed to heating at 40 °C (68% ee), 70 °C (43% ee), and sonicating (41% ee). Additionally, solvent loss was also minimized with the FFMR, which showed 9% mass loss, as compared to sonicating, which showed a significant 62% mass loss.

The energy efficient recovery and recycling of water is important for future demands, especially in locations with limited access to fresh water. Forward osmosis (FO) has become a popular water treatment and desalination method due to its low energy requirements.<sup>466</sup> In FO, an aqueous feed solution is separated from a draw solute (DS) by a semipermeable membrane. The osmotic pressure difference between the two solutions results in water from the feed passing through the membrane to the DS, without contaminants passing through. DSs typically consist of solutions of sugars, inorganic and organic salts, gases, or other materials.<sup>467</sup> The subsequent removal of the DS from the purified water is usually achieved by distillation, heat stripping, or further membrane separations; however, these processes require significant amounts of energy or expensive materials.<sup>468,469</sup>

The bicarbonate salts of SHSs have high osmotic pressures and have been shown to function as effective DSs.<sup>470</sup> Separation of the SHS from the purified water can be achieved by thermolytically removing the CO<sub>2</sub> from the solution, to regenerate the base as a separate phase that can be recycled. Tertiary amines have been examined as DSs; however, not all amines produce an osmotic-driven flux across semipermeable membranes. These SHS draw solutes have been termed “non-osmotic SPS”, while amines that are able to produce an osmotic driven flux are termed “osmotic SPS”.<sup>464,471</sup> Typically, tertiary amines that react with one single CO<sub>2</sub> molecule function as draw solutes and are osmotic; however, when multiple tertiary



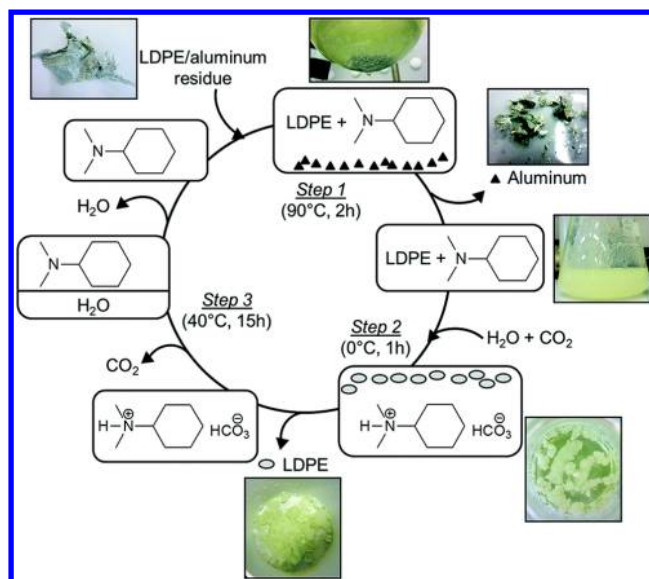
amines react with one single  $\text{CO}_2$  molecule, the amines do not function as draw solutes and are nonosmotic.

Wendt et al. have developed a process model for SPS-FO (note: in this case, the switchable solvents are named SPS, even though they experience a phase separation from water on  $\text{CO}_2$  degassing) desalination and treatment of waste waters from oil and gas drilling.<sup>472</sup> The energy requirements and capital and operational costs were calculated for a process using the dimethylcyclohexylamine (DMCHA) bicarbonate salt,  $[\text{DMCA-H}][\text{HCO}_3^-]$ , as a draw solute; see Figure 51. The total energy requirements for SPS-FO seawater desalination ( $\text{NaCl} = 0.6 \text{ mol/kg}$ ) were found to be significantly lower than for other thermal desalination processes, and compared favorably with industrial seawater reverse osmosis (RO) desalination. Depending on the degasser temperatures, SPS-FO was calculated to consume 2.4–4.3  $\text{kWh/m}^3$  for >90% water recovery, while RO has an electrical energy consumption of 4–6  $\text{kWh/m}^3$  for ~50% recovery.

Although switchable solvents do appear to be promising draw solutes for FO, there are a number of associated issues. Stone et al. observed the degradation of cellulose triacetate (CTA) FO membranes with a  $[\text{DMCA-H}][\text{HCO}_3^-]$  draw solute.<sup>470</sup> As a result, aqueous feeds with  $\geq 1.0 \text{ mol/kg}$  of  $\text{NaCl}$  were found to contain up to 1.8 wt % of DMCA, the solubility limit of the free amine in water, due to reverse diffusion through the membrane. Reimund et al. further investigated the stability of several RO membranes and one FO polyamide thin film composite (TFC) membrane in concentrated  $[\text{DMCA-H}][\text{HCO}_3^-]$ .<sup>473</sup> Their results showed variable membrane stability and poor performance for the FO membrane in long-term exposure studies. Fortunately, a 1-cyclohexylpiperidine (CHP)-based switchable solvent has been proposed as alternatives to the aggressive DMCA draw solutes.<sup>474</sup> CHP has osmotic pressures comparable to those of DMCA and releases  $\text{CO}_2$  at a lower temperature (70 °C). In addition, the flux performance is comparable to DMCA, and polyamide TFC membranes appear to be stable over long periods in the presence of CHP draw solutes.

Multilayer materials are versatile, cheap, and durable packaging materials that are popular in the food industry for aseptic packaging.<sup>475</sup> Unfortunately, recycling multilayer materials is problematic as they are composed of several plastic-laminated layers that are difficult to separate.<sup>476</sup> Furthermore, the quality of the recovered components largely determines their commercial value, and hence successful recycling methods must avoid material degradation. Chemical-based processes exploit the solubility of the polymer films in organic solvents to separate the layered materials under mild operating conditions. However, the best solvents for polymer dissolution are often toxic, harmful organic solvents (e.g., toluene, xylenes, and hexane<sup>477</sup>), which must be removed and disposed of, or recycled by energy intensive distillations.

Samorì et al. have therefore assessed the use of switchable solvents based on DMCHA for the separation of depapered multilayer packaging materials composed of aluminum foil laminated with low-density polyethylene (LDPE); see Figure 52.<sup>478</sup> In this process, LDPE is first dissolved in DMCHA (step 1, 90 °C, 2 h), and the Al is removed by filtration. The hydrophobic amine can then be switched to its hydrophilic form using carbonated water (step 2, 0 °C, 1 h), causing LDPE to precipitate from solution. The ammonium carbonate can be switched back to the hydrophobic amine by removal of  $\text{CO}_2$  (step 3, 40 °C, 15 h), and water can be removed by separating



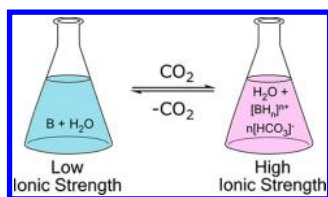
**Figure 52.** Separation of depapered multilayer materials composed of aluminum and LDPE using a DMCHA switchable solvent system, as reported by Samorì et al. Reproduced with permission from ref 479. Copyright 2017 The Royal Society of Chemistry.

the layers, allowing the solvent to be reused. Laboratory-based experiments have shown that the proposed three-step process can recover 70–90% LDPE and >99% Al, of which 86% is metallic Al (i.e., there is little oxidation). However, despite high recovery rates and high purity, the process is limited by increasing viscosity for high sample loadings (<10 wt %) and poor solvent recovery; only 80% of DMCHA is recovered after one process cycle.

A preliminary cradle-to-gate LCA showed that the SHS process compares favorably to other waste treatment processes (landfill, pyrolysis, and formic acid treatment) in six impact categories (climate change, human toxicity, particulate matter formation, environmental toxicity, land occupation, and fossil fuel depletion). For example, the SHS process can reduce  $\text{CO}_2$  emissions by –648.2 kg, by preventing further raw materials processing, while formic acid treatment reduced  $\text{CO}_2$  emissions by only –576.1 kg  $\text{CO}_2$ . The SHS-based process reduces the global environmental load by –8% to –35% (depending on the energy mix), as compared to other methods.

During  $\text{CO}_2$  exposure, the increasing concentration of alkylammonium bicarbonate salt in the aqueous layer may result in increased solubility of the hydrophobic amine in the aqueous layer, through hydrotropic effects.<sup>459</sup> Furthermore, although SHS organic bases form secondary hydrophobic phases, they may still exhibit low solubility in water. Issues can therefore arise during the switching process, most notably, contamination of the aqueous phase with toxic organic bases, or solvent loss over time.

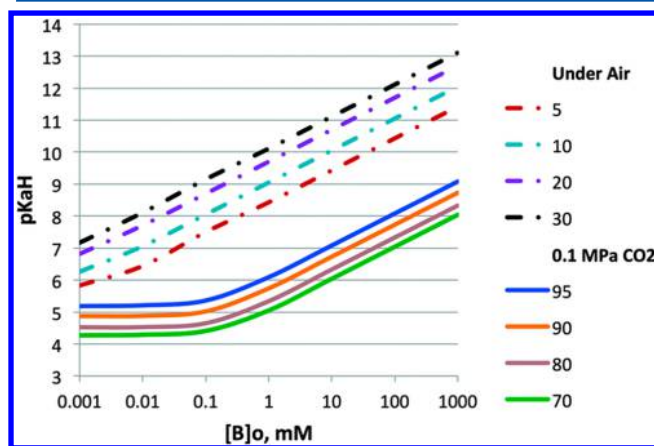
**6.3.3. Switchable Water (SW).** As with SHS, the introduction of  $\text{CO}_2$  gas to switchable water leads to the formation of ammonium bicarbonate salts. However, for switchable water, the organic base, which is most often an amine, is water miscible, and therefore in the absence of  $\text{CO}_2$  the system exists as a single phase; see Figure 53. The  $\text{CO}_2$  trigger thus results in a significant change in ionic strength, rather than polarity shifts or water miscibility. Consequently, the solubility of organic compounds in SW decreases, and therefore these systems may be used for the energy efficient



**Figure 53.** Switchable water experiences an increase in ionic strength when exposed to  $\text{CO}_2$ .

removal or purification of water-soluble organics via salting out effects.<sup>480</sup> Because the disposal of salt solutions can be costly, SW has been presented as a reusable alternative to traditional salt solutions for post reaction purifications and recycling.<sup>425</sup> Other physical changes in switchable water also occur; for example, upon  $\text{CO}_2$  bubbling, the conductivity and viscosity of the solution also increase.<sup>481</sup> Brief overviews of switchable water have been presented in 2015<sup>26</sup> and 2016;<sup>482</sup> however, the majority of investigations into switchable solvents have mostly focused on the popular SHS.

When triggered, switchable water does not experience any phase changes. Therefore, switchable water represents a simplified system that may be modeled far easier than SHS. For instance, Alshamrani et al. have predicted the basicities required for the high conversion of monobasic amines into bicarbonate salts using equilibrium calculations.<sup>460</sup> Figure 54



**Figure 54.**  $\text{pK}_{\text{aH}}$  required for a base to have a specified % protonation at a given concentration ( $[\text{Bo}]$ ) in water at 25 °C in both air (dashed lines) and 0.1 MPa  $\text{CO}_2$  (solid lines). Reproduced with permission from ref 460. Copyright 2016 The Royal Society of Chemistry.

shows the concentration-dependent % protonation of a base in air (dashed lines) and the % protonation in 0.1 MPa of  $\text{CO}_2$  (solid lines) at 25 °C. An ideal switchable functional group (SFG) would have a low percentage of protonation in air (<5%), and a high percentage protonation in  $\text{CO}_2$  (>95%), at a given concentration of base ( $[\text{B}]_0$ ). Therefore, any base should have a  $\text{pK}_{\text{aH}}$  below the red dashed line, but above the solid blue line. The authors state the importance of such figures for guiding the selection of an appropriate base for a certain application.

The ability to change solvent properties with the introduction of a  $\text{CO}_2$  trigger offers many advantages for chemical processes, mainly regarding separations and product isolations. However, these advantages are irrelevant if switchable solvents, whether ionic or neutral, are slowly lost during processing as additional energy is needed to remove solvent

contaminants from either product or waste streams. Because the toxicity of amines can dramatically change depending on their structures,<sup>483–485</sup> predictive models are an important part of SPS, SHS, and switchable water development. The environmental fate of amines is also poorly understood,<sup>486,487</sup> although current growth in postcombustion  $\text{CO}_2$  capture has resulted in increased interest in amine emissions.<sup>488</sup>

Predictive models play important roles in identifying environmentally friendly switchable solvents, further helping to guide their development toward more sustainable options. Simple, cheap, and readily available solvents clearly have significant advantages over more synthetically complicated alternatives. For this reason, switchable solvents are superior to many other neoteric solvents. However, as stated previously, cradle-to-grave LCAs are also important for any chemical process. As switchable solvents are relatively new, detailed knowledge of their life cycles is still insufficient. Likewise, green metric analyses of switchable solvent processes are also insufficient to draw comparisons to other solvents. Hence, predictive models play a significant role in switchable solvent development, not only regarding their ESH properties, but also the performance of the solvent in each specific application.

## 7. FUTURE OUTLOOK

Highlights from the 2017 *Faraday Discussion* titled “Bio-resources: Feeding a sustainable Chemical Industry” have been summarized by Brandt-Talbot and Weigand, to ensure that the conclusions and impressions from the discussion can reach a wider audience.<sup>489</sup> The conference report conveys the recurring themes throughout the meeting, one of which has been a recurring theme throughout this Review, economic feasibility. This point has been exemplified by the attendance of companies and the formation of start-up companies from the academic research presented at the Faraday Discussion. In general, this signifies that researchers are now aware that process economics are a crucial part of a sustainable chemical industry. Given the drive by the bioresource community, the concluding impressions echoed the importance of green metrics, safety, and environmental impacts for future bioresource developments. In 2017, Beller et al. published an essay for the 10-year anniversary special of *ChemSusChem* on the most cited papers from the journal in past decade.<sup>490</sup> The authors highlighted the overwhelming focus on new materials, rather than solutions to existing problems such as waste management, environmental technologies, and sustainable assessment methodologies. The importance of process intensification for existing chemical processes was also stressed as this can produce significant advances in sustainable processes over a short period of time. Subramaniam et al. have also emphasized the importance of LCAs and technoeconomic assessments during the early stages of process development to identify the “hotspots” of environmental impact.<sup>491</sup>

These messages are similar to those made by Jessop in 2010,<sup>68</sup> when researchers were urged to consider whether they were studying the best solvent for the environment and to use methods of assessing their environmental impacts. This Review has demonstrated that progress has been made toward these goals. Rather than following the green chemistry principles as instructions or commandments, sustainable chemistry is now encouraging a holistic approach to ensure that future developments are optimized throughout the entire supply chain. This ethos has become an integral part of the alternative solvent community. The green principles state that the use of

solvents should be made unnecessary wherever possible.<sup>25</sup> However, while this general guideline is excellent when applied to large-scale processes employing reaction solvents such as chloroform or hexane, for other processes it may be detrimental.

In the short term, chemical processes may be improved by replacing toxic solvents with traditional, safer alternatives, in combination with process intensification. However, beyond incremental changes, future chemical processes will depend on lowering energy demands, preventing waste, reducing emissions, and using renewable materials. The properties of alternative solvents can be exploited to achieve these goals. However, sustainable solvents are one facet of sustainable chemistry, and many other strategies are being developed to help advance sustainable chemistry.<sup>492–498</sup> Although renewability should be a feature of future sustainable solvents, it should not be the only one. Current options in the green and sustainable solvent tool-kit span a diverse range of physicochemical properties. Most traditional organic solvents can now be replaced by a neoteric solvent. However, the important point to consider is whether those options are truly sustainable alternatives. Furthermore, although one solvent can enable a more sustainable chemical process, its application to a different chemical process may increase environmental impacts or negatively affect process economics. Solvents should therefore be chosen on a process-by-process basis, and all alternatives should be considered.

The intersection of sustainability and economic pressures can be a determining factor in the adoption of a more sustainable solvent system. This can be a synergistic rather than competitive situation if economic and environmental factors are used as part of the solvent design process itself. Economically driven solvent design often leads to reduced environmental impact because of the shortened synthesis tree; environmental impact is dependent on both the precursor materials and the properties of the final product solvent. Additionally, an efficient process is not only better for the economics of a solvent-based process, but it is invariably better for the environment; lower cost is almost always a tell-tale sign of less energy usage, less waste production, and lower material usage. Cost can be a stand-in for green-ness under process design conditions, although sustainability requires a broader analysis.

Environmentally driven solvent design (making something renewable, biodegradable, or less toxic), while laudable, usually leads to the need for costly extractions from feedstocks (also producing waste) and often a more complex synthesis. This can lead to an overall less sustainable solvent or process than the petrochemical alternative if efficiency considerations are not taken into account. The economic impact is usually a far more telling sign of solvent performance (at least from an LCA perspective), and even if it is a gain in the environmental sustainability of the solvent once made, the provenance of the solvent must also be considered. The environmental benefit of having a renewable, biodegradable, and less toxic solvent can be compromised by loss in process efficiency, which could drive both economics and overall sustainability of the process down considerably.

However, because a sustainable chemical process is dependent on both the environmental and the economic (or societal) factors and benefits, economic design can lead to better advances, unless the process produces or uses extremely toxic or very persistent chemicals. The balance between economic

and environmental factors is therefore normally in favor of economics, but there is a caveat: toxicity and CO<sub>2</sub> emissions are not normally properly accounted for in a strictly economic analysis. Therefore, these “hidden costs” must be properly weighted against the gains from other areas if an informed choice is to be made as to which solvent truly leads to the most sustainable process.

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### Notes

The authors declare no competing financial interest.

### Biographies

Dr. Coby James Clarke received his Master's degree in 2011 under the supervision of Pete Licence at the University of Nottingham. He later earned his Ph.D. in 2015 in the same group, where he studied ionic liquid surfaces using XPS. Coby subsequently joined Jason Hallett's research group in the Department of Chemical Engineering at Imperial College London as part of a Frontier Engineering programme devoted to scaling up synthetic biology. His research is primarily focused toward protein stabilization in ionic liquids; however, other research interests include the thermal behavior and surface characterization of ionic liquids.

Wei-Chien Tu is currently a doctorate student in the Department of Chemical Engineering at Imperial College London. She received an M.Res. in Green Chemistry from Imperial College in 2014. Her research focus includes lignocellulosic biomass pretreatment using ionic liquids and the development of cellulose and cellulose-derived products. She earned a dual B.A. with Honors from the University of Chicago in 2000 in Psychology and East Asian Languages and Civilizations. She then completed a 10 year career in the financial services industry.

Oliver Levers is a Ph.D. student within the Institute of Chemical Biology, Imperial College London. He received his M.Chem. from the University of York in 2013, and an M.Res. in Chemical Biology from Imperial College London in 2015. Oliver's research interests include soil chemistry and soil biology, and he is currently working on the utilization of lignocellulosic materials in an agricultural context.

