GREEN CHEMISTRY

Laurea Magistrale in Scienze Chimiche

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6 CFU – AA 2017-2018

Green Chemistry 06

SOLVENTS IN GREEN CHEMISTRY I

Solvents in Green Chemistry

Use safer solvents and auxiliaries

Solvents in Green Chemistry

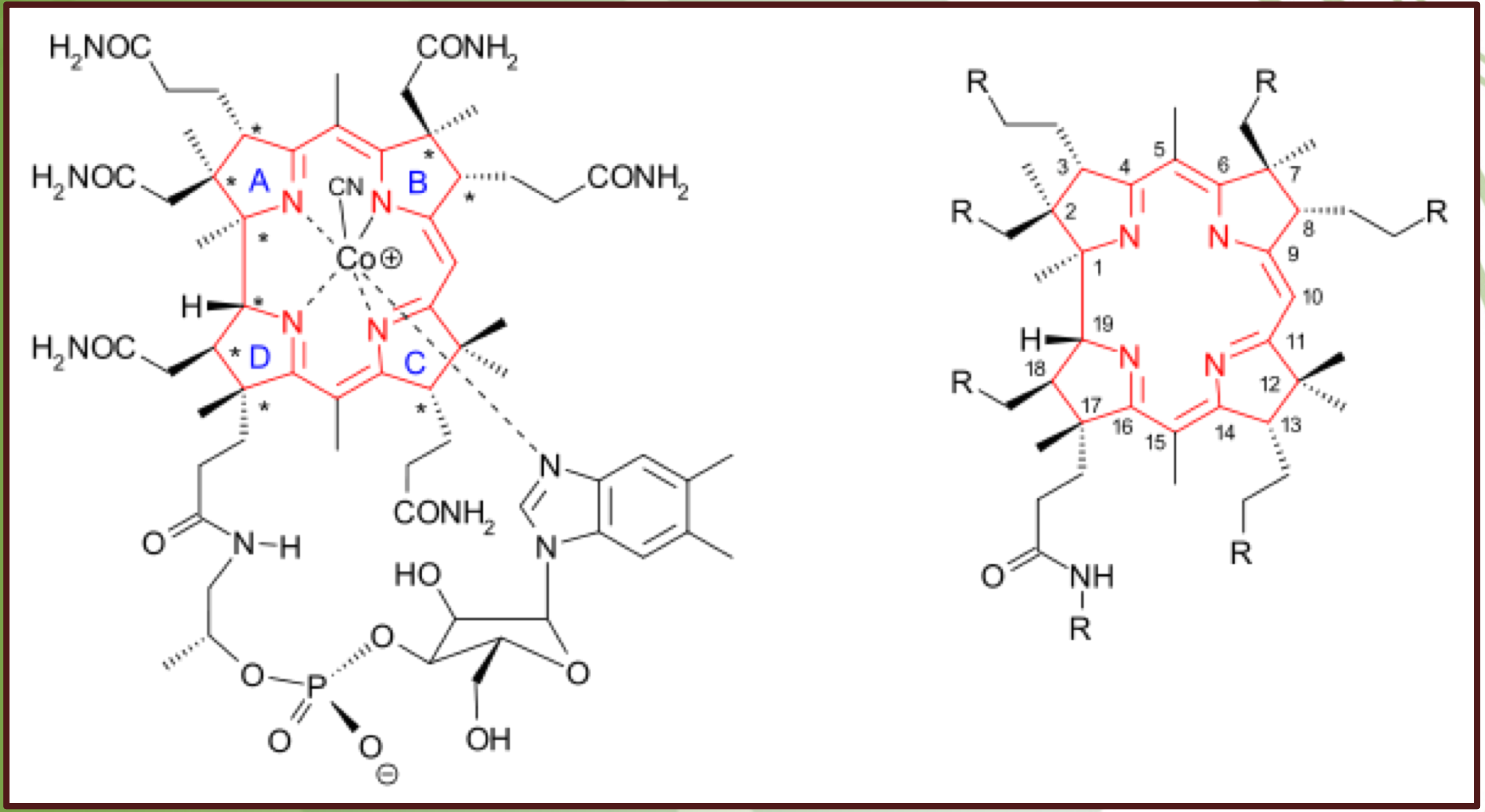
An immediate and obvious approach toward large-scale waste reduction is to minimize or eradicate auxiliary substances (those that do not appear in the desired product). A significant ancillary in many processes is the solvent, which usually provides a medium for reactant dissolution. Research into low-solvent or solvent-free reactivity is therefore currently of great interest.

Solvents in Green Chemistry

Employment of solvents in chemical reactivity stretches back many centuries. "*Corpora non agunt nisi fluida seu soluta*" (Aristotele) [“Compounds that are not fluid or dissolved, do not react”]. As more solvents became available to chemists it was further noted that not only are solvents a necessity, but choosing the correct solvent for a particular reaction is of even greater importance.

Solvents in Green Chemistry

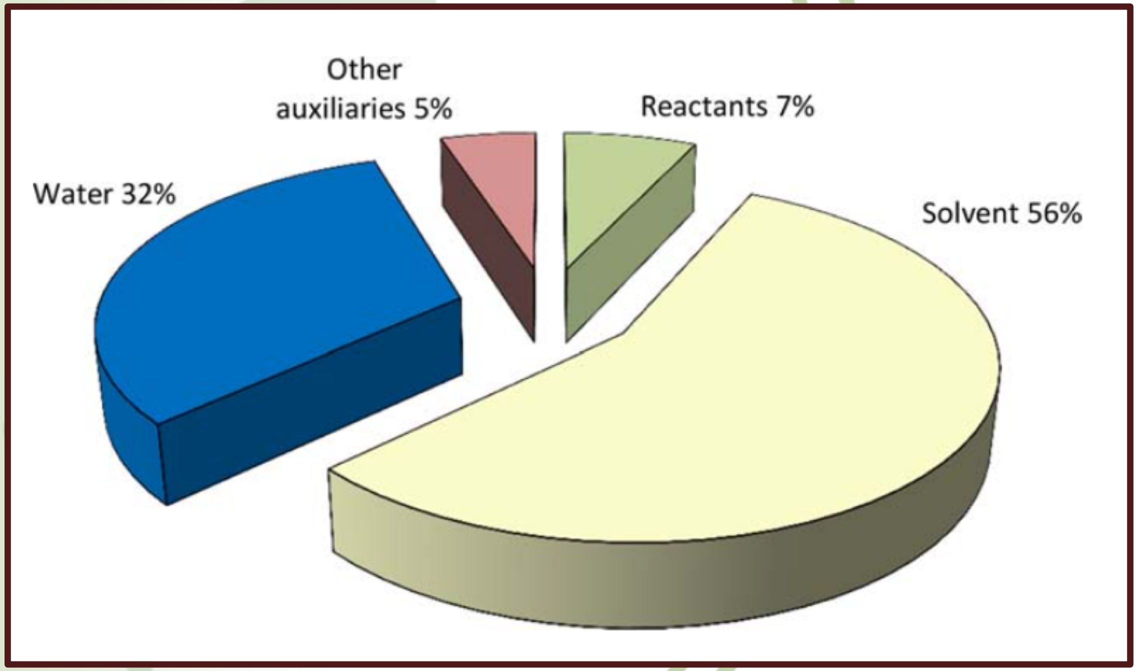
Woodward and Eschenmoser's Vitamin B12 synthesis



37 synthetic steps and 20 different organic solvents

Solvents in Green Chemistry

- Solvents represent roughly 56% of the total mass used in pharmaceutical manufacturing.
- For every kilogram of active pharmaceutical ingredient (API) produced 22 kg of solvent are needed
- GlaxoSmithKline developed guidelines for which solvents are safe to use and which solvents should be avoided



Solvents in Green Chemistry

The criteria that are generally considered when assessing the environmental credentials of a solvent include:

- Carbon footprint
- Biodegradability
- Solubility in water (solvents that are immiscible with water are less likely to contaminate aqueous waste streams)

Solvents in Green Chemistry

The criteria that are generally considered when assessing the environmental credentials of a solvent include:

- Whether it gives rise to volatile organic compounds (VOCs) (solvents with higher boiling points are less likely to have this issue)
- Whether the solvent is easy to recycle (distillation is less energy intensive for lower boiling solvents)
- Whether the solvent is produced from a renewable feedstock

Solvents in Green Chemistry

Additionally, safety criteria can be incorporated, including the solvent’s:

- Stability
- Flammability (or flash point)
- Toxicity (human and environmental)

Solvents in Green Chemistry

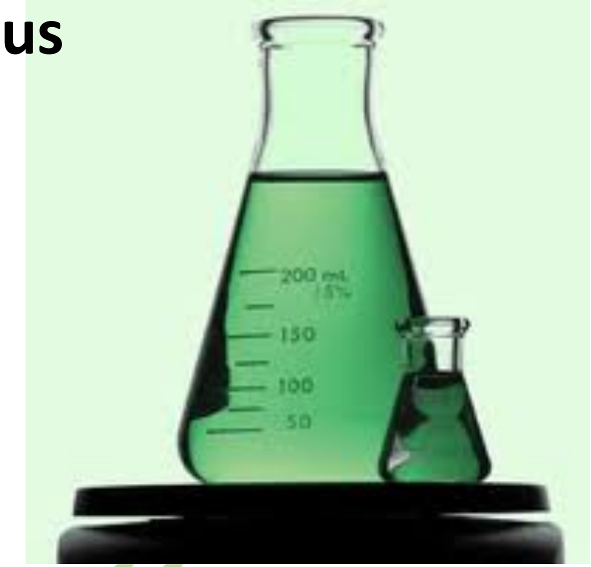
Alternative solvents suitable for green chemistry are those that have low toxicity, are easy to recycle, are inert and do not contaminate the product.

There is no perfect green solvent that can be applied to all situations

Solvents in Green Chemistry

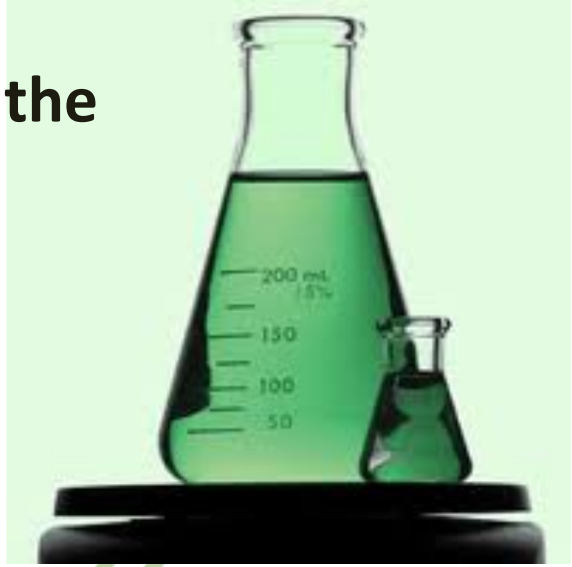
There is still debate about what constitutes a "green solvent" and which solvents are truly environmentally benign.

Recycling the solvent is another strategy that is employed by many companies. However, because current recycling methods are not very efficient there is only approximately a 50-80% recovery rate, thus recycling is not a sustainable option.



Solvents in Green Chemistry

A **green and sustainable solvent** can be defined as a solvent that addresses environmental issues, contributes to the optimization of the overall process, and is cost-effective. Specific process considerations must include reaction rates, product yields and selectivity, product separation, and recycling strategies for both the catalyst and the solvent.



Solvents in Green Chemistry

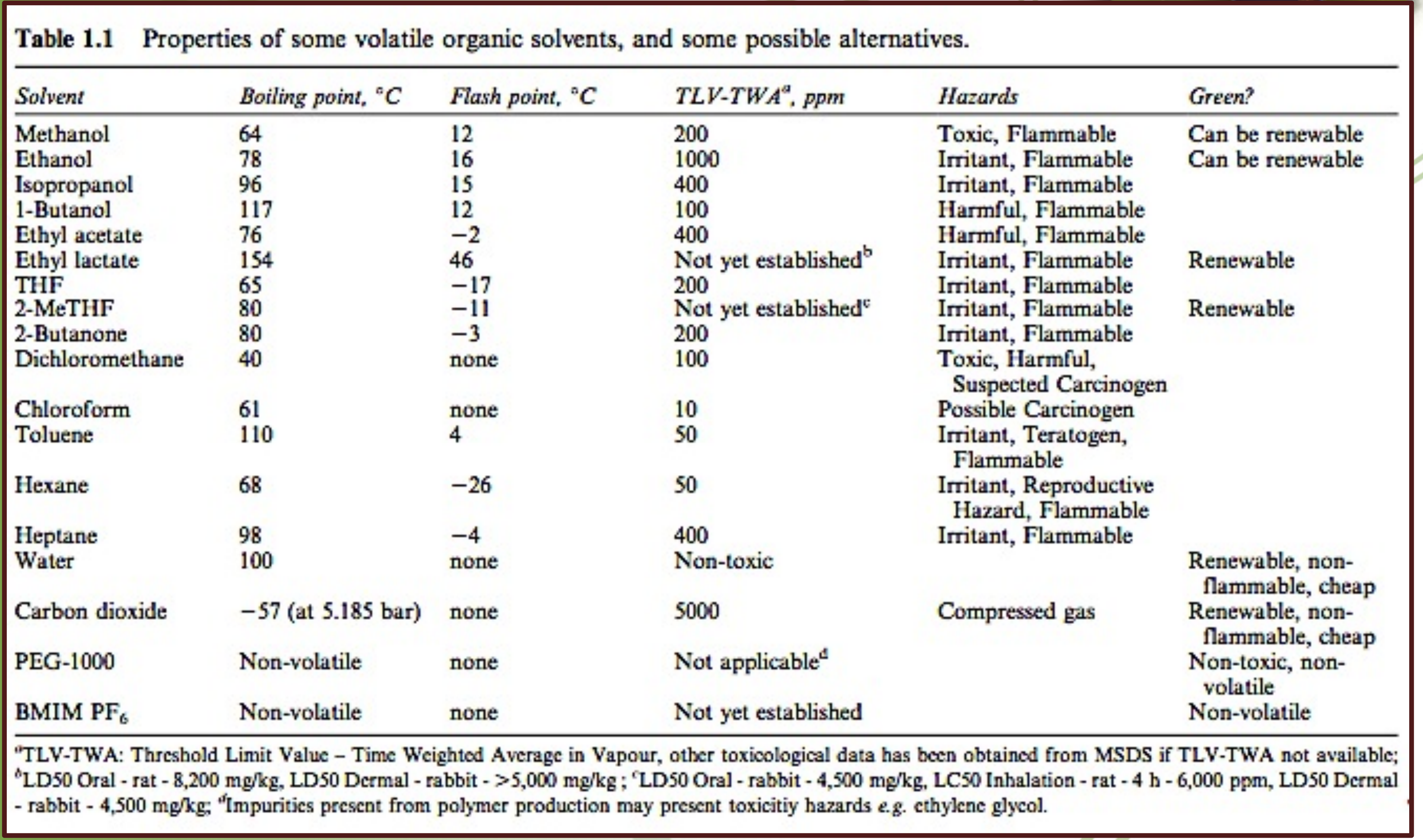


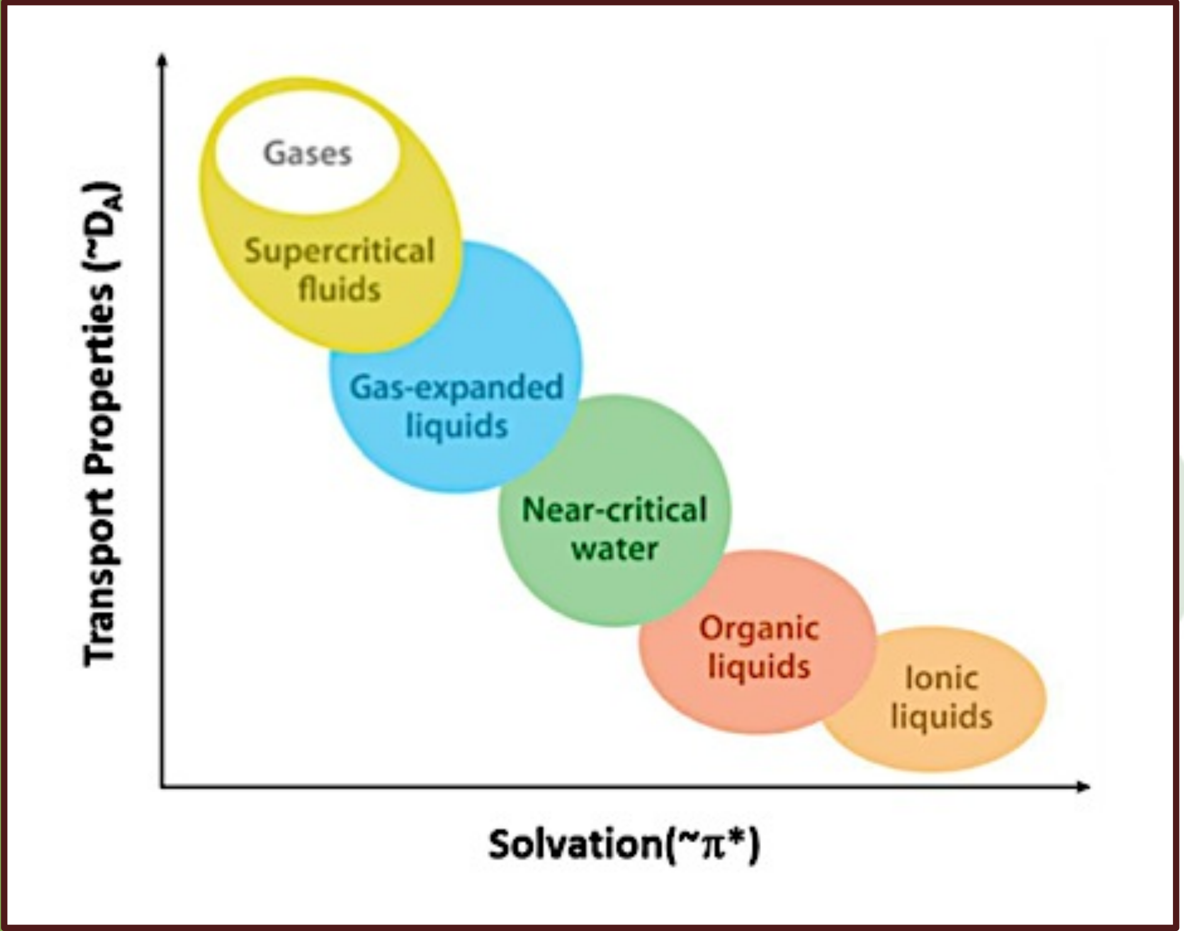
Table 1.1 Properties of some volatile organic solvents, and some possible alternatives.

Solvent	*Boiling point, °C*	*Flash point, °C*	*TLV-TWA[a], ppm*	*Hazards*	*Green?*
Methanol	64	12	200	Toxic, Flammable	Can be renewable
Ethanol	78	16	1000	Irritant, Flammable	Can be renewable
Isopropanol	96	15	400	Irritant, Flammable	
1-Butanol	117	12	100	Harmful, Flammable	
Ethyl acetate	76	−2	400	Harmful, Flammable	
Ethyl lactate	154	46	Not yet established[b]	Irritant, Flammable	Renewable
THF	65	−17	200	Irritant, Flammable	
2-MeTHF	80	−11	Not yet established[c]	Irritant, Flammable	Renewable
2-Butanone	80	−3	200	Irritant, Flammable	
Dichloromethane	40	none	100	Toxic, Harmful, Suspected Carcinogen	
Chloroform	61	none	10	Possible Carcinogen	
Toluene	110	4	50	Irritant, Teratogen, Flammable	
Hexane	68	−26	50	Irritant, Reproductive Hazard, Flammable	
Heptane	98	−4	400	Irritant, Flammable	
Water	100	none	Non-toxic		Renewable, non-flammable, cheap
Carbon dioxide	−57 (at 5.185 bar)	none	5000	Compressed gas	Renewable, non-flammable, cheap
PEG-1000	Non-volatile	none	Not applicable[d]		Non-toxic, non-volatile
BMIM PF_6	Non-volatile	none	Not yet established		Non-volatile

[a] TLV-TWA: Threshold Limit Value – Time Weighted Average in Vapour, other toxicological data has been obtained from MSDS if TLV-TWA not available; [b] LD50 Oral - rat - 8,200 mg/kg, LD50 Dermal - rabbit - >5,000 mg/kg ; [c] LD50 Oral - rabbit - 4,500 mg/kg, LC50 Inhalation - rat - 4 h - 6,000 ppm, LD50 Dermal - rabbit - 4,500 mg/kg; [d] Impurities present from polymer production may present toxicitiy hazards *e.g.* ethylene glycol.

