

Chlorinated Solvents: Their Advantages, Disadvantages and Alternatives in Organic and Medicinal Chemistry

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Abstract

Chlorinated solvents were once, and in many places are still, ubiquitous in chemistry laboratories. This review explores the properties that led to such widespread use; why there is now an increasing drive to minimize usage, and what alternatives are currently available.

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List of Abbreviations

Abbreviation	Definition
ACS	American Chemical Society
API	Active Pharmaceutical Ingredient
BF ₄	Tetrafluoroborate
BOC	<i>tert</i> -butyloxycarbonyl
BOC ₂ O	Di- <i>tert</i> -butyl dicarbonate
<i>t</i> -BuOH	<i>tert</i> -Butyl alcohol
CCl ₄	Carbon tetrachloride
CH ₃ CN	Acetonitrile
CHCl ₃	Chloroform
CICAD	Concise International Chemical Assessment Documents
CNS	Central Nervous System
COSMO-RS	COnductor like Screening MOdel for Real Solvents

CPME	Cyclopentyl methyl ether
DABAL-Me ₃	Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]-octane
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
DAST	(Diethylamino)sulfur trifluoride
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DES	Deep-eutectic solvents
DIBAL	Diisobutylaluminum hydride
DIC	<i>N,N'</i> -Diisopropylcarbodiimide
DMA/DMAc	Dimethylacetamide
DMC	Dimethyl Carbonate
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DOM	Directed Orto Metalation
EHS	Environmental, Health & Safety
EPA	Environmental Protection Agency (USA)
Et ₃ N	Triethylamine
EtOAc	Ethyl Acetate
EtOH	Ethanol
EU	European Union
GCI	Green Chemistry Institute
GCIPR	Green Chemistry Institute Pharmaceutical Roundtable
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GSK	GlaxoSmithKline
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
HFIP	Hexafluoroisopropanol

HMTA	Hexamethylenetetramine
HPLC	High-Performance Liquid Chromatography
HSP	Hansen Solubility Parameters
HWE	Horner–Wadsworth–Emmons
IARC	International Agency for Research on Cancer
ICSC	International Chemical Safety Cards
IPA	<i>Iso</i> -propanol
MeOH	Methanol
MSDS	Material Safety Data Sheets
NBP	<i>N</i> -Butylpyrrolidinone
NBS	<i>N</i> -Bromosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NHC	<i>N</i> -Heterocyclic Carbene
NMP	<i>N</i> -Methylpyrrolidinone
NMR	Nuclear Magnetic Resonance
OPR&D	Organic Process Research & Development
PEG	Polyethylene Glycol
PET	Positron Emission Tomography
PF ₆	Hexafluorophosphate
PI3K	Phosphoinositide 3-kinases
PMI	Process Mass Intensity
PPE	Personal Protective Equipment
RCM	Ring Closing Metathesis
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RNA	Ribonucleic acid
RSC	Royal Society of Chemistry
SDS	Safety Data Sheet
T ₃ P	Propanephosphonic Acid Anhydride

TBAF	Tetrabutylammonium Fluoride
TBME	tert-Butyl Methyl Ether
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMO	2,2,5,5-tetramethyloxolane
TMS	Tetramethylsilyl
TPGS-750-	
M	DL- α -Tocopherol Methoxypolyethylene Glycol Succinate
VOC	Volatile Organic Carbon
WEL	Workplace Exposure Limit
WHO	World Health Organisation

1.0 Introduction

Chlorinated solvents that are commonly employed in organic and medicinal chemistry include dichloromethane (DCM), chloroform, 1,2-dichloroethane (DCE), carbon tetrachloride (CCl₄), chlorobenzene, 1,2-dichlorobenzene, 1,1,1-trichloroethane and trichloroethylene. Of these, DCM and chloroform have found most widespread usage in synthetic organic chemistry laboratories. Outside of synthetic organic chemistry, chlorinated solvents see widespread use in the manufacture of silicon, as degreasers, paint strippers and general cleaning applications.¹ In 2007, finding and publicizing alternatives to halogenated solvents was identified by the ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) as a key theme in which more research was required.² Similarly, in 2018 the same research theme was identified once again by the ACS GCIPR as an ongoing concern.³ Thus, it has been made clear that viable alternatives to halogenated solvents need to be identified and that this is a high priority concern for many pharmaceutical companies.³ The motivation for identifying alternatives to

halogenated solvents are manifold and include environmental health and safety concerns, economical and disposal costs, and regulatory and legal frameworks.³

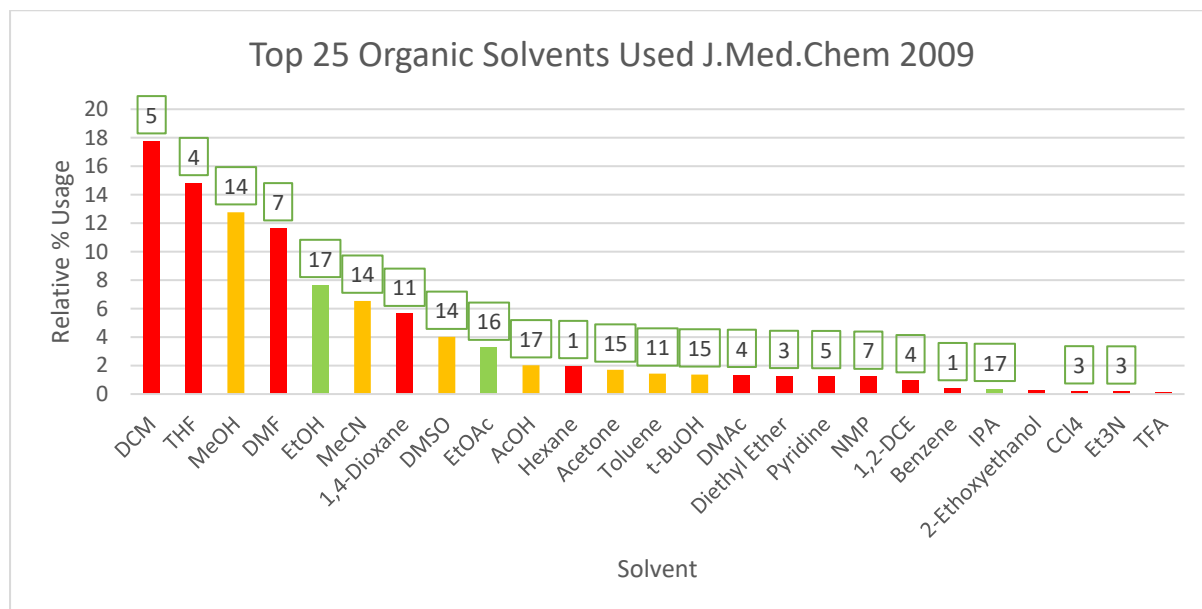


Fig. 1: Proportion of solvent usage of J. Med. Chem. issues 1-2 in 2009 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color coded using a traffic light metric: Green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).⁴ EHS scores are those determined by Prat et al⁵; the higher the score, the more favorable the EHS profile of the solvent. Scores for 2-Ethoxyethanol and TFA are unknown.

To determine how the solvent usage landscape may have changed over the past decade, a poll of solvent usage in J. Med. Chem. for the first two issues published in 2009 was conducted to establish baseline usage in a typical medicinal chemistry journal⁶. It was found that 19% of all reactions reported (3282 reactions in 129 documents) involved the use of a chlorinated solvent with DCM being the most common (~18%), followed by DCE (~1%) and CCl₄ (~0.2%). Chloroform did not appear in the top 25 most common solvents (0.04%), Fig. 1.

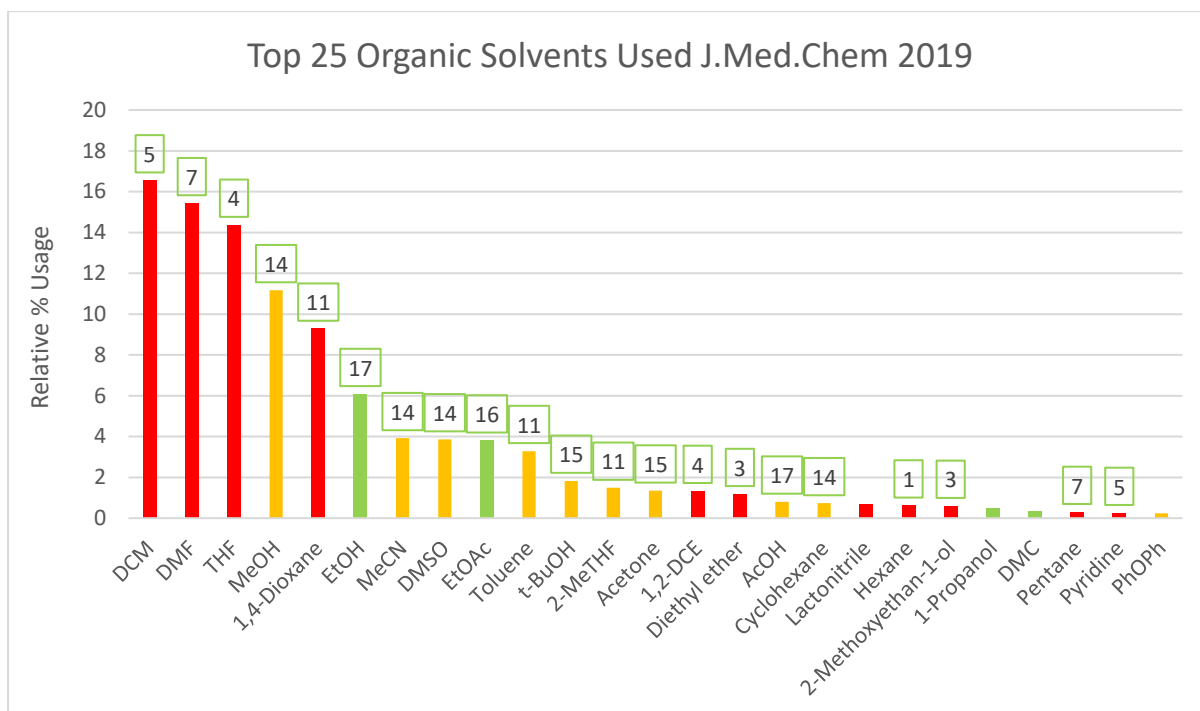


Fig. 2: Proportion of solvent usage of J. Med. Chem. issues 1-2 in 2019 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color coded using a traffic light metric: Green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).⁴ EHS scores are those determined by Prat et al⁵; the higher the score, the more favorable the EHS profile of the solvent. Color codes for decane and undecane are unknown. Solvent scores for lactonitrile, 1-propanol, dimethyl carbonate (DMC) and diphenyl ether (PhOPh) are unknown.

The same search was applied to solvent usage in J. Med. Chem. publications 2019 and the results were almost identical, Fig. 2⁶; chlorinated solvents made up 18% of all solvents used, with DCM remaining the most popular (16.6%) followed by DCE (1.3%) and then chloroform (0.2%). Declining use of CCl₄ was observed (down to just 0.01% compared to 0.2% in 2009). Other changes that can be seen are the appearance of cyclohexane and dimethyl carbonate in the top 25 (both of which are considered somewhat greener, safer and more sustainable alternatives in their respective classes,⁴ examples of which are discussed in section 4.0).

It comes as a surprise that in the intervening ten years between ACS roundtable publications that chlorinated solvent usage in pre-clinical medicinal chemistry has not

appreciably changed, even with the concomitant growth and expansion of the field of Green Chemistry and direct emphasis on the importance of safe and sustainable solvent selection being highlighted by pharmaceutical companies.³

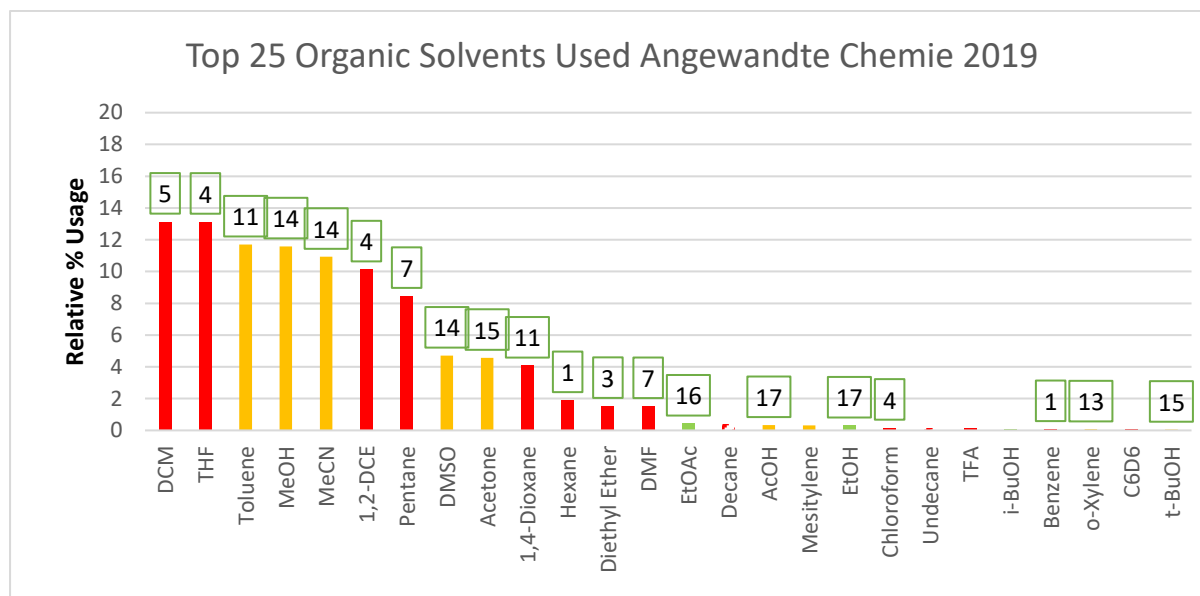


Fig. 3: Proportion of solvent usage in *Angewandte Chemie* publications, issue 1, 2019⁷ with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color coded using a traffic light metric: Green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).⁴ EHS scores are those determined by Prat et al⁵; the higher the score, the more favorable the EHS profile of the solvent. Color codes for decane and undecane are unknown. Solvent scores for decane, mesitylene, undecane, TFA, iBuOH and C₆D₆ are unknown.

Solvent usage analysis was then conducted on archetypal organic chemistry research journal *Angewandte Chemie* for 2019, issue 1, to assess whether general solvent usage trends differed between organic and medicinal chemistry research disciplines. The results portray a slightly different picture, Fig. 3. In total, 111 papers containing 8441 reactions were analyzed and showed that DCM and THF were the most popular solvents employed. Toluene also featured far more prominently as the third most popular choice, whereas DMF and 1,4-dioxane appeared far less, thus highlighting their prominent use in medicinal chemistry and drug discovery. The major difference regarding chlorinated solvent usage is the far more prevalent use of DCE (6th most popular) which featured in 10% of the

reactions analyzed. These differences highlight the variety, focus and prevalence of various solvents across both organic and medicinal chemistry research disciplines. The individual solvent usage trends may be further explained and rationalized by the types of reactions and transformations conducted, see section 4.2 *vide infra*.

When carrying out analysis of solvent usage in the Journal of Organic Process Research and Development (OPR&D) publications for 2019 we can see a very different distribution of solvents (Fig. 4) when compared to both Fig. 3. Of note is that chlorinated solvents only make up ~10% of the solvents used and that DCM still remains the most popular (8.6%), followed by chloroform (1.6%). DCE does not feature in the top 25 solvents. The overall chlorinated solvent usage in OPR&D is half that of J. Med. Chem., thus a very different solvent usage landscape can be observed when comparing the two fields (

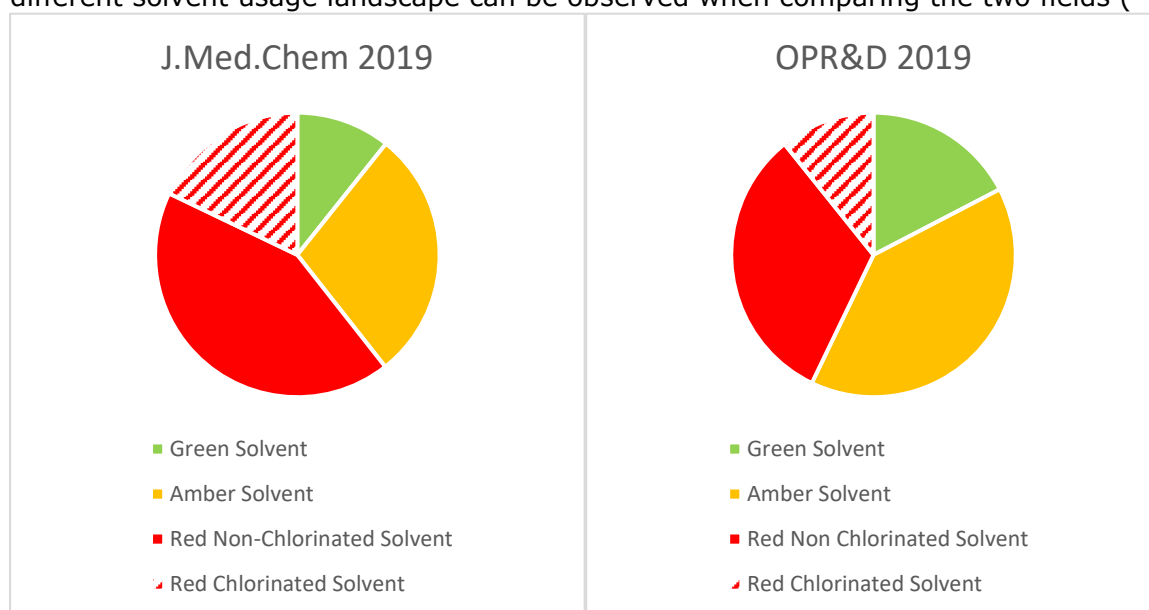


Fig. 5), i.e. a lot less "red" solvents are utilized in OPR&D publications.

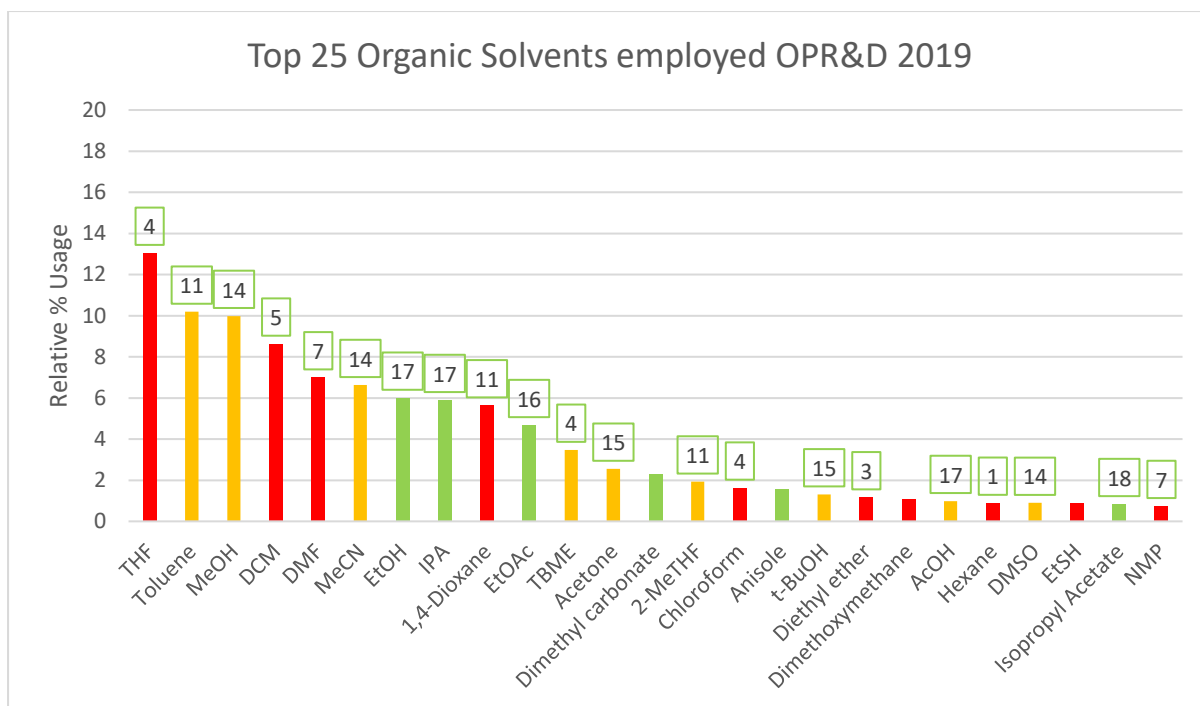


Fig. 4: Proportion of solvent usage of all OPR&D publications in 2019 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color coded using a traffic light metric: Green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).⁴ EHS scores are those determined by Prat et al⁵; the higher the score, the more favorable the EHS profile of the solvent. Color codes for decane and undecane are unknown. Solvent scores for dimethyl carbonate, anisole, dimethoxymethane and ethanethiol are unknown.

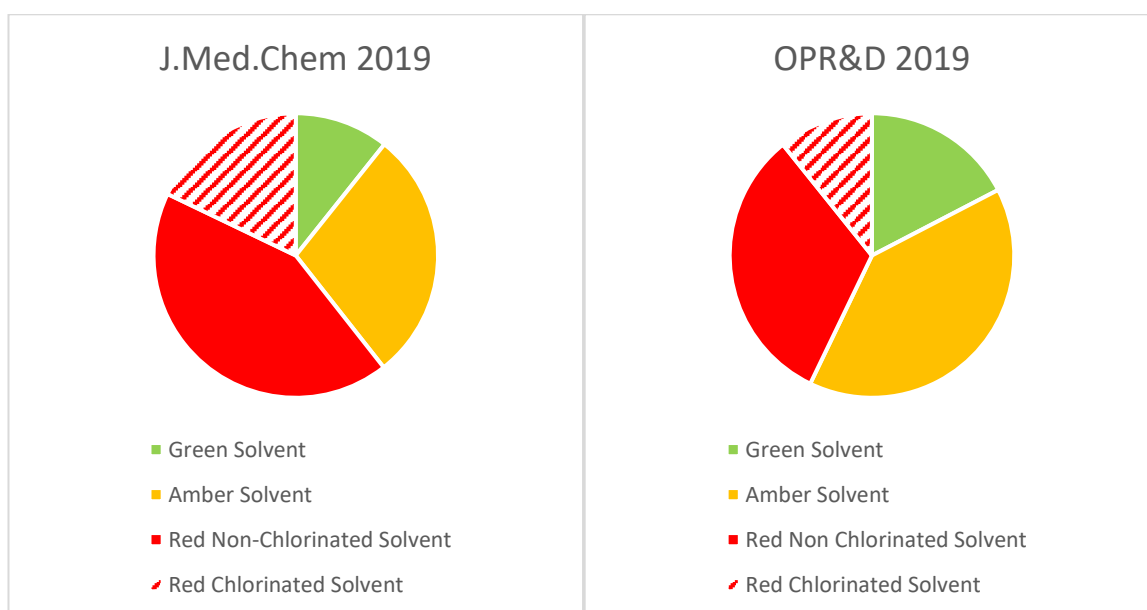


Fig. 5: Top 25 organic solvents employed J.Med.Chem. 2019 (left) vs OPR&D 2019 (right). Solvents categorized by a traffic light metric: Green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).⁴

The reason for the different solvent usage landscapes may be attributed to the policies that many process chemistry departments have in actively trying to avoid the use of chlorinated solvents.⁸ Since 2012, OPR&D editorial policy has been such that papers containing strongly undesirable solvents (including CCl₄ and chloroform) will only be considered if accompanied by an analysis of alternatives, or if a convincing justification for their use is presented.⁹ Solvent use in process chemistry for the period of 1997-2012 has previously been reviewed and the declining use of chloroform has been well highlighted.¹⁰ Advances in green and sustainable chemistry are also highlighted in OPR&D's publications entitled: "Green Chemistry Articles of Interest to the Pharmaceutical Industry".¹¹ The series, which has been published 1-2 times a year since 2008¹², captures items that are believed to be of significant importance to the wider pharmaceutical industry and is an excellent platform for showcasing and highlighting state of the art green and sustainable chemistry developments.