Dr. Andreas Bröhl was born in 1986 in Cologne, Germany. He received his diploma degree in chemistry from the University of Cologne in 2012. He conducted his graduate studies at the University of Cologne and was a visiting Ph.D. student at the University of Notre Dame in the United States. He received his Ph.D. degree in 2016. In the same year, he joined Jason Hallett's group at Imperial College London as a postdoctoral research associate. His research is focused on understanding interactions of proteins with ionic liquids, and how these interactions can be steered by chemical modifications of the protein surfaces.

Dr. Jason Hallett is Reader in Sustainable Chemical Technology within the Department of Chemical Engineering at Imperial College London. He did his B.S. degree in Chemical Engineering at the University of Maine and Ph.D. in Chemical Engineering at the Georgia Institute of Technology under the direction of Prof. Charles Eckert and Prof. Charles Liotta. He joined the Department of Chemistry at Imperial College in 2006 as a Marshall-Sherfield Postdoctoral Research Fellow, and later became a Research Lecturer in 2008. He joined the



Department of Chemical Engineering as a Senior Lecturer in 2014 before becoming Reader in 2016 and currently leads a group of 10 postdocs and 15 Ph.D. students with a focus on solvent design for reduced environmental impact in chemical processes. This has included the development of cost-effective designer solvents (ionic liquids) for large-scale applications. He is also the director of the Imperial Network of Excellence in Industrial Biotechnology.

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## REFERENCES

- (1) United Nations General Assembly. *Transforming Our World: The 2030 Agenda for Sustainable Development*; 2015.
- (2) Cséfalvay, E.; Akién, G. R.; Qi, L.; Horváth, I. T. Definition and Application of Ethanol Equivalent: Sustainability Performance Metrics for Biomass Conversion to Carbon-Based Fuels and Chemicals. *Catal. Today* **2015**, *239*, 50–55.
- (3) Glavic, P.; Lukman, R. Review of Sustainability Terms and Their Definitions. *J. Cleaner Prod.* **2007**, *15*, 1875–1885.
- (4) <http://www.acs.org/content/acs/en/sustainability/understandingsustainability.html> (accessed Sep 9, 2017).
- (5) Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Sherwood, J. Opportunities for Bio-Based Solvents Created as Petrochemical and Fuel Products Transition Towards Renewable Resources. *Int. J. Mol. Sci.* **2015**, *16*, 17101–17159.
- (6) Buncel, E.; Stairs, R.; Wilson, H. In *The Role of the Solvent in Chemical Reactions*; Compton, R. G., Davies, S. S., Evans, J., Eds.; Oxford University Press: UK, 2003.
- (7) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011.
- (8) Abou-Shehade, S.; Clark, J. H.; Paggiola, G.; Sherwood, J. Tunable Solvents: Shades of Green. *Chem. Eng. Process.* **2016**, *99*, 88–96.
- (9) Sheldon, R. A. Green Solvents for Sustainable Organic Synthesis: State of the Art. *Green Chem.* **2005**, *7*, 267–278.
- (10) Roschangar, F.; Colberg, J.; Dunn, P. J.; Gallou, F.; Hayler, J. D.; Koenig, S. G.; Kopach, M. E.; Leahy, D. K.; Mergelsberg, I.; Tucker, J. L.; et al. A Deeper Shade of Green: Inspiring Sustainable Drug Manufacturing. *Green Chem.* **2017**, *19*, 281–285.
- (11) Savelski, M. J.; Slater, C. S.; Tozzi, P. V.; Wisniewski, C. M. On the Simulation, Economic Analysis, and Life Cycle Assessment of Batch-Mode Organic Solvent Recovery Alternatives for the Pharmaceutical Industry. *Clean Technol. Environ. Policy* **2017**, *19*, 2467–2477.
- (12) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. Perspective on Solvent Use in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2007**, *11*, 133–137.
- (13) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. Updating and Further Expanding GSK's Solvent Sustainability Guide. *Green Chem.* **2016**, *18*, 3879–3890.
- (14) Sheldon, R. A. The E Factor: Fifteen Years On. *Green Chem.* **2007**, *9*, 1273–1283.
- (15) Sheldon, R. A. The E Factor 25 Years On: The Rise of Green Chemistry and Sustainability. *Green Chem.* **2017**, *19*, 18–43.
- (16) Kerton, F.; Marriott, R. Chapter 2. Green Solvents - Legislation and Certification. *RSC Green Chemistry*; The Royal Society of Chemistry: UK, 2013; pp 31–50.
- (17) Leedham Elvidge, E. C.; Oram, D. E.; Laube, J. C.; Baker, A. K.; Montzka, S. A.; Humphrey, S.; O'Sullivan, D. A.; Brenninkmeijer, C. A. M. Increasing Concentrations of Dichloromethane, CH<sub>2</sub>Cl<sub>2</sub>, Inferred From CARIBIC Air Samples Collected 1998–2012. *Atmos. Chem. Phys.* **2015**, *15*, 1939–1958.
- (18) Welton, T. Solvents and Sustainable Chemistry. *Proc. R. Soc. London, Ser. A* **2015**, *471*, 1–26.
- (19) Horváth, I. T.; Cséfalvay, E.; Mika, L. T.; Debreczeni, M. Sustainability Metrics for Biomass-Based Carbon Chemicals. *ACS Sustainable Chem. Eng.* **2017**, *5*, 2734–2740.
- (20) Do, J. L.; Friščić, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3*, 13–19.
- (21) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; et al. Mechanochemistry: Opportunities for New and Cleaner Synthesis. *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- (22) Stolle, A. Technical Implications of Organic Syntheses in Ball Mills. *RSC Green Chemistry Series*; Royal Society of Chemistry: UK, 2015; Vol. 31, pp 241–276.
- (23) Pollet, P.; Eckert, C. A.; Liotta, C. L. Solvents For Sustainable Chemical Processes. *Green Chem.* **2014**, *16*, 1034–1055.
- (24) Cvjetko Bubalo, M.; Vidović, S.; Radojčić Redovniković, I.; Jokić, S. Green Solvents for Green Technologies. *J. Chem. Technol. Biotechnol.* **2015**, *90*, 1631–1639.
- (25) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: UK, 1998.
- (26) Anastas; Constable; Gallou; Hamann; Gladysz; Jessop; Koenig; Krische; Lipshutz; Ritter; et al. Green Chemistry Issue. *Aldrichimica Acta* **2015**, *48*.
- (27) Kirchhoff, M. M. Promoting Sustainability Through Green Chemistry. *Resour., Conserv. Recycl.* **2005**, *44*, 237–243.
- (28) Fegade, S. L.; Tremblay, J. P. Dispute Over Designating an Ionic Liquid as a Green Solvent. *Chem. Eng. J.* **2015**, *273*, 668.
- (29) Winterton, N. Green Chemistry: Deliverance or Distraction? *Clean Technol. Environ. Policy* **2016**, *18*, 991–1001.
- (30) Sáez-Martínez, F. J.; Lefebvre, G.; Hernández, J. J.; Clark, J. H. Drivers of Sustainable Cleaner Production and Sustainable Energy Options. *J. Cleaner Prod.* **2016**, *138*, 1–7.
- (31) Duić, N.; Urbaniec, K.; Huisingh, D. Components and Structures of the Pillars of Sustainability. *J. Cleaner Prod.* **2015**, *88*, 1–12.
- (32) Dudukovic, M. P. Frontiers in Reactor Engineering. *Science (Washington, DC, U. S.)* **2009**, *325* (5941), 698–701.
- (33) Subramaniam, B. Exploiting Neoteric Solvents for Sustainable Catalysis and Reaction Engineering: Opportunities and Challenges. *Ind. Eng. Chem. Res.* **2010**, *49*, 10218–10229.
- (34) Capello, C.; Fischer, U.; Hungerbühler, K. What Is a Green Solvent? A Comprehensive Framework for the Environmental Assessment of Solvents. *Green Chem.* **2007**, *9*, 927–934.
- (35) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK's Solvent Selection Guide – Embedding Sustainability Into Solvent Selection Starting at Medicinal Chemistry. *Green Chem.* **2011**, *13*, 854–862.
- (36) Diorazio, L. J.; Hose, D. R. J.; Adlington, N. K. Toward a More Holistic Framework for Solvent Selection. *Org. Process Res. Dev.* **2016**, *20*, 760–773.
- (37) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; et al. Green Chemistry Tools to Influence a Medicinal Chemistry and Research Chemistry Based Organisation. *Green Chem.* **2008**, *10*, 31–36.
- (38) Prat, D.; Pardigon, O.; Flemming, H. W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; et al. Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes. *Org. Process Res. Dev.* **2013**, *17*, 1517–1525.
- (39) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehade, S.; Dunn, P. J. CHEM21 Selection Guide of Classical and Less Classical-Solvents. *Green Chem.* **2016**, *18*, 288–296.
- (40) Jessop, P. G. Searching for Green Solvents. *Green Chem.* **2011**, *13*, 1391.
- (41) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. Metrics to “Green” Chemistry—Which Are the Best? *Green Chem.* **2002**, *4*, 521–527.

- (42) Van Aken, K.; Strekowski, L.; Patiny, L. EcoScale, a Semi-Quantitative Tool to Select an Organic Preparation Based on Economical and Ecological Parameters. *Beilstein J. Org. Chem.* **2006**, *2*, 1–7.
- (43) Hoffmann, V. H.; Hungerbu, K.; Mcrae, G. J. Multiobjective Screening and Evaluation of Chemical Process Technologies. *Ind. Eng. Chem. Res.* **2001**, *40*, 4513–4524.
- (44) Trost, B. M. The Atom Economy-A Search for Synthetic Efficiency. *Science (Washington, DC, U. S.)* **1991**, *254*, 1471–1477.
- (45) Trost, B. M.; Toste, F. D.; Greenman, K. Atom Economy. Palladium-Catalyzed Formation of Coumarins by Addition of Phenols and Alkynoates via a Net C-H Insertion. *J. Am. Chem. Soc.* **2003**, *125*, 4518–4526.
- (46) Sheldon, R. A. Fundamentals of Green Chemistry: Efficiency in Reaction Design. *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.
- (47) Calvo-Flores, F. G. Sustainable Chemistry Metrics. *ChemSusChem* **2009**, *2*, 905–919.
- (48) Unruh, D.; Pabst, K.; Schaub, G. Fischer–Tropsch Synfuels from Biomass: Maximizing Carbon Efficiency and Hydrocarbon Yield. *Energy Fuels* **2010**, *24*, 2634–2641.
- (49) Jae, J.; Tompsett, G. A.; Lin, Y.-C.; Carlson, T. R.; Shen, J.; Zhang, T.; Yang, B.; Wyman, C. E.; Conner, W. C.; Huber, G. W. Depolymerization of Lignocellulosic Biomass to Fuel Precursors: Maximizing Carbon Efficiency by Combining Hydrolysis with Pyrolysis. *Energy Environ. Sci.* **2010**, *3*, 358–365.
- (50) Galuszka, A.; Migaszewski, Z. M.; Konieczka, P.; Namieśnik, J. Analytical Eco-Scale for Assessing the Greenness of Analytical Procedures. *TrAC, Trends Anal. Chem.* **2012**, *37*, 61–72.
- (51) Rao, V. K.; Reddy, S. S.; Krishna, B. S.; Naidu, K. R. M.; Raju, C. N.; Ghosh, S. K. Synthesis of Schiff's Bases in Aqueous Medium: A Green Alternative Approach With Effective Mass Yield and High Reaction Rates. *Green Chem. Lett. Rev.* **2010**, *3*, 217–223.
- (52) Bui, V. P.; Hansen, T. V.; Stenström, Y.; Hudlicky, T. Direct Biocatalytic Synthesis of Functionalized Catechols: A Green Alternative to Traditional Methods With High Effective Mass Yield. *Green Chem.* **2000**, *2*, 263–265.
- (53) Sheldon, R. A. Organic Synthesis - Past, Present and Future. *Chem. Ind.* **1992**, 903–906.
- (54) Sheldon, R. A. Consider the Environmental Quotient. *CHEMTECH* **1994**, *24*, 38–47.
- (55) Tobiszewski, M.; Marć, M.; Galuszka, A.; Namieśnik, J. Green Chemistry Metrics with Special Reference to Green Analytical Chemistry. *Molecules* **2015**, *20*, 10928–10946.
- (56) Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry to Drive More Sustainable Processes. *Org. Process Res. Dev.* **2011**, *15*, 912–917.
- (57) Gómez-Biagi, R. F.; Dicks, A. P. Assessing Process Mass Intensity and Waste via an Aza-Baylis–Hillman Reaction. *J. Chem. Educ.* **2015**, *92*, 1938–1942.
- (58) Curzons, A. D.; Mortimer, D. N.; Constable, D. J. C.; Cunningham, V. L. So You Think Your Process Is Green, How Do You Know? — Using Principles of Sustainability to Determine What Is Green — a Corporate Perspective. *Green Chem.* **2001**, *3*, 1–6.
- (59) Dunn, P. J.; Galvin, S.; Hettenbach, K. The Development of an Environmentally Benign Synthesis of Sildenafil Citrate (Viagra™) and Its Assessment by Green Chemistry Metrics. *Green Chem.* **2004**, *6*, 43–48.
- (60) Andraos, J. Unification of Reaction Metrics for Green Chemistry: Applications to Reaction Analysis. *Org. Process Res. Dev.* **2005**, *9*, 149–163.
- (61) Andraos, J. Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to Reaction Discovery. *Org. Process Res. Dev.* **2005**, *9*, 404–431.
- (62) Curzons, A. D.; Jiménez-González, C.; Duncan, A. L.; Constable, D. J. C.; Cunningham, V. L. Fast Life Cycle Assessment of Synthetic Chemistry (FLASC™) Tool. *Int. J. Life Cycle Assess.* **2007**, *12*, 272–280.
- (63) Klöpffer, W. Life Cycle Assessment as Part of Sustainability Assessment for Chemicals. *Environ. Sci. Pollut. Res.* **2005**, *12*, 173–177.
- (64) Kralisch, D.; Ott, D.; Gericke, D. Rules and Benefits of Life Cycle Assessment in Green Chemical Process and Synthesis Design: A Tutorial Review. *Green Chem.* **2015**, *17*, 123–145.
- (65) Hellweg, S.; Fischer, U.; Scheringer, M.; Hungerbühler, K. Environmental Assessment of Chemicals: Methods and Application to a Case Study of Organic Solvents. *Green Chem.* **2004**, *6*, 418–427.
- (66) Reinhardt, D.; Ilgen, F.; Kralisch, D.; König, B.; Kreisel, G. Evaluating the Greenness of Alternative Reaction Media. *Green Chem.* **2008**, *10*, 1170–1181.
- (67) Jin, S.; Byrne, F.; McElroy, C. R.; Sherwood, J.; Clark, J. H.; Hunt, A. J. Challenges in the Development of Bio-Based Solvents: A Case Study on methyl(2,2-Dimethyl-1,3-Dioxolan-4-yl)methyl Carbonate as an Alternative Aprotic Solvent. *Faraday Discuss.* **2017**, *202*, 157–173.
- (68) Jessop, P. G. Searching for Green Solvents. *Green Chem.* **2011**, *13*, 1391–1398.
- (69) Jin, S.; Byrne, F.; McElroy, C. R.; Sherwood, J.; Clark, J. H.; Hunt, A. J. Challenges in the Development of Bio-Based Solvents: A Case Study on methyl(2,2-Dimethyl-1,3-Dioxolan-4-yl)methyl Carbonate as an Alternative Aprotic Solvent. *Faraday Discuss.* **2017**, *202*, 157–173.
- (70) Sheldon, R. A. Catalysis and Pollution Prevention. *Chem. Ind.* **1997**, *1*, 12–15.
- (71) George, A.; Brandt, A.; Tran, K.; Zahari, S. M. S. N. S.; Klein-Marcuschamer, D.; Sun, N.; Sathitsuksanoh, N.; Shi, J.; Stavila, V.; Parthasarathi, R.; et al. Design of Low-Cost Ionic Liquids for Lignocellulosic Biomass Pretreatment. *Green Chem.* **2015**, *17* (3), 1728–1734.
- (72) Chen, L.; Sharifzadeh, M.; Mac Dowell, N.; Welton, T.; Shah, N.; Hallett, J. P. Inexpensive Ionic Liquids: [HSO<sub>4</sub>]<sup>−</sup>-Based Solvent Production at Bulk Scale. *Green Chem.* **2014**, *16* (6), 3098–3106.
- (73) Brandt-Talbot, A.; Gschwend, F. J. V.; Fennell, P. S.; Lammens, T. M.; Tan, B.; Weale, J.; Hallett, J. P. An Economically Viable Ionic Liquid for the Fractionation of Lignocellulosic Biomass. *Green Chem.* **2017**, *19* (13), 3078–3102.
- (74) Harris, K. R.; Kanakubo, M. Self-Diffusion Coefficients and Related Transport Properties for a Number of Fragile Ionic Liquids. *J. Chem. Eng. Data* **2016**, *61*, 2399–2411.
- (75) Lin, H.; Freeman, B. D. Gas Solubility, Diffusivity and Permeability in Poly(ethylene Oxide). *J. Membr. Sci.* **2004**, *239* (1), 105–117.
- (76) García, G.; Aparicio, S.; Ullah, R.; Atilhan, M. Deep Eutectic Solvents: Physicochemical Properties and Gas Separation Applications. *Energy Fuels* **2015**, *29*, 2616–2644.
- (77) Zhang, Y.; Bakshi, B. R.; Demessie, E. S. Life Cycle Assessment of an Ionic Liquid versus Molecular Solvents and Their Applications. *Environ. Sci. Technol.* **2008**, *42*, 1724–1730.
- (78) Sheldon, R. A. Green Chemistry and Resource Efficiency: Towards a Green Economy. *Green Chem.* **2016**, *18*, 3180–3183.
- (79) Clark, J. H.; Farmer, T. J.; Herrero-Davila, L.; Sherwood, J. Circular Economy Design Considerations For Research and Process Development in the Chemical Sciences. *Green Chem.* **2016**, *18*, 3914–3934.
- (80) Sherwood, J.; Clark, J. H.; Farmer, T. J.; Herrero-Davila, L.; Moity, L. Recirculation: A New Concept to Drive Innovation in Sustainable Product Design for Bio-Based Products. *Molecules* **2017**, *22*, 1–17.
- (81) Zuin, V. G. Circularity in Green Chemical Products, Processes and Services: Innovative Routes Based on Integrated Eco-Design and Solution Systems. *Curr. Opin. Green Sus. Chem.* **2016**, *2*, 40–44.
- (82) GrandViewResearch. *White Biotechnology Market Report Analysis By Product (Biofuels, Biomaterials, Biochemicals, Industrial Enzymes), By Application (Bioenergy, Food & Feed Additives, Pharmaceutical Ingredients, Personal Care & Household Products) And Segment Forecasts To 20; 2016.*

