CHEMICAL REVIEWS

pubs.acs.org/CR

Review

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

Andrew Jordan,* Patrick Stoy, and Helen F. Sneddon*

Cite This: *Chem. Rev.* 2021, 121, 1582–1622

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

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.

CONTENTS

Received: July 6, 2020
Published: December 22, 2020

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

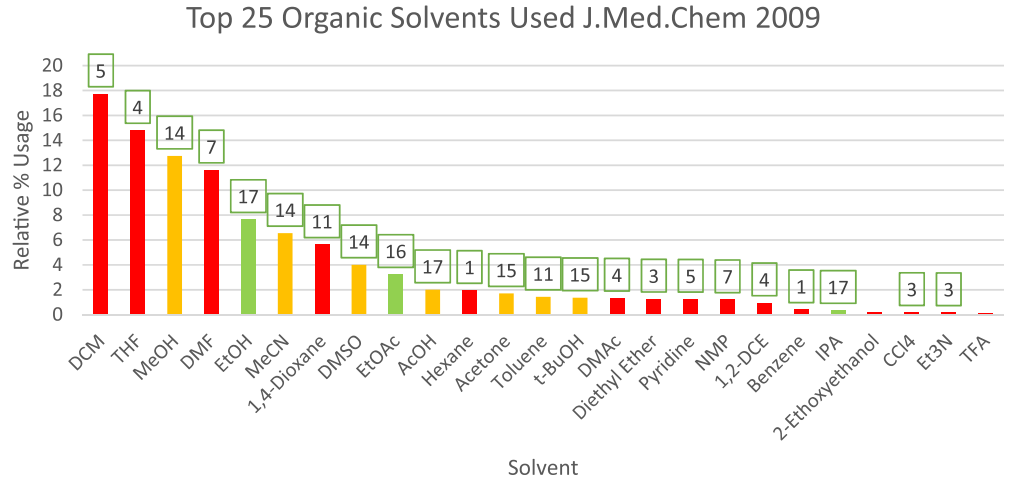


Figure 1. Proportion of solvent usage of *J. Med. Chem.* issues 1 and 2 in 2009 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color-coded using a traffic light metric: green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).[4] The EHS scores are those determined by Prat et al.;[5] the higher the score, the more favorable the EHS profile of the solvent. The scores for 2-ethoxyethanol and TFA are unknown.

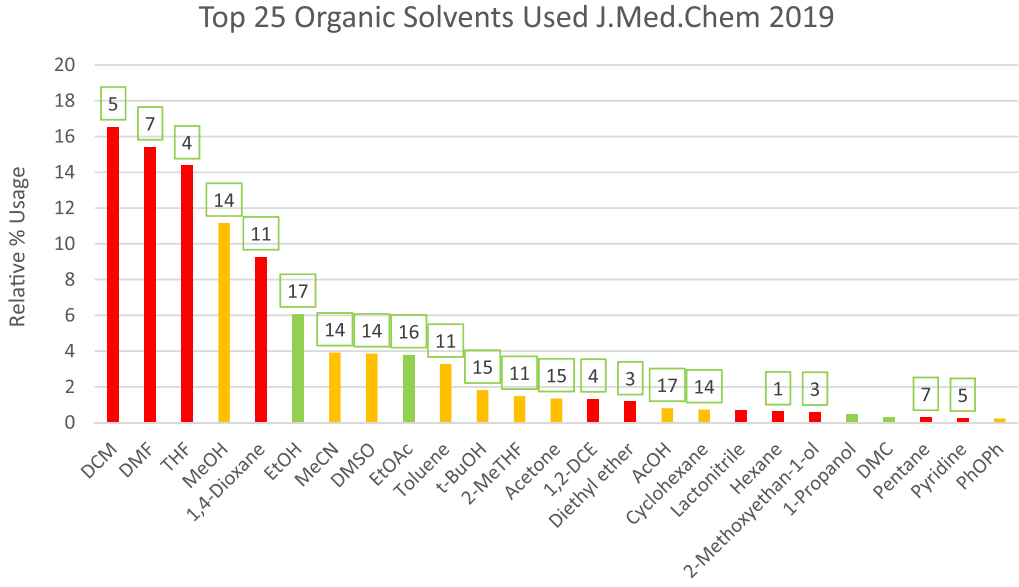


Figure 2. Proportion of solvent usage of *J. Med. Chem.* issues 1 and 2 in 2019 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color-coded using a traffic light metric: green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).[4] The EHS scores are those determined by Prat et al.;[5] the higher the score, the more favorable the EHS profile of the solvent. The color codes for decane and undecane are unknown. The solvent scores for lactonitrile, 1-propanol, dimethyl carbonate (DMC), and diphenyl ether (PhOPh) are unknown.

1.0. INTRODUCTION

Chlorinated solvents that are commonly employed in organic and medicinal chemistry include dichloromethane (DCM), chloroform, 1,2-dichloroethane (DCE), carbon tetrachloride (CCl_4), chlorobenzene, 1,2-dichlorobenzene, 1,1,1-trichloroethane, and trichloroethylene. Of these, DCM and chloroform have found the 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 in 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

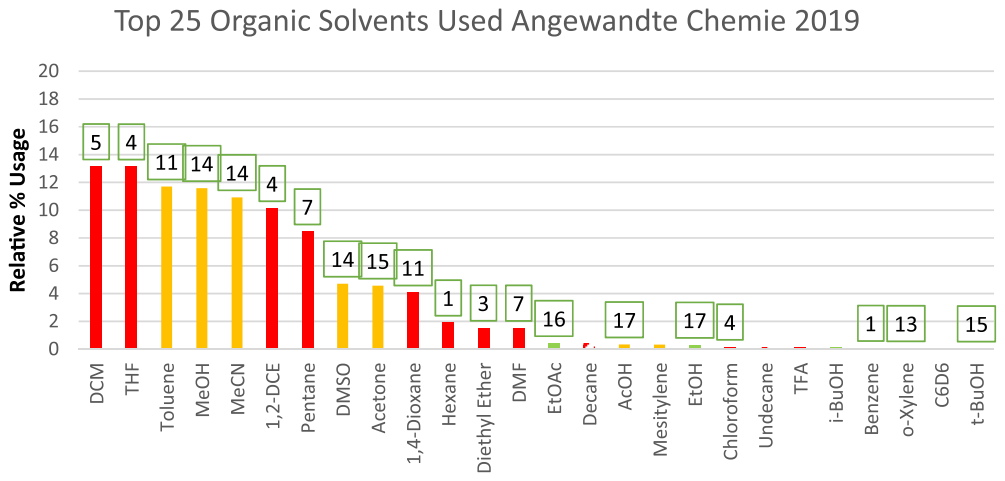


Figure 3. Proportion of solvent usage in *Angewandte Chemie* for 2019, issue 1,[7] with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color-coded using a traffic light metric: green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).[4] The EHS scores are those determined by Prat et al.;[5] the higher the score, the more favorable the EHS profile of the solvent. The color codes for decane and undecane are unknown. The solvent scores for decane, mesitylene, undecane, TFA, iBuOH, and C_6D_6 are unknown.

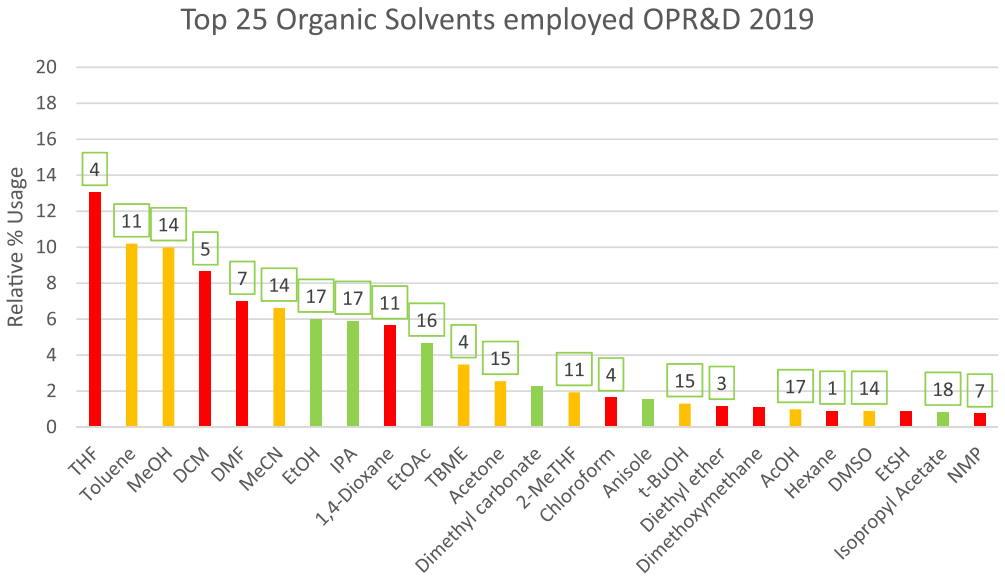


Figure 4. Proportion of solvent usage of all *OPR&D* publications in 2019 with summarized environmental health and safety (EHS) score data label (green box). Solvent bars have been color-coded using a traffic light metric: green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).[4] The EHS scores are those determined by Prat et al..;[5] the higher the score, the more favorable the EHS profile of the solvent. The color codes for decane and undecane are unknown. The solvent scores for dimethyl carbonate, anisole, dimethoxymethane, and ethanethiol are unknown.

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]

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 journal.[6] 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 CCl_4 (~0.2%). Chloroform did not appear in the top 25 most common solvents (0.04%), Figure 1.

The same search was applied to solvent usage in *J. Med. Chem.* publications in 2019, and the results were almost identical, Figure 2;[6] 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 CCl_4 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 10 years between ACS roundtable publications that chlorinated solvent usage in

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

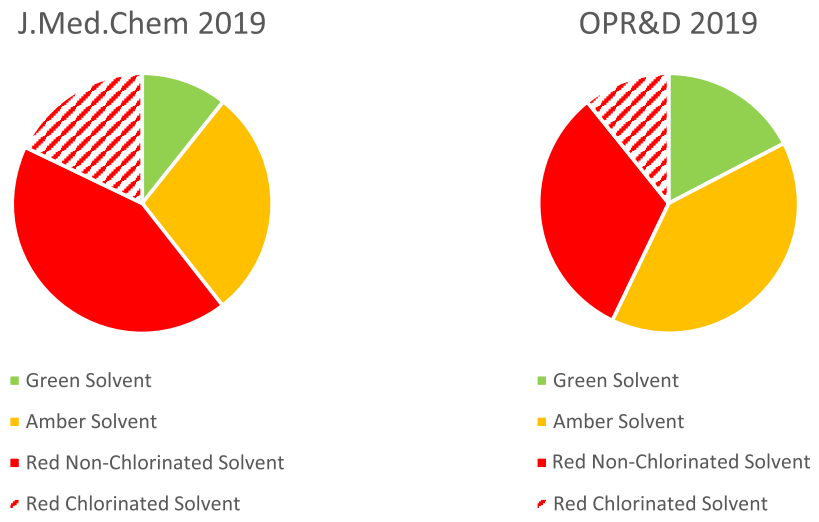


Figure 5. Top 25 organic solvents employed in *J. Med. Chem.* 2019 (left) vs *OPR&D* 2019 (right). Solvents have been categorized by a traffic light metric: green = recommended (few issues), amber = problematic (some issues), red = hazardous (major issues).[4]

preclinical 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]

Solvent usage analysis was then conducted on the 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, Figure 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 was 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 *Organic Process Research and Development* (*OPR&D*) publications for 2019, we can see a very different distribution of solvents (Figure 4) when compared to both Figures 2 and 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 (Figure 5); i.e., a lot less "red" solvents are utilized in *OPR&D* publications.

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 CCl_4 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 one to two times a year since 2008,[12] 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 third most popular solvent to eighth.[13] Similarly, by 2015, Pfizer had not transferred a process to manufacturing that involved a halogenated solvent for at least eight years[10] 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) process;[17] 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 and 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 toward 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

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]

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 nonpolar 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 (Table 2) or indeed by the Kamlet−Taft parameters (Table 3).

The numerical values assigned to each HSP category allow for intuitive categorization of solvents based on whether they are nonpolar 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 (three-dimensional representations of solvent space) and the calculation, prediction, and optimization of solvent blends.[26,27]

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.

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 eq 1, and is based on linear free energy relationships. The uppercase values represent solute

Table 1. Common Organic Solvents, in Order of Decreasing E_T^N as an Empirical Parameter of Solvent Polarity[23,a]

solvent	ε_r[b]	$\mu/(10^{-30}$ Cm)[c]	E_T^N[d]
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
t-butanol	12.47	5.5	0.389
N,*N*-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**
t-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**
n-heptane	1.92 (20 °C)	0.0	0.012
n-hexane	1.88	0.0	0.009
cyclohexane	2.02 (20 °C)	0.0	0.006

[a]Chlorinated solvents are highlighted in bold. [b]Relative permittivity (commonly referred to as dielectric constant) of the pure liquid at 25 °C unless followed by another temperature in parentheses. [c]Dipole moment in Coulombmeter (Cm), measured in benzene, carbon tetrachloride, 1,4-dioxane, or *n*-hexane at 20−30 °C. [d]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.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Table 2. Hansen Solubility Parameter (HSP) Values for Some Commonly Used Chlorinated Solvents, from refs 23 and 25 unless Noted Otherwise[a]

solvent	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	19	4.3	2.0
1,2-dichlorobenzene	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

[a]HSP can be used to describe the intermolecular interactions between solvent and solute. There are three parameter categories: dispersion, i.e., van der Waals forces (δD), polarity (δP), and hydrogen bonding (δH).

Table 3. Kamlet–Taft Parameters for Some Commonly Used Chlorinated Solvents[a]

solvent	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

[a]From ref 29 unless noted otherwise.[28,29]

descriptors, described in Table 4. The lowercase 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 as 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.

Abraham model log P calculation:

$$\log P = c + eE + sS + aA + bB + vV \quad (1)$$

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

Abraham model solubility prediction:

$$\log S_s = \log S_w c + eE + sS + aA + bB + vV \quad (2)$$

where $\log S_s$ = molar concentration of solute in solvent and $\log S_w$ = molar concentration 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 physicochemical 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., hexafluoroisoporpanol (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 physicochemical 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 Autoignition Temperatures. 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. CCl_4 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 the absence of a flash point.[41]

Table 4. Abraham's Parameters for a Number of Chlorinated Solvents[31,a]

solvent	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

[a]Solute descriptors are E, S, A, B, V, or L. E is the solute excess molar refractivity ($cm^3\ mol^{-1}$)/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 ($cm^3\ mol^{-1}$)/100 for use in liquid–liquid partition calculations, and L is a gas–liquid partition coefficient to n-hexadecane at 298.2 K.[32]

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

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 workup 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*.

Table 5. Melting Points and Boiling Points of Selected Chlorinated Solvents[38,39]

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 6. Flash Points and Autoignition Temperatures of Common Solvents[39,a]

solvent	flash point (°C)	autoignition 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

[a]Chlorinated solvents are highlighted in bold.

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 flammability or non-flammability of many chlorinated solvents also contributed to their widespread adoption over more flammable hydrocarbon solvents.[42] For example 1,1,1-trichlorethane, 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 strippers.[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 toxicities of these additives were unknown, (2) water intense processes are often higher energy processes, (3) contaminated aqueous waste is often disposed of into the sewer, and (4) 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 has long been considered.

2.1.3. UV−Vis, Viscosity, and Refractive Index. Chlorinated solvents are frequently employed as chromatography solvents especially in flash chromatography applications. The UV cutoff for DCM is sufficiently low that a standard fixed wavelength UV lamp emitting at 254 nm will not cause DCM to absorb appreciably (Table 7). Furthermore, the ability of DCM to dissolve a wide variety of polar and nonpolar substrates and its ease of removal by evaporation have led it to become one of the most popular chromatography solvents for decades.[46]

Table 7. UV Cutoff Wavelengths,[44] **Refractive Index,**[39,45] **and Viscosity**[39,44] **of Some Common Solvents**[a]

solvent	nm	viscosity (cP), 25 °C	refractive 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

[a]Wavelength at which the solvent absorbs 1.0 AU in a 10 mm cell. Chlorinated solvents are highlighted in bold.

2.1.4. Economic Considerations—Cost of Chlorinated Solvents. The apparent low cost of chlorinated solvents such as DCM and chlorobenzene has 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 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 phasing out of this solvent due to its ozone depleting potential.[47] Economy of scale is evident as the pricing of 2.5 L of DCM amounts to

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Table 8. Typical Costs per Liter of Common Chlorinated Solvents and Greener More Sustainable Solvents as of June 2020[48,a]

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

[a]Note CCl_4 is only sold at £80.30/100 mL via Sigma-Aldrich making the cost £803.00/L. Prices correct at time of publishing.

£13.80/L. Also included are some greener and more sustainable solvents for comparative purposes. Of note is that the cost per liter of EtOAc is not much more expensive than DCM and that IPA is only 30 p per L more expensive than DCM. However, other greener solvents such as anisole, CPME, and 2-MeTHF are considerably more expensive than DCM, Table 8.

2.2. Summary

In summary, chlorinated solvents occupy a privileged solvent space. Their physicochemical properties such as low boiling point, 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.

Table 9. Categorization of Some Common Chlorinated Solvents by H-Phrases according to the Work of McElroy et al.[72,a]

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	SDS 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, H411, H410, 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

[a]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 min TWA.[53] All SDS references checked as of January 7, 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.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

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 has recently reassessed the EHS profile of CCl_4. In a draft assessment, it was stated that there is little concern to users of CCl_4, 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, was up 2 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 (1) the 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 h time-weighted average) to chloroform, chlorobenzene, and CCl_4 is 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, that for acetone is 500 ppm, and that for 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 people 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, and 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 trichloroethylene[56] and chloroform.[59] Each of the chlorinated solvents described in Table 10 is considered toxic to the aquatic environment with the exception of DCM. Release to the environment is 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/h (with no more than 20 mg/m^3 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 the temperature of 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 the 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]

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 nonstabilized 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 base 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 led to detonation, causing destruction to the immediate work environment and injury (noncritical) to two chemists.[78] Other similar incidents involving chlorinated

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Table 10. World Health Organization (WHO) Classifications of Some Common Chlorinated Organic Solvents, Their Short-Term and Long-Term Effects, and Generalized Environmental Impacts[a]

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
dichloromethane	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
1,2-dichloroethane	possible CNS, liver, kidney toxin, probable carcinogen	The vapor is irritating to the eyes, skin, and respiratory tract. Inhalation may cause lung edema. 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
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 and 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Table 10. continued

[a]Source information: Concise International Chemical Assessment Document (CICAD) WHO[73] and International Chemical Safety Card (ICSC) International Labour Organization (ILO)/WHO.[74]

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. While this is not usually a problem for small splashes of DCM (though the aforementioned ability of chlorinated solvents to defat 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-ethylenedioxypyrrole through a researcher's nitrile gloves*". The compound polymerized on the chemist's hands, blackening the skin.[80] The toxicity of the compound was unknown. As with all laboratory operations, appropriate understanding 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 2018[81] and 2020.[82] Nonstabilized DCM degrades over time and is often stabilized with alkanes such as amylene or cyclohexane/cyclohexene.[77]

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-dichlorbenzene 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 among 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 and 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 possible,[83] and solvent processes should be designed to be solvent-economical.[85] Finally, as recently described in *ACS Sustainable Chemistry & 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 disproportionally 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 Figure 6 and Figure 7. These guides are constantly evolving and being developed by industry and academic research groups to aid chemists in making more judicial decisions in solvent selection. As in-depth discussions and reviews of solvent selection guides have already been

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

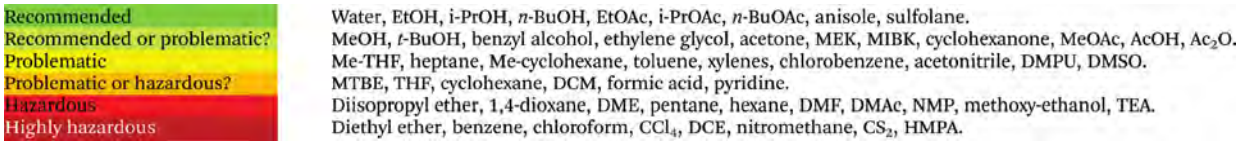


Figure 6. Color-coded classification of solvents based on a survey of publicly available solvent guides.[88] Reprinted with permission from ref 88. Copyright 2017 The Royal Society of Chemistry under Creative Commons 3.0 license [https://creativecommons.org/licenses/by-nc/3.0/].