Significant changes in solvent usage practices have also been observed on industrial scale pharmaceutical chemistry. In the period of 2000-2005 the GSK Pilot plant reduced its reliance on DCM from being its 3rd most popular solvent to 8th.¹³ Similarly, by 2015 Pfizer had not transferred a process to manufacturing that involved a halogenated solvent for at least eight years¹⁰ and had reduced their use of chloroform in small molecule drug discovery from 1150 kg in Q4 2007 to just 21 kg in Q4 2008.¹⁴

The expanding use of greener and more sustainable solvents in chemical processes has been thoroughly reviewed by Clarke *et al.* in 2017.¹⁵ More recently Sharma *et al.* have examined green chemistry practices in the pharmaceutical industry.¹⁶ Even though less chlorinated solvent usage may be observed in process and industrial pharmaceutical chemistry, it still remains significant and the challenges of finding "drop in" replacements for chlorinated solvents such as DCM and DCE have been acknowledged.³

Solvents typically constitute the biggest percentage of the mass intensity of an Active Pharmaceutical Ingredient (API) process¹⁷; around 56% of the mass intensity of an API process can be attributed to organic solvent.¹⁸ If water is included as part of the solvent mass intensity calculation then between 80-90% of an entire API process mass intensity can be attributed to solvent.¹³ It is typical for reactions to be conducted at increasingly higher concentrations as they are scaled up, and with process refinement and optimization, the total use of solvent does decrease across the development phases towards product launch.¹⁹ Consequently, the volume of chlorinated solvents used also decreases across the development phase showing that the primary users of chlorinated solvents are those working in preclinical R&D. Not only are reactions typically more dilute earlier in the R&D pipeline, but they may require solvent intensive purification protocols. It is evident that solvent remains an enormous contributing factor in the sustainability credentials of a pharmaceutical product once the whole discovery and development process is taken into account.

Solvents have long been recognized as one of the biggest contributors to the cradle-to-gate life cycle impact of pharmaceutical products.²⁰ It is therefore reasonable that if trying to minimize the environmental impact of either an individual route, or more broadly the whole of an operational R&D facility, solvent choice should be one of the first options to consider. Given the prevalence of chlorinated solvent usage, it is worth considering their advantages and disadvantages, especially those of DCM as the most widely used chlorinated solvent in pharmaceutical R&D. The following sections discuss the advantages (section 2.0) and disadvantages (section 3.0) of the use of chlorinated solvents and is followed by an in-depth analysis of the viable alternatives to chlorinated solvents in organic and medicinal chemistry transformations (Section 4.0).

2.0 Advantages of Chlorinated Solvents

2.1 Physico-Chemical Properties and Relevant Applications

2.1.1 Solvent Polarity Descriptors

When looking for the ideal solvent for a particular purpose, a variety of different properties must be considered. One of the most fundamental is whether the liquid concerned solubilizes the solute of interest. Solvent polarity is a common term to describe and assess the ability of a solvent to solvate dissolved charged or neutral, apolar or dipolar species. It is not always easy to quantify. The relative permittivity (or dielectric constant) can be used as a measure of polarity; however, it regards solvents as having no structure and comprising an isotropic continuum. As such, it ignores solvent/solvent interactions or solvent/solute interactions. Dipole moments also do not provide a complete picture as the charge distribution may lead to quadrupole or higher multipole moments which might be relevant.²¹ Empirical parameters are therefore sometimes used to give a measure of solvent polarity e.g. from spectroscopic measurements (Table 1), and have been promoted as useful tools for making more informed solvent replacements.²²

Solvent	ϵ_r^a	$\mu / (10^{-30} \text{ Cm})^b$	$E_T^N^c$
Water	78.36	6.2	1.000
Methanol	32.66	9.6	0.762
2-Methoxyethanol	16.93	6.8	0.657
Ethanol	24.55	5.5	0.654
Acetic Acid	6.17 (20 °C)	5.6	0.648
2-Propanol	19.92	5.5	0.546
Propylene carbonate	64.92	16.5	0.472
Acetonitrile	35.94	13.0	0.460
Dimethyl sulfoxide	46.45	13.5	0.444
<i>t</i> -Butanol	12.47	5.5	0.389
<i>N,N</i> -Dimethylformamide	36.71	12.7	0.386

1-Methylpyrrolidin-2-one	32.2	13.6	0.355
Acetone	20.56	9.0	0.355
1,2-Dichloroethane	10.36 (18 °C)	6.1	0.327
Dichloromethane	8.93	3.8	0.309
Pyridine	12.91	7.9	0.302
Chloroform	4.89	3.8	0.259
1,2-Dimethoxyethane	7.20	5.7	0.231
Ethyl acetate	6.02	5.9	0.228
Tetrahydrofuran	7.58	5.8	0.207
Chlorobenzene	5.62	5.6	0.188
1,2-Dichlorobenzene	9.93	8.3	0.225
1,1,1-Trichloroethane	7.25 (20 °C)	5.7	0.17
1,4-Dioxane	2.21	1.5	0.164
Trichloroethylene	3.42 (16 °C)	2.7	0.160
<i>t</i> -Butyl methyl ether	4.5 (20 °C)	4.1	0.124
Diethyl Ether	4.20	3.8	0.117
Toluene	2.38	1.0	0.099
Carbon tetrachloride	2.24	0.0	0.052
Triethylamine	2.42 (20 °C)	2.2	0.043
Tetrachloroethene	2.5 (21 °C)	0.0	0.043
<i>n</i> -Heptane	1.92 (20 °C)	0.0	0.012
<i>n</i> -Hexane	1.88	0.0	0.009
Cyclohexane	2.02 (20 °C)	0.0	0.006

Table 1: Common organic solvents, in order of decreasing E_T^N as an empirical parameter of solvent polarity.²³ Chlorinated solvents highlighted in red. ^a Relative permittivity (commonly referred to as dielectric constant) of the pure liquid at 25 °C unless followed by another temperature in parentheses. ^b Dipole moment in Coulombmeter (Cm), measured in benzene, carbon tetrachloride, 1,4-dioxane or *n*-hexane at 20 - 30 °C. ^c Normalized E_T^N values derived from the transition energy at 25 °C of the long wavelength visible absorption of a standard pyridinium *N*-phenolate betaine dye

(normalized between water and TMS as extreme reference solvents) i.e. Normalized Reichardt parameter.

The consideration of dipole moments and higher multipole moments can lead chlorinated solvents, such as DCM, to be considered as more polar than their relative permittivity would initially suggest. It is this ability of DCM to act as a relatively non-polar eluent, yet one that dissolves a broad range of chemical compounds, which has made it such an attractive solvent for chromatography.²⁴ These solubility phenomena may be further rationalized by their Hansen solubility parameters or indeed by the Kamlet-Taft parameters.

Solvents	δD	δP	δH
Chloroform	17.8	3.1	5.7
Dichloromethane	17	7.3	7.1
1,2-Dichloroethane	18	7.4	4.1
Chlorobenzene ²³	19	4.3	2.0
1,2-Dichlorobenzene ²⁵	19.2	6.3	3.3
1,1,1-Trichloroethane	16.8	4.3	2.0
Trichloroethylene	18	3.1	5.3
Tetrachloroethylene	18.3	5.7	0.0
Carbon tetrachloride	17.8	0	0.6

Table 2: Hansen solubility parameter (HSP) values for some commonly used chlorinated solvents, from ref [24-25] unless noted otherwise. HSP can be used to describe the inter-molecular interactions between solvent and solute. There are three parameter categories: dispersion i.e. Van der Waals forces (δD), polarity (δP) and hydrogen bonding (δH).

The numerical values assigned to each HSP category allow for intuitive categorization of solvents based on whether they are non-polar or polar protic/aprotic. Additionally the Hansen solubility parameters can be used to assess the characteristics of solvent blends based on weighted averages of the values in each category.²⁶ A useful excel sheet is available online for the calculation of HSP spheres (3 dimensional representations of solvent space) and the calculation, prediction and optimization of solvent blends.²⁶⁻²⁷

Solvents	π^*	β	α
Chloroform	0.58	0.00	0.44
Dichloromethane	0.82	0.00	0.30
1,2-Dichloroethane	0.81	0.00	0.00
Chlorobenzene	0.71	0.07	0.00
1,2-Dichlorobenzene ²⁸	0.80	0.03	0.00
1,1,1-Trichloroethane	0.49	0.00	0.00
Trichloroethylene	0.53	0.00	0.00
Tetrachloroethylene	0.28	0.00	0.00
Carbon tetrachloride	0.28	0.00	0.00

Table 3: Kamlet-Taft parameters for some commonly used chlorinated solvents. From ref [27] unless noted otherwise ²⁸⁻²⁹

Other frameworks within which solvents can be described include Kamlet-Taft, which describes polarity based on solvatochromic relationships between solvent and a number of test dyes. The measurements separately describe the dipolarity/polarizability (π^*), hydrogen-bonding acidity (donor) (α) and hydrogen-bonding basicity (acceptor) (β) of the solvent. All three of these properties contribute to the overall polarity of the solvent.³⁰ As can be seen from Table 3 both chloroform and DCM are the only chlorinated solvents from this selection to have any hydrogen-bonding acidity character i.e. an ability to act as a H-bond donor.

Solvents **E** **S** **A** **B** **V** **L**

Chloroform	0.43	0.49	0.15	0.02	0.6167	2.48
Dichloromethane	0.39	0.57	0.10	0.05	0.4943	2.019
1,2-Dichloroethane	0.42	0.64	0.10	0.11	0.6352	2.573
Chlorobenzene	0.718	0.65	0	0.07	0.8388	3.657
1,2-Dichlorobenzene	0.872	0.78	0	0.04	0.9612	4.518
1,1,1-Trichloroethane	0.37	0.41	0	0.09	0.7576	2.733
Trichloroethylene	0.52	0.37	0.08	0.03	0.7146	2.997
Tetrachloroethylene	0.64	0.44	0	0	0.837	3.584
Carbon tetrachloride	0.46	0.38	0	0	0.7391	2.823

Table 4: Abraham's parameters for a number of chlorinated solvents.³¹ Solute descriptors are: E, S, A, B, V or L. E is the solute excess molar refractivity ($\text{cm}^3\text{mol}^{-1}$)/10, S is the solute dipolarity/polarizability, A is the sum of H bond acidity, B is the sum of H bond basicity. V is the McGowan characteristic volume ($\text{cm}^3\text{mol}^{-1}$)/100 for use in liquid-liquid partition calculations. L is a gas-liquid partition coefficient to *n*-hexadecane at 298.2 °K.³²

The Abraham solvation model is a method of describing solvents and was developed to aid in predicting partition coefficients for conventional organic solvents and for predicting drug molecule partition across membranes etc.³²⁻³³ The Abraham model describes solvent log P i.e. solvent/water partition coefficient according to Equation 1 and is based on linear free energy relationships. The upper-case values represent solute descriptors, described below Table 4. The lower case values (c, e, s, a, b, v/l) are solvent coefficient values that are complementary to water-solvent or gas-solvent systems of interest.³⁴ These coefficient values are experimentally determined using linear regression from partition and solubility experiments of solvent and solutes with known Abraham descriptors. The coefficients have also been reported by Abraham et al.³⁵ The intercept, c, is not set to zero and represents other information not described by these parameters. As can be seen from Table 4, chloroform and DCM are described as having some hydrogen bond acidity character (A). Trichloroethylene is also described having weak hydrogen bond acidity which was not described under Kamlet-Taft, Table 3. Similarly, weak hydrogen bond basicity (B) is described for many of the solvents in Table 4.

$$\log P = c + e E + s S + a A + b B + v V$$

Equation 1: Abraham model Log P calculation.

By extension, the model can allow for prediction of the aqueous-organic partition coefficient of organic molecules in various solvents according to Equation 2.

$$\log S_s = \log S_w c + e E + s S + a A + b B + v V$$

Equation 2: Abraham model solubility prediction. *Log S_s* = molar conc. of solute in solvent. *Log S_w* = molar conc. of solute in water

Predicted Abraham's solubility parameters have been used by Bradley *et al.* to predict the properties of a number of sustainable solvents and used to suggest potential replacements.

³⁶ An online database of Abraham's solubility parameters is available online and contains over 3000 entries.³¹

2.1.1.1 C-H Bond activation

Due to the specific solubilizing and physico-chemical characteristics of chlorinated - and other halogenated - solvents, they have found themselves in a unique position in the field of C-H bond activation chemistry. The key features that many of the solvents employed in C-H bond activation possess include a high polarity character in combination with both hydrophilic and hydrophobic moieties e.g. hexafluoroisopropanol (HFIP) and trichloroethanol. Some solvents, such as HFIP and trichloroethanol also contain an acidic OH group which overall leads to desirable H-bond donation capability.³⁷ Due to the unique blend of physico-chemical properties required for C-H bond activation chemistry, finding alternative solvents that meet these requirements is extremely challenging and is further discussed in section 4.2.5.1.

2.1.2 Melting Points, Boiling Points, Flammability, Flash Points and Auto-ignition Temperatures.

Solvent	m.p.	b.p.
1,2-Dichloroethane	-36 °C	84 °C

Dichloromethane	-95 °C	40 °C
Chloroform	-64 °C	61 °C
Chlorobenzene	-45 °C	132 °C
1,2-Dichlorobenzene	-17 °C	180 °C
1,1,1-Trichloroethane	-33 °C	74 °C
Trichloroethylene	-73 °C	87 °C
Tetrachloroethylene	-22 °C	121 °C
Carbon tetrachloride	-23 °C	77 °C

Table 5: Melting points and boiling points of selected chlorinated solvents.³⁸⁻³⁹

Chlorinated solvents can sometimes offer safety advantages over non-chlorinated solvents through their lack of flammability, which can be seen in their flash points and autoignition temperatures (Table 6). Indeed, chloroform has been used as a fire extinguishing agent in its own right.⁴⁰ There may also be times when the conductivity and dipole moment (or lack thereof) can favor chlorinated solvents for certain purposes. CCl₄ may once have been favored as a dry cleaning agent, not only for its solubilizing properties, but also for home dry cleaning use due to absence of a flash point.⁴¹

The low melting point of chlorinated solvents (Table 5) has made them suitable choices for low temperature reactions, and their low boiling points have contributed to their popularity as work-up and purification solvents, as they can easily be evaporated. High volatility however also contributes significantly to health and safety concerns which will be discussed later in section 3.0, *vide infra*.

Solvent	Flash Point / °C	Auto-ignition Temperature /°C
1,2-Dichloroethane	13	413
1,1,1-Trichloroethane	>93	537
Acetone	-17	465
Acetonitrile	6	524
Carbon tetrachloride	None	528

Chlorobenzene	28	590
1,2-Dichlorobenzene	66	648
Chloroform	None	613
Cyclohexane	-20	260
Dichloromethane	None	605
Diethyl Ether	-45	175
Ethanol	13	363
Ethyl Acetate	-4	427
Heptane	-4	204
Hexane	-22	225
Methanol	10	455
Tetrahydrofuran	-21	215
Tetrachloroethylene	None	>650
Trichloroethylene	None	410
Toluene	4	480

Table 6: Flash points and auto-ignition temperatures of common solvents.³⁹ Chlorinated solvents highlighted in red.

2.1.2.1 Cleaning Applications

Outside of organic and medicinal chemistry the low boiling points, high volatility and ability to solubilize a wide variety of organic materials have led to chlorinated solvents being used in cleaning applications. Perceived worker safety benefits due to the low/non-flammability of many chlorinated solvents also contributed to their widespread adoption over more flammable hydrocarbon solvents.⁴² For example 1,1,1-trichloroethane, trichloroethylene and DCM have historically seen widespread use in vapor degreasing, electronics and cold cleaning applications and tetrachloroethylene has seen widespread use as a dry cleaning fluid. DCM has also been a popular component of paint stripper.⁴² The alternatives to these chlorinated solvents in cleaning applications, discussed in the exemplary review by Wolf *et al.* in 1991, were mostly aqueous based processes utilizing unspecified cleaning additives (most likely surfactants for degreasing etc.).⁴² Major considerations were

highlighted including that (1) the toxicity of these additives were unknown, (2) water intense processes are often higher energy processes, (3) that contaminated aqueous waste is often disposed of into the sewer and (4) that alternatives can often be incompatible with the application hardware e.g. aerosol degreasers designed specifically for chlorinated solvents. Thus, the issue of whether solvent and process alternatives are compatible and safer have long been considered.

2.1.3 UV-Vis, Viscosity and Refractive Index

Solvent	nm ^a	Viscosity (cP) Refractive	
		25 °C	Index 20 °C
1,2-Dichloroethane	226	0.779	1.442
Acetone	330	0.306	1.359
Acetonitrile	190	0.369	1.344
Carbon tetrachloride	265	0.908	1.457
Chlorobenzene	287 ⁴³	0.753	1.525
1,2-Dichlorobenzene	295 ⁴³	1.324 ³⁹	1.549 ³⁹
Chloroform	245	0.537	1.443
Cyclohexane	210	0.894	1.427
Dichloromethane	235	0.413	1.424
Diethyl Ether	218	0.224	1.352
Ethanol	210	1.074	1.361
Ethyl Acetate	255	0.423	1.372
Heptane	197	0.387	1.388
Hexane	210	0.300	1.375
Methanol	205	0.544	1.328
Tetrachloroethylene	290	0.844	1.506 ³⁹
1,1,1-Trichloroethane	-	0.793	1.503
Trichloroethylene	273 ³⁹	0.545	1.438 ³⁹
Tetrahydrofuran	220	0.456	1.407

Toluene	286	0.560	1.497
Water	191	0.890	1.333

Table 7: UV cut-off wavelengths,⁴⁴ refractive index,^{39, 45} and viscosity^{39, 44} of some common solvents. Wavelength at which the solvent absorbs 1.0 AU in a 10-mm cell. Chlorinated solvents highlighted in red.

Chlorinated solvents are frequently employed as chromatography solvents especially in flash chromatography applications. The UV cut-off for DCM is sufficiently low that a standard fixed wavelength UV lamp emitting at 254 nm will not cause DCM to absorb appreciably. Furthermore, the ability of DCM to dissolve a wide variety of polar and non-polar substrates and its ease of removal by evaporation have lead it to become one of the most popular chromatography solvents for decades.⁴⁶

2.1.4 Economic Considerations – Cost of Chlorinated Solvents

The apparent low cost of chlorinated solvents such as DCM and chlorobenzene have clearly contributed to their popularity, however these costs do not take into account either the cost of chilled storage where needed, or the cost of incinerating and scrubbing for volatile organic compounds (VOCs), *vide infra*. Of note is the considerably higher cost of carbon tetrachloride, which should inevitably promote further reductions in its in R&D environments (Table 8). 1,1,1-Trichloroethane was also no longer available for purchase from Sigma Aldrich at the time of writing and may reflect the phase out of this solvent due to its ozone depleting potential.⁴⁷ Economy of scale is evident as the pricing of 2.5L of DCM amounts to £13.80 per liter. Also included are some greener and more sustainable solvents for comparative purposes. Of note is that the cost per L of EtOAc is not much more expensive than DCM and IPA is only 30 p more expensive. However, other greener solvents such as anisole, CPME and 2-MeTHF are considerably more expensive than DCM, Table 8.

Solvent	Cost per L 2020	Cost for Cheapest 2.5 L
---------	-----------------	-------------------------

1,2-Dichloroethane	£49.10	£88.00
1,1,1-Trichloroethane	-	-
Dichloromethane	£22.00	£34.50
Chloroform	£37.90	£70.40
Chlorobenzene	£28.30	£50.10
1,2-Dichlorobenzene	£27.80	£57.70
Trichloroethylene	£79.00	£165.00
Tetrachloroethylene	£38.90	£81.40
Carbon tetrachloride	£803.00 (£80.30 per 100 mL)	-
Some Popular Green Solvents:		
Ethyl Acetate (EtOAc)	£26.90	£46.20
Isopropyl Alcohol (IPA)	£22.30	£36.50
Dimethyl Carbonate	£33.90	£131.00
Methyl Isobutyl ketone (MiBK)	£44.40	£103.00
Anisole	£59.20	£68.50
Cyclopentyl methyl ether (CPME)	£79.50	-
2-Methyl tetrahydrofuran (2-MeTHF)	£47.80	£99.20

Table 8: Typical costs per liter of common chlorinated solvents and greener more sustainable solvents as of June 2020.⁴⁸Note CCl₄ is only sold at £80.30 per 100 mL via Sigma Aldrich making the cost per liter £803.00 per L. Prices correct at time of publishing.

2.2 Summary

In summary, chlorinated solvents occupy a privileged solvent space. Their physico-chemical properties such as low boiling points, general non-flammability and unique blend of polarity descriptors in conjunction with general availability and low-cost have led to their widespread use, worldwide, for nearly a century. One factor behind the popularity of chlorinated solvents, which should not be underestimated, is the wealth of existing precedence for reactions conducted in chlorinated solvents. It is logical that chemists seek

close precedence in the literature before trying reactions, and in many cases, time may preclude solvent screens to optimize reactions, or such optimization may be unnecessary once a product has been obtained. In this way, the past prevalence of chlorinated solvents in the literature can lead to a self-reinforcing popularity of these solvents. In some cases, the use of chlorinated solvents may have been necessary, or have given the best results, however, in many cases it may have been the only solvent tried.

Any attempt to try to address the trends in solvent usage must therefore seek to popularize when alternatives to chlorinated solvents can be used. Also of critical importance is whether the alternatives are actually safer and more sustainable than the solvent undergoing replacement. As such, the remainder of this review aims to highlight the disadvantages of using chlorinated solvents and to promote the use of alternatives.

3.0 Disadvantages of Chlorinated Solvents

Having discussed the benefits of the use of chlorinated solvents that have led to their historical prominence as solvents of choice, we must now discuss the myriad of disadvantages from a health and safety, environmental and sustainability perspective. The use of chlorinated solvents is incongruous with the 12 Principles of Green Chemistry which suggests that we employ "Safer Solvents".⁴⁹ The reasons for these safety concerns are outlined in this section.