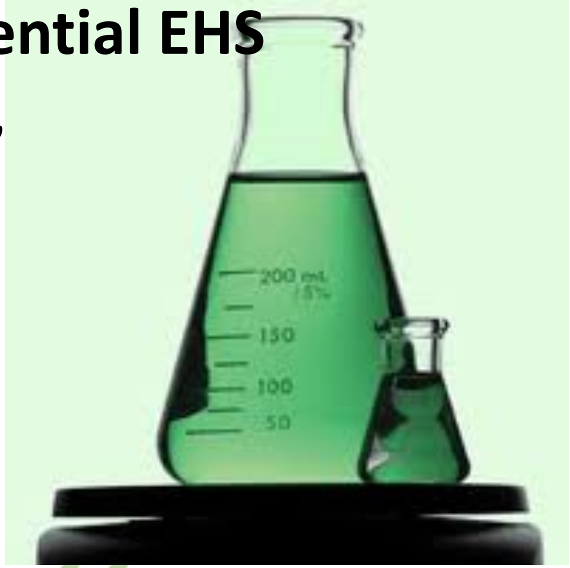
Solvents in Green Chemistry

Compromise of transport ability and solvent power for various types of solvents

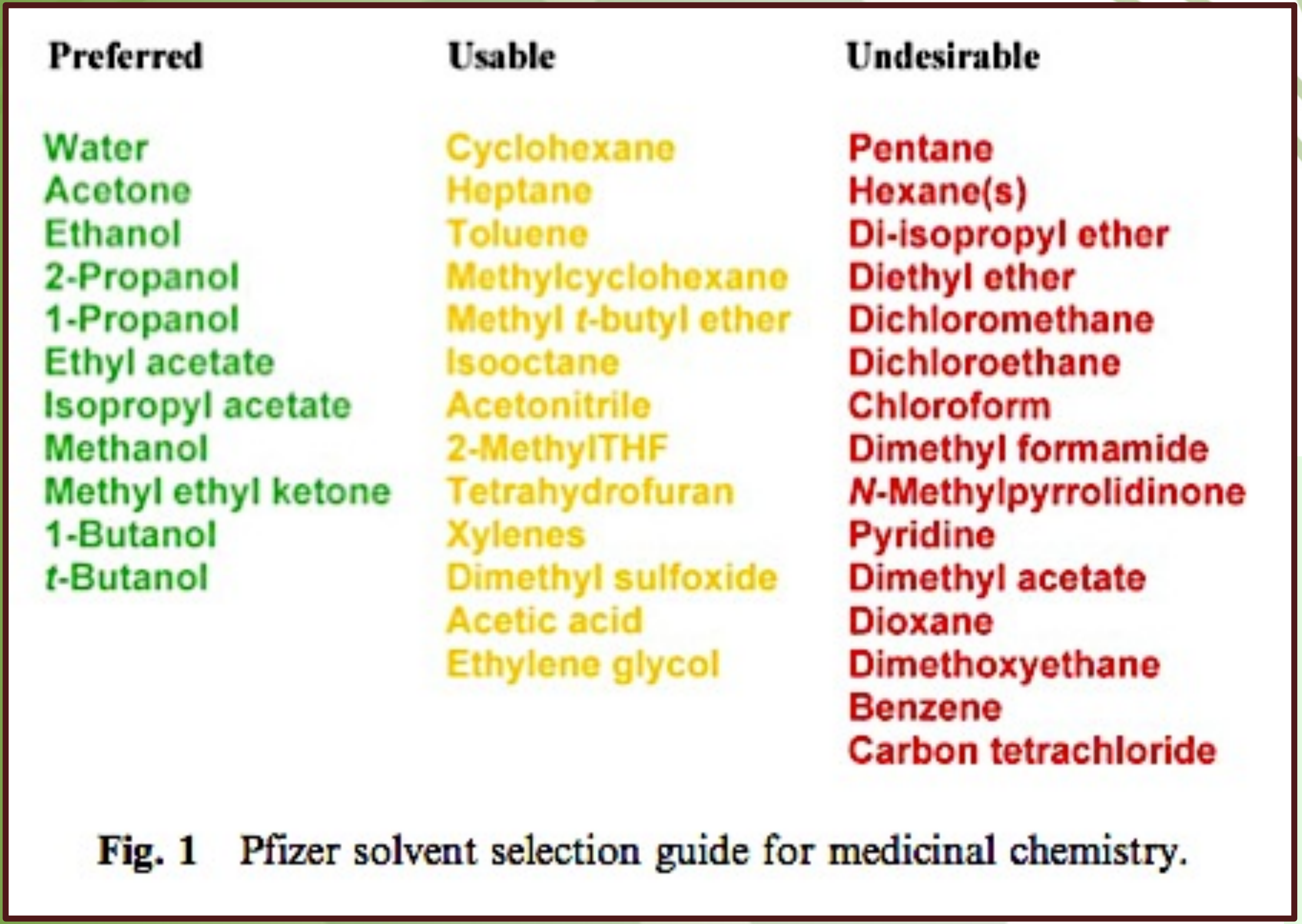


Solvents in Green Chemistry

Worker safety: including carcinogenicity, mutagenicity, reprotoxicity, skin absorption/sensitization, and toxicity;
Process safety: including flammability, potential for high emissions through high vapour pressure, static charge, potential for peroxide formation and odour issues.
Environmental and regulatory considerations: including ecotoxicity and ground water contamination, potential EHS regulatory restrictions, ozone depletion potential, photoreactive potential.
(Pfizer)



Solvents in Green Chemistry



Preferred

- Water
- Acetone
- Ethanol
- 2-Propanol
- 1-Propanol
- Ethyl acetate
- Isopropyl acetate
- Methanol
- Methyl ethyl ketone
- 1-Butanol
- *t*-Butanol

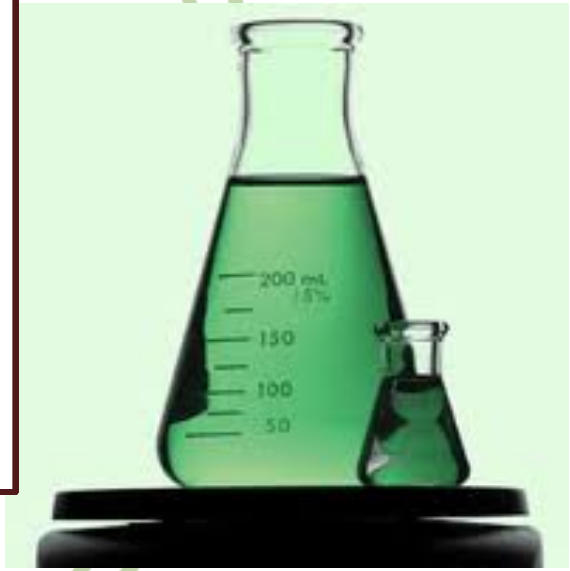
Usable

- Cyclohexane
- Heptane
- Toluene
- Methylcyclohexane
- Methyl *t*-butyl ether
- Isooctane
- Acetonitrile
- 2-MethylTHF
- Tetrahydrofuran
- Xylenes
- Dimethyl sulfoxide
- Acetic acid
- Ethylene glycol

Undesirable

- Pentane
- Hexane(s)
- Di-isopropyl ether
- Diethyl ether
- Dichloromethane
- Dichloroethane
- Chloroform
- Dimethyl formamide
- *N*-Methylpyrrolidinone
- Pyridine
- Dimethyl acetate
- Dioxane
- Dimethoxyethane
- Benzene
- Carbon tetrachloride

Fig. 1 Pfizer solvent selection guide for medicinal chemistry.



Solvents in Green Chemistry

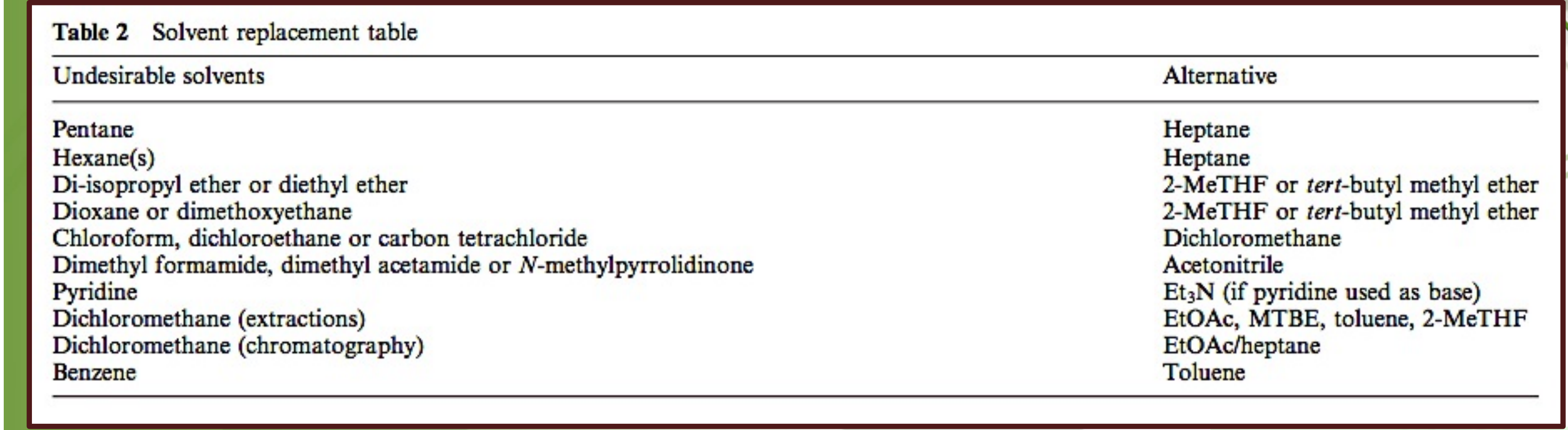
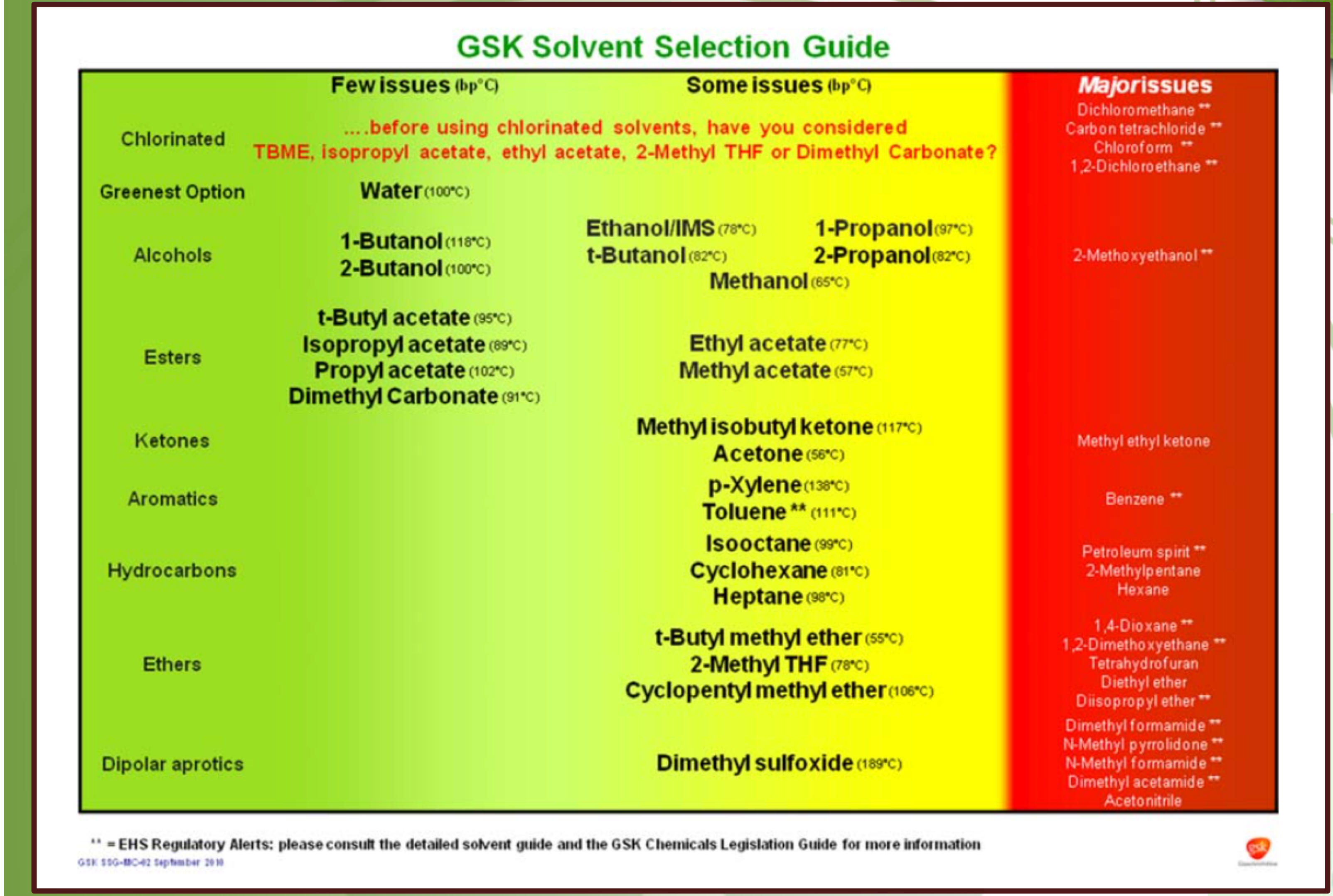


Table 2 Solvent replacement table

Undesirable solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-MeTHF or *tert*-butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or *tert*-butyl methyl ether
Chloroform, dichloroethane or carbon tetrachloride	Dichloromethane
Dimethyl formamide, dimethyl acetamide or *N*-methylpyrrolidinone	Acetonitrile
Pyridine	Et_3N (if pyridine used as base)
Dichloromethane (extractions)	EtOAc, MTBE, toluene, 2-MeTHF
Dichloromethane (chromatography)	EtOAc/heptane
Benzene	Toluene

Solvents in Green Chemistry

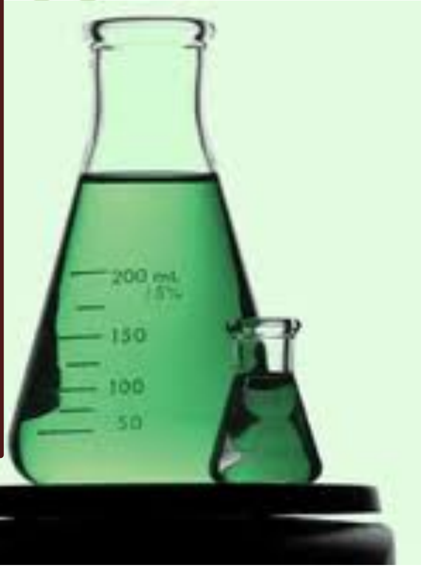


GSK Solvent Selection Guide

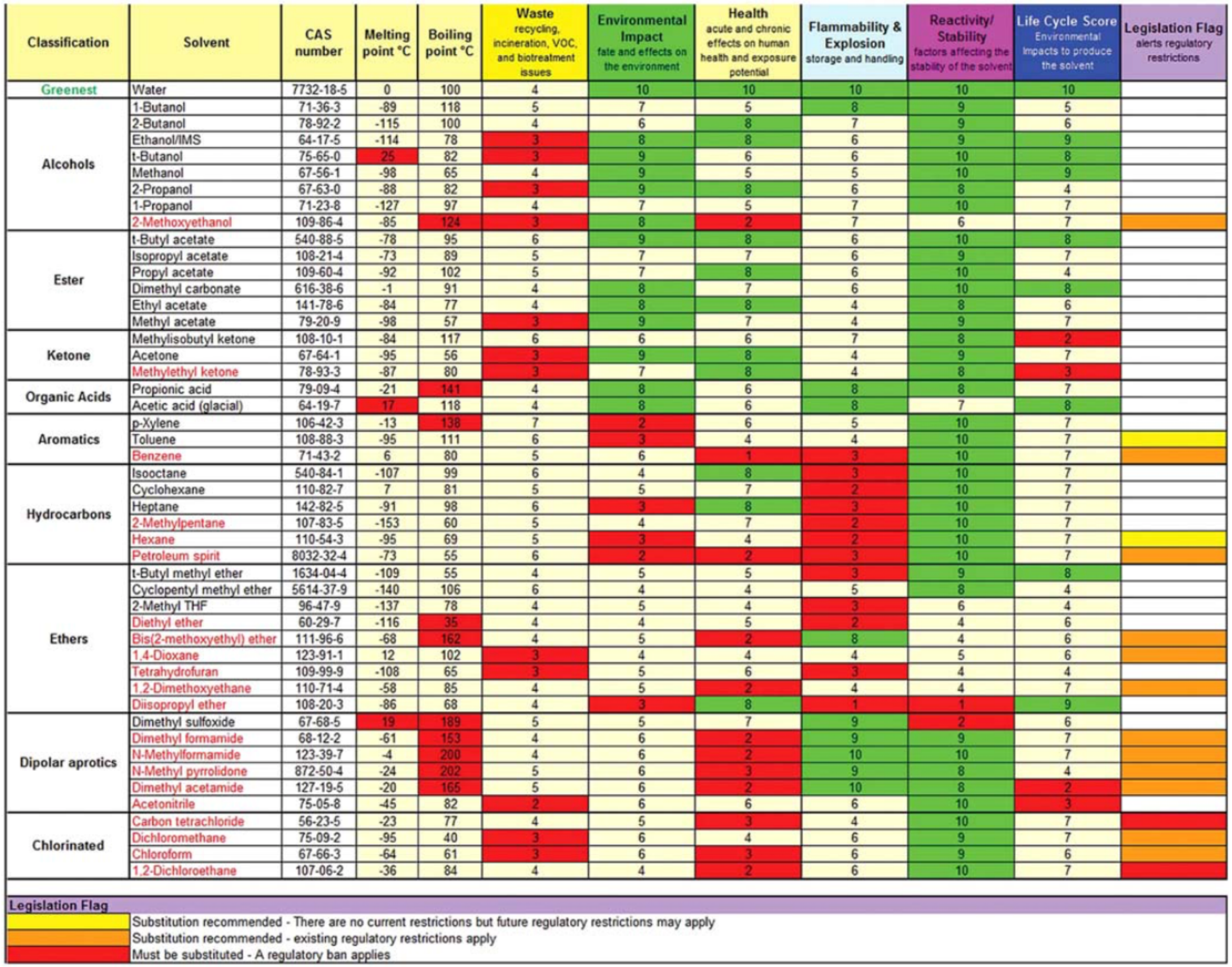
	Few issues (bp°C)	Some issues (bp°C)	*Major* issues
Chlorinated	….before using chlorinated solvents, have you considered TBME, isopropyl acetate, ethyl acetate, 2-Methyl THF or Dimethyl Carbonate?		Dichloromethane ** Carbon tetrachloride ** Chloroform ** 1,2-Dichloroethane **
Greenest Option	Water (100°C)		
Alcohols	1-Butanol (118°C) 2-Butanol (100°C)	Ethanol/IMS (78°C) t-Butanol (82°C) 1-Propanol (97°C) 2-Propanol (82°C) Methanol (65°C)	2-Methoxyethanol **
Esters	t-Butyl acetate (95°C) Isopropyl acetate (89°C) Propyl acetate (102°C) Dimethyl Carbonate (91°C)	Ethyl acetate (77°C) Methyl acetate (57°C)	
Ketones		Methyl isobutyl ketone (117°C) Acetone (56°C)	Methyl ethyl ketone
Aromatics		p-Xylene (138°C) Toluene ** (111°C)	Benzene **
Hydrocarbons		Isooctane (99°C) Cyclohexane (81°C) Heptane (98°C)	Petroleum spirit ** 2-Methylpentane Hexane
Ethers		t-Butyl methyl ether (55°C) 2-Methyl THF (78°C) Cyclopentyl methyl ether (106°C)	1,4-Dioxane ** 1,2-Dimethoxyethane ** Tetrahydrofuran Diethyl ether Diisopropyl ether **
Dipolar aprotics		Dimethyl sulfoxide (189°C)	Dimethyl formamide ** N-Methyl pyrrolidone ** N-Methyl formamide ** Dimethyl acetamide ** Acetonitrile

** = EHS Regulatory Alerts: please consult the detailed solvent guide and the GSK Chemicals Legislation Guide for more information

GSK SSG-MC-02 September 2010

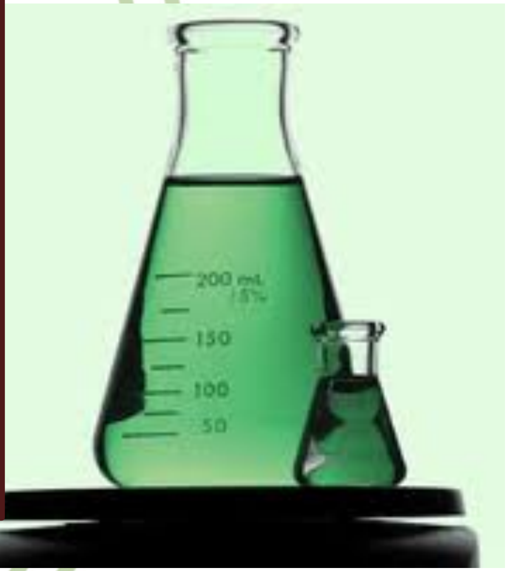


Solvents in Green Chemistry



Classification	Solvent	CAS number	Melting point °C	Boiling point °C	Waste recycling, incineration, VOC, and biotreatment issues	Environmental Impact fate and effects on the environment	Health acute and chronic effects on human health and exposure potential	Flammability & Explosion storage and handling	Reactivity/ Stability factors affecting the stability of the solvent	Life Cycle Score Environmental Impacts to produce the solvent	Legislation Flag alerts regulatory restrictions
Greenest	Water	7732-18-5	0	100	4	10	10	10	10	10	
Alcohols	1-Butanol	71-36-3	-89	118	5	7	5	8	9	5	
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6	
	Ethanol/IMS	64-17-5	-114	78	3	8	8	6	9	9	
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8	
	Methanol	67-56-1	-98	65	4	9	5	5	10	9	
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4	
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7	
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7	🟧
Ester	t-Butyl acetate	540-88-5	-78	95	6	9	8	6	10	8	
	Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
	Propyl acetate	109-60-4	-92	102	5	7	8	6	10	4	
	Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
	Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
	Methyl acetate	79-20-9	-98	57	3	9	7	4	9	7	
Ketone	Methylisobutyl ketone	108-10-1	-84	117	6	6	6	7	8	2	
	Acetone	67-64-1	-95	56	3	9	8	4	9	7	
	Methylethyl ketone	78-93-3	-87	80	3	7	8	4	8	3	
Organic Acids	Propionic acid	79-09-4	-21	141	4	8	6	8	8	7	
	Acetic acid (glacial)	64-19-7	17	118	4	8	6	8	7	8	
Aromatics	p-Xylene	106-42-3	-13	138	7	2	6	5	10	7	
	Toluene	108-88-3	-95	111	6	3	4	4	10	7	🟨
	Benzene	71-43-2	6	80	5	6	1	3	10	7	🟧
Hydrocarbons	Isooctane	540-84-1	-107	99	6	4	8	3	10	7	
	Cyclohexane	110-82-7	7	81	5	5	7	2	10	7	
	Heptane	142-82-5	-91	98	6	3	8	3	10	7	
	2-Methylpentane	107-83-5	-153	60	5	4	7	2	10	7	
	Hexane	110-54-3	-95	69	5	3	4	2	10	7	🟨
	Petroleum spirit	8032-32-4	-73	55	6	2	2	3	10	7	🟧
Ethers	t-Butyl methyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
	Cyclopentyl methyl ether	5614-37-9	-140	106	6	4	4	5	8	4	
	2-Methyl THF	96-47-9	-137	78	4	5	4	3	6	4	
	Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6	
	Bis(2-methoxyethyl) ether	111-96-6	-68	162	4	5	2	8	4	6	🟧
	1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6	🟧
	Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4	
	1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7	🟧
	Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9	
Dipolar aprotics	Dimethyl sulfoxide	67-68-5	19	189	5	5	7	9	2	6	
	Dimethyl formamide	68-12-2	-61	153	4	6	2	9	9	7	🟧
	N-Methylformamide	123-39-7	-4	200	4	6	2	10	10	7	🟧
	N-Methyl pyrrolidone	872-50-4	-24	202	5	6	3	9	8	4	🟧
	Dimethyl acetamide	127-19-5	-20	165	5	6	2	10	8	2	🟧
	Acetonitrile	75-05-8	-45	82	2	6	6	6	10	3	
Chlorinated	Carbon tetrachloride	56-23-5	-23	77	4	5	3	4	10	7	🟥
	Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	🟧
	Chloroform	67-66-3	-64	61	3	6	3	6	9	6	🟧
	1,2-Dichloroethane	107-06-2	-36	84	4	4	2	6	10	7	🟥