- (83) Dornburg, V.; Hermann, B. G.; Patel, M. K. Scenario Projections for Future Market Potentials of Biobased Bulk Chemicals. *Environ. Sci. Technol.* **2008**, *42* (7), 2261–2267.
- (84) Berndes, G.; Hoogwijk, M.; van den Broek, R. The Contribution of Biomass in the Future Global Energy Supply: A Review of 17 Studies. *Biomass Bioenergy* **2003**, *25* (1), 1–28.
- (85) BERINGER, T.; LUCHT, W.; SCHAPHOFF, S. Bioenergy Production Potential of Global Biomass Plantations under Environmental and Agricultural Constraints. *GCB Bioenergy* **2011**, *3* (4), 299–312.
- (86) Fischer, G. N.; Prieler, S.; Van Velthuisen, H.; Berndes, G.; Faaij, A.; Londo, M.; De Wit, M. Biofuel Production Potentials in Europe: Sustainable Use of Cultivated Land and Pastures, Part II: Land Use Scenarios the Sum of EU15 and EU12; EU27. *Biomass Bioenergy* **2009**, *34*, 173–187.
- (87) <http://biofuel.org.uk/biofuel-facts.html> (accessed Sep 12, 2017).
- (88) Cherubini, F.; Ulgiati, S. Crop Residues as Raw Materials for Biorefinery Systems - A LCA Case Study. *Appl. Energy* **2010**, *87*, 47–57.
- (89) Maity, S. K. Opportunities, Recent Trends and Challenges of Integrated Biorefinery: Part I. *Renewable Sustainable Energy Rev.* **2015**, *43*, 1427–1445.
- (90) Maity, S. K. Opportunities, Recent Trends and Challenges of Integrated Biorefinery: Part II. *Renewable Sustainable Energy Rev.* **2015**, *43*, 1446–1466.
- (91) Jerome, F.; Luque, R. In *Bio-Based Solvents*; Jerome, F., Luque, R., Eds.; Wiley: New York, 2017.
- (92) Shanks, B. H.; Keeling, P. L. Bioprivileged Molecules: Creating Value from Biomass. *Green Chem.* **2017**, *19* (14), 3177–3185.
- (93) Paggiola, G.; Van Stempvoort, S.; Bustamante, J.; Vega Barbero, J. M.; Hunt, A. J.; Clark, J. H. Can Bio-Based Chemicals Meet Demand? Global and Regional Case-Study Around Citrus Waste-Derived Limonene as a Solvent for Cleaning Applications. *Biofuels, Bioprod. Biorefin.* **2016**, *10*, 686–698.
- (94) Ciriminna, R.; Lomeli-Rodriguez, M.; Demma Carà, P.; Lopez-Sanchez, J. A.; Pagliaro, M. Limonene: A Versatile Chemical of the Bioeconomy. *Chem. Commun.* **2014**, *50*, 15288–15296.
- (95) Tobiszewski, M.; Namieśnik, J.; Pena-Pereira, F. Environmental Risk-Based Ranking of Solvents Using the Combination of a Multimedia Model and Multi-Criteria Decision Analysis. *Green Chem.* **2017**, *19*, 1034–1042.
- (96) Commission Regulation (EU) No. 348/2013. *Off. J. Eur. Union* **2013**, L 108/1.
- (97) Fiorentino, G.; Ripa, M.; Ulgiati, S. Chemicals From Biomass: Technological Versus Environmental Feasibility. A Review. *Biofuels, Bioprod. Biorefin.* **2017**, *11*, 195–214.
- (98) Brandt, A.; Gräsvik, J.; Hallett, J. P.; Welton, T. Deconstruction of Lignocellulosic Biomass with Ionic Liquids. *Green Chem.* **2013**, *15*, 550–583.
- (99) Farran, A.; Cai, C.; Sandoval, M.; Xu, Y.; Liu, J.; Hernaiz, M. J.; Linhardt, R. J. Green Solvents in Carbohydrate Chemistry: From Raw Materials to Fine Chemicals. *Chem. Rev.* **2015**, *115* (14), 6811–6853.
- (100) Nagamori, M.; Funazukuri, T. Glucose Production by Hydrolysis of Starch under Hydrothermal Conditions. *J. Chem. Technol. Biotechnol.* **2004**, *79* (3), 229–233.
- (101) HAISSIG, B. E.; DICKSON, R. E. Starch Measurement in Plant Tissue Using Enzymatic Hydrolysis. *Physiol. Plant.* **1979**, *47* (2), 151–157.
- (102) Onda, A.; Ochi, T.; Yanagisawa, K. Selective Hydrolysis of Cellulose into Glucose over Solid Acid Catalysts. *Green Chem.* **2008**, *10* (10), 1033.
- (103) Kunamneni, A.; Singh, S. Response Surface Optimization of Enzymatic Hydrolysis of Maize Starch for Higher Glucose Production. *Biochem. Eng. J.* **2005**, *27* (2), 179–190.
- (104) Hegner, J.; Pereira, K. C.; DeBoef, B.; Lucht, B. L. Conversion of Cellulose to Glucose and Levulinic Acid via Solid-Supported Acid Catalysis. *Tetrahedron Lett.* **2010**, *51* (17), 2356–2358.
- (105) Pace, V.; Hoyos, P.; Castoldi, L.; Domínguez De María, P.; Alcántara, A. R. 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry. *ChemSusChem* **2012**, *5* (8), 1369–1379.
- (106) Alonso, D. M.; Wettstein, S. G.; Dumesic, J. A. Gamma-Valerolactone, a Sustainable Platform Molecule Derived from Lignocellulosic Biomass. *Green Chem.* **2013**, *15*, 584–595.
- (107) Fegyverneki, D.; Orha, L.; Láng, G.; Horváth, I. T. Gamma-Valerolactone-Based Solvents. *Tetrahedron* **2010**, *66*, 1078–1081.
- (108) Antonucci, V.; Coleman, J.; Ferry, J. B.; Johnson, N.; Mathe, M.; Scott, J. P.; Xu, J. Toxicological Assessment of 2-Methyltetrahydrofuran and Cyclopentyl Methyl Ether in Support of Their Use in Pharmaceutical Chemical Process Development. *Org. Process Res. Dev.* **2011**, *15* (4), 939–941.
- (109) Bozell, J. J.; Moens, L.; Elliott, D. C.; Wang, Y.; Neuenschwander, G. G.; Fitzpatrick, S. W.; Bilski, R. J.; Jarnefeld, J. L. Production of Levulinic Acid and Use as a Platform Chemical for Derived Products. *Resour. Conserv. Recycl.* **2000**, *28* (3–4), 227–239.
- (110) Ashcroft, C. P.; Dunn, P. J.; Hayler, J. D.; Wells, A. S. Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997–2012. *Org. Process Res. Dev.* **2015**, *19*, 740–747.
- (111) Slater, C. S.; Savelski, M. J.; Hitchcock, D.; Cavanagh, E. J. Environmental Analysis of the Life Cycle Emissions of 2-Methyl Tetrahydrofuran Solvent Manufactured From Renewable Resources. *J. Environ. Sci. Health, Part A: Toxic/Hazard. Subst. Environ. Eng.* **2016**, *51*, 487–494.
- (112) Khoo, H. H.; Wong, L. L.; Tan, J.; Isoni, V.; Sharratt, P. Synthesis of 2-Methyl Tetrahydrofuran from Various Lignocellulosic Feedstocks: Sustainability Assessment via LCA. *Resour. Conserv. Recycl.* **2015**, *95*, 174–182.
- (113) Hayes, D. J.; Fitzpatrick, S.; Hayes, M. H. B.; Ross, J. R. H. The Biofine Process – Production of Levulinic Acid, Furfural, and Formic Acid from Lignocellulosic Feedstocks. *Biorefineries-Industrial Processes and Products*; Wiley-VCH Verlag GmbH: New York, 2008; pp 139–164.
- (114) Mondal, M.; Bora, U. Eco-Friendly Suzuki–Miyaura Coupling of Arylboronic Acids to Aromatic Ketones Catalyzed by the Oxime-Palladacycle in Biosolvent 2-MeTHF. *New J. Chem.* **2016**, *40* (4), 3119–3123.
- (115) Monticelli, S.; Castoldi, L.; Murgia, I.; Senatore, R.; Mazzeo, E.; Wackerlig, J.; Urban, E.; Langer, T.; Pace, V. Recent Advancements on the Use of 2-Methyltetrahydrofuran in Organometallic Chemistry. *Monatsh. Chem.* **2017**, *148*, 37–48.
- (116) Wright, W. R. H.; Palkovits, R. Development of Heterogeneous Catalysts for the Conversion of Levulinic Acid to  $\gamma$ -Valerolactone. *ChemSusChem* **2012**, *5* (9), 1657–1667.
- (117) Omoriy, U.; Page, S.; Hallett, J.; Miller, P. W. Homogeneous Catalyzed Reactions of Levulinic Acid: To Gamma-Valerolactone and beyond. *ChemSusChem* **2016**, *9*, 2037–2047.
- (118) Demirbas, A. Future Hydrogen Economy and Policy. *Energy Sources, Part B* **2017**, *12*, 172–181.
- (119) Khetkorn, W.; Rastogi, R. P.; Incharoensakdi, A.; Lindblad, P.; Madamwar, D.; Pandey, A.; Larroche, C. Microalgal Hydrogen Production – A Review. *Bioresour. Technol.* **2017**, *243*, 1194–1206.
- (120) Singh, L.; Wahid, Z. a. Methods for Enhancing Bio-Hydrogen Production from Biological Process: A Review. *J. Ind. Eng. Chem.* **2015**, *21*, 70–80.
- (121) Zhang, Z. Synthesis of  $\gamma$ -Valerolactone from Carbohydrates and Its Applications. *ChemSusChem* **2016**, *9* (2), 156–171.
- (122) Zhou, H.; Song, J.; Kang, X.; Hu, J.; Yang, Y.; Fan, H.; Meng, Q.; Han, B. One-Pot Conversion of Carbohydrates into Gamma-Valerolactone Catalyzed by Highly Cross-Linked Ionic Liquid Polymer and Co/TiO<sub>2</sub>. *RSC Adv.* **2015**, *5* (20), 15267–15273.
- (123) Deng, J.; Wang, Y.; Pan, T.; Xu, Q.; Guo, Q.-X.; Fu, Y. Conversion of Carbohydrate Biomass to  $\gamma$ -Valerolactone by Using Water-Soluble and Reusable Iridium Complexes in Acidic Aqueous Media. *ChemSusChem* **2013**, *6* (7), 1163–1167.



- (124) Cui, J.; Tan, J.; Deng, T.; Cui, X.; Zheng, H.; Zhu, Y.; Li, Y. Direct Conversion of Carbohydrates to  $\gamma$ -Valerolactone Facilitated by a Solvent Effect. *Green Chem.* **2015**, *17* (5), 3084–3089.
- (125) Wong, C. Y. Y.; Choi, A. W.-T.; Lui, M. Y.; Fridrich, B.; Horváth, A. K.; Mika, L. T.; Horváth, I. T. Stability of Gamma-Valerolactone under Neutral, Acidic, and Basic Conditions. *Struct. Chem.* **2017**, *28* (2), 423–429.
- (126) Luterbacher, J. S.; Rand, J. M.; Alonso, D. M.; Han, J.; Youngquist, J. T.; Maravelias, C. T.; Pfeleger, B. F.; Dumesic, J. A. Nonenzymatic Sugar Production from Biomass Using Biomass-Derived  $\gamma$ -Valerolactone. *Science (Washington, DC, U. S.)* **2014**, *343* (6168), 277–280.
- (127) Klein-Marcuschamer, D.; Oleskowicz-Popiel, P.; Simmons, B. A.; Blanch, H. W. The Challenge of Enzyme Cost in the Production of Lignocellulosic Biofuels. *Biotechnol. Bioeng.* **2012**, *109*, 1083–1087.
- (128) Luterbacher, J. S.; Azarpira, A.; Motagamwala, A. H.; Lu, F.; Ralph, J.; Dumesic, J. A. Lignin Monomer Production Integrated into the Gamma-Valerolactone Sugar Platform. *Energy Environ. Sci.* **2015**, *8*, 2657–2663.
- (129) Azadi, P.; Carrasquillo-Flores, R.; Pagán-Torres, Y. J.; Gürbüz, E. I.; Farnood, R.; Dumesic, J. A. Green Chemistry Catalytic Conversion of Biomass Using Solvents Derived from Lignin. *Green Chem.* **2012**, *14*, 1573.
- (130) Liu, X.; Yan, P.; Xu, W.; Zhang, Z. C.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; et al. Structure Dependent Toxicity of Lignin Phenolics and PEG Detoxification in VHG Ethanol Fermentation. *RSC Adv.* **2016**, *6* (102), 99924–99932.
- (131) Han, J. Process Design and Techno-Economic Evaluation for Catalytic Production of Cellulosic  $\gamma$ -Valerolactone Using Lignin Derived Propyl Guaiacol. *J. Ind. Eng. Chem.* **2017**, *52*, 218–223.
- (132) Han, J. Biorenewable Strategy for Catalytic  $\epsilon$ -Caprolactam Production Using Cellulose- and Hemicellulose-Derived  $\gamma$ -Valerolactone. *ACS Sustainable Chem. Eng.* **2017**, *5* (2), 1892–1898.
- (133) Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanari, D.; Marrocchi, A.; Drees, M.; Facchetti, A.; Vaccaro, L. A Biomass-Derived Safe Medium to Replace Toxic Dipolar Solvents and Access Cleaner Heck Coupling Reactions. *Green Chem.* **2015**, *17* (1), 365–372.
- (134) Lancaster, M. *Green Chemistry: An Introductory Text*. RSC Paperbacks; Royal Society of Chemistry: UK, 2007.
- (135) Yan, K.; Yang, Y.; Chai, J.; Lu, Y. Catalytic Reactions of Gamma-Valerolactone: A Platform to Fuels and Value-Added Chemicals. *Appl. Catal., B* **2015**, *179*, 292–304.
- (136) Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H. Dihydrolevoglucosenone (Cyrene) as a Bio-Based Alternative for Dipolar Aprotic Solvents. *Chem. Commun.* **2014**, *50* (68), 9650–9652.
- (137) George Huber, P. W.; Krishna, S. H.; McClelland, D. J.; Rashke, Q. A.; Dumesic, J. A.; Huber, G. W. Green Chemistry Cutting-Edge Research for a Greener Sustainable Future Hydrogenation of Levoglucosenone to Renewable Chemicals. *Green Chem.* **2017**, *19*, 1197–1408.
- (138) Su, Y.; Brown, H. M.; Huang, X.; Zhou, X.; Amonette, J. E.; Zhang, Z. C. Single-Step Conversion of Cellulose to 5-Hydroxymethylfurfural (HMF), a Versatile Platform Chemical. *Appl. Catal., A* **2009**, *361* (1–2), 117–122.
- (139) He, J.; Liu, M.; Huang, K.; Walker, T. W.; Maravelias, C. T.; Dumesic, J. A.; Huber, G. W. Production of Levoglucosenone and 5-Hydroxymethylfurfural from Cellulose in Polar Aprotic Solvent–water Mixtures. *Green Chem.* **2017**, *19* (15), 3642–3653.
- (140) Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H. Dihydrolevoglucosenone (Cyrene) as a Bio-Based Alternative for Dipolar Aprotic Solvents. *Chem. Commun.* **2014**, *50* (68), 9650–9652.
- (141) Zhang, J.; White, G. B.; Ryan, M. D.; Hunt, A. J.; Katz, M. J. Dihydrolevoglucosenone (Cyrene) As a Green Alternative to *N,N*-Dimethylformamide (DMF) in MOF Synthesis. *ACS Sustainable Chem. Eng.* **2016**, *4* (12), 7186–7192.
- (142) Mistry, L.; Mapesa, K.; Bousfield, T. W.; Camp, J. E. Synthesis of Ureas in the Bio-Alternative Solvent Cyrene. *Green Chem.* **2017**, *19*, 2123.
- (143) Salavagione, H. J.; Sherwood, J.; De Bruyn, M.; Budarin, V. L.; Ellis, G. J.; Clark, J. H.; Shuttleworth, P. S. Green Chemistry Cutting-Edge Research for a Greener Sustainable Future Identification of High Performance Solvents for the Sustainable Processing of Graphene. *Green Chem.* **2017**, *19* (11), 2465–2698.
- (144) Wilson, K. L.; Kennedy, A. R.; Murray, J.; Greatrex, B.; Jamieson, C.; Watson, A. J. B. Scope and Limitations of a DMF Bio-Alternative within Sonogashira Cross-Coupling and Cacchi-Type Annulation. *Beilstein J. Org. Chem.* **2016**, *12* (1), 2005–2011.
- (145) *Ionic Liquids in Synthesis*; Welton, T., Wasserscheid, P., Eds.; Wiley-VCH: New York, 2008.
- (146) Wilkes, J. S. A Short History of Ionic Liquids—from Molten Salts to Neoteric Solvents. *Green Chem.* **2002**, *4*, 73–80.
- (147) Armstrong, J. P.; Hurst, C.; Jones, R. G.; Licence, P.; Lovelock, K. R. J.; Satterley, C. J.; Villar-Garcia, I. J. Vapourisation of Ionic Liquids. *Phys. Chem. Chem. Phys.* **2007**, *9*, 982–990.
- (148) Perez de los Rios, A.; Irabien, A.; Hollmann, F.; Hernandez Fernandez, F. J. Ionic Liquids: Green Solvents for Chemical Processing. *J. Chem.* **2013**, *2013*, 1–2.
- (149) Welton, T. Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. *Chem. Rev.* **1999**, *99* (8), 2071–2084.
- (150) Sheldon, R. Catalytic Reactions in Ionic Liquids. *Chem. Commun.* **2001**, 2399–2407.
- (151) Kralisch, D.; Stark, A.; Koersten, S.; Kreisel, G.; Ondruschka, B. Energetic, Environmental and Economic Balances: Spice up Your Ionic Liquid Research Efficiency. *Green Chem.* **2005**, *7*, 301–309.
- (152) Martins, I. C. B.; Oliveira, M. C.; Diogo, H. P.; Branco, L. C.; Duarte, M. T. MechanoAPI-ILs: Pharmaceutical Ionic Liquids Obtained through Mechanochemical Synthesis. *ChemSusChem* **2017**, *10* (7), 1360–1363.
- (153) Namboodiri, V. V.; Varma, R. S. Solvent-Free Sonochemical Preparation of Ionic Liquids. *Org. Lett.* **2002**, *4* (18), 3161–3163.
- (154) Varma, R. S.; Namboodiri, V. V. An Expeditious Solvent-Free Route to Ionic Liquids Using Microwaves. *Chem. Commun.* **2001**, *7*, 643–644.
- (155) Fernandez, A. A.; Dongen, M. J. A. Van; Blanco-ania, D.; Kouwer, P. H. J. A Facile Route to Hydrophilic Ionic Liquids. *RSC Adv.* **2014**, *4*, 30267–30273.
- (156) Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Pitner, W. R.; Seddon, K. R.; Rogers, R. D.; Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; et al. Efficient, Halide Free Synthesis of New, Low Cost Ionic Liquids: 1,3-Dialkylimidazolium Salts Containing Methyl- and Ethyl-Sulfate Anions. *Green Chem.* **2002**, *4* (5), 407–413.
- (157) Liu, R.; Zhang, P.; Zhang, S.; Yan, T.; Xin, J.; Zhang, X. Ionic Liquids and Supercritical Carbon Dioxide: Green and Alternative Reaction Media for Chemical Processes. *Rev. Chem. Eng.* **2016**, *32* (6), 587–609.
- (158) Richardson, S. D.; Ternes, T. A. Water Analysis: Emerging Contaminants and Current Issues. *Anal. Chem.* **2011**, *83* (12), 4616–4648.
- (159) Chatel, G.; Naffrechoux, E.; Draye, M. Avoid the PCB Mistakes: A More Sustainable Future for Ionic Liquids. *J. Hazard. Mater.* **2017**, *324*, 773–780.
- (160) Stolte, S.; Matzke, M.; Arning, J. (Eco)Toxicology and Biodegradation of Ionic Liquids. *Ionic Liquids Completely UnCOILED*; John Wiley & Sons, Inc.: New York, 2015; pp 189–208.
- (161) Stolte, S.; Arning, J.; Bottin-Weber, U.; Müller, A.; Pitner, W.-R.; Welz-Biermann, U.; Jastorff, B.; Ranke, J. Effects of Different Head Groups and Functionalised Side Chains on the Cytotoxicity of Ionic Liquids. *Green Chem.* **2007**, *9* (7), 760–767.