3.1 Health Effects, Environmental Concerns and Laboratory Safety

It has long been known that chlorinated solvents such as CCl_4 and chloroform have potentially serious toxicological effects on organic life including carcinogenic effects, damage to health through chronic exposure, specific organ toxicity, reproductive damage, neurotoxicity, risk of asphyxiation, flammability of certain solvents and ozone depleting effects.⁴² Indeed, chloroform and trichlorethylene were employed as an anesthetic during the 20th century due to their abilities to suppress the central nervous system (CNS).⁵⁰ The major health effects and hazards are outlined in Table 9 and it is quite evident that commonly used chlorinated solvents pose a considerable health risk to users and the

environment.¹ Growing bodies of literature are further reinforcing the strong link between exposure to certain chlorinated solvents and cancer e.g. the exposure of workers in the printing industry in Japan to 1,2-dichloropropane and the associated development of cholangiocarcinoma (cancer of the bile duct).⁵¹ Somewhat worryingly, the US EPA have recently re-assessed the EHS profile of CCl₄. In a draft assessment, it was stated that there is little concern to users of CCl₄, as long as appropriate PPE is worn. However, this assessment does not take into account exposure to the general population through industrial emissions, which as of 2016, were up two orders of magnitude higher in the USA than expected.⁵² Thus, the full life cycle of each and every solvent should be considered as populations as a whole, and not just solvent end users, can be affected.

Inhalation is the primary mode through which occupational exposure to chlorinated solvents occurs and exposure limits have been imposed by various regulatory bodies and through government legislation.⁵³ The severity of the damage caused by exposure depends on a combination of factors including the (1) specific chemical(s) exposed to, (2) the concentration of the chemical in the air and (3) the length and frequency of the exposure.⁵⁴ Thus, the severity of exposure can be categorized accordingly: (1) situations immediately dangerous to life, (2) acute health effects, and (3) chronic health effects. To adequately combat the potentially detrimental health effects of exposure to chlorinated solvents, strict exposure limits are required (Table 9), e.g. long-term exposure (8 hours time-weighted average) to chloroform, chlorobenzene and CCl₄ are both just 1 ppm. DCM has been set at 100 ppm. To put this into context with other traditional organic solvents: according to the same legislation, long-term WEL for IPA is 400 ppm, acetone is 500 ppm and ethanol is 1000 ppm. Short-term exposure limits are usually set to help prevent acute effects such as eye irritation, which can occur after just a few minutes.⁵³

The short and long-term effects of exposure to chlorinated solvents on the person and the environment are described in Table 10. Short-term effects on the person include CNS suppression, nausea, vomiting and eye irritation. Furthermore, kidney and liver damage due to the metabolic pathways of many of the chlorinated solvents is reported. Reductive

metabolism of chloroform can lead to the formation of highly reactive dichloromethyl radicals CHCl_2^* ,⁵⁵ whereas oxidative metabolism can generate phosgene and subsequently HCl.⁵⁵ Trichloroethylene and metabolites of trichloroethylene have been shown to be themselves mutagenic and genotoxic and damaging to the liver and kidneys.⁵⁶ CCl_4 can be metabolized to the highly reactive trichloromethyl radical CCl_3^* .⁵⁷ Long-term exposure to CCl_4 is associated with toxicity, carcinogenicity, liver and kidney damage.⁵⁸ Long-term exposure to trichloroethylene can result in fatigue, irritability and mental and memory disturbances. Increased risk to the unborn child has also been reported for long-term exposure to trichloroethylene⁵⁶ and chloroform⁵⁹. Each of the chlorinated solvents described in Table 10 are considered toxic to the aquatic environment with the exception of DCM. Release to the environment are strongly advised against for trichloroethylene, tetrachloroethylene and chlorobenzene. CCl_4 has an ozone depleting potential (ODP2) of 0.82 (relative to CCl_3F which is set as 1).⁶⁰ Finally, to reduce the potential harm that halogenated solvents can cause, the emission of any halogenated solvents with a hazard statement of H341 or H351 is now restricted under EU regulation to 100 g/hour (with no more than 20 mg/m³ of any one individual halogenated component).⁶¹ Furthermore EU regulations require that hazardous waste containing >1% halogenated components must be burnt at a temperature of at least 1100 °C, as opposed to 850 °C required for non-halogenated waste.⁶¹ Combustion products from chlorinated waste streams for example can include HCl and Cl_2 ⁶² and appropriate scrubbing must be utilized before flue gases can be discharged to atmosphere. Even on a research scale, chlorinated solvent waste is more expensive to dispose of than non-chlorinated waste; it can be up to 40% more expensive to dispose of.⁶³

Solvent	Highly Explosive Red Flag	Highly Explosive Amber Flag	Explosive thermal runaway Red Flag	Explosive thermal runaway Amber Flag	Toxic Red Flag	Toxic Amber Flag	Long Term toxicity Red Flag	Long Term toxicity Amber Flag	Environmental implications Red Flag	Environmental implications Amber Flag	GHS Pictograms	WEL Long term ppm	WEL Short-term ppm	SD Ref
	H200, H201, H202, H203	H205, H220, H224	H230, H240, H250	H241	H300, H310, H330	H301, H311, H331	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373	H400, H410, H411, H420	H401, H412				
Chloroform						H331	H372	H351, H361d		H412		2	-	64
Dichloromethane								H351				100	200	65
1,2-Dichloroethane						H331	H350					5	-	66
Chlorobenzene									H411			1	3	67
1,2-Dichlorobenzene									H400, H410			25	50	68
1,1,1-Trichloroethane						H301, H311, H331	H370	H351	H420			100	200	47, 69
Trichloroethylene							H350	H341		H412		100	150	70
Tetrachloroethylene								H351	H411			20	40	71
Carbon tetrachloride						H301, H311, H331	H372	H351	H420	H412		1	5	58

Table 9: Categorization of some common chlorinated solvents by H-phrases according to the work of McElroy et al.⁷² Workplace Exposure Limit (WEL) according to UK EH40/2005 Workplace exposure limits. Long-term exposure = 8 h time-weighted average (TWA). Short-term exposure = 15 minutes

TWA.⁵³ All SDS references checked as of 01/07/2020. The information provided here does not constitute an alternative to conducting a risk assessment of any solvents used, or sourcing an up to date SDS from your chemical supplier.

Solvent	Classification	Short Term Exposure	Long-term Exposure	Environmental Impact	Ref
Chloroform	Possible CNS, liver, kidney toxin, carcinogen	Irritates the eyes. The substance may cause effects on the central nervous system liver and kidneys. The effects may be delayed. Medical observation is indicated.	The liquid defats the skin. The substance may have effects on the liver and kidneys. This substance is possibly carcinogenic to humans.	The substance is toxic to aquatic organisms.	ICSC 27
	Possible CNS and liver toxin, carcinogen	The substance is irritating to the eyes, skin and respiratory tract. If swallowed the substance may cause vomiting and could result in aspiration pneumonitis. The substance may cause effects on the central nervous system, blood, liver, heart and lungs. Exposure could cause carbon monoxide poisoning. This may result in impaired functions. Exposure at high concentrations could cause lowering of consciousness and death. The effects may be delayed.	The substance may have effects on the central nervous system. This substance is probably carcinogenic to humans.	N/A	CICAD 58 ICSC 0058
Dichloromethane	Possible CNS, liver, kidney toxin, probable carcinogen	The vapor is irritating to the eyes, skin and respiratory tract. Inhalation may cause lung oedema. The substance may cause effects on the kidneys and liver. This may result in impaired functions, liver damage and kidney damage. Exposure at high concentrations could cause lowering of consciousness and death. The effects may be delayed.	Repeated or prolonged contact with skin may cause dermatitis. The substance may have effects on the liver and kidneys, resulting in impaired functions. This substance is possibly carcinogenic to humans.	The substance is harmful to aquatic organisms.	ICSC 0250 CICAD 01
1,2-Dichloroethane					

Chlorobenzene	Confirmed animal carcinogen with unknown relevance to humans	The substance is irritating to the eyes and the skin. If this liquid is swallowed, aspiration into the lungs may result in chemical pneumonitis. The substance may cause effects on the central nervous system, resulting in lowering of consciousness.	The liquid defats the skin. The substance may have effects on the liver and kidneys	The substance is harmful to aquatic organisms. It is strongly advised not to let the chemical enter into the environment.	ICSC 0642
1,2-Dichlorobenzene	Not classifiable as a human carcinogen	The substance is irritating to the eyes, skin and respiratory tract. The substance may cause effects on the central nervous system and liver. Exposure could cause lowering of consciousness	The substance defats the skin, which may cause dryness or cracking. The substance may have effects on the kidneys and blood.	The substance is toxic to aquatic organisms. Bioaccumulation of this chemical may occur in fish. It is strongly advised not to let the chemical enter into the environment.	ICSC 1066
1,1,1-Trichloroethane	Possible cardiac, CNS, liver, kidney toxin	The substance is mildly irritating to the eyes, respiratory tract and skin. The substance may cause effects on the central nervous system. This may result in lowering of consciousness. Exposure at high levels could cause cardiac dysrhythmia	The substance defats the skin, which may cause dryness or cracking	The substance is harmful to aquatic organisms	ICSC 0079
Trichloroethylene	Possible CNS, liver, kidney toxin, probable carcinogen	The substance is irritating to the eyes, skin and respiratory tract. If swallowed the substance may cause vomiting and could result in aspiration pneumonitis. The substance may cause effects on the central nervous system, liver and kidneys. This may result in impaired functions. Exposure at high concentrations could cause unconsciousness.	Repeated or prolonged contact with skin may cause dermatitis. The substance may have effects on the central nervous system. This may result in fatigue, irritability and mental and memory disturbances. The substance may have effects on the liver, kidneys and immune system. This substance is carcinogenic to humans. Causes toxicity to human reproduction or development.	The substance is harmful to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.	ICSC 0081

Tetrachloroethylene	Possible CNS, liver, kidney toxin, probable carcinogen	The substance is irritating to the eyes, skin and respiratory tract. If swallowed the substance may cause vomiting and could result in aspiration pneumonitis. The substance may cause effects on the central nervous system. Exposure at high levels could cause unconsciousness.	Repeated or prolonged contact with skin may cause dermatitis. The substance may have effects on the liver, kidneys and central nervous system. This substance is probably carcinogenic to humans.	The substance is toxic to aquatic organisms. The substance may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter into the environment.	ICSC 0076
Carbon tetrachloride	Possible CNS, liver, kidney toxin, carcinogen	The substance is irritating to the eyes. The substance may cause effects on the liver, kidneys and central nervous system. This may result in unconsciousness. Medical observation is indicated.	Repeated or prolonged contact with skin may cause dermatitis. This substance is possibly carcinogenic to humans.	The substance is harmful to aquatic organisms. Avoid release to the environment because of its impact on the ozone layer.	ICSC 0024

Table 10: World Health Organization (WHO) classifications of some common chlorinated organic solvents, their short-term and long-term effects and generalized environmental impacts. Source information: Concise International Chemical Assessment Document (CICAD) WHO.⁷³ Source information International Chemical Safety Card (ICSC) International Labour Organization (ILO)/WHO.⁷⁴

3.2 Laboratory Safety Concerns

Many of the chlorinated solvents commonly employed in organic chemistry laboratories have chemical incompatibilities and serious safety concerns regarding their use.⁷⁵⁻⁷⁶ A number of case studies are highlighted below demonstrating areas where two of the most commonly employed chlorinated solvents (DCM and chloroform) should definitely be avoided.

3.2.1 Chloroform

Chloroform is usually stabilized with ethanol or amylene. Long term storage of non-stabilized chloroform leads to a reaction with air (in combination with heat and light) to produce phosgene and HCl.⁷⁷ Chloroform, similar to DCM, is incompatible with azide ions, having the propensity to form triazidomethane. The dangers of triazidomethane are highlighted in section 3.2.2 using diazidomethane as a case study.⁷⁸ Chloroform can also react violently with methanol and acetone in the presence of a strong bases and can also react explosively with sodium and sodium methoxide.⁷⁵

3.2.2 Dichloromethane

In 2008, an explosion in a scale-up facility was reported by Conrow *et al.* involving DCM and sodium azide. The explosion was due to the accidental formation of diazidomethane from residual DCM carried through from a previous step and sodium azide from the step in question. Azeotropic distillation of diazidomethane with residual water during removal of solvent by rotary evaporation (20 L rotary evaporator) occurred at the end of the reaction. The accumulation of diazidomethane in the receiving flask and condenser lead to detonation causing destruction to the immediate work environment and injury (non-critical) to two chemists.⁷⁸ Other similar incidents involving chlorinated solvents and azides have also been reported in the literature. As such, there is a general danger associated with the use of chlorinated solvents in sequences that involve the use of azides and this has been highlighted by OPR&D as a significant safety concern.⁷⁹

DCM penetration of nitrile gloves is a common problem encountered by chemists. Whilst this is not usually a problem for small splashes of DCM (though the aforementioned ability

of chlorinated solvents to de-fat the skin should be noted), what can occur is that DCM can carry other chemicals through the gloves themselves. An incident occurred in 2014 where “DCM carried 3,4-ethylenedioxy pyrrole through a researcher’s nitrile gloves”. The compound polymerized on the chemists hands, blackening the skin.⁸⁰ Toxicity of the compound was unknown. As with all laboratory operations, appropriate understandings of the choice and limitations of personal protective equipment (PPE) is essential. Subcutaneous injection of DCM can also lead to localized necrosis reported separately in 2018⁸¹ and 2020⁸². Non-stabilized DCM degrades over time and is often stabilized with alkanes such as amylene or cyclohexane/cyclohexene⁷⁷

3.2.3 1,2-Dichloroethane, Chlorobenzene and 1,2-Dichlorobenzene

Unlike the other chlorinated solvents listed here, DCE is flammable with a flash point of 13 °C, chlorobenzene has a flashpoint of 28 °C, and 1,2-dichlorobenzene has a flashpoint of 66 °C (Table 5).

4.0 Viable alternatives to chlorinated solvents for different situations – Solvent Selection Guides

All solvents have advantages and disadvantages. In many ways the “greenest” solvent i.e. the safest, most sustainable, most economical solvent, is not to use one at all.⁸³ Recognizing the advantages that solvents possess in permitting material transfer, solubilizing substrates and reagents, diluting reactions, moderating exotherms, and permitting purification amongst others, it may be useful to consider some alternatives to the chlorinated solvents previously described. When it comes to solvent selection there are three key considerations. The first is the technical suitability of the solvent for the process i.e. is it compatible with the process; does it provide the desired solubilization of reaction mass? The second is whether the solvent complies with environmental health and safety policies.⁸⁴ Solvents chosen should be as safe and innocuous as possible⁸³ and solvent processes should be designed to be solvent-economical.⁸⁵ Finally, as recently described in ACS Sustainable Chemistry and Engineering, a sustainable process should

meet a triple bottom-line: "A product or process should respond to a need in society. Delivery of the product or process should not disproportionately impact our environment. The process that delivers the product should be economically viable".⁸⁶ Thus, cost should be considered.

The following section highlights the tools, resources and many case studies of how greener, safer, more sustainable solvents can be successfully employed in common organic and medicinal chemistry reactions.

To aid chemists in selecting solvents that can potentially improve the sustainability of reactions/processes many solvent selection guides have been produced,^{4, 87-101} examples of which are depicted in Fig. 6 and Fig. 7. These guides are constantly evolving and being developed by industry and academic research groups to aid chemists in making more judicious decisions in solvent selection. As in-depth discussions and reviews of solvent selection guides have already been published^{5, 15, 89, 102-104}, some as recently as 2018, the authors feel that any further discussion in this area would be superfluous to the already comprehensive literature available.

Recommended	Water, EtOH, <i>i</i> -PrOH, <i>n</i> -BuOH, EtOAc, <i>i</i> -PrOAc, <i>n</i> -BuOAc, anisole, sulfolane.
Recommended or problematic?	MeOH, <i>t</i> -BuOH, benzyl alcohol, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, MeOAc, AcOH, Ac ₂ O.
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, DMPU, DMSO.
Problematic or hazardous?	MTBE, THF, cyclohexane, DCM, formic acid, pyridine.
Hazardous	Diisopropyl ether, 1,4-dioxane, DME, pentane, hexane, DMF, DMAc, NMP, methoxy-ethanol, TEA.
Highly hazardous	Diethyl ether, benzene, chloroform, CCl ₄ , DCE, nitromethane, CS ₂ , HMPA.

Fig. 6: Color coded classification of solvents based on a survey of publicly available solvent guides.⁸⁸ Reprinted with permission from ref [87]. Copyright 2016, The Royal Society of Chemistry under Creative Commons 3.0 license [<https://creativecommons.org/licenses/by-nc/3.0/>]

With a wealth of solvent selection information available, choosing an appropriate solvent for a process (or choosing a potential solvent replacement) has never been as well informed a process as it is now. An excellent starting point resource is the "MedChem Tips and Tricks" website hosted by the ACS GCI which includes an excellent decision tree for assisting compound purification, solvent and reagent advice, as well as energy and reaction methodology advice.¹⁰⁵ An NMR residual solvents reference guide has also been

produced by GSK cataloguing the ^1H and ^{13}C chemical shifts of 80 solvents, including many green solvents (recorded in 6 different deuterated solvents). Furthermore, the greenness of each of the deuterated solvents is also assessed; D_2O is recommended as solvent of choice where possible whereas CDCl_3 should be avoided if possible.¹⁰⁶

The following sections (4.1-4.3) provide an in-depth and case-specific resource regarding solvent usage in many of the commonly employed organic and medicinal chemistry processes and transformations. Case studies where chlorinated solvents have been successfully replaced are highlighted to provide guidance and a potential framework for those seeking to do likewise in other processes. A concise guide summarizing this section accompanies this manuscript as Supporting Information. Table S1 comprises a "Unified Solvent Selection Guide for Reactions of Importance to Medicinal Chemistry". The authors have chosen not to include areas such as ionic liquids, deep-eutectic solvents, super critical CO_2 or enzymatic synthesis as these areas are so well developed that they would warrant reviews of their own. We would like to point readers towards some relevant reviews on the topics. For ionic liquids,¹⁰⁷⁻¹¹⁴ deep-eutectic solvents¹¹⁵⁻¹²⁰, super critical CO_2 ¹²¹⁻¹²⁵, and enzymatic synthesis in organic chemistry¹²⁶⁻¹³⁰.

Class	Solvent	Conclusion (Pfizer)	Conclusion (GSK)	Conclusion (Sanofi)
Esters	Methyl acetate		Some issues	Substitution advisable
	Ethyl acetate	Preferred	Some issues	Recommended
	<i>n</i> -Propyl acetate		Few issues	Recommended
	<i>i</i> -Propyl acetate	Preferred	Few issues	Recommended
Ethers	THF	Usable	Major issues	Substitution advisable
	2-MeTHF	Usable	Some issues	Recommended
	TBME	Usable	Some issues	Substitution advisable
	CPME		Some issues	Substitution requested
	Diethyl ether	Undesirable	Major issues	
	Di- <i>i</i> -propyl ether	Undesirable	Major issues	Substitution advisable
	1,2-DME	Undesirable	Major issues	Substitution requested
Ketones	1,4-Dioxane	Undesirable	Major issues	Substitution requested
	Acetone	Preferred	Some issues	Recommended
	Methylethyl ketone	Preferred	Major issues	Recommended
	MIBK		Some issues	Recommended
Halo-genated	Dichloromethane	Undesirable	Major issues	Substitution advisable
	1,2-Dichloroethane	Undesirable	Major issues	
	Chloroform	Undesirable	Major issues	
	CCl_4	Undesirable	Major issues	
Miscellaneous	Water	Preferred	Few issues	Recommended
	Acetic acid	Usable		Substitution advisable
	Pyridine	Undesirable		Substitution advisable

Class	Solvent	Conclusion (Pfizer)	Conclusion (GSK)	Conclusion (Sanofi)
Alcohols	Methanol	Preferred	Some issues	Recommended
	Ethanol	Preferred	Some issues	Recommended
	1-Propanol	Preferred	Some issues	Recommended
	<i>i</i> -Propanol	Preferred	Some issues	Recommended
	1-Butanol	Preferred	Few issues	Recommended
	2-Butanol		Few issues	Recommended
	<i>t</i> -Butanol	Preferred	Some issues	Substitution advisable
	Ethylene glycol	Usable		Substitution advisable
	2-Methoxyethanol		Major issues	Substitution requested
	<i>n</i> -Pentane	Undesirable		Banned
Hydro-carbons	Hexane(s)	Undesirable	Major issues	Substitution requested
	Cyclohexane	Usable	Some issues	Substitution advisable
	Methylcyclohexane	Usable		Substitution advisable**
	Heptane	Usable	Some issues	Substitution advisable
	Isooctane	Usable	Some issues	
	Benzene	Undesirable	Major issues	
	Toluene	Usable	Some issues	Substitution advisable
Dipolar aprotic	Xylene(s)	Usable	Some issues	Substitution advisable
	DMSO	Usable	Some issues	Substitution advisable
	Acetonitrile	Usable	Major issues	Recommended
	DMF	Undesirable	Major issues	Substitution requested
	DMAc*	Undesirable	Major issues	Substitution requested
	NMP	Undesirable	Major issues	Substitution requested

Fig. 7: Excerpts from the "unified, generalized, solvent selection guides for medicinal chemists".¹⁰²

Adapted from ref [102]. Copyright 2016, Springer Open under Creative Commons Attribution 4.0 International License [<http://creativecommons.org/licenses/by/4.0/>].

A summary of the advice provided in the following section is also included in the Supporting Information of this publication. See "Unified Solvent Selection Guide for Reactions of Importance to Medicinal Chemistry" in the Supporting Information.

4.1 Silica Gel Chromatography

In medicinal chemistry and academic environments, one of the largest consumptions of DCM typically results from its use as a chromatography solvent in silica gel chromatography.²⁴ As previously discussed in section 2.0, DCM is employed as a non-polar chromatography mobile phase component primarily due to its ability to dissolve a wide range of organic molecules and ease of removal due to its volatility. DCM is commonly used in conjunction with methanol as the polar eluent. Eluent pH can also be modified as required with additives such as ammonia or acetic acid. Due to the health risks associated with DCM and the increased cost in disposal of chlorinated waste²⁴, avoiding the use of halogenated solvents has become an area that has received significant attention for a number of pharmaceutical companies.^{3, 131}

Alternatives to DCM/methanol eluent systems have been published which highlight the ease in which the traditional system can be replaced with a drop-in replacement.⁴⁶ In 2012 Taygerly *et al.* (Amgen) published a guide to replacing DCM/MeOH with both two and three component solvent mixtures.⁴⁶ DCM was replaced with heptane(s) and the polar component MeOH was replaced with ethyl acetate (EtOAc), or for more polar compounds a premixed EtOAc:ethanol solution (in a 3:1 ratio). The system was developed using a set of twenty-six drug-like molecules (nine neutral, eight basic and nine acidic) to determine R_f values in both DCM/MeOH and greener solvent systems to build an appropriate model of "relative eluting strength" for potential solvent replacements. Systems requiring pH adjustment had an appropriate amount of ammonia or acetic acid added. The results are depicted in a series of visual guides which make an excellent benchtop reference for chemist e.g. Fig. 8 (for acidic and basic compounds see the original publication⁴⁶). The visual guides produced will be familiar to chemists that have employed the equielutropic diagrams produced by Neher *et al.* (1964) for choosing alternative, but similar strength,

elution systems for thin-layer chromatography (TLC).¹³² Commercial sources of pre-mixed 3:1 EtOAc:ethanol are now available specifically for chromatography applications.¹³³

The University of Nottingham (UoN) has been hosting drug discovery activities analogous to those undertaken in pharmaceutical companies for ten years as part of both its Teaching and Learning (T&L) activities¹³⁴⁻¹³⁶ and also as part of its R&D portfolio¹³⁷⁻¹⁴¹. As of September 2019, the GSK Carbon Neutral Laboratory for Sustainable Chemistry, University of Nottingham project laboratory (which hosts 16 organic and medicinal research chemists, graduate and undergraduate students when at full capacity) has ceased its use of chlorinated solvents for all chromatographic applications except for rare cases involving solubility issues. On average, 20-25 flash chromatographic separations are conducted each week using a Biotage SP4 to purify new investigational medicinal chemistry drug molecules, synthetic natural products and their intermediates. The transition to chromatography free from chlorinated solvent was built upon the aforementioned guide by Taygerly *et al.* and has been a huge success to date. Of note is the willingness of chemists who are earlier in their careers - especially undergraduate student chemists who have little experience of or familiarity with chlorinated solvents in chromatography - to readily adapt to new working practices. It is apparent that chemists in early career stages have less prejudice or preference towards what more experienced chemists would consider "traditional" or "standard" elution systems. It is hoped that the success of this pilot scheme (which also includes replacements for other solvents and reagents of concern e.g. DMF) in an industry influenced academic drug discovery setting will help convince other chemists in the wider field and industry to adopt safer, cleaner,

more sustainable practices. Solvent usage practices may have changed but drug discovery has continued unimpeded.