Class	Solvent	Conclusion (Pfizer)	Conclusion (GSK)	Conclusion (Sanofi)
Esters	Methyl acetate		Some issues	Substitution advisable
	Ethyl acetate	Preferred	Some issues	Recommended
	n-Propyl acetate		Few issues	Recommended
	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*-propyl ether	Undesirable	Major issues	Substitution advisable
	1,2-DME	Undesirable	Major issues	Substitution requested
	1,4-Dioxane	Undesirable	Major issues	Substitution requested
Ketones	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	
Miscellan-eous	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-Propanol	Preferred	Some issues	Recommended
	1-Butanol	Preferred	Few issues	Recommended
	2-Butanol		Few issues	Recommended
	t-Butanol	Preferred	Some issues	Substitution advisable
	Ethylene glycol	Usable		Substitution advisable
	2-Methoxyethanol		Major issues	Substitution requested
Hydro-carbons	*n*-Pentane	Undesirable		Banned
	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
	Xylene(s)	Usable	Some issues	Substitution advisable
Dipolar aprotic	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

Figure 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].

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.

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" Web site 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 ^{1}H 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 the 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, supercritical 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 toward some relevant reviews on the topics. For ionic liquids, see refs 107−114 ; for deep eutectic solvents, see refs 115−120; for supercritical CO_2, see refs 121−125; and for enzymatic synthesis in organic chemistry, see refs 126−130.

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 nonpolar 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 waste,[24] 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 26 drug-like molecules (9 neutral, 8 basic, and 9 acidic) to determine R_f values in both DCM/MeOH and greener solvent systems to

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

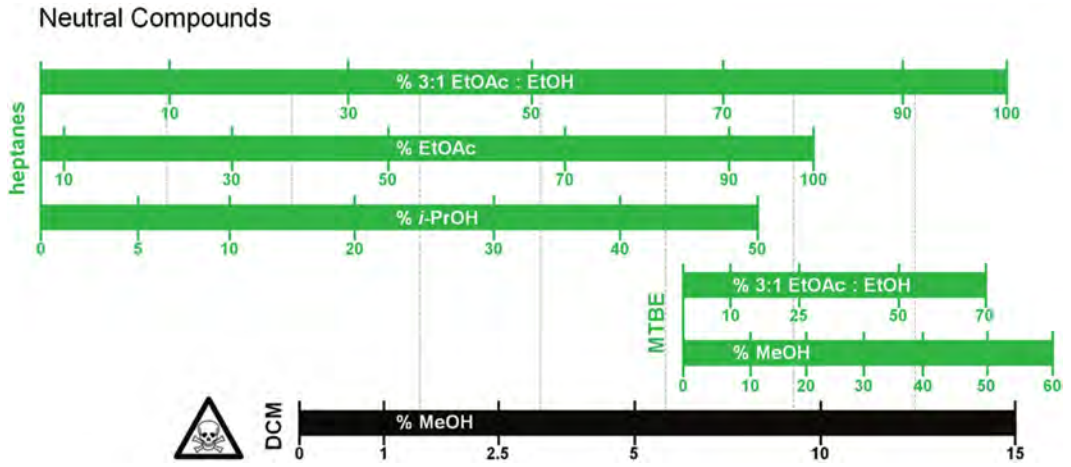


Figure 8. Relative eluting strengths of green chromatography solvent mixtures (neutral compounds).[46] Adapted from ref 46. Copyright 2012 The Royal Society of Chemistry.

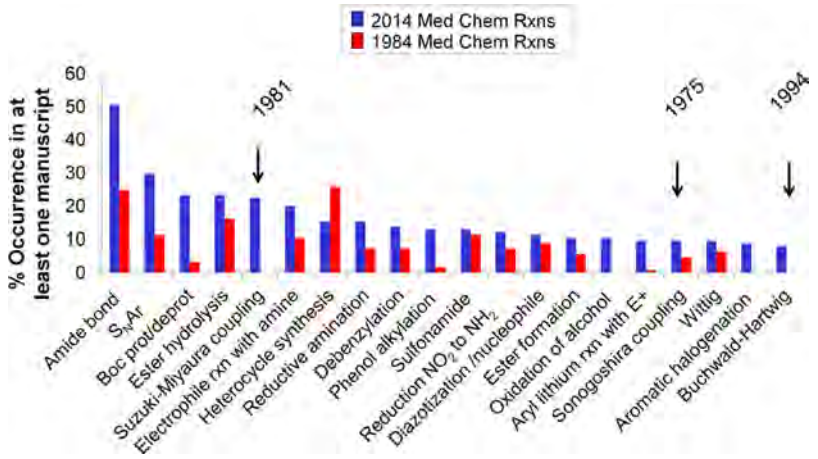


Figure 9. Prominence and variety of organic chemistry reactions used in medicinal chemistry.[142] The years highlighted represent the year of publication/disclosure of the relevant named reactions. Reproduced with permission from ref 142. Copyright 2016 American Chemical Society.

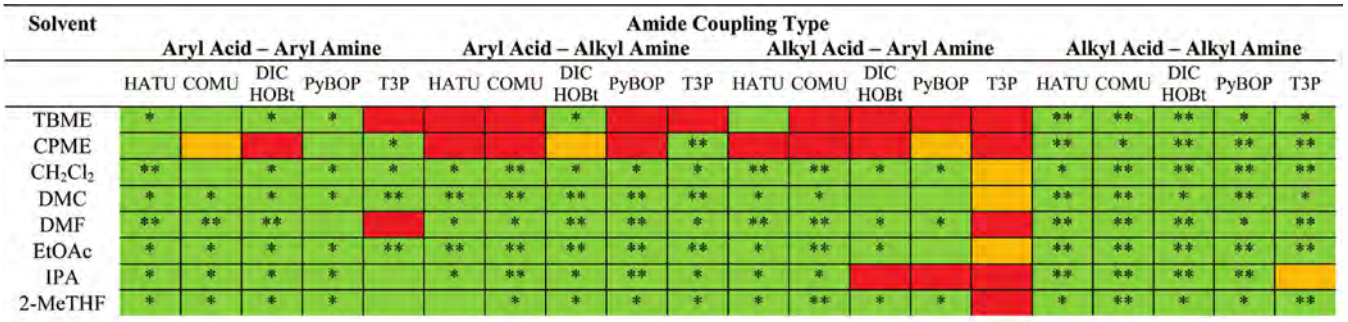
build an appropriate model of "relative eluting strength" for potential solvent replacements. Systems requiring pH adjustment had an appropriate amount of ammonia or acetic acid added. The results are depicted in a series of visual guides which make an excellent benchtop reference for chemists, e.g., Figure 8 (for acidic and basic compounds, see the original publication[46]). 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 premixed 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 10 years as part of both its teaching and learning (T&L) activities[134−136] and also as part of its R&D portfolio.[137−141] 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 and 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 toward 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 a collaborative industry-academia 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.

4.2. Commonly Employed Transformations in Medicinal Chemistry

Depicted in Figure 9 are the most commonly encountered organic transformations employed by medicinal chemists according to Brown et al.[142] Figure 9 is also in good agreement

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622



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

Figure 10. Solvent–reagent selection guide for the formation of amide bonds.[146] Reproduced with permission from ref 146. Copyright 2013 The Royal Society of Chemistry.

with the most commonly employed functional groups in bioactive molecules, as determined by Ertl et al.[143] With respect to Figure 9, the following section will discuss the use of chlorinated solvents in these reaction classes and highlight efforts toward 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.

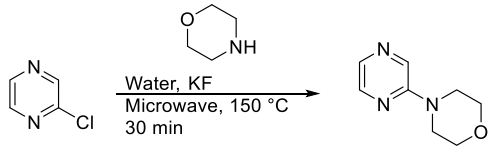
4.2.1. Amide Formation. Amide bond formation is one of the most commonly conducted transformations in synthetic medicinal chemistry.[142] Amide bonds are usually formed from amines and either acid chlorides or carboxylic acids with the utilization of a coupling reagent (though efforts toward catalytic[144] and enzymatic[145] 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 (Figure 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 a benefit in terms of sustainability and safety, as amide bond formation remains one of the most widely used transformations to date.

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 toluene,[149] 2-MeTHF,[150] and *iso*-propyl acetate.[151] Solvent-free reaction conditions have also been described.[152]

Solid supported peptide synthesis routinely employs DCM or DMF both as reaction solvent and during postreaction 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 racemization 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. 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 occur,[156] 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

Scheme 1. Example of an S_NAr Reaction Conducted Metal Free in Water/KF[155]



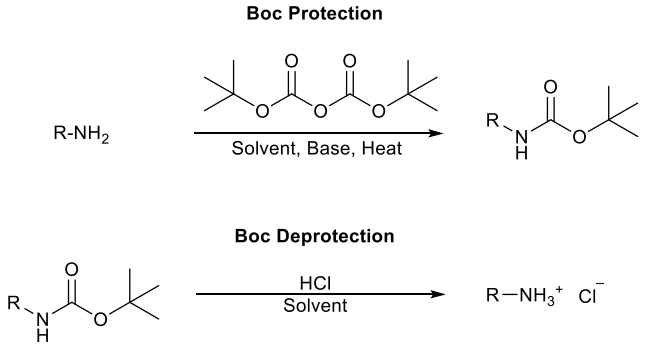
favored over transition-metal-catalyzed cross-coupling methods for the formation of C–O/N/S bonds in process chemistry whenever possible.[156] Solvent effects on the S_NAr reaction have been well documented and include regiosomeric and selectivity effects.[156–158] Solvent choices for rapid reactivity rely on the ability of the solvent to enhance the nucleophile's nucleophilicity while also being able to accept hydrogen bonds.[157] Selectivity when employing an aromatic system with multiple

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

potential reactive sites may benefit from nonpolar 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 diaminopyrimidines 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 min.[159] Isley et al. have demonstrated that S_NAr reactions could be performed under micellar conditions using K_3PO_4 in 2 wt % TPGS-750-M 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 of 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 Boc_2O (Scheme 2).[163] The

Scheme 2. Typical BOC Protection and Deprotection Reaction Conditions



most commonly employed organic solvent for this transformation is DCM with nearly one-third of reactions reported in this solvent. The 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*-termini 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 publications.[165−167] 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.

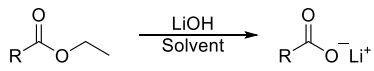
Multiple methods to carry out Boc deprotection are available, including but not limited to acid deprotection with HCl[168] or TFA,[169] thermal deprotection,[161] $CeCl_3·7H_2O$−NaI,[170] ball-milling,[171] and boiling water.[172] Similar to Boc protection, conventional acid-catalyzed deprotection relies heavily on DCM, which is reported as the reaction solvent in almost half of the examples examined.[163] The 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 incident.[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 to be used directly in multistep reaction sequences,[176] 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 the currently available literature, Boc protection and deprotection 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

Scheme 3. Typical Hydroxide-Mediated Hydrolysis of an Ethyl Ester[178]



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 esters,[179] and enzymatic hydrolysis.[180] 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]

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

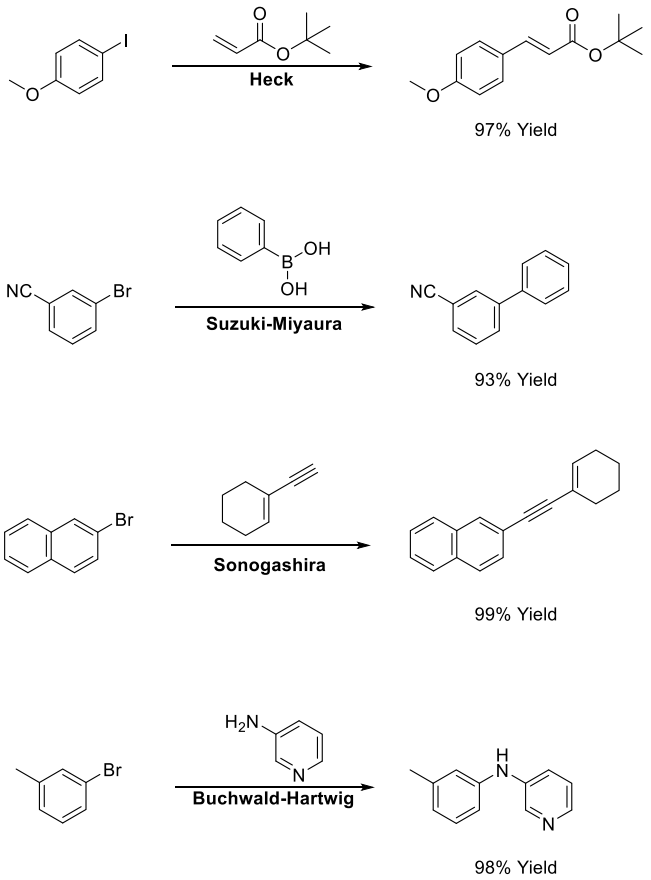
https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

EtOH and IPA are already exemplified in base hydrolysis applications.

Acid hydrolysis (HCl, TFA, etc.) appears to employ DCM most frequently as the 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 1970s, the myriad transformations made possible by these reactions (Scheme 4)

Scheme 4. A Selection of Pd-Catalyzed Cross-Coupling Reactions Conducted in TPGS-750-M and Water at Room Temperature[214]



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 a significant impact in pharmaceutical and medicinal chemistry include the Buchwald–Hartwig amination (1994).[184] Other C–N bond formations such as aromatic nitrile[185] and nitro[186] 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 chemistry by Robinson et al.[140] 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 yields.[192] 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 makes the task of choosing greener and more sustainable solvents somewhat challenging.

A brief examination of all cross-coupling reaction types using Reaxys involving monohalogenated benzene as substrate gave a set of 1630 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 Figure 7).[102] One potential replacement for polar aprotic solvents is the biobased 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 toward 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 biomass derived solvents,[196] aqueous conditions, or water–organic solvent mixtures.[197] Similarly, efforts toward 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 cosolvent, ethanol and aqueous-micellar conditions. Suzuki reactions in pure water,[200] water ligand free,[201] and aqueous with an organic cosolvent[202] have also been reported. Progress in metal-mediated/catalyzed reactions in water has also been extensively reviewed 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 among other examples.[204] Cyclic carbonates have also been successfully employed as solvents in asymmetric allylic alkylations reactions[205] 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 Ismael et al.[207] In their study, 16 renewable/biomass/CO_2 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

shown to be compatible as well, though they possess considerably higher levels of toxicity compared to DMC.[207]

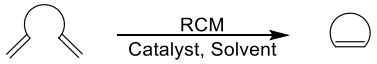
Solvent effects have also been examined in the Buchwald−Hartwig amination reaction, which commonly employs 1,4-dioxane, toluene, or other hydrocarbon solvents.[183] *iso*-Propanol has been reported as a greener and more sustainable alternative to dioxane, and reactions using *iso*-propanol have been conducted successfully on the kilogram scale.[208] *t*-BuOH has been successfully employed as a reaction solvent in a Buchwald−Hartwig amination[209] and amidation.[210] 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 among 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]

The aforementioned 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 Lipshutz 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 "Lipshutz" 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 do not always require a complicated reaction mixture: "*No organic solvents and no heating; just add water.*"[215]

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, CH_3CN, γ-valerolactone,[218] and cumene[37] (though neither THF nor CH_3CN 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 physicochemical 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 more favorably (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 November 22, 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. 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

Scheme 5. Olefin Metathesis to Give Ring Closed Product



(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 a 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, Figure 11.[221]

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]

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 biobased, biodegradable low-toxicity solvent) in conjunction with microwave heating conditions.[222] Lipshutz et al. have also demonstrated successful RCM in aqueous-surfactant conditions, recycling the aqueous surfactant phase eight 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 encompass a truly enormous category of potential reaction types including but not limited to nucleophilic substitution reactions with halide/pseudohalide leaving groups, acid chlorides, and 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, which is discussed in section 4.2.17.

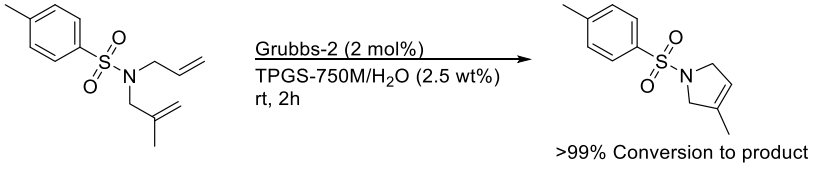
The challenge of replacing dipolar aprotic solvents, which is outside the scope of this review, is being addressed. Recent publications have shown that many less toxic, biocompatible solvents exist that can potentially be employed as replacement solvents for polar aprotics. These include *N*-butylpyrrolidinone

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

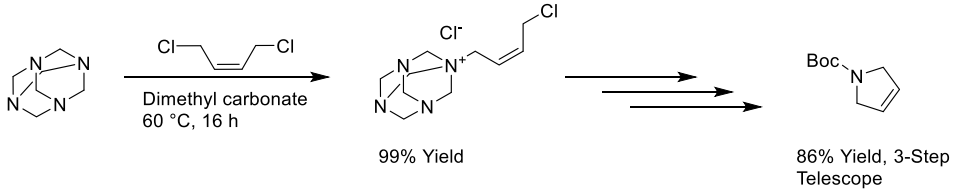
Entry	Catalyst	GC yield [%] MeOH	i-PrOH	AcOEt	DMC	CPME	2-MeTHF	DCM[c]
1	H-II	38	31	97	93	73	38	97
2	N-II	9	11*	94	85	79	49	96
3	E-II	8	9	66	79	20	37	95
4	G-II	15	16	97	98	80	35	92
5	Ind-II	3*	15*	96	98	69	38	93
6	H-II′	58	88	96	93	90	90	93
7	N-II′	45	85	96	99	97	97	88*
8	E-II′	57	86	98	99	97	97	91
9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

Figure 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.

Scheme 6. RCM Conducted in TPGS-750-M[214]



Scheme 7. Employing the Delépine Reaction in the Scaled-up Synthesis of *N*-(*tert*-Butyloxycarbonyl)-3-pyrroline[224,225]

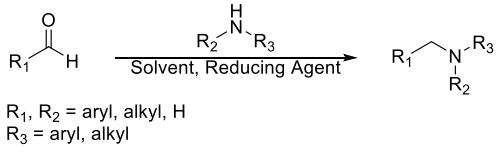


(NBP), aforementioned cyclic carbonates, biobased Cyrene,[223] and γ-valerolactone.[196] When it comes to solvent selection for amine−electrophile reactions, some general guidance may be provided. When selecting potential solvents, avoid chlorinated solvents, and if a polar aprotic solvent is required, then one of the aforementioned replacements such as a cyclic carbonate, NBP, Cyrene, or γ-valerolactone should be included in any solvent screening conducted. For example, Cyrene has been shown to be an effective polar aprotic alternative in urea formation[148] 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.