Legislation Flag	
🟨	Substitution recommended - There are no current restrictions but future regulatory restrictions may apply
🟧	Substitution recommended - existing regulatory restrictions apply
🟥	Must be substituted - A regulatory ban applies



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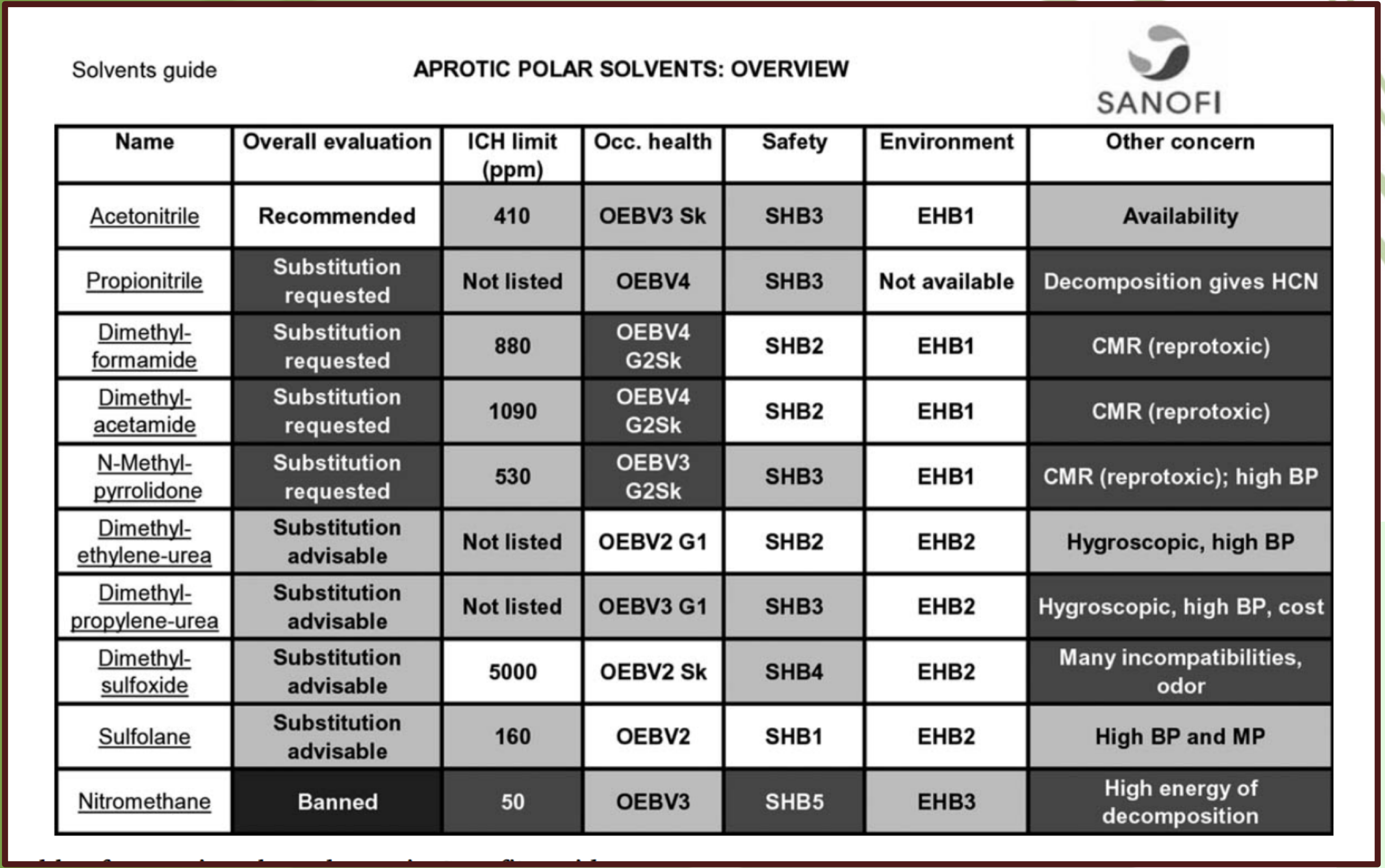
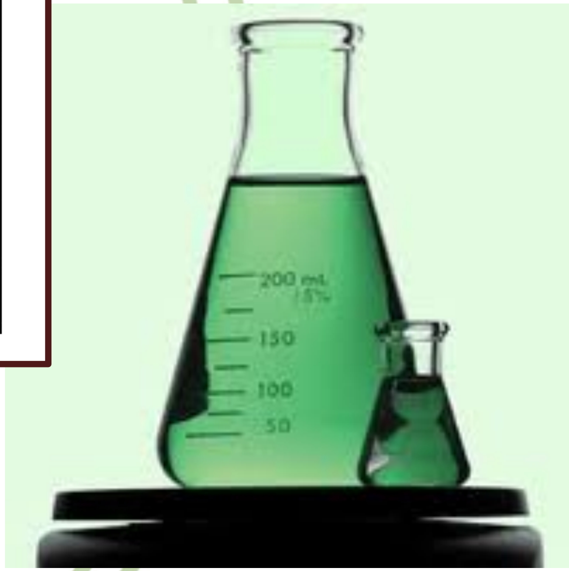


Solvents guide

APROTIC POLAR SOLVENTS: OVERVIEW

SANOFI

Name	Overall evaluation	ICH limit (ppm)	Occ. health	Safety	Environment	Other concern
Acetonitrile	**Recommended**	**410**	**OEBV3 Sk**	**SHB3**	**EHB1**	**Availability**
Propionitrile	**Substitution requested**	**Not listed**	**OEBV4**	**SHB3**	**Not available**	**Decomposition gives HCN**
Dimethyl-formamide	**Substitution requested**	**880**	**OEBV4 G2Sk**	**SHB2**	**EHB1**	**CMR (reprotoxic)**
Dimethyl-acetamide	**Substitution requested**	**1090**	**OEBV4 G2Sk**	**SHB2**	**EHB1**	**CMR (reprotoxic)**
N-Methyl-pyrrolidone	**Substitution requested**	**530**	**OEBV3 G2Sk**	**SHB3**	**EHB1**	**CMR (reprotoxic); high BP**
Dimethyl-ethylene-urea	**Substitution advisable**	**Not listed**	**OEBV2 G1**	**SHB2**	**EHB2**	**Hygroscopic, high BP**
Dimethyl-propylene-urea	**Substitution advisable**	**Not listed**	**OEBV3 G1**	**SHB3**	**EHB2**	**Hygroscopic, high BP, cost**
Dimethyl-sulfoxide	**Substitution advisable**	**5000**	**OEBV2 Sk**	**SHB4**	**EHB2**	**Many incompatibilities, odor**
Sulfolane	**Substitution advisable**	**160**	**OEBV2**	**SHB1**	**EHB2**	**High BP and MP**
Nitromethane	**Banned**	**50**	**OEBV3**	**SHB5**	**EHB3**	**High energy of decomposition**



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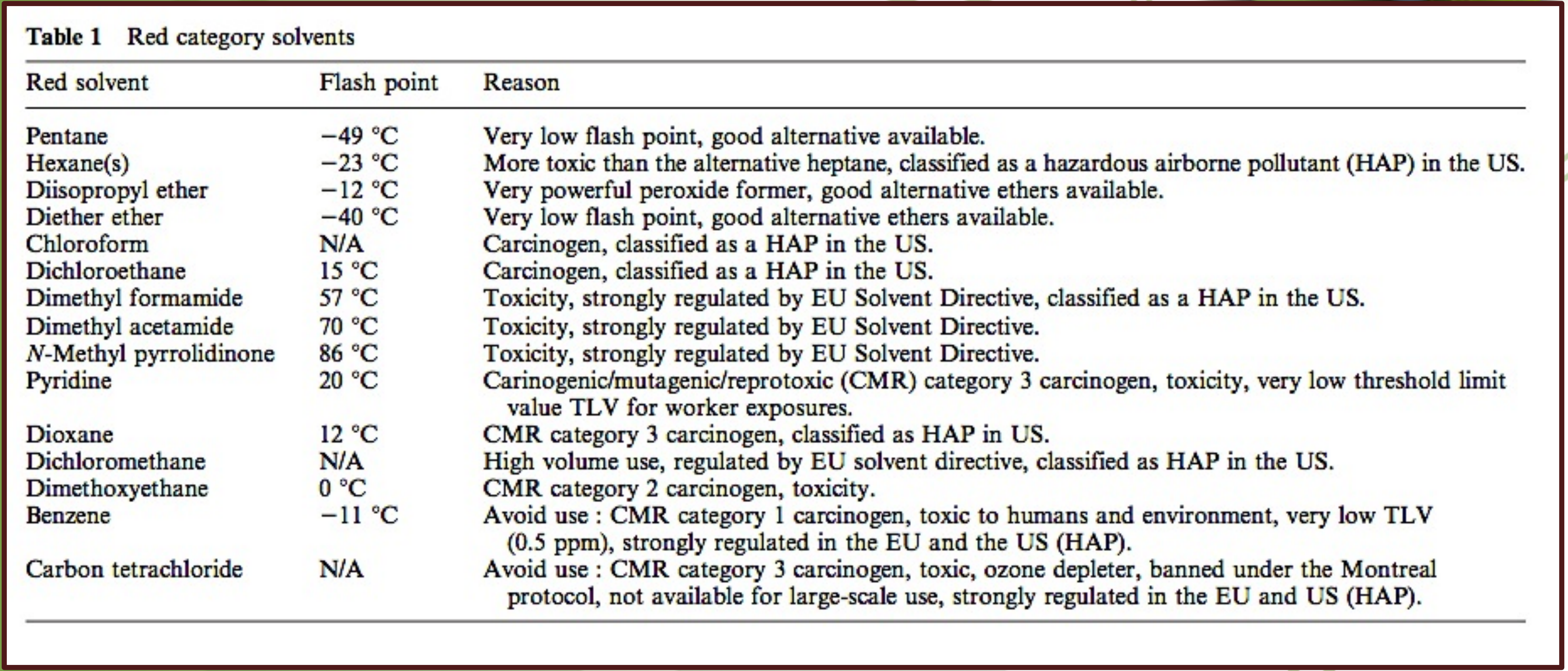


Table 1 Red category solvents

Red solvent	Flash point	Reason
Pentane	−49 °C	Very low flash point, good alternative available.
Hexane(s)	−23 °C	More toxic than the alternative heptane, classified as a hazardous airborne pollutant (HAP) in the US.
Diisopropyl ether	−12 °C	Very powerful peroxide former, good alternative ethers available.
Diether ether	−40 °C	Very low flash point, good alternative ethers available.
Chloroform	N/A	Carcinogen, classified as a HAP in the US.
Dichloroethane	15 °C	Carcinogen, classified as a HAP in the US.
Dimethyl formamide	57 °C	Toxicity, strongly regulated by EU Solvent Directive, classified as a HAP in the US.
Dimethyl acetamide	70 °C	Toxicity, strongly regulated by EU Solvent Directive.
N-Methyl pyrrolidinone	86 °C	Toxicity, strongly regulated by EU Solvent Directive.
Pyridine	20 °C	Carinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, very low threshold limit value TLV for worker exposures.
Dioxane	12 °C	CMR category 3 carcinogen, classified as HAP in US.
Dichloromethane	N/A	High volume use, regulated by EU solvent directive, classified as HAP in the US.
Dimethoxyethane	0 °C	CMR category 2 carcinogen, toxicity.
Benzene	−11 °C	Avoid use : CMR category 1 carcinogen, toxic to humans and environment, very low TLV (0.5 ppm), strongly regulated in the EU and the US (HAP).
Carbon tetrachloride	N/A	Avoid use : CMR category 3 carcinogen, toxic, ozone depleter, banned under the Montreal protocol, not available for large-scale use, strongly regulated in the EU and US (HAP).

The flash point of a volatile material is the lowest temperature at which it can vaporize to form an ignitable mixture in air. Measuring a flash point requires an ignition source.
HAP: Hazardous Air Pollutants
The threshold limit value (TLV) of a chemical substance is a level to which it is believed a worker can be exposed day after day for a working lifetime without adverse health effects.

Solvents in Green Chemistry

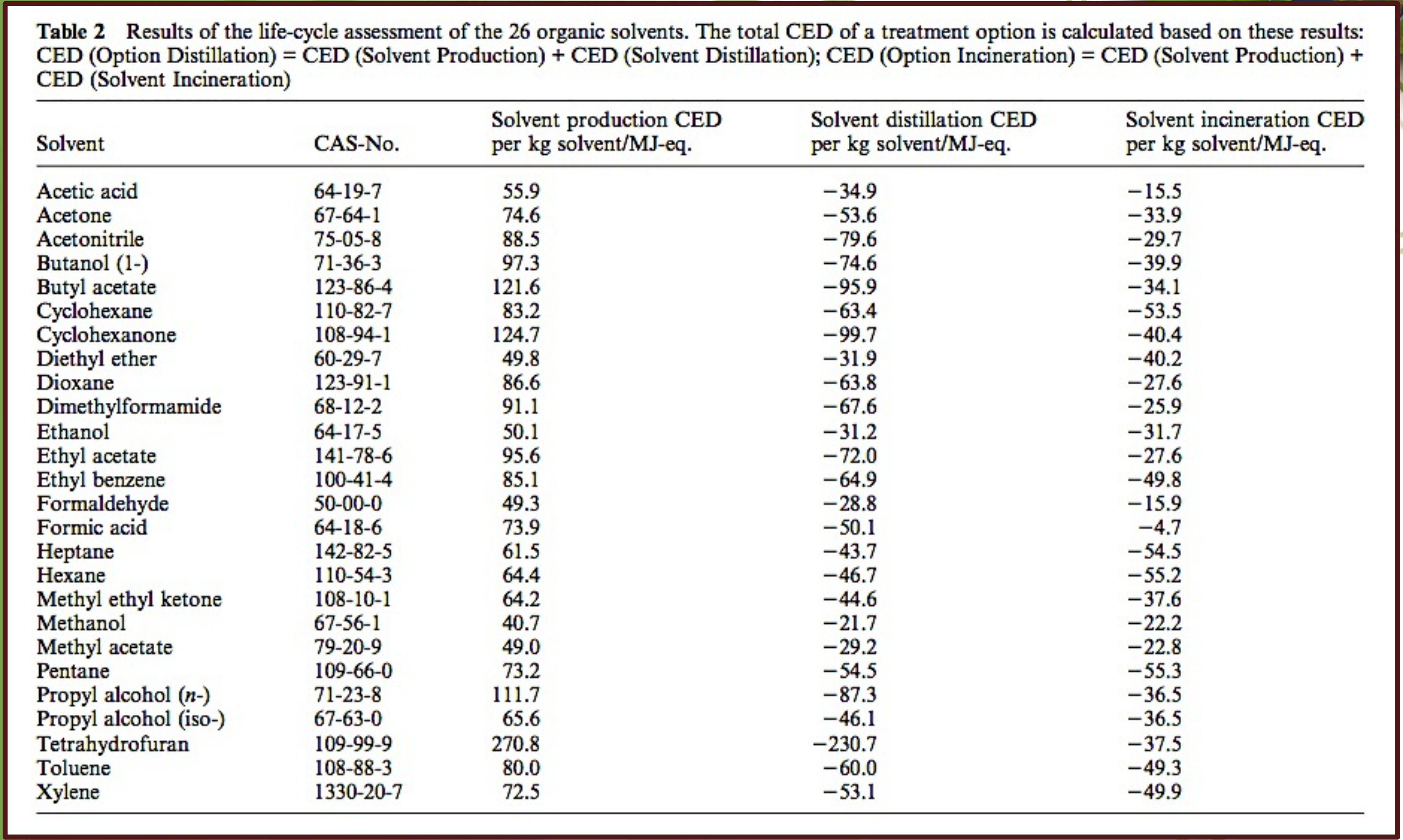
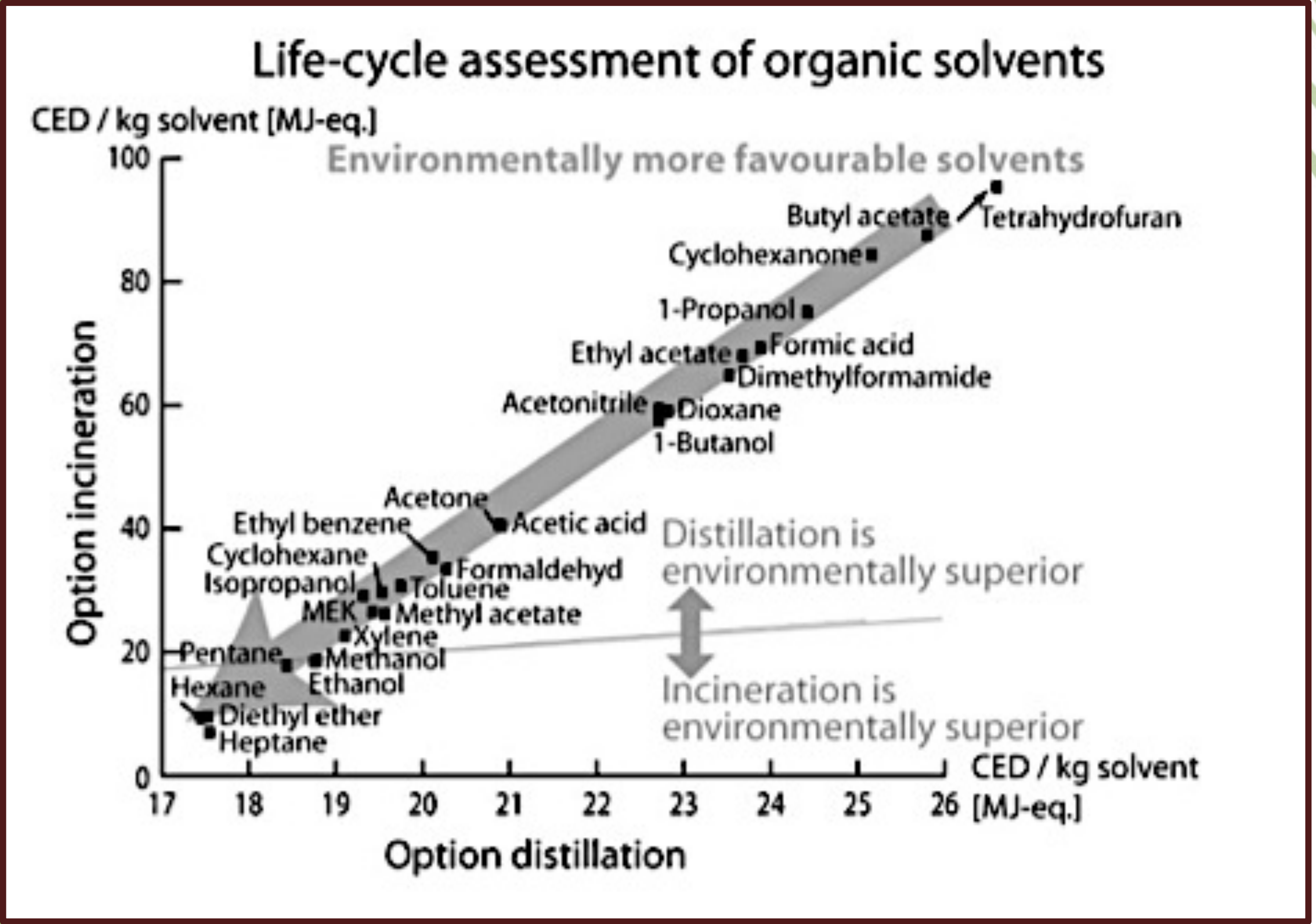


Table 2 Results of the life-cycle assessment of the 26 organic solvents. The total CED of a treatment option is calculated based on these results: CED (Option Distillation) = CED (Solvent Production) + CED (Solvent Distillation); CED (Option Incineration) = CED (Solvent Production) + CED (Solvent Incineration)