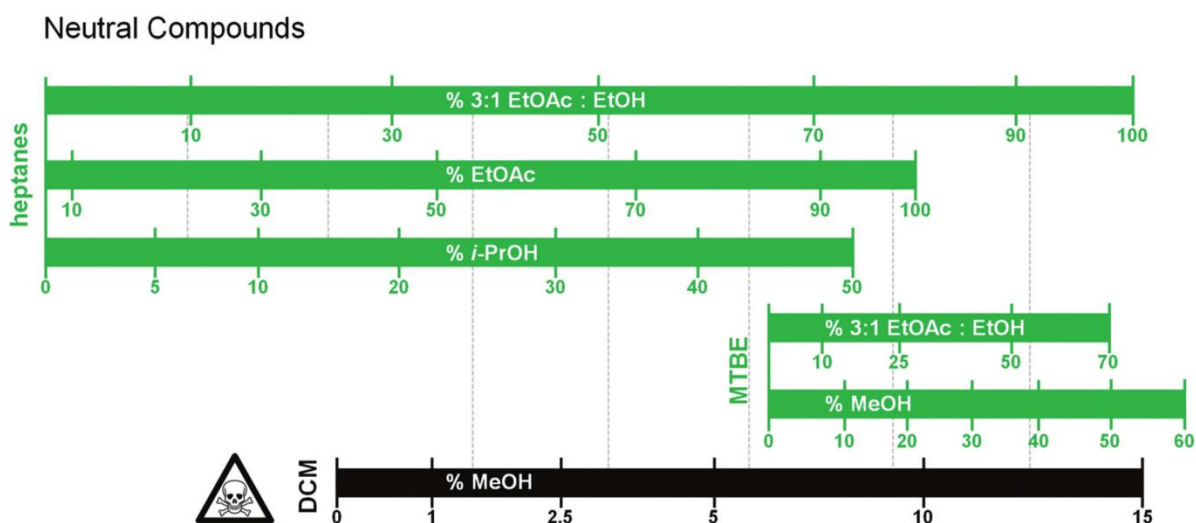


Fig. 8: Relative eluting strengths of green chromatography solvent mixtures (neutral compounds).⁴⁶ Adapted from ref [46]. Copyright 2012, The Royal Society of Chemistry.

4.2 Commonly Employed Transformations in Medicinal Chemistry

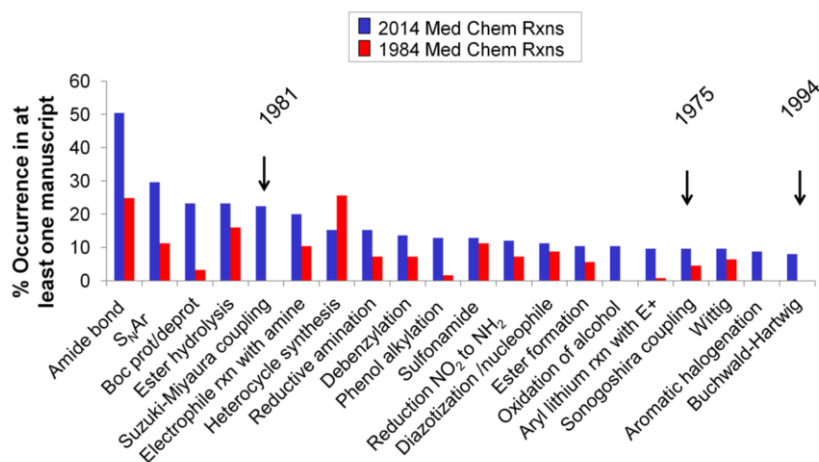


Fig. 9: Prominence and variety of organic chemistry reactions used in medicinal chemistry.¹⁴² The years highlighted represent the year of publication/disclosure of the relevant named reactions. Reproduced with permission from <https://pubs.acs.org/doi/10.1021/acs.jmedchem.5b01409>. Further permissions related to the material excerpted should be directed to the ACS.

Depicted in Fig. 9 are the most commonly encountered organic transformations employed by medicinal chemists according to Brown *et al.*¹⁴² Fig. 9 is also in good agreement with the most commonly employed functional groups in bioactive molecules as determined by Ertl *et al.*¹⁴³ With respect to Fig. 9, the following section will discuss the use of chlorinated solvents in these reaction classes and highlight efforts towards discovering suitable greener, more sustainable solvent replacements. Not all reaction classes rely on chlorinated solvents and though not strictly within the remit of this review, highlighted examples of greener and more sustainable reaction conditions and solvents will be highlighted.

It is important to note that, as previously mentioned at the beginning of section 4.0, it may be possible to swap a chlorinated solvent for an alternative but it is critical that the impact of an entire process is taken into account before deciding whether a replacement solvent and the new process is actually a sustainability improvement.

Note: the order of appearance of each category is roughly by order of prevalence of use in medicinal chemistry except for Section 4.2.5 which pools multiple cross-coupling methodologies together and Section 4.2.17 which combines alcohol deoxyhalogenation with other halogenation methodologies. Less commonly employed methodologies are also interspersed throughout as are a number of case studies on successful solvent replacement investigations.

4.2.1 Amide formation

Amide bond formation is one of the most commonly conducted transformations in synthetic medicinal chemistry.¹⁴² Amide bonds are usually formed from amines and either acid chlorides or carboxylic acids with the utilization of a coupling reagent (though efforts towards catalytic¹⁴⁴ and enzymatic¹⁴⁵ amide bond formation are well documented). The most widespread solvents employed for amide bond formation employing coupling reagents are either DMF or DCM.¹⁴⁶ In 2012, Watson *et al.* as part of an ongoing collaboration between GSK and the University of Strathclyde, evaluated a number of potential replacement solvents for amide coupling reactions. Their study found that

dimethyl carbonate, EtOAc and 2-MeTHF all performed well as reaction solvents across a range of substrates and coupling reagents, with broadly equivalent rates of reaction and yields when compared to DCM and DMF. A visual solvent-reagent selection guide for amine and carboxylic acid classes was prepared as a result of this study (Fig. 10), providing a useful bench reference for organic and medicinal chemists. Employing such a guide as a standard in academic and industrial research programs would have benefit in terms of sustainability and safety as amide bond formation remains one of the most widely used transformations to date.

Solvent	Amide Coupling Type																				
	Aryl Acid – Aryl Amine				Aryl Acid – Alkyl Amine				Alkyl Acid – Aryl Amine				Alkyl Acid – Alkyl Amine								
	HATU	COMU	DIC HOBT	PyBOP	T3P	HATU	COMU	DIC HOBT	PyBOP	T3P	HATU	COMU	DIC HOBT	PyBOP	T3P	HATU	COMU	DIC HOBT	PyBOP	T3P	
TBME	*		*	*				*								**	**	**	*	*	
CPME					*					**						**	*	**	**	**	
CH ₂ Cl ₂	**		*	*	*	*	*	*	*	*	*	*	*	*	*	*	**	**	**	**	**
DMC	*	*	*	*	**	**	**	**	**	*	*	*	*	*	*	*	**	**	*	**	*
DMF	**	**	**	*		*	*	**	**	*	*	*	*	*	*	*	**	**	**	*	**
EtOAc	*	*	*	*	**	**	**	**	**	*	*	*	*	*	*	*	**	**	**	**	**
IPA	*	*	*	*		*	*	*	**	*	*	*	*	*	*	*	**	**	**	**	*
2-MeTHF	*	*	*	*		*	*	*	*	*	*	**	*	*	*	*	**	**	*	*	**

^a Key: Red = <50% conv., orange = 50–70% conv., green = >70% conv.; * Indicates 100% conv. within 4 h. ** Indicates 100% conv. within 1 h.

Fig. 10: Solvent-Reagent selection guide for the formation of amide bonds.¹⁴⁶ Reproduced with permission. [146] - Reproduced by permission of The Royal Society of Chemistry.

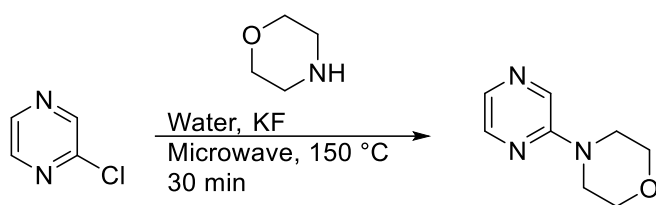
More recent developments have also shown that the biomass derived dihydrolevoglucosenone (Cyrene) can be employed as an effective, safer, polar aprotic solvent for use in amide coupling.¹⁴⁷ Amide formation *via* acid chlorides is a commonly employed synthetic strategy and Bousfield *et al.* have demonstrated that Cyrene can be employed as a reaction medium with facile isolation of products in many cases *via* precipitation simply by the addition of water.¹⁴⁸ Aqueous-organic biphasic conditions, e.g. Schotten-Baumann type conditions, have also been employed in the synthesis of amides. Conditions entirely avoiding chlorinated solvents as the organic phase have been reported utilizing instead toluene¹⁴⁹ 2-MeTHF¹⁵⁰ and *iso*-propyl acetate¹⁵¹. Solvent-free reaction conditions have also been described.¹⁵²

Solid supported peptide synthesis routinely employs DCM or DMF as both reaction solvent and during post-reaction workup to wash solid supported products clean. In 2017 North

et al. demonstrated that propylene carbonate could effectively replace DMF/DCM in both solid and solution phase synthesis of polypeptides with yields and degrees of racemisation comparable to products prepared in DMF.¹⁵³ The degree of swelling of some commonly employed solid-phase synthesis resins (Merrifield and Hypogel 200) in green solvents has also been reported.¹⁵⁴

4.2.2 Nucleophilic aromatic substitutions S_NAr

Scheme 1: Example of an S_NAr reaction conducted metal free in water/KF.¹⁵⁵



The S_NAr reaction is a convenient method by which nucleophiles can displace leaving groups in aryl ring systems. The aromatic ring system must be sufficiently electron deficient to allow nucleophilic attack to occur¹⁵⁶ e.g. nitro functional groups ortho or para to a halide leaving group or a system such as pyrazine, pyrimidine etc. (Scheme 1). The S_NAr reaction is also favoured over transition metal catalyzed cross-coupling methods for the formation of C-O/N/S bonds in process chemistry whenever possible.¹⁵⁶ Solvent effects on the S_NAr reaction have been well documented and include regiosomeric and selectivity effects.¹⁵⁶⁻¹⁵⁸ Solvent choices for rapid reactivity rely on the ability of the solvent to enhance the nucleophiles nucleophilicity whilst also being able to accept hydrogen bonds.¹⁵⁷ Selectivity when employing an aromatic system with multiple potential reactive sites may benefit from non-polar solvents such as toluene.¹⁵⁶ In 2013 Walsh *et al.* published S_NAr methodology using water and KF heated under conventional and microwave conditions.¹⁵⁵ Numerous amine nucleophiles were successfully reacted with a variety of halo-pyridines, -pyrazines, -pyrimidines and -quinazolines to give aminated products in moderate to excellent yields though reactions using di-aminopyrimidines gave unpredictable yields. Overall, the transformations using this KF/water system have shown

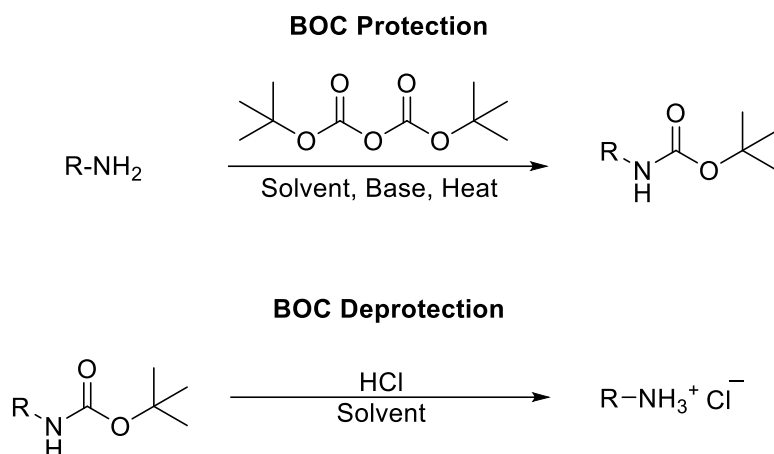
that transition metal catalysis may be an entirely unnecessary requirement in some cases.¹⁵⁵ Similarly, S_NAr reactions have been conducted in EtOH for the formation of 2-anilinopyridines under microwave conditions in moderate to excellent yields in just 10 minutes.¹⁵⁹ Isley *et al.* have demonstrated that S_NAr reactions could be performed under micellar conditions using K₃PO₄ in 2 wt.% TPGS-750M surfactant in water. Reactions proceeded smoothly at temperature ranges from room temperature to 45 °C and conditions were suited to N, O and S nucleophiles. Moderate to excellent yields were observed as was recyclability and low E-factor of the micellar system, furthermore one pot tandem S_NAr reactions followed by nitro reduction were demonstrated.¹⁶⁰

4.2.3 BOC-Protection/Deprotection

tert-Butyloxycarbonyl (BOC) protection/deprotection ranks as no.3 in the most commonly employed reactions in medicinal chemistry.¹⁶¹ *tert*-Butyloxycarbonyl is also one the most commonly employed amine protecting groups at the process chemistry stage, followed by benzyl and CBz protecting groups.¹⁶² A brief search of the literature using Reaxys shows that there are over 24k reported BOC protections of amines using BOC₂O (Scheme 2).¹⁶³ The top five most commonly employed organic solvents for this transformation are DCM with nearly one third of reactions reported in this solvent. Next most popular are THF, 1,4-dioxane, MeOH and DMF, all of which, except for MeOH, are solvents of concern and should be replaced where possible. Biphasic mixtures of water and organic solvent are also prevalent and are commonly employed in examples where the *N*-terminus of amino acid carboxylic acids are undergoing protection. Examples employing greener solvents are present throughout the literature and include water (biphasic/binary mixture with an organic solvent), EtOH, *tert*-butyl alcohol, EtOAc, IPA, acetone, butan-1-ol and 2-MeTHF, in total making up ~12% of the entire body of literature. Solvent-free reactions at ambient temperature have also been reported employing catalytic amounts of molecular iodine.¹⁶⁴ Gratifyingly, greener solvent choices for BOC-protection have been exemplified in a number of medicinal chemistry publications¹⁶⁵⁻¹⁶⁷. Therefore, when it comes to this often-

employed transformation, there is a body of literature already in existence to assist in making well-informed, safer, more sustainable solvent choices.

Scheme 2: Typical BOC protection and deprotection reaction conditions.



Multiple methods to carry out BOC deprotection are available, including but not limited to acid deprotection with HCl¹⁶⁸ or TFA¹⁶⁹, thermal deprotection¹⁶¹, CeCl₃·7H₂O - NaI¹⁷⁰, ball-milling,¹⁷¹ and boiling water¹⁷². Similar to BOC-protection, conventional acid catalyzed deprotection relies heavily on DCM, reported as reaction solvent in almost half of the examples examined.¹⁶³ Next most popular are 1,4-dioxane MeOH, EtOAc, and THF. Water features prominently again as biphasic or binary aqueous-organic mixtures. The presence of EtOAc in the top five most commonly employed organic solvents is promising and may be due to the commercial availability of HCl-EtOAc solutions, a combination long employed for BOC-deprotection.¹⁷³ With literature precedent of more sustainable, non-chlorinated solvents being employed successfully for BOC-deprotection, chemists may be able to move away from traditional methods employing DCM and 1,4-dioxane especially with the commercial availability of HCl solutions in EtOAc, IPA, EtOH, MeOH, 1-butanol, and CPME.¹⁷⁴ Regarding the use of methanolic HCl, a recent incident report has highlighted its intrinsic instability on storage leading to spontaneous degassing and spraying out of a bottle leading to a near miss.¹⁷⁵ Ethanolic HCl was examined for the same behavior and was found to be a much safer alternative.¹⁷⁵

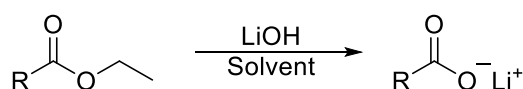
Thermal deprotection in batch or flow, offers multiple benefits in that aqueous workup or free-basing of amines can be avoided thus reducing waste and allowing for the compounds use directly in multistep reaction sequences¹⁷⁶, as long as the compound undergoing deprotection is otherwise thermally stable to the heating conditions.¹⁶¹ Thermal deprotection can also be conducted under solvent free conditions.¹⁷⁷

Overall, from analysis of currently available literature, BOC protection and de-protection should be entirely feasible in non-chlorinated solvents especially greener more sustainable solvents, substrate solubility permitting.

4.2.4 Ester Hydrolysis

Ester hydrolysis to furnish carboxylic acids (Scheme 3) is another of the most commonly employed transformations in medicinal chemistry. Common methods to achieve this transformation are well described in "Greene's protective groups in organic synthesis"¹⁷⁸ and include but are not limited to aqueous acid hydrolysis, dry acid hydrolysis of *tert*-butyl esters, base hydrolysis, hydrogenolysis of benzylic esters¹⁷⁹, and enzymatic hydrolysis¹⁸⁰. Reaxys reports over 605k published examples of ester hydrolysis thus providing an enormous body of literature to assist in making informed solvent selection choices.¹⁸¹

Scheme 3: Typical hydroxide mediated hydrolysis of an ethyl ester.¹⁷⁸



According to the same search criteria,¹⁸¹ base-mediated hydrolysis (NaOH, LiOH, KOH etc.) most commonly employs MeOH (41%), THF (40%), water (as a single solvent or as a binary mixture, often THF), EtOH, 1,4-dioxane, and DMF as solvents.¹⁸¹ DCM makes up just over 10% of this overall solvent landscape. Therefore, greener alternatives such as MeOH and EtOH and IPA are already exemplified in base hydrolysis applications.

Acid hydrolysis (HCl, TFA etc.) appears to employ DCM most frequently as organic solvent of choice, most likely to avoid trans-esterification issues involved with using alcohols as

solvent. Nearly one third of all acid catalyzed deprotections were carried out in DCM.¹⁸¹ The next most popular are THF, MeOH, EtOH, 1,4-dioxane and DMF. Nearly all TFA deprotection reactions (70%) employed DCM as solvent, though deprotection using TFA in water is possible.¹⁸² Similar to the picture portrayed for base hydrolysis reactions, the literature suggests that greener alternatives such as aqueous combinations of alcohols (e.g. MeOH, EtOH, and IPA) can all be viable solvent options for conducting this reaction.

4.2.5 Cross-Coupling – Suzuki-Miyaura, Heck, Negishi, Buchwald-Hartwig

Since the advent of palladium catalyzed cross-coupling methodologies in the 1970's, the myriad transformations made possible by these reactions (Scheme 4) have become a driving force in medicinal chemistry, natural product and fine chemical synthesis.¹⁸³ Later additions to the Pd catalyzed reaction manifold that have had significant impact in pharmaceutical and medicinal chemistry include the Buchwald-Hartwig amination (1994).¹⁸⁴ Other C-N bond formation such as aromatic nitrile¹⁸⁵ and nitro¹⁸⁶ synthesis are also possible via Pd catalysis.

More recently copper-based methodologies such as the Chan-Evans-Lam reaction have been employed as a late stage functionalization tool in medicinal chemistry¹⁴⁰ Developments by Ma and co-workers have led to new Cu catalyzed C-N and C-O bond forming methodologies that have been applied in organic and medicinal chemistry.¹⁸⁷⁻¹⁸⁹ A review on the topic is also available.¹⁹⁰

Solvent effects in Pd catalyzed cross-coupling reactions have been extensively reviewed by Sherwood *et al.*¹⁸³ Each of the individual cross-coupling methodologies have their own distinct variables and nuances that can be explored when conducting reaction optimization such as solvent, ligand, base, temperature and reaction time.¹⁹¹ Solvent choice can have profound effects on cross-coupling reaction rates, selectivity and yields¹⁹². Due to the complexity and multiple variables involved in palladacycle chemistry, Sherwood *et al.* have determined that "*rarely is the choice of solvent decided by the solubility of the product in a cross-coupling reaction*".¹⁸³ This level of complexity and variability make the task of choosing greener and more sustainable solvents somewhat challenging.