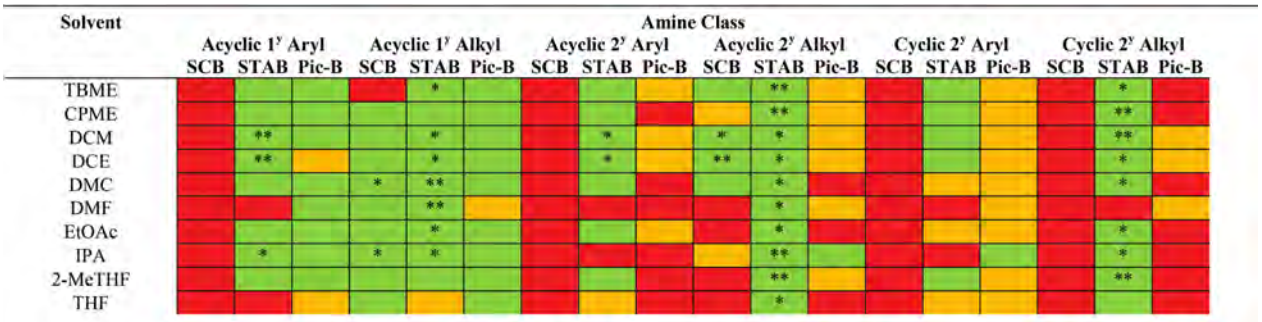
4.2.6.1. Delépine Reaction. The Delépine reaction is a traditional synthetic method for the formation of primary amines via the reaction of hexamethylenetetramine (HMTA) with an alkyl halide (Scheme 7). It is contemporaneous to the Gabriel synthesis of amine formation. One obvious drawback to the use 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 the 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. Reductive amination of carbonyl containing compounds is a commonly used, robust transformation in organic/medicinal chemistry for the derivatization 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-dichlorethane and DCM among the most frequently encountered.[226] Research in this area has subsequently led to the generation of a solvent selection guide for

Scheme 8. Generic Reductive Amination Chemistry Using Aryl/Alkyl Aldehydes/Amines

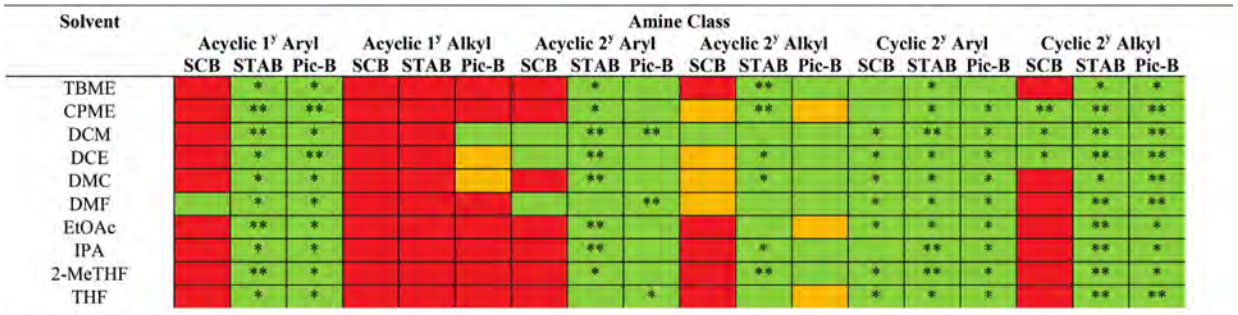


https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622



[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 = $NaBH_3CN$, STAB = $NaBH(OAc)_3$, Pic-B = picoline–borane complex.

Figure 12. Evaluation of alternative solvents and reagents for reductive amination of aryl aldehydes.[226] Reproduced with permission from ref 226. Copyright 2013 The Royal Society of Chemistry.



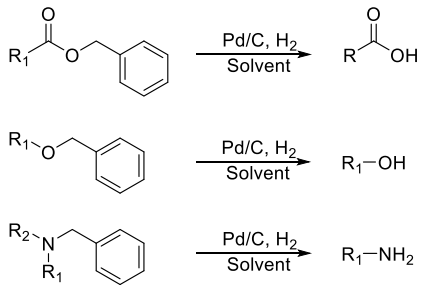
[a] Key: red = <50% conv., orange = 50–70% conv., green = >70% conv. *Indicates 100% conv. within 4 h. **Indicates 100% conv. within 1 h. SCB = $NaBH_3CN$, STAB = $NaBH(OAc)_3$, Pic-B = picoline–borane complex.

Figure 13. Evaluation of alternative solvents and reagents for reductive amination of alkyl aldehydes.[226] Reproduced with permission from ref 226. Copyright 2013 The Royal Society of Chemistry.

conducting reductive aminations using borane-based reductants (Figure 12 and Figure 13). 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]

4.2.8. Debenzylation. 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]

Scheme 9. Generic *O*- and *N*-Debenzylation Reactions

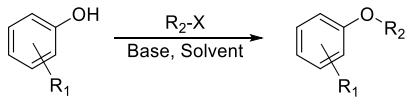


4.2.9. Heteroatom Alkylation/Arylation. Heteroatom alkylation/arylation is one of the most prominent reaction types in medicinal chemistry.[162] *O*-Functionalization features less frequently than other *N*-alkylation (section 4.2.6), though it still remains an important transformation in the synthesis of ethers, the purpose of which can be functionalization or protection, i.e., benzylic ethers (section 4.2.8). *S*-Alkylation/arylation is less frequently encountered than both *O*- and *N*-alkylation/arylation.[162] Some direct *N*-arylation methods are already discussed in section 4.2.5; i.e., Buchwald–Hartwig amination and *N*-alkylation via reductive amination are 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 the 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

Scheme 10. Generic Phenol Alkylation Reaction



needed is a 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 (toluene,[149] 2-MeTHF,[150] and *iso*-propyl acetate[151]).

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 solvents[231] (though THF is a much more common solvent in traditionalMitsunobu reactions than DCM due to the higher rate of reaction it facilitates).[232]

4.2.10. Sulfonamide Formation. Sulfonamide containing drugs were among the first antibacterial agents to be used systematically in modern medicine to great effect, e.g., Prontosil (Figure 14), the first sulfonamide drug which was discovered in

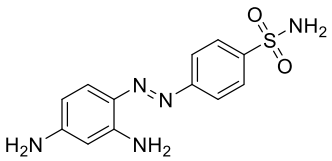
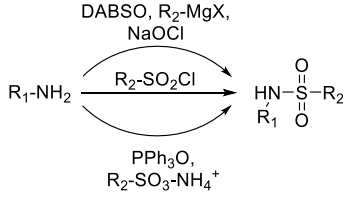


Figure 14. Prontosil, the first commercial sulfonamide drug.[233]

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]

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 (Scheme 11), 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

Scheme 11. Various Methods of Sulfonamide Synthesis[a]



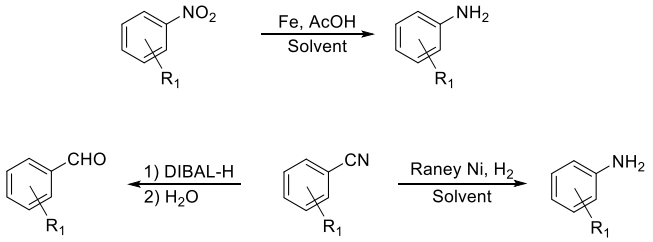
[a]Adapted from ref 235. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA. DABSO = 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct.

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 sulfinate 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 of relying on 2-MeTHF and isopropyl acetate.[151]

4.2.11. NO_x and Nitrile Reduction. 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 NH_2 (Scheme 12).[162] Reduction using H_2 is

Scheme 12. Generic NO_x and Nitrile Reductions



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 debenzylation 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-mediated[240] or trichlorosilane reductions.[241] 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 solvent selection guides.[239] EtOAc is also a possible choice.[242] If alternative

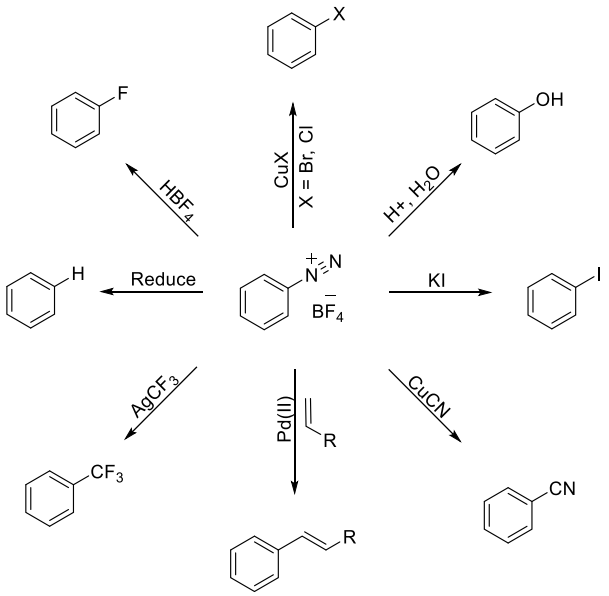
https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

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 $CuFe_2O_4$ nanoparticles,[243] and iron pincer complexes have been shown to be excellent catalysts in H_2 reduction of nitriles employing *iso*-PrOH as solvent.[244]

4.2.11.1. Other Reducing Reagents—General Use. For other reduction types utilizing $LiAlH_4$, 2-MeTHF[245] has been shown to be an excellent alternative to THF, with $LiAlH_4$ solutions now available as commercial preparations in 2-MeTHF.[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, is a convenient method for rapidly derivatizing aromatic rings with functional groups such as halides, CF_3, OH, and CN among 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[247,248]



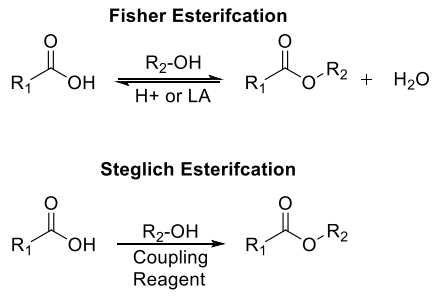
Reactions involving diazonium salts are unpopular in process chemistry environments with only 12 publications in *OPR&D* containing aryl diazonium compounds having been published since 2009.[249] The reasons for this dearth of diazonium containing compounds on scale are well understood; in a 2019 publication 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 often far more stable than their respective BF_4 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 BF_4 salts themselves can be conducted in EtOH,[251] 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, CH_3CN, and DMF.[253] Sandmeyer reactions are traditionally conducted in their respective aqueous halide acid solutions as per the 1926 preparation described by Fry and Grote.[254] 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 $NaNO_2$ in water or MeOH (for $NaNO_2$ reaction) at room temperature to give the respective aryl halide or nitro compound. Reaction times were rapid (<4 h) 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–Matsuda[256,257] and Suzuki–Miyaura[258,259] 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. 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-Me_3,[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). Fischer esterification generally employs a carboxylic acid

Scheme 14. Fischer and Steglich Esterification



and an alcohol to form an ester in the presence of acid[262] or a Lewis acid.[263] Steglich esterification differs in that the reaction is not carried out under acidic conditions; instead, coupling agents 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

Figure 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 of water with 2 wt % TPGS-750-M surfactant.[268] Reproduced with permission from ref 268. Copyright 2019 The Royal Society of Chemistry.

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 methods, and transition-metal-catalyzed methods, 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 CH_3CN, and they mirror 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 (H_2SO_4 and HCl being the most popular).[267] It is suggested, if Steglich esterification conditions are required, that inspiration be taken from the solvent−reagent selection guide described for amide bond formation (Figure 10) to assist in more judicial 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 determined.

4.2.13.1. Thioester Formation. Thioester formation is a much less commonly employed transformation than traditional ester bond formation, yet it 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 Jordan 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 (Figure 10) and reductive amination (Figure 12 and Figure 13) solvent selection guides, was produced (Figure 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 T_3P, a more sustainable and safer amide coupling reagent than DIC/DCC,[269] was a suitable reagent to promote this transformation.[268]

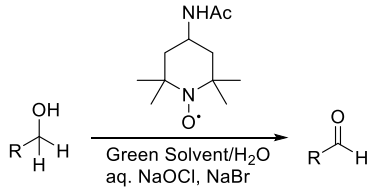
4.2.14. Oxidation. *4.2.14.1. Alcohols.* Selective oxidation of alcohols to carbonyl compounds is a transformation of significant importance,[270,271] yet it is a transformation that is less often employed in large-scale drug manufacturing (which predominantly carries out sulfide oxidation rather than 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 (Scheme 15). 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 cocatalyst (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 alone;[273] this work

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Scheme 15. *N*-Oxy-Catalyzed Bleach Oxidation of Alcohols in Greener Solvents[a]

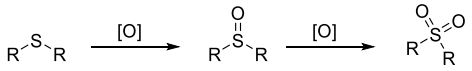


[a]Reproduced with permission from ref 270. Copyright 2011 Royal Society of Chemistry.

is however indicative of the radical and ground-breaking direction in which solvent selection can potentially be taken.[274]

4.2.14.2. Sulfides. 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-

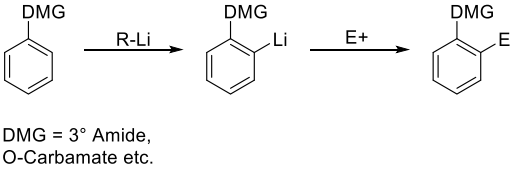
Scheme 16. Oxidation of Sulfides to Sulfoxide and Sulfones[275]



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. Aryl lithium species are incredibly useful intermediates similar in reactivity to other organometallic reagents such as Grignard, Gillman, 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;

Scheme 17. Reactions of Aryl Lithium Species with a Broad Variety of Electrophiles Can Be Achieved via Directed Ortho Metalation (DoM)[a]

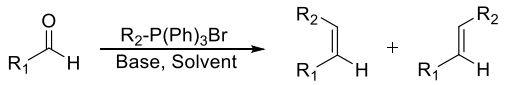


[a]Adapted from ref 276. Copyright 1990 American Chemical Society.

the pyrophoric nature of butyl lithium reagents 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 cylopentyl 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. 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 (PPh_3, alkyl halides, and base).[284] Reaction conditions are thoroughly established in the literature, and stereochemical control of *E*/*Z* alkenes (Scheme 18) is well documented through multiple derivatives

Scheme 18. Generic Wittig Olefination of an Aldehyde to Give a Mixture of *E*- and *Z*-Isomers



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 phosphorus 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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

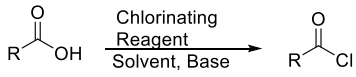
proceeded fastest in MeOH and slowest in THF and CH_3CN. Most significantly, the Wittig reaction proceeded fastest in water over all organic solvents with the exception of MeOH, even though the reactions were conducted as suspensions. The protocol published by El-Batta et al. demonstrated that excellent yields (up to 99%) and stereochemical control (up to 98% *E*-selectivity) for aqueous Wittig reactions can be achieved at room temperature (40 min to 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.[291−293]

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, water is included as part of any potential green solvent screen. Ethanol,[294] MeOH,[290] and EtOAc[295] should also be considered for inclusion. Other developments in the field of olefination may also be considered including recently developed decarbonylative olefination which avoids phosphorus-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 and 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 and 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. Acid chloride synthesis from the respective carboxylic acid (Scheme 19) is a long

Scheme 19. Acid Chloride Formation



employed step in amide bond synthesis[148] (see section 4.2.1) and ester synthesis[297] (section 4.2.13). Chlorinating reagents that are among the most popular include highly reactive $SOCl_2$, $(COCl)_2$, 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 have shown that the biobased 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 a kg scale has also been effectively demonstrated in 2-MeTHF (catalytic amounts of DMF).[299]

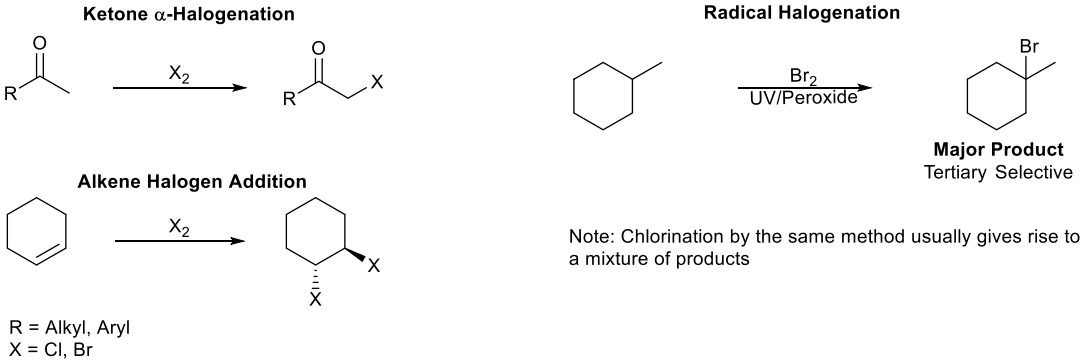
4.2.17.2. Aliphatic Halogenation. Aliphatic halogenation, as the namesake suggests, involves the replacement of a hydrocarbon hydrogen atom with a halide. The predominant reaction types used to facilitate this transformation are free radical halogenation or halogenation addition reactions to alkenes, alkynes, or carbonyl compounds with sufficiently acidic protons at the α-position (Scheme 20). 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 toxicitiy.[300] However, examples do exist such as the antibiotic Clindamycin, the steroid Mometasone furoate, the 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]

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 under either acidic or basic conditions. Low-pH conditions aid in promoting monohalogenation, while basic pH generally promotes exhaustive halogenation, an example of which is the haloform reaction.[302] Selective monobromination 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 among 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 Br_2-CHCl_3 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 $CHCl_3$ to facilitate a Br_2 bromination step in a reported enantioselective synthesis of Epibatidine.[305] EtOAc has also been successfully employed as reaction solvent in a Br_2 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-MeTHF,[307] EtOH,[308] and EtOAc.[309] *N*-Halosuccinimide-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 $NaBr/NaBrO_3$ 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]

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

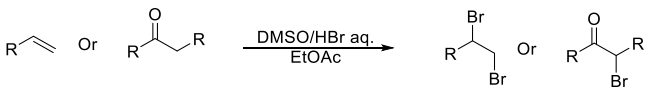
Scheme 20. Various Methods of Aliphatic Halogenation



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 Br_2 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 Br_2 are predominantly chlorinated solvents in the following order (most occurrences): chloroform, CCl_4, and DCM.[314] Examples employing non-chlorinated solvents do exist such as the dibromination of methyl acrylate in acetone (89% yield using 1 equiv of Br_2).[315]

One modern synthetic development that avoids the use of chlorinated solvents entirely is the DMSO-based oxidative bromination methodology (Scheme 21) such as that developed

Scheme 21. DMSO-Based Oxidative Bromination



by Song et al.[316] The methodology represents a further development of currently existing O_2 and H_2O_2 oxidative halogenation methods such as oxidative ketone bromination "on water".[317] The oxidative bromination system employs HBr as a bromine source and takes place using EtOAc as a solvent, giving moderate to high yields of vicinal dibromides when alkenes and alkynes are used as substrates. Similarly, α-Br ketones can be furnished in excellent yields. The substrate scope, avoidance of molecular bromine, and use of non-chlorinated solvents make this a 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 H_2O_2 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 Br_2-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 CCl_4 to the position of go-to solvent.[325,326] CCl_4 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 carbonate[333] have also been demonstrated as 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 process.[335] Oxidative benzylic bromination solvent screening has also been examined by Mestres et al. who have shown that this transformation could potentially be carried out in isopropyl acetate (~66% yield) or methyl pivalate (80% yield) as opposed to CCl_4 (quantitative).[336] Flow chemistry advancements have also shown that this transformation can be conducted in CH_3CN/AcOH.[337] Thus, it is suggested that alternative solvents are screened in benzylic bromination reactions before the use of CCl_4 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 Br_2 with CCl_4 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 reaction[339] which is a method that can be employed to convert a carboxylic acid silver salt to an alkyl bromide with loss of CO_2 and proceeds *via* a radical process. The Hunsdiecker reaction is also traditionally conducted in CCl_4,

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

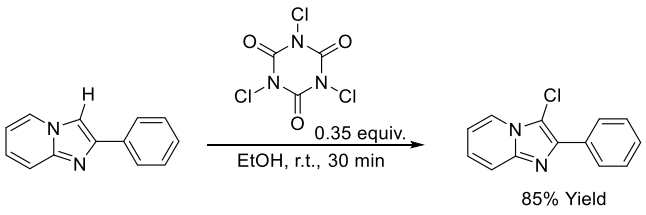
though high-yielding solvent-free examples have been reported.[339] Other elements of radical chemistry outside the scope of this review such as reduction of organohalides and C−C bond formation are reviewed by Togo in the book chapter "Free Radicals for Green Chemistry" with a good number of transformations 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 and 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 H_2O_2.[342] The reactions were conducted in MeOH EtOH, water, or were solvent-free, and demonstrated good yields. Some work was required to tune selectivity and 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 NH_4I) 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 min) across a wide range of heteroaryl imidazoles (Scheme 22).

