

# EVALUATION OF GREEN TECHNIQUES FOR ORGANIC SYNTHESIS

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## ABSTRACT

The green chemistry philosophy has aroused great interest within the ranks of solvent chemists. The challenge set by its demand for increased mass and energy efficiency coupled with environmental benevolence has been met, at least in part, by various solutions in the collective guise of the so-called neoteric solvents. What gives solvents their apparent high priority within the sphere of green chemistry relative to other chemicals is the volume in which they are used. A typical lab-scale organic reaction will be conducted as a solution, and purification by way of recrystallization or chromatography will also require a solvent. The total mass of solvent used throughout a synthetic procedure will inevitably outweigh the contribution of all other chemicals to the anticipated waste stream [1]. As such any valuable attributes possessed by a solvent need to be balanced against human and ecological toxicity alongside other pollution and safety concerns prior to use.

**KEYWORDS:** Green Techniques, Organic Synthesis, chemistry, solvent.

## INTRODUCTION

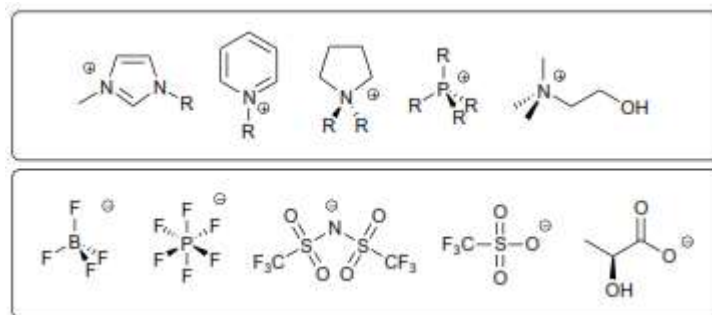
The solvent substitutions will have a considerable influence on any life cycle considerations. A life cycle assessment (LCA) is constructed by accounting for all sources of environmental damage caused by the existence of a product, from its inception to its eventual destruction. Within the context of a chemical's lifespan, the LCA stage of most interest to chemists is the process by which it is made. Because of the relative mass of solvent typically required, the LCA of the solvent will account for much of the environmental impact attributed to the synthesis of a chemical product. Therefore to claim a reaction, or the product itself to be green, any solvents used must certainly be green themselves. This perspective should be balanced against the benefits a solvent can have upon a reaction.

Preferential equilibrium positions, accelerated reaction rates, greater product selectivity, facile catalyst separation, and the optimisation of other parameters can be achieved through the choice of solvent [2]. With so many factors to consider, deciding upon the most favourable solvent for a given transformation can only be achieved with some exertion from the chemist. Academics have adopted their own biases towards particular solvents, and although this attitude is beneficial as regards to the elucidation of solvent effects and their synthetic versatility, it does not consider whether that solvent is the greenest option from a LCA perspective, but rather how advantageous the application of that solvent is in the narrower scope of selectivity enhancements or perhaps catalyst activity. What follows is an introduction to the manufacturing routes and green properties of ionic liquids, supercritical carbon dioxide, water, Perfluorinated solvents, and bio-derived alternatives to conventional petroleum solvents. Justification for applying these classes of solvent to organic synthesis and medicinal chemistry is then established via the use of reaction case studies.

## ORIGINS OF THE NEOTERIC SOLVENTS

### Ionic Liquids

If the number of articles and reviews associated with them is taken as a measure of significance within the field, then room temperature ionic liquids have arguably been at the forefront of the green solvent initiative [3]. With a virtually innumerable selection of cations and anions available, it is believed that any of a huge range of physical properties and environmental characteristics could manifest themselves in the form of a unique solvent, suited to specific chemistries and mirroring the current intellectual climate regarding environmentalism within the chemical industry (Figure 1). Suitable for the construction of ionic liquids are bulky asymmetric ions with a delocalised charge, although cation and anion need not both adhere to these requirements. Frequently used cations are based on 1,3- dialkylimidazolium ions, but other petroleum derived cations exist based on ammonium, pyridinium, and phosphonium structural motifs, among others. Complementing the selection of available ions are some potentially bio-derived species such as the lactate anion, possibly useful for the creation of biodegradable solvents. In the synthesis of an ionic liquid, formation of the desired cation is not typically accompanied by the corresponding anion. The reaction of chloroalkanes with nucleophiles such as methylimidazole for example to give organocations obviously yields the chloride salt, typically a solid at room temperature. Anion metathesis with another salt completes the synthesis. To their detriment, the reactions required for the manufacture of an ionic liquid do not usually go to completion, are performed in an organic solvent, and the anion metathesis step results in the stoichiometric production of an inorganic salt waste product.