A brief examination of all cross-coupling reaction types using Reaxys involving mono-halogenated benzene as substrate gave a set of 1,630 reactions. Only 3% used DCM as reaction solvent.¹⁹³ It would appear that the elevated temperatures that cross-coupling reactions are often conducted in precludes the use of low boiling chlorinated solvents such as DCM and chloroform. More popular “go-to” solvents appear to be THF, DMF, toluene, water, acetonitrile, 1,4-dioxane and DMAc. THF, DMF, 1,4-dioxane and DMAc are all solvents with associated issues that require replacement (see Fig. 7)¹⁰². One potential replacement for polar aprotic solvents is the bio-based solvent Cyrene which has been successfully employed as reaction solvent in multiple cross-coupling methodologies.¹⁹⁴⁻¹⁹⁵

Though not strictly within the scope of this review (as low usage of chlorinated solvents within cross-coupling reactions has been observed) it is worth discussing efforts towards improving cross-coupling sustainability. In 2018 Akhtar *et al.* published a comprehensive review of environmentally friendly synthetic strategies for Sonogashira cross-coupling reactions which includes examples of reactions conducted solvent-free, or employing bio-mass derived solvents,¹⁹⁶ aqueous conditions, or water-organic solvent mixtures.¹⁹⁷ Similarly, efforts towards developing greener methodologies for Heck,¹⁹⁸ Chan–Lam, Stille and Suzuki cross-coupling reactions have been reviewed by Yousaf *et al.*¹⁹⁹ The examples reviewed share similarities to the aforementioned Sonogashira review and include propylene carbonate, pure aqueous, aqueous with organic co-solvent, ethanol and aqueous-micellar conditions. Suzuki reactions in pure water²⁰⁰, water, water ligand free²⁰¹, and aqueous with an organic co-solvent²⁰² have also been reported. Progress in metal mediated/catalyzed reactions in water has also been extensively review by Zhou *et al* (2019).²⁰³ Nickel-catalyzed Suzuki-Miyaura reactions have been conducted successfully in green solvents such as EtOAc, *i*-PrOAc and 2-MeTHF amongst other examples.²⁰⁴ Cyclic carbonates have also been successfully employed as solvent in asymmetric allylic alkylations reactions²⁰⁵ as well as direct arylation of heteroaromatics.²⁰⁶ Other Pd catalyzed processes such as aminocarbonylation, alkoxycarbonylation and carbonylative coupling of boronic acids and aryl bromides have been recently investigated by Aya *et al.*²⁰⁷ In their

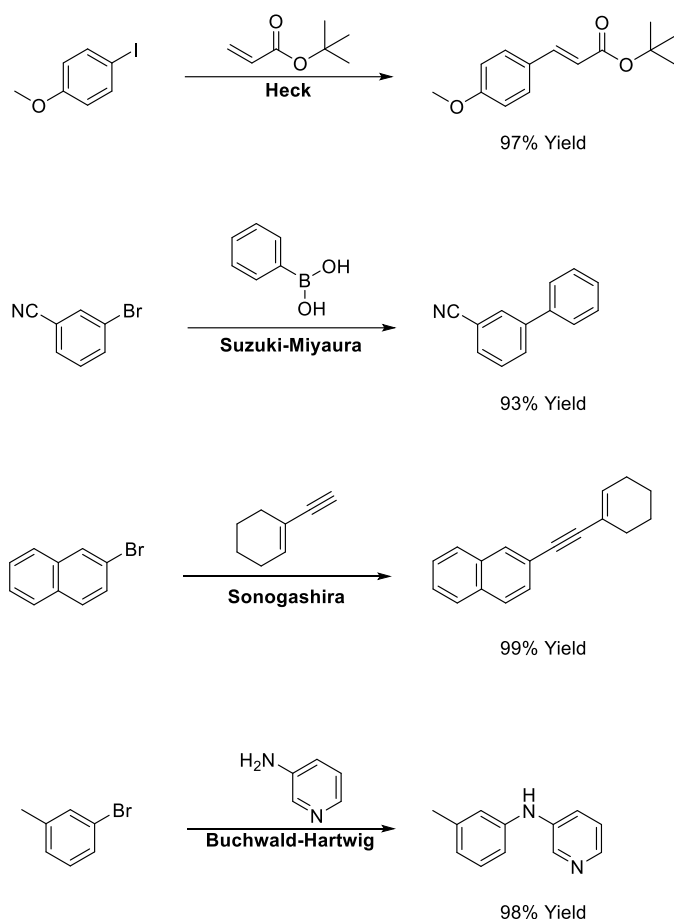
study, 16 renewable/biomass/CO₂ derived reaction solvents were examined; aminocarbonylation and aminocarbonylation were shown to work well in DMC and the carbonylative coupling proceeded well in *p*-cymene. Other terpene derived solvents such as limonene and α -pinene were shown to be compatible as well, though possess considerably higher levels of toxicity compared to DMC.²⁰⁷

Solvent effects have also been examined in the Buchwald-Hartwig amination reaction, which commonly employs 1,4 dioxane, toluene or other hydrocarbon solvents.¹⁸³ *iso*-Propanol has been reported as a greener and more sustainable alternative to dioxane and reactions using *iso*-propanol have been conducted successfully on kilogram scale²⁰⁸. *t*-BuOH has been successfully employed as a reaction solvent in a Buchwald-Hartwig amination²⁰⁹ and amidation²¹⁰. Solvent-free protocols have also been successfully demonstrated.²¹¹ Fischmeister *et al.* have reviewed and highlighted the potential for using carbonate solvents, PEG-water combinations, and EtOAc amongst other green solvents, in many Pd and Ru C-H bond functionalizing reactions.²¹² Ethanol has also been successfully employed as solvent in Heck-Matsuda reactions.²¹³

Both reviews highlight the advances and successes achieved in the cross-coupling field in employing aqueous and aqueous-surfactant/micellar systems. Proponents of the field such as Lipschutz *et al.* have enjoyed success performing cross-coupling reactions in water and the recyclable surfactant TPGS-750-M (commercially available) at room temperature.²¹⁴ Somewhat surprisingly Negishi coupling was also shown to be entirely possible in aqueous media without prior formation of organozinc reagents.²¹⁵ Kilogram scale Suzuki-Miyaura cross-coupling reactions have been successfully conducted using this system thus highlighting its generality and versatility in industrial settings as well.²¹⁶ Wagner *et al.* have also further refined and expanded the scope and breadth of Buchwald-Hartwig amination reactions possible using "Lipschutz" conditions.²¹⁷ Furthermore, Cohen *et al.* have demonstrated Pd catalyzed cyanation of aryl halides in aqueous media.¹⁸⁵ Although reaction optimization will always be an important part of cross-coupling reactions, the successful and broad variety of examples and methodologies that can employ aqueous

surfactant reaction conditions shows that you don't always require a complicated reaction mixture: "No organic solvents and no heating; just add water."²¹⁵

*Scheme 4: A selection of Pd-catalyzed cross-coupling reactions conducted in TPGS-750-M and water at room temperature.*²¹⁴



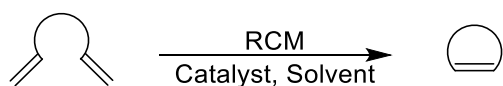
4.2.5.1 C-H Bond Activation

Metal catalyzed direct C-H activation often relies on halogenated solvents such as DCE, tetrachloroethylene, trichloroethanol and hexafluoroisopropanol (HFIP). The topic is well reviewed by Sherwood *et al*²¹⁸, and more recently by Yu *et al*.³⁷ Notable examples of emerging replacement solvents used under specific reaction conditions in C-H bond activation reactions include THF, CH₃CN, γ -valerolactone²¹⁸ and cumene³⁷ (though neither THF nor CH₃CN are considered sustainable alternatives)⁴. 2-MeTHF has also been demonstrated as an excellent reaction solvent in Ru catalyzed direct C-H photoarylation.²¹⁹

Due to the unique blend of physico-chemical properties that are conducive to C-H bond activation, properties that some chlorinated solvents conveniently possess (see section 2.1.1.1), it is challenging to find drop-in replacements. The properties often include high polarity characteristics in conjunction with hydrophilic and hydrophobic moieties, and acidic OH groups. The challenge arises from the complexity in attempting to find a solvent that combines all of the above properties and features but does not include some form of halogenated functional group. One potential replacement solvent has emerged in the form of cumene which has been identified as an excellent alternative non-halogenated solvent for C-H activation in reactions where oxidation and redox processes are limiting factors.³⁷ Cumene also scores favourably (amber) in comparison to other halogenated solvents according to the GSK solvent sustainability guide.⁴ If C-H bond activation research is to develop unimpeded then a concerted effort to identify further potential replacement solvents must be continued.²¹⁸ Finding effective replacements for DCE is also of significant importance as under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation this solvent is “of very high concern requiring authorisation before it is used”. Its sunset date was 22/11/2017 i.e. it can no longer be used in processes unless special authorization is granted to the user.²²⁰

4.2.5.2 Olefin Metathesis

Scheme 5: Olefin Metathesis to give ring closed product.



Olefin metathesis is a powerful methodology employed for the formation of alkenes and is often used in the pharmaceutical industry in olefin ring-closing metathesis (RCM) to form unsaturated ring structures from two alkenes (Scheme 5) or cross metathesis of two different alkenes (CM).²²¹ The reaction is often catalyzed by a ruthenium derived catalyst-ligand system such as Grubbs, Hoveyda-Grubbs or indenylidene. Of serious concern however is the widespread use of DCE as reaction solvent as well as DCM. To assess

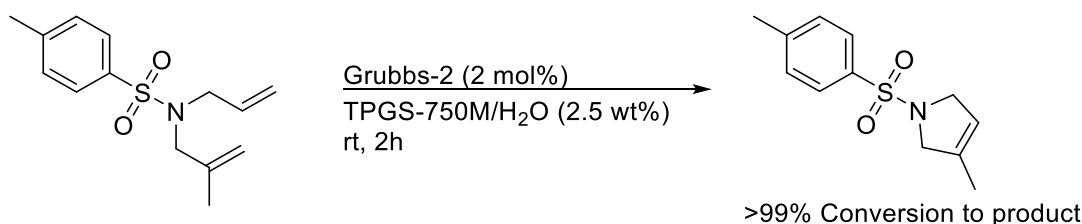
whether solvent alternatives were possible, Skowerski *et al.* have developed a solvent selection guide for olefin metathesis using greener and more sustainable solvents that can be used in conjunction with a variety of catalysts, Fig. 11.²²¹

Entry	Catalyst	GC yield [%]						
		MeOH	i-PrOH	AcOEt	DMC	CPME	2-MeTHF	DCM ^f
1	H-II	28	31	97	93	73	38	97
2	N-II	9	11*	94	85	79	49	96
3	E-II	8	9	66	79	20	37	95
4	G-II	15	16	97	98	80	35	92
5	Ind-II	3*	15*	96	98	69	38	93
6	H-II'	58	88	96	93	90	90	93
7	N-II'	45	85	96	99	97	97	88*
8	E-II'	57	86	98	99	97	97	91
9	G-II'	19	31	88	97	85	84	91
10	Ind-II'	8*	51*	92	98	89	93	95

Fig. 11: Illustrative representation of RCM catalyzed by various Ru catalysts in green solvents at 40 °C.²²¹ G = Grubbs, H = Hoveyda-Grubbs, Ind = indenylidne, E = "Scorpio" catalyst. II = (SIMes) NHC ligand, II' = SIPr NHC ligand. Key: Red – yield <50%; yellow – yield 51-90%; green – yield >90%. Adapted with permission from ref [221]. Copyright 2014, The Royal Society of Chemistry.

Skowerski *et al.* were able to show that for RCM, CM and enyne metathesis, reactions could be carried out in non-degassed, non-distilled solvents such as EtOAc and dimethylcarbonate giving comparable yields and scope to benchmark solvent DCM.²²¹

Scheme 6: RCM conducted in TPGS-750-M.²¹⁴



Further efforts in employing green solvents in olefin RCM have been published by Bakhrou *et al.* who effectively demonstrated that RCM could be conducted in glycerol (a bio-based, biodegradable low-toxicity solvent) in conjunction with microwave heating conditions.²²² Lipschutz *et al.* have also demonstrated successful RCM in aqueous-surfactant conditions,

recycling the aqueous surfactant phase 8 times with no loss of percentage conversion (Scheme 6).²¹⁴

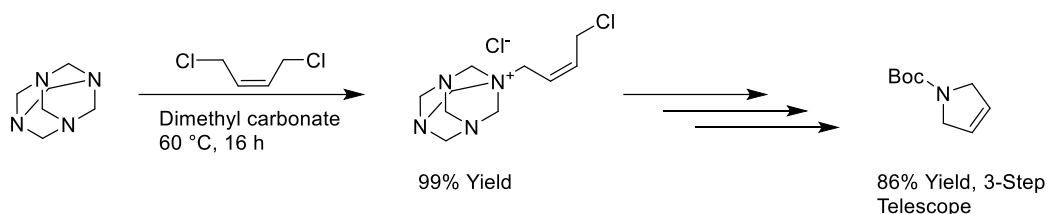
4.2.6 Electrophile Reaction with Amine – Amines as nucleophiles

Reactions of amines with electrophiles encompasses a truly enormous category of potential reaction types including but not limited to nucleophilic substitution reactions with halide/pseudohalide leaving groups, acid chlorides, acid anhydrides and addition to ketones/aldehyde to form imines. For S_N2 type reactions, polar aprotic solvents are most often the primary solvent choice thus acetonitrile, DMF, DMAc and NMP see extensive use in these reaction classes. However, chlorinated solvents such as DCM and chloroform also see widespread use in electrophilic reactions with amines such as amine acylation as discussed in section 4.2.1. (i.e. amide bond formation), reductive amination *via* imine formation which is discussed in section 4.2.7, and the *in situ* generation of acid chlorides section 4.2.17.

The challenge of replacing dipolar aprotic solvents, which is outside the scope of this review, is being addressed. Recent publications have shown that many less-toxic, biocompatible solvents exist that can potentially be employed as replacement solvents for polar aprotics. These include *N*-butylpyrrolidinone (NBP), aforementioned cyclic carbonates, bio-based Cyrene²²³, and γ -valerolactone¹⁹⁶. When it comes to solvent selection for amine-electrophile reactions, some general guidance may be provided. When selecting potential solvents avoid chlorinated solvents and if a polar aprotic is required then one of the aforementioned replacements such as a cyclic carbonate, NBP, Cyrene or γ -valerolactone should be included in any solvent screening conducted. E.g. Cyrene has been shown to be an effective polar aprotic alternative in urea formation¹⁴⁸ and in amide formation from acid chlorides.¹⁴⁸ An example of how simple steps can be employed in successfully replacing chlorinated solvents in an amine electrophile reaction is outlined below in section 4.2.6.1.

4.2.6.1 Delépine Reaction

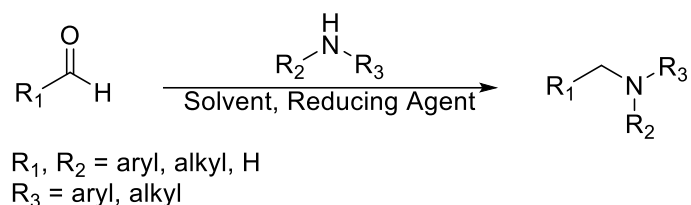
Scheme 7: Employing the Delépine reaction in the scaled-up synthesis of *N*-(*tert*-butyloxycarbonyl)-3-pyrroline.²²⁴



The Delépine reaction is a traditional synthetic method for the formation of primary amines *via* the reaction of hexamethylenetetramine (HMTA) with an alkyl halide. It is contemporaneous to the Gabriel synthesis of amine formation. One obvious drawback to the use of the Delépine reaction for amine synthesis is that chloroform is the reported solvent of choice with ~6-7% of reported Delépine reactions taking place in a solvent that could be considered sustainable. A second drawback is the release of formaldehyde during HMTA salt hydrolysis which cannot be avoided and must be adequately risk assessed before being conducted. Formaldehyde and NH_4Cl release also lead to poor atom economy. The need to discover greener, more sustainable solvent conditions for this reaction came as the result of an ongoing medicinal chemistry/green chemistry collaboration between the University of Nottingham and GSK. A solvent screen was conducted for the Delépine reaction by Jordan *et al.* and it was discovered that a number of greener, more sustainable solvents (dimethylcarbonate, isopropyl acetate, Cyrene, cyclopentanone, EtOAc, isopropanol) could act as effective replacements for chloroform. Of note was that HMTA did not fully solubilize in any of the replacement solvents, yet reaction still proceeded effectively as suspensions to give products of excellent yields and purity. The optimized methodology relied on dimethyl carbonate as solvent and a wide range of HMTA salts were synthesized to emphasize the robustness of the methodology.²²⁵

4.2.7 Reductive Amination

Scheme 8: Generic reductive amination chemistry using aryl/alkyl aldehydes/amines.



Reductive amination of carbonyl containing compounds is a commonly used, robust transformation in organic/medicinal chemistry for the derivatisation and functionalization of amines (

Scheme 8). In 2013, a survey conducted by Watson *et al.* showed that chlorinated solvents were heavily employed as reaction solvent for reductive aminations with 1,2-dichloroethane and DCM amongst the most frequently encountered.²²⁶ Research in this area has subsequently led to the generation of a solvent selection guide for conducting reductive aminations using borane-based reductants (Fig. 10 & Fig. 12). It was discovered that EtOAc was a broadly comparable solvent to DCE for sodium triacetoxyborohydride mediated reductive aminations. Dimethyl carbonate, isopropyl alcohol and 2-MeTHF also appeared to be viable alternatives in many instances.²²⁶ The importance of identifying DCE replacements is discussed in further detail in section 4.2.5.1 Imine formation, the first step in carbonyl reductive amination, can also be conducted in ethyl lactate as was effectively demonstrated by the work of Bennett *et al.* in which a number of aryl aldimines were synthesized in ethyl lactate/water mixtures with products conveniently precipitating from solution.²²⁷

Solvent	Amine Class																	
	Acyclic 1° Aryl			Acyclic 1° Alkyl			Acyclic 2° Aryl			Acyclic 2° Alkyl			Cyclic 2° Aryl			Cyclic 2° Alkyl		
	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B
TBME				*					**							*		
CPME									**							**		
DCM	**			*			*		*							**		
DCE	**			*			*		**	*						*		
DMC				*	**				*							*		
DMF				**					*							*		
EtOAc				*					*							*		
IPA	*			*	*				**							*		
2-MeTHF									**							**		
THF									*							*		

^a Key: red = <50% conv., orange = 50–70% conv., green = >70% conv. *Indicates 100% conv. within 4 h. **Indicates 100% conv. within 1 h. SCB = NaBH₃CN, STAB = NaBH(OAc)₃, Pic-B = picoline–borane complex.

Fig. 12: Evaluation of alternative solvents and reagents for reductive amination of aryl aldehydes.²²⁶

[226] - Reproduced by permission of The Royal Society of Chemistry.

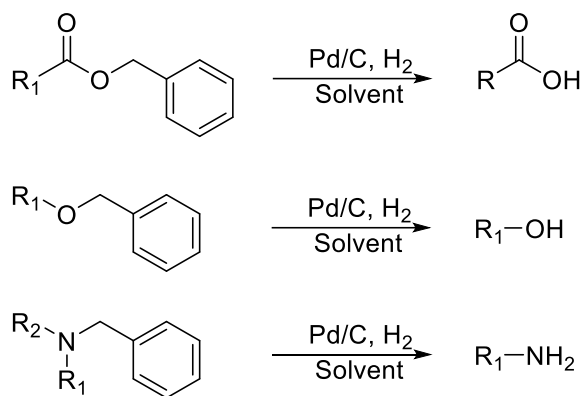
Solvent	Amine Class																	
	Acyclic 1° Aryl			Acyclic 1° Alkyl			Acyclic 2° Aryl			Acyclic 2° Alkyl			Cyclic 2° Aryl			Cyclic 2° Alkyl		
	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B	SCB	STAB	Pic-B
TBME		*	*					*		**			*		*		*	
CPME	**	**						*		**			*	*	*	**	**	
DCM	**	*					**	**				*	**	*	*	**	**	
DCE	*	**					**	**		*		*	*	*	*	**	**	
DMC	*	*					**	**		*		*	*	*	*	*	**	
DMF	*	*					**	**		*		*	*	*	*	**	**	
EtOAc	**	*					**	**		*		*	*	*	*	**	*	
IPA	*	*					**	**		*		*	*	*	*	**	*	
2-MeTHF	**	*					*	*		**		*	**	*	*	**	*	
THF	*	*					*	*		*		*	*	*	*	**	**	

^a Key: red = <50% conv., orange = 50–70% conv., green = >70% conv. *Indicates 100% conv. within 4 h. **Indicates 100% conv. within 1 h. SCB = NaBH₃CN, STAB = NaBH(OAc)₃, Pic-B = picoline–borane complex.

Fig. 13: Evaluation of alternative solvents and reagents for reductive amination of alkyl aldehydes.²²⁶ [226] - Reproduced by permission of The Royal Society of Chemistry.

4.2.8 Debenzylation

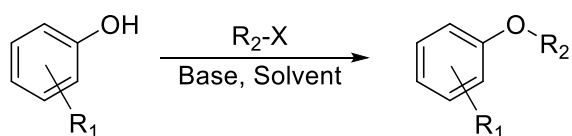
Scheme 9: Generic O- and N- debenzylation reactions.



Benzyl group hydrogenolysis is a commonly encountered deprotection reaction (Scheme 9). The most commonly employed solvent for ester debenzylation is MeOH (42%), followed by THF, EtOH, EtOAc, water (as a single solvent or as a binary mixture), DCM (12%) and DMF.²²⁸ The enormous availability of debenzylation reactions available in the literature (>32k including both *N*- and *O*- debenzylation) shows that more sustainable solvents such as EtOH, EtOAc, or water if solubility permits, can be employed for this deprotection step. Although MeOH is a more sustainable alternative than DCM, there are flammability issues when used in conjunction with reducing metals such as Pd/C, thus its use should be avoided.²²⁹

4.2.9 Heteroatom alkylation/arylation

Scheme 10: Generic phenol alkylation reaction



Heteroatom alkylation/arylation is one of the most prominent reaction types in medicinal chemistry.¹⁶² *O*- functionalization features less frequently than other *N*-alkylation (section 4.2.6.) though still remains an important transformation in the synthesis of ethers. The purpose of which can be functionalization or protection i.e. benzylic ether (section 4.2.8). *S*- alkylation/arylation is less frequently encountered than both *O*- and *N*-.¹⁶² Some direct

N-arylation methods are already discussed in section 4.2.5 i.e. Buchwald-Hartwig amination, *N*-alkylation via reductive amination is discussed in section 4.2.7.

Phenol, alcohol, and thiol alkylation can be achieved *via* traditional S_N2 type chemistry i.e. the use of a base to deprotonate the alcohol/thiol to an alkoxide/thiolate followed by the addition of an electrophile such as an alkyl halide (Scheme 10). Solvent choices for phenol alkylation rely on DMF (35%) as solvent of choice followed by acetone (23%), THF, water, DCM (12%), ethanol and acetonitrile.²³⁰ DCM/water mixtures are often employed in biphasic reaction mixtures though DCM itself is not a requirement, all that is generally needed is a solvent that is an organic solvent that is immiscible with water such as toluene. It is our suggestion that if biphasic/Schotten-Baumann conditions are going to be employed then avoid chlorinated solvents and attempt the use of a non chlorinated-alternative (that is compatible with the reaction conditions) such as those mentioned in section 4.2.1 (toluene¹⁴⁹ 2-MeTHF¹⁵⁰ and *iso*-propyl acetate¹⁵¹).

Other methods that can be employed to achieve heteroatom alkylation include the Mitsunobu reaction which has traditionally been associated with high waste and challenging purification steps.²³¹ Recent advances have seen Beddoe *et al.* develop an organocatalytic Mitsunobu reaction that effectively overcomes many of these concerns and can be conducted in toluene or xylenes, completely avoiding the use of chlorinated solvents²³¹ (though THF is a much more common solvent in the Mitsunobu reaction than DCM due to the higher rate of reaction it facilitates)²³².

4.2.10 Sulfonamide Formation

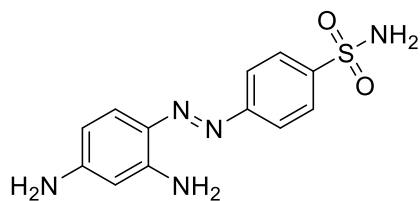
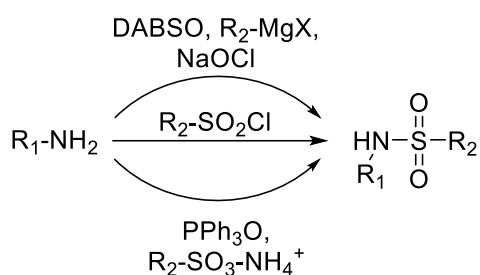


Fig. 14: Prontosil, the first commercial sulfonamide drug.²³³

Sulfonamide containing drugs were amongst the first antibacterial agents to be used systematically in modern medicine to great effect e.g. Prontosil (Fig. 14), the first sulfonamide drug which was discovered in 1932.²³³ Sulfonamides are also convenient isosteric replacements for carboxylic acids and can be rapidly and diversely functionalized.²³⁴ As such, the sulfonamide functional group is a key moiety that is featured in a wide range of molecules including antibacterial, antifungal, anticancer and antiviral drugs.²³⁵

Scheme 11: Various methods of sulfonamide synthesis. Adapted from ²³⁵. DABSO = 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct.