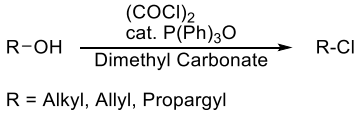
Scheme 22. Heteroarene Selective Halogenation Using Trichloroisocyanuric Acid in EtOH



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.

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 byproduct. 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 (Scheme 23).[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]

Scheme 23. Catalytic Appel Chlorination Reaction[a]



[a]Adapted from ref 345. Copyright 2020 American Chemical Society.

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 has 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 $Et_3N{\cdot}3HF$. One of the most popular nucleophilic fluorinating reagents is tetrabutylammonium fluoride

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(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 deoxyfluorination, 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 is also reported. For reactions employing TBAF, THF was the most prominent solvent followed by DCM and CH_3CN. The popularity of THF may be due to the commercial availability of TBAF−THF solutions. The reactivity and nature of deoxyfluorination chemistry obviously precludes the use of alcohols as solvents. Sparse use of greener solvents exists, though EtOAc appears to have been successfully employed as solvent for both DAST-[356] and Deoxofluor-[357] 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 CuF_2 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 (CuF_2 addition) using water. Formation of the activated *O*-alkylisourea is believed to act as a Lewis-basic site from which CuF_2 can coordinate, 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 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 toward 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 a 50 g scale is described, possessing a mass intensity (MI) of just 9, 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 a more sustainable and scalable synthetic option. The potential for sustainable F_2 chemistry is further discussed by Harsanyi 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-CF_3 and CF_2H 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 BF_4 or PF_6 salt which when heated undergoes fluorination with loss of N_2. The Wallach reaction is a fluorination technique 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 CH_3CN. Due to the driving reaction conditions that are usually required, lower-boiling chlorinated solvents are not usual choices.[371] S_NAr chemistry is further discussed in section 4.2.2, *vide supra*.

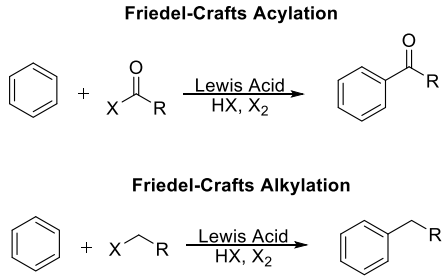
4.2.17.7.4. Benzylic Fluorination. Benzylic fluorination is a fluorination technique that can often be achieved via free radical methods due to the ability of benzylic carbon centers to stabilize radicals. Problems are often encountered using traditional fluorination procedures, e.g., competitive S_N1 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 has 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. 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 alkylation[372] and

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

acylation[373] via the Friedel–Crafts reactions, Scheme 24. The ability to rapidly and reliably conduct many important

Scheme 24. Friedel–Crafts Alkylation and Acylation Reactions



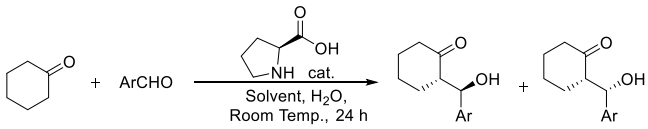
functional group transformations/installations from simple substrates via well-established reaction pathways has led to EAS being one of the oldest and most popular methods of C–C bond formation/functionalization in organic chemistry.

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 CCl_4 and chlorobenzene (in the dual role of reagent and solvent) also occurs.[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/bromo-benzene, 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 $TiCl_4$,[376] zinc,[377] and ZnO[378] 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 heating[379] or by microwave-assisted methods.[377]

Another alternative is aqueous-based reactions. In 2018, Sadiq et al. published a review of Friedel–Crafts reactions in aqueous media,[380] which is itself a considerable challenge, as traditional Lewis acid catalysts such as $AlCl_3$ 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. Three-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 have been demonstrated on the 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 only moderate (61%).[382] Heterogeneous catalysis using zeolite ZSM-5 has allowed for Friedel–Crafts alkylation of benzene in 95% aqueous ethanol.[383] Hydrophobic polypeptide resin bound trifluoroacetic acid has demonstrated some promising results with good yields obtained for the reaction of 4-nitrocinnamaldehyde with *N*-methylindole 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, the authors of the aforementioned review, Sadiq et al., conclude that Friedel–Crafts reactions in water "*could possibly be carried out under variable conditions*".[380] However, 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 (Scheme 25). The original "Hajos–

Scheme 25. Proline-Catalyzed Aldol Reactions in Aqueous Carbonate Solvents[385]



Parrish–Eder–Sauer–Wiechert reaction", as the asymmetric transformation is also known, was developed throughout the 1970s 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 2000s.[384]

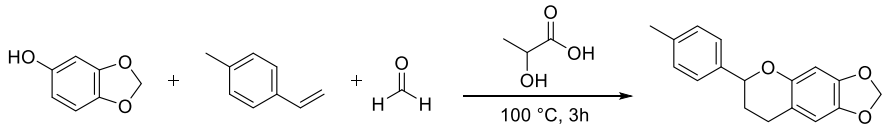
Propylene carbonate has been shown by North et al. to be a viable replacement solvent for polar aprotic and chlorinated solvents in proline-catalyzed asymmetric aldol reactions.[385] Reported yields were good along with excellent stereocontrol observed, comparable and in some cases exceeding results 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. While 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 ee'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. In 2012, Yang et al. demonstrated that lactic acid, a biobased green solvent, was an effective medium in which numerous multicomponent reactions could be conducted. Reaction types included three-component combinations of styrene–aldehyde–phenol/*N*,*N*-dialkylacetoacetamides (Scheme 26), aldehyde–aniline–alkynes, salicylaldehydes and diethyl acetylenedicarboxylates, and Friedländer annulations.[387] All of the reported examples outperformed traditionally employed solvent acetic acid with enhanced reaction rates also observed. Lactic acid was also easily recycled in a number of cases where products were less polar making this an excellent case study in the use of biobased 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 8.

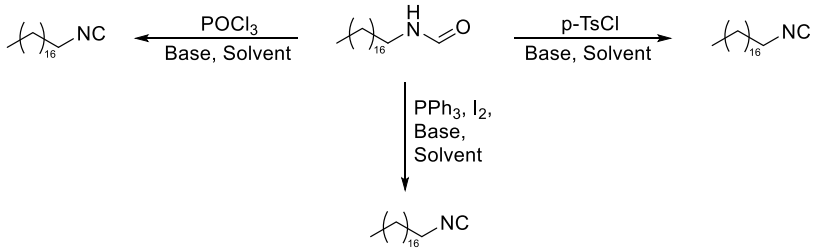
4.2.19.3. Isocyanide Synthesis. A comprehensive analysis of the synthesis of aliphatic isocyanides was conducted by Waibel et al. in 2020 and includes reaction methodology such as

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

Scheme 26. Three-Component Reaction of Styrene, Phenol, and Aldehyde Using Lactic Acid as Solvent[387]



Scheme 27. Sustainable Isocyanide Synthesis Examined by Waibel et al.[388]



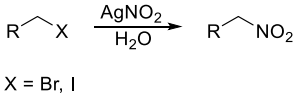
formamide dehydration using *p*-toluenesulfonyl chloride (*p*-TsCl), Ugi reaction conditions utilizing $POCl_3$, and Wang conditions using PPh_3 and I_2 (dehydrating conditions similar to Appel conditions), Scheme 27.[388] DCM was employed as a benchmark solvent for these reaction types and was shown 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 10 formamides to isocyanides was performed using these conditions; products were obtained in high yields (Table 11) and excellent purities, though the reaction times were longer than those in DCM (overnight vs 2 h).

Table 11. A Selection of Greener and More Sustainable Non-Chlorinated Solvents Utilized in Isocyanide Formation Methodologies by Waibel et al.[388]

method	solvent	yield %
Ugi ($POCl_3$)	2-MeTHF, EtOAc, dimethyl carbonate	94, 90, 90
Wang (PPh_3 + I_2)	2-MeTHF	93
p-TsCl	dimethyl carbonate	89

4.2.19.4. Conversion of Primary Alkyl Halides to Nitroalkanes. Nitroalkanes are a group of significant importance to the fine chemicals and pharmaceutical industry, e.g., as nitroaldol/Henry reaction components for the formation of *β*-nitro alcohols[389] and as amine precursors accessible via nitro reduction, and have found historical use in the synthesis and preparation of dies 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 a NO_2 source which is reacted with an alkyl halide of choice, often conducted in diethyl ether[392] when using $AgNO_2$, or DMF[393] when employing $NaNO_2$. Both solvents are solvents of concern.[4] In 2004, Ballini et al. reported the first examples of conducting this transformation, using $AgNO_2$, in water (Scheme 28).[390] Treating the alkyl halide (Br and I) of choice with $AgNO_2$ in water furnished a variety of nitro alkanes in moderate to good yields. Reaction times were generally short (30 min to 5 h, though one benzylic bromide substrate took 24 h to reach 53% yield), and temperatures ranged from room temperature to

Scheme 28. Nitroalkane Synthesis from Alkyl Halides in Water



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 straightforward, 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 has published an exemplary account of how they have successfully developed a computer aided multiparameter 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 phyisicochemical parameters.[84] Similarly, AsztraZeneca has 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 physicochemical 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 recrystallization 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 (×10 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 toward *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

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582–1622

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]

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 computational modeling. This body of work eventually led to the identification of "Cygnet 0.0", Figure 16, a biobased solvent

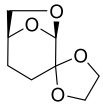


Figure 16. Cygnet 0.0, part of a larger family of "Cygnets" derived from levoglucosenone.[398]

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 proprties.[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 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 have illustrated, 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/replacement guides can all be used in conjunction with each other 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 is restricted, so it is with this mind-set that the authors of this review propose that chlorinated solvents are only used as solvents in organic and 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 have 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 toward sustainable solvent choices in our respective fields. 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 toward more environmentally sustainable solvent practices over the past 10 years. It is time now for preclinical medicinal chemistry and research organic chemists to adapt their practices to a research landscape that is increasingly being scrutinized for its sustainability. Precedent exists for changing habits—benzene and CCl_4 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 organic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrev.0c00709.

A summarized, printable table of potential solvent replacements for reactions of importance to medicinal and organic chemistry, as discussed in section 4.0 (PDF)

AUTHOR INFORMATION

Corresponding Authors

Andrew Jordan − *GlaxoSmithKline Carbon Neutral Laboratory for Sustainable Chemistry, Jubilee Campus, University of Nottingham, Nottingham NG7 2GA, U.K.*; orcid.org/0000-0002-2964-5043; Email: andrew.jordan@nottingham.ac.uk

Helen F. Sneddon − *GSK, Medicines Research Centre, Stevenage, Hertfordshire SG1 2NY, U.K.*; Email: helen.f.sneddon@gsk.com

Author

Patrick Stoy − *Drug Design and Selection, Platform and Technology Sciences, GlaxoSmithKline, Collegeville, Pennsylvania 19426, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrev.0c00709

Notes

The authors declare no competing financial interest.

Biographies

Andrew Jordan studied Chemical and Pharmaceutical Science at Dublin City University (2008−2012) before completing his PhD in 2016 at the same institute in Green and Organic Chemistry under the supervision of Prof. Nicholas Gathergood and Dr Andrew Kellett. Following on from life as a University researcher, Andrew joined GSK, Cork, as a technical development chemist before moving to the UK to work for Charnwood Molecular as a process and development chemist. He currently works as a GSK postdoctoral research fellow at the University of Nottingham conducting green and medicinal chemistry research at the interface between academia and industry, a unique position that gives the best of both worlds.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Patrick Stoy, a third-generation organic chemist, received his BS in Chemistry from the University of Chicago and PhD in Organic Chemistry from the University of Michigan in the area of dipolar cycloaddition and alkaloid total synthesis. Beginning his career at Bristol Myers Squibb in cardiovascular medicinal chemistry, he later joined GlaxoSmithKline and worked on numerous drug discovery targets and therapeutic areas. As Director of Medical Chemistry, Dr Stoy led an integrated Lead Generation group with a focus on applying new approaches such as AI and Lean Operations. After 15 years in large pharma, in 2019, Patrick founded the Leaping Cat Pharma Solutions LLC consulting group, and in 2020, he joined Medical Affairs at Janssen Oncology.

Helen F. Sneddon studied Natural Sciences at Christ's College, Cambridge, and obtained her PhD from the University of Cambridge under the supervision of Professor Steven V. Ley. Following postdoctoral studies at the University of California, Irvine, with Professor Larry Overman, she joined GSK in Stevenage, UK. While at GSK, she has developed a particular interest in Green Chemistry as applied to the Pharmaceutical Industry, including solvent and reagent selection, metrics, and the development of more efficient transformations. She is currently on the editorial board of the journal *Green Chemistry* and on the editorial advisory board of the journal *ACS Sustainable Chemistry & Engineering*. She is an author of over 50 peer-reviewed publications, a Fellow of the Royal Society of Chemistry, and a visiting professor of Sustainable Chemistry at the University of Nottingham.

ACKNOWLEDGMENTS

The authors would like to thank the EPSRC for funding via Prosperity Partnership EP/S035990/1 and GlaxoSmithKline for postdoctoral funding. We would also like to kindly thank Nicholas Bennett for helpful discussions in preparation of this manuscript and Emmet Jordan for creating the Table of Contents graphic.

LIST OF ABBREVIATIONS

ACS	American Chemical Society
API	active pharmaceutical ingredient
BF_4	tetrafluoroborate
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
t-BuOH	*tert*-butyl alcohol
CCl_4	carbon tetrachloride
CH_3CN	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	*N*,*N*′-diisopropylcarbodiimide
DMA/DMAc	dimethylacetamide
DMC	dimethyl carbonate
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DOM	directed ortho metalation
EHS	Environmental, Health & Safety
EPA	Environmental Protection Agency (USA)
Et_3N	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 Labeling 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	*iso*-propanol
MeOH	methanol
MSDS	material safety data sheets
NBP	*N*-butylpyrrolidinone
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMP	*N*-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_3P	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 Organization

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

REFERENCES

(1) Ruder, A. M. Potential Health Effects of Occupational Chlorinated Solvent Exposure. *Ann. N. Y. Acad. Sci.* **2006**, *1076*, 207−227.

(2) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Key green chemistry research areas—a perspective from pharmaceutical manufacturers. *Green Chem.* **2007**, *9*, 411−420.

(3) Bryan, M. C.; Dunn, P. J.; Entwistle, D.; Gallou, F.; Koenig, S. G.; Hayler, J. D.; Hickey, M. R.; Hughes, S.; Kopach, M. E.; Moine, G.; Richardson, P.; Roschangar, F.; Steven, A.; Weiberth, F. J. Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chem.* **2018**, *20*, 5082−5103.

(4) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. Updating and further expanding GSK's solvent sustainability guide. *Green Chem.* **2016**, *18*, 3879−3890.

(5) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546−4551.

(6) SciFinder search of *J. Med. Chem.* issues 1 and 2 in 2009 and issues 1 and 2 in 2019. Result sets were analyzed using the SciFinder "Solvent" filter (accessed April 13, 2020).

(7) SciFinder search of *Angewandte Chemie* volume 58, issue 1 in 2019. Result sets were analyzed using the SciFinder "Solvent" filter (accessed April 13, 2020).

(8) Dunn, P. J. The importance of Green Chemistry in Process Research and Development. *Chem. Soc. Rev.* **2012**, *41*, 1452−1461.

(9) Organic Process Research & Development Scope and Editorial Policy. http://pubsapp.acs.org/paragonplus/submission/oprdfk/oprdfk_scope.pdf (accessed March 30, 2020).

(10) Ashcroft, C. P.; Dunn, P. J.; Hayler, J. D.; Wells, A. S. Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997−2012. *Org. Process Res. Dev.* **2015**, *19*, 740−747.

(11) Braun, M.-G.; Diorazio, L.; Fraunhoffer, K.; Hayler, J.; Hickey, M.; Latham, J.; Lovelle, L. E.; McLaws, M.; Parsons, A. T.; Richardson, P.; Roiban, G.-D.; Roosen, P. C.; Steven, A.; Terrett, J. A.; White, T.; Yin, J. Green Chemistry Articles of Interest to the Pharmaceutical Industry. *Org. Process Res. Dev.* **2020**, *24*, 334−346.

(12) Challenger, S.; Dudin, L.; DaSilva, J.; Dunn, P.; Govaerts, T.; Hayler, J.; Hinkley, B.; Houpis, Y.; Hunter, T.; Jellet, L.; Leazer, J. L.; Lorenz, K.; Mathew, S.; Rammeloo, T.; Sudini, R.; Wan, Z.; Welch, C.; Wells, A.; Vance, J.; Xie, C.; Zhang, F. Green Chemistry Articles of Interest to the Pharmaceutical Industry. *Org. Process Res. Dev.* **2008**, *12*, 807−816.

(13) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. Perspective on Solvent Use in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2007**, *11*, 133−137.

(14) Dunn, P. J.; Wells, A. S.; Williams, M. T. Future Trends for Green Chemistry in the Pharmaceutical Industry. *Green Chemistry in the Pharmaceutical Industry*; Wiley: 2010; pp 333−355.

(15) Clarke, C. J.; Tu, W.-C.; Levers, O.; Bröhl, A.; Hallett, J. P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* **2018**, *118*, 747−800.

(16) Sharma, S.; Das, J.; Braje, W. M.; Dash, A. K.; Handa, S. A Glimpse into Green Chemistry Practices in the Pharmaceutical Industry. *ChemSusChem* **2020**, *13*, 2806.

(17) Jiménez-González, C.; Constable, D. J. C.; Ponder, C. S. Evaluating the "Greenness" of chemical processes and products in the pharmaceutical industry—a green metrics primer. *Chem. Soc. Rev.* **2012**, *41*, 1485−1498.

(18) Jimenez-Gonzalez, C.; Ponder, C. S.; Broxterman, Q. B.; Manley, J. B. Using the Right Green Yardstick: Why Process Mass Intensity Is Used in the Pharmaceutical Industry To Drive More Sustainable Processes. *Org. Process Res. Dev.* **2011**, *15*, 912−917.

(19) GCIPR Informex 2011 PMI Tool. https://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/Convergent-PMI-Presentation.pptx (accessed March 24, 2020).

(20) Jiménez-González, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds. *Int. J. Life Cycle Assess.* **2004**, *9*, 114−121.

(21) Schmid, R. Recent Advances in the Description of the Structure of Water, the Hydrophobic Effect, and the Like-Dissolves-Like Rule. *Highlights in Solute-Solvent Interactions*; Springer: 2002; pp 84−86.

(22) Jessop, P. G.; Jessop, D. A.; Fu, D.; Phan, L. Solvatochromic parameters for solvents of interest in green chemistry. *Green Chem.* **2012**, *14*, 1245−1259.

(23) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2003.

(24) Peterson, E. A.; Dillon, B.; Raheem, I.; Richardson, P.; Richter, D.; Schmidt, R.; Sneddon, H. F. Sustainable chromatography (an oxymoron?). *Green Chem.* **2014**, *16*, 4060−4075.

(25) Appendix C3 - Estimation of HSP from Multilevel Data—Bitumen. In *Cleaning with Solvents*; Durkee, J. B., Ed.; William Andrew Publishing: 2014; p 584.

(26) Díaz de los Ríos, M.; Hernández Ramos, E. Determination of the Hansen solubility parameters and the Hansen sphere radius with the aid of the solver add-in of Microsoft Excel. *SN Applied Sciences* **2020**, *2*, 676.

(27) HSP_Calculations.xlsx. https://www.hansen-solubility.com/contents/HSP_Calculations.xlsx (accessed June 18, 2020).