- (162) Ranke, J.; Müller, A.; Bottin-Weber, U.; Stock, F.; Stolte, S.; Arning, J.; Störmann, R.; Jastorff, B. Lipophilicity Parameters for Ionic Liquid Cations and Their Correlation to in Vitro Cytotoxicity. *Ecotoxicol. Environ. Saf.* **2007**, *67*, 430–438.
- (163) Piotrowska, A.; Syguda, A.; Wyrwas, B.; Chrzanowski, Ł.; Heipieper, H. J. Toxicity Evaluation of Selected Ammonium-Based Ionic Liquid Forms with MCPP and Dicamba Moieties on *Pseudomonas Putida*. *Chemosphere* **2017**, *167* (7), 114–119.
- (164) Luo, Y. R.; San-Hu, W.; Li, X. Y.; Yun, M. X.; Wang, J. J.; Sun, Z. J. Toxicity of Ionic Liquids on the Growth, Reproductive Ability, and ATPase Activity of Earthworm. *Ecotoxicol. Environ. Saf.* **2010**, *73*, 1046–1050.
- (165) Shao, Y.; Du, Z.; Zhang, C.; Zhu, L.; Wang, J.; Wang, J. Acute Toxicity of Imidazole Nitrate Ionic Liquids with Varying Chain Lengths to Earthworms (*Eisenia Foetida*). *Bull. Environ. Contam. Toxicol.* **2017**, *99*, 213–217.
- (166) Cvjetko Bubalo, M.; Radošević, K.; Radojčić Redovniković, I.; Halambek, J.; Gaurina Srček, V. A Brief Overview of the Potential Environmental Hazards of Ionic Liquids. *Ecotoxicol. Environ. Saf.* **2014**, *99*, 1–12.
- (167) Wang, C.; Wei, Z.; Wang, L.; Sun, P.; Wang, Z. Assessment of Bromide-Based Ionic Liquid Toxicity toward Aquatic Organisms and QSAR Analysis. *Ecotoxicol. Environ. Saf.* **2015**, *115*, 112–118.
- (168) Montalbán, M. G.; Hidalgo, J. M.; Collado-González, M.; Diaz Banos, F. G.; Villora, G. Assessing Chemical Toxicity of Ionic Liquids on *Vibrio Fischeri*: Correlation with Structure and Composition. *Chemosphere* **2016**, *155*, 405–414.
- (169) Ghanem, O. Ben; Mutalib, M. I. A.; Lévêque, J. M.; El-Harbawi, M. Development of QSAR Model to Predict the Ecotoxicity of *Vibrio Fischeri* Using COSMO-RS Descriptors. *Chemosphere* **2017**, *170*, 242–250.
- (170) Perales, E.; García, C. B.; Lomba, L.; Aldea, L.; García, J. I.; Giner, B. Comparative Ecotoxicology Study of Two Neoteric Solvents: Imidazolium Ionic Liquid vs. Glycerol Derivative. *Ecotoxicol. Environ. Saf.* **2016**, *132*, 429–434.
- (171) Aldea, L.; García, J. I.; Mayoral, J. A. Multiphase Enantioselective Kharasch–Sosnovsky Allylic Oxidation Based on Neoteric Solvents and Copper Complexes of Ditopic Ligands. *Dalt. Trans.* **2012**, *41*, 8285–8289.
- (172) Aldea, L.; Fraile, J. M.; García-Marín, H.; García, J. I.; Herrerías, C. I.; Mayoral, J. a.; Pérez, I. Study of the Recycling Possibilities for Azabis(oxazoline)–cobalt Complexes as Catalysts for Enantioselective Conjugate Reduction. *Green Chem.* **2010**, *12* (3), 435.
- (173) Reid, E.S.J.; Prydderch, H.; Spulak, M.; Shimizua, S.; Walker, A. J.; Gathergood, N. Green Profiling of Aprotic versus Protic Ionic Liquids: Synthesis and Microbial Toxicity of Analogous Structures. *Sustain. Chem. Pharm.* **2017**, *7*, 17.
- (174) Costa, S. P. F.; Azevedo, A. M. O.; Pinto, P. C. A. G.; Saraiva, M. L. M. F. S. Environmental Impact of Ionic Liquids: Recent Advances in (Eco)toxicology and (Bio)degradability. *ChemSusChem* **2017**, *10*, 2321–2347.
- (175) Deng, Y.; Beadham, I.; Ghavre, M.; Costa Gomes, M. F.; Gathergood, N.; Husson, P.; Légeret, B.; Quilty, B.; Sancelme, M.; Besse-Hoggan, P. When Can Ionic Liquids Be Considered Readily Biodegradable? Biodegradation Pathways of Pyridinium, Pyrrolidinium and Ammonium-Based Ionic Liquids. *Green Chem.* **2015**, *17* (3), 1479–1491.
- (176) Hou, X. D.; Liu, Q. P.; Smith, T. J.; Li, N.; Zong, M. H. Evaluation of Toxicity and Biodegradability of Cholinium Amino Acids Ionic Liquids. *PLoS One* **2013**, *8* (3), e59145.
- (177) Prydderch, H.; Haif, A.; Spulak, M.; Quilty, B.; Kümmeler, K.; Heise, A.; Gathergood, N. Mandelic Acid Derived Ionic Liquids: Synthesis, Toxicity and Biodegradability. *RSC Adv.* **2017**, *7* (4), 2115–2126.
- (178) Bhadani, A.; Iwabata, K.; Sakai, K.; Koura, S.; Sakai, H.; Abe, M. Sustainable Oleic and Stearic Acid Based Biodegradable Surfactants. *RSC Adv.* **2017**, *7* (17), 10433–10442.
- (179) Haif, A.; Jordan, A.; Westphal, J.; Logunova, E.; Gathergood, N.; Kümmeler, K.; Smiglak, M.; Pringle, J. M.; Lu, X.; Han, L.; et al. On the Way to Greener Ionic Liquids: Identification of a Fully Mineralizable Phenylalanine-Based Ionic Liquid. *Green Chem.* **2016**, *18* (16), 4361–4373.
- (180) Mehrkesh, A.; Karunanithi, A. T. Life-Cycle Perspectives on Aquatic Ecotoxicity of Common Ionic Liquids. *Environ. Sci. Technol.* **2016**, *50* (13), 6814–6821.
- (181) Cuéllar-Franca, R. M.; García-Gutiérrez, P.; Taylor, S. F. R.; Hardacre, C.; Azapagic, A. A Novel Methodology for Assessing the Environmental Sustainability of Ionic Liquids Used for CO<sub>2</sub> Capture. *Faraday Discuss.* **2016**, *192* (0), 283–301.
- (182) Amado Alviz, P. L.; Alvarez, A. J. Comparative Life Cycle Assessment of the Use of an Ionic Liquid ([Bmim]Br) versus a Volatile Organic Solvent in the Production of Acetylsalicylic Acid. *J. Cleaner Prod.* **2016**, *168*, 1614.
- (183) Cevalco, G.; Chiappe, C. Are Ionic Liquids a Proper Solution to Current Environmental Challenges? *Green Chem.* **2014**, *16*, 2375–2385.
- (184) Garcia, M. T.; Gathergood, N.; Scammells, P. J. Biodegradable Ionic Liquids: Part II. Effect of the Anion and Toxicology. *Green Chem.* **2005**, *7*, 9–14.
- (185) Gathergood, N.; Scammells, P. J.; Garcia, M. T. Biodegradable Ionic Liquids: Part III. The First Readily Biodegradable Ionic Liquids. *Green Chem.* **2006**, *8*, 156–160.
- (186) Coleman, D.; Gathergood, N. Biodegradation Studies of Ionic Liquids. *Chem. Soc. Rev.* **2010**, *39*, 600–637.
- (187) Hulsbosch, J.; De Vos, D. E.; Binnemans, K.; Ameloot, R. Biobased Ionic Liquids: Solvents for a Green Processing Industry? *ACS Sustainable Chem. Eng.* **2016**, *4*, 2917–2931.
- (188) Pernak, J.; Czerniak, K.; Biedziak, A.; Marcinkowska, K.; Praczyk, T.; Erfurt, K.; Chrobok, A. Herbicidal Ionic Liquids Derived from Renewable Sources. *RSC Adv.* **2016**, *6*, 52781–52789.
- (189) Plechkova, N. V.; Seddon, K. R. Applications of Ionic Liquids in the Chemical Industry. *Chem. Soc. Rev.* **2008**, *37*, 123–150.
- (190) Baral, N. R.; Shah, A. Techno-Economic Analysis of Cellulose Dissolving Ionic Liquid Pretreatment of Lignocellulosic Biomass for Fermentable Sugars Production. *Biofuels, Bioprod. Biorefin.* **2016**, *10* (1), 70–88.
- (191) Sklavounos, E.; Helminen, J. K. J.; Kyllönen, L.; Kilpeläinen, I.; King, A. W. T. Ionic Liquids: Recycling. *Encyclopedia of Inorganic and Bioinorganic Chemistry*; John Wiley & Sons, Ltd.: New York, 2011.
- (192) Kuzmina, O.; Hallett, J. P. In *Application, Purification, and Recovery of Ionic Liquids*, 1st ed.; Kuzmina, O., Hallett, J. P., Eds.; Elsevier: New York, 2016.
- (193) Deetlefs, M.; Seddon, K. R. Assessing the Greenness of Some Typical Laboratory Ionic Liquid Preparations. *Green Chem.* **2009**, *12*, 17.
- (194) Ebel, K.; Koehler, H.; Gamer, A. O.; Jäckh, R. Imidazole and Derivatives. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2000.
- (195) Socha, A. M.; Parthasarathi, R.; Shi, J.; Pattathil, S.; Whyte, D.; Bergeron, M.; George, A.; Tran, K.; Stavila, V.; Venkatachalam, S.; et al. Efficient Biomass Pretreatment Using Ionic Liquids Derived from Lignin and Hemicellulose. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, E3587–E3595.
- (196) Kilpeläinen, I.; Xie, H.; King, A.; Granstrom, M.; Heikkinen, S.; Argyropoulos, D. S. Dissolution of Wood in Ionic Liquids. *J. Agric. Food Chem.* **2007**, *55*, 9142–9148.
- (197) Reddy, P. A Critical Review of Ionic Liquids for the Pretreatment of Lignocellulosic Biomass. *S. Afr. J. Sci.* **2015**, *111* (11/12), 1–9.
- (198) Yoo, C. G.; Pu, Y.; Ragauskas, A. J. Ionic Liquids: Promising Green Solvents for Lignocellulosic Biomass Utilization. *Curr. Opin. Green Sus. Chem.* **2017**, *5*, 5–11.
- (199) Gadilohar, B. L.; Shankarling, G. S. Choline Based Ionic Liquids and Their Applications in Organic Transformation. *J. Mol. Liq.* **2017**, *227*, 234–261.
- (200) Cheng, F.; Wang, H.; Chatel, G.; Gurau, G.; Rogers, R. D. Facile Pulp of Lignocellulosic Biomass Using Choline Acetate. *Bioresour. Technol.* **2014**, *164*, 394–401.

- (201) Hou, X. D.; Xu, J.; Li, N.; Zong, M. H. Effect of Anion Structures on Cholinium Ionic Liquids Pretreatment of Rice Straw and the Subsequent Enzymatic Hydrolysis. *Biotechnol. Bioeng.* **2015**, *112* (1), 65–73.
- (202) Sun, N.; Parthasarathi, R.; Socha, A. M.; Shi, J.; Zhang, S.; Stavila, V.; Sale, K. L.; Simmons, B. A.; Singh, S. Understanding Pretreatment Efficacy of Four Cholinium and Imidazolium Ionic Liquids by Chemistry and Computation. *Green Chem.* **2014**, *16* (5), 2546–2557.
- (203) Liszka, M. J.; Kang, A.; Konda, N. V. S. N. M.; Tran, K.; Gladden, J. M.; Singh, S.; Keasling, J. D.; Scown, C. D.; Lee, T. S.; Simmons, B. A.; et al. Switchable Ionic Liquids Based on Di-Carboxylic Acids for One-Pot Conversion of Biomass to an Advanced Biofuel. *Green Chem.* **2016**, *18*, 4012–4021.
- (204) Konda, N.; Shi, J.; Singh, S.; Blanch, H. W.; Simmons, B. A.; Klein-Marcuschamer, D. Understanding Cost Drivers and Economic Potential of Two Variants of Ionic Liquid Pretreatment for Cellulosic Biofuel Production. *Biotechnol. Biofuels* **2014**, *7* (1), 86.
- (205) Xu, F.; Sun, J.; Konda, N. V. S. N. M.; Shi, J.; Dutta, T.; Scown, C. D.; Simmons, B. A.; Singh, S. Transforming Biomass Conversion with Ionic Liquids: Process Intensification and the Development of a High-Gravity, One-Pot Process for the Production of Cellulosic Ethanol. *Energy Environ. Sci.* **2016**, *9* (3), 1042–1049.
- (206) Mondal, D.; Sharma, M.; Quental, M. V.; Tavares, A. P. M.; Prasad, K.; Freire, M. G. Suitability of Bio-Based Ionic Liquids for the Extraction and Purification of IgG Antibodies. *Green Chem.* **2016**, *18*, 6071–6081.
- (207) Low, D.; O'Leary, R.; Pujar, N. S. Future of Antibody Purification. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2007**, *848* (1), 48–63.
- (208) Fukaya, Y.; Iizuka, Y.; Sekikawa, K.; Ohno, H. Bio Ionic Liquids: Room Temperature Ionic Liquids Composed Wholly of Biomaterials. *Green Chem.* **2007**, *9* (11), 1155.
- (209) Morandeira, L.; Álvarez, M. S.; Markiewicz, M.; Stolte, S.; Rodríguez, A.; Sanromán, M. Á.; Deive, F. J. Testing True Choline Ionic Liquid Biocompatibility from a Biotechnological Standpoint. *ACS Sustainable Chem. Eng.* **2017**, *5*, 8302.
- (210) Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jérôme, F. Deep Eutectic Solvents: Syntheses, Properties and Applications. *Chem. Soc. Rev.* **2012**, *41*, 7108–7146.
- (211) Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. *Chem. Rev.* **2014**, *114*, 11060–11082.
- (212) Ge, X.; Gu, C.; Wang, X.; Tu, J. Deep Eutectic Solvents (DESs)-Derived Advanced Functional Materials for Energy and Environmental Applications: Challenges, Opportunities, and Future Vision. *J. Mater. Chem. A* **2017**, *5*, 8209–8229.
- (213) Smith, E. L. Deep Eutectic Solvents (DESs) and the Metal Finishing Industry: Where Are They Now? *Trans. Inst. Met. Finish.* **2013**, *91* (5), 241–248.
- (214) Mbous, Y. P.; Hayyan, M.; Hayyan, A.; Wong, W. F.; Hashim, M. A.; Looi, C. Y. Applications of Deep Eutectic Solvents in Biotechnology and bioengineering—Promises and Challenges. *Biotechnol. Adv.* **2017**, *35*, 105–134.
- (215) Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. Deep Eutectic Solvents Formed between Choline Chloride and Carboxylic Acids: Versatile Alternatives to Ionic Liquids. *J. Am. Chem. Soc.* **2004**, *126*, 9142–9147.
- (216) Li, G.; Jiang, Y.; Liu, X.; Deng, D. New Levulinic Acid-Based Deep Eutectic Solvents: Synthesis and Physicochemical Property Determination. *J. Mol. Liq.* **2016**, *222*, 201–207.
- (217) Dai, Y.; van Spronsen, J.; Witkamp, G. J.; Verpoorte, R.; Choi, Y. H. Natural Deep Eutectic Solvents as New Potential Media for Green Technology. *Anal. Chim. Acta* **2013**, *766*, 61–68.
- (218) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. Natural Deep Eutectic Solvents - Solvents for the 21st Century. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063–1071.
- (219) Gutiérrez, M. C.; Ferrer, M. L.; Mateo, C. R.; Monte, F. Del Freeze-Drying of Aqueous Solutions of Deep Eutectic Solvents: A Suitable Approach to Deep Eutectic Suspensions of Self-Assembled Structures. *Langmuir* **2009**, *25*, 5509–5515.
- (220) Crawford, D. E.; Wright, L. A.; James, S. L.; Abbott, A. P. Efficient Continuous Synthesis of High Purity Deep Eutectic Solvents by Twin Screw Extrusion. *Chem. Commun.* **2016**, *52*, 4215–4218.
- (221) Crawford, D. E.; Miskimmin, C. K. G.; Albadarin, A. B.; Walker, G.; James, S. L. Organic Synthesis by Twin Screw Extrusion (TSE): Continuous, Scalable and Solvent-Free. *Green Chem.* **2017**, *19*, 1507–1518.
- (222) Crawford, D. E. Extrusion - Back to the Future: Using an Established Technique to Reform Automated Chemical Synthesis. *Beilstein J. Org. Chem.* **2017**, *13*, 65–75.
- (223) Pena-Pereira, F.; Namieśnik, J. Ionic Liquids and Deep Eutectic Mixtures: Sustainable Solvents for Extraction Processes. *ChemSusChem* **2014**, *7*, 1784–1800.
- (224) Jenkin, G. R. T.; Al-Bassam, A. Z. M.; Harris, R. C.; Abbott, A. P.; Smith, D. J.; Holwell, D. A.; Chapman, R. J.; Stanley, C. J. The Application of Deep Eutectic Solvent Ionic Liquids for Environmentally-Friendly Dissolution and Recovery of Precious Metals. *Miner. Eng.* **2016**, *87*, 18–24.
- (225) Durand, E.; Lecomte, J.; Villeneuve, P. From Green Chemistry to Nature: The Versatile Role of Low Transition Temperature Mixtures. *Biochimie* **2016**, *120*, 119–123.
- (226) Alomar, M. K.; Hayyan, M.; Alsaadi, M. A.; Akib, S.; Hayyan, A.; Hashim, M. A. Glycerol-Based Deep Eutectic Solvents: Physical Properties. *J. Mol. Liq.* **2016**, *215*, 98–103.
- (227) Hayyan, A.; Mjalli, F. S.; Alnashef, I. M.; Al-Wahaibi, T.; Al-Wahaibi, Y. M.; Hashim, M. A. Fruit Sugar-Based Deep Eutectic Solvents and Their Physical Properties. *Thermochim. Acta* **2012**, *541*, 70–75.
- (228) Fischer, V.; Kunz, W. Properties of Sugar-Based Low-Melting Mixtures. *Mol. Phys.* **2014**, *112*, 1241–1245.
- (229) Abbott, A. P.; Harris, R. C.; Ryder, K. S.; D'Agostino, C.; Gladden, L. F.; Mantle, M. D. Glycerol Eutectics as Sustainable Solvent Systems. *Green Chem.* **2011**, *13*, 82–90.
- (230) Leoneti, A. B.; Aragão-Leoneti, V.; de Oliveira, S. V. W. B. Glycerol as a by-Product of Biodiesel Production in Brazil: Alternatives for the Use of Unrefined Glycerol. *Renewable Energy* **2012**, *45*, 138–145.
- (231) Ardi, M. S.; Aroua, M. K.; Hashim, N. A. Progress, Prospect and Challenges in Glycerol Purification Process: A Review. *Renewable Sustainable Energy Rev.* **2015**, *42*, 1164–1173.
- (232) Moity, L.; Benazzouz, A.; Molinier, V.; Nardello-Rataj, V.; Elmekaddem, M. K.; de Caro, P.; Thiébaud-Roux, S.; Gerbaud, V.; Marion, P.; Aubry, J.-M. Glycerol Acetals and Ketals as Bio-Based Solvents: Positioning in Hansen and COSMO-RS Spaces, Volatility and Stability towards Hydrolysis and Autoxidation. *Green Chem.* **2015**, *17* (3), 1779–1792.
- (233) Dai, Y.; Witkamp, G. J.; Verpoorte, R.; Choi, Y. H. Tailoring Properties of Natural Deep Eutectic Solvents with Water to Facilitate Their Applications. *Food Chem.* **2015**, *187*, 14–19.
- (234) Guajardo, N.; Domínguez de María, H. P.; Ahumada, K.; Schreiber, R. A.; Ramírez-Tagle, R.; Crespo, F. A.; Carlesi, C. Water as Cosolvent: Nonviscous Deep Eutectic Solvents for Efficient Lipase-Catalyzed Esterifications. *ChemCatChem* **2017**, *9*, 1393–1396.
- (235) Germani, R.; Orlandini, M.; Tiecco, M.; Del Giacco, T. Novel Low Viscous, Green and Amphiphilic N-Oxides/phenylacetic Acid Based Deep Eutectic Solvents. *J. Mol. Liq.* **2017**, *240*, 233–239.
- (236) Hayyan, M.; Hashim, M. A.; Hayyan, A.; Al-Saadi, M. A.; AlNashef, I. M.; Mirghani, M. E. S.; Saheed, O. K. Are Deep Eutectic Solvents Benign or Toxic? *Chemosphere* **2013**, *90*, 2193–2195.
- (237) Wen, Q.; Chen, J. X.; Tang, Y. L.; Wang, J.; Yang, Z. Assessing the Toxicity and Biodegradability of Deep Eutectic Solvents. *Chemosphere* **2015**, *132*, 63–69.
- (238) Hayyan, M.; Hashim, M. A.; Al-Saadi, M. A.; Hayyan, A.; AlNashef, I. M.; Mirghani, M. E. S. Assessment of Cytotoxicity and Toxicity for Phosphonium-Based Deep Eutectic Solvents. *Chemosphere* **2013**, *93*, 455–459.