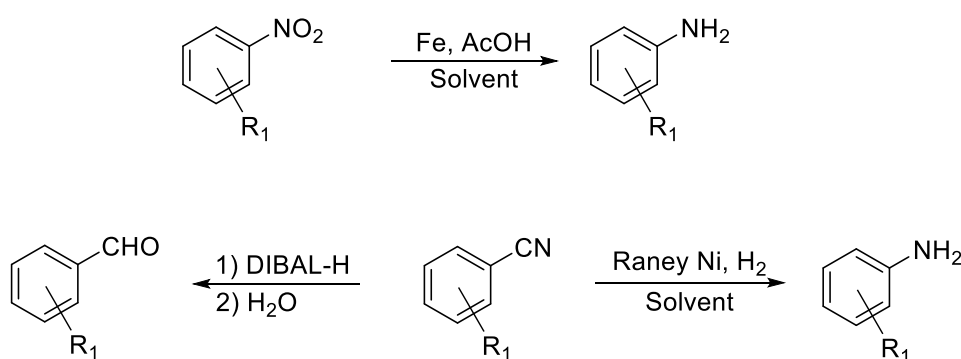
Sulfonamide formation *via* the reaction of a sulfonyl chloride with an appropriate nucleophile is one of the most popular methods for the formation of sulfonamides and could be considered analogous to amide formation *via* an acid chloride. As with acid chloride reactions, DCM is one of the most popular solvents that is employed for this transformation (63%).⁸² Key advances that have improved the sustainability of the synthesis of sulfonamides are aqueous-biphasic reaction conditions and reactions in water. Sulfonamide synthesis from sulfonyl chlorides using pH 8 buffered water has been successfully demonstrated at up to 100 g scale with excellent yields using water-soluble carboxylic acid containing substrates.²³⁶ Products were isolated by precipitation and filtration by adjusting the pH to 2.0. Sulfonamide and sulfonazide synthesis from sulfonyl chlorides has also been effectively demonstrated by Jafarpour *et al.* in both ethanol and water, giving excellent yields in very short reaction times (minutes), outperforming other conventional methods.²³⁷ Excellent yields are also possible using EtOAc instead of DCM.²³⁸ Sulfonamide synthesis from sodium sulfinat and nitroarenes in water has been

demonstrated by Eid *et al.*, isolating products simply by filtration, though water solubility of starting materials limited the scope of this methodology.²³⁵

Flow synthesis of sulfonamides is another area in which modern synthetic techniques have greatly contributed. Gioiello *et al.* have effectively demonstrated a flow method for the synthesis of sulfonamides (39 examples) in excellent yields and purities using water/acetone/PEG 400 mixtures as the solvent. Furthermore, exemplary solvent and surfactant recycling were demonstrated for their scaled up synthesis of target molecule probenecid, giving the final compound in 78% yield and 95% purity with a final E-factor of 0.66.²³⁴ Biphasic conditions have also been employed in the synthesis of sulfonamides to excellent effect avoiding chlorinated solvents instead relying on 2-MeTHF and isopropyl acetate.¹⁵¹

4.2.11 NO_x and Nitrile Reduction

Scheme 12: Generic NO_x and Nitrile reductions.



Reduction reactions as a whole are generally encountered more frequently than oxidations in process and scale-up chemistry for reasons which are elaborated in section 4.2.14.¹⁶² If reductive amination and benzylic protecting group reductions are ignored, then the most frequently encountered reduction types are imine/nitrile to amine and NO_x to NH₂.¹⁶² Reduction using H₂ is the most atom efficient method when compared to other hydride-based reduction methods and the most commonly employed method for NO_x reductions.¹⁶²

Similar to the results observed for debenzoylation reactions, section 4.2.8, the most commonly employed solvents are methanol and ethanol followed by THF and EtOAc.²³⁹ DCM only appears to feature prominently in other non-hydrogenation based reductions such as zinc mediated²⁴⁰ or trichlorosilane reductions²⁴¹. The use of ethanol is to be encouraged over MeOH, as it is a safer alternative than methanol for Pd/C based reductions as is discussed in section 4.2.8 *vide supra*.

The combination of iron with acetic acid is another of the most commonly employed methods that can be used for nitro reduction and it would appear that ethanol is the most commonly employed solvent (52%), one of the most preferred solvent choices in the aforementioned guides.²³⁹ EtOAc is also a possible choice.²⁴² If alternative reduction methods such as borohydride are required for nitrile/imine reduction then inspiration may be gleaned from section 4.2.7 concerning reductive amination and the potential that exists for screening greener more sustainable solvents and not relying on DCE. Newly developed methods such as borohydride reduction of nitro and nitriles in water have been developed that are catalyzed by magnetically retrievable CuFe₂O₄ nanoparticles²⁴³ and iron pincer complexes have been shown to be excellent catalysts in H₂ reduction of nitriles employing *iso*-PrOH as solvent.²⁴⁴

4.2.11.1 Other Reducing Reagents – General Use

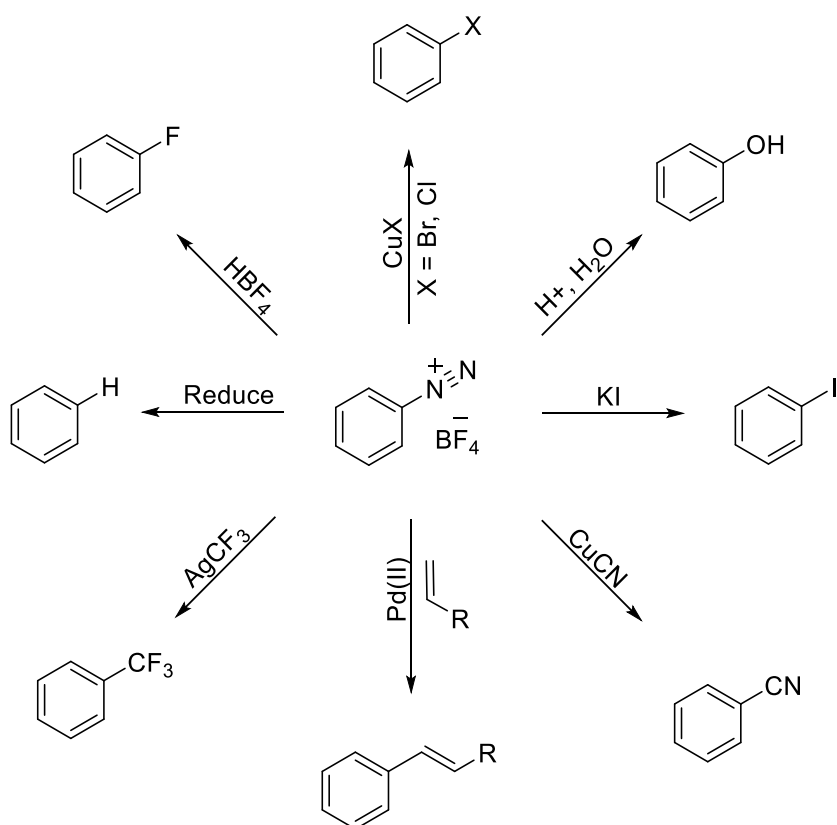
For other reduction types utilizing LiAlH₄ for example, 2-MeTHF²⁴⁵ has been shown to be an excellent alternative to THF, with 2-MeTHF LiAlH₄ solutions commercially available.²⁴⁶ Similarly DIBAL-H is often used in conjunction with hydrocarbon solvents. Other commonly employed reducing agents are already covered in section 4.2.7 regarding their use in reductive amination reactions and may provide guidance and inspiration for more judicious solvent selection outside of reductive amination transformations.

4.2.12 Diazotization

Diazotization, reactions of azo containing compounds and diazonium salts *via* transformations such as the Sandmeyer reaction, are a convenient method for rapidly derivatizing aromatic rings with functional groups such as halides, CF₃, OH and CN

amongst others (Scheme 13). Diazonium salts are also useful coupling partners in the Heck-Matsuda and Suzuki-Miyaura reactions.^{213, 247}

Scheme 13: Some common transformations that can be achieved using diazonium salts.^{248, 247}



Reactions involving diazonium salts are unpopular in process chemistry environments with only 12 publications in OPR&D containing aryl diazonium compounds having been published since 2009.²⁴⁹ The reasons for this dearth of diazonium containing compounds

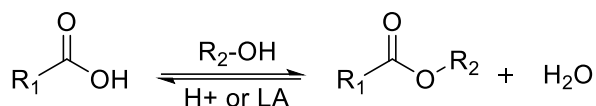
on scale are well understood; in a 2019 publication by Bondarev *et al.* it is noted that diazonium compounds have “*such disadvantages as a poor storage stability in the solid state and a propensity to explosively decompose upon heating, photo-irradiation, or mechanical stress*”.²⁵⁰ Such physical properties severely limit their use especially on a large/industrial scale. (Note: Bondarev *et al.* have shown that triflate diazonium salts are far more stable than their respective BF₄ and tosylate analogues.)²⁵⁰

Transformations involving diazonium salts remain popular in medicinal chemistry as they provide a route to rapidly access multiple functional groups from one common intermediate. The synthesis of diazonium BF₄ salts themselves can be conducted in EtOH²⁵¹ and diazonium tosylate salt formation using solid supported nitrite and acetic acid has also been reported.²⁵² Polar protic and aprotic solvents are most often employed for transformations involving diazonium salts including water, CH₃CN, DMF.²⁵³ Sandmeyer reactions are traditionally conducted in their respective aqueous halide acid solutions as per the 1926 preparation described by Fry and Grote²⁵⁴ Aqueous halide acids are still technically halogenated solvents and suffer from the same issues regarding waste disposal and incineration (see section 3.1). Filimonov *et al.* have shown that it is possible to react diazonium tosylate salts with either KI, KBr, or NaNO₂ in water or MeOH (for NaNO₂ reaction) at room temperature to give the respective aryl halide or nitro compound. Reaction times were rapid (<4 hours) and gave excellent yields.²⁵² Similarly, in 2018 Gholap published a gram scale synthesis of aryl iodides from diazonium fluoroborate salts using metal free conditions in a KI/water solution.²⁵⁵ Heck-Matsuda²⁵⁶⁻²⁵⁷ and Suzuki-Miyaura²⁵⁸⁻²⁵⁹ type coupling reactions both appear to be feasible when methanol and ethanol are used as solvent, both of which are favorable choices when it comes to green and sustainable reaction conditions, though ethanol is preferred.⁴ Electrochemical methods for carrying out the Sandmeyer reaction have also been developed.²⁶⁰

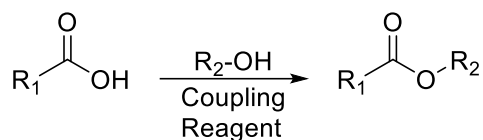
4.2.13 Ester Formation

Scheme 14: Fisher and Steglich Esterification.

Fisher Esterification



Steglich Esterification



Ester formation is often conducted to facilitate the protection of a carboxylic acid i.e. a protecting group strategy. Generally simple alkyl esters such as methyl and ethyl are employed to achieve this.¹⁶² Esters are also useful intermediates which can undergo reduction to their respective alcohol, can be utilized in direct amide bond formation via reaction with reagent DABAL-Me₃,²⁶¹ and can also be useful in C-C bond formation *via* Claisen condensation, one of the most popular methods of C-C bond formation after Pd catalyzed cross-coupling.¹⁶²

Two of the most prevalent methods for the formation of esters are the Fischer esterification and Steglich esterification (Scheme 14). Fisher esterification generally employs a carboxylic acid and an alcohol to form an ester in the presence of acid²⁶² or a Lewis acid²⁶³. Steglich esterification differs in that the reaction is not carried out under acidic conditions, instead a coupling agent such as those found in amide synthesis are employed to activate a carboxylic acid which then undergoes nucleophilic attack by an alcohol to form the desired ester.²⁶⁴ Esters can also be synthesized *via* the condensation of an acid chloride (see section 4.2.17) with an alcohol. Apart from the traditional methods of ester synthesis, a myriad of other protocols (some esoteric) have been developed and are well reviewed by Matsumoto *et al.* including base/acid catalyzed transesterification, solid supported reagents, Lewis acid catalysts, the Mitsunobu esterification, enzymatic methods, ionic liquid catalysts, electrochemical, transition metal catalyzed, to name but a selection.²⁶⁵ Ester formation is often employed as a key transformation in natural product synthesis thus the requirement and drive to develop such a diverse portfolio of methods.²⁶⁶

A brief survey of ester formation methods employed in *J. Med. Chem.* for the period of 2009-2019 shows that carbodiimide and hydroxybenzotriazol-1-ol derived reagents are the most commonly employed for Steglich esterification.²⁶⁷ Solvents used for these types of reactions are predominantly DCM, DMF, THF and CH₃CN and mirrors the trend observed in section 4.2.1 for amide formation.²⁶⁷ Conversely, conducting the same survey in OPR&D publications for the same period shows that esterification reactions are chiefly conducted using acid catalyzed conditions (H₂SO₄ and HCl being the most popular).²⁶⁷ It is suggested that if Steglich esterification conditions are required, that inspiration be taken from the solvent-reagent selection guide described for amide bond formation (Fig. 10) to assist in more judicious solvent selection. An example of where this approach has been successfully employed is highlighted in section 4.2.13.1; a case study in how greener and more sustainable solvent-reagent conditions for the formation of thioesters *via* a Steglich type reaction were discovered.

4.2.13.1 Thioester Formation

Thioester formation is a much less commonly employed transformation than traditional ester bond formation yet finds use in natural product synthesis as a convenient method of mildly forming aldehydes *via* the Fukuyama reduction as opposed to the use of DIBAL-H or Rosenmund conditions.²⁶⁸ The sustainability of thioester formation came under scrutiny in a 2018 publication by Sneddon *et al.* as the result of the need to form a thioester as part of a collaborative medicinal chemistry program between the UoN and GSK. A review of currently available literature showed that at the time the most commonly employed solvents for thioester formation were DCM and DMF, followed by THF, in conjunction with a coupling reagent such as would be used in amide bond formation (DIC and DCC were prevalent). A guide, similar to the amide (Fig. 10) and reductive amination (Fig. 12 & Fig. 13) solvent selection guides, was produced (Fig. 15). It was discovered that chlorinated solvents (and DMF) could easily be replaced with safer, more sustainable alternatives such as cyclopentanone and dimethyl carbonate. Improved solvent-reagent conditions gave comparable yields and conversion times to those already quoted in the

literature. It was also demonstrated that T₃P, a more sustainable and safer amide coupling reagent than DIC/DCC²⁶⁹, was a suitable reagent to promote this transformation.²⁶⁸

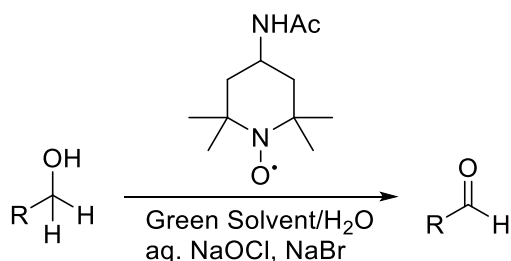
Solvent	Reaction 1: Aryl Thiol – Alkyl Acid				Reaction 2: Aryl Thiol – Aryl Acid				Reaction 3: Alkyl Thiol – Alkyl Acid				Reaction 4: Alkyl Thiol – Aryl Acid			
	T ₃ P	HATU	CDI	EDC-HCl	T ₃ P	HATU	CDI	EDC-HCl	T ₃ P	HATU	CDI	EDC-HCl	T ₃ P	HATU	CDI	EDC-HCl
DMC	**	**	**	*	**	**	*	*	**	**	*	*	**	*	*	*
CycP†	**	**	**	*	**	**	*	*	**	**	*	*	**	*	*	*
EtOAc	*	**	**	*	**	**	*	*	**	**	*	*	**	*	*	*
Water††	*	*	*	*	N/A	N/A	N/A	N/A	*	*	*	*	N/A	N/A	N/A	N/A
CPME	*	*	*	*	**	**	*	*	**	**	*	*	**	*	*	*
2-MeTHF	**	**	**	*	**	**	*	*	**	**	*	*	**	*	*	*
CH ₃ CN	**	**	**	*	**	*	*	*	**	**	*	*	**	*	*	*
DMF	*	**	**	*	**	**	*	*	**	**	*	*	**	*	*	*
DCM	**	**	**	*	*	**	*	*	**	**	*	*	**	*	*	*

Fig. 15: Thioester formation by solvent and coupling reagent type. Red = <50% conv., orange = 50–70% conv., green = >70% conv.; * Indicates >90% conv. within 4 h. ** Indicates >90% conv. within 1 h. †Cyclopentanone (CycP). †† 1 mL water with 2 wt.% TPGS 750 M surfactant.²⁶⁸ [268] - Reproduced by permission of The Royal Society of Chemistry.

4.2.14 Oxidation

4.2.14.1 Alcohols

Scheme 15: N-oxy catalyzed bleach oxidation of alcohols in greener solvents. Reproduced with permission.²⁷⁰



Selective oxidation of alcohols to carbonyl compounds is a transformation of significant importance,²⁷⁰⁻²⁷¹ yet it is a transformation that is less often employed in large-scale drug

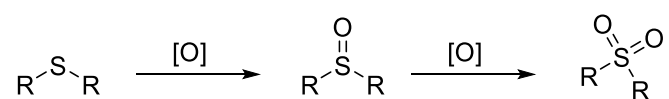
manufacturing (which predominantly carries out sulfide oxidation rather than alcohol oxidation).¹⁶² The most commonly employed oxidants are oxygen, hydrogen peroxide and sodium hypochlorite. Of those used, oxygen is usually avoided on scale due to the inherent flammability and safety issues.^{270, 272} It is due to these safety issues that oxidation chemistry is less often employed than reduction chemistry on scale as a whole. Furthermore, heavy metal contamination from many oxidation processes can be problematic in the manufacturing of APIs.¹⁶² More recently, *tert*-butyl hydroperoxide has been employed as a safer alternative to hydrogen peroxide.

In 2011, Sheldon *et al.* explored alternatives to DCM for *N*-oxy catalyzed bleach oxidations of various alcohol substrates. It was found that methyl acetate and isopropyl acetate gave results comparable to, or in some cases better than DCM. The choice of the *N*-oxy catalyst (TEMPO, AA-TEMPO, or PIPO) and co-catalyst (NaBr or borax) did however require optimization between substrates, and the authors were not able to recommend a unified set of conditions for all alcohols.²⁷⁰

More recently, Delorme *et al.* have developed a method for the selective, electrochemical TEMPO-catalyzed, oxidation of alcohols using a variety of ionic liquids as solvents. It was demonstrated that ionic liquid reaction kinetics and selectivity were superior to the organic solvent benchmark acetonitrile. Ionic liquids themselves cannot be considered inherently green and sustainable on the merit of low volatility alone²⁷³; this work is indicative of the radical and ground breaking direction in which solvent selection can be taken.²⁷⁴

4.2.14.2 Sulfides

*Scheme 16: Oxidation of sulfides to sulfoxide and sulfones.*²⁷⁵

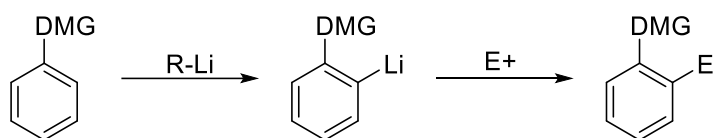


Oxidation of sulfides is an important and common transformation employed in the pharmaceutical industry and is used to access sulfoxides and sulfones (Scheme 16).¹⁶²

Sato *et al.* have reported organic solvent- and halogen-free biphasic conditions that effectively achieve this transformation.²⁷⁵ The reported oxidation conditions employed a biphasic aqueous system comprising the organic substrate itself, aqueous hydrogen peroxide, acidic promoter and a phase-transfer catalyst. Catalyst loadings were low at 0.1 mol% and the reaction conditions gave excellent yields. At 100 g scale diphenyl sulfide was smoothly converted to diphenylsulfone (96% yield).

4.2.15 Aryl Lithium Reaction with Electrophile

Scheme 17: Reactions of aryl lithium species with a broad variety of electrophiles can be achieved via directed ortho metalation (DoM).²⁷⁶



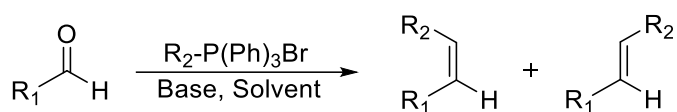
DMG = 3° Amide,
O-Carbamate etc.

Aryl lithium species are incredibly useful intermediates similar in reactivity to other organometallic reagents such as Grignard, Gilman and other organolithium species. Organolithium species reactivity as nucleophiles encompasses a broad portfolio of reactions including 1,2-addition to carbonyl compounds, carbolithiation reactions across alkene and alkynes, and S_N2 type reactions with alkyl halides.²⁷⁶⁻²⁷⁸ Aryl lithium species are formed *via* "lithiation", i.e. lithium hydrogen exchange of an aryl hydrogen atom with an appropriate reagent such as n-BuLi. Aryl lithiation can also be conducted in a site specific manner by directed ortho metalation (DOM).²⁷⁶ The resulting aryl lithium species can be quenched with an electrophile to give access to a wide range of substituents (Scheme 17). This methodology is attractive as it allows rapid access to a broad variety of functional groups from one common intermediate. There are however considerable hazards associated with the use of lithium reagents, the pyrophoric nature of butyl lithium

is noteworthy having come to prominence in mainstream media in 2008/2009 after the tragic death of researcher Sheharbano Sangji.²⁷⁹ Organolithium reagents are most often commercially available as alkane or ethereal solutions. Ethers can undergo coordination to alkyllithium reagents due to the Lewis basicity of oxygen and some reactions involving alkyllithium can take place faster and are higher yielding due to this coordinating effect.²⁷⁸ The potential for carbene formation from halogenated solvents generally precludes their use in organolithium reactions.²⁸⁰⁻²⁸¹ Directed ortho-lithiation is however entirely possible in cyclopentyl methyl ether (CPME), a safer more sustainable solvent alternative to common ethers.²⁸² CPME has also proven to be an excellent ether replacement in many other organometallic reactions such as Grignard, carbenoid, and LAH reductions.²⁸³ The guidance that can be provided for these transformations is that if you require an ether, then try CPME or 2-MeTHF before THF. If you require an alkane solvent then heptane and cyclohexane are both preferable to hexane or petroleum ether.⁴ 2-MeTHF has also been highlighted as a suitable alternative solvent in many other organometallic processes and reactions such as Grignard and Reformatsky reactions.²⁴⁵

4.2.16 Wittig

Scheme 18: Generic Wittig Olefination of an aldehyde to give a mixture of E- and Z-isomers.