(28) Kamlet-Taft solvent parameters. http://www.stenutz.eu/chem/solv26.php (accessed June 18, 2020).

(29) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters, .pi.*, .alpha., and.beta., and some methods for simplifying the generalized solvatochromic equation. *J. Org. Chem.* **1983**, *48*, 2877−2887.

(30) Kamlet, M. J.; Taft, R. W. Linear solvation energy relationships. Part 3. Some reinterpretations of solvent effects based on correlations with solvent π^* and α values. *J. Chem. Soc., Perkin Trans. 2* **1979**, 349−356.

(31) Bradley, J.-C.; Acree, W.; Lang, A. Compounds with known Abraham descriptors. DOI: 10.6084/m9.figshare.1176994.

(32) Bradley, J.-C.; Abraham, M. H.; Acree, W. E., Jr.; Lang, A. S. Predicting Abraham model solvent coefficients. *Chem. Cent. J.* **2015**, *9*, 12.

(33) Bradley, J.-C.; Abraham, M. H.; Acree, W. E.; Lang, A. S. I. D.; Beck, S. N.; Bulger, D. A.; Clark, E. A.; Condron, L. N.; Costa, S. T.; Curtin, E. M.; Kurtu, S. B.; Mangir, M. I.; McBride, M. J. Determination of Abraham model solute descriptors for the monomeric and dimeric forms of trans-cinnamic acid using measured solubilities from the Open Notebook Science Challenge. *Chem. Cent. J.* **2015**, *9*, 11.

(34) Karunasekara, T.; Poole, C. F. Determination of descriptors for fragrance compounds by gas chromatography and liquid−liquid partition. *J. Chromatogr. A* **2012**, *1235*, 159−165.

(35) Abraham, M. H.; Smith, R. E.; Luchtefeld, R.; Boorem, A. J.; Luo, R.; Acree, W. E. Prediction of Solubility of Drugs and Other Compounds in Organic Solvents. *J. Pharm. Sci.* **2010**, *99*, 1500−1515.

(36) Bradley, J.-C.; Abraham, M. H.; Acree, W. E.; Lang, A. S. I. D. Predicting Abraham model solvent coefficients. *Chem. Cent. J.* **2015**, *9*, 12.

(37) Yu, C.; Sanjosé-Orduna, J.; Patureau, F. W.; Pérez-Temprano, M. H. Emerging unconventional organic solvents for C−H bond and related functionalization reactions. *Chem. Soc. Rev.* **2020**, *49*, 1643−1652.

(38) Common Solvents Used in Organic Chemistry: Table of Properties. https://www.organicdivision.org/wp-content/uploads/2016/12/organic_solvents.html (accessed March 26, 2020).

(39) Knovel Solvents Database. http://app.knovel.com/web/toc.v/cid:kpKSAPD005/viewerType:toc/root_slug:knovel-solvents---a-properties-database (accessed May 4, 2020).

(40) Chloroform: general information. https://www.gov.uk/government/publications/chloroform-properties-incident-management-and-toxicology/chloroform-general-information (accessed March 24, 2020).

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(41) Roethe, H. E. *Safe use and storage of gasoline and kerosene on the farm*. United States. Dept. of Agriculture: 1945; Vol. *1678*.
(42) Wolf, K.; Yazdani, A.; Yates, P. Chlorinated solvents: will the alternatives be safer? *J. Air Waste Manage. Assoc.* **1991**, *41*, 1055−61.
(43) Physical Properties of Solvents. https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/General_Information/labbasics_pg144.pdf (accessed May 4, 2020).
(44) Viscosity of Liquids. In *CRC Handbook of Chemistry and Physics, Internet Version 2005*, 91st ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2005; pp 6−186.
(45) HPLC Solvent Properties - Laserchrom. http://www.laserchrom.co.uk/LaserchromHPLC-HPLCSolventGuide.htm (accessed March 26, 2020).
(46) Taygerly, J. P.; Miller, L. M.; Yee, A.; Peterson, E. A. A convenient guide to help select replacement solvents for dichloromethane in chromatography. *Green Chem.* **2012**, *14*, 3020−3025.
(47) 1,1,1-Trichloroethane SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=40010-U&brand=SUPELCO&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D71-55-6%26interface%3DAll%26N%3D0%26mode%3Dpartialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(48) Prices quoted for cheapest 1 L bottles on the Aldrich Web site with a purity of at least 99%.
(49) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
(50) Wawersik, J. History of chloroform anesthesia. *Anaesthesiol. Reanim.* **1997**, *22*, 144−52.
(51) Some Chemicals Used as Solvents and in Polymer Manufacture. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*; International Agency for Research on Cancer: Lyon, France, 2017.
(52) U.S. carbon tetrachloride emissions exceed expectations. *C&EN Global Enterprise* **2016**, *94*, 11−12.
(53) EH40/2005 Workplace exposure limits. https://www.hse.gov.uk/pUbns/priced/eh40.pdf (accessed March 27, 2020).
(54) Solvent vapour degreasing plant. https://www.hse.gov.uk/pubns/eis47.pdf (accessed March 27, 2020).
(55) Chloroform - Toxicological Review. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/338535/Chloroform_Toxicological_Overview.pdf (accessed March 27, 2020).
(56) Elkin, E. R.; Harris, S. M.; Su, A. L.; Lash, L. H.; Loch-Caruso, R. Placenta as a target of trichloroethylene toxicity. *Environ. Sci. Process. Impacts* **2020**, *22*, 472−486.
(57) Weber, L. W.; Boll, M.; Stampfl, A. Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Crit. Rev. Toxicol.* **2003**, *33*, 105−36.
(58) Carbon Tetrachloride SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=289116&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3Dcarbon%2Btetrachloride%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(59) Wennborg, H.; Bodin, L.; Vainio, H.; Axelsson, G. Pregnancy outcome of personnel in Swedish biomedical research laboratories. *J. Occup. Environ. Med.* **2000**, *42*, 438−46.
(60) Ozone Depleting Substances. https://www.epa.gov/ozone-layer-protection/ozone-depleting-substances (accessed March 30, 2020).
(61) Directive 2010/75/eu of the european parliament and of the council of 24 November 2010 on industrial emissions (integrated pollution prevention and control). http://data.europa.eu/eli/dir/2010/75/2011-01-06 (accessed May 4, 2020).
(62) Lou, J. C.; Chang, Y. S. Thermal oxidation of chloroform. *Combust. Flame* **1997**, *109*, 188−197.
(63) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. *J. Med. Chem.* **2013**, *56*, 6007−6021.
(64) Chloroform SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=C2432&brand=SIGALD&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D67-66-3%26interface%3DCAS%2520No.%26N%3D0%2B%26mode%3Dpartialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct%26gclid%3DEAIaIQobChMIfLeqsm66AIVBLTtCh0_owcIEAAYASAAEgK6q_D_BwE (accessed July 1, 2020).
(65) DCM SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=270997&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3Ddichloromethane%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(66) 1,2-DCE SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=284505&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D1%252C2-Dichloroethane%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(67) Chlorobenzene SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=284513&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3DChlorobenzene%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(68) 1,2-Dichlorobenzene SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=240664&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D1%252C2-dichlorobenzene%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(69) 1,1,1-Trichloroethane SDS No. 2. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=T54704&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2Ft54704%3Flang%3Den (accessed July 1, 2020).
(70) Trichloroethylene SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=251402&brand=SIGALD&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3DTrichloroethylene%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct (accessed July 1, 2020).
(71) Tetrachloroethylene SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=371696&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F371696%3Flang%3Den (accessed July 1, 2020).

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(72) McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J. H. Towards a holistic approach to metrics for the 21st century pharmaceutical industry. *Green Chem.* **2015**, *17*, 3111−3121.
(73) WHO CICAD. https://www.who.int/ipcs/publications/cicad/en/ (accessed May 5, 2020).
(74) ILO/WHO ICSC. https://www.ilo.org/dyn/icsc/showcard.home (accessed May 5, 2020).
(75) Luttrell, W. E. Toxic tips: Chloroform. *Chem. Health Saf.* **2005**, *12*, 36−37.
(76) Luttrell, W. E. Toxic tips: 1,1,1-Trichloroethane. *Chem. Health Saf.* **2002**, *9*, 32−33.
(77) Stabilizer Systems. https://www.sigmaaldrich.com/chemistry/solvents/learning-center/stabilizer-systems.html (accessed March 31, 2020).
(78) Conrow, R. E.; Dean, W. D. Diazidomethane Explosion. *Org. Process Res. Dev.* **2008**, *12*, 1285−1286.
(79) am Ende, D. J.; Vogt, P. F. Safety Notables: Information from the Literature. *Org. Process Res. Dev.* **2004**, *8*, 1045−1048.
(80) Consequences of Poor Glove Choice. https://cenblog.org/the-safety-zone/2014/11/consequences-of-poor-glove-choice/ (accessed March 31, 2020).
(81) Sanprasert, K.; Tangtrongchitr, T.; Krairojananan, N. Dichloromethane Injection: Case Report. *Asia Pac. J. Med. Toxicol.* **2018**, *7*, 84−85.
(82) Vidal, S. Safety First: A Recent Case of a Dichloromethane Injection Injury. *ACS Cent. Sci.* **2020**, *6*, 83−86.
(83) Erythropel, H. C.; Zimmerman, J. B.; de Winter, T. M.; Petitjean, L.; Melnikov, F.; Lam, C. H.; Lounsbury, A. W.; Mellor, K. E.; Janković, N. Z.; Tu, Q.; Pincus, L. N.; Falinski, M. M.; Shi, W.; Coish, P.; Plata, D. L.; Anastas, P. T. The Green ChemisTREE: 20 years after taking root with the 12 principles. *Green Chem.* **2018**, *20*, 1929−1961.
(84) Piccione, P. M.; Baumeister, J.; Salvesen, T.; Grosjean, C.; Flores, Y.; Groelly, E.; Murudi, V.; Shyadligeri, A.; Lobanova, O.; Lothschütz, C. Solvent Selection Methods and Tool. *Org. Process Res. Dev.* **2019**, *23*, 998−1016.
(85) Zimmerman, J. B.; Anastas, P. T.; Erythropel, H. C.; Leitner, W. Designing for a green chemistry future. *Science* **2020**, *367*, 397−400.
(86) Allen, D. T.; Gathergood, N.; Licence, P.; Subramaniam, B. Expectations for Manuscripts Contributing to the Field of Solvents in ACS Sustainable Chemistry & Engineering. *ACS Sustainable Chem. Eng.* **2020**, *8*, 14627−14629.
(87) Tobiszewski, M.; Namieśnik, J.; Pena-Pereira, F. Environmental risk-based ranking of solvents using the combination of a multimedia model and multi-criteria decision analysis. *Green Chem.* **2017**, *19*, 1034−1042.
(88) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016**, *18*, 288−296.
(89) Diorazio, L. J.; Hose, D. R. J.; Adlington, N. K. Toward a More Holistic Framework for Solvent Selection. *Org. Process Res. Dev.* **2016**, *20*, 760−773.
(90) Tobiszewski, M.; Tsakovski, S.; Simeonov, V.; Namieśnik, J.; Pena-Pereira, F. A solvent selection guide based on chemometrics and multicriteria decision analysis. *Green Chem.* **2015**, *17*, 4773−4785.
(91) Prat, D.; Pardigon, O.; Flemming, H.-W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; Hosek, P. Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes. *Org. Process Res. Dev.* **2013**, *17*, 1517−1525.
(92) MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents. *Green Chem.* **2012**, *14*, 3016−3019.
(93) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK's solvent selection guide − embedding sustainability into solvent selection starting at medicinal chemistry. *Green Chem.* **2011**, *13*, 854−862.
(94) Capello, C.; Fischer, U.; Hungerbühler, K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents. *Green Chem.* **2007**, *9*, 927−934.
(95) Jiménez-González, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. Expanding GSK's Solvent Selection Guide—application of life cycle assessment to enhance solvent selections. *Clean Technol. Environ. Policy* **2004**, *7*, 42−50.
(96) Curzons, A. D.; Constable, D. C.; Cunningham, V. Solvent selection guide: A guide to the integration of environmental, health and safety criteria into the selection of solvents. *Clean Technol. Environ. Policy* **1999**, *1*, 82−90.
(97) Barwick, V. J. Strategies for solvent selection — a literature review. *TrAC, Trends Anal. Chem.* **1997**, *16*, 293−309.
(98) Solvent Selection Tool. https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry/solvent-tool.html (accessed March 31, 2020).
(99) ACS GCI Pharmaceutical Roundtable Solvent Selection Guide Version 2.0. http://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html (accessed March 31, 2020).
(100) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chem.* **2008**, *10*, 31−36.
(101) López-Porfiri, P.; Gorgojo, P.; Gonzalez-Miquel, M. Green Solvent Selection Guide for Biobased Organic Acid Recovery. *ACS Sustainable Chem. Eng.* **2020**, *8*, 8958.
(102) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chem. Processes* **2016**, *4*, 7.
(103) Eastman, H. E.; Jamieson, C.; Watson, A. J. B. Development of solvent selection guides. *Aldrichimica Acta* **2015**, *48*, 51−55.
(104) Sneddon, H. F.; Scott, J. L. Green Solvents. In *Green Techniques for Organic Synthesis and Medicinal Chemistry*; Zhang, W., Cue, B. W., Jr., Eds.; Wiley: 2018; pp 21−42.
(105) MedChem Tips and Tricks. https://www.acsgcipr.org/tools-for-innovation-in-chemistry/medchem-tips-and-tricks/ (accessed May 7, 2020).
(106) Gottlieb, H. E.; Graczyk-Millbrandt, G.; Inglis, G. G. A.; Nudelman, A.; Perez, D.; Qian, Y.; Shuster, L. E.; Sneddon, H. F.; Upton, R. J. Development of GSK's NMR guides − a tool to encourage the use of more sustainable solvents. *Green Chem.* **2016**, *18*, 3867−3878.
(107) Welton, T. Ionic liquids in catalysis. *Coord. Chem. Rev.* **2004**, *248*, 2459−2477.
(108) Galinski, M.; Lewandowski, A.; Stepniak, I. Ionic liquids as electrolytes. *Electrochim. Acta* **2006**, *51*, 5567−5580.
(109) Parvulescu, V. I.; Hardacre, C. Catalysis in ionic liquids. *Chem. Rev.* **2007**, *107*, 2615−2665.
(110) van Rantwijk, F.; Sheldon, R. A. Biocatalysis in ionic liquids. *Chem. Rev.* **2007**, *107*, 2757−2785.
(111) Greaves, T. L.; Drummond, C. J. Protic ionic liquids: Properties and applications. *Chem. Rev.* **2008**, *108*, 206−237.
(112) Plechkova, N. V.; Seddon, K. R. Applications of ionic liquids in the chemical industry. *Chem. Soc. Rev.* **2008**, *37*, 123−150.
(113) Olivier-Bourbigou, H.; Magna, L.; Morvan, D. Ionic liquids and catalysis: Recent progress from knowledge to applications. *Appl. Catal., A* **2010**, *373*, 1−56.
(114) Hallett, J. P.; Welton, T. Room-Temperature Ionic Liquids: Solvents for Synthesis and Catalysis. 2. *Chem. Rev.* **2011**, *111*, 3508−3576.
(115) Liu, P.; Hao, J. W.; Mo, L. P.; Zhang, Z. H. Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. *RSC Adv.* **2015**, *5*, 48675−48704.
(116) Paiva, A.; Craveiro, R.; Aroso, I.; Martins, M.; Reis, R. L.; Duarte, A. R. C. Natural Deep Eutectic Solvents - Solvents for the 21st Century. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063−1071.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(117) Carriazo, D.; Serrano, M. C.; Gutierrez, M. C.; Ferrer, M. L.; del Monte, F. Deep-eutectic solvents playing multiple roles in the synthesis of polymers and related materials. *Chem. Soc. Rev.* **2012**, *41*, 4996−5014.
(118) Zhang, Q. H.; Vigier, K. D.; Royer, S.; Jerome, F. Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.* **2012**, *41*, 7108−7146.
(119) Wagle, D. V.; Zhao, H.; Baker, G. A. Deep Eutectic Solvents: Sustainable Media for Nanoscale and Functional Materials. *Acc. Chem. Res.* **2014**, *47*, 2299−2308.
(120) Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. *Chem. Rev.* **2014**, *114*, 11060−11082.
(121) Cooper, A. I. Polymer synthesis and processing using supercritical carbon dioxide. *J. Mater. Chem.* **2000**, *10*, 207−234.
(122) Leitner, W. Supercritical carbon dioxide as a green reaction medium for catalysis. *Acc. Chem. Res.* **2002**, *35*, 746−756.
(123) Beckman, E. J. Supercritical and near-critical CO2 in green chemical synthesis and processing. *J. Supercrit. Fluids* **2004**, *28*, 121−191.
(124) Munshi, P.; Bhaduri, S. Supercritical CO2: a twenty-first century solvent for the chemical industry. *Curr. Sci.* **2009**, *97*, 63−72.
(125) Reverchon, E.; De Marco, I. Supercritical fluid extraction and fractionation of natural matter. *J. Supercrit. Fluids* **2006**, *38*, 146−166.
(126) Koeller, K. M.; Wong, C. H. Enzymes for chemical synthesis. *Nature* **2001**, *409*, 232−240.
(127) Kim, Y.; Park, J.; Kim, M. J. Dynamic Kinetic Resolution of Amines and Amino Acids by Enzyme-Metal Cocatalysis. *ChemCatChem* **2011**, *3*, 271−277.
(128) Hollmann, F.; Arends, I. Enzyme Initiated Radical Polymerizations. *Polymers* **2012**, *4*, 759−793.
(129) Xue, R.; Woodley, J. M. Process technology for multi-enzymatic reaction systems. *Bioresour. Technol.* **2012**, *115*, 183−195.
(130) Agarwal, V.; Miles, Z. D.; Winter, J. M.; Eustaquio, A. S.; El Gamal, A. A.; Moore, B. S. Enzymatic Halogenation and Dehalogenation Reactions: Pervasive and Mechanistically Diverse. *Chem. Rev.* **2017**, *117*, 5619−5674.
(131) Watson, W. J. W. How do the fine chemical, pharmaceutical, and related industries approach green chemistry and sustainability? *Green Chem.* **2012**, *14*, 251−259.
(132) Neher, R. *Thin Layer Chromatography*; Elsevier: Amsterdam, The Netherlands, 1964.
(133) New Alternative to Chlorinated Solvents - Fisher Chemical Ethyl Acetate Ethanol 3:1 Solution. https://beta-static.fishersci.ca/content/dam/fishersci/en_US/documents/programs/scientific/technical-documents/data-sheets/fisher-chemical-new-3-to-1-Ethyl-Acetate-Datasheet.pdf (accessed April 3, 2020).
(134) Barnes, L.; Blaber, H.; Brooks, D. T. K.; Byers, L.; Buckley, D.; Byron, Z. C.; Chilvers, R. G.; Cochrane, L.; Cooney, E.; Damian, H. A.; Francis, L.; He, D. F.; Grace, J. M. J.; Green, H. J.; Hogarth, E. J. P.; Jusu, L.; Killalea, C. E.; King, O.; Lambert, J.; Lee, Z. J.; Lima, N. S.; Long, C. L.; Mackinnon, M. L.; Mahdy, S.; Matthews-Wright, J.; Millward, M. J.; Meehan, M. F.; Merrett, C.; Morrison, L.; Parke, H. R. I.; Payne, C.; Payne, L.; Pike, C.; Seal, A.; Senior, A. J.; Smith, K. M.; Stanelyte, K.; Stillibrand, J.; Szpara, R.; Taday, F. F. H.; Threadgould, A. M.; Trainor, R. J.; Waters, J.; Williams, O.; Wong, C. K. W.; Wood, K.; Barton, N.; Gruszka, A.; Henley, Z.; Rowedder, J. E.; Cookson, R.; Jones, K. L.; Nadin, A.; Smith, I. E.; Macdonald, S. J. F.; Nortcliffe, A. Free-Wilson Analysis of Comprehensive Data on Phosphoinositide-3-kinase (PI3K) Inhibitors Reveals Importance of N-Methylation for PI3K delta Activity. *J. Med. Chem.* **2019**, *62*, 10402−10422.
(135) McInally, T.; Macdonald, S. J. F. Unusual Undergraduate Training in Medicinal Chemistry in Collaboration between Academia and Industry. *J. Med. Chem.* **2017**, *60*, 7958−7964.
(136) Macdonald, S. J. F.; Fray, M. J.; McInally, T. Passing on the medicinal chemistry baton: training undergraduates to be industry-ready through research projects between the University of Nottingham and GlaxoSmithKline. *Drug Discovery Today* **2016**, *21*, 880−887.
(137) Oglic, D.; Oatley, S. A.; Macdonald, S. J. F.; McInally, T.; Garnett, R.; Hirst, J. D.; Gartner, T. Active Search for Computer-aided Drug Design. *Mol. Inf.* **2018**, *37*, 1700130.
(138) Tipping, W. J.; Tshuma, N.; Adams, J.; Haywood, H. T.; Rowedder, J. E.; Fray, M. J.; McInally, T.; Macdonald, S. J. F.; Oldham, N. J. Relative Binding Affinities of Integrin Antagonists by Equilibrium Dialysis and Liquid Chromatography-Mass Spectrometry. *ACS Med. Chem. Lett.* **2015**, *6*, 221−224.
(139) Adams, J.; Anderson, E. C.; Blackham, E. E.; Chiu, Y. W. R.; Clarke, T.; Eccles, N.; Gill, L. A.; Haye, J. J.; Haywood, H. T.; Hoenig, C. R.; Kausas, M.; Le, J.; Russell, H. L.; Smedley, C.; Tipping, W. J.; Tongue, T.; Wood, C. C.; Yeung, J.; Rowedder, J. E.; Fray, M. J.; McInally, T.; Macdonald, S. J. F. Structure Activity Relationships of alpha(v) Integrin Antagonists for Pulmonary Fibrosis by Variation in Aryl Substituents. *ACS Med. Chem. Lett.* **2014**, *5*, 1207−1212.
(140) Robinson, H.; Oatley, S.; Rowedder, J.; Slade, P.; Macdonald, S.; Argent, S.; Hirst, J.; McInally, T.; Moody, C. J. Late stage functionalization via Chan-Lam amination: rapid access to potent and selective integrin inhibitors. *Chem. - Eur. J.* **2020**, *26*, 7678.
(141) Guest, E. E.; Oatley, S. A.; Macdonald, S. J. F.; Hirst, J. D. Molecular Simulation of $\alpha v\beta 6$ Integrin Inhibitors. *J. Chem. Inf. Model.* **2020**, *60*, 5487.
(142) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443−4458.
(143) Ertl, P.; Altmann, E.; McKenna, J. M. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J. Med. Chem.* **2020**, *63*, 8408−8418.
(144) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. Catalytic amide formation from non-activated carboxylic acids and amines. *Chem. Soc. Rev.* **2014**, *43*, 2714−2742.
(145) Goswami, A.; Van Lanen, S. G. Enzymatic strategies and biocatalysts for amide bond formation: tricks of the trade outside of the ribosome. *Mol. BioSyst.* **2015**, *11*, 338−353.
(146) MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and N, N-dimethylformamide. *Green Chem.* **2013**, *15*, 596−600.
(147) Wilson, K. L.; Murray, J.; Jamieson, C.; Watson, A. J. B. Cyrene as a bio-based solvent for HATU mediated amide coupling. *Org. Biomol. Chem.* **2018**, *16*, 2851−2854.
(148) Bousfield, T. W.; Pearce, K. P. R.; Nyamini, S. B.; Angelis-Dimakis, A.; Camp, J. E. Synthesis of amides from acid chlorides and amines in the bio-based solvent Cyrene. *Green Chem.* **2019**, *21*, 3675−3681.
(149) Jordan, A.; Haiß, A.; Spulak, M.; Karpichev, Y.; Kümmerer, K.; Gathergood, N. Synthesis of a series of amino acid derived ionic liquids and tertiary amines: green chemistry metrics including microbial toxicity and preliminary biodegradation data analysis. *Green Chem.* **2016**, *18*, 4374−4392.
(150) Brown Ripin, D. H.; Vetelino, M. 2-Methyltetrahydrofuran as an Alternative to Dichloromethane in 2-Phase Reactions. *Synlett* **2003**, *2003*, 2353−2353.
(151) White, T. D.; Berglund, K. D.; Groh, J. M.; Johnson, M. D.; Miller, R. D.; Yates, M. H. Development of a Continuous Schotten−Baumann Route to an Acyl Sulfonamide. *Org. Process Res. Dev.* **2012**, *16*, 939−957.
(152) Ghosh, S.; Das, J. Benzoylation of Amines *sans* Alkali: A Green Protocol in Neat Phase. *Org. Chem. Int.* **2010**, *2010*, 743186.
(153) Lawrenson, S. B.; Arav, R.; North, M. The greening of peptide synthesis. *Green Chem.* **2017**, *19*, 1685−1691.
(154) Ran, Y.; Byrne, F.; Ingram, I. D. V.; North, M. Resin Swelling in Mixed Solvents Analysed using Hansen Solubility Parameter Space. *Chem. - Eur. J.* **2019**, *25*, 4951−4964.
(155) Walsh, K.; Sneddon, H. F.; Moody, C. J. Amination of Heteroaryl Chlorides: Palladium Catalysis or SNAr in Green Solvents? *ChemSusChem* **2013**, *6*, 1455−1460.
(156) Sythana, S. K.; Naramreddy, S. R.; Kavitake, S.; Ch, V. K.; Bhagat, P. R. Nonpolar Solvent a Key for Highly Regioselective SNAr