**Figure 1.** Common or other otherwise valuable ionic liquid cations (top) and anions (bottom) where R– represents an alkyl group.

### Supercritical Carbon Dioxide (scCO<sub>2</sub>)

In contrast to some ionic liquids, the claim to greenness made by supercritical carbon dioxide (scCO<sub>2</sub>) is not hampered by a poor LCA. In fact carbon dioxide can be intercepted from industrial waste streams, and as a result its reuse as a solvent is not regarded as having a net gain on carbon emissions [5]. Carbon dioxide becomes a supercritical fluid at a temperature of at least 31.1 °C at pressures equal or greater to 73.8 bar [6]. A supercritical fluid (SCF) is characterised by properties that lie between that observed for the liquid and gaseous states. For example, the density and viscosity of a substance are found to decrease from the liquid state to the SCF state, and again from the SCF state to the gaseous state (Table 1) [7]. It is these and other quirky properties that extend interest in scCO<sub>2</sub> beyond simple green arguments. Aside from the possible but minor risk of asphyxiation, the use of carbon dioxide instead of typical liquid solvents has many health, safety, and environmental benefits [8].

**Table 1. Magnitude of selected properties belonging to different states of carbon dioxide.**

Property	Liquid	SCF	Gas
Density /g cm <sup>-3</sup>	10 <sup>0</sup>	10 <sup>-1</sup>	10 <sup>-3</sup>
Viscosity /Pa s	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>
Diffusivity /cm <sup>2</sup> s <sup>-1</sup>	10 <sup>-5</sup>	10 <sup>-3</sup>	10 <sup>-1</sup>

### Water

Water can also be utilised in the supercritical state as a solvent, but is typically used in the more familiar liquid state. Both water and CO<sub>2</sub> are naturally occurring inorganic solvents. Because they reside at the opposite extremes of solvent polarity, they offer an interesting platform for solvent optimisation studies beyond the use of organic solvents. The most celebrated application of an aqueous solvent within academic circles is perhaps the DielsAlder reaction, which benefits from the infamous hydrophobic effect [9]. Within the chemical industries the Ruhrchemie/Rhône-Poulenc „oxo“ process (a hydroformylation to give butyraldehyde) is widely applauded for its efficient and clean aqueous phase chemistry [10]. Akin to scCO<sub>2</sub>, the LCA describing water prior to its utilisation (i.e. cradle-to-gate) consists only of purification and distribution stages. Additionally any solvent-based health

concerns can be dismissed upon a solvent substitution in favour of water. Unfortunately due to reactivity and solubility issues water is not a suitable solvent for many chemical transformations, and as such the scope for applications is somewhat limited. Having said this, the low solubility of substrates in water is not always an unsurpassable restriction, with several “on-water” reactions reported in the literature [11].

### **Perfluorinated Solvents**

Arising from the ongoing quest for improved process efficiency in organic synthetic protocols, fluoruous biphasic systems (FBSs) have been shown to provide a means of recycling a catalyst-containing reaction medium, from which products can be easily extracted. Perfluorinated solvents include those based on alkanes such as perfluoroheptane and perfluoromethylcyclohexane, as well as perfluoropolyethers. Perfluorinated alkanes are typically immiscible with organic solvents at room temperature. This is due to a lack of polarisability and the rigid conformations they adopt. As a result perfluorinated alkanes can only engage in poor intermolecular interactions, and accordingly are regarded as less polar than even hydrocarbons [12]. Although a perfluorinated solvent can be used in a reaction without a complementary second liquid phase (organic or perhaps aqueous), typically the reaction will be designed so that the product will not be associated with the fluoruous phase, even if the reaction occurs in this non-polar environment. Accordingly, reactions that increase the polarity of a substrate are suited to this technology for purposes of product extraction. Oxidations and hydroformylations are examples of transformations that may potentially benefit from the use of a perfluorinated solvent. Further assisting these procedures are the high molar solubilities ( $\text{/mol.dm}^{-3}$ ) of gases in this class of solvent. However due to the high molecular weight of typical perfluorinated solvents molal solubilities ( $\text{/mol.kg}^{-1}$ ) are not extraordinary [13].