The Wittig reaction is a powerful transformation in the chemists' toolbox used to convert ketones and aldehydes to alkenes. The reagents required to carry out the transformation are relatively inexpensive (PPh₃, alkyl halides and base).²⁸⁴ Reaction conditions are thoroughly established in literature and stereochemical control of E/Z alkenes (Scheme 18) are well documented through multiple derivatives of the Wittig reaction such as the Schlosser modification,²⁸⁵ Horner-Wadsworth-Emmons reaction (HWE),²⁸⁶ and "Boden's conditions"²⁸⁷. Drawbacks to the Wittig manifold of reactions include the generation of

stoichiometric amounts of PPh_3O waste, which can lead to laborious purification steps to ensure its complete removal. Due to the wasteful nature of the Wittig reaction, pioneering research into developing catalytic Wittig reactions has been conducted.^{284, 288} One popular strategy that involves catalysis in the phosphorous component is *in situ* redox recycling of PPh_3O P(V) back to PPh_3 P(III).²⁸⁸ The stereochemical outcome of the Wittig reaction can be significantly influenced by the nature of the ylide and the specific solvent-reaction conditions. Pandolfi *et al.* reported dramatic changes in stereoselectivity when screening various solvents using Boden's reaction conditions i.e. potassium bases in conjunction with 18-crown-6.²⁸⁷ Note: 18-crown-6 is itself a solvent of concern, possessing acute oral toxicity.²⁸⁹

Chlorinated solvents such as DCM, chloroform and CCl_4 do find use in the Wittig reaction.²⁹⁰ The solvent effects of a number of conventional organic solvents and aqueous suspensions were reported as part of a study in 2007 by El-Batta *et al.*²⁹⁰ DCM performed well in a model HWE-Wittig reaction between aldehydes (*o*-anisaldehyde and cinnamaldehyde) and methoxycarbonylmethylenetriphenylphosphorane. It was observed as a general trend that the Wittig reaction proceeded fastest in MeOH and slowest in THF and CH_3CN . Most significantly, the Wittig reaction proceeded fastest in water over all organic solvents with the exception of MeOH, even though the reactions were conducted as suspensions. The protocol published by El-Batta *et al.* demonstrated that excellent yields (up to 99%) and stereochemical control (up to 98% *E*-selectivity) for aqueous Wittig reactions can be achieved at room temperature (40 min – 2 h).²⁹⁰ A total of 24 one-pot Wittig reactions encompassing a broad variety of substrates was included as part of this study. The authors concluded that "*these results further support the suggestion that water should be routinely considered as a medium for organic synthesis, for reasons both of environmental consideration and of chemical efficacy*".²⁹⁰ As a teaching and learning exercise, both solvent-free and aqueous Wittig reactions based on this type of reaction are now conducted.^{291-292, 293}

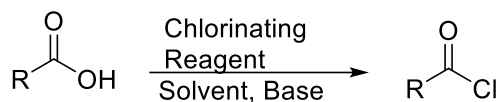
Due to the level of complexity associated with stereochemical outcomes, ylide stabilization and solubilization of inorganic bases it is very difficult to provide unified guidance for choosing alternative solvents. It is suggested that as part of solvent screening for Wittig reaction optimization that water is included as part of any potential green solvent screen. Ethanol²⁹⁴, MeOH,²⁹⁰ and EtOAc²⁹⁵ should also be considered for inclusion. Other developments in the field of olefination may also be considered including recently developed decarbonylative olefination which avoids phosphorous based reagents entirely.²⁹⁶

4.2.17 Halogenation – Acid Chlorides, Aliphatic Halogenation, Aromatic Halogenation, Alcohol Halogenation, Fluorination

Halogenation of organic molecules can serve many purposes including activation of functional groups to their corresponding leaving groups e.g. alcohols to their respective alkyl halides, carboxylic acids to acid chlorides. Aromatic halogenation can serve to provide reactive intermediates for cross-coupling reactions or to alter ring electronics/sterics. Fluorination is a commonly employed tactic to replace H atoms in drug molecules with more lipophilic isosteric replacements and can be used to block site-specific metabolism or in the development of positron emission tomography (PET) ligands.¹⁴² Halogenation remains one of the most common functional group additions made during drug molecule synthesis.¹⁶² In the following sections, halogenation of carboxylic acids, aliphatic and aromatic substrates will be discussed. Fluorination will be discussed separately in section 4.2.17.7.

4.2.17.1 Acid Chloride Formation

Scheme 19: Acid chloride formation.



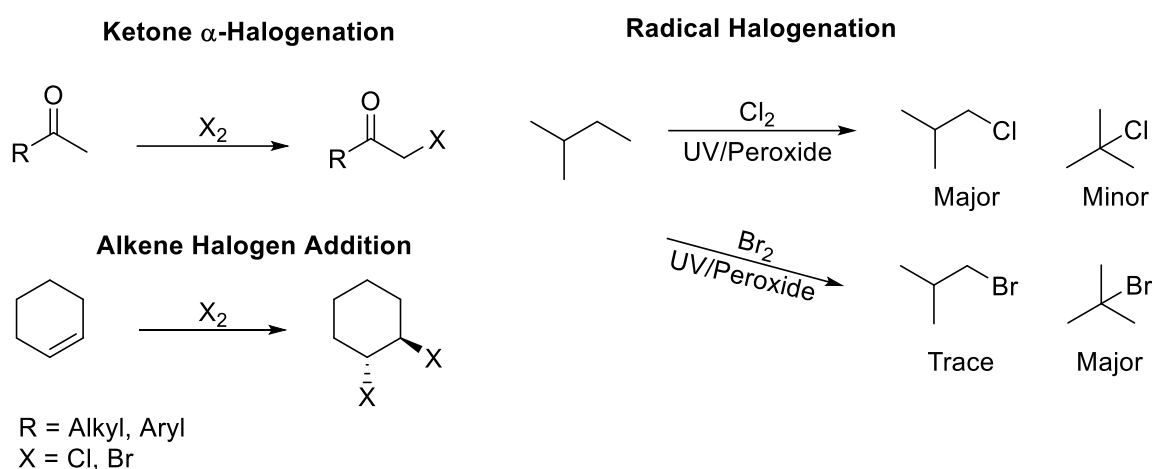
Acid chloride synthesis from the respective carboxylic acid (Scheme 19) is a long employed step in amide bond synthesis¹⁴⁸ (see section 4.2.1) and ester synthesis²⁹⁷ (section 4.2.13). Chlorinating reagents that are amongst the most popular include highly reactive SOCl_2 , $(\text{COCl})_2$ and POCl_5 , thus the solvents chosen must be compatible with the highly electrophilic chlorinating reagents i.e. not polar protic solvents.²⁹⁸ The most commonly employed solvent is unsurprisingly DCM; other choices include THF, toluene and benzene.²⁹⁸ Often catalytic amounts of DMF are also included.²⁹⁸ Recent advances in alternative solvent availability and judicious solvent selection has shown that the bio-based solvent Cyrene can be used as a direct replacement for polar-aprotic solvents for this transformation.¹⁴⁸ Bousfield *et al.* demonstrated that acid chlorides could be easily synthesized and reacted *in situ* with amine nucleophiles to give amides in excellent yields. Products were often isolable by precipitation from the reaction mixtures upon addition of water.¹⁴⁸ Acid chloride synthesis on kg scale has also been effectively demonstrated in 2-MeTHF (catalytic amounts of DMF).²⁹⁹

4.2.17.2 Aliphatic Halogenation

Aliphatic halogenation as the namesake suggests, involves the replacement of a hydrocarbon hydrogen atom with a halide. The predominant reaction types used to facilitate this transformation are free radical halogenation or halogenation addition reactions to alkenes, alkynes or carbonyl compounds with sufficiently acidic protons at the α -position. Aromatic halogenation methods are discussed later (section 4.2.17.5). Aliphatic halogenation to form an alkyl chloride, bromide or iodide is a transformation most often employed to form reactive halide intermediates but will rarely feature as a functional group in a drug molecule due to associated reactivity and toxicity.³⁰⁰ However, examples do exist such as antibiotic Clindamycin, steroid Mometasone furoate, artificial sweetener Sucralose and a number of natural products.^{300,301} Alkyl halides are also present in some

natural products. As a functional group they have even been declared as “underexplored motifs in medicine” in a recent review by Gál *et al.*³⁰⁰

Scheme 20: Various methods of aliphatic halogenation.



4.2.17.3 Ketone Halogenation and Halogen Addition Reactions

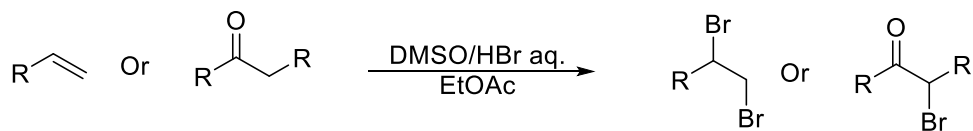
α -Halogenation of ketones is a convenient method for rapidly accessing α -Cl/Br/I ketones. Reactions can be conducted in either acidic or basic conditions. Low pH conditions aid in promoting monohalogenation whilst basic pH generally promotes exhaustive halogenation, an example of which is the haloform reaction.³⁰² Selective mono-bromination of the α -H of a ketone is a key synthetic step in the synthesis of Salbutamol, an inhaled compound used in the treatment of asthma and chronic obstructive pulmonary disease.³⁰³

The most popular reagents employed for the formation of α -Br ketones are Br_2 or *N*-bromosuccinimide (NBS) and an acid catalyst such as acetic acid or HBr .³⁰⁴ The use of Br_2 is undesirable due to its associated health and safety concerns.²⁶⁹ DCM, THF and chloroform are amongst the most popular solvents employed to carry out Br_2 mediated transformations and the first example in this review that includes chloroform as one of the most prominent solvents (not just from legacy examples but still currently a popular

solvent choice with 163 published examples in 2019 alone using Br₂ - CHCl₃ reaction conditions).³⁰⁴ Clearly, the formation of α-Br ketones is relying on legacy methodology to facilitate this transformation. More sustainable solvent choices are sparsely reported but do include MeOH replacing CHCl₃ to facilitate a Br₂ bromination step in a reported enantioselective synthesis of Epibatidine.³⁰⁵ EtOAc has also been successfully employed as reaction solvent in a Br₂ α- bromination reaction with an excellent yield of 85.9% reported.³⁰⁶ Bromination employing Cu(II)Br as reagent can effectively be conducted in a number of alternative solvents including 2-MeTHF³⁰⁷, EtOH³⁰⁸ and EtOAc³⁰⁹. *N*-halo succinimide mediated halogenation (Cl, Br and I) can similarly be conducted in non-chlorinated solvents such as EtOAc and catalyzed by Amberlyst-15 to give halogenated products in excellent yields and short reaction times with recycling of the Amberlyst-15 acid catalyst possible.³¹⁰ Safer brominating reagents such as the NaBr/NaBrO₃ system developed by Adimurthy *et al.* have been reported but reactions were initially conducted in dioxane and DCM,³¹¹ though these conditions have since been improved to use acetic acid.³¹²

Alkene/alkyne halogenation is often conducted with the aim of forming vicinal dibromides, which are useful synthetic precursors. The most common method of conducting this transformation is similar to that employed for α-halogenation of ketones i.e. addition of Br₂ across double or triple bonds.³¹³ The environmental, health and safety aspects of modern developments in conducting electrophilic bromination are thoroughly discussed by Eissen *et al.*³¹³ Solvents employed for electrophilic alkene bromination using Br₂ are predominantly chlorinated solvents in the following order (most occurrences): chloroform, CCl₄ and DCM.³¹⁴ Examples employing non-chlorinated solvents do exist such as the dibromination of methyl acrylate in acetone (89% yield using 1 equivalent of Br₂).³¹⁵

Scheme 21: DMSO-based oxidative bromination.



One modern synthetic development that avoids the use of chlorinated solvents entirely is DMSO-based oxidative bromination methodology (Scheme 21) such as that developed by Song *et al.*³¹⁶ The methodology represents a further development of currently existing O₂ and H₂O₂ oxidative halogenation methods such as oxidative ketone bromination “on water”³¹⁷. The oxidative bromination system employs HBr as bromine source and takes place using EtOAc as solvent giving moderate to high yields of vicinal dibromides when alkenes and alkynes are used as substrates. Similarly, α-Br ketones were furnished in excellent yields. The substrate scope, avoidance of molecular bromine, and use of non-chlorinated solvents, make this very attractive methodology to accomplish a wide variety of electrophilic bromination reactions.³¹⁶ Oxidative chlorination is much more difficult to achieve due to the higher oxidation potential of HCl in H₂O₂ systems thus selectivity can be difficult to achieve.³¹⁸

It is recommended that a substantially safer, more environmentally friendly, chlorinated solvent-free methodology such as the DMSO-based oxidative transformation outlined above is attempted before reverting to Br₂ based methodologies. Further oxidative halogenation methods are well reviewed by Podgoršek *et al.*³¹⁸ For an extensive review of electrophilic iodination methods, see Stavber *et al.* 2008.³¹⁹ Alternative methods for the formation of alkyl halides include the Finkelstein reaction.³²⁰ The Finkelstein reaction is an S_N2 reaction in which one alkyl halide is exchanged for another e.g. alkyl chloride to alkyl iodide transformations are usually accomplished using NaI in acetone, exploiting the insolubility of the NaCl formed during the reaction to drive the transformation to completion.

4.2.17.4 Free-Radical Halogenation

Free radical halogenation can be employed as a general C-H functionalization method. In general, superior selectivity of radical brominations is observed over chlorinations due to

the Hammond postulate and also the inverse relationship between selectivity and reactivity.³²¹ NBS in conjunction with a radical initiator remains the most popular and widespread method for radical bromination of benzylic C-H and allylic C-H groups i.e. a Wohl-Ziegler type of reaction.³²²⁻³²⁴ Due to the reactivity of halide radicals, solvents themselves must be unreactive making solvent choice challenging and promoting CCl₄ to the position of go to solvent.³²⁵⁻³²⁶ CCl₄ was almost exclusively employed by Ziegler in the original studies of this reaction.³²⁷ Benzene is another popular choice as it generally does not undergo radical attack in the presence of peroxides.³²⁷

Throughout the literature available on radical benzylic bromination reactions employing NBS, a number have been successfully carried out using cyclohexane as solvent.³²⁸⁻³³⁰ Other methods such as "on water" benzylic bromination,³³¹ the use of MeOAc as solvent,³³² and microwave assisted benzylic bromination in EtOAc and diethyl carbonate³³³ have also shown to be successful approaches, as have solvent-free methods.³³⁴ Benzylic bromination may be achieved alternatively using tribromoisocyanuric acid in EtOAc without the need for catalysts or initiators, a considerably safer and greener process.³³⁵ Oxidative benzylic bromination solvent screening has also been examined by Mestres *et al.* and showed that this transformation could potentially be carried out in isopropyl acetate (~66% yield) or methyl pivalate (80% yield) compared to CCl₄ (quantitative).³³⁶ Flow chemistry advancements have also shown that this transformation can be conducted in CH₃CN/AcOH.³³⁷ Thus, it is suggested that alternative solvents are screened in benzylic bromination reactions before the use of CCl₄ is ever considered. Note: Hazardous incompatibilities have been identified with NBS and a number of conventional organic solvents such as DMF and DMA including autocatalytic behavior on heating.³³⁸

There appears to be a lack of greener solvents that can be used for alkane C-H bond radical bromination. The most popular methods of facilitating this transformation include both NBS and Br₂ with CCl₄ as solvent. This transformation therefore remains an area of concern for green and sustainable chemistry. Other methods for the formation of alkyl halides include the Hunsdiecker reaction³³⁹ which is a method that can be employed to convert a

carboxylic acid silver salt to an alkyl bromide with loss of CO₂ and proceeds *via* a radical process. The Hunsdiecker reaction is also traditionally conducted in CCl₄ though high yielding solvent-free examples have been reported.³³⁹ Other elements of radical chemistry outside the scope of this review such as reduction of organohalides and C-C bond formation are reviewed by Togo in the book chapter "Free Radicals for Green Chemistry" with a good number of transformations carried out in alcohols, water and solvent-free.³⁴⁰ The challenge of finding greener solvent conditions for Wohl-Ziegler reactions is also noted. Generally, it has been viewed that solvent selection plays little effect on free radical chemistry, that a reaction should work just as well in benzene as it would in EtOH,³⁴⁰ however this misconception has been reviewed and challenged as "folklore" in the work of Litwinienko *et al.*³⁴¹

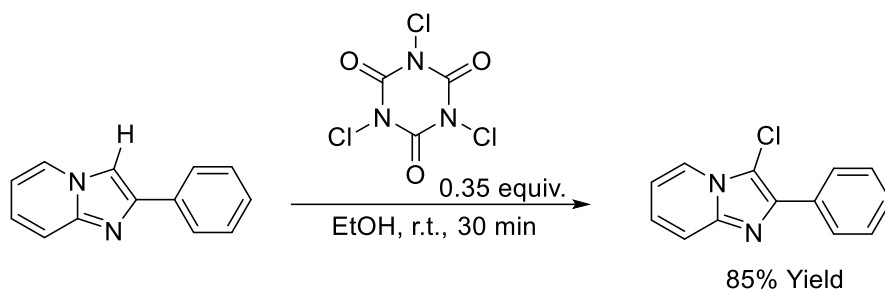
4.2.17.5 Aromatic Halogenation

A greener halogenation system for the synthesis of brominated aromatics has been evaluated by Kajorinne *et al.* using a combination of HBr and H₂O₂.³⁴² The reactions were conducted in methanol, ethanol, water, or were solvent-free and demonstrated good yields, though some work was required to tune selectivity. The conditions were not general to all halides with bromine working much better than iodine and chlorine.

Halogenated solvent-free aryl halide synthesis has also been accomplished by Song *et al.* employing the combination of dimethyl sulfoxide (stoichiometric, not as solvent) and HBr (or NH₄I) in EtOAc. The system developed allows for excellent yields and regioselectivity of arylbromides and iodides and has been employed across a wide variety of substrates including heteroarenes.³⁴³

Recently, Neto *et al.* have utilized trihaloisocyanuric acids as aromatic halogenating reagents for the regioselective halogenation of imidazoles using ethanol as solvent.³⁴⁴ Chlorination, bromination and iodination were all demonstrated, giving excellent yields in short reaction times (30 minutes) across a wide range of heteroaryl imidazoles. (Scheme 22).

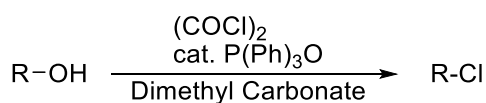
Scheme 22: Heteroarene selective halogenation using trichloroisocyanuric acid in EtOH.



4.2.17.6 Alcohol Halogenation/Deoxyhalogenation –Appel Reaction

Alcohol halogenation or deoxyhalogenation, e.g. *via* the Appel reaction, is a useful transformation for accessing alkyl, allylic and propargylic halides from their respective alcohols, thus avoiding radical halogenation methodologies. A recently published case study in screening greener and sustainable solvents for a catalytic Appel reaction is outlined below.

Scheme 23: Catalytic Appel chlorination reaction.³⁴⁵



R = Alkyl, Allyl, Propargyl

The Appel reaction is a convenient method with which to activate alcohols by converting them into their respective halides i.e. deoxyhalogenation. The original methodology involves the reaction of triphenylphosphine with CCl_4 to form a reactive chlorophosphonium species (CPS). CPS then reacts with various alcohols to form the respective alkyl chloride and triphenylphosphine as a by-product. CCl_4 may also be replaced with carbon tetrabromide to give the respective bromination. More recently, a catalytic version of the reaction methodology was developed by Denton *et al.* replacing CCl_4 with chloroform and employing triphenylphosphine as an organocatalyst significantly reducing the amount of waste produced.³⁴⁶⁻³⁴⁷ Further developments and improvements to the sustainability of the catalytic Appel reaction were published by Jordan *et al.* in 2020 which effectively removed the need for chlorinated solvents in the Appel deoxyhalogenation by replacing it with

dimethylcarbonate.³⁴⁵ Yields and conversions were comparable to contemporary methodology and the improved conditions were used to synthesize a number of building block-like molecules up to 10 mmol scale, chromatography free with excellent catalyst recovery, (no further scale-up was attempted though the authors see no reason to stop at 10 mmol).³⁴⁵

4.2.17.7 Fluorination

Fluorination represents a very important transformation in medicinal chemistry. Fluorine is a commonly employed isosteric replacement for hydrogen atoms and can be used to block site specific metabolism and alter other aspects of drug distribution and clearance.³⁴⁸ β -F atoms can also be used to modulate amine basicity.³⁴⁹ ^{19}F -NMR and ^{18}F -PET diagnostic medical techniques also rely on fluorinated drug molecules. Fluorination techniques have undergone considerable development over the past 10-20 years and are already thoroughly reviewed in the literature.³⁵⁰⁻³⁵⁴ Traditional methods of fluorination up until a few decades ago relied on either F_2 gas or KF. Problems with selectivity and harshness of reaction conditions meant use of F_2 restricted the potential substrate scope that could be used. Similarly problems with the poor reactivity of KF limited its use.³⁵³ The advent of organic fluorinating reagents such as diethylaminosulfur trifluoride (DAST), Selectfluor and *N*-fluoropyridinium salts have facilitated a new wave of selective fluorination chemistry.³⁵³ However, inherent issues with the safety and sustainability of these reagents exists thus driving investigation into greener more sustainable fluorination chemistry. Modern developments include transition-metal insertion of F into C-H bonds, and carbon radical generation followed by F-atom transfer.³⁵⁰ The most commonly employed fluorinating reagents in medicinal chemistry are well described in the review published by Yerien *et al.*³⁵² Functional group transformations and their respective reaction conditions and reagents are well reviewed by Ritter *et al.*³⁵³ Due to the immense body of literature available on fluorination techniques, discussing solvents used for each method would require its own review. Therefore, this section will focus on the most commonly employed reagents and techniques that are applicable to medicinal chemistry/drug discovery.

4.2.17.7.1 Nucleophilic Fluorination

Nucleophilic fluorination involves an electrophilic substrate with a suitable leaving group and a source of nucleophilic fluoride ion. There are numerous sources of nucleophilic fluorinating reagents such as inorganic KF and CsF, and HF derived reagents such as HF/pyridine and Et₃N.3HF. One of the most popular nucleophilic fluorinating reagents is tetrabutylammonium fluoride (TBAF).³⁵⁴ Deoxyfluorination is another nucleophilic fluorination strategy with reagents such as DAST, and the more recently developed Deoxo-Fluor, facilitating this transformation. Deoxyfluorination allows for access to alkyl fluorides and allylic fluorides from the respective alcohols.³⁵⁴ HF/Pyridine and DAST are reagents with major issues and it is suggested that alternatives should be used if possible. For deoxy-fluorination, DAST is the most popular reagent followed by TBAF.³⁵⁵ DAST reactions overwhelmingly employ DCM as reaction solvent, though the use of THF and toluene are also reported. For reactions employing TBAF, THF was the most prominent solvent followed by DCM and CH₃CN. The popularity of THF may be due to the commercial availability of TBAF-THF solutions. The reactivity and nature of deoxy-fluorination chemistry obviously precludes the use of alcohols as solvents. Sparse use of greener solvents exist though EtOAc appears to have been successfully employed as solvent for both DAST³⁵⁶ and Deoxofluor³⁵⁷ mediated deoxyfluorination by a number of pharmaceutical companies.