Reaction in the Case of 2,4-Difluoronitrobenzene. *Org. Process Res. Dev.* **2014**, *18*, 912−918.
(157) Gazitúa, M.; Tapia, R. A.; Contreras, R.; Campodónico, P. R. Effect of the nature of the nucleophile and solvent on an SNAr reaction. *New J. Chem.* **2018**, *42*, 260−264.
(158) El Guesmi, N.; Berionni, G.; Asghar, B. H. Electronic and solvent effects on kinetics of S(N)Ar substitution reactions of substituted anilines with 2,6-bis(trifluoromethanesulfonyl)-4-nitroanisole in MeOH-Me(2)SO mixtures of varying composition: one reaction with two mechanistic pathways. *Monatsh. Chem.* **2013**, *144*, 1537−1545.
(159) Campestre, C.; Keglevich, G.; Kóti, J.; Scotti, L.; Gasbarri, C.; Angelini, G. Microwave-assisted simple synthesis of 2-anilinopyrimidines by the reaction of 2-chloro-4,6-dimethylpyrimidine with aniline derivatives. *RSC Adv.* **2020**, *10*, 12249−12254.
(160) Isley, N. A.; Linstadt, R. T. H.; Kelly, S. M.; Gallou, F.; Lipshutz, B. H. Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis. *Org. Lett.* **2015**, *17*, 4734−4737.
(161) Li, B.; Li, R.; Dorff, P.; McWilliams, J. C.; Guinn, R. M.; Guinness, S. M.; Han, L.; Wang, K.; Yu, S. Deprotection of N-Boc Groups under Continuous-Flow High-Temperature Conditions. *J. Org. Chem.* **2019**, *84*, 4846−4855.
(162) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347.
(163) Boc and De-Boc Reaxys Search as of April 17, 2020.
(164) Varala, R.; Nuvula, S.; Adapa, S. R. Molecular Iodine-Catalyzed Facile Procedure for N-Boc Protection of Amines. *J. Org. Chem.* **2006**, *71*, 8283−8286.
(165) Huang, H.; Martásek, P.; Roman, L. J.; Silverman, R. B. Synthesis and Evaluation of Peptidomimetics as Selective Inhibitors and Active Site Probes of Nitric Oxide Synthases. *J. Med. Chem.* **2000**, *43*, 2938−2945.
(166) Sestito, S.; Daniele, S.; Nesi, G.; Zappelli, E.; Di Maio, D.; Marinelli, L.; Digiacomo, M.; Lapucci, A.; Martini, C.; Novellino, E.; Rapposelli, S. Locking PDK1 in DFG-out conformation through 2-oxo-indole containing molecules: Another tools to fight glioblastoma. *Eur. J. Med. Chem.* **2016**, *118*, 47−63.
(167) Gajewski, M.; Seaver, B.; Esslinger, C. S. Design, synthesis, and biological activity of novel triazole amino acids used to probe binding interactions between ligand and neutral amino acid transport protein SN1. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4163−4166.
(168) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. A stereoselective synthesis of sphingosine, a protein kinase c inhibitor. *Tetrahedron Lett.* **1988**, *29*, 3037−3040.
(169) Kawabata, E.; Kikuchi, K.; Urano, Y.; Kojima, H.; Odani, A.; Nagano, T. Design and Synthesis of Zinc-Selective Chelators for Extracellular Applications. *J. Am. Chem. Soc.* **2005**, *127*, 818−819.
(170) Marcantoni, E.; Massaccesi, M.; Torregiani, E.; Bartoli, G.; Bosco, M.; Sambri, L. Selective Deprotection of N-Boc-Protected tert-Butyl Ester Amino Acids by the CeCl3·7H2O−NaI System in Acetonitrile. *J. Org. Chem.* **2001**, *66*, 4430−4432.
(171) Margetić, D.; Đud, M. Solvent-Free Mechanochemical Deprotection of N-Boc Group. *Int. J. Org. Chem.* **2017**, *07*, 140−144.
(172) Wang, J.; Liang, Y.-L.; Qu, J. Boiling water-catalyzed neutral and selective N-Boc deprotection. *Chem. Commun.* **2009**, 5144−5146.
(173) Stahl, G. L.; Walter, R.; Smith, C. W. General procedure for the synthesis of mono-N-acylated 1,6-diaminohexanes. *J. Org. Chem.* **1978**, *43*, 2285−2286.
(174) Sigma Aldrich HCl Solutions. https://www.sigmaaldrich.com/catalog/search?term=Hydrogen+chloride+solution&interface=All&N=0&mode=match%20partialmax&lang=en&region=GB&focus=product (accessed April 8, 2020).
(175) Hardouin, C.; Lemaitre, S. Safety Case Study. Intrinsic Instability of Concentrated Solutions of Alcoholic Hydrogen Chloride: Potential Hazards Associated with Methanol. *Org. Process Res. Dev.* **2020**, *24*, 867−871.
(176) Bogdan, A. R.; Charaschanya, M.; Dombrowski, A. W.; Wang, Y.; Djuric, S. W. High-Temperature Boc Deprotection in Flow and Its Application in Multistep Reaction Sequences. *Org. Lett.* **2016**, *18*, 1732−1735.
(177) Rawal, V. H.; Cava, M. P. Thermolytic removal of t-butyloxycarbonyl (Boc) protecting group on indoles and pyrroles. *Tetrahedron Lett.* **1985**, *26*, 6141−6142.
(178) Wuts, P. G. M. *Greene's protective groups in organic synthesis*, 5th ed.; Wiley: Hoboken, NJ, 2014; pp 699−700.
(179) Dardoize, F.; Goasdoué, C.; Goasdoué, N.; Laborit, H. M.; Topall, G. 4-Hydroxybutyric acid (and analogues) derivatives of D-glucosamine. *Tetrahedron* **1989**, *45*, 7783−7794.
(180) Boaz, N. W. Enzymatic desymmetrization of cis-1,3-cyclohexanedicarboxylic acid diesters. *Tetrahedron: Asymmetry* **1999**, *10*, 813−816.
(181) Ester Deprotection Reaxys Search as of April 21, 2020.
(182) Iwai, N.; Nakayama, K.; Oku, J.; Kitazume, T. Synthesis and antibacterial activity of alaremycin derivatives for the porphobilinogen synthase. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2812−2815.
(183) Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slattery, J. M. Solvent effects in palladium catalysed cross-coupling reactions. *Green Chem.* **2019**, *21*, 2164−2213.
(184) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-catalyzed formation of carbon-nitrogen bonds. Reaction intermediates and catalyst improvements in the hetero cross-coupling of aryl halides and tin amides. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970.
(185) Cohen, D. T.; Buchwald, S. L. Mild Palladium-Catalyzed Cyanation of (Hetero)aryl Halides and Triflates in Aqueous Media. *Org. Lett.* **2015**, *17*, 202−205.
(186) Fors, B. P.; Buchwald, S. L. Pd-Catalyzed Conversion of Aryl Chlorides, Triflates, and Nonaflates to Nitroaromatics. *J. Am. Chem. Soc.* **2009**, *131*, 12898−12899.
(187) Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. CuI/Oxalic Diamide Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amines. *J. Am. Chem. Soc.* **2015**, *137*, 11942−11945.
(188) Fan, M.; Zhou, W.; Jiang, Y.; Ma, D. CuI/Oxalamide Catalyzed Couplings of (Hetero)aryl Chlorides and Phenols for Diaryl Ether Formation. *Angew. Chem., Int. Ed.* **2016**, *55*, 6211−6215.
(189) Xia, S.; Gan, L.; Wang, K.; Li, Z.; Ma, D. Copper-Catalyzed Hydroxylation of (Hetero)aryl Halides under Mild Conditions. *J. Am. Chem. Soc.* **2016**, *138*, 13493−13496.
(190) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C−N, C−O, C−S, and C−C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136−16179.
(191) Bullock, K. M.; Mitchell, M. B.; Toczko, J. F. Optimization and Scale-Up of a Suzuki−Miyaura Coupling Reaction: Development of an Efficient Palladium Removal Technique. *Org. Process Res. Dev.* **2008**, *12*, 896−899.
(192) Espinet, P.; Echavarren, A. M. The Mechanisms of the Stille Reaction. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704−4734.
(193) Cross-Coupling Reaxys Search as of April 20, 2020.
(194) Wilson, K. L.; Kennedy, A. R.; Murray, J.; Greatrex, B.; Jamieson, C.; Watson, A. J. B. Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation. *Beilstein J. Org. Chem.* **2016**, *12*, 2005−2011.
(195) Wilson, K. L.; Murray, J.; Jamieson, C.; Watson, A. J. B. Cyrene as a Bio-Based Solvent for the Suzuki−Miyaura Cross-Coupling. *Synlett* **2018**, *29*, 650−654.
(196) Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanari, D.; Marrocchi, A.; Drees, M.; Facchetti, A.; Vaccaro, L. A biomass-derived safe medium to replace toxic dipolar solvents and access cleaner Heck coupling reactions. *Green Chem.* **2015**, *17*, 365−372.
(197) Akhtar, R.; Zahoor, A. F.; Parveen, B.; Suleman, M. Development of environmental friendly synthetic strategies for Sonogashira cross coupling reaction: An update. *Synth. Commun.* **2019**, *49*, 167−192.
(198) Parker, H. L.; Sherwood, J.; Hunt, A. J.; Clark, J. H. Cyclic Carbonates as Green Alternative Solvents for the Heck Reaction. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1739−1742.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(199) Yousaf, M.; Zahoor, A. F.; Akhtar, R.; Ahmad, M.; Naheed, S. Development of green methodologies for Heck, Chan−Lam, Stille and Suzuki cross-coupling reactions. *Mol. Diversity* **2019**.
(200) Hoffmann, I.; Blumenröder, B.; Onodi neé Thumann, S.; Dommer, S.; Schatz, J. Suzuki cross-coupling in aqueous media. *Green Chem.* **2015**, *17*, 3844−3857.
(201) Li, Z.; Gelbaum, C.; Heaner, W. L.; Fisk, J.; Jaganathan, A.; Holden, B.; Pollet, P.; Liotta, C. L. Palladium-Catalyzed Suzuki Reactions in Water with No Added Ligand: Effects of Reaction Scale, Temperature, pH of Aqueous Phase, and Substrate Structure. *Org. Process Res. Dev.* **2016**, *20*, 1489−1499.
(202) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. Aqueous-Phase, Palladium-Catalyzed Cross-Coupling of Aryl Bromides under Mild Conditions, Using Water-Soluble, Sterically Demanding Alkylphosphines. *J. Org. Chem.* **2004**, *69*, 7919−7927.
(203) Zhou, F.; Li, C.-J. En route to metal-mediated and metal-catalysed reactions in water. *Chem. Sci.* **2019**, *10*, 34−46.
(204) Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. Nickel-Catalyzed Suzuki−Miyaura Couplings in Green Solvents. *Org. Lett.* **2013**, *15*, 3950−3953.
(205) Schäffner, B.; Holz, J.; Verevkin, S. P.; Börner, A. Organic Carbonates as Alternative Solvents for Palladium-Catalyzed Substitution Reactions. *ChemSusChem* **2008**, *1*, 249−253.
(206) Dong, J. J.; Roger, J.; Verrier, C.; Martin, T.; Le Goff, R.; Hoarau, C.; Doucet, H. Carbonates: eco-friendly solvents for palladium-catalysed direct arylation of heteroaromatics. *Green Chem.* **2010**, *12*, 2053−2063.
(207) Ismael, A.; Gevorgyan, A.; Skrydstrup, T.; Bayer, A. Renewable Solvents for Palladium-Catalyzed Carbonylation Reactions. *Org. Process Res. Dev.* **2020**, *24*, 2665.
(208) Affouard, C.; Crockett, R. D.; Diker, K.; Farrell, R. P.; Gorins, G.; Huckins, J. R.; Caille, S. Multi-Kilo Delivery of AMG 925 Featuring a Buchwald−Hartwig Amination and Processing with Insoluble Synthetic Intermediates. *Org. Process Res. Dev.* **2015**, *19*, 476−485.
(209) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-Catalyzed C−N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655.
(210) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. An efficient system for the Pd-catalyzed cross-coupling of amides and aryl chlorides. *Tetrahedron* **2009**, *65*, 6576−6583.
(211) Topchiy, M. A.; Asachenko, A. F.; Nechaev, M. S. Solvent-Free Buchwald−Hartwig Reaction of Aryl and Heteroaryl Halides with Secondary Amines. *Eur. J. Org. Chem.* **2014**, *2014*, 3319−3322.
(212) Fischmeister, C.; Doucet, H. Greener solvents for ruthenium and palladium-catalysed aromatic C−H bond functionalisation. *Green Chem.* **2011**, *13*, 741−753.
(213) Sarkar, S. M.; Rahman, M. L.; Chong, K. F.; Yusoff, M. M. Poly(hydroxamic acid) palladium catalyst for heck reactions and its application in the synthesis of Ozagrel. *J. Catal.* **2017**, *350*, 103−110.
(214) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature. *J. Org. Chem.* **2011**, *76*, 4379−4391.
(215) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature Without Prior Formation of Organozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 15592−15593.
(216) Parmentier, M.; Wagner, M.; Wickendick, R.; Baenziger, M.; Langlois, A.; Gallou, F. A General Kilogram Scale Protocol for Suzuki−Miyaura Cross-Coupling in Water with TPGS-750-M Surfactant. *Org. Process Res. Dev.* **2020**, *24*, 1536−1542.
(217) Wagner, P.; Bollenbach, M.; Doebelin, C.; Bihel, F.; Bourguignon, J.-J.; Salomé, C.; Schmitt, M. t-BuXPhos: a highly efficient ligand for Buchwald−Hartwig coupling in water. *Green Chem.* **2014**, *16*, 4170−4178.
(218) Sherwood, J. European Restrictions on 1,2-Dichloroethane: C−H Activation Research and Development Should Be Liberated and not Limited. *Angew. Chem., Int. Ed.* **2018**, *57*, 14286−14290.
(219) Sagadevan, A.; Charitou, A.; Wang, F.; Ivanova, M.; Vuagnat, M.; Greaney, M. F. Ortho C−H arylation of arenes at room temperature using visible light ruthenium C−H activation. *Chem. Sci.* **2020**, *11*, 4439−4443.
(220) 1,2-Dichloroethane ECHA Substance Infocard. https://echa.europa.eu/substance-information/-/substanceinfo/100.003.145 (accessed April 1, 2020).
(221) Skowerski, K.; Białecki, J.; Tracz, A.; Olszewski, T. K. An attempt to provide an environmentally friendly solvent selection guide for olefin metathesis. *Green Chem.* **2014**, *16*, 1125−1130.
(222) Bakhrou, N.; Lamaty, F.; Martinez, J.; Colacino, E. Ring-closing metathesis in glycerol under microwave activation. *Tetrahedron Lett.* **2010**, *51*, 3935−3937.
(223) Sherwood, J.; De bruyn, M.; Constantinou, A.; Moity, L.; McElroy, C. R.; Farmer, T. J.; Duncan, T.; Raverty, W.; Hunt, A. J.; Clark, J. H. Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents. *Chem. Commun.* **2014**, *50*, 9650−9652.
(224) Rajesh, T.; Azeez, S. A.; Naresh, E.; Madhusudhan, G.; Mukkanti, K. Practical One-Pot and Large-Scale Synthesis of N-(tert-Butyloxycarbonyl)-3-pyrroline. *Org. Process Res. Dev.* **2009**, *13*, 638−640.
(225) Jordan, A.; Huang, S.; Sneddon, H. F.; Nortcliffe, A. Assessing the Limits of Sustainability for the Delépine Reaction. *ACS Sustainable Chem. Eng.* **2020**, *8*, 12746−12754.
(226) McGonagle, F. I.; MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. Development of a solvent selection guide for aldehyde-based direct reductive amination processes. *Green Chem.* **2013**, *15*, 1159−1165.
(227) Bennett, J. S.; Charles, K. L.; Miner, M. R.; Heuberger, C. F.; Spina, E. J.; Bartels, M. F.; Foreman, T. Ethyl lactate as a tunable solvent for the synthesis of aryl aldimines. *Green Chem.* **2009**, *11*, 166−168.
(228) Benzylic Ester Reaxys Search as of April 21, 2020.
(229) Pd/C SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=205699&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F205699%3Flang%3Den (accessed April 17, 2020).
(230) Phenol Alkylation Reaxys Search as of April 21, 2020.
(231) Beddoe, R. H.; Andrews, K. G.; Magné, V.; Cuthbertson, J. D.; Saska, J.; Shannon-Little, A. L.; Shanahan, S. E.; Sneddon, H. F.; Denton, R. M. Redox-neutral organocatalytic Mitsunobu reactions. *Science* **2019**, *365*, 910−914.
(232) Camp, D.; Harvey, P. J.; Jenkins, I. D. The effect of solvent polarity on the rate of the Mitsunobu esterification reaction. *Tetrahedron* **2015**, *71*, 3932−3938.
(233) Prontosil. https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/prontosil (accessed April 22, 2020).
(234) Gioiello, A.; Rosatelli, E.; Teofrasti, M.; Filipponi, P.; Pellicciari, R. Building a Sulfonamide Library by Eco-Friendly Flow Synthesis. *ACS Comb. Sci.* **2013**, *15*, 235−239.
(235) Eid, N.; Karamé, I.; Andrioletti, B. Straightforward and Sustainable Synthesis of Sulfonamides in Water under Mild Conditions. *Eur. J. Org. Chem.* **2018**, *2018*, 5016−5022.
(236) Deng, X.; Mani, N. S. A facile, environmentally benign sulfonamide synthesis in water. *Green Chem.* **2006**, *8*, 835−838.
(237) Jafarpour, M.; Rezaeifard, A.; Golshani, T. A Green, Catalyst-Free Method for the Synthesis of Sulfonamides and Sulfonylazides. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *186*, 140−148.
(238) Muraglia, M.; Franchini, C.; Corbo, F.; Scilimati, A.; Tortorella, V.; Sinicropi, M. S.; De Luca, A.; De Bellis, M.; Camerino, D. C. Synthesis of beta-proline like derivatives and their evaluation as sodium channel blockers. *J. Heterocycl. Chem.* **2007**, *44*, 1099−1103.
(239) Nitro Reduction Reaxys Search as of April 22, 2020.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(240) Chen, B.; Wang, P.; Jin, Q.; Tang, X. Chemoselective reduction and self-immolation based FRET probes for detecting hydrogen sulfide in solution and in cells. *Org. Biomol. Chem.* **2014**, *12*, 5629−5633.
(241) Porta, R.; Puglisi, A.; Colombo, G.; Rossi, S.; Benaglia, M. Continuous-flow synthesis of primary amines: Metal-free reduction of aliphatic and aromatic nitro derivatives with trichlorosilane. *Beilstein J. Org. Chem.* **2016**, *12*, 2614−2619.
(242) Whritenour, D. C.; Brenek, S. J.; Tom, N. J. An Improved Procedure for the Reduction of 2,4-Dinitrobenzaldehyde to 2,4-Diaminobenzaldehyde with Iron and Acetic Acid under Dose-Controlled Conditions. *Org. Process Res. Dev.* **2001**, *5*, 539−541.
(243) Zeynizadeh, B.; Mohammad Aminzadeh, F.; Mousavi, H. Green and convenient protocols for the efficient reduction of nitriles and nitro compounds to corresponding amines with NaBH4 in water catalyzed by magnetically retrievable CuFe2O4 nanoparticles. *Res. Chem. Intermed.* **2019**, *45*, 3329−3357.
(244) Bornschein, C.; Werkmeister, S.; Wendt, B.; Jiao, H.; Alberico, E.; Baumann, W.; Junge, H.; Junge, K.; Beller, M. Mild and selective hydrogenation of aromatic and aliphatic (di)nitriles with a well-defined iron pincer complex. *Nat. Commun.* **2014**, *5*, 4111.
(245) Aycock, D. F. Solvent Applications of 2-Methyltetrahydrofuran in Organometallic and Biphasic Reactions. *Org. Process Res. Dev.* **2007**, *11*, 156−159.
(246) Lithium aluminum hydride solution, 2-MeTHF. https://www.sigmaaldrich.com/catalog/product/aldrich/703508?lang=en&region=GB (accessed April 30, 2020).
(247) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. Evolution and Synthetic Applications of the Heck−Matsuda Reaction: The Return of Arenediazonium Salts to Prominence. *Eur. J. Org. Chem.* **2011**, *2011*, 1403−1428.
(248) Hodgson, H. H. The Sandmeyer Reaction. *Chem. Rev.* **1947**, *40*, 251−277.
(249) Diazonium Salt Reaxys Search as of April 23, 2020.
(250) Bondarev, A. A.; Naumov, E. V.; Kassanova, A. Z.; Krasnokutskaya, E. A.; Stankevich, K. S.; Filimonov, V. D. First Study of the Thermal and Storage Stability of Arenediazonium Triflates Comparing to 4-Nitrobenzenediazonium Tosylate and Tetrafluoroborate by Calorimetric Methods. *Org. Process Res. Dev.* **2019**, *23*, 2405−2415.
(251) Theunissen, C.; Métayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin-Mingot, A.; Thibaudeau, S.; Evano, G. Keteniminium Ion-Initiated Cascade Cationic Polycyclization. *J. Am. Chem. Soc.* **2014**, *136*, 12528−12531.
(252) Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K.-W. Unusually Stable, Versatile, and Pure Arenediazonium Tosylates: Their Preparation, Structures, and Synthetic Applicability. *Org. Lett.* **2008**, *10*, 3961−3964.
(253) Sandmeyer-like Reaxys Search as of April 23, 2020.
(254) Fry, H. S.; Grote, I. W. A Standardization of the Sandmeyer Reaction, With Special Applications. *J. Am. Chem. Soc.* **1926**, *48*, 710−714.
(255) Gholap, S. S. An Efficient Gram Scale Synthesis of Aryl Iodides from Aryl Diazofluoroborates in Water under Mild Conditions. *Lett. Org. Chem.* **2018**, *15*, 594−599.
(256) Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Roglans, A. First Heck Reaction with Arenediazonium Cations with Recovery of Pd-Triolefinic Macrocyclic Catalyst. *Org. Lett.* **2003**, *5*, 1559−1561.
(257) Taylor, J. G.; Correia, C. R. D. Stereoselective Synthesis of Unsymmetrical *β*,*β*-Diarylacrylates by a Heck−Matsuda Reaction: Versatile Building Blocks for Asymmetric Synthesis of *β*,*β*-Diphenylpropanoates, 3-Aryl-indole, and 4-Aryl-3,4-dihydro-quinolin-2-one and Formal Synthesis of (−)-Indatraline. *J. Org. Chem.* **2011**, *76*, 857−869.
(258) Laudien, J.; Fouquet, E.; Zakri, C.; Felpin, F.-X. A Multi-Task Palladium Catalyst Involved in Heck-Reduction-Cyclization Sequences for the Preparation of 4-Benzyl-1,2-dihydroisoquinolin-3-ones: An Unusual Homogeneous-Heterogeneous Sustainable Approach. *Synlett* **2010**, *2010*, 1539−1543.
(259) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. Palladium catalyzed Heck reaction of arenediazonium tetrafluoroborate salts with Baylis−Hillman adducts: production of *α*-benzyl-*β*-keto esters. *Tetrahedron Lett.* **2006**, *47*, 1325−1328.
(260) Liu, Q.; Sun, B.; Liu, Z.; Kao, Y.; Dong, B.-W.; Jiang, S.-D.; Li, F.; Liu, G.; Yang, Y.; Mo, F. A general electrochemical strategy for the Sandmeyer reaction. *Chem. Sci.* **2018**, *9*, 8731−8737.
(261) Dubois, N.; Glynn, D.; McInally, T.; Rhodes, B.; Woodward, S.; Irvine, D. J.; Dodds, C. On DABAL-Me3 promoted formation of amides. *Tetrahedron* **2013**, *69*, 9890−9897.
(262) Fischer, E.; Speier, A. Darstellung der Ester. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3252−3258.
(263) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. Direct ester condensation from a 1:1 mixture of carboxylic acids and alcohols catalyzed by hafnium(IV) or zirconium(IV) salts. *Tetrahedron* **2002**, *58*, 8179−8188.
(264) Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.
(265) Matsumoto, K.; Yanagi, R.; Oe, Y. Recent Advances in the Synthesis of Carboxylic Acid Esters, Carboxylic Acid - Key Role in Life Sciences. In *Carboxylic Acid - Key Role in Life Sciences*; IntechOpen: 2018.
(266) Tsakos, M.; Schaffert, E. S.; Clement, L. L.; Villadsen, N. L.; Poulsen, T. B. Ester coupling reactions − an enduring challenge in the chemical synthesis of bioactive natural products. *Nat. Prod. Rep.* **2015**, *32*, 605−632.
(267) Esterification Reaxys Search as of April 24, 2020.
(268) Jordan, A.; Sneddon, H. F. Development of a solvent-reagent selection guide for the formation of thioesters. *Green Chem.* **2019**, *21*, 1900−1906.
(269) Adams, J. P.; Alder, C. M.; Andrews, I.; Bullion, A. M.; Campbell-Crawford, M.; Darcy, M. G.; Hayler, J. D.; Henderson, R. K.; Oare, C. A.; Pendrak, I.; Redman, A. M.; Shuster, L. E.; Sneddon, H. F.; Walker, M. D. Development of GSK's reagent guides − embedding sustainability into reagent selection. *Green Chem.* **2013**, *15*, 1542−1549.
(270) Janssen, M. H. A.; Chesa Castellana, J. F.; Jackman, H.; Dunn, P. J.; Sheldon, R. A. Towards greener solvents for the bleach oxidation of alcohols catalysed by stable N-oxy radicals. *Green Chem.* **2011**, *13*, 905−912.
(271) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. Green, Catalytic Oxidations of Alcohols. *Acc. Chem. Res.* **2002**, *35*, 774−781.
(272) Harre, M.; Haufe, R.; Nickisch, K.; Weinig, P.; Weinmann, H.; Kinney, W. A.; Zhang, X. Some Reaction Safety Aspects of Ruthenium-Catalyzed Allylic Oxidations of Δ-5-Steroids in the Pilot Plant. *Org. Process Res. Dev.* **1998**, *2*, 100−104.
(273) Jordan, A.; Gathergood, N. Biodegradation of ionic liquids − a critical review. *Chem. Soc. Rev.* **2015**, *44*, 8200−8237.
(274) Delorme, A. E.; Sans, V.; Licence, P.; Walsh, D. A. Tuning the Reactivity of TEMPO during Electrocatalytic Alcohol Oxidations in Room-Temperature Ionic Liquids. *ACS Sustainable Chem. Eng.* **2019**, *7*, 11691−11699.
(275) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. Oxidation of sulfides to sulfoxides and sulfones with 30% hydrogen peroxide under organic solvent- and halogen-free conditions. *Tetrahedron* **2001**, *57*, 2469−2476.
(276) Snieckus, V. Directed ortho metalation. Tertiary amide and O-carbamate directors in synthetic strategies for polysubstituted aromatics. *Chem. Rev.* **1990**, *90*, 879−933.
(277) Capriati, V.; Perna, F. M.; Salomone, A. The Great Beauty" of organolithium chemistry: a land still worth exploring. *Dalton Trans.* **2014**, *43*, 14204−14210.
(278) Wietelmann, U.; Klett, J. 200 Years of Lithium and 100 Years of Organolithium Chemistry. *Z. Anorg. Allg. Chem.* **2018**, *644*, 194−204.
(279) Kemsley, J. Researcher Dies After Lab Fire - UCLA research assistant burned in incident with tert-butyl lithium. https://cen.acs.org/articles/87/web/2009/01/Researcher-Dies-Lab-Fire.html (accessed April 24, 2020).
(280) Closs, G. L. Carbenes from Alkyl Halides and Organolithium Compounds. IV.1 Formation of Alkylcarbenes from Methylene