- (239) Hayyan, M.; Looi, C. Y.; Hayyan, A.; Wong, W. F.; Hashim, M. A. In Vitro and in Vivo Toxicity Profiling of Ammonium-Based Deep Eutectic Solvents. *PLoS One* **2015**, *10* (2), 1–18.
- (240) de Moraes, P.; Gonçalves, F.; Coutinho, J. A. P.; Ventura, S. P. M. Ecotoxicity of Cholinium-Based Deep Eutectic Solvents. *ACS Sustainable Chem. Eng.* **2015**, *3*, 3398–3404.
- (241) Juneidi, I.; Hayyan, M.; Hashim, M. A. Evaluation of Toxicity and Biodegradability for Cholinium-Based Deep Eutectic Solvents. *RSC Adv.* **2015**, *5*, 83636–83647.
- (242) Hayyan, M.; Mbous, Y. P.; Looi, C. Y.; Wong, W. F.; Hayyan, A.; Salleh, Z.; Mohd-Ali, O. Natural Deep Eutectic Solvents: Cytotoxic Profile. *SpringerPlus* **2016**, *5*, 913.
- (243) Mbous, Y. P.; Hayyan, M.; Wong, W. F.; Looi, C. Y.; Hashim, M. A. Unraveling the Cytotoxicity and Metabolic Pathways of Binary Natural Deep Eutectic Solvent Systems. *Sci. Rep.* **2017**, *7*, 41257.
- (244) Gutiérrez, M. C.; Ferrer, M. L.; Yuste, L.; Rojo, F.; Monte, F. Del Bacteria Incorporation in Deep-Eutectic Solvents through Freezedrying. *Angew. Chem., Int. Ed.* **2010**, *49*, 2158–2162.
- (245) Zamani, P.; Khosropour, A. R. A Combination of Natural Deep Eutectic Solvents and Microflow Technology: A Sustainable Innovation for the Tandem Synthesis of 3-Aminohexahydrocoumarins. *Green Chem.* **2016**, *18*, 6450–6455.
- (246) Li, X.; Row, K. H. Development of Deep Eutectic Solvents Applied in Extraction and Separation. *J. Sep. Sci.* **2016**, *39*, 3505–3520.
- (247) Ruesgas-Ramón, M.; Figueroa-Espinoza, M. C.; Durand, E. Application of Deep Eutectic Solvents (DES) for Phenolic Compounds Extraction: Overview, Challenges, and Opportunities. *J. Agric. Food Chem.* **2017**, *65*, 3591–3601.
- (248) Jiang, W.; Dong, L.; Liu, W.; Guo, T.; Li, H.; Yin, S.; Zhu, W.; Li, H. Biodegradable Choline-like Deep Eutectic Solvents for Extractive Desulfurization of Fuel. *Chem. Eng. Process.* **2017**, *115*, 34–38.
- (249) Sintra, T. E.; Nasirpour, M.; Siopa, F.; Rosatella, A. A.; Gonçalves, F.; Coutinho, J. A. P.; Afonso, C. A. M.; Ventura, S. P. M. Ecotoxicological Evaluation of Magnetic Ionic Liquids. *Ecotoxicol. Environ. Saf.* **2017**, *143*, 315–321.
- (250) van Osch, D. J. G. P.; Zubeir, L. F.; van den Bruinhorst, A.; Rocha, M. A. A.; Kroon, M. C. Hydrophobic Deep Eutectic Solvents as Water-Immiscible Extractants. *Green Chem.* **2015**, *17*, 4518–4521.
- (251) Duan, L.; Dou, L.-L.; Guo, L.; Li, P.; Liu, E.-H. Comprehensive Evaluation of Deep Eutectic Solvents in Extraction of Bioactive Natural Products. *ACS Sustainable Chem. Eng.* **2016**, *4*, 2405–2411.
- (252) Florindo, C.; Branco, L. C.; Marrucho, I. M. Development of Hydrophobic Deep Eutectic Solvents for Extraction of Pesticides from Aqueous Environments. *Fluid Phase Equilib.* **2017**, *448*, 135–142.
- (253) Cvjetko Bubalo, M.; Ćurko, N.; Tomašević, M.; Kovačević Ganić, K.; Radojčić Redovniković, I. Green Extraction of Grape Skin Phenolics by Using Deep Eutectic Solvents. *Food Chem.* **2016**, *200*, 159–166.
- (254) Bosiljkov, T.; Dujmić, F.; Cvjetko Bubalo, M.; Hribar, J.; Vidrih, R.; Brnčić, M.; Zlatić, E.; Radojčić Redovniković, I.; Jokić, S. Natural Deep Eutectic Solvents and Ultrasound-Assisted Extraction: Green Approaches for Extraction of Wine Lees Anthocyanins. *Food Bioprod. Process.* **2017**, *102*, 195–203.
- (255) Chen, J.; Liu, M.; Wang, Q.; Du, H.; Zhang, L. Deep Eutectic Solvent-Based Microwave-Assisted Method for Extraction of Hydrophilic and Hydrophobic Components from Radix Salviae Miltiorrhizae. *Molecules* **2016**, *21*, 1383.
- (256) Ji, Y.; Hou, Y.; Ren, S.; Yao, C.; Wu, W. Removal of the Neutral Oil Entrained in Deep Eutectic Solvents Using an Anti-Extraction Method. *Fuel Process. Technol.* **2017**, *160*, 27–33.
- (257) Haerens, K.; Matthijs, E.; Binnemans, K.; Van der Bruggen, B. Electrochemical Decomposition of Choline Chloride Based Ionic Liquid Analogues. *Green Chem.* **2009**, *11*, 1357–1365.
- (258) Nguyen, H. T.; Tran, P. H. An Extremely Efficient and Green Method for the Acylation of Secondary Alcohols, Phenols and Naphthols with a Deep Eutectic Solvent as the Catalyst. *RSC Adv.* **2016**, *6*, 98365–98368.
- (259) Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. Bio-Renewable Enantioselective Aldol Reaction in Natural Deep Eutectic Solvents. *Green Chem.* **2016**, *18*, 1724–1730.
- (260) Padvi, S. A.; Dalal, D. S. Choline chloride–ZnCl<sub>2</sub>: Recyclable and Efficient Deep Eutectic Solvent for the [2 + 3] Cycloaddition Reaction of Organic Nitriles with Sodium Azide. *Synth. Commun.* **2017**, *47*, 779–787.
- (261) Khandelwal, S.; Tailor, Y. K.; Kumar, M. Deep Eutectic Solvents (DESS) as Eco-Friendly and Sustainable Solvent/catalyst Systems in Organic Transformations. *J. Mol. Liq.* **2016**, *215*, 345–386.
- (262) Marset, X.; Pérez, J. M.; Ramón, D. J. Cross-Dehydrogenative Coupling Reaction Using Copper Oxide Impregnated on Magnetite in Deep Eutectic Solvents. *Green Chem.* **2016**, *18*, 826–833.
- (263) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions. *Angew. Chem., Int. Ed.* **2016**, *55*, 16145–16148.
- (264) Ab Rani, M. A.; Borduas, N.; Colquhoun, V.; Hanley, R.; Johnson, H.; Larger, S.; Lickiss, P. D.; Llopis-Mestre, V.; Luu, S.; Mogstad, M.; et al. The Potential of Methylsiloxanes as Solvents for Synthetic Chemistry Applications. *Green Chem.* **2014**, *16*, 1282–1296.
- (265) Heldebrandt, D. J.; Witt, H. N.; Walsh, S. M.; Ellis, T.; Rauscher, J.; Jessop, P. G. Liquid Polymers as Solvents for Catalytic Reductions. *Green Chem.* **2006**, *8*, 807–815.
- (266) Harrell, M. L.; Malinski, T.; Torres-López, C.; Gonzalez, K.; Suriboot, J.; Bergbreiter, D. E. Alternatives for Conventional Alkane Solvents. *J. Am. Chem. Soc.* **2016**, *138*, 14650–14657.
- (267) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. Polyethylene Glycol and Solutions of Polyethylene Glycol as Green Reaction Media. *Green Chem.* **2005**, *7*, 64–82.
- (268) Watson, G. K.; Jones, N. The Biodegradation of Polyethylene Glycols by Sewage Bacteria. *Water Res.* **1977**, *11*, 95–100.
- (269) Sarkar, S.; Basak, P.; Adhikari, B. Biodegradation of Polyethylene Glycol-Based Polyether Urethanes. *Polym.-Plast. Technol. Eng.* **2011**, *50*, 80–88.
- (270) Kawai, F.; Yamanaka, H. Biodegradation of Polyethylene Glycol by Symbiotic Mixed Culture (Obligate Mutualism). *Arch. Microbiol.* **1986**, *146*, 125–129.
- (271) Mansour, F. R.; Zhou, L.; Danielson, N. D. Applications of Poly(Ethylene)Glycol (PEG) in Separation Science. *Chromatographia* **2015**, *78*, 1427–1442.
- (272) Zhu, Y.; Romain, C.; Williams, C. K. Sustainable Polymers from Renewable Resources. *Nature* **2016**, *540*, 354–362.
- (273) Pereira, B.; Zhang, H.; De Mey, M.; Lim, C. G.; Li, Z. J.; Stephanopoulos, G. Engineering a Novel Biosynthetic Pathway in Escherichia Coli for Production of Renewable Ethylene Glycol. *Biotechnol. Bioeng.* **2016**, *113*, 376–383.
- (274) Gong, J.; You, F. Value-Added Chemicals from Microalgae: Greener, More Economical, or Both? *ACS Sustainable Chem. Eng.* **2015**, *3*, 82–96.
- (275) Sun, J.; Liu, H. Selective Hydrogenolysis of Biomass-Derived Xylitol to Ethylene Glycol and Propylene Glycol on Supported Ru Catalysts. *Green Chem.* **2011**, *13*, 135–142.
- (276) Asenjo, J. A.; Andrews, B. A. Aqueous Two-Phase Systems for Protein Separation: A Perspective. *J. Chromatogr. A* **2011**, *1218*, 8826–8835.
- (277) Pereira, J. F. B.; Kurnia, K. A.; Freire, M. G.; Coutinho, J. A. P.; Rogers, R. D. Controlling the Formation of Ionic-Liquid-Based Aqueous Biphasic Systems by Changing the Hydrogen-Bonding Ability of Polyethylene Glycol End Groups. *ChemPhysChem* **2015**, *16*, 2219–2225.
- (278) Passos, H.; Luís, A.; Coutinho, J. A. P.; Freire, M. G. Thermoreversible (Ionic-Liquid-Based) Aqueous Biphasic Systems. *Sci. Rep.* **2016**, *6* (20276), 1–7.
- (279) Harris, J.; Daugulis, A. J. Biocompatibility of Low Molecular Weight Polymers for Two-Phase Partitioning Bioreactors. *Biotechnol. Bioeng.* **2015**, *112*, 2450–2458.