Solvent	CAS-No.	Solvent production CED per kg solvent/MJ-eq.	Solvent distillation CED per kg solvent/MJ-eq.	Solvent incineration CED per kg solvent/MJ-eq.
Acetic acid	64-19-7	55.9	−34.9	−15.5
Acetone	67-64-1	74.6	−53.6	−33.9
Acetonitrile	75-05-8	88.5	−79.6	−29.7
Butanol (1-)	71-36-3	97.3	−74.6	−39.9
Butyl acetate	123-86-4	121.6	−95.9	−34.1
Cyclohexane	110-82-7	83.2	−63.4	−53.5
Cyclohexanone	108-94-1	124.7	−99.7	−40.4
Diethyl ether	60-29-7	49.8	−31.9	−40.2
Dioxane	123-91-1	86.6	−63.8	−27.6
Dimethylformamide	68-12-2	91.1	−67.6	−25.9
Ethanol	64-17-5	50.1	−31.2	−31.7
Ethyl acetate	141-78-6	95.6	−72.0	−27.6
Ethyl benzene	100-41-4	85.1	−64.9	−49.8
Formaldehyde	50-00-0	49.3	−28.8	−15.9
Formic acid	64-18-6	73.9	−50.1	−4.7
Heptane	142-82-5	61.5	−43.7	−54.5
Hexane	110-54-3	64.4	−46.7	−55.2
Methyl ethyl ketone	108-10-1	64.2	−44.6	−37.6
Methanol	67-56-1	40.7	−21.7	−22.2
Methyl acetate	79-20-9	49.0	−29.2	−22.8
Pentane	109-66-0	73.2	−54.5	−55.3
Propyl alcohol (*n*-)	71-23-8	111.7	−87.3	−36.5
Propyl alcohol (iso-)	67-63-0	65.6	−46.1	−36.5
Tetrahydrofuran	109-99-9	270.8	−230.7	−37.5
Toluene	108-88-3	80.0	−60.0	−49.3
Xylene	1330-20-7	72.5	−53.1	−49.9

CED: cumulative energy demand

Solvents in Green Chemistry



Solvents in Green Chemistry

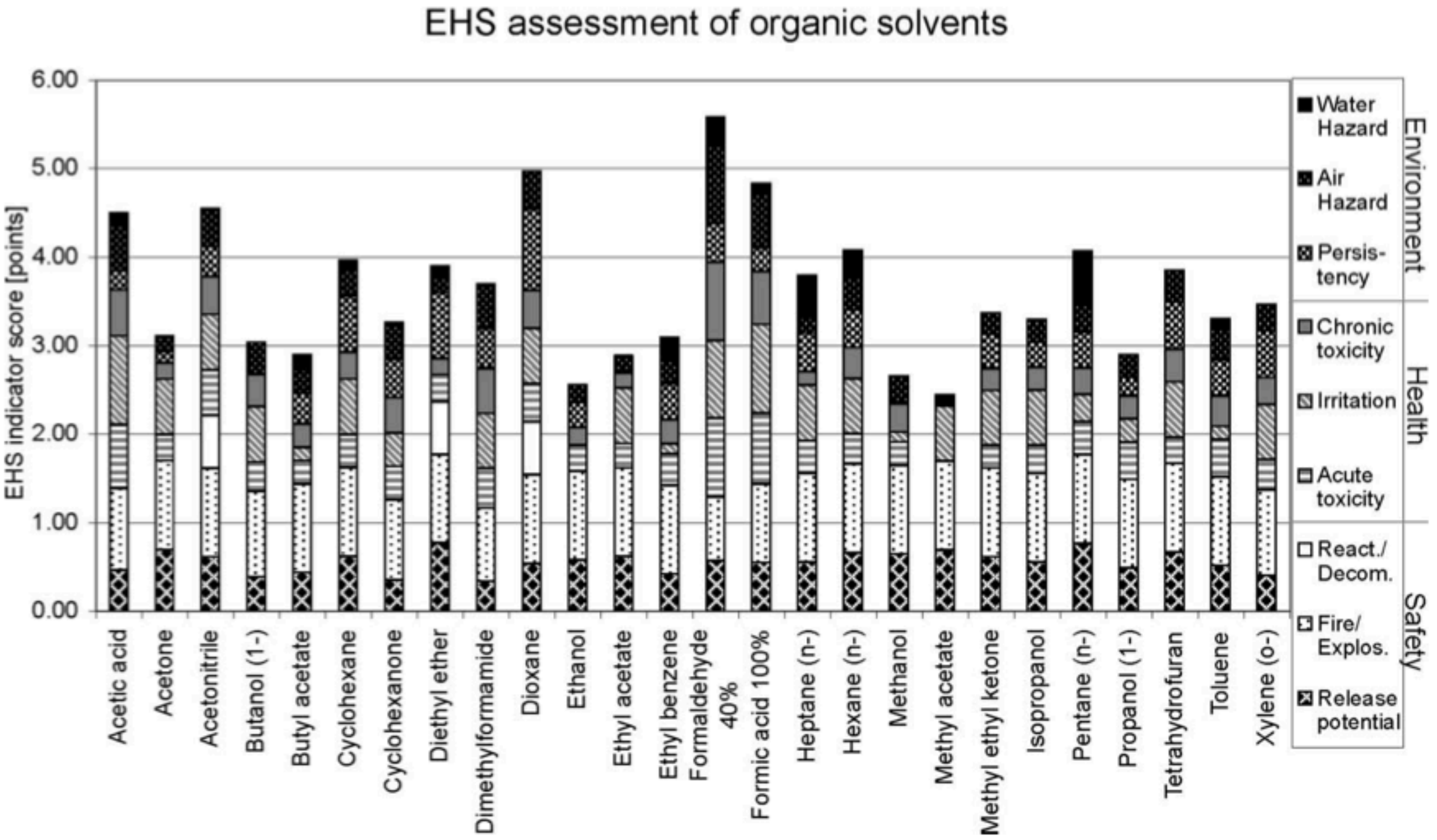
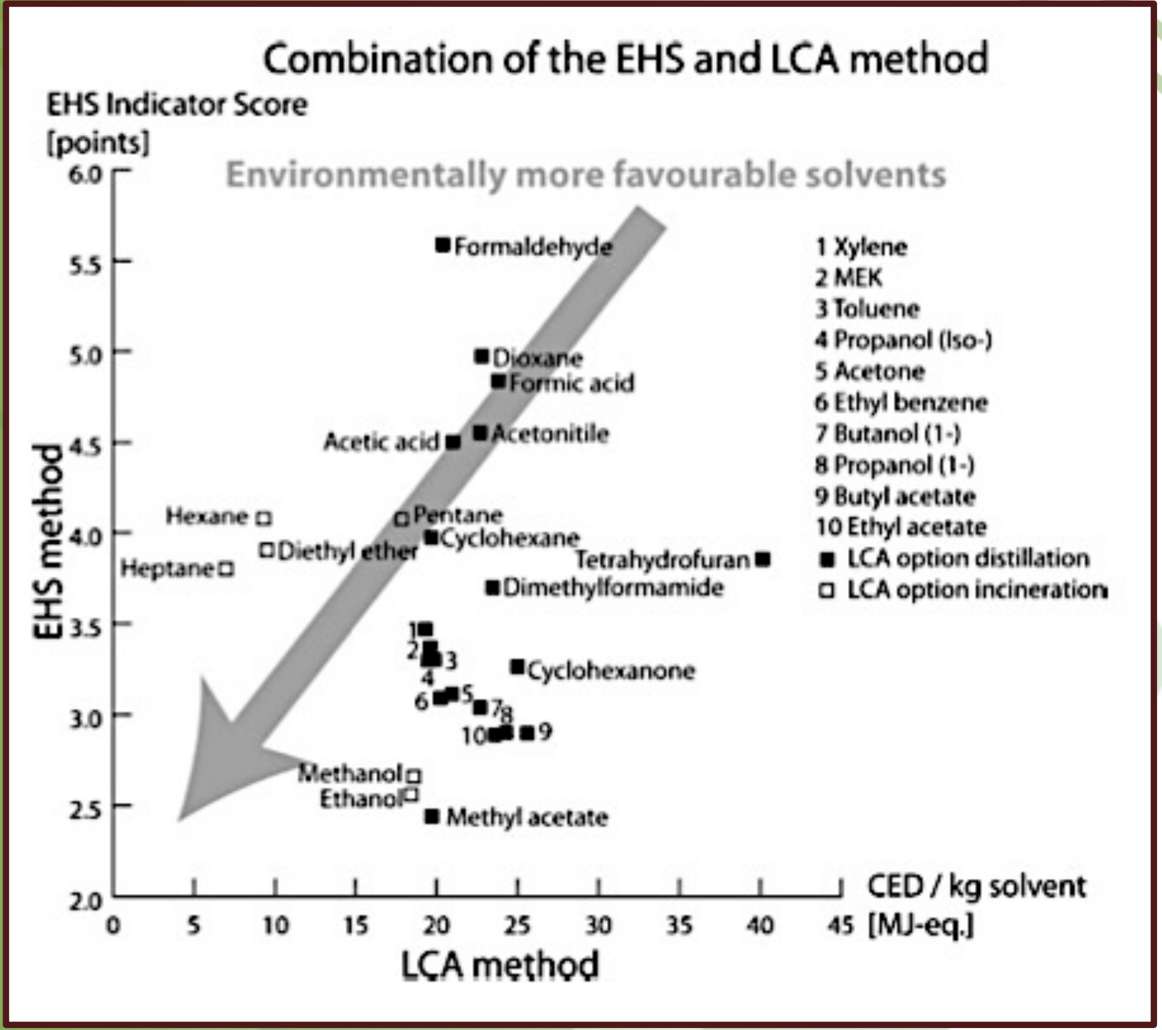
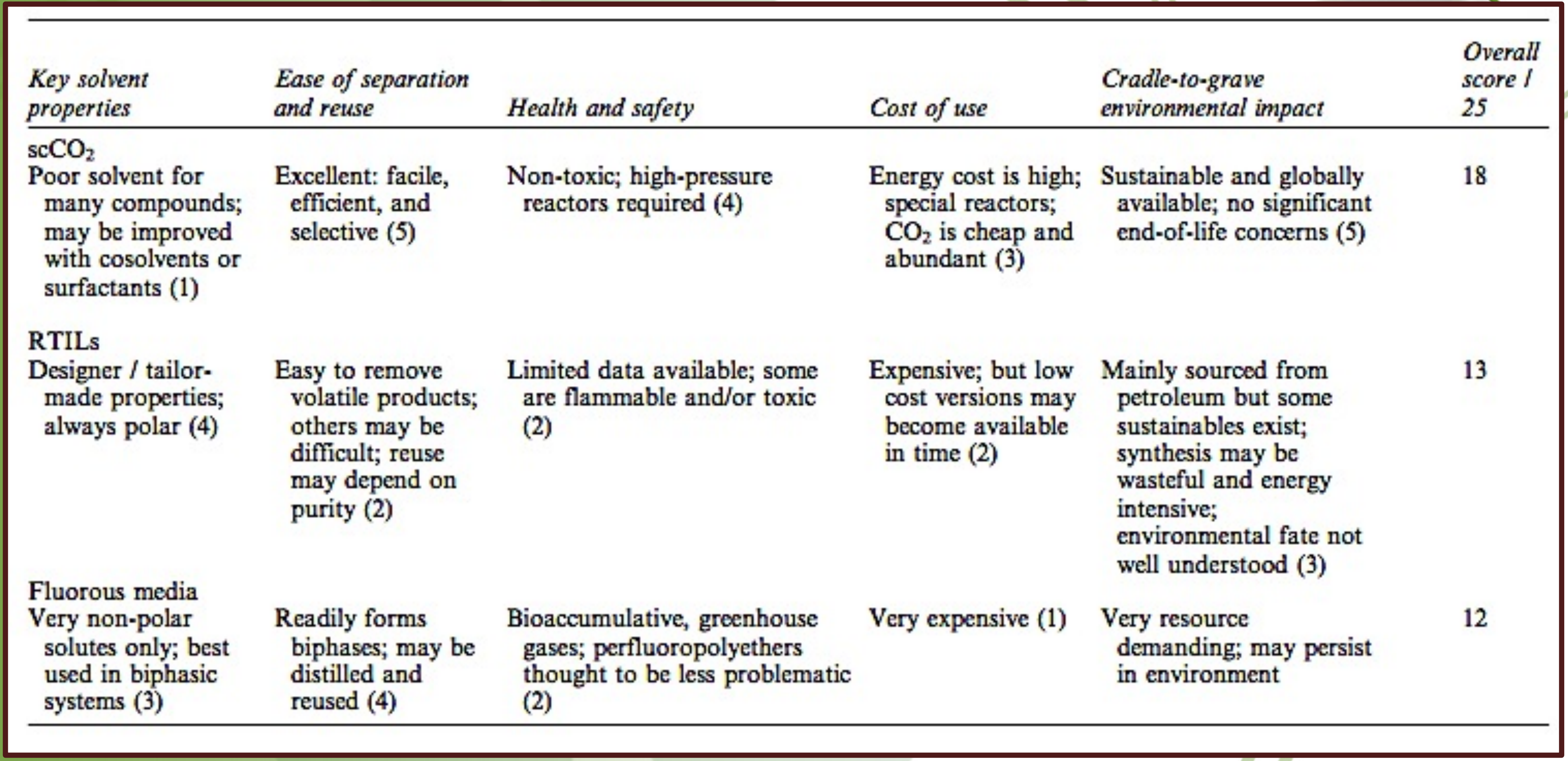


Fig. 2 Results of the EHS method for the 26 pure organic solvents (step (1) in the framework for the assessment of green solvents). The EHS result score is composed of environmental indicators (water and air hazard, persistency), as well as indicators for health (chronic and acute toxicity and irritation) and safety (reaction/decomposition, fire/explosion, release potential) hazards. The results were calculated using the EHS-Tool.[14]

Solvents in Green Chemistry



Solvents in Green Chemistry



Key solvent properties	*Ease of separation and reuse*	*Health and safety*	*Cost of use*	*Cradle-to-grave environmental impact*	*Overall score / 25*
$scCO_2$ Poor solvent for many compounds; may be improved with cosolvents or surfactants (1)	Excellent: facile, efficient, and selective (5)	Non-toxic; high-pressure reactors required (4)	Energy cost is high; special reactors; CO_2 is cheap and abundant (3)	Sustainable and globally available; no significant end-of-life concerns (5)	18
RTILs Designer / tailor-made properties; always polar (4)	Easy to remove volatile products; others may be difficult; reuse may depend on purity (2)	Limited data available; some are flammable and/or toxic (2)	Expensive; but low cost versions may become available in time (2)	Mainly sourced from petroleum but some sustainables exist; synthesis may be wasteful and energy intensive; environmental fate not well understood (3)	13
Fluorous media Very non-polar solutes only; best used in biphasic systems (3)	Readily forms biphases; may be distilled and reused (4)	Bioaccumulative, greenhouse gases; perfluoropolyethers thought to be less problematic (2)	Very expensive (1)	Very resource demanding; may persist in environment	12

Solvents in Green Chemistry

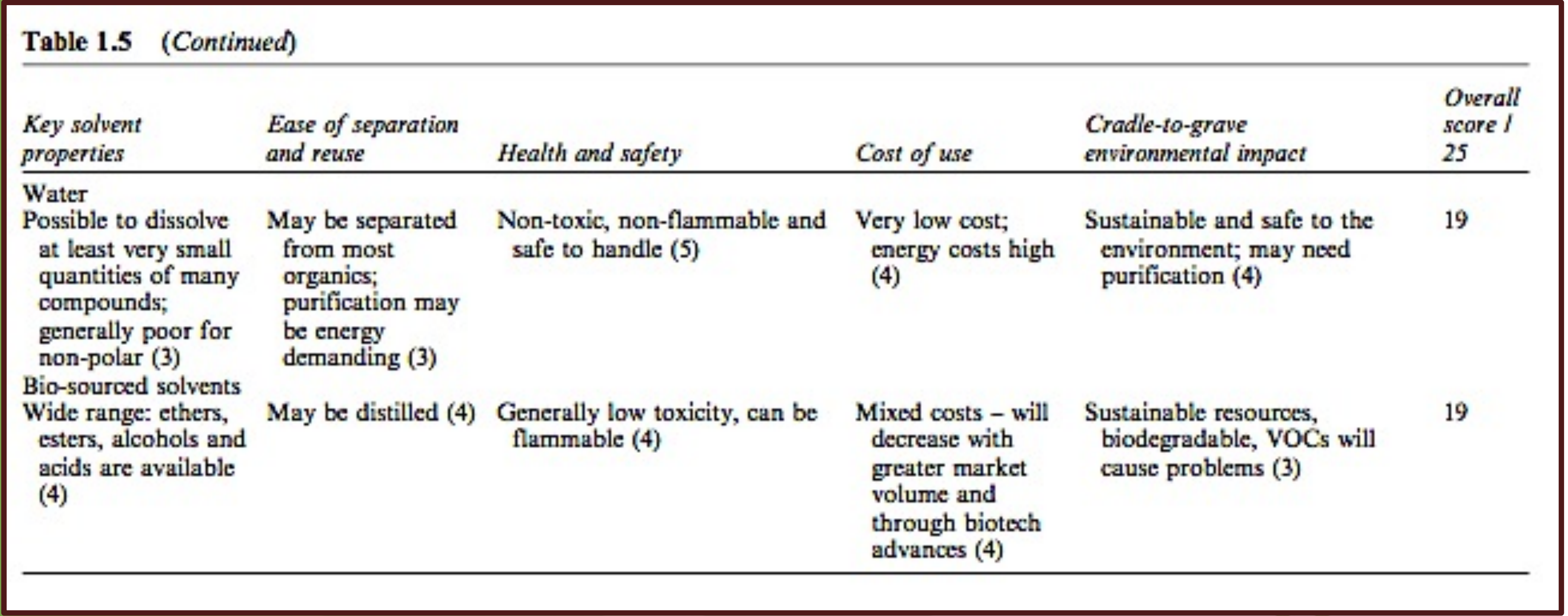
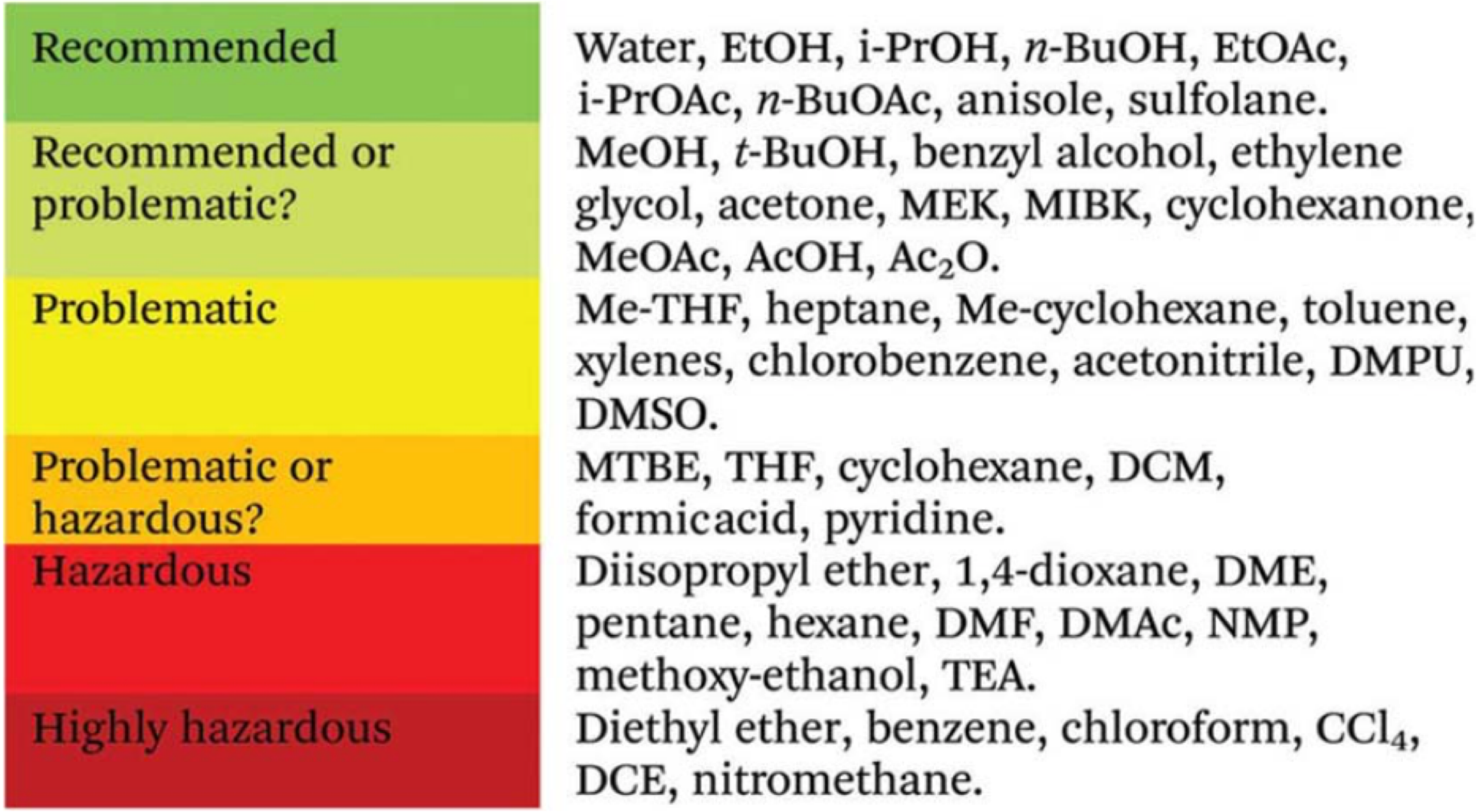


Table 1.5 (*Continued*)

Key solvent properties	*Ease of separation and reuse*	*Health and safety*	*Cost of use*	*Cradle-to-grave environmental impact*	*Overall score / 25*
Water					
Possible to dissolve at least very small quantities of many compounds; generally poor for non-polar (3)	May be separated from most organics; purification may be energy demanding (3)	Non-toxic, non-flammable and safe to handle (5)	Very low cost; energy costs high (4)	Sustainable and safe to the environment; may need purification (4)	19
Bio-sourced solvents					
Wide range: ethers, esters, alcohols and acids are available (4)	May be distilled (4)	Generally low toxicity, can be flammable (4)	Mixed costs – will decrease with greater market volume and through biotech advances (4)	Sustainable resources, biodegradable, VOCs will cause problems (3)	19

Solvents in Green Chemistry



Recommended	Water, EtOH, i-PrOH, *n*-BuOH, EtOAc, i-PrOAc, *n*-BuOAc, anisole, sulfolane.
Recommended or problematic?	MeOH, *t*-BuOH, benzyl alcohol, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, MeOAc, AcOH, Ac_2O.
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, DMPU, DMSO.
Problematic or hazardous?	MTBE, THF, cyclohexane, DCM, formicacid, pyridine.
Hazardous	Diisopropyl ether, 1,4-dioxane, DME, pentane, hexane, DMF, DMAc, NMP, methoxy-ethanol, TEA.
Highly hazardous	Diethyl ether, benzene, chloroform, CCl_4, DCE, nitromethane.