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

Chloride and Alkyllithium Compounds2. *J. Am. Chem. Soc.* **1962**, *84*, 809−813.
(281) Closs, G. L.; Closs, L. E. Carbenes from Alkyl Halides and Organolithium Compounds. I. Synthesis of Chlorocyclopropanes1. *J. Am. Chem. Soc.* **1960**, *82*, 5723−5728.
(282) Mallardo, V.; Rizzi, R.; Sassone, F. C.; Mansueto, R.; Perna, F. M.; Salomone, A.; Capriati, V. Regioselective desymmetrization of diaryltetrahydrofurans via directed ortho-lithiation: an unexpected help from green chemistry. *Chem. Commun.* **2014**, *50*, 8655−8658.
(283) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. Cyclopentyl Methyl Ether as a New and Alternative Process Solvent. *Org. Process Res. Dev.* **2007**, *11*, 251−258.
(284) Lao, Z.; Toy, P. H. Catalytic Wittig and aza-Wittig reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 2577−2587.
(285) Tsukamoto, M.; Schlosser, M. Ylid Modeling as the Key to a cis-Selective Synthesis of Stilbenes. *Synlett* **1990**, *1990*, 605−608.
(286) Wadsworth, W.S., Jr. Synthetic Applications of Phosphoryl-Stabilized Anions. *Org. React.* **2005**, DOI: 10.1002/0471264180.or025.02.
(287) Pandolfi, E. M.; López, G. V.; Días, E.; Seoane, G. A. Solvent Effect in the Wittig Reaction Under Boden's Conditions. *Synth. Commun.* **2003**, *33*, 2187−2196.
(288) O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J. Breaking the Ring through a Room Temperature Catalytic Wittig Reaction. *Chem. - Eur. J.* **2013**, *19*, 5854−5858.
(289) 18-crown-6 SDS. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=274984&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F274984%3Flang%3Den (accessed July 1, 2020).
(290) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters from Mixing Aldehydes, α-Bromoesters, and Ph3P in Aqueous NaHCO3. *J. Org. Chem.* **2007**, *72*, 5244−5259.
(291) Morsch, L. A.; Deak, L.; Tiburzi, D.; Schuster, H.; Meyer, B. Green Aqueous Wittig Reaction: Teaching Green Chemistry in Organic Teaching Laboratories. *J. Chem. Educ.* **2014**, *91*, 611−614.
(292) Leung, S. H.; Angel, S. A. Solvent-Free Wittig Reaction: A Green Organic Chemistry Laboratory Experiment. *J. Chem. Educ.* **2004**, *81*, 1492.
(293) Robertson, F. J. A Highly Versatile One-Pot Aqueous Wittig Reaction. *World J. Chem. Educ.* **2016**, *4*, 101−106.
(294) Chiellini, G.; Rapposelli, S.; Zhu, J.; Massarelli, I.; Saraceno, M.; Bianucci, A. M.; Plum, L. A.; Clagett-Dame, M.; DeLuca, H. F. Synthesis and biological activities of vitamin D-like inhibitors of CYP24 hydroxylase. *Steroids* **2012**, *77*, 212−223.
(295) Alonso-Fernández, J.; Benaiges, C.; Casas, E.; Alibés, R.; Bayón, P.; Busqué, F.; Álvarez-Larena, Á.; Figueredo, M. Synthetic studies on Stemona alkaloids. Construction of the sessilifoliamides B and C and 1,12-secostenine skeleton. *Tetrahedron* **2016**, *72*, 3500−3524.
(296) Ainembabazi, D.; Reid, C.; Chen, A.; An, N.; Kostal, J.; Voutchkova-Kostal, A. Decarbonylative Olefination of Aldehydes to Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 696−699.
(297) Van Waes, F. E. A.; Drabowicz, J.; Cukalovic, A.; Stevens, C. V. Efficient and catalyst-free condensation of acid chlorides and alcohols using continuous flow. *Green Chem.* **2012**, *14*, 2776−2779.
(298) Acid Chloride Reaxys Search as of April 27, 2020.
(299) Hanson, R. L.; Johnston, R. M.; Goldberg, S. L.; Parker, W. L.; Goswami, A. Enzymatic Preparation of an R-Amino Acid Intermediate for a γ-Secretase Inhibitor. *Org. Process Res. Dev.* **2013**, *17*, 693−700.
(300) Gál, B.; Bucher, C.; Burns, N. Z. Chiral Alkyl Halides: Underexplored Motifs in Medicine. *Mar. Drugs* **2016**, *14*, 206.
(301) Chung, W.-j.; Vanderwal, C. D. Stereoselective Halogenation in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2016**, *55*, 4396−4434.
(302) Fuson, R. C.; Bull, B. A. The Haloform Reaction. *Chem. Rev.* **1934**, *15*, 275−309.
(303) Salbutamol Synthesis. https://www.sciencedirect.com/topics/chemistry/albuterol (accessed April 20, 2020).
(304) a-Halo Ketone Reaxys Search as of April 28, 2020.
(305) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C.; Temesvári-Major, E.; Blaskó, G. A practical enantioselective synthesis of epibatidine. *Tetrahedron* **1996**, *52*, 11053−11062.
(306) Narayana, B.; Vijaya Raj, K. K.; Ashalatha, B. V.; Kumari, N. S. Synthesis of Some New 4-(2-Chloropyridin-4-yl)-N-Aryl-1,3-Thiazol-2-Amine Derivatives as Possible Antifungal and Antibacterial Agents. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 7−14.
(307) Sanivarapu, S.; Vaddiraju, N.; Velide, L. Synthesis and anti-inflammatory activity of 1,2−3-substituted 2a1,4,5-triazacyclopenta-[cd]indene derivatives. *Med. Chem. Res.* **2019**, *28*, 1461−1470.
(308) Shi, L.; Hu, A.; Xu, J.; Jiang, Y. Design, Synthesis and Biological Evaluation of 2-(2-Aryl-morpholino-4-yl)ethyl Esters of Indomethacin as Potential Cyclooxygenase-2 (COX-2) Inhibitors. *Chin. J. Chem.* **2012**, *30*, 1339−1344.
(309) Sahin, Z.; Ertas, M.; Berk, B.; Biltekin, S. N.; Yurttas, L.; Demirayak, S. Studies on non-steroidal inhibitors of aromatase enzyme; 4-(aryl/heteroaryl)-2-(pyrimidin-2-yl)thiazole derivatives. *Bioorg. Med. Chem.* **2018**, *26*, 1986−1995.
(310) Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. Amberlyst-15®-promoted efficient 2-halogenation of 1,3-keto-esters and cyclic ketones using N-halosuccinimides. *Tetrahedron Lett.* **2005**, *46*, 623−626.
(311) Adimurthy, S.; Ramachandraiah, G.; Bedekar, A. V.; Ghosh, S.; Ranu, B. C.; Ghosh, P. K. Eco-friendly and versatile brominating reagent prepared from a liquid bromine precursor. *Green Chem.* **2006**, *8*, 916−922.
(312) Adimurthy, S.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. An alternative method for the regio- and stereoselective bromination of alkenes, alkynes, toluene derivatives and ketones using a bromide/bromate couple. *Green Chem.* **2008**, *10*, 232−237.
(313) Eissen, M.; Lenoir, D. Electrophilic Bromination of Alkenes: Environmental, Health and Safety Aspects of New Alternative Methods. *Chem. - Eur. J.* **2008**, *14*, 9830−9841.
(314) Alkene/Alkyne Reaxys Search as of April 28, 2020.
(315) Casiraghi, A.; Valoti, E.; Suigo, L.; Artasensi, A.; Sorvillo, E.; Straniero, V. How Reaction Conditions May Influence the Regioselectivity in the Synthesis of 2,3-Dihydro-1,4-benzoxathiine Derivatives. *J. Org. Chem.* **2018**, *83*, 13217−13227.
(316) Song, S.; Li, X.; Sun, X.; Yuan, Y.; Jiao, N. Efficient bromination of olefins, alkynes, and ketones with dimethyl sulfoxide and hydrobromic acid. *Green Chem.* **2015**, *17*, 3285−3289.
(317) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. Bromination of ketones with H2O2−HBr "on water. *Green Chem.* **2007**, *9*, 1212−1218.
(318) Podgoršek, A.; Zupan, M.; Iskra, J. Oxidative Halogenation with "Green" Oxidants: Oxygen and Hydrogen Peroxide. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424−8450.
(319) Stavber, S.; Jereb, M.; Zupan, M. Electrophilic Iodination of Organic Compounds Using Elemental Iodine or Iodides. *Synthesis* **2008**, *2008*, 1487−1513.
(320) Finkelstein, H. Darstellung organischer Jodide aus den entsprechenden Bromiden und Chloriden. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528−1532.
(321) Scala, A. A. Free Radical Halogenation, Selectivity, and Thermodynamics: The Polanyi Principle and Hammond's Postulate. *J. Chem. Educ.* **2004**, *81*, 1661.
(322) Wohl, A. Bromierung ungesättigter Verbindungen mit N-Brom-acetamid, ein Beitrag zur Lehre vom Verlauf chemischer Vorgänge. *Ber. Dtsch. Chem. Ges. B* **1919**, *52*, 51−63.
(323) Ziegler, K.; Schenck, G.; Krockow, E. W.; Siebert, A.; Wenz, A.; Weber, H. Die Synthese des Cantharidins. *Justus Liebigs Annalen der Chemie* **1942**, *551*, 1−79.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622