- (280) Moreno-Pérez, S.; Orrego, A. H.; Romero-Fernández, M.; Trobo-Maseda, L.; Martins-Deoliveira, S.; Munilla, R.; Fernández-Lorente, G.; Guisan, J. M. Intense PEGylation of Enzyme Surfaces: Relevant Stabilizing Effects. *Methods Enzymol.* **2016**, 571, 55–72.
- (281) Vafaezadeh, M.; Hashemi, M. M. Polyethylene Glycol (PEG) as a Green Solvent for Carbon-Carbon Bond Formation Reactions. *J. Mol. Liq.* **2015**, 207, 73–79.
- (282) Kong, D.-L.; He, L.-N.; Wang, J.-Q. Polyethylene Glycol-Enhanced Chemoselective Synthesis of Organic Carbamates from Amines, CO<sub>2</sub>, and Alkyl Halides. *Synth. Commun.* **2011**, 41, 3298–3307.
- (283) Ohki, T.; Harada, M.; Okada, T. Structural and Thermodynamic Aspects of Ionic Solvation in Concentrated Aqueous Poly(ethylene Glycol). *J. Phys. Chem. B* **2007**, 111, 7245–7252.
- (284) Rogers, R. D.; Zhang, J.; Bauer, C. B. Effects of Choice of Anion (X = Cl<sup>-</sup>, SCN<sup>-</sup>, NO<sub>3</sub><sup>-</sup>) and Polyethylene Glycol (PEG) Chain Length on the Local and Supramolecular Structures of LnX<sub>3</sub>/PEG Complexes. *J. Alloys Compd.* **1997**, 249, 41–48.
- (285) Billault, I.; Pessel, F.; Petit, A.; Turgis, R.; Scherrmann, M.-C. Investigation of the copper(I) Catalyzed Azide-Alkyne Cycloaddition Reactions (CuAAC) in Molten PEG2000. *New J. Chem.* **2015**, 39, 1986–1995.
- (286) Priyadarshani, N.; Suriboot, J.; Bergbreiter, D. E. Recycling Pd Colloidal Catalysts Using Polymeric Phosphine Ligands and Polyethylene as a Solvent. *Green Chem.* **2013**, 15, 1361–1367.
- (287) Yedage, S. L.; Bhanage, B. M. Ru(II)/PEG-400 as a Highly Efficient and Recyclable Catalytic Media for Annulation and Olefination Reactions via C–H Bond Activation. *Green Chem.* **2016**, 18, 5635–5642.
- (288) Zhao, H.; Zhang, T.; Yan, T.; Cai, M. Recyclable and Reusable [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub>/Cu(OAc)<sub>2</sub>/PEG-400/H<sub>2</sub>O System for Oxidative C–H Bond Alkenylations: Green Synthesis of Phthalides. *J. Org. Chem.* **2015**, 80, 8849–8855.
- (289) Feu, K. S.; de la Torre, A. F.; Silva, S.; de Moraes Junior, M. A. F.; Corrêa, A. G.; Paixão, M. W. Polyethylene Glycol (PEG) as a Reusable Solvent Medium for an Asymmetric Organocatalytic Michael Addition. Application to the Synthesis of Bioactive Compounds. *Green Chem.* **2014**, 16, 3169–3174.
- (290) Tiwari, A. R.; Bhanage, B. M. Polythene Glycol (PEG) as a Reusable Solvent System for the Synthesis of 1,3,5-Triazines via Aerobic Oxidative Tandem Cyclization of Benzylamines and N-Substituted Benzylamines with Amidines under Transition Metal-Free Conditions. *Green Chem.* **2016**, 18, 144–149.
- (291) Gu, Y. Multicomponent Reactions in Unconventional Solvents: State of the Art. *Green Chem.* **2012**, 14, 2091–2128.
- (292) Kumari, S.; Khurana, J. M. One-Pot Four Component Condensation for the Synthesis of Novel Dispirooxindole Pyrrolidine Linked 1,2,3-Triazoles via Stereo- and Regioselective [3 + 2] Cycloaddition Reaction in PEG-400. *Heteroat. Chem.* **2016**, 27, 396–403.
- (293) Khan, M. N.; Karamthulla, S.; Choudhury, L. H.; Haque Faizi, M. S. Ultrasound Assisted Multicomponent Reactions: A Green Method for the Synthesis of Highly Functionalized Selenopyridines Using Reusable Polyethylene Glycol as Reaction Medium. *RSC Adv.* **2015**, 5, 22168–22172.
- (294) Bhattacharyya, B.; Kundu, A.; Das, A.; Dhara, K.; Guchhait, N. One-Pot Protocol for J-Aggregated Anthraimidazoleiones Catalyzed by Phosphotungstic Acid in PEG-400 under Aerobic Condition. *RSC Adv.* **2016**, 6 (26), 21907–21916.
- (295) Díaz-Cruz, C.; Almonso Nuñez, G.; Espinoza-Gómez, H.; Flores-López, L. Z. Effect of Molecular Weight of PEG or PVA as Reducing-Stabilizing Agent in the Green Synthesis of Silver-Nanoparticles. *Eur. Polym. J.* **2016**, 83, 265–277.
- (296) Chen, M.; Wang, W.; Wu, X. One-Pot Green Synthesis of Water-Soluble Carbon Nanodots with Multicolor Photoluminescence from Polyethylene Glycol. *J. Mater. Chem. B* **2014**, 2 (25), 3937.
- (297) Ng, Y. H.; Di Lena, F.; Chai, C. L. L. Atom Transfer Radical Polymerization (ATRP) of Methyl Methacrylate Mediated by iron(II) Chloride in the Presence of Polyethers as Both Solvents and Ligands. *Macromol. Res.* **2012**, 20, 552–558.
- (298) Perrier, S.; Gemici, H.; Li, S. Poly(ethylene Glycol) as Solvent for Transition Metal Mediated Living Radical Polymerisation. *Chem. Commun.* **2004**, 604–605.
- (299) Matsuoka, S.; Kikuno, T.; Takagi, K.; Suzuki, M. Poly(ethylene Glycol)-Induced Acceleration of Free Radical Polymerization of Methyl Methacrylate: Effects of Highly Viscous Solvent and Kinetic Study. *Polym. J.* **2010**, 42, 368–374.
- (300) Gao, C.; Zhou, H.; Qu, Y.; Wang, W.; Khan, H.; Zhang, W. In Situ Synthesis of Block Copolymer Nanoassemblies via Polymerization-Induced Self-Assembly in Poly(ethylene Glycol). *Macromolecules* **2016**, 49, 3789–3798.
- (301) Hong, M.; Chen, E. Y.-X. Chemically Recyclable Polymers: A Circular Economy Approach to Sustainability. *Green Chem.* **2017**, 19, 3692–3706.
- (302) Vekariya, R. H.; Patel, H. D. Sulfonated Polyethylene Glycol (PEG-OSO<sub>3</sub>H) as a Polymer Supported Biodegradable and Recyclable Catalyst in Green Organic Synthesis: Recent Advances. *RSC Adv.* **2015**, 5, 49006–49030.
- (303) Hayashi, Y. Pot Economy and One-Pot Synthesis. *Chem. Sci.* **2016**, 7, 866–880.
- (304) Eckert, C. A.; Knutson, B. L.; Debenedetti, P. G. Supercritical Fluids as Solvents for Chemical and Materials Processing. *Nature* **1996**, 383, 313–318.
- (305) Jessop, P. G.; Ikariya, T.; Noyori, R. Homogeneous Catalysis in Supercritical Fluids. *Chem. Rev.* **1999**, 99, 475–493.
- (306) Kerton, F. *Alternative Solvents for Green Chemistry*; The Royal Society of Chemistry: UK, 2009.
- (307) Herrero, M.; Mendiola, J. A.; Ibanez, E. Gas Expanded Liquids and Switchable Solvents. *Curr. Opin. Green Sus. Chem.* **2017**, 5, 24–30.
- (308) Subramaniam, B.; Chaudhari, R. V.; Chaudhari, A. S.; Akien, G. R.; Xie, Z. Supercritical Fluids and Gas-Expanded Liquids as Tunable Media for Multiphase Catalytic Reactions. *Chem. Eng. Sci.* **2014**, 115, 3–18.
- (309) Jessop, P. G.; Jessop, D. A.; Fu, D.; Phan, L. Solvatochromic Parameters for Solvents of Interest in Green Chemistry. *Green Chem.* **2012**, 14, 1245–1259.
- (310) Wyatt, V. T.; Bush, D.; Lu, J.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. Determination of Solvatochromic Solvent Parameters for the Characterization of Gas-Expanded Liquids. *J. Supercrit. Fluids* **2005**, 36, 16–22.
- (311) Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. Sustainable Reactions in Tunable Solvents. *J. Phys. Chem. B* **2004**, 108, 18108–18118.
- (312) Baiker, A. Supercritical Fluids in Heterogeneous Catalysis. *Chem. Rev.* **1999**, 99, 453–473.
- (313) Marcus, Y. Solvatochromic Probes in Supercritical Fluids. *J. Phys. Org. Chem.* **2005**, 18, 373–384.
- (314) Gurina, D. L.; Antipova, M. L.; Odintsova, E. G.; Petrenko, V. E. The Study of Peculiarities of Parabens Solvation in Methanol- and Acetone-Modified Supercritical Carbon Dioxide by Computer Simulation. *J. Supercrit. Fluids* **2017**, 126, 47–54.
- (315) Gurina, D. L.; Odintsova, E. G.; Golubev, V. A.; Antipova, M. L.; Petrenko, V. E. Features of Solvation of Phenolic Acids in Supercritical Carbon Dioxide Modified by Methanol and Acetone. *J. Supercrit. Fluids* **2017**, 124, 50–56.
- (316) Herrero, M.; Mendiola, J. A.; Cifuentes, A.; Ibáñez, E. Supercritical Fluid Extraction: Recent Advances and Applications. *J. Chromatogr. A* **2010**, 1217, 2495–2511.
- (317) Reverchon, E.; De Marco, I. Supercritical Fluid Extraction and Fractionation of Natural Matter. *J. Supercrit. Fluids* **2006**, 38, 146–166.
- (318) Pinelo, M.; Ruiz-Rodríguez, A.; Sineiro, J.; Señoráns, F. J.; Reglero, G.; Núñez, M. J. Supercritical Fluid and Solid-Liquid Extraction of Phenolic Antioxidants From Grape Pomace: A Comparative Study. *Eur. Food Res. Technol.* **2007**, 226, 199–205.
- (319) Santos, E. R. M.; Oliveira, H. N. M.; Oliveira, E. J.; Azevedo, S. H. G.; Jesus, A. A.; Medeiros, A. M.; Dariva, C.; Sousa, E. M. B. D. Supercritical Fluid Extraction of Rumex Acetosa L. Roots: Yield,



Composition, Kinetics, Bioactive Evaluation and Comparison With Conventional Techniques. *J. Supercrit. Fluids* **2017**, *122*, 1–9.

(320) Villanueva Bermejo, D.; Angelov, I.; Vicente, G.; Stateva, R. P.; Rodriguez García-Risco, M.; Reglero, G.; Ibañez, E.; Fornari, T. Extraction of Thymol from Different Varieties of Thyme Plants Using Green Solvents. *J. Sci. Food Agric.* **2015**, *95*, 2901–2907.

(321) Liu, X. L.; Zhao, M. M.; Wang, J. S.; Luo, W. Antimicrobial and Antioxidant Activity of Emblica Extracts Obtained by Supercritical Carbon Dioxide Extraction and Methanol Extraction. *J. Food Biochem.* **2009**, *33*, 307–330.

(322) Lu, Y.; Mu, B.; Zhu, B.; Wu, K.; Gou, Z.; Li, L.; Cui, L.; Liang, N. Comparison of Supercritical Fluid Extraction and Liquid Solvent Extraction on Antitumor Diterpenoid from *Pteris Semipinnata* L. *Sep. Sci. Technol.* **2012**, *47*, 2436–2443.

(323) Marañón, J. P.; Manikandan, S.; Priya, B.; Gurumoorthis, P. Box-Behnken Design Based Multi-Response Analysis and Optimization of Supercritical Carbon Dioxide Extraction of Bioactive Flavonoid Compounds From Tea (*Camellia Sinensis* L.) Leaves. *J. Food Sci. Technol.* **2015**, *52* (1), 92–104.

(324) Hedayati, A.; Ghoreishi, S. M. Supercritical Carbon Dioxide Extraction of Glycyrrhizic Acid From Licorice Plant Root Using Binary Entrainer: Experimental Optimization via Response Surface Methodology. *J. Supercrit. Fluids* **2015**, *100*, 209–217.

(325) Santos, P.; Aguiar, A. C.; Barbero, G. F.; Rezende, C. A.; Mart?nez, J. Supercritical Carbon Dioxide Extraction of Capsaicinoids From Malagueta Pepper (*Capsicum Frutescens* L.) Assisted by Ultrasound. *Ultrason. Sonochem.* **2015**, *22*, 78–88.

(326) Bertuol, D. A.; Machado, C. M.; Silva, M. L.; Calgaro, C. O.; Dotto, G. L.; Tanabe, E. H. Recovery of Cobalt from Spent Lithium-Ion Batteries Using Supercritical Carbon Dioxide Extraction. *Waste Manage.* **2016**, *51*, 245–251.

(327) Brunner, G. Applications of Supercritical Fluids. *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 321–342.

(328) Vigano, J.; Zabet, G. L.; Martinez, J. Supercritical Fluid and Pressurized Liquid Extractions of Phytonutrients from Passion Fruit by-Products: Economic Evaluation of Sequential Multi-Stage and Single-Stage Processes. *J. Supercrit. Fluids* **2017**, *122*, 88–98.

(329) de Aguiar, A. C.; Osorio-Tobón, J. F.; Silva, L. P. S.; Barbero, G. F.; Martínez, J. Economic Analysis of Oleoresin Production from Malagueta Peppers (*Capsicum Frutescens*) by Supercritical Fluid Extraction. *J. Supercrit. Fluids* **2018**, *133* (September 2017), 86–93.

(330) Rocha-Urbe, J. A.; Novelo-Pérez, J. I.; Ruiz-Mercado, A. C. Cost Estimation for CO<sub>2</sub> Supercritical Extraction Systems and Manufacturing Cost for Habanero Chili. *J. Supercrit. Fluids* **2014**, *93*, 38–41.

(331) Rosa, P. T. V.; Meireles, M. A. A. Rapid Estimation of the Manufacturing Cost of Extracts Obtained by Supercritical Fluid Extraction. *J. Food Eng.* **2005**, *67* (1–2), 235–240.

(332) *Scale-up of Extraction Processes*; Rostagno, M. A., Prado, J. M., Eds.; Royal Society of Chemistry: UK, 2013.

(333) Zabet, G. L.; Bitencourte, I. P.; Tres, M. V.; Meireles, M. A. A. Process Intensification for Producing Powdered Extracts Rich in Bioactive Compounds: An Economic Approach. *J. Supercrit. Fluids* **2017**, *119*, 261–273.

(334) Kurniawansyah, F.; Mammucari, R.; Tandia, A.; Foster, N. R. Scale – Up and Economic Evaluation of the Atomized Rapid Injection Solvent Extraction Process. *J. Supercrit. Fluids* **2017**, *127*, 208–216.

(335) Moncada, J.; Tamayo, J. A.; Cardona, C. A. Techno-Economic and Environmental Assessment of Essential Oil Extraction from Oregano (*Origanum Vulgare*) and Rosemary (*Rosmarinus Officinalis*) in Colombia. *J. Cleaner Prod.* **2016**, *112*, 172–181.

(336) Razi Parjikaiei, B.; Errico, M.; Bahij El-Houri, R.; Mantell, C.; Frette, X. C.; Christensen, K. V. Process Design and Economic Evaluation of Green Extraction Methods for Recovery of Astaxanthin from Shrimp Waste. *Chem. Eng. Res. Des.* **2017**, *117*, 73–82.

(337) Todd, R.; Baroutian, S. A Techno-Economic Comparison of Subcritical Water, Supercritical CO<sub>2</sub> and Organic Solvent Extraction of Bioactives from Grape Marc. *J. Cleaner Prod.* **2017**, *158*, 349–358.

(338) Jessop, P. G.; Ikariya, T.; Noyori, R. Homogeneous Catalytic Hydrogenation of Supercritical Carbon Dioxide. *Nature* **1994**, *368*, 231–233.

(339) Jessop, P.; Hsiao, Y.; Ikariya, T.; Noyori, R. Catalytic Production of Dimethylformamide from Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **1994**, *116*, 8851–8852.

(340) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. Homogeneous Catalysis in Supercritical Fluids: Hydrogenation of Supercritical Carbon Dioxide to Formic Acid, Alkyl Formates, and Formamides. *J. Am. Chem. Soc.* **1996**, *118*, 344–355.

(341) Yilmaz, F.; Mutlu, A.; Ünver, H.; Kurta, M.; Kani, I. Hydrogenation of Olefins Catalyzed by Pd(II) Complexes Containing a Perfluoroalkylated S,O-Chelating Ligand in Supercritical CO<sub>2</sub> and Organic Solvents. *J. Supercrit. Fluids* **2010**, *54*, 202–209.

(342) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. Asymmetric Catalytic Hydrogenation Reactions in Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **1995**, *117*, 8277–8278.

(343) Xiao, J.; Nefkens, S. C. A.; Jessop, P. G.; Ikariya, T.; Noyori, R. Asymmetric Hydrogenation of  $\alpha,\beta$ -Unsaturated Carboxylic Acids in Supercritical Carbon Dioxide. *Tetrahedron Lett.* **1996**, *37*, 2813–2816.

(344) Hu, Y.; Birdsall, D. J.; Stuart, A. M.; Hope, E. G.; Xiao, J. Ruthenium-Catalysed Asymmetric Hydrogenation with Fluoroalkylated BINAP Ligands in Supercritical CO<sub>2</sub>. *J. Mol. Catal. A: Chem.* **2004**, *219*, 57–60.

(345) Lyubimov, S. E.; Rastorguev, E. A.; Petrovskii, P. V.; Kelbysheva, E. S.; Loim, N. M.; Davankov, V. A. Iridium-Catalyzed Asymmetric Hydrogenation of Imines in Supercritical Carbon Dioxide Using Phosphite-Type Ligands. *Tetrahedron Lett.* **2011**, *52*, 1395–1397.

(346) Berthod, M.; Mignani, G.; Lemaire, M. New Perfluoroalkylated BINAP Usable as a Ligand in Homogeneous and Supercritical Carbon Dioxide Asymmetric Hydrogenation. *Tetrahedron: Asymmetry* **2004**, *15*, 1121–1126.

(347) Earley, J. H.; Bourne, R. A.; Watson, M. J.; Poliakov, M. Continuous Catalytic Upgrading of Ethanol to N-Butanol and > C<sub>4</sub> Products over Cu/CeO<sub>2</sub> Catalysts in Supercritical CO<sub>2</sub>. *Green Chem.* **2015**, *17*, 3018–3025.

(348) Piqueras, C. M.; Puccia, V.; Vega, D. A.; Volpe, M. A. Selective Hydrogenation of Cinnamaldehyde in Supercritical CO<sub>2</sub> over Me–CeO<sub>2</sub> (Me = Cu, Pt, Au): Insight of the Role of Me–Ce Interaction. *Appl. Catal., B* **2016**, *185*, 265–271.

(349) Rathke, J. W.; Klingler, R. J.; Krause, T. R. Propylene Hydroformylation in Supercritical Carbon Dioxide. *Organometallics* **1991**, *10*, 1350–1355.

(350) Koch, D.; Leitner, W. Rhodium-Catalyzed Hydroformylation in Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **1998**, *120*, 13398–13404.

(351) Koeken, A. C. J.; Smeets, N. M. B. A Bulky Phosphite Modified Rhodium Catalyst for Efficient Hydroformylation of Disubstituted Alkenes and Macromonomers in Supercritical Carbon Dioxide. *Catal. Sci. Technol.* **2013**, *3* (4), 1036.

(352) Lyubimov, S. E.; Rastorguev, E. A.; Lubentsova, K. I.; Korlyukov, A. A.; Davankov, V. A. Rhodium-Containing Hypercross-Linked Polystyrene as a Heterogeneous Catalyst for the Hydroformylation of Olefins in Supercritical Carbon Dioxide. *Tetrahedron Lett.* **2013**, *54*, 1116–1119.

(353) Chapman, A. O.; Akien, G. R.; Arrowsmith, N. J.; Licence, P.; Poliakov, M. Continuous Heterogeneous Catalytic Oxidation of Primary and Secondary Alcohols in scCO<sub>2</sub>. *Green Chem.* **2010**, *12*, 310–315.

(354) Hou, Z.; Theysen, N.; Leitner, W. Palladium Nanoparticles Stabilised on PEG-Modified Silica as Catalysts for the Aerobic Alcohol Oxidation in Supercritical Carbon Dioxide. *Green Chem.* **2007**, *9*, 127–132.

(355) Ciriminna, R.; Campestrini, S.; Pagliaro, M. FluoroGel: A Versatile Catalyst for Aerobic Alcohol Oxidation in Supercritical Carbon Dioxide. *Org. Biomol. Chem.* **2006**, *4*, 2637–2641.