Solvents in Green Chemistry

Solvent Polarity

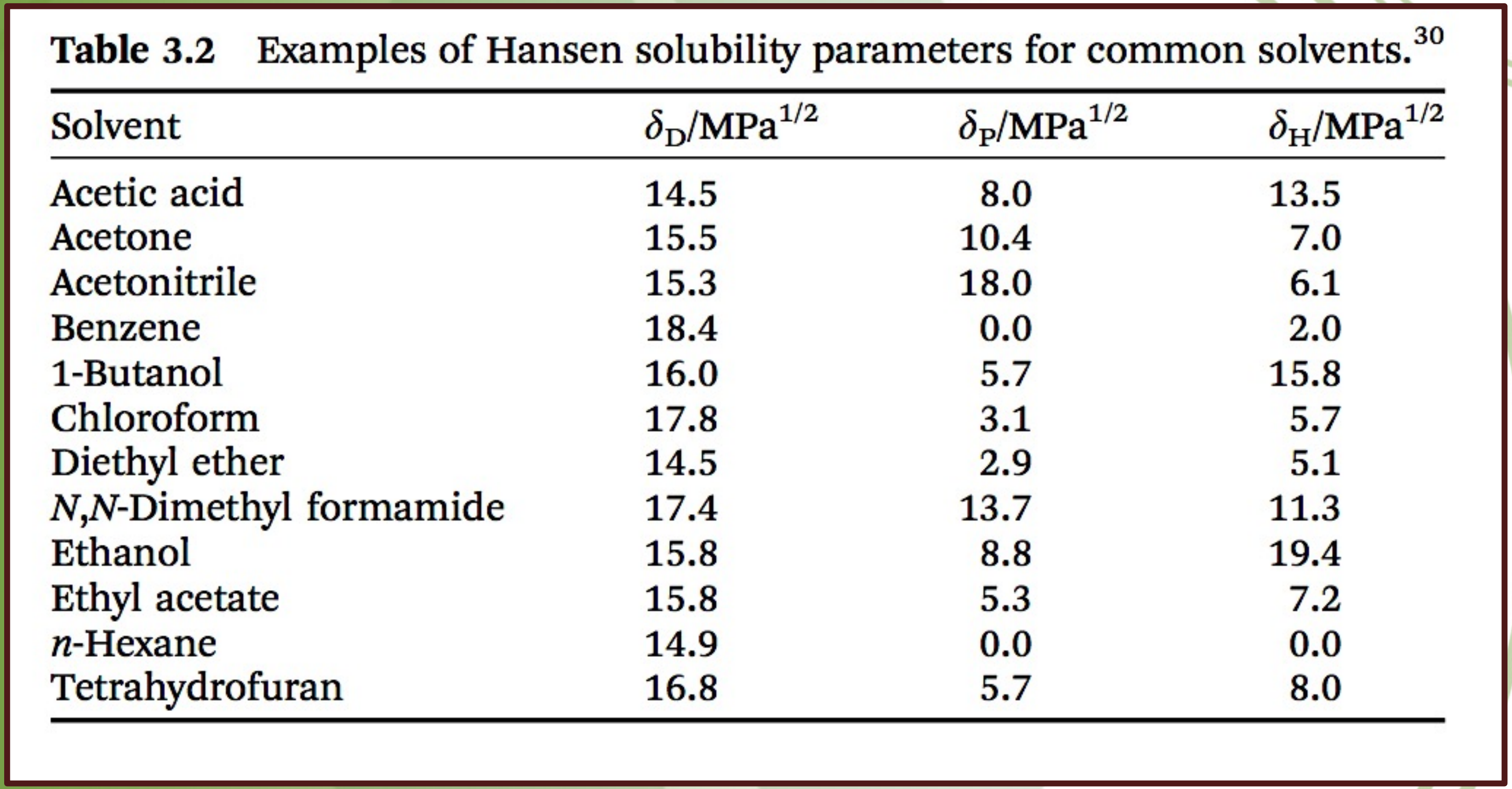


Table 3.2 Examples of Hansen solubility parameters for common solvents.[30]

Solvent	δ_D/MPa$^{1/2}$	δ_P/MPa$^{1/2}$	δ_H/MPa$^{1/2}$
Acetic acid	14.5	8.0	13.5
Acetone	15.5	10.4	7.0
Acetonitrile	15.3	18.0	6.1
Benzene	18.4	0.0	2.0
1-Butanol	16.0	5.7	15.8
Chloroform	17.8	3.1	5.7
Diethyl ether	14.5	2.9	5.1
N,*N*-Dimethyl formamide	17.4	13.7	11.3
Ethanol	15.8	8.8	19.4
Ethyl acetate	15.8	5.3	7.2
n-Hexane	14.9	0.0	0.0
Tetrahydrofuran	16.8	5.7	8.0

SOLVENT-FREE CHEMISTRY

INTRODUCTION

Green Chemistry 06.01

Introduction

The greenest solvent, in terms of reducing waste, is no solvent

Introduction

A dry solid phase reaction is solvent-free, also a reaction where there is a liquid present, but it is not acting as a solvent (i.e., nothing is dissolved in it) is also solvent-free

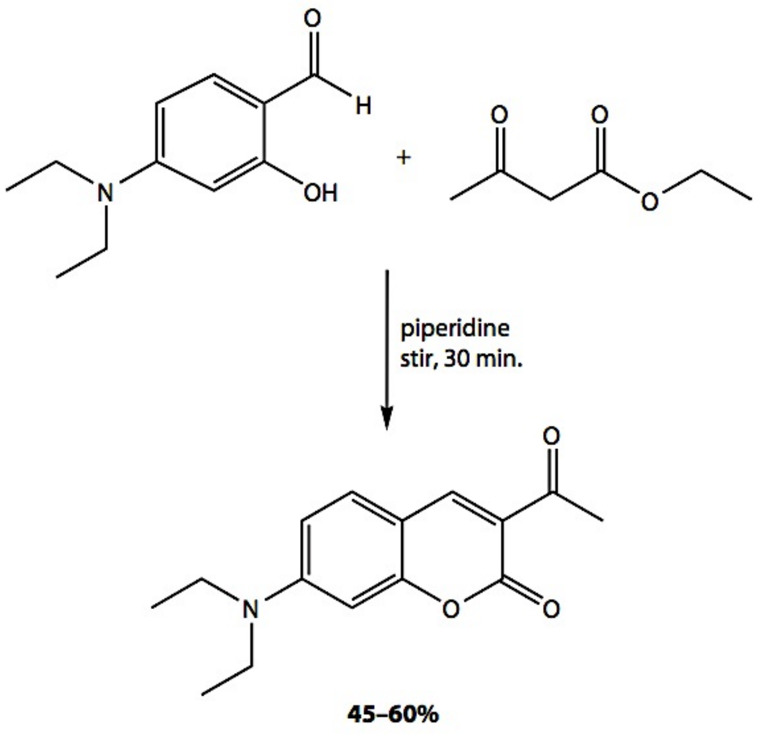
Welton 2006

Introduction

A dry solid phase reaction is solvent-free, also a reaction where there is a liquid present, but it is not acting as a solvent (i.e., nothing is dissolved in it) is also solvent-free
Welton 2006

Solvent-free?

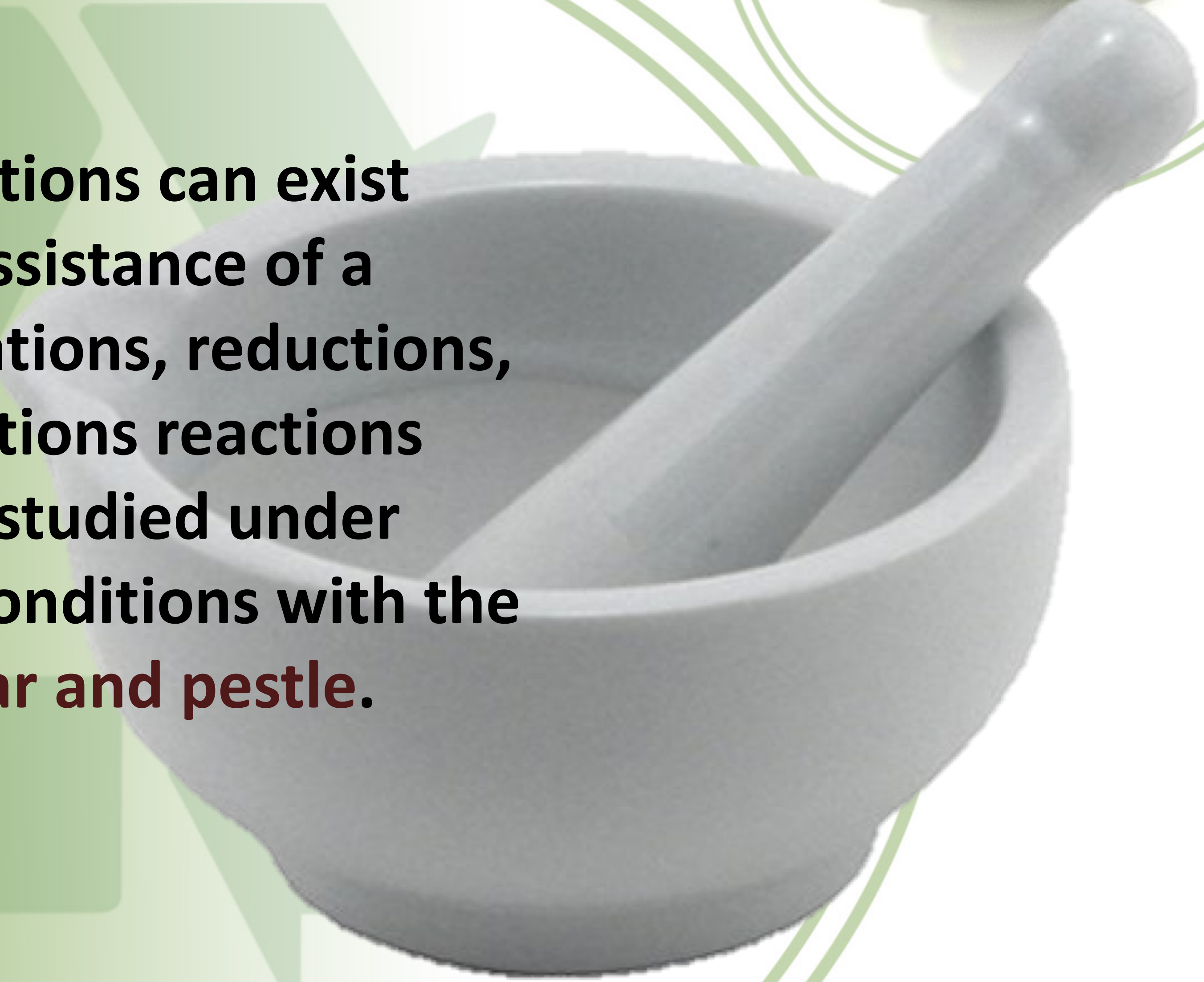
β-ketoester (0.53 mL, 4.15 mmol) is present in excess of the salicylaldehyde derivative (0.4 g, 2.07 mmol). As ethyl acetoacetate is a liquid at room temperature, it is clearly participating as both reagent and solvent.



Solvent-free?

In many solvent-free approaches, VOCs are used to extract and purify the product, and therefore the reaction may be solvent free but often the process as a whole does use solvents.

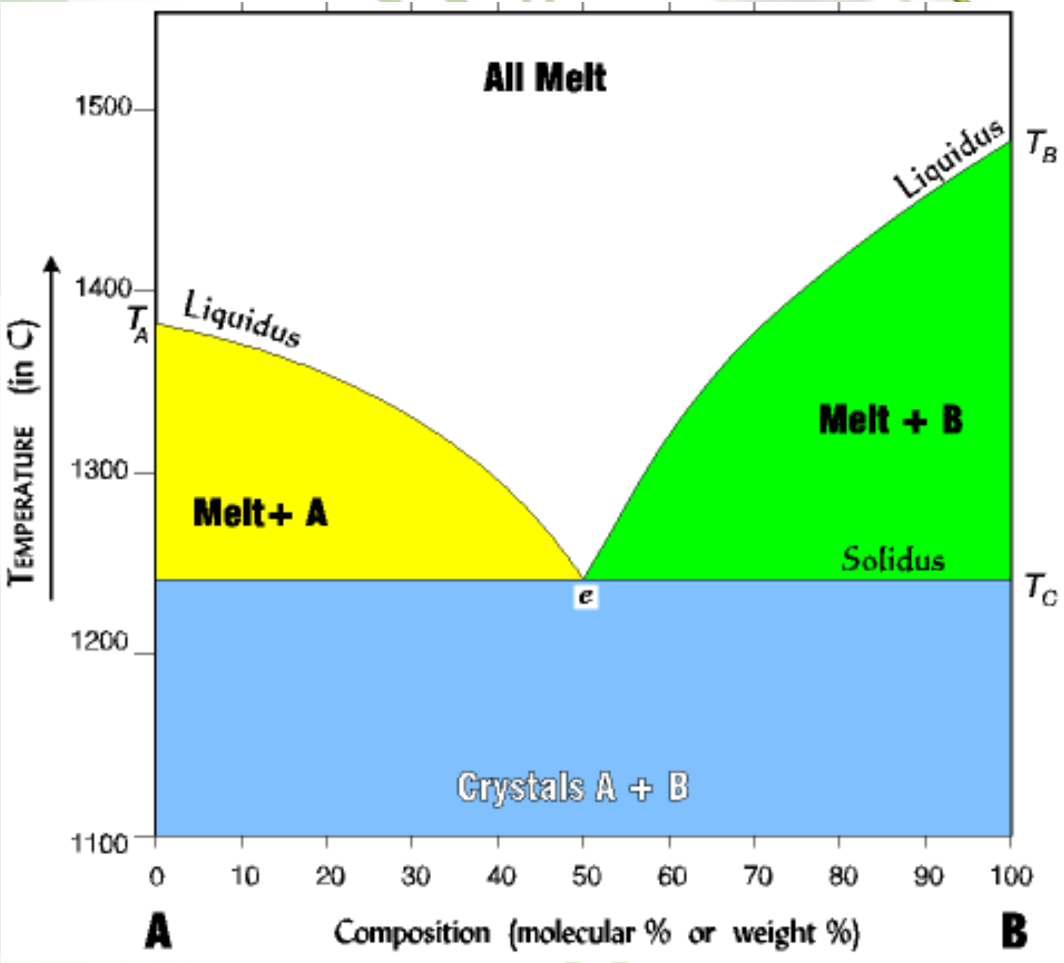
Mortar and Pestle



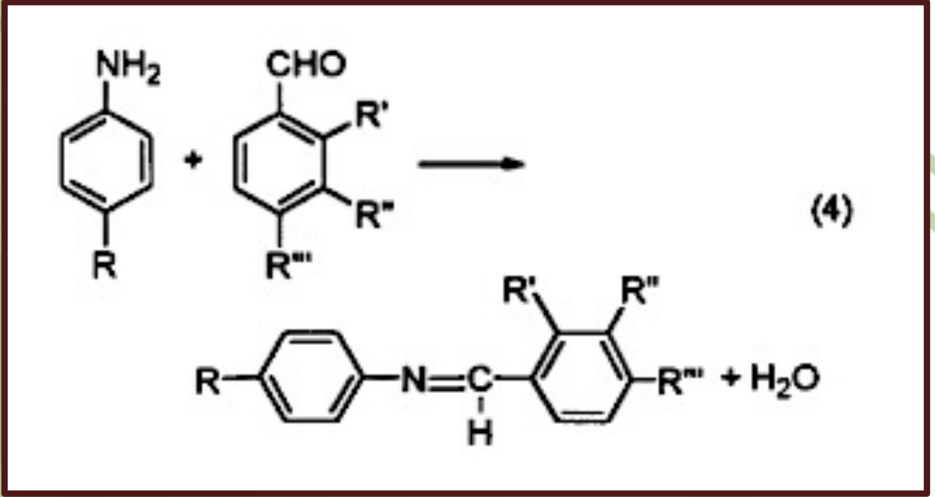
Chemical reactions can exist without the assistance of a solvent. Oxidations, reductions, and condensations reactions have all been studied under solvent-free conditions with the use of a mortar and pestle.

Mortar and Pestle

Only reagents that form a eutectic melt when combined gave the desired product.



Mortar and Pestle



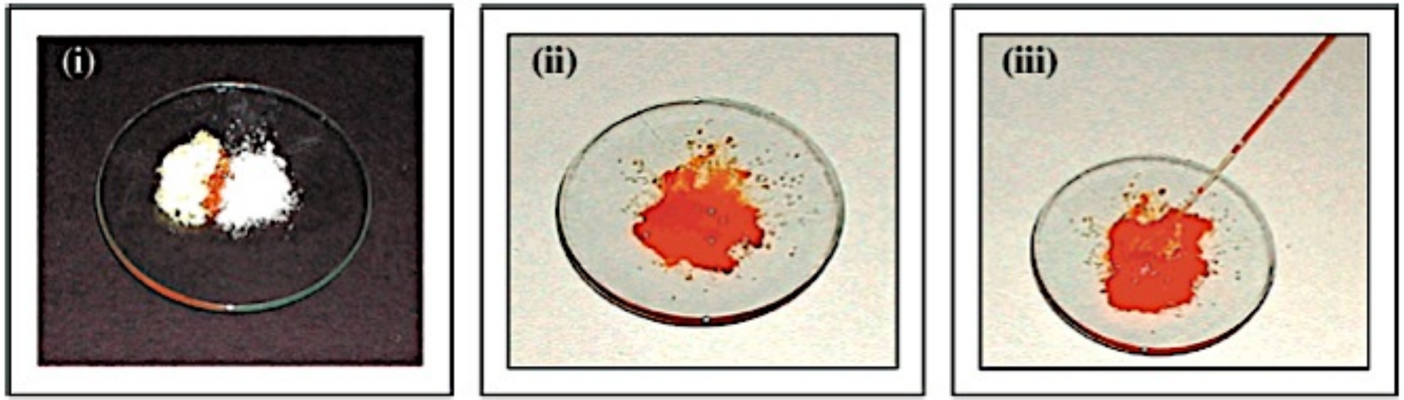
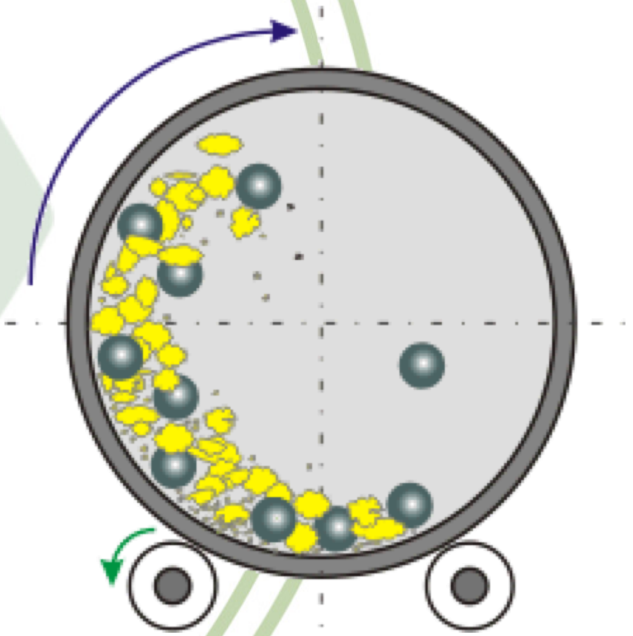


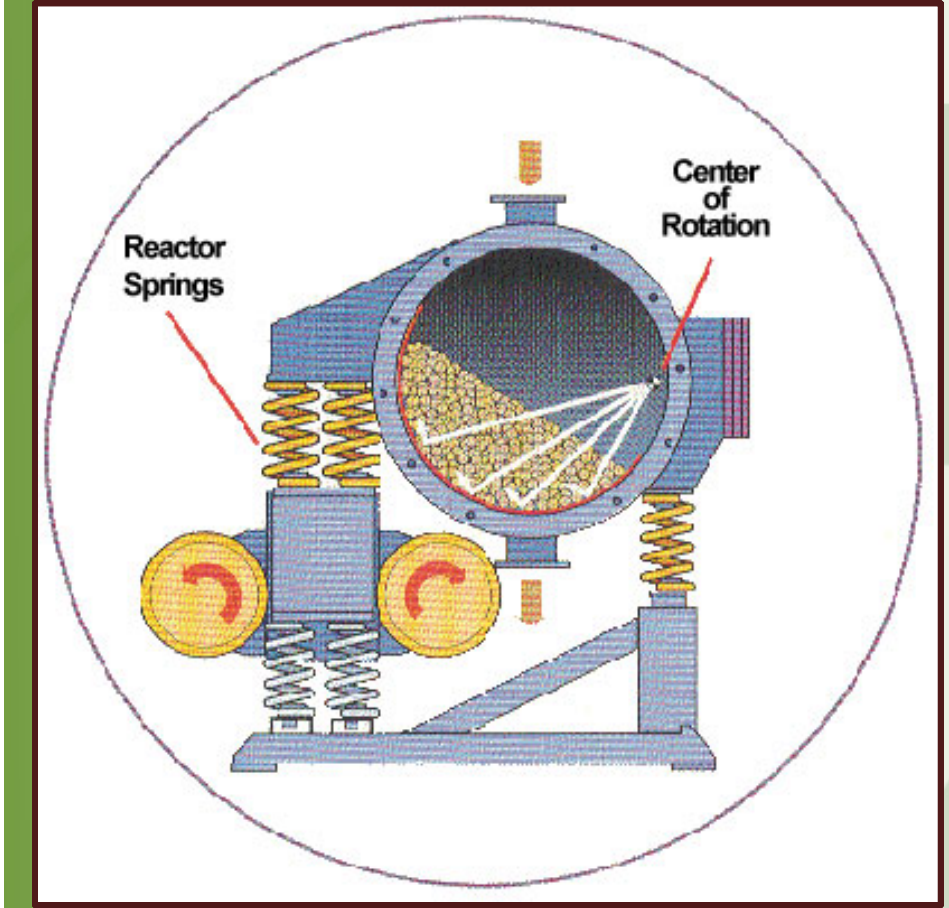
Figure 3. 4-Aminotoluene and 2-hydroxy-3-methoxybenzaldehyde ground independently and mixed at room temperature. (i) Immediately after the powders contact one other an orange, liquid phase forms. (ii) After merely mixing with a glass rod the entire mass is a homogeneous liquid. Time elapsed is approximately 2 min and the Petri dish has been shifted from a dark to a light background immediately post mixing of the powders. (iii) The orange, liquid phase is so fluid that it may be drawn into a pasteur pipet. Solid, orange azomethine product rapidly crystallizes from the liquid phase as the reaction proceeds and the entire mass is a wet crystalline solid in less than 10 min.