An improved method of deoxyfluorination has been recently demonstrated by Sood *et al.* using inorganic fluorinating reagent CuF₂ in conjunction with amide coupling reagent diisopropylcarbodiimide.³⁵⁸ The reaction is carried out as a two part telescope, the first step (alcohol activation) is performed using CPME as solvent and the second step (CuF₂ addition) using water. Formation of the activated *O*-alkylisourea is believed to act as a Lewis-basic site from which CuF₂ can co-ordinate, thus facilitating intermolecular F-transfer. The methodology was amenable to a variety of primary and secondary alcohols as substrates, though yields of secondary alcohols were moderate when compared to primary, and radiolabeling was also demonstrated.³⁵⁸

4.2.17.7.2 Electrophilic Fluorination

Electrophilic fluorination is the reaction between a nucleophilic substrate and an electrophilic fluorine source. Commonly employed reagents include Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), *N*-fluorobenzenesulfonimide (NFSi), Accufluor (1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate), and fluoro pyridinium salts.³⁵² The most popular solvent used to facilitate Selectfluor reactions is not a chlorinated solvent but rather acetonitrile, owing to the poor solubility of the reagent in almost anything but polar solvents.³⁵⁹ To find greener electrophilic fluorination conditions one must move away from organic solvents and look towards some of the more recent advancements in this area: electrophilic fluorination in water. Stavber *et al.* have reported direct electrophilic fluorination of carbonyl compounds in water and under solvent-free conditions.³⁶⁰ In their work, a number of 1,3-dicarbonyl compounds were effectively fluorinated at the α -position using a number of commonly employed electrophilic fluorinating reagents such as Selectfluor and NFSi.³⁶⁰ Due to the good stability of Selectfluor in water at ambient temperatures, this reagent solvent combination has facilitated many electrophilic fluorination transformations which are well reviewed by Yang *et al.*³⁶¹ Electrophilic fluorination using NFSi in water appears to be the most agreeable set of conditions that avoids the use of organic solvent entirely and employs what is considered to be a safer fluorinating reagent.²⁶⁹ An example of a more sustainable copper catalyzed direct fluorination by F_2 has been reported by Willis *et al.*³⁶² In their publication the routine synthesis of a fluoromalonate building block on 50 g scale is described, possessing a mass intensity (MI) of just nine whereas comparable literature methods utilizing NFSI had a calculated MI of 316. With appropriate engineering and safety controls, Cu catalyzed direct fluorination with F_2 could be considered as sustainable and scalable synthetic option. The potential for sustainable F_2 chemistry is further discussed by Antal *et al.*³⁶³ complementary to an economic and green chemistry metric evaluation.³⁶⁴

4.2.17.7.3 Aryl Fluorination

Aryl fluorination is a useful transformation for installing Ar-F bonds, either from C_{Ar}-H or C_{Ar}-X bonds and is a moiety that is present in a number of currently marketed drug molecules such as Lapatanib, Gefitinib and Vandetanib.³⁵² Direct C_{Ar}-H fluorination has been developed by Lou *et al.* using palladium-catalyzed fluorination with NFSi in EtOAc. This methodology represents an excellent development with facile and site-selective C-H fluorination possible across a broad substrate scope with high functional group tolerance and moderate to excellent yields possible.³⁶⁵

Aryl fluorination of C_{Ar}-X bonds where X is a halide or pseudohalide *via* Pd or Cu catalyzed methods is well reviewed by Yerien *et al.*³⁵² This technique has undergone considerable development over the past decade with a number of late-stage fluorination techniques for drug discovery having also been developed.^{353, 366} Aryl-CF₃ and CF₂H are often introduced to molecules via cross-coupling methodologies as well.³⁶⁷⁻³⁶⁸ Solvents used for metal-catalyzed aryl fluorination are as varied as those discussed in section 4.2.5 on cross-coupling methodologies and include cyclohexane, TBME, toluene and 2-MeTHF.³⁶⁹⁻³⁷⁰

Non-metal catalyzed aryl fluorination reactions included the Balz-Schiemann reaction and the Wallach reaction. The Balz-Schiemann reaction is actually a nucleophilic fluorination strategy that utilizes an aryl diazonium BF₄ or PF₆ salt which when heated undergoes fluorination with loss of N₂. The Wallach reaction is a fluorination techniques that uses aryl triazenes which undergo fluorination when treated with HF/pyridine. Both techniques are somewhat limited in substrate scope due to the harsh reaction conditions.³⁵⁴

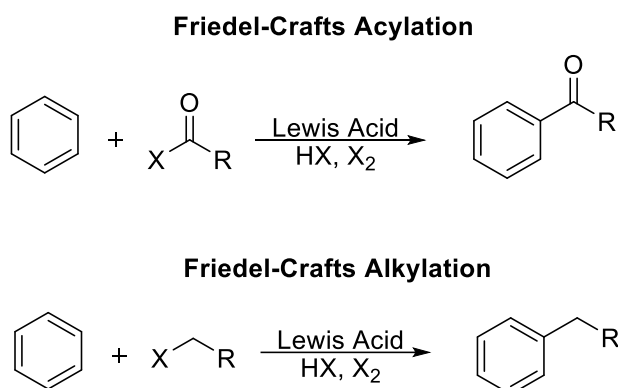
The S_NAr reaction is often utilized in generating aryl fluorides from electron deficient arenes containing leaving groups such as chloro or nitro. A nucleophilic fluorine source is required such as KF etc. and solvent choices are often high boiling including sulfolane, toluene, water, DMF and CH₃CN. Due to the driving reaction conditions usually required, lower boiling chlorinated solvents are not usual choices.³⁷¹ S_NAr chemistry is further discussed in section 4.2.2, *vide supra*.

4.2.17.7.4 Benzylic Fluorination

Benzylic fluorination is a fluorination technique that can often be achieved *via* free-radical methods due to the ability of benzylic carbon centers to stabilize radicals. Problems are often encountered using traditional fluorination procedures e.g. competitive S_N1 elimination to form styrenes. Dozens of examples of benzylic fluorination methods are described by Champagne *et al.* in their exemplary review of monofluorination techniques.³⁵⁴ Fe, Mn and Pd catalyzed methods have all been employed to some degree of success, as have light generated radical fluorination. There is no general consensus on solvent selection as the methods employed encompass a broad variety of techniques.³⁵⁴

4.2.18 Friedel Crafts Acylation/Alkylation

Scheme 24: Friedel-Crafts alkylation and acylation reactions.



Electrophilic aromatic substitution (EAS), also known as the S_EAr reaction, is a classical reaction manifold that involves the replacement of an aryl hydrogen atom by an electrophile. The transformations achievable under this manifold include aromatic halogenation, sulfonation, nitration, and alkylation³⁷² and acylation³⁷³ via the Friedel-Crafts reactions, Scheme 24. The ability to rapidly and reliably conduct many important functional group transformations/installations from simple substrates via well-established reaction pathways has led to EAS being one of the oldest and most popular methods of C-C bond formation/functionalization in organic chemistry.

A survey of solvents employed for Friedel-Crafts acylation reactions shows that the most commonly employed solvent for this transformation is DCM (32%). Carbon disulfide (12%), 1,2-dichloroethane (8%) and nitrobenzene (3%) also feature in many examples. Utilization of other chlorinated solvents such as CCl₄ and chlorobenzene (in the dual role of reagent and solvent) also occur.³⁷⁴ It is clear from this survey that the Friedel-Crafts reactions are still relying heavily on solvents of serious concern. This is of no surprise as the generally accepted synthetic methodology has often been to employ an excess of the hydrocarbon that is undergoing substitution such as benzene, toluene or chloro/bromobenzene, as is noted in the 1935 review on the same matter.³⁷⁵ When a solvent is required, an inert one is required to avoid reaction with the Lewis acid and herein lies the challenge of discovering appropriate alternatives for this reaction. One successfully employed strategy is to employ solvent free methods. These have long been known and reactions can be conducted by grinding the reagents together giving a fused mass.³⁷⁵ Modern advances in solvent-free Friedel-Crafts acylation reactions have shown TiCl₄³⁷⁶, zinc³⁷⁷ and ZnO³⁷⁸ to be excellent catalysts for promoting this reaction giving excellent conversions to product in very short reaction times (often seconds to minutes) either through conventional heating³⁷⁹, or microwave assisted³⁷⁷.

Another alternative is aqueous based reactions. In 2018, Sadiq *et al.* published a review of Friedel-Crafts reactions in aqueous media³⁸⁰, which is itself a considerable challenge as traditional Lewis acid catalysts such as AlCl₃ react violently with water. Strategies to achieve this transformation include both aqueous compatible homogeneous and heterogeneous acid catalysis, reactions in basic aqueous media and catalyst free conditions. 3-component aza-Friedel-Crafts reactions have been successfully conducted in water using decanoic acid as an acid catalyst to give substituted indoles in good to excellent yields and has been demonstrated on gram scale.³⁸¹ Friedel-Crafts alkylation reactions have been carried out using aqueous slurries of mesoporous particles, such as alumina or silica, with Lewis acidic character. The reported system allowed for the reaction of *t*-butyl benzyl chloride with sodium salicylate though the isolated yields were moderate

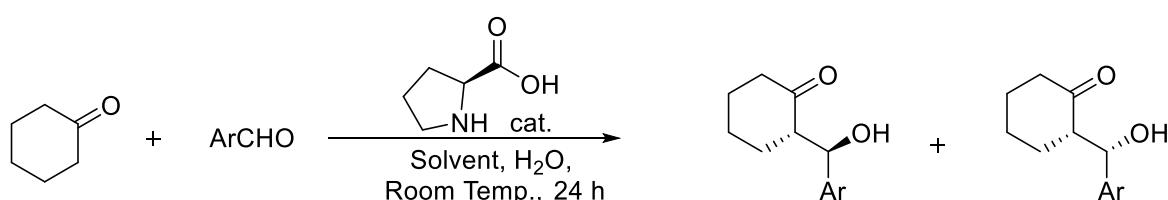
(61%).³⁸² Heterogeneous catalysis using zeolite ZSM-5 has allowed for Friedel-Crafts alkylation of benzene in 95% aqueous ethanol.³⁸³ Hydrophobic poly-peptide resin bound trifluoroacetic acid has demonstrated some promising results with good yields obtained for the reaction of 4-nitrocinnamaldehyde with *N*-methyl indole in water. The chiral nature of the peptide tether also introduced asymmetric induction to the reaction and up to 88% ee was observed for the same transformation.³⁷⁹ Overall, authors of the aforementioned review, Sadiq *et al.*, conclude that Friedel-Crafts reactions in water “*could possibly be carried out under variable conditions*”.³⁸⁰ Though, as of yet, there are no unified conditions to conduct this transformation in water.

4.2.19 Other Highlights in Green and Sustainable Reaction Development

4.2.19.1 Proline catalyzed aldol

The proline catalyzed aldol reaction is a significant transformation in organic chemistry for a number of reasons, not least its synthetic usefulness. The original “Hajos–Parrish–Eder–Sauer–Wiechert reaction” as the asymmetric transformation is also known, was developed throughout the 1970’s and represents a landmark discovery in the field of organocatalysis, though exploration of this field as a whole did not really take off until the early 2000’s.³⁸⁴

Scheme 25: Proline catalyzed aldol reactions in aqueous carbonate solvents. ³⁸⁵

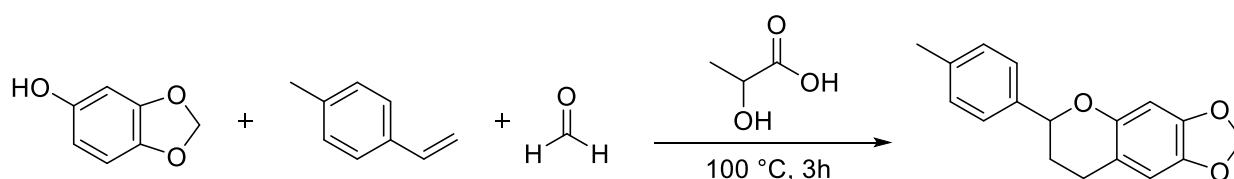


Propylene carbonate has been shown by North *et al.* to be a viable replacement solvent for polar aprotic and chlorinated solvents in proline catalyzed asymmetric aldol reactions.³⁸⁵ Reported yields were good along with excellent stereocontrol observed, comparable and in some cases exceeding results reported under other solvent/reaction conditions. North *et al.* have also demonstrated that propylene carbonate can replace DCM in proline catalyzed hydrazinations of aldehydes and ketones. Whilst the yield and enantiomeric excess (ee) were diminished compared to DCM at room temperature,

reducing the temperature and increasing the time allowed good yields and e.e.s to be obtained. The use of enantiomerically pure propylene carbonate did not appear to offer any advantage over the racemic solvent.³⁸⁶

4.2.19.2 Lactic Acid Multicomponent Reactions

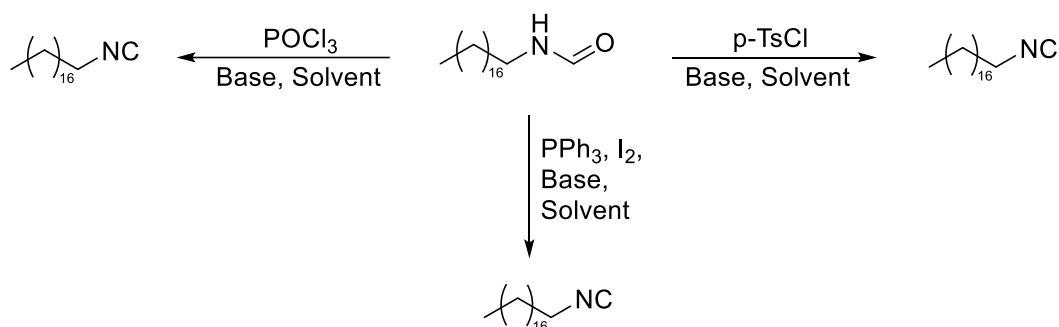
Scheme 26: 3-Component reaction of styrene, phenol and aldehyde using lactic acid as solvent.³⁸⁷



In 2012 Yang *et al.* demonstrated that lactic acid, a bio-based green solvent, was an effective medium in which numerous multi component reactions could be conducted including three component styrene-aldehyde-phenol/*N,N*-dialkylacetoacetamide reactions (Scheme 26), aldehydes-anilines-alkyne, salicylaldehydes and diethyl acetylenedicarboxylate, and Friedländer annulations.³⁸⁷ All of the examples synthesized outperformed traditionally employed solvent acetic acid with enhanced reaction rates also observed. The lactic acid was also easily recycled in a number of cases where products were less polar and makes this an excellent case study in the use of bio-based solvents as a versatile reaction medium. Further work on Friedländer annulations has been conducted by Anderson *et al.* who have reported optimized conditions utilizing water as solvent. The requirement for stoichiometric quantities of proline organocatalyst was also removed giving a very favorable PMI of eight.

4.2.19.3 Isocyanide Synthesis

Scheme 27: Sustainable isocyanide synthesis examined by Waibel *et al.* ³⁸⁸



A comprehensive analysis of the synthesis of aliphatic isocyanides was conducted by Waibel *et al.* in 2020 and includes reaction methodology such as formamide dehydration using *p*-toluenesulfonyl chloride (*p*-TsCl), Ugi reaction conditions utilizing POCl_3 , and Wang conditions using PPh_3 and I_2 (dehydrating conditions similar to Appel conditions), Scheme 27.³⁸⁸ DCM was employed as a benchmark solvent for these reaction types and was shown to be an excellent solvent for the Ugi and *p*-TsCl reactions but performed poorly under Wang conditions. Analysis of alternative reaction conditions using green chemistry metrics combined with screening of greener and more sustainable solvents led to the determination that the use of *p*-TsCl in combination with dimethyl carbonate was an excellent reagent-solvent combination (E-factor of 7.41). Dehydration of ten formamides to isocyanides were performed using these conditions; products were obtained in high yields and excellent purities though reaction times were longer than in DCM (overnight vs 2 hours).

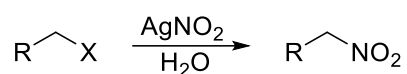
Method	Solvent	Yield %
Ugi (POCl_3)	2-MeTHF, EtOAc, Dimethyl Carbonate	94, 90, 90

Wang (PPh ₃ + I ₂)	2-MeTHF	93
<i>p</i> -TsCl	Dimethyl Carbonate	89

Table 11: A selection of greener and more sustainable non-chlorinated solvents utilized in isocyanide formation methodologies by Waibel *et al.*³⁸⁸

4.2.19.4 Conversion of Primary Alkyl Halides to Nitroalkanes

Scheme 28: Nitroalkane synthesis from alkyl halides in water.



X = Br, I

Nitroalkanes are a group of significant importance to the fine chemicals and pharmaceutical industry e.g. as nitro-aldol/Henry reaction components for the formation of β -nitro alcohols³⁸⁹ and as amine precursors accessible via nitro reduction, and have found historical use in the synthesis and preparation of dyes and explosives.³⁹⁰ One of the most widely used methods to furnish nitroalkanes is the Victor-Meyer reaction.³⁹¹ This reaction employs silver nitrite (or sodium nitrite) as NO₂ source which is reacted with an alkyl halide of choice, often conducted in diethyl ether³⁹² when using AgNO₂ or DMF³⁹³ when employing NaNO₂. Both solvents are solvents of concern.⁴ In 2004 Ballini *et al* reported the first examples of conducting this transformation, using AgNO₂, in water.³⁹⁰ Treating the alkyl halide (Br and I) of choice with AgNO₂ in water furnished a variety of nitro alkanes in moderate to good yields. Reaction times were generally short (30 min – 5 h, though one benzylic bromide substrate took 24 hours to reach 53% yield) and temperatures ranged from room temperature to 60 °C. The process is a marked improvement over traditional reactions involving e.g. DMF. The reaction times reported are claimed to be shorter, workup is more straight forward, yields are superior and alkyl nitrite impurity levels were minimized.³⁹⁰

4.3 Solvent Selection Tools

Other than the aforementioned solvent selection guides and examples outlined in section 4.0, a number of advancements have been made in aiding solvent selection such as *in silico* assisted solvent selection and solvent property prediction for the discovery of new and bespoke solvents. Recently, Syngenta have published an exemplary account of how they have successfully developed a computer aided multi-parameter solvent selection tool and deployed it across multiple sites (in-house). The tool has aided and accelerated decision making in solvent replacement by generating lists of similar solvents to the one that requires replacing, with attempts to match desired physico-chemical parameters.⁸⁴ Similarly, AsztraZeneca have released a freely available online solvent selection tool in association with the ACS GCIPR.⁹⁹ The tool allows for interactive solvent selection and replacement based on solvent physico-chemical and EHS properties and uses a visual map of chemical space to allow for informed decision-making. Selections of solvents can also be downloaded as .csv files for ease of import into other software packages e.g. supporting process chemistry Design of Experiments (DoE). For assisting solvent selection in recrystallisation processes, Eli Lilly published an account in 2019 describing their success in implementing *in silico* methods to both reduce employee time required for crystallization method development (20% reduction) and API wastage (x10 reduction).³⁹⁴ Machine learning has also been successfully utilized and implemented in solvent selection for asymmetric catalytic processes.³⁹⁵ Beyond selection tools, efforts have also been directed towards *in silico* methods of calculating solvent physicochemical properties and actually predicting the structures of potential new solvents with tailor made properties i.e. *in silico* solvent design and prediction of Kamlet-Abboud-Taft solvatochromic parameters.³⁹⁶ Such techniques have aided researchers as part of the ReSolve project in their utilization of 2,2,5,5-tetramethyloxolane (TMO) as an alternative solvent for hazardous hydrocarbons.³⁹⁷

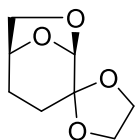


Fig. 16: Cygnet 0.0, part of a larger family of "Cygnet" derived from levoglucosenone. ³⁹⁸

Similarly, the "Cygnet" family of solvents, derived from levoglucosenone (the precursor to polar aprotic solvent Cyrene) were identified through a rational design approach using predicted Hansen solubility parameters and COSMO-RS computation modelling. This body of work eventually led to the identification of "Cygnet 0.0", Fig. 16, a bio-based solvent that occupies a unique area of the Hansen space and has been successfully demonstrated as a potential DCM replacement and a viable solvent in both Heck and S_NAr reactions.³⁹⁸ Predictive methods such as Abraham's solvent parameters have also been used by Bradley *et al.* to predict the properties of dozens of sustainable solvents. The same study includes potential solvent replacements for current solvents of concern based on predicted properties.³⁶ Similarly, over 40 solvents exhibiting favorable EHS profiles were identified using a HSP space-filling design to give a set of green solvents that are evenly spread around the Hansen space.³⁹⁹ Software such as HSPiP can also be employed to determine Hansen solubility parameters.⁵⁵ Computational methods and tools for solvent selection are an invaluable tool for chemists and should aid in designing safer and more sustainable chemical processes.

5.0 General Guidance and Conclusion

As the variety of solvents and examples listed in the preceding sections illustrates, there is no one "drop-in" alternative for chlorinated solvents. However, a number of companies and research groups have sought to provide generalized guidance to improve the chances of successful solvent replacements, even in areas where there is no literature precedent. Computational methods, online tools and solvent swapping guides can all be used in conjunction to assist the end user in making more informed solvent selection choices. Further to the guidance provided, literature examples of more sustainable solvent choices for nearly every transformation that is common to medicinal chemistry exist. The wealth

of literature available can and should be used to make changes to default practices. Just because DCM is the most commonly used solvent in a reaction does not mean that it is the best solvent for a reaction; indeed – what “best” means will likely vary greatly depending on the circumstances. The only way to break the status quo of chlorinated solvents being the “go to” is to encourage individual chemists to make these changes themselves, review the literature for their reactions in different solvents and make an informed decision, not just a convenient one. A time may come where the use of chlorinated solvents such as DCM are restricted so it with this mind-set that the authors of this review propose that chlorinated solvents are only used as solvents in medicinal chemistry research where literature and/or experimental results suggest that other alternatives are not viable. It has already been highlighted that the legislative restrictions on chlorinated solvent use has the potential to hamper scale-up of C-H activation methodology, a situation that needs to be addressed through a concerted effort to discover safer, more sustainable alternatives. Enough examples and research have already been conducted that show that we can begin to make the transition towards sustainable solvent choices as a field. Change must come, and must now be promoted from the ground up, not just from within industry. As we have already seen, industry and process chemistry have been transitioning towards more environmentally sustainable solvent practices over the past ten years. It is time now for pre-clinical medicinal chemistry to adapt its practices to a research landscape that is increasingly being scrutinized for its sustainability. Precedent exists for changing habits, benzene and CCl₄ usage has undergone dramatic reduction over the preceding decades due to EHS concerns. Chemical research inevitably overcomes these challenges and restrictions by innovation, adaptation and outreach to inform the wider community of lessons learned. It is with this hopeful view that we conclude our review of chlorinated solvent usage in medicinal chemistry.

6.0 Associated Content

A summarized, printable table of potential solvent replacements for reactions of importance to medicinal and organic chemistry, as discussed in Section 4.0, are provided in the Supporting Information Table S1.

7.0 Acknowledgements

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Author Biographies

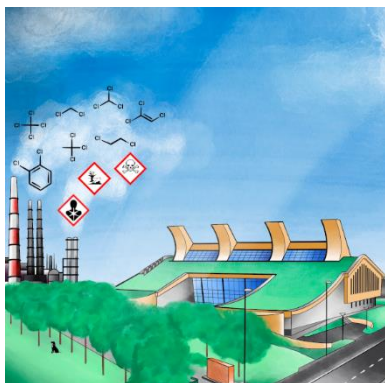
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