(356) Maayan, G.; Ganchegui, B.; Leitner, W.; Neumann, R. Selective Aerobic Oxidation in Supercritical Carbon Dioxide Catalyzed by the



- HSPV2Mo10O40 Polyoxometalate. *Chem. Commun.* **2006**, 2230–2232.
- (357) Jiang, H. F.; Jia, L. Q.; Li, J. H. Wacker Reaction in Supercritical Carbon Dioxide. *Green Chem.* **2000**, 2, 161–164.
- (358) Oakes, R. S.; Clifford, A. A.; Bartle, K. D.; Pett, M. T.; Rayner, C. M. Sulfur Oxidation in Supercritical Carbon Dioxide: Dramatic Pressure Dependant Enhancement of Diastereoselectivity for Sulfoxidation of Cysteine Derivatives. *Chem. Commun.* **1999**, 247–248.
- (359) Haas, G.; Kolis, J. W. The Diastereoselective Epoxidation of Olefins in Supercritical Carbon Dioxide. *Tetrahedron Lett.* **1998**, 39, 5923–5926.
- (360) Erdem, O.; Guzel, B. Synthesis of New Perfluorinated Binaphthyl Mn(III) Complexes and Epoxidation of Styrene in Supercritical Carbon Dioxide. *J. Supercrit. Fluids* **2014**, 85, 6–10.
- (361) Olmos, A.; Asensio, G.; Perez, P. J. Homogeneous Metal-Based Catalysis in Supercritical Carbon Dioxide as Reaction Medium. *ACS Catal.* **2016**, 6, 4265–4280.
- (362) Fernandes, R. R.; Lasri, J.; da Silva, M. F. C. G.; Palavra, A. M. F.; da Silva, J. A. L.; da Silva, J. J. R. F.; Pombeiro, A. J. L. Oxadiazoline and Ketoimine Palladium(II) Complexes as Highly Efficient Catalysts for Suzuki-Miyaura Cross-Coupling Reactions in Supercritical Carbon Dioxide. *Adv. Synth. Catal.* **2011**, 353, 1153–1160.
- (363) Early, T. R.; Gordon, R. S.; Carroll, M. A.; Holmes, A. B.; Shute, R. E.; McConvey, I. F. Palladium-Catalysed Cross-Coupling Reactions in Supercritical Carbon Dioxide. *Chem. Commun.* **2001**, 1966–1967.
- (364) Jiang, H. F.; Wang, A. Z. Copper-Catalyzed Cross-Coupling Reactions of Bromoalkynols with Terminal Alkynes in Supercritical Carbon Dioxide. *Synthesis* **2007**, 11, 1649–1654.
- (365) Lyubimov, S. E.; Kuchurov, I. V.; Vasil'ev, A. A.; Tyutyunov, A. A.; Kalinin, V. N.; Davankov, V. A.; Zlotin, S. G. The Use of a New Carboranylamidophosphite Ligand in the Asymmetric Pd-Catalysed Allylic Alkylation in Organic Solvents and Supercritical Carbon Dioxide. *J. Organomet. Chem.* **2009**, 694, 3047–3049.
- (366) Bo, H.; Hu, Y.; Li, D. Facile and Efficient Suzuki-Miyaura Coupling Reaction of Aryl Halides Catalyzed by Pd2(dba)3 in Ionic Liquid/supercritical Carbon Dioxide Biphasic System. *J. Mol. Liq.* **2016**, 218, 429–433.
- (367) Gava, R.; Olmos, A.; Noverges, B.; Varea, T.; Álvarez, E.; Belderrain, T. R.; Caballero, A.; Asensio, G.; Pérez, P. J. Discovering Copper for Methane C-H Bond Functionalization. *ACS Catal.* **2015**, 5, 3726–3730.
- (368) Zhang, W.; He, X.; Ren, B.; Jiang, Y.; Hu, Z. Cu(OAc)-2\*H2O—An Efficient Catalyst for Huisgen-Click Reaction in Supercritical Carbon Dioxide. *Tetrahedron Lett.* **2015**, 56, 2472–2475.
- (369) Badgujar, K. C.; Bhanage, B. M. The Green Metric Evaluation and Synthesis of Diesel-Blend Compounds from Biomass Derived Levulinic Acid in Supercritical Carbon Dioxide. *Biomass Bioenergy* **2016**, 84, 12–21.
- (370) Savi, T.; Mazutti, M. A.; Luccio, M. Di; Oliveira, D. De; Oliveira, J. V. Enzymatic Synthesis of Soybean Biodiesel Using Supercritical Carbon Dioxide as Solvent in a Continuous Expanded-Bed Reactor. *J. Supercrit. Fluids* **2015**, 97, 16–21.
- (371) Liu, X.; Coutelier, O.; Harrison, S.; Tassaing, T.; Marty, J. D.; Destarac, M. Enhanced Solubility of Polyvinyl Esters in scCO2 by Means of Vinyl Trifluorobutylate Monomer. *ACS Macro Lett.* **2015**, 4, 89–93.
- (372) Chakraborty, S.; Colón, Y. J.; Snurr, R. Q.; Nguyen, S. T. Hierarchically Porous Organic Polymers: Highly Enhanced Gas Uptake and Transport through Templated Synthesis. *Chem. Sci.* **2015**, 6, 384–389.
- (373) Maleki, H.; Duraes, L.; Portugal, A. Synthesis of Mechanically Reinforced Silica Aerogels via Surface-Initiated Reversible Addition-Fragmentation Chain Transfer (RAFT) Polymerization. *J. Mater. Chem. A* **2015**, 3, 1594–1600.
- (374) Kuang, T. R.; Mi, H. Y.; Fu, D. J.; Jing, X.; Chen, B. Y.; Mou, W. J.; Peng, X. F. Fabrication of Poly(lactic Acid)/graphene Oxide Foams with Highly Oriented and Elongated Cell Structure via Unidirectional Foaming Using Supercritical Carbon Dioxide. *Ind. Eng. Chem. Res.* **2015**, 54, 758–768.
- (375) De Marco, L.; Rossmann, M.; Prosapio, V.; Reverchon, E.; Braeuer, A. Control of Particle Size, at Micrometric and Nanometric Range, Using Supercritical Antisolvent Precipitation from Solvent Mixtures: Application to PVP. *Chem. Eng. J.* **2015**, 273, 344–352.
- (376) Zhao, J.; Liu, Z.; Li, H.; Hu, W.; Zhao, C.; Zhao, P.; Shi, D. Development of a Highly Active Electrocatalyst via Ultra Fine Pd Nanoparticles Dispersed on Pristine Graphene. *Langmuir* **2015**, 31, 2576–2583.
- (377) Jimenez, C.; Garcia, J.; Camarillo, R.; Martinez, F.; Rincon, J. Electrochemical CO2 Reduction to Fuels Using Pt/CNT Catalysts Synthesized in Supercritical Medium. *Energy Fuels* **2017**, 31, 3038–3046.
- (378) Sánchez-Vicente, Y.; Stevens, L. A.; Pando, C.; José, M.; Snape, C. E.; Drage, T. C.; Cabañas, A. A New Sustainable Route in Supercritical CO2 to Functionalize Silica SBA-15 with 3-Amino-propyltrimethoxysilane as Material for Carbon Capture. *Chem. Eng. J.* **2015**, 264, 886–898.
- (379) Hoibye, L.; Clauson-Kaas, J.; Wenzel, H.; Larsen, H. F.; Jacobsen, B. N.; Dalgaard, O. Sustainability Assessment of Advanced Wastewater Treatment Technologies. *Water Sci. Technol.* **2008**, 58 (5), 963–968.
- (380) Kurniawan, T. A.; Chan, G. Y. S.; Lo, W. H.; Babel, S. Physico-Chemical Treatment Techniques for Wastewater Laden with Heavy Metals. *Chem. Eng. J.* **2006**, 118 (1–2), 83–98.
- (381) Zheng, H.; Xu, Y.; Zhang, J.; Xiong, X.; Yan, J.; Zheng, L. An Ecofriendly Dyeing of Wool with Supercritical Carbon Dioxide Fluid. *J. Cleaner Prod.* **2017**, 143, 269–277.
- (382) Ranganathan, K.; Karunakaran, K.; Sharma, D. C. Recycling of Wastewaters of Textile Dyeing Industries Using Advanced Treatment Technology and Cost Analysis-Case Studies. *Resour. Conserv. Recycl.* **2007**, 50 (3), 306–318.
- (383) Fernandez Cid, M. V.; van Spronsen, J.; van der Kraan, M.; Veugelers, W. J. T.; Woerlee, G. F.; Witkamp, G. J. Excellent Dye Fixation on Cotton Dyed in Supercritical Carbon Dioxide Using Fluorotriazine Reactive Dyes. *Green Chem.* **2005**, 7, 609–616.
- (384) Elmaaty, T. A.; El-Aziz, E. A. Supercritical Carbon Dioxide as a Green Media in Textile Dyeing: A Review. *Text. Res. J.* **2017**, 0, 1–29.
- (385) Xiao, H.; Zhao, T.; Li, C. H.; Li, M. Y. Eco-Friendly Approaches for Dyeing Multiple Type of Fabrics with Cationic Reactive Dyes. *J. Cleaner Prod.* **2017**, 165, 1499–1507.
- (386) Zhang, Y. Q.; Wei, X. C.; Long, J. J. Ecofriendly Synthesis and Application of Special Disperse Reactive Dyes in Waterless Coloration of Wool with Supercritical Carbon Dioxide. *J. Cleaner Prod.* **2016**, 133, 746–756.
- (387) Zheng, H.; Zhang, J.; Yan, J.; Zheng, L. An Industrial Scale Multiple Supercritical Carbon Dioxide Apparatus and Its Eco-Friendly Dyeing Production. *J. CO2 Util.* **2016**, 16, 272–281.
- (388) Zheng, H.; Zhang, J.; Zheng, L. Optimization of an Ecofriendly Dyeing Process in an Industrialized Supercritical Carbon Dioxide Unit for Acrylic Fibers. *Text. Res. J.* **2017**, 87, 1818–1827.
- (389) Eren, H. A.; Avinc, O.; Eren, S. Supercritical Carbon Dioxide for Textile Applications and Recent Developments. *IOP Conf. Ser.: Mater. Sci. Eng.* **2017**, 254, 82011.
- (390) Hu, J.; Deng, W. Application of Supercritical Carbon Dioxide for Leather Processing. *J. Cleaner Prod.* **2016**, 113, 931–946.
- (391) Peng, S.; Li, T.; Tang, Z.; Shi, J.; Zhang, H. Comparative Life Cycle Assessment of Remanufacturing Cleaning Technologies. *J. Cleaner Prod.* **2016**, 137, 475–489.
- (392) Jessop, P. G.; Subramaniam, B. Gas-Expanded Liquids. *Chem. Rev.* **2007**, 107, 2666–2694.
- (393) Akien, G. R.; Poliakoff, M. A Critical Look at Reactions in Class I and II Gas-Expanded Liquids Using CO2 and Other Gases. *Green Chem.* **2009**, 11, 1083–1100.
- (394) Subramaniam, B.; Akien, G. R. Sustainable Catalytic Reaction Engineering with Gas-Expanded Liquids. *Curr. Opin. Chem. Eng.* **2012**, 1, 336–341.

- (395) Jin, H.; Subramaniam, B. Homogeneous Catalytic Hydroformylation of 1-Octene in CO<sub>2</sub>-Expanded Solvent Media. *Chem. Eng. Sci.* **2004**, *59*, 4887–4893.
- (396) Jin, H.; Subramaniam, B.; Ghosh, A.; Tunge, J. Intensification of Catalytic Olefin Hydroformylation in CO<sub>2</sub>-Expanded Media. *AIChE J.* **2006**, *52*, 2575–2581.
- (397) Fang, J.; Jin, H.; Ruddy, T.; Pennybaker, K.; Fahey, D.; Subramaniam, B. Economic and Environmental Impact Analyses of Catalytic Olefin Hydroformylation in CO<sub>2</sub>-Expanded Liquid (CXL) Media. *Ind. Eng. Chem. Res.* **2007**, *46*, 8687–8692.
- (398) Xie, Z.; Subramaniam, B. Development of a Greener Hydroformylation Process Guided by Quantitative Sustainability Assessments. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2748–2757.
- (399) Jana, R.; Tunge, J. A. A Homogeneous, Recyclable Rhodium(I) Catalyst for the Hydroarylation of Michael Acceptors. *Org. Lett.* **2009**, *11*, 971–974.
- (400) Xu, G.; Wei, H.; Ren, Y.; Yin, J.; Wang, A.; Zhang, T. Chemoselective Hydrogenation of 3-Nitrostyrene over a Pt/FeOx Pseudo-Single-Atom-Catalyst in CO<sub>2</sub>-Expanded Liquids. *Green Chem.* **2016**, *18*, 1332–1338.
- (401) Hoang, H. N.; Nagashima, Y.; Mori, S.; Kagechika, H.; Matsuda, T. CO<sub>2</sub>-Expanded Bio-Based Liquids as Novel Solvents for Enantioselective Biocatalysis. *Tetrahedron* **2017**, *73*, 2984–2989.
- (402) Sioumkrou, E.; Galindo, A.; Adjiman, C. S. On the Optimal Design of Gas-Expanded Liquids Based on Process Performance. *Chem. Eng. Sci.* **2014**, *115*, 19–30.
- (403) Lu, J.; Lazzaroni, M. J.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Tunable Solvents for Homogeneous Catalyst Recycle. *Ind. Eng. Chem. Res.* **2004**, *43*, 1586–1590.
- (404) Lu, J.; Lazzaroni, M. J.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Tunable Solvents for Homogeneous Catalyst Recycle. *Ind. Eng. Chem. Res.* **2004**, *43*, 1586–1590.
- (405) Broering, J. M.; Hill, E. M.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A.; Bommarius, A. S. Biocatalytic Reaction and Recycling by Using CO<sub>2</sub>-Induced Organic-Aqueous Tunable Solvents. *Angew. Chem., Int. Ed.* **2006**, *45*, 4670–4673.
- (406) Hill, E. M.; Broering, J. M.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Coupling Chiral Homogeneous Biocatalytic Reactions with Benign Heterogeneous Separation. *Green Chem.* **2007**, *9*, 888–893.
- (407) Hallett, J. P.; Ford, J. W.; Jones, R. S.; Pollet, P.; Thomas, C. A.; Liotta, C. L.; Eckert, C. A. Hydroformylation Catalyst Recycle with Gas-Expanded Liquids. *Ind. Eng. Chem. Res.* **2008**, *47*, 2585–2589.
- (408) Reynolds, S. R.; Markland, K. A.; Rood, J.; Leonard, E.; Saunders, S. R. Manipulating Ligand–nanoparticle Interactions and Catalytic Activity through Organic-Aqueous Tunable Solvent Recovery. *RSC Adv.* **2016**, *6*, 78496–78504.
- (409) Al-Hamimi, S.; Abellan Mayoral, A.; Cunico, L. P.; Turner, C. Carbon Dioxide Expanded Ethanol Extraction: Solubility and Extraction Kinetics of  $\alpha$ -Pinene and Cis-Verbenol. *Anal. Chem.* **2016**, *88*, 4336–4345.
- (410) Rodríguez-Pérez, C.; Mendiola, J. A.; Quirantes-Piné, R.; Ibáñez, E.; Segura-Carretero, A. Green Downstream Processing Using Supercritical Carbon Dioxide, CO<sub>2</sub>-Expanded Ethanol and Pressurized Hot Water Extractions for Recovering Bioactive Compounds from Moringa Oleifera Leaves. *J. Supercrit. Fluids* **2016**, *116*, 90–100.
- (411) Chhouk, K.; Uemori, C.; Wahyudiono; Kanda, H.; Goto, M. Extraction of Phenolic Compounds and Antioxidant Activity from Garlic Husk Using Carbon Dioxide Expanded Ethanol. *Chem. Eng. Process.* **2017**, *117*, 113–119.
- (412) José, M.; Reyes, F. A.; Mendiola, J. A.; Iba, E. Astaxanthin Extraction from Haematococcus Pluvialis Using CO<sub>2</sub>-Expanded Ethanol. *J. Supercrit. Fluids* **2014**, *92*, 75–83.
- (413) Paudel, A.; Jessop, M. J.; Stubbs, S. H.; Champagne, P.; Jessop, P. G. Extraction of Lipids from Microalgae Using CO<sub>2</sub>-Expanded Methanol and Liquid CO<sub>2</sub>. *Bioresour. Technol.* **2015**, *184*, 286–290.
- (414) Yang, Y. H.; Klinthong, W.; Tan, C. S. Optimization of Continuous Lipid Extraction from Chlorella Vulgaris by CO<sub>2</sub>-Expanded Methanol for Biodiesel Production. *Bioresour. Technol.* **2015**, *198*, 550–556.
- (415) Wang, H. C.; Klinthong, W.; Yang, Y. H.; Tan, C. S. Continuous Extraction of Lipids from Schizochytrium Sp. by CO<sub>2</sub>-Expanded Ethanol. *Bioresour. Technol.* **2015**, *189*, 162–168.
- (416) Wang, T. H.; Hsu, C. L.; Huang, C. H.; Hsieh, Y. K.; Tan, C. S.; Wang, C. F. Environmental Impact of CO<sub>2</sub>-Expanded Fluid Extraction Technique in Microalgae Oil Acquisition. *J. Cleaner Prod.* **2016**, *137*, 813–820.
- (417) Lardon, L.; Helias, A.; Sialve, B.; Steyer, J.-P.; Bernard, O. Policy Analysis Life-Cycle Assessment of Biodiesel Production from Microalgae. *Environ. Sci. Technol.* **2009**, *43*, 6475–6481.
- (418) Liu, D.; Cheng, E.; Yang, Z. DNA-Based Switchable Devices and Materials. *NPG Asia Mater.* **2011**, *3*, 109–114.
- (419) Blanco, V.; Leigh, D. A.; Marcos, V. Artificial Switchable Catalysts. *Chem. Soc. Rev.* **2015**, *44*, 5341–5370.
- (420) Jessop, P. G.; Mercer, S. M.; Heldebrant, D. J. CO<sub>2</sub>-Triggered Switchable Solvents, Surfactants, and Other Materials. *Energy Environ. Sci.* **2012**, *5*, 7240–7253.
- (421) Jones, C. D.; Steed, J. W. Gels with Sense: Supramolecular Materials That Respond to Heat, Light and Sound. *Chem. Soc. Rev.* **2016**, *45*, 6546–6596.
- (422) Hallett, J. P.; Pollet, P.; Liotta, C. L.; Eckert, C. A. Reversible in Situ Catalyst Formation. *Acc. Chem. Res.* **2008**, *41* (3), 458–467.
- (423) Liu, H.; Lin, S.; Feng, Y.; Theato, P. CO<sub>2</sub>-Responsive Polymer Materials. *Polym. Chem.* **2017**, *8*, 12–23.
- (424) Grosseheilmann, J.; Vanderveen, J. R.; Jessop, P. G.; Kragl, U. Switchable-Hydrophilicity Solvents for Product Isolation and Catalyst Recycling in Organocatalysis. *ChemSusChem* **2016**, *9*, 696–702.
- (425) Mercer, S. M.; Robert, T.; Dixon, D. V.; Jessop, P. G. Recycling of a Homogeneous Catalyst Using Switchable Water. *Catal. Sci. Technol.* **2012**, *2*, 1315–1318.
- (426) Zhang, J.; Misch, R.; Tan, Y.; Agar, D. W. Novel Thermomorphic Biphasic Amine Solvents for CO<sub>2</sub> Absorption and Low-Temperature Extractive Regeneration. *Chem. Eng. Technol.* **2011**, *34*, 1481–1489.
- (427) Mathias, P. M.; Afshar, K.; Zheng, F.; Bearden, M. D.; Freeman, C. J.; Andrea, T.; Koech, P. K.; Kutnyakov, I.; Zwoster, A.; Smith, A. R.; et al. Improving the Regeneration of CO<sub>2</sub>-Binding Organic Liquids with a Polarity Change. *Energy Environ. Sci.* **2013**, *6*, 2233–2242.
- (428) Heldebrant, D. J.; Koech, P. K.; Rainbolt, J. E.; Zheng, F.; Smurthwaite, T.; Freeman, C. J.; Oss, M.; Leito, I. Performance of Single-Component CO<sub>2</sub>-Binding Organic Liquids (CO<sub>2</sub>BOLs) for Post Combustion CO<sub>2</sub> Capture. *Chem. Eng. J.* **2011**, *171*, 794–800.
- (429) Zhuang, Q.; Clements, B.; Dai, J.; Carrigan, L. Ten Years of Research on Phase Separation Absorbents for Carbon Capture: Achievements and next Steps. *Int. J. Greenhouse Gas Control* **2016**, *52*, 449–460.
- (430) Samorì, C.; Pezzolesi, L.; Barreiro, D. L.; Galletti, P.; Pasteris, A.; Tagliavini, E. Synthesis of New Polyethoxylated Tertiary Amines and Their Use as Switchable Hydrophilicity Solvents. *RSC Adv.* **2014**, *4*, 5999–6008.
- (431) Vanderveen, J. R.; Durelle, J.; Jessop, P. G. Design and Evaluation of Switchable-Hydrophilicity Solvents. *Green Chem.* **2014**, *16*, 1187–1197.
- (432) Cantu, D. C.; Lee, J.; Lee, M. S.; Heldebrant, D. J.; Koech, P. K.; Freeman, C. J.; Rousseau, R.; Glezakou, V. A. Dynamic Acid/Base Equilibrium in Single Component Switchable Ionic Liquids and Consequences on Viscosity. *J. Phys. Chem. Lett.* **2016**, *7*, 1646–1652.
- (433) Blasucci, V.; Hart, R.; Mestre, V. L.; Hahne, D. J.; Burlager, M.; Huttenhower, H.; Thio, B. J. R.; Pollet, P.; Liotta, C. L.; Eckert, C. A. Single Component, Reversible Ionic Liquids for Energy Applications. *Fuel* **2010**, *89*, 1315–1319.
- (434) Yamada, T.; Lukac, P. J.; Yu, T.; Weiss, R. G. Reversible, Room-Temperature, Chiral Ionic Liquids. Amidinium Carbamates Derived from Amidines and Amino-Acid Esters with Carbon Dioxide. *Chem. Mater.* **2007**, *19*, 4761–4768.