Mechanochemistry

Ball milling is a procedure in which solid reactants are placed inside a vessel, in the absence of solvent, along with one or more ball bearings. Planetary mills and vibratory mills are two of the most utilized mills for conducting solvent-free chemical reactions.



Mechanochemistry



Vibratory mill

Planetary Mill

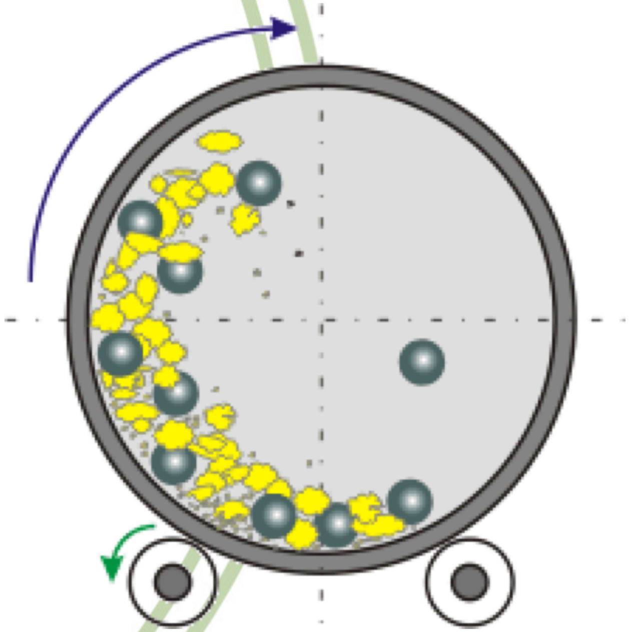
Mechanochemistry

Ball milling reactions are considered to occur in a two-step process.

- **Activation step: the particles are reduced to a size suitable for reaction.**
- **Ignition step: ball collisions cause a chemical reaction to occur.**

There are various aspects that govern the rate of these two steps.

- **mechanical operation of the mill**
- **mechanics of individual collisions**
- **chemical process**
- **structural changes**
- **defect formations.**

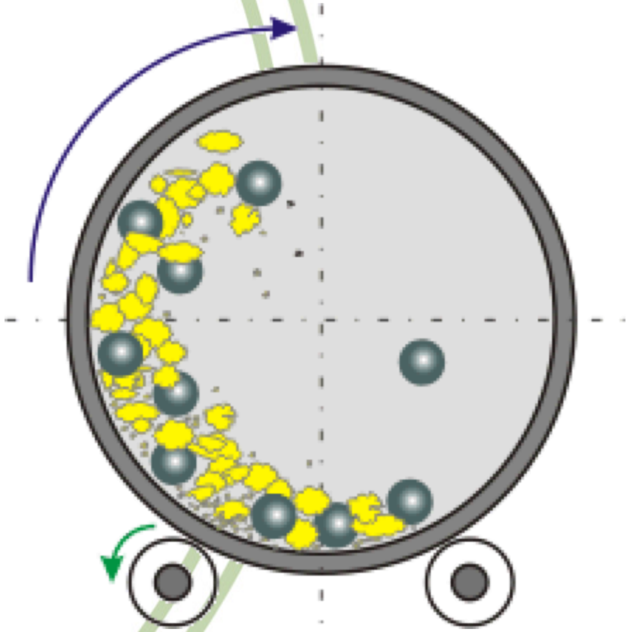


Mechanochemistry

Factors such as:

- milling time,
- milling speed,
- ball to powder ratio (i e , mass of the solids to the mass of the balls),
- atmosphere,
- temperature of the mill

all play an integral role in this novel technique.



Mechanochemistry

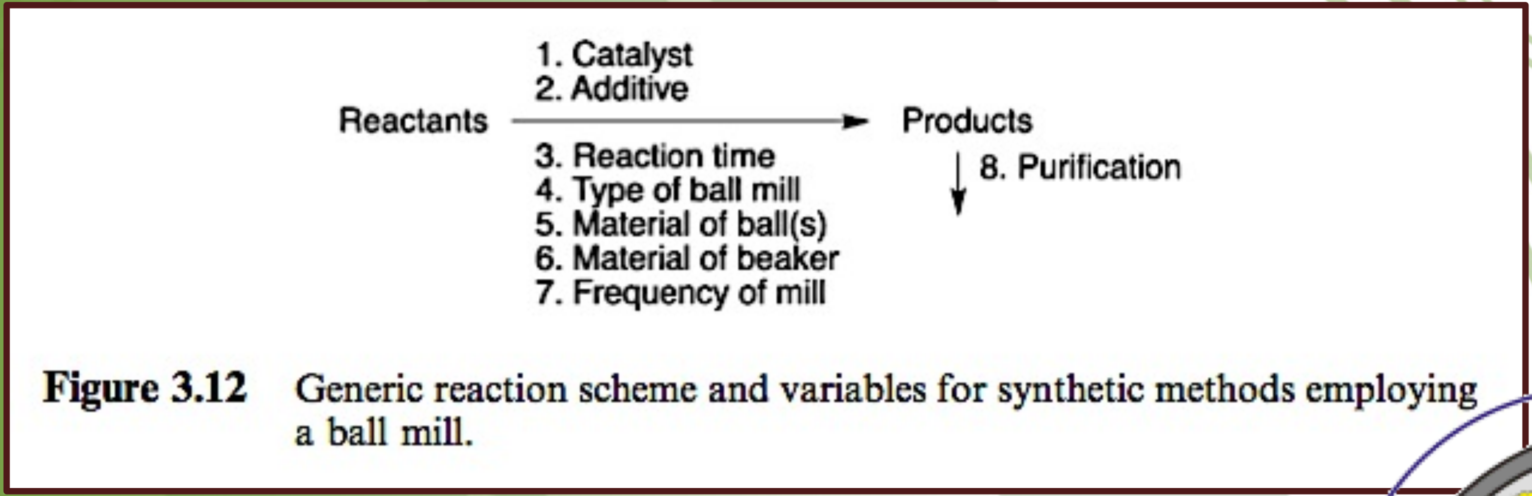
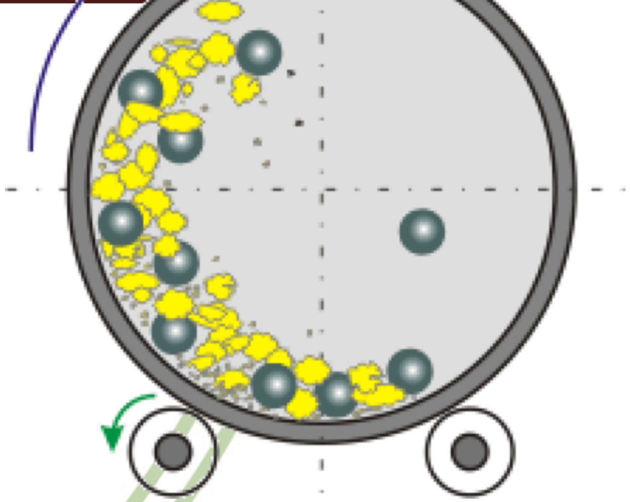


Figure 3.12 Generic reaction scheme and variables for synthetic methods employing a ball mill.



Examples

Solvent-free methods have been used extensively in supramolecular chemistry, coordination chemistry and the formation of transition-metal clusters and polymers

Examples

Solvent Free: r.t.; 10 min;
Water: 100°C; 4 weeks

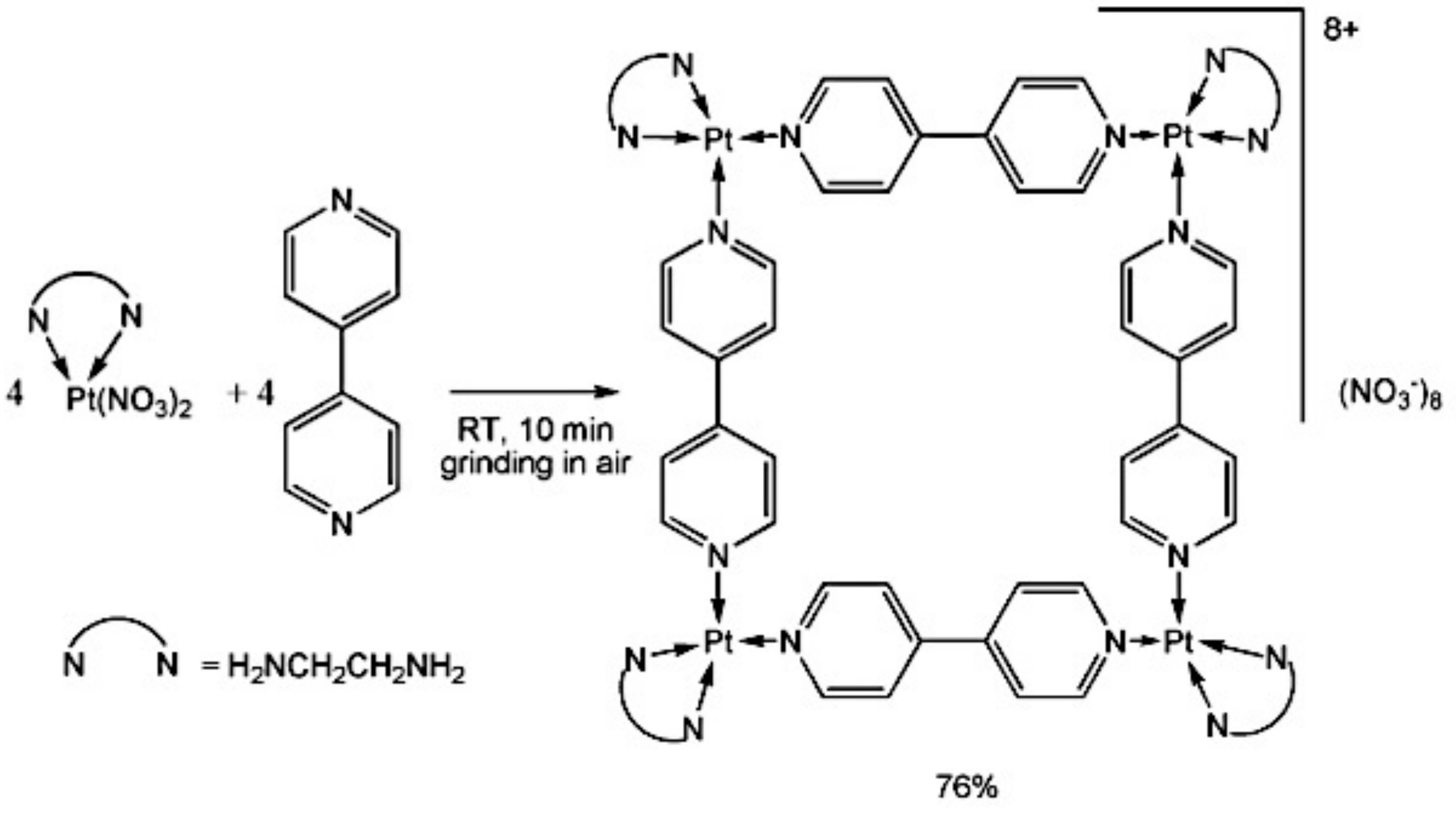
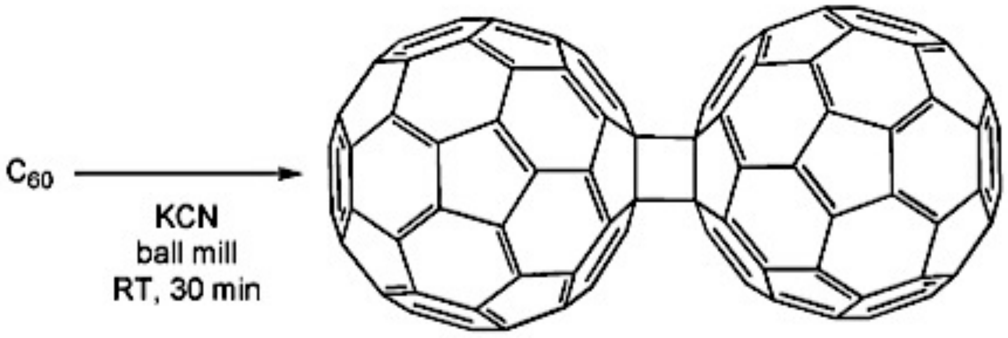


Figure 3.1 Solvent-free supramolecular self assembly of a metallo-square.

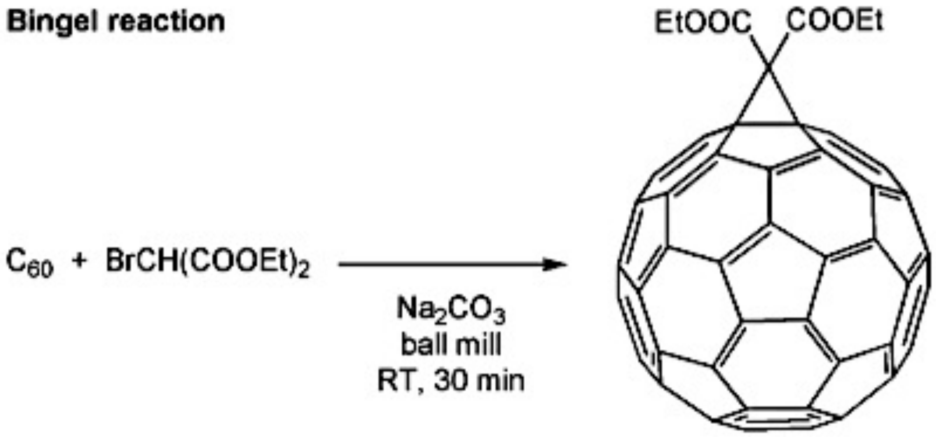
Examples

Fullerene [2+2] cycloaddition



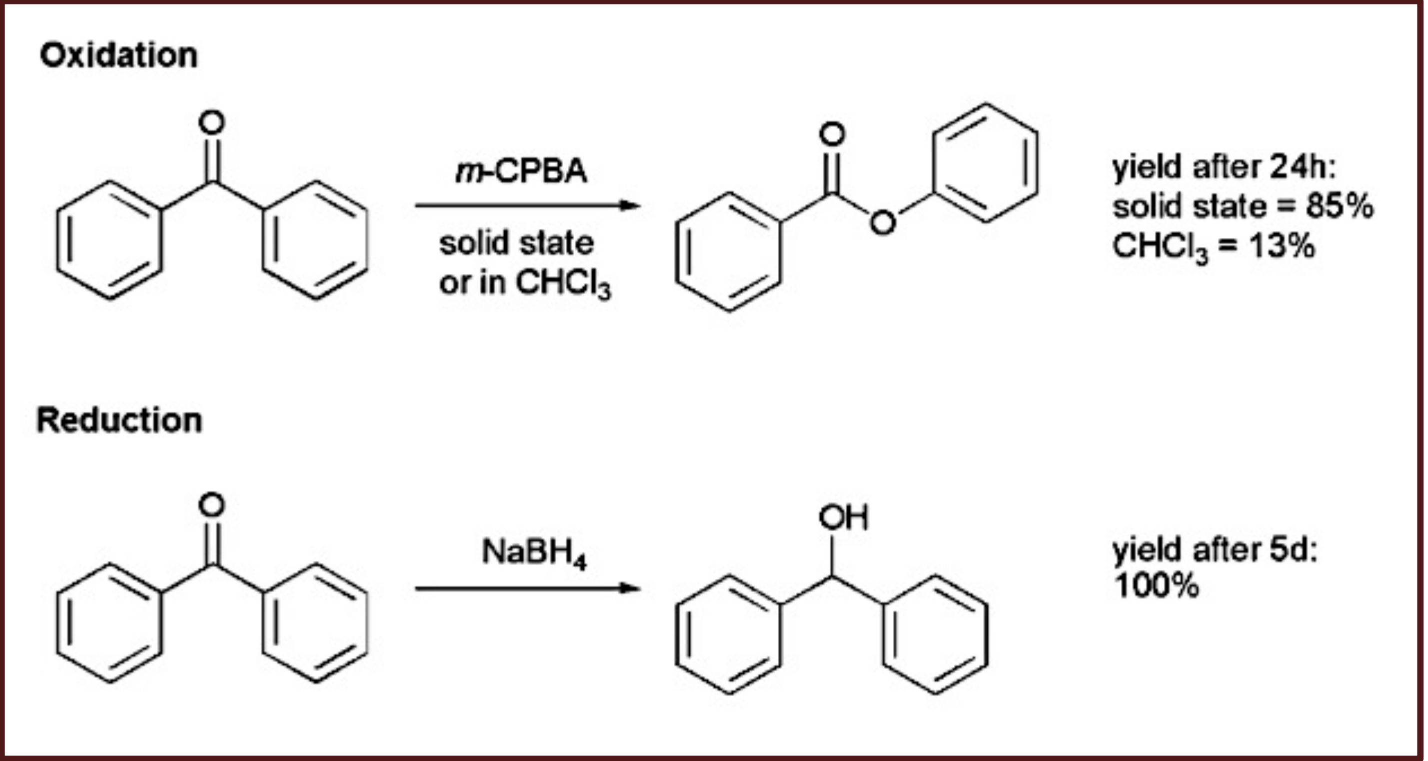
Isolated yield, 30%

Bingel reaction



Purified by column chromatography
toluene/petroleuem ether
Isolated yield, 78%

Examples

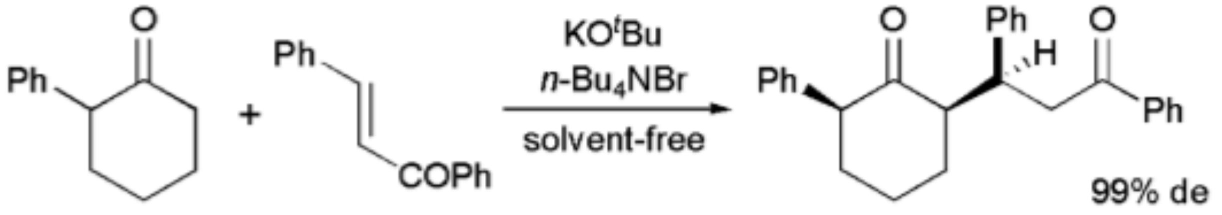


yield after 24h:
solid state = 85%
$CHCl_3$ = 13%

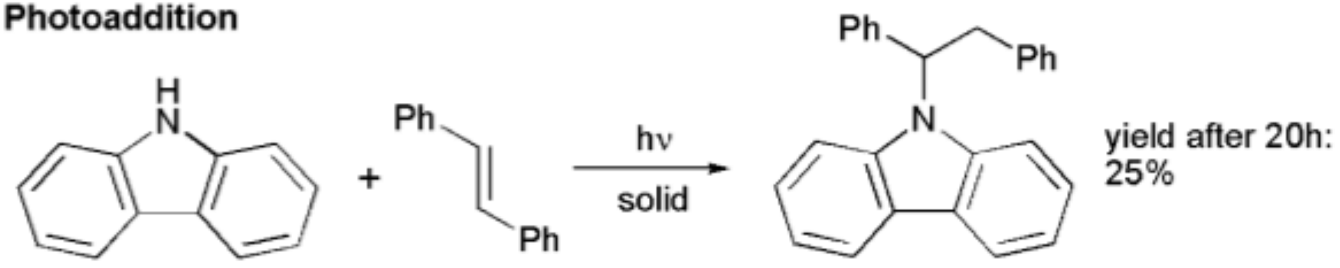
yield after 5d:
100%

Examples

Michael Addition



Photoaddition



Examples

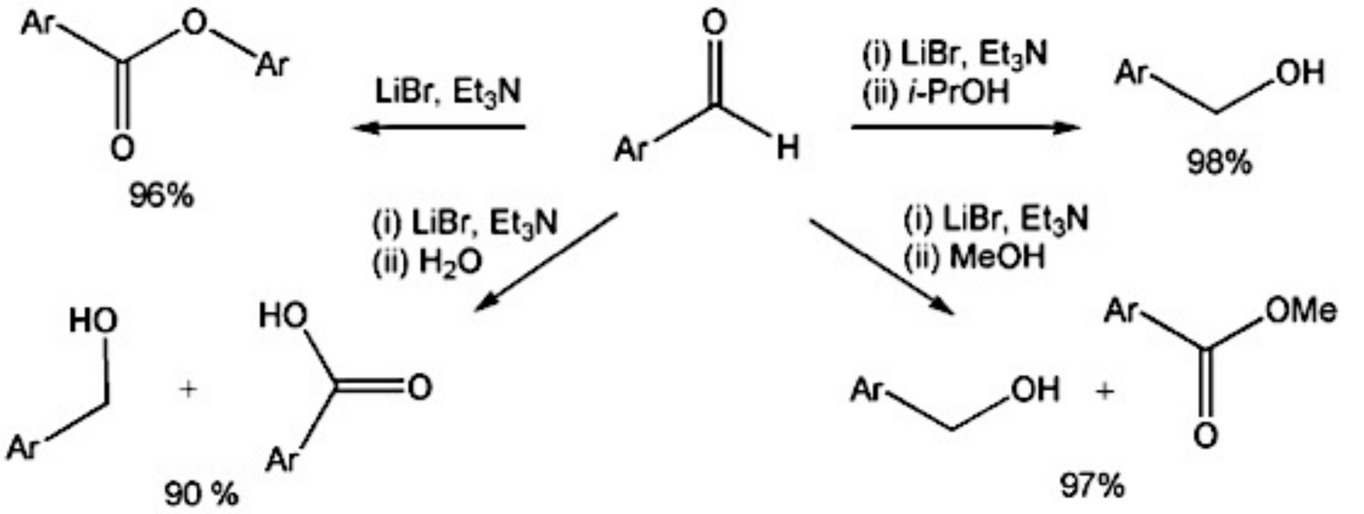


Figure 3.8 Solvent-free Cannizzaro, Tischenko and Meerwein–Ponndorf–Verley reactions.