## **APPLICATION OF GREEN SOLVENTS**

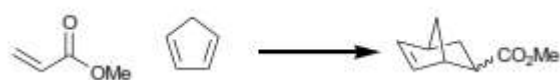
### **Synthetic Organic Chemistry Overview**

Assessing the success of solvent substitutions can be a somewhat complicated exercise, within which personal bias and the selective use and interpretation of metrics must be accounted for. It is also difficult to find reactions performed under identical conditions that only vary in the choice of solvent. Nevertheless certain reactions are favoured by green solvent chemists, and so many examples of certain transformations are available for scrutiny. Inevitably this academic favouritism has yielded discussions similar to that which follow, often numerous times. Slightly rarer however are comparisons across the neoteric and otherwise green solvents for a specific reaction, with arguments commonly divided by solvent class. This being so, the objective of this work is to address the issue of solvent selection from a life cycle perspective, regardless of the solvent's origin, for specific applications. The chemistries examined within are (1) the Diels-Alder reaction, (2) palladium catalysed cross-couplings, and (3) ring-closing metathesis. The manufacturing stages of the different solvent classes have already been addressed, and so for the following transformations a discussion of any end-of-life issues for suitable solvents will complete the holistic LCA approach advocated throughout this study.

## Diels-Alder Cycloaddition

The Diels-Alder reaction is an obvious target for green chemists as it is both synthetically useful and has been shown to benefit from the application of aqueous solvents. Conversely, from an ungreen perspective lithium perchlorate in diethyl ether (LPDE) is also a respected solvent system due to the benefits of its catalytic nature and high internal pressure [46-47]. This leaves us with an interesting dichotomy in which Diels-Alder cycloadditions can be performed in either water, usually regarded as a green solvent, or LPDE to take advantage of the inherent kinetic profile of the reaction, which usually favours both high pressure and hydrogen bond stabilising environments. The overriding issue with LPDE is the flammability and peroxide forming capability of the ether. The lithium perchlorate adds to waste concerns, although this argument also applies to aqueous systems utilising additives such as lithium chloride [48]. However substrate conversions and product selectivity can be improved by substituting water with LPDE, which raises a question over the relative importance of employing green solvents at the expense of reaction productivity [49].

Having just advocated aqueous cycloadditions, it is disappointing to concede that this viewpoint is not always shared by organic chemists. A popular review describing the application of the Diels-Alder reaction in the synthesis of natural products rarely presents a reaction that is not performed in either an aromatic or a chlorinated solvent [50]. This is probably due to a lack of concern regarding solvent effects within the organic synthesis community and the sensitivity of the delicate reactants in equal measure. This is unfortunate as these classes of solvent are subject to ever increasing scrutiny, illustrated by the restrictions imposed on benzene and carbon tetrachloride within industry [51]. It will be further measures like this that eventually force the hand of organic synthetic chemists to adopt greener protocols. It should also be made clear that the rate of Diels-Alder reactions are typically slow in these solvents, where it is not uncommon for reaction durations to be reported in days rather than hours. The advances made by using water as a solvent have inspired cycloaddition chemistry in other green solvents, also yet to be adopted by synthetic chemists. The default cycloaddition reaction system used to assess the performance of solvents tends to be that of cyclopentadiene and methyl acrylate, giving rise to both endo- and exo- products. In the absence of this specific example other reactions will be discussed when necessary.

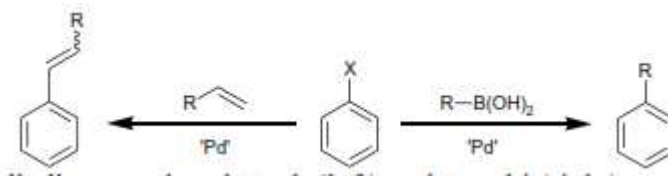


**Figure 2.** Reference reaction for probing solvent effects between methyl acrylate and cyclopentadiene.

## Cross-Coupling

Palladium catalysed cross-coupling reactions are regularly conducted in high-boiling dipolar aprotic solvents in order to dissolve the reaction components, which range from greasy hydrocarbons to inorganic salt additives. This combination of solvating prowess and access to high reaction temperatures is highly regarded, especially by those

performing Heck cross-coupling reactions. However the teratogenicity of solvents such as N,Ndimethylformamide (DMF) introduces an extra and unnecessary risk into these versatile and widely practiced reactions. Our emphasis will be placed on the Suzuki and Heck variants of the general cross-coupling procedure, as these protocols have an obvious advantage within the realm of green chemistry over their stoichiometric metal utilising counterparts such as the Stille (tin), Negishi (zinc), and Kumada (magnesium) coupling reactions (Figure3). Having said this, academic work does exist in which the quantities of tin required in the Stille reaction can be reduced to catalytic amounts [65]. Nevertheless, even if atom economy says otherwise, stoichiometric boron waste (i.e. the Suzuki reaction) would be preferable to most chemists when the alternative is a smaller amount of tin waste.