- (435) Vinci, D.; Donaldson, M.; Hallett, J. P.; John, E. A.; Pollet, P.; Thomas, C. A.; Grilly, J. D.; Jessop, P. G.; Liotta, C. L.; Eckert, C. A. Piperylene Sulfone: A Labile and Recyclable DMSO Substitute. *Chem. Commun.* **2007**, 1427–1429.
- (436) Marus, G. A.; Vyhmeister, E.; Pollet, P.; Donaldson, M. E.; Llopis-Mestre, V.; Faltermeier, S.; Roesel, R.; Tribo, M.; Gelbaum, L.; Liotta, C. L.; et al. Sustainable and Scalable Synthesis of Piperylene Sulfone: A “volatile” and Recyclable DMSO Substitute. *Ind. Eng. Chem. Res.* **2011**, *50*, 23–27.
- (437) Behr, A.; Kleyensteiber, A.; Becker, M. A Novel Approach to Selecting Thermomorphic Multicomponent Solvent Systems (TMS) for Hydroaminomethylation Reactions. *Chem. Eng. Process.* **2013**, *69*, 15–23.
- (438) McBride, K.; Gaide, T.; Vorholt, A.; Behr, A.; Sundmacher, K. Thermomorphic Solvent Selection for Homogeneous Catalyst Recovery Based on COSMO-RS. *Chem. Eng. Process.* **2015**, *99*, 97–106.
- (439) Jessop, P. P. G.; Heldebrant, D. J. D.; Li, X.; Eckert, C. A. C.; Liotta, C. C. L. Green Chemistry: Reversible Nonpolar-to-Polar Solvent. *Nature* **2005**, *436*, 1102.
- (440) Phan, L.; Chiu, D.; Heldebrant, D. J.; Huttenhower, H.; John, E.; Li, X.; Pollet, P.; Wang, R.; Eckert, C. A.; Liotta, C. L.; et al. Switchable Solvents Consisting of Amidine/alcohol or Guanidine/alcohol Mixtures. *Ind. Eng. Chem. Res.* **2008**, *47*, 539–545.
- (441) Yamada, T.; Lukac, P. J.; George, M.; Weiss, R. G. Reversible, Room-Temperature Ionic Liquids. Amidinium Carbamates Derived from Amidines and Aliphatic Primary Amines with Carbon Dioxide. *Chem. Mater.* **2007**, *19*, 967–969.
- (442) Phan, L.; Andreatta, J. R.; Horvey, L. K.; Edie, C. F.; Luco, A. L.; Mirchandani, A.; Darensbourg, D. J.; Jessop, P. G. Switchable-Polarity Solvents Prepared with a Single Liquid Component. *J. Org. Chem.* **2008**, *73*, 127–132.
- (443) Heldebrant, D. J.; Yonker, C. R.; Jessop, P. G.; Phan, L. Organic Liquid CO<sub>2</sub> Capture Agents with High Gravimetric CO<sub>2</sub> Capacity. *Energy Environ. Sci.* **2008**, *1*, 487–493.
- (444) Samorì, C.; Torri, C.; Samorì, G.; Fabbri, D.; Galletti, P.; Guerrini, F.; Pistocchi, R.; Tagliavini, E. Extraction of Hydrocarbons from Microalga *Botryococcus Braunii* with Switchable Solvents. *Bioresour. Technol.* **2010**, *101*, 3274–3279.
- (445) Hart, R.; Pollet, P.; Hahne, D. J.; John, E.; Llopis-mestre, V.; Blasucci, V.; Huttenhower, H.; Leitner, W.; Eckert, C. A.; Liotta, C. L. Benign Coupling of Reactions and Separations with Reversible Ionic Liquids. *Tetrahedron* **2010**, *66*, 1082–1090.
- (446) Phan, L.; Brown, H.; White, J.; Hodgson, A.; Jessop, P. G. Soybean Oil Extraction and Separation Using Switchable or Expanded Solvents. *Green Chem.* **2009**, *11*, 53–59.
- (447) Naeemullah; Shah, F.; Kazi, T. G.; Afridi, H. I.; Khan, A. R.; Arain, S. S.; Arain, M. S.; Panhwar, A. H. Switchable Dispersive Liquid–liquid Microextraction for Lead Enrichment: A Green Alternative to Classical Extraction Techniques. *Anal. Methods* **2016**, *8*, 904–911.
- (448) Eta, V.; Mikkola, J. P. Deconstruction of Nordic Hardwood in Switchable Ionic Liquids and Acylation of the Dissolved Cellulose. *Carbohydr. Polym.* **2016**, *136*, 459–465.
- (449) Anugwom, I.; Eta, V.; Virtanen, P.; Mäki-Arvela, P.; Hedenström, M.; Hummel, M.; Sixta, H.; Mikkola, J. P. Switchable Ionic Liquids as Delignification Solvents for Lignocellulosic Materials. *ChemSusChem* **2014**, *7*, 1170–1176.
- (450) Soudham, V. P.; Raut, D. G.; Anugwom, I.; Brandberg, T.; Larsson, C.; Mikkola, J. P. Coupled Enzymatic Hydrolysis and Ethanol Fermentation: Ionic Liquid Pretreatment for Enhanced Yields. *Biotechnol. Biofuels* **2015**, *8*, 135.
- (451) Khokarale, S. G.; Le-That, T.; Mikkola, J. P. Carbohydrate Free Lignin: A Dissolution-Recovery Cycle of Sodium Lignosulfonate in a Switchable Ionic Liquid System. *ACS Sustainable Chem. Eng.* **2016**, *4*, 7032–7040.
- (452) Xue, D.; Mu, Y.; Mao, Y.; Yang, T.; Xiu, Z. Kinetics of DBU-Catalyzed Transesterification for Biodiesel in the DBU-Ethanol Switchable-Polarity Solvent. *Green Chem.* **2014**, *16*, 3218–3223.
- (453) Cao, X.; Xie, H.; Wu, Z.; Shen, H.; Jing, B. Phase-Switching Homogeneous Catalysis for Clean Production of Biodiesel and Glycerol from Soybean and Microbial Lipids. *ChemCatChem* **2012**, *4*, 1272–1278.
- (454) Bao, J.; Liu, Y.; Parnas, R.; Liang, B.; Lu, H. Inter-Solubility of Product Systems in Biodiesel Production from *Jatropha Curcas* L. Oil with the Switchable Solvent DBU/methanol. *RSC Adv.* **2015**, *5*, 8311–8317.
- (455) Troter, D. Z.; Todorović, Z. B.; Đokić-Stojanović, D. R.; Stamenković, O. S.; Veljković, V. B. Application of Ionic Liquids and Deep Eutectic Solvents in Biodiesel Production: A Review. *Renewable Sustainable Energy Rev.* **2016**, *61*, 473–500.
- (456) Leung, D. Y. C.; Wu, X.; Leung, M. K. H. A Review on Biodiesel Production Using Catalyzed Transesterification. *Appl. Energy* **2010**, *87*, 1083–1095.
- (457) Lourinho, G.; Brito, P. Advanced Biodiesel Production Technologies: Novel Developments. *Rev. Environ. Sci. Bio/Technol.* **2015**, *14*, 287–316.
- (458) Jessop, P. G.; Phan, L.; Carrier, A.; Robinson, S.; Dürr, C. J.; Harjani, J. R. A Solvent Having Switchable Hydrophilicity. *Green Chem.* **2010**, *12*, 809–814.
- (459) Durelle, J.; Vanderveen, J. R.; Jessop, P. G. Modelling the Behaviour of Switchable-Hydrophilicity Solvents. *Phys. Chem. Chem. Phys.* **2014**, *16*, 5270–5275.
- (460) Alshamrani, A. K.; Vanderveen, J. R.; Jessop, P. G.; Jessop, P. G.; Heldebrant, D. J.; Xiaowang, L.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G.; Jessop, P. G.; et al. A Guide to the Selection of Switchable Functional Groups for CO<sub>2</sub>-Switchable Compounds. *Phys. Chem. Chem. Phys.* **2016**, *18*, 19276–19288.
- (461) Bougie, F.; Iliuta, M. C. Sterically Hindered Amine-Based Absorbents for the Removal of CO<sub>2</sub> from Gas Streams. *J. Chem. Eng. Data* **2012**, *57*, 635–669.
- (462) Durelle, J.; Vanderveen, J. R.; Quan, Y.; Chalifoux, C. B.; Kostin, J. E.; Jessop, P. G.; Vanderveen, J. R.; Durelle, J.; Jessop, P. G.; Durelle, J.; et al. Extending the Range of Switchable-Hydrophilicity Solvents. *Phys. Chem. Chem. Phys.* **2015**, *17*, 5308–5313.
- (463) Vanderveen, J. R.; Patiny, L.; Chalifoux, C. B.; Jessop, M. J.; Jessop, P. G. A Virtual Screening Approach to Identifying the Greenest Compound for a Task: Application to Switchable-Hydrophilicity Solvents. *Green Chem.* **2015**, *17*, 5182–5188.
- (464) Wilson, A. D.; Stewart, F. F. Structure–function Study of Tertiary Amines as Switchable Polarity Solvents. *RSC Adv.* **2014**, *4*, 11039–11049.
- (465) Li, H.; Wang, B.; Deng, L. Enantioselective Nitroaldol Reaction of Alpha-Ketoesters Catalyzed by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2006**, *128*, 732–733.
- (466) Shaffer, D. L.; Werber, J. R.; Jaramillo, H.; Lin, S.; Elimelech, M. Forward Osmosis: Where Are We Now? *Desalination* **2015**, *356*, 271–284.
- (467) Cai, Y.; Hu, X. M. A Critical Review on Draw Solute Development for Forward Osmosis. *Desalination* **2016**, *391*, 16–29.
- (468) Luo, H.; Wang, Q.; Zhang, T. C.; Tao, T.; Zhou, A.; Chen, L.; Bie, X. A Review on the Recovery Methods of Draw Solute in Forward Osmosis. *J. Water Process Eng.* **2014**, *4*, 212–223.
- (469) Ge, Q.; Ling, M.; Chung, T. S. Draw Solutions for Forward Osmosis Processes: Developments, Challenges, and Prospects for the Future. *J. Membr. Sci.* **2013**, *442*, 225–237.
- (470) Stone, M. L.; Rae, C.; Stewart, F. F.; Wilson, A. D. Switchable Polarity Solvents as Draw Solute for Forward Osmosis. *Desalination* **2013**, *312*, 124–129.
- (471) Wilson, A. D.; Orme, C. J. Concentration Dependent Speciation and Mass Transport Properties of Switchable Polarity Solvents. *RSC Adv.* **2015**, *5*, 7740–7751.
- (472) Wendt, D. S.; Orme, C. J.; Mines, G. L.; Wilson, A. D. Energy Requirements of the Switchable Polarity Solvent Forward Osmosis (SPS-FO) Water Purification Process. *Desalination* **2015**, *374*, 81–91.
- (473) Reimund, K. K.; Coscia, B. J.; Arena, J. T.; Wilson, A. D.; McCutcheon, J. R. Characterization and Membrane Stability Study for



the Switchable Polarity Solvent N,N-Dimethylcyclohexylamine as a Draw Solute in Forward Osmosis. *J. Membr. Sci.* **2016**, *501*, 93–99.

(474) Orme, C. J.; Wilson, A. D. 1-Cyclohexylpiperidine as a Thermolytic Draw Solute for Osmotically Driven Membrane Processes. *Desalination* **2015**, *371*, 126–133.

(475) Quintavalla, S.; Vicini, L. Antimicrobial Food Packaging in Meat Industry. *Meat Sci.* **2002**, *62*, 373–380.

(476) Tartakowski, Z. Recycling of Packaging Multilayer Films: New Materials for Technical Products. *Resour., Conserv. Recycl.* **2010**, *55*, 167–170.

(477) Cervantes-Reyes, A.; Nunez-Pineda, A.; Barrera-Diaz, C.; Varela-Guerrero, V.; Martinez-Barrera, G.; Cuevas-Yanez, E. Solvent Effect in the Polyethylene Recovery from Multilayer Postconsumer Aseptic Packaging. *Waste Manage.* **2015**, *38*, 61–64.

(478) Samori, C.; Cespi, D.; Blair, P.; Galletti, P.; Malferrari, D.; Passarini, F.; Vassura, I.; Tagliavini, E. Application of Switchable Hydrophilicity Solvents for Recycling Multilayer Packaging Materials. *Green Chem.* **2017**, *19*, 1714–1720.

(479) Samori, C.; Cespi, D.; Blair, P.; Galletti, P.; Malferrari, D.; Passarini, F.; Vassura, I.; Tagliavini, E. Application of Switchable Hydrophilicity Solvents for Recycling Multilayer Packaging Materials. *Green Chem.* **2017**, *19*, 1714–1720.

(480) Mercer, S. M.; Jessop, P. G. Switchable Water”: Aqueous Solutions of Switchable Ionic Strength. *ChemSusChem* **2010**, *3*, 467–470.

(481) Su, X.; Cunningham, M. F.; Jessop, P. G. Switchable Viscosity Triggered by CO<sub>2</sub> Using Smart Worm-like Micelles. *Chem. Commun.* **2013**, *49*, 2655–2657.

(482) Darabi, A.; Jessop, P. G.; Cunningham, M. F. CO<sub>2</sub>-Responsive Polymeric Materials: Synthesis, Self-Assembly, and Functional Applications. *Chem. Soc. Rev.* **2016**, *45*, 4391–4436.

(483) Greim, H.; Bury, D.; Klimisch, H.-J.; Oeben-Negele, M.; Ziegler-Skylakakis, K. TOXICITY OF ALIPHATIC AMINES: STRUCTURE-ACTIVITY RELATIONSHIP. *Chemosphere* **1998**, *36*, 271–295.

(484) Benigni, R.; Passerini, L. Carcinogenicity of the Aromatic Amines: From Structure-Activity Relationships to Mechanisms of Action and Risk Assessment. *Mutat. Res., Rev. Mutat. Res.* **2002**, *511*, 191–206.

(485) Chung, K. T.; Kirkovsky, L.; Kirkovsky, A.; Purcell, W. P. Review of Mutagenicity of Monocyclic Aromatic Amines: Quantitative Structure-Activity Relationships. *Mutat. Res., Rev. Mutat. Res.* **1997**, *387*, 1–16.

(486) Poste, A. E.; Grung, M.; Wright, R. F. Amines and Amine-Related Compounds in Surface Waters: A Review of Sources, Concentrations and Aquatic Toxicity. *Sci. Total Environ.* **2014**, *481*, 274–279.

(487) Lee, D. Y.; Wexler, A. S. Atmospheric Amines - Part III: Photochemistry and Toxicity. *Atmos. Environ.* **2013**, *71*, 95–103.

(488) Mazari, S. A.; Si Ali, B.; Jan, B. M.; Saeed, I. M.; Nizamuddin, S. An Overview of Solvent Management and Emissions of Amine-Based CO<sub>2</sub> Capture Technology. *Int. J. Greenhouse Gas Control* **2015**, *34*, 129–140.

(489) Brandt-Talbot, A.; Weigand, L. Highlights from the Faraday Discussion: Bio-Resources: Feeding a Sustainable Chemical Industry. *Chem. Commun.* **2017**, *53*, 12848–12856.

(490) Beller, M.; Centi, G.; Sun, L. Chemistry Future: Priorities and Opportunities from the Sustainability Perspective. *ChemSusChem* **2017**, *10*, 6–13.

(491) Subramaniam, B.; Helling, R. K.; Bode, C. J. Quantitative Sustainability Analysis: A Powerful Tool to Develop Resource-Efficient Catalytic Technologies. *ACS Sustainable Chem. Eng.* **2016**, *4*, 5859–5865.

(492) Varma, R. S. Greener and Sustainable Trends in Synthesis of Organics and Nanomaterials. *ACS Sustainable Chem. Eng.* **2016**, *4*, 5866–5878.

(493) Lupacchini, M.; Mascitti, A.; Giachi, G.; Tonucci, L.; D'Alessandro, N.; Martinez, J.; Colacino, E. Sonochemistry in Non-

Conventional, Green Solvents or Solvent-Free Reactions. *Tetrahedron* **2017**, *73*, 609–653.

(494) Sheldon, R. A.; Pereira, P. C. Biocatalysis Engineering: The Big Picture. *Chem. Soc. Rev.* **2017**, *46*, 2678–2691.

(495) Utikar, R. P.; Ranade, V. V. Intensifying Multiphase Reactions and Reactors: Strategies and Examples. *ACS Sustain. ACS Sustainable Chem. Eng.* **2017**, *5*, 3607–3622.

(496) Lohr, T. L.; Marks, T. J. Orthogonal Tandem Catalysis. *Nat. Chem.* **2015**, *7*, 477–482.

(497) Matlin, S. A.; Mehta, G.; Hopf, H.; Krief, A. The Role of Chemistry in Inventing a Sustainable Future. *Nat. Chem.* **2015**, *7*, 941–943.

(498) Hernáiz, M. J.; Alcántara, A. R.; García, J. I.; Sinisterra, J. V. Applied Biotransformations in Green Solvents. *Chem. - Eur. J.* **2010**, *16*, 9422–9437.