Examples

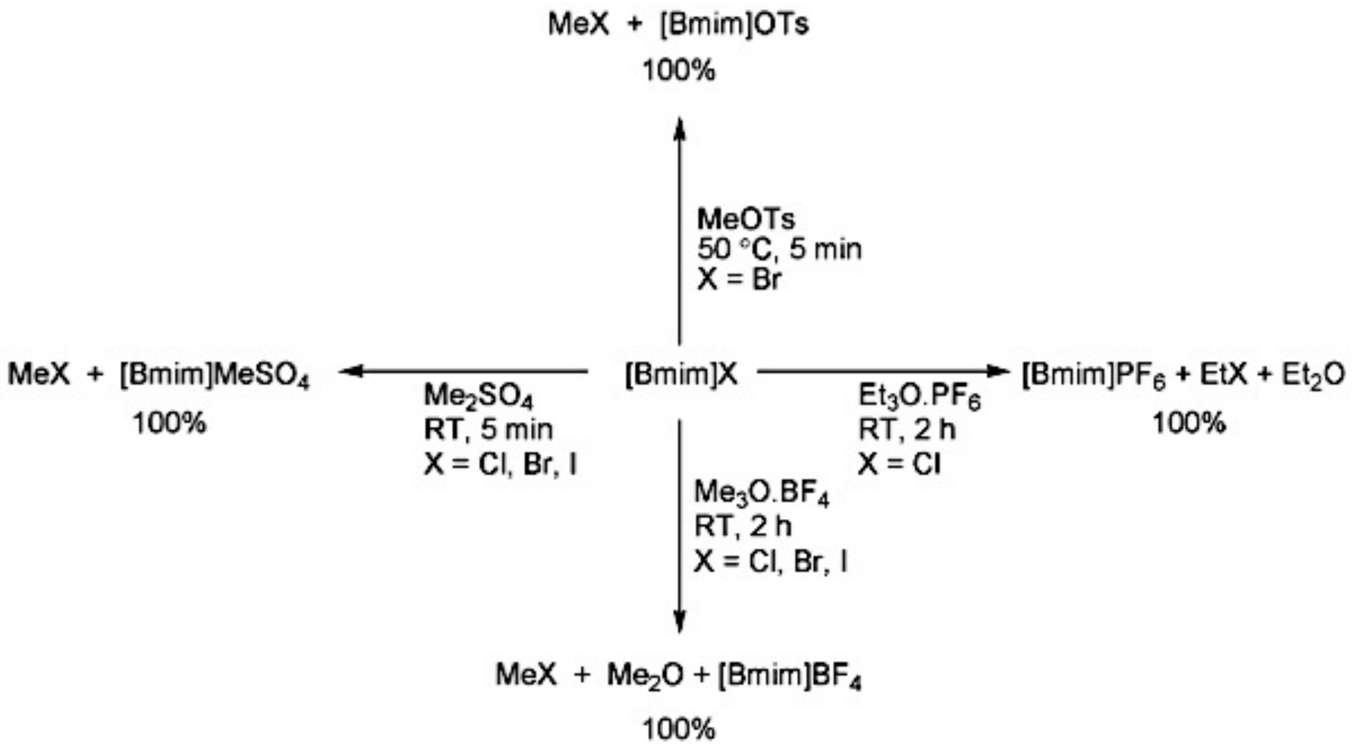
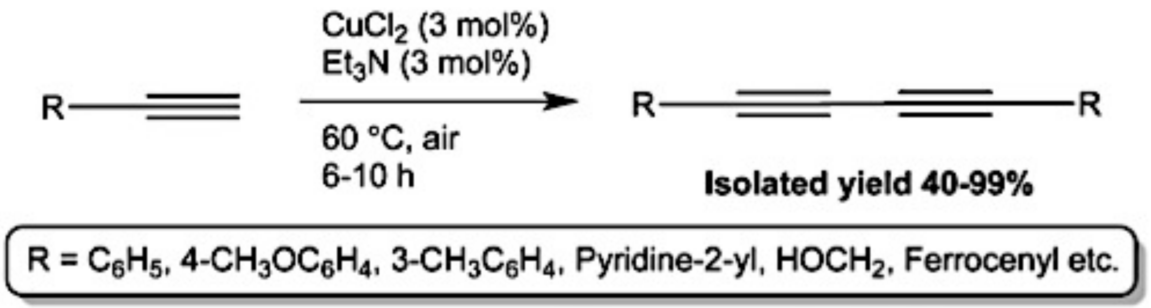


Figure 3.11 Quantitative synthesis of 1-butyl-3-methylimidazolium [Bmim] ionic liquids *via* solvent-free anion metathesis.

Examples

Catalytic Transformation



R = C_6H_5, 4-$CH_3OC_6H_4$, 3-$CH_3C_6H_4$, Pyridine-2-yl, $HOCH_2$, Ferrocenyl etc.

Figure 3.13 Solvent-free synthesis of 1,3-diynes.

Examples

Catalytic Transformation

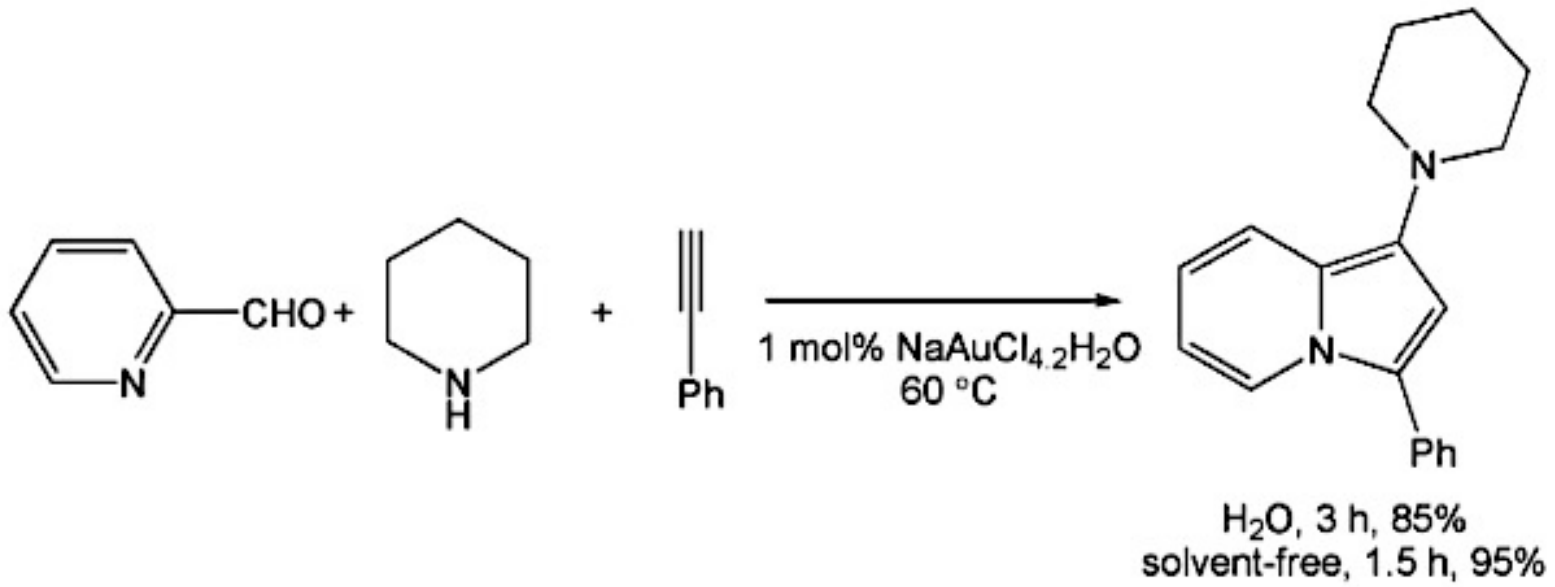
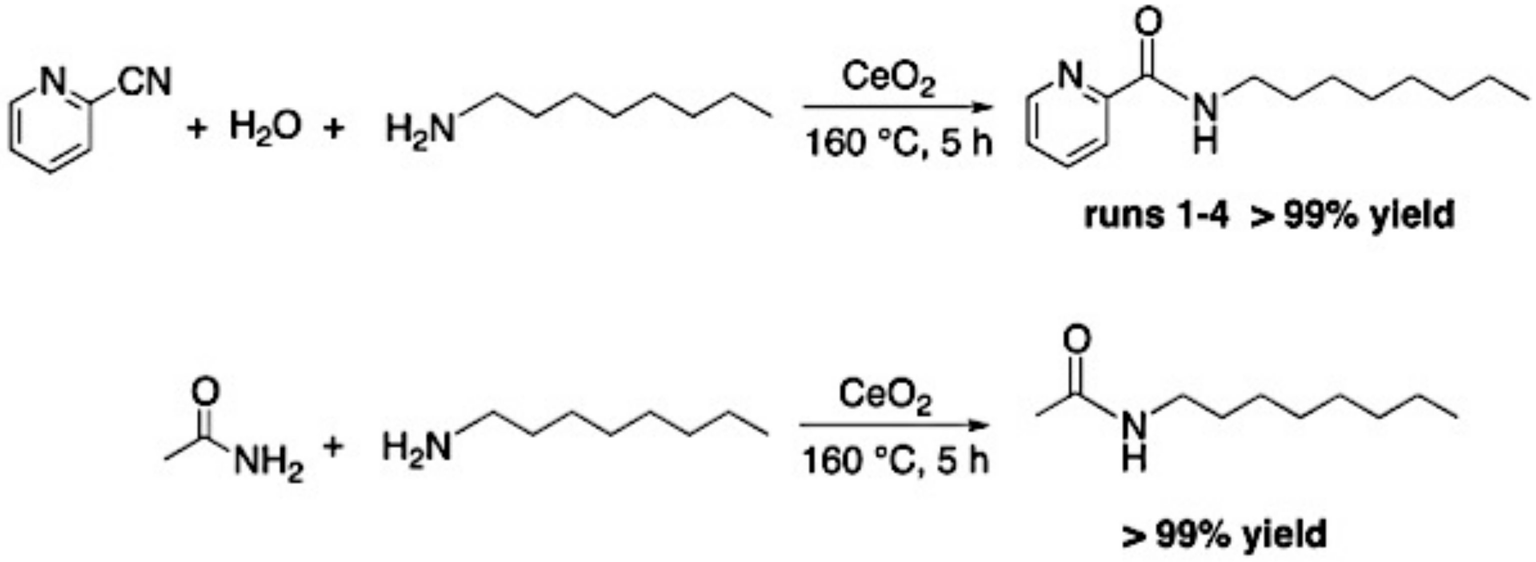


Figure 3.15 Gold-catalysed three-component coupling reaction in water and under solvent-free conditions.

Examples



runs 1-4 >99% yield

>99% yield

Figure 3.18 Ceria-catalysed preparation of amides under solvent-free conditions.

Examples

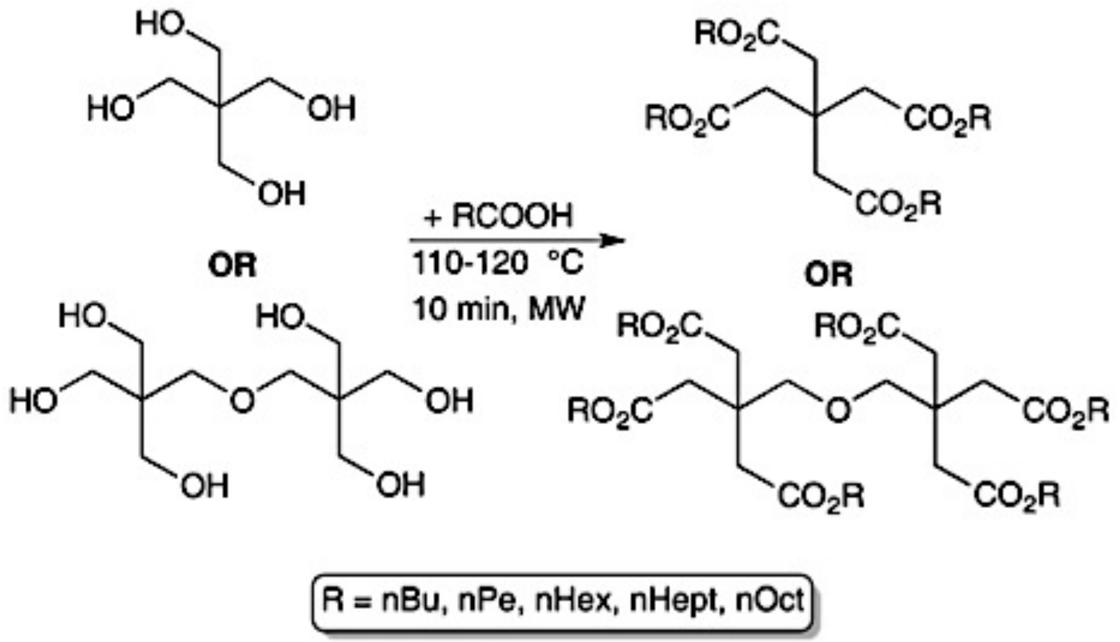


Figure 3.25 Direct esterification of polyols with fatty acids to yield lubricating oils.

Examples

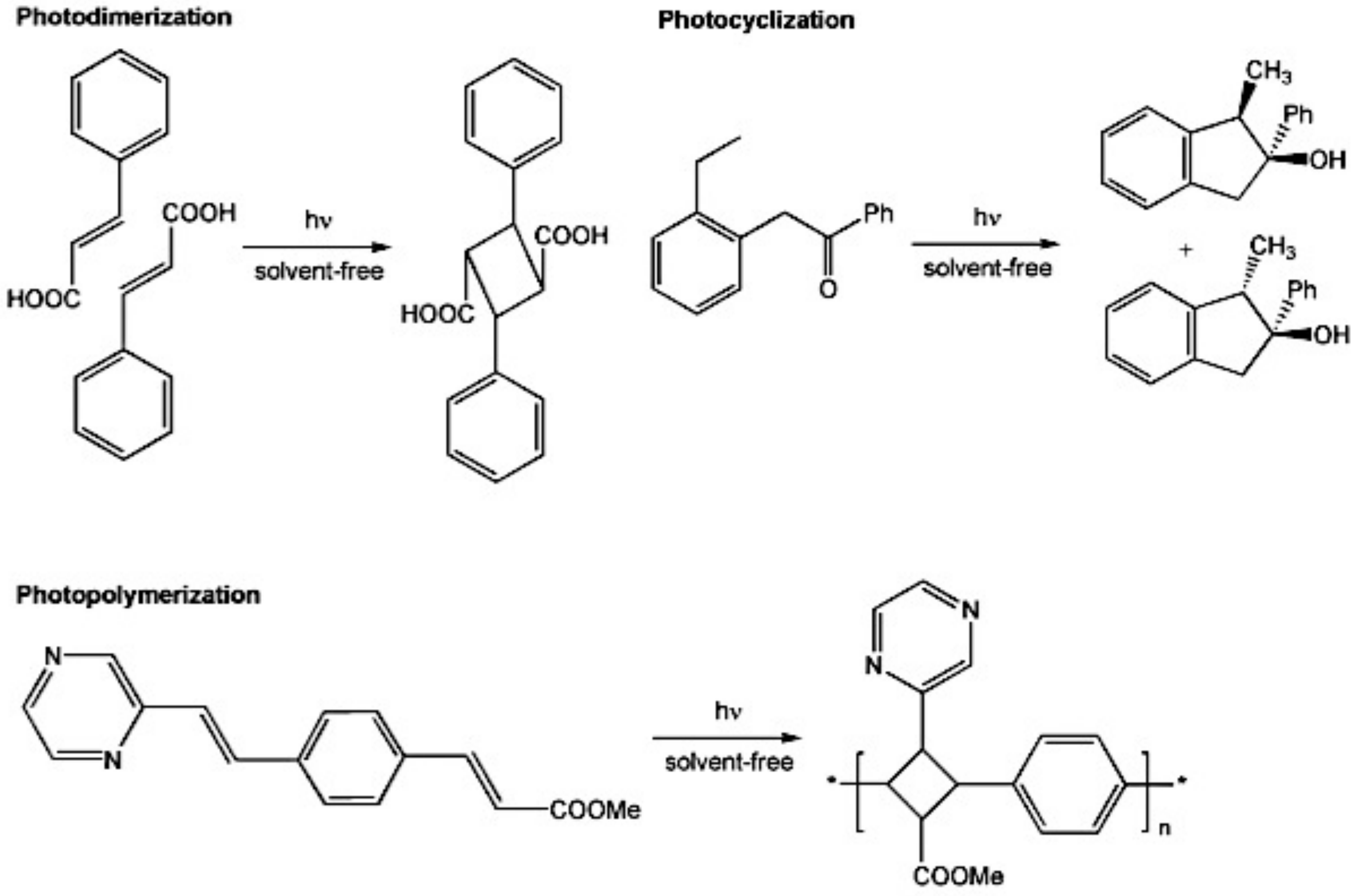
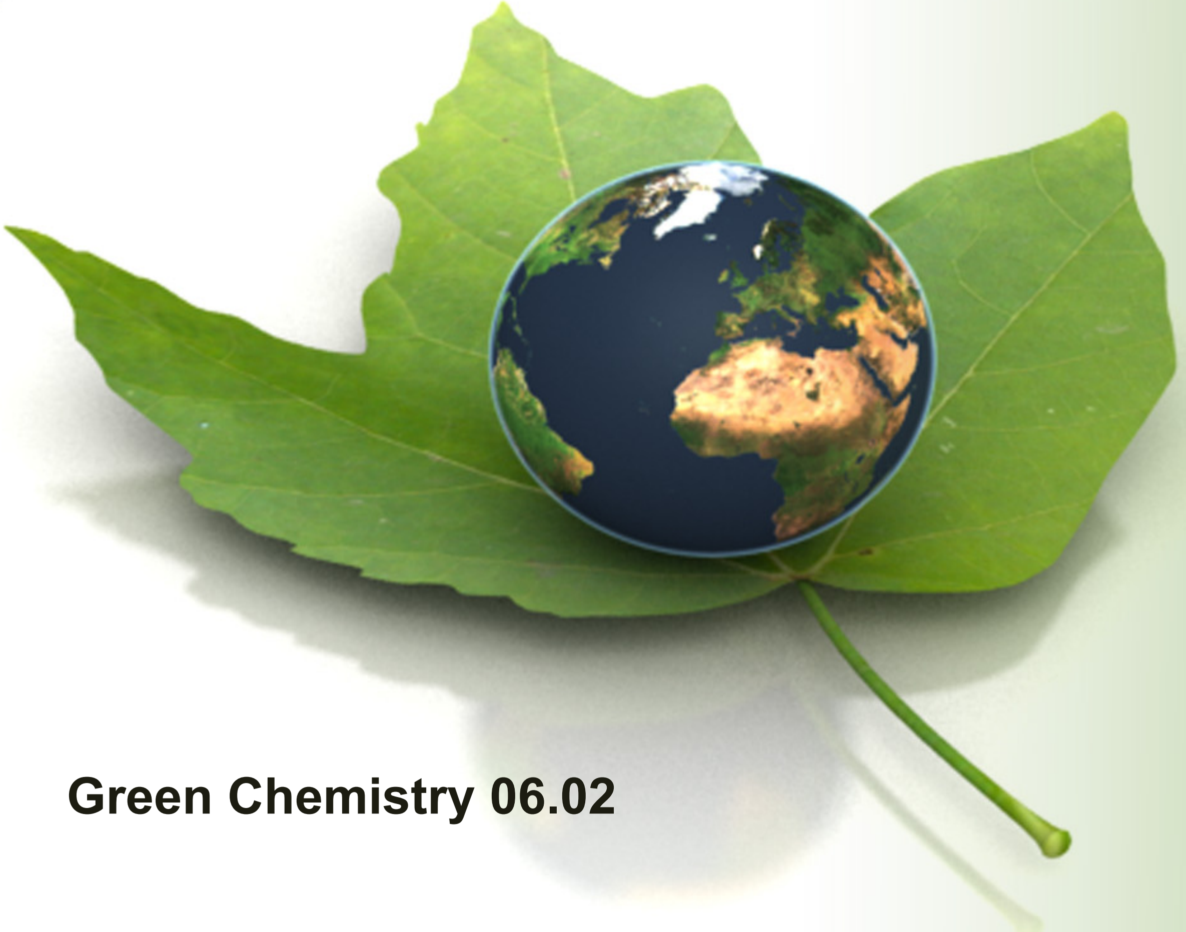


Figure 3.22 Some typical solvent-free photochemical reactions.