(324) Wang, Z. Wohl-Ziegler Bromination. In *Comprehensive Organic Name Reactions and Reagents*, Wang, Z., Ed.; 2010, DOI: 10.1002/9780470638859.conrr680.
(325) Marcos, C. F.; Neo, A. G.; Díaz, J.; Martínez-Caballero, S. A Safe and Green Benzylic Radical Bromination Experiment. *J. Chem. Educ.* **2020**, *97*, 582−585.
(326) Alkane Radical Halogenation Reaxys Search as of April 28, 2020.
(327) Djerassi, C. Brominations with N-Bromosuccinimide and Related Compounds. *Chem. Rev.* **1948**, *43*, 271−317.
(328) Dehimat, Z. I.; Paşahan, A.; Tebbani, D.; Yaşar, S.; Özdemir, İ. Synthesis of sterically hindered N-benzyladamantyl substituted benzimidazol-2-ylidene palladium complexes and investigation of their catalytic activity in aqueous medium. *Tetrahedron* **2017**, *73*, 5940−5945.
(329) Krishnamurthy, M.; Schirle, N. T.; Beal, P. A. Screening helix-threading peptides for RNA binding using a thiazole orange displacement assay. *Bioorg. Med. Chem.* **2008**, *16*, 8914−8921.
(330) Krishnamurthy, M.; Simon, K.; Orendt, A. M.; Beal, P. A. Macrocyclic Helix-Threading Peptides for Targeting RNA. *Angew. Chem., Int. Ed.* **2007**, *46*, 7044−7047.
(331) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. Visible light induced 'on water' benzylic bromination with N-bromosuccinimide. *Tetrahedron Lett.* **2006**, *47*, 1097−1099.
(332) Amijs, C. H. M.; van Klink, G. P. M.; van Koten, G. Carbon tetrachloride free benzylic brominations of methyl aryl halides. *Green Chem.* **2003**, *5*, 470−474.
(333) Pingali, S. R. K.; Upadhyay, S. K.; Jursic, B. S. Microwave-assisted benzyl mono- and dibromination in diethyl carbonate as environmentally friendly alternative to radical bromination in carbon tetrachloride. *Green Chem.* **2011**, *13*, 928−933.
(334) Jereb, M.; Zupan, M.; Stavber, S. Visible-Light-Promoted Wohl−Ziegler Functionalization of Organic Molecules with N-Bromosuccinimide under Solvent-Free Reaction Conditions. *Helv. Chim. Acta* **2009**, *92*, 555−566.
(335) de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. Tribromoisocyanuric acid as a green reagent for benzylic bromination of alkylarenes. *Tetrahedron Lett.* **2015**, *56*, 6843−6845.
(336) Mestres, R.; Palenzuela, J. High atomic yield bromine-less benzylic bromination. *Green Chem.* **2002**, *4*, 314−316.
(337) Bonfield, H. E.; Williams, J. D.; Ooi, W. X.; Leach, S. G.; Kerr, W. J.; Edwards, L. J. A Detailed Study of Irradiation Requirements Towards an Efficient Photochemical Wohl-Ziegler Procedure in Flow. *ChemPhotoChem.* **2018**, *2*, 938−944.
(338) Shimizu, S.; Imamura, Y.; Ueki, T. Incompatibilities between N-Bromosuccinimide and Solvents. *Org. Process Res. Dev.* **2014**, *18*, 354−358.
(339) Johnson, R. G.; Ingham, R. K. The Degradation Of Carboxylic Acid Salts By Means Of Halogen - The Hunsdiecker Reaction. *Chem. Rev.* **1956**, *56*, 219−269.
(340) Togo, H. 12 - Free Radicals for Green Chemistry. In *Advanced Free Radical Reactions for Organic Synthesis*; Togo, H., Ed.; Elsevier Science: Amsterdam, The Netherlands, 2004; pp 247−256.
(341) Litwinienko, G.; Beckwith, A. L. J.; Ingold, K. U. The frequently overlooked importance of solvent in free radical syntheses. *Chem. Soc. Rev.* **2011**, *40*, 2157−2163.
(342) Kajorinne, J. K.; Steers, J. C. M.; Merchant, M. E.; MacKinnon, C. D. Green halogenation reactions for (hetero)aromatic ring systems in alcohol, water, or no solvent. *Can. J. Chem.* **2018**, *96*, 1087−1091.
(343) Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. Efficient and Practical Oxidative Bromination and Iodination of Arenes and Heteroarenes with DMSO and Hydrogen Halide: A Mild Protocol for Late-Stage Functionalization. *Org. Lett.* **2015**, *17*, 2886−2889.
(344) Neto, J. S. S.; Balaguez, R. A.; Franco, M. S.; de Sá Machado, V. C.; Saba, S.; Rafique, J.; Galetto, F. Z.; Braga, A. L. Trihaloisocyanuric acids in ethanol: an eco-friendly system for the regioselective halogenation of imidazo-heteroarenes. *Green Chem.* **2020**, *22*, 3410−3415.
(345) Jordan, A.; Denton, R. M.; Sneddon, H. F. Development of a More Sustainable Appel Reaction. *ACS Sustainable Chem. Eng.* **2020**, *8*, 2300−2309.
(346) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. Catalytic Phosphorus(V)-Mediated Nucleophilic Substitution Reactions: Development of a Catalytic Appel Reaction. *J. Org. Chem.* **2011**, *76*, 6749−6767.
(347) Denton, R. M.; An, J.; Adeniran, B. Phosphine oxide-catalysed chlorination reactions of alcohols under Appel conditions. *Chem. Commun.* **2010**, *46*, 3025−3027.
(348) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. Metabolism of fluorine-containing drugs. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443−70.
(349) Fjelbye, K.; Marigo, M.; Clausen, R. P.; Jørgensen, E. B.; Christoffersen, C. T.; Juhl, K. Elucidation of fluorine's impact on pKa and in vitro Pgp-mediated efflux for a series of PDE9 inhibitors. *MedChemComm* **2018**, *9*, 893−896.
(350) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C−H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824−14848.
(351) Cheng, Q.; Ritter, T. New Directions in C-H Fluorination. *Trends Chem.* **2019**, *1*, 461−470.
(352) Yerien, D. E.; Bonesi, S.; Postigo, A. Fluorination methods in drug discovery. *Org. Biomol. Chem.* **2016**, *14*, 8398−8427.
(353) Neumann, C. N.; Ritter, T. Late-Stage Fluorination: Fancy Novelty or Useful Tool? *Angew. Chem., Int. Ed.* **2015**, *54*, 3216−3221.
(354) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174.
(355) Deoxy-Fluorination Reaxys Search as of April 30, 2020.
(356) Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Ridgill, M. P.; Shaw, D. E. 2-aryl indole derivatives and their use as therapeutic agents. U.S. Patent 2001/0039286A1, November 8, 2001.
(357) Hewawasam, P.; Kadow, J. F.; Lopez, O. D.; Meanwell, N. A.; Tu, Y.; Wang, A. X.; Xu, N.; Gupta, S. V. S. A. K.; Srinivasu, P.; Kumar, I. G.; Kumar, P. S.; Belema, M.; Fridell, R. A.; Gao, M.; Lemm, J. A.; O'boyle, D. R., II; Sun, J.-h.; Wang, C.; Wang, Y.-k. Hepatitis C Virus Inhibitors. U.S. Patent 2013/0183269A1, July 18, 2013.
(358) Sood, D. E.; Champion, S.; Dawson, D. M.; Chabbra, S.; Bode, B. E.; Sutherland, A.; Watson, A. J. B. Deoxyfluorination with CuF2: Enabled by Using a Lewis Base Activating Group. *Angew. Chem., Int. Ed.* **2020**, *59*, 8460−8463.
(359) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. Selectfluor: mechanistic insight and applications. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212.
(360) Stavber, G.; Stavber, S. Towards Greener Fluorine Organic Chemistry: Direct Electrophilic Fluorination of Carbonyl Compounds in Water and Under Solvent-Free Reaction Conditions. *Adv. Synth. Catal.* **2010**, *352*, 2838−2846.
(361) Yang, L.; Dong, T.; Revankar, H. M.; Zhang, C.-P. Recent progress on fluorination in aqueous media. *Green Chem.* **2017**, *19*, 3951−3992.
(362) Willis, N. J.; Fisher, C. A.; Alder, C. M.; Harsanyi, A.; Shukla, L.; Adams, J. P.; Sandford, G. Sustainable synthesis of enantiopure fluorolactam derivatives by a selective direct fluorination − amidase strategy. *Green Chem.* **2016**, *18*, 1313−1318.
(363) Harsanyi, A.; Sandford, G. Organofluorine chemistry: applications, sources and sustainability. *Green Chem.* **2015**, *17*, 2081−2086.
(364) Harsanyi, A.; Sandford, G. Fluorine gas for life science syntheses: green metrics to assess selective direct fluorination for the synthesis of 2-fluoromalonate esters. *Green Chem.* **2015**, *17*, 3000−3009.
(365) Lou, S.-J.; Chen, Q.; Wang, Y.-F.; Xu, D.-Q.; Du, X.-H.; He, J.-Q.; Mao, Y.-J.; Xu, Z.-Y. Selective C−H Bond Fluorination of Phenols with a Removable Directing Group: Late-Stage Fluorination of 2-Phenoxyl Nicotinate Derivatives. *ACS Catal.* **2015**, *5*, 2846−2849.
(366) Campbell, M. G.; Ritter, T. Late-Stage Fluorination: From Fundamentals to Application. *Org. Process Res. Dev.* **2014**, *18*, 474−480.

(367) Oishi, M.; Kondo, H.; Amii, H. Aromatic trifluoromethylation catalytic in copper. *Chem. Commun.* **2009**, 1909−1911.
(368) Fier, P. S.; Hartwig, J. F. Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides. *J. Am. Chem. Soc.* **2012**, *134*, 5524−5527.
(369) Lee, H. G.; Milner, P. J.; Buchwald, S. L. Pd-Catalyzed Nucleophilic Fluorination of Aryl Bromides. *J. Am. Chem. Soc.* **2014**, *136*, 3792−3795.
(370) Sather, A. C.; Buchwald, S. L. The Evolution of Pd(0)/Pd(II)-Catalyzed Aromatic Fluorination. *Acc. Chem. Res.* **2016**, *49*, 2146−2157.
(371) Aryl SnAr Fluorination Reaxys Search as of April 30, 2020.
(372) Wang, Z. Friedel-Crafts Alkylation. *Comprehensive Organic Name Reactions and Reagents*, Wang, Z., Ed.; 2010, DOI: 10.1002/9780470638859.conrr249.
(373) Wang, Z. Friedel-Crafts Acylation. *Comprehensive Organic Name Reactions and Reagents*, Wang, Z., Ed.; 2010, DOI: 10.1002/9780470638859.conrr248.
(374) Electrophilic Aromatic Substitution Reaxys Search as of June 19, 2020.
(375) Calloway, N. O. The Friedel-Crafts Syntheses. *Chem. Rev.* **1935**, *17*, 327−392.
(376) Bensari, A.; Zaveri, N. T. Titanium(IV) Chloride-Mediated Ortho-Acylation of Phenols and Naphthols. *Synthesis* **2003**, *2003*, 0267−0271.
(377) Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. Zinc Mediated Friedel-Crafts Acylation in Solvent-Free Conditions under Microwave Irradiation. *Synthesis* **2003**, *2003*, 2877−2881.
(378) Sarvari, M. H.; Sharghi, H. Reactions on a Solid Surface. A Simple, Economical and Efficient Friedel−Crafts Acylation Reaction over Zinc Oxide (ZnO) as a New Catalyst. *J. Org. Chem.* **2004**, *69*, 6953−6956.
(379) Akagawa, K.; Yamashita, T.; Sakamoto, S.; Kudo, K. Friedel−Crafts-type alkylation in aqueous media using resin-supported peptide catalyst having polyleucine. *Tetrahedron Lett.* **2009**, *50*, 5602−5604.
(380) Sadiq, Z.; Iqbal, M.; Hussain, E. A.; Naz, S. Friedel-Crafts reactions in aqueous media and their synthetic applications. *J. Mol. Liq.* **2018**, *255*, 26−42.
(381) Shirakawa, S.; Kobayashi, S. Carboxylic Acid Catalyzed Three-Component Aza-Friedel−Crafts Reactions in Water for the Synthesis of 3-Substituted Indoles. *Org. Lett.* **2006**, *8*, 4939−4942.
(382) Bohström, Z.; Härelind, H.; Holmberg, K. Friedel−Crafts alkylation of sodium salicylate with 4-tert butylbenzyl chloride performed in aqueous dispersions of mesoporous oxides. *J. Mol. Catal. A: Chem.* **2013**, *366*, 171−178.
(383) Yuan, J.-J. Alkylation of benzene with aqueous solution of ethanol over ZSM-5 catalysts. *Indian J. Chem. Technol.* **2006**, *13*, 334−340.
(384) MacMillan, D. W. C. The advent and development of organocatalysis. *Nature* **2008**, *455*, 304−308.
(385) North, M.; Pizzato, F.; Villuendas, P. Organocatalytic, Asymmetric Aldol Reactions with a Sustainable Catalyst in a Green Solvent. *ChemSusChem* **2009**, *2*, 862−865.
(386) North, M.; Omedes-Pujol, M. Catalytic, asymmetric cyanohydrin synthesis in propylene carbonate. *Tetrahedron Lett.* **2009**, *50*, 4452−4454.
(387) Yang, J.; Tan, J.-N.; Gu, Y. Lactic acid as an invaluable bio-based solvent for organic reactions. *Green Chem.* **2012**, *14*, 3304−3317.
(388) Waibel, K. A.; Nickisch, R.; Möhl, N.; Seim, R.; Meier, M. A. R. A more sustainable and highly practicable synthesis of aliphatic isocyanides. *Green Chem.* **2020**, *22*, 933−941.
(389) Wang, Z. Henry Reaction. *Comprehensive Organic Name Reactions and Reagents*, Wang, Z., Ed.; 2010, DOI: 10.1002/9780470638859.conrr308.
(390) Ballini, R.; Barboni, L.; Giarlo, G. The First Conversion of Primary Alkyl Halides to Nitroalkanes under Aqueous Medium. *J. Org. Chem.* **2004**, *69*, 6907−6908.
(391) Wang, Z. Victor Meyer Reaction. *Comprehensive Organic Name Reactions and Reagents*, Wang, Z., Ed.; 2010, DOI: 10.1002/9780470638859.conrr642.
(392) Addo, J. K.; Teesdale-Spittle, P.; Hoberg, J. O. Synthesis of 3-Nitropropanol Homologues. *Synthesis* **2005**, *2005*, 1923−1925.
(393) Christov, P. P.; Hawkins, E. K.; Kett, N. R.; Rizzo, C. J. Simplified synthesis of individual stereoisomers of the 4-hydroxynonenal adducts of deoxyguanosine. *Tetrahedron Lett.* **2013**, *54*, 4289−4291.
(394) Tan, J. S.; Hilden, L. R.; Merritt, J. M. Applications of In Silico Solvent Screening and an Interactive Web-Based Portal for Pharmaceutical Crystallization Process Development. *J. Pharm. Sci.* **2019**, *108*, 2621−2634.
(395) Amar, Y.; Schweidtmann, A. M.; Deutsch, P.; Cao, L.; Lapkin, A. Machine learning and molecular descriptors enable rational solvent selection in asymmetric catalysis. *Chem. Sci.* **2019**, *10*, 6697−6706.
(396) Sherwood, J.; Granelli, J.; McElroy, C. R.; Clark, J. H. A Method of Calculating the Kamlet−Abboud−Taft Solvatochromic Parameters Using COSMO-RS. *Molecules* **2019**, *24*, 2209.
(397) Pellis, A.; Byrne, F. P.; Sherwood, J.; Vastano, M.; Comerford, J. W.; Farmer, T. J. Safer bio-based solvents to replace toluene and tetrahydrofuran for the biocatalyzed synthesis of polyesters. *Green Chem.* **2019**, *21*, 1686−1694.
(398) Alves Costa Pacheco, A.; Sherwood, J.; Zhenova, A.; McElroy, C. R.; Hunt, A. J.; Parker, H. L.; Farmer, T. J.; Constantinou, A.; De bruyn, M.; Whitwood, A. C.; Raverty, W.; Clark, J. H. Intelligent Approach to Solvent Substitution: The Identification of a New Class of Levoglucosenone Derivatives. *ChemSusChem* **2016**, *9*, 3503−3512.
(399) Benazzouz, A.; Moity, L.; Pierlot, C.; Sergent, M.; Molinier, V.; Aubry, J.-M. Selection of a Greener Set of Solvents Evenly Spread in the Hansen Space by Space-Filling Design. *Ind. Eng. Chem. Res.* **2013**, *52*, 16585−16597.

https://dx.doi.org/10.1021/acs.chemrev.0c00709
Chem. Rev. 2021, 121, 1582−1622