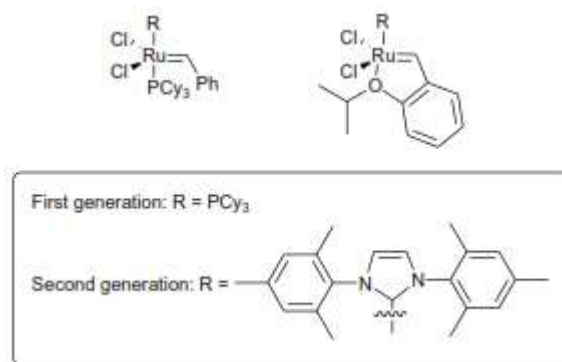
**Figure 3. Generic palladium catalysed Heck (left) and Suzuki (right) reactions.**

Ionic liquids have understandably been the focus of many studies, such is their broad appeal. A proven advantage to ionic liquids (shared with perfluorinated solvents) is the potential for the development of a reclaimable catalyst-solvent reaction phase that can be reused in subsequent runs. If the catalyst is ionic and not preferentially soluble in water then a recyclable medium becomes feasible. Perhaps the definitive example of this was developed by Earle and co-workers and applied to the Heck reaction [66]. The reaction is conducted in a hydrophobic ionic liquid, after which the product can be extracted into a low polarity molecular solvent, and the base additive (now neutralised with the hydrogen halide X R B(OH) R 2 'Pd' 'Pd' R R by-product of the reaction) is removed with a water wash.

### Ring Closing Metathesis

Our discussion of the Stille cross-coupling reaction has been intentionally restricted because of the benefits of the Suzuki reaction in analogous transformations. However  $sp^2$ - $sp^2$  couplings, especially for the synthesis of macrocycles, were first achievable via Stille coupling where other methods had failed [85]. However this procedure has been supplanted by Pd(OAc)<sub>2</sub> HN OMe OMe O O HN OMe OMe O O in recent times by ruthenium catalysed olefin metathesis, typified by the advances made with the different generations of Grubbs and Hoveyda catalysts (Figure 10) [86]. Both atom economy and the benevolence of waste streams have typically been improved with the transition from Stille coupling to olefin metathesis. However this is not to say that olefin metathesis is immune from the pressures of solvent selection and green chemistry. There is much scope for solvent improvement, especially to overcome two particular issues that arise from the use of ruthenium centred catalysts. Again mirroring the complications of the Stille reaction, traces of ruthenium in isolated products is problematic. The permissible levels of ruthenium contamination are as low as 10 ppm for pharmaceutical applications [87]. Secondly the reclamation of

this metal for reuse would be desirable from a monetary perspective, and as apparent from previous case studies the neoteric solvents offer modes of catalyst recycling conducive to this aim.



**Figure 4. Grubbs (top left) and Hoveyda (top right) type olefin metathesis catalysts.**

Although other forms of metathesis exist (ring opening, ring opening polymerisation, and cross metathesis), ring closing metathesis, henceforth abbreviated to RCM, is prevalent enough in the literature to form the basis of this overview. The RCM of diallyl tosylamide is the most practised cyclisation of this sort and will be scrutinised as our primary example (Figure 11). Based on review articles it appears that approximately 75% of procedures involve chlorinated solvents (predominately DCM) and about 25% use either benzene or toluene [88-90]. The reason for this is well justified, as catalyst decomposition is minimised in non-polar solvents [91]. However the acceleration to RCM reactions that can be provided by protic solvents such as acetic acid overwhelms any loss of catalyst activity within the context of a single experimental run [92]. Obviously this would have to be reassessed if the catalyst is to be reclaimed for further experiments.

## CONCLUSION

The emergence of a sustained and growing interest in green chemistry has led to the inception and application of a new generation of solvents, as well as a resurgence of aqueous phase synthetic chemistry. Ionic liquids, supercritical fluids, and perfluorinated solvents have all been found to have attributes amenable to novel and intriguing academic research, especially with regards to catalyst function and recycling. However the neoteric solvents are yet to impose themselves upon the chemical industry. The most high profile use of ionic liquids is probably the BASIL™ process designed by BASF, in which waste acid is neutralised by methylimidazole to give an easily removable liquid by-product [3]. The solvent is not ionic. Likewise the most obvious scCO<sub>2</sub> facilitated process is the decaffeination of coffee rather than a synthetic application [108-110]. Considering its other applications in extractions and chromatography, it might be fair to say that scCO<sub>2</sub> has enjoyed the most success as a solvent out of those examined within this work. Perfluorinated solvents are yet to make an impact on the same scale as their neoteric cousins, and this will be the case for the foreseeable future unless a significant advance is made that overcomes all the economic, operational, and environmental concerns they generate. Consequently biosolvents may gain some impetus in the near future as more research groups develop or otherwise infer „like-for-like“ replacements for conventional

solvents. Because biosolvents possess no significant structural deviations from the various functionalities that give petrosolvents such versatility, their introduction into synthetic chemistry is not hindered by a need for proof of concept studies or apprehension from research chemists.

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