SUPERCRITICAL FLUIDS

Introduction

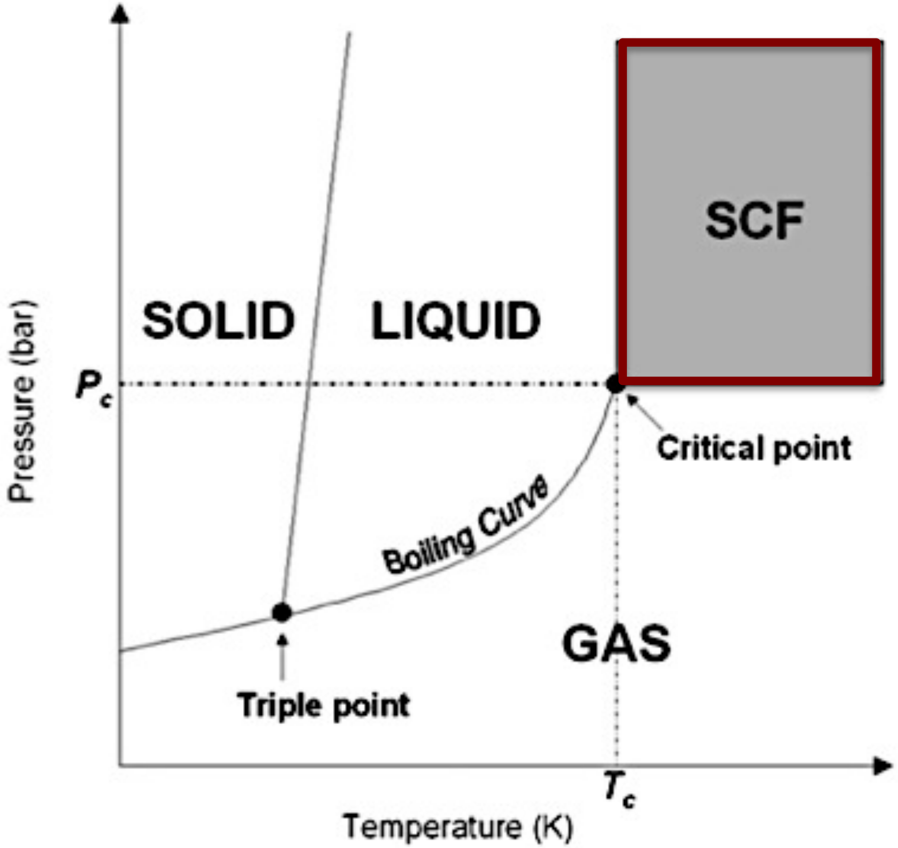


Green Chemistry 06.02

Introduction

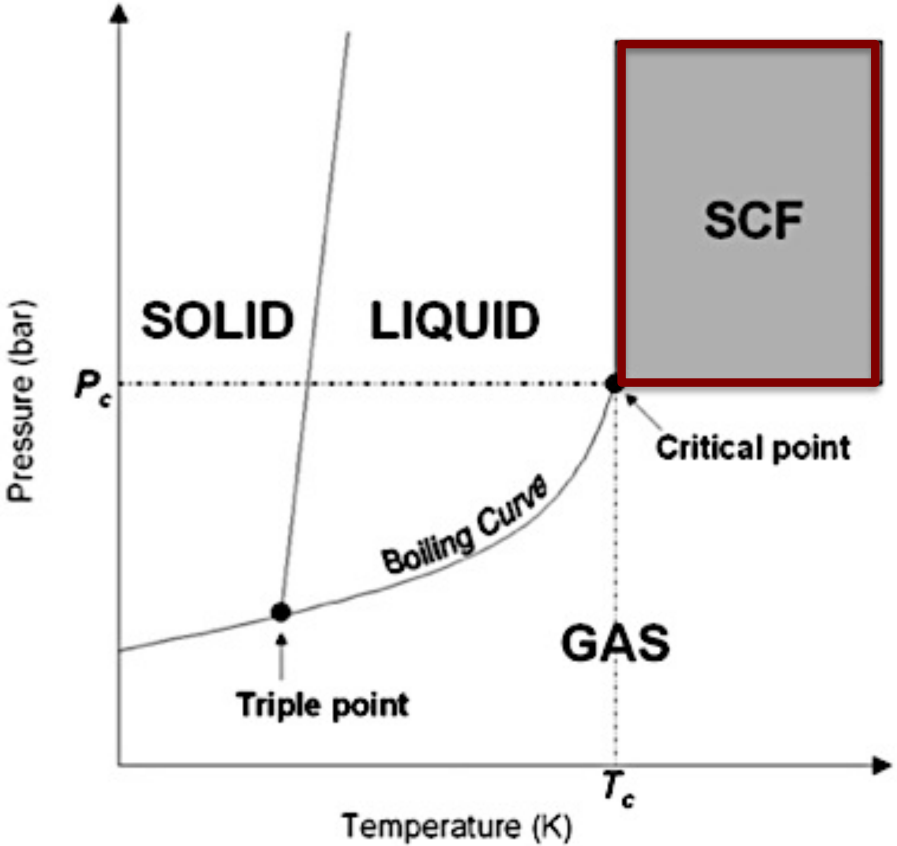
What is a SCF?

Substances enter the SCF phase above their critical pressures (Pc) and temperatures (Tc),



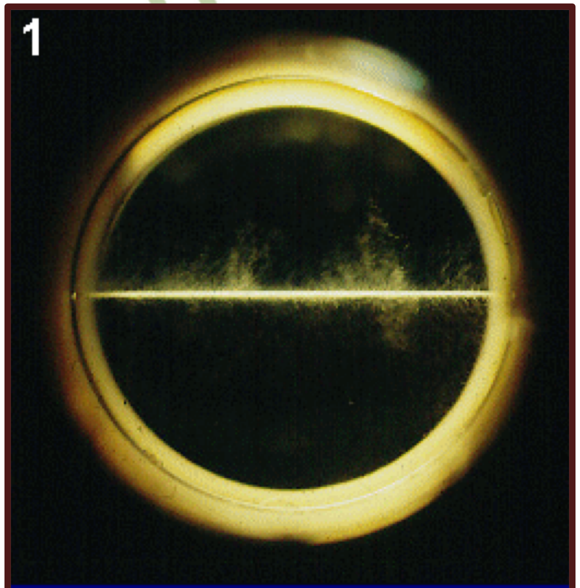
Introduction

The critical point of a SCF represents the highest temperature and pressure at which the substance can exist as a vapour and liquid in equilibrium.



Introduction

The densities of the two phases converge and become identical, the distinction between gas and liquid disappears, and the boiling curve comes to an end at the critical point.



Below the critical parameters, two distinct phases exist

Introduction

No distinct gas or liquid phase can exist above the critical point, and the SCF phase has a unique combination of properties from both gas and liquid states

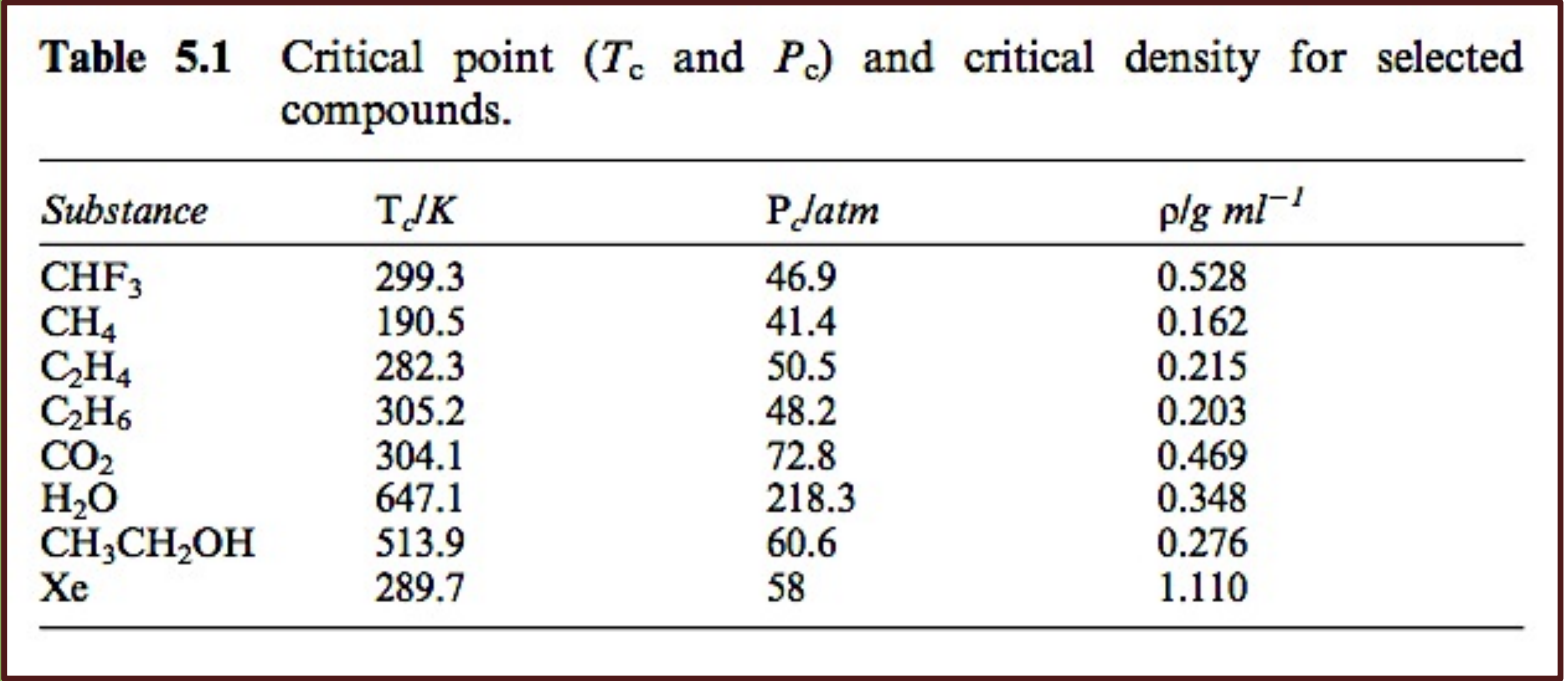


Table 5.1 Critical point (T_c and P_c) and critical density for selected compounds.

Substance	T_c/*K*	P_c/*atm*	*ρ/g ml⁻¹*
CHF_3	299.3	46.9	0.528
CH_4	190.5	41.4	0.162
C_2H_4	282.3	50.5	0.215
C_2H_6	305.2	48.2	0.203
CO_2	304.1	72.8	0.469
H_2O	647.1	218.3	0.348
CH_3CH_2OH	513.9	60.6	0.276
Xe	289.7	58	1.110

Introduction

- At liquid-like densities SCFs exhibit low viscosity and high diffusion rates, like a gas;
- Conventional solvents require very large pressure changes to vary their density, whereas the density of a SCF changes significantly upon increasing pressure;
- Solubility in a SCF is related to density, therefore this medium has the added benefit of being tunable, and hence the solubility of species can be directly controlled.

Introduction

- **Purification** or reaction **quenching** can thus be achieved by reducing solvent density and precipitating the product;
- Varying the density can also affect the **selectivity** and **outcome** of some chemical reactions;
- Lower than supercritical pressures of gases can be used to expand organic solvents and lead to the formation of a **gas-expanded liquid (GXL) phase**.

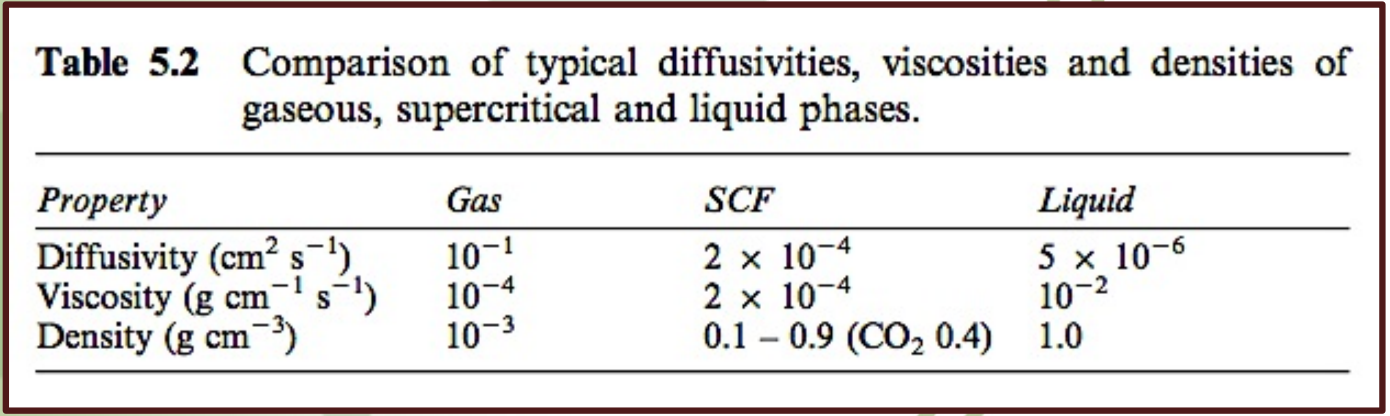


Table 5.2 Comparison of typical diffusivities, viscosities and densities of gaseous, supercritical and liquid phases.

Property	*Gas*	*SCF*	*Liquid*
Diffusivity ($cm^2\ s^{-1}$)	10^{-1}	2×10^{-4}	5×10^{-6}
Viscosity ($g\ cm^{-1}\ s^{-1}$)	10^{-4}	2×10^{-4}	10^{-2}
Density ($g\ cm^{-3}$)	10^{-3}	0.1 – 0.9 (CO_2 0.4)	1.0

Introduction

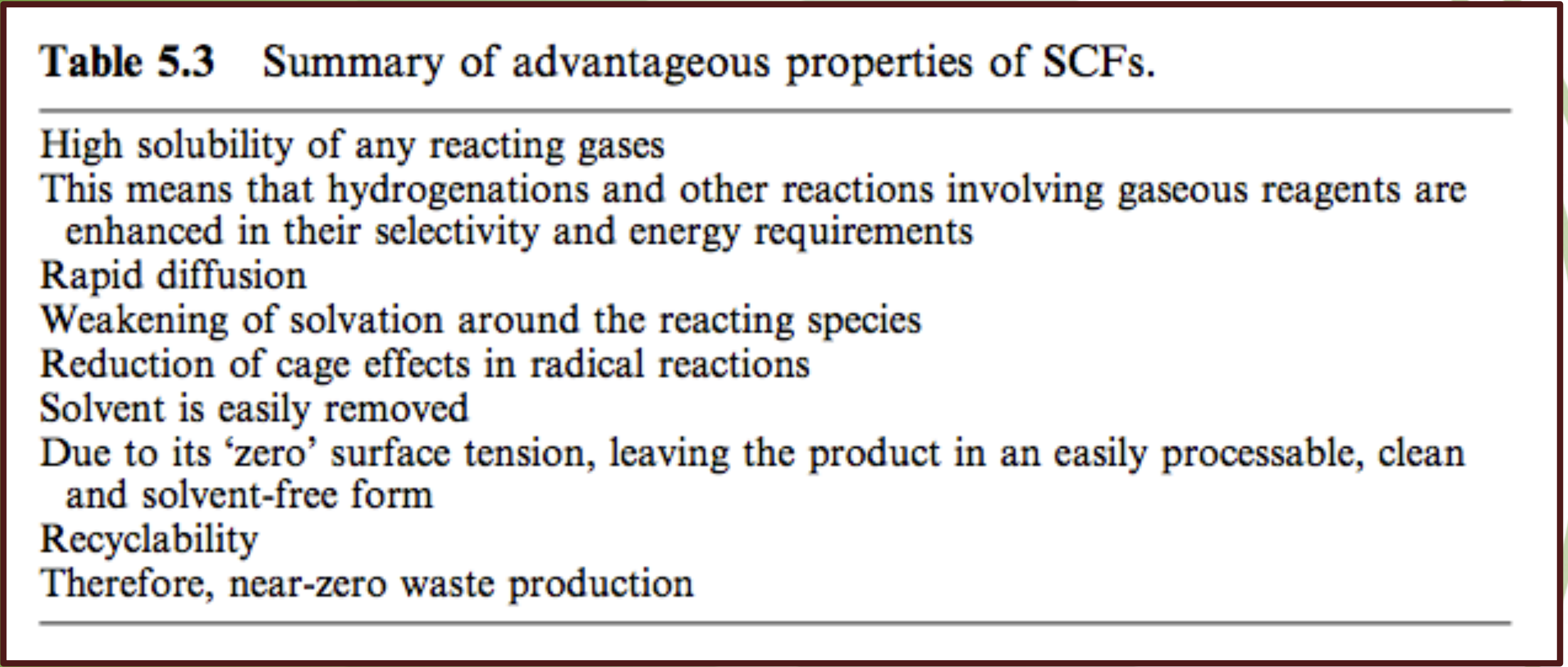


Table 5.3 Summary of advantageous properties of SCFs.

High solubility of any reacting gases
This means that hydrogenations and other reactions involving gaseous reagents are enhanced in their selectivity and energy requirements
Rapid diffusion
Weakening of solvation around the reacting species
Reduction of cage effects in radical reactions
Solvent is easily removed
Due to its 'zero' surface tension, leaving the product in an easily processable, clean and solvent-free form
Recyclability
Therefore, near-zero waste production

SUPERCRITICAL FLUIDS

Supercritical Carbon Dioxide

Supercritical and Liquid Carbon Dioxide

- Inexpensive;
- Obtained as a byproduct of fermentation and combustion;
- Nontoxic and not a VOC;
- Nonflammable and relatively inert;
- React with nucleophiles (e.g. carbamic acid formation from amines);
- Cannot be oxidized and therefore oxidation reactions using air or O_2 as the oxidant have been intensively investigated;
- Inert to free-radical chemistry, in contrast to many conventional solvents;

Supercritical and Liquid Carbon Dioxide

- **Product isolation to total dryness is achieved by simple evaporation;**
- **Given the critical point of carbon dioxide, most processes reported to date have been conducted in a pressure regime between 100–200 bar;**

Supercritical and Liquid Carbon Dioxide

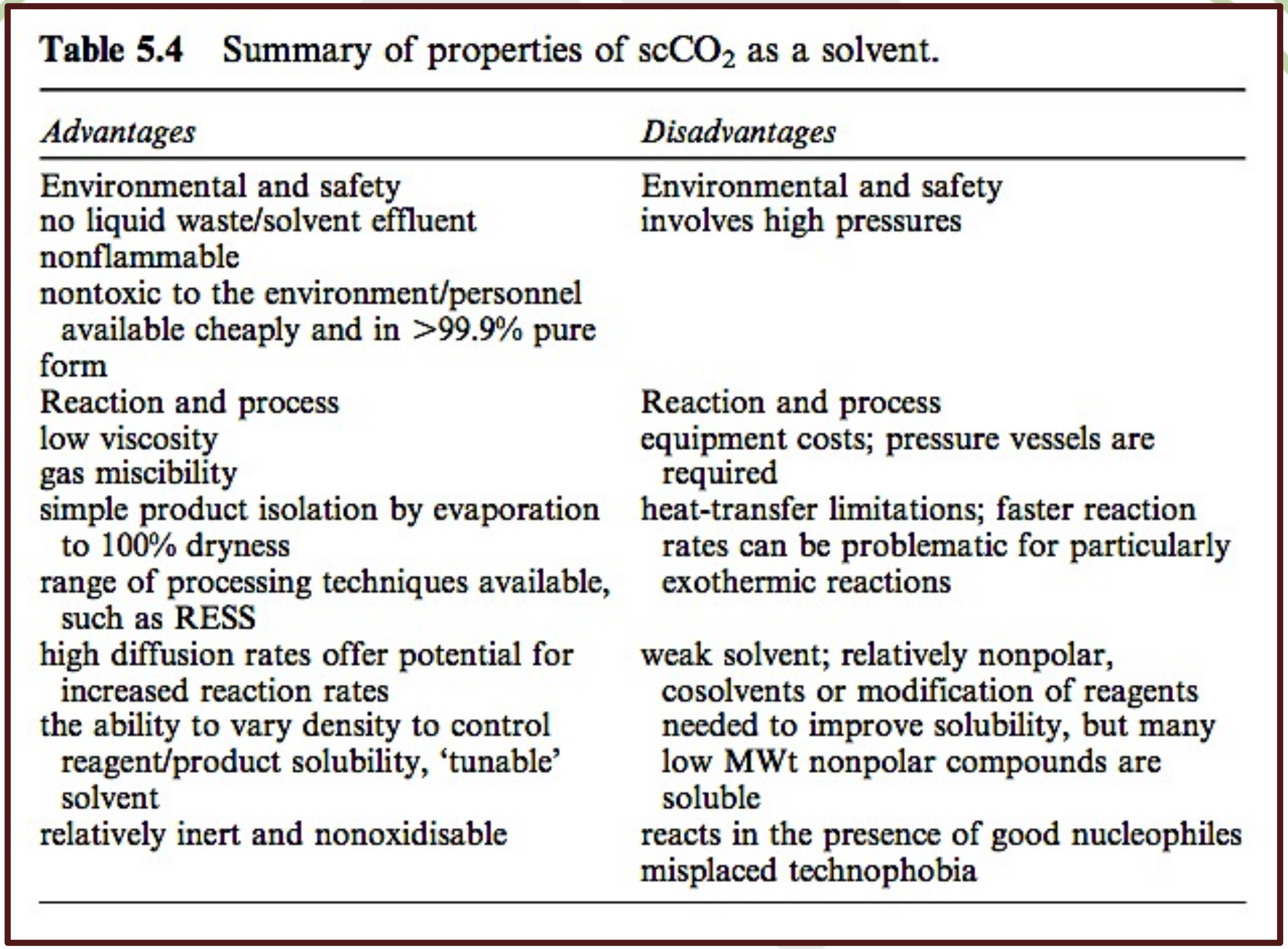


Table 5.4 Summary of properties of $scCO_2$ as a solvent.

Advantages	*Disadvantages*
Environmental and safety	Environmental and safety
no liquid waste/solvent effluent	involves high pressures
nonflammable	
nontoxic to the environment/personnel	
available cheaply and in >99.9% pure form	
Reaction and process	Reaction and process
low viscosity	equipment costs; pressure vessels are required
gas miscibility	
simple product isolation by evaporation to 100% dryness	heat-transfer limitations; faster reaction rates can be problematic for particularly exothermic reactions
range of processing techniques available, such as RESS	
high diffusion rates offer potential for increased reaction rates	weak solvent; relatively nonpolar, cosolvents or modification of reagents needed to improve solubility, but many low MWt nonpolar compounds are soluble
the ability to vary density to control reagent/product solubility, 'tunable' solvent	
relatively inert and nonoxidisable	reacts in the presence of good nucleophiles
	misplaced technophobia

Solubility in $scCO_2$

All gases are miscible with SCFs

This is particularly important for catalysis in SCFs and particularly $scCO_2$
[For example, the concentration of hydrogen in a supercritical mixture of hydrogen (85 bar) and carbon dioxide (120 bar) at 50 °C is 3.2 M, whereas the concentration of hydrogen in THF under the same pressure is merely 0.4 M]

Solubility in $scCO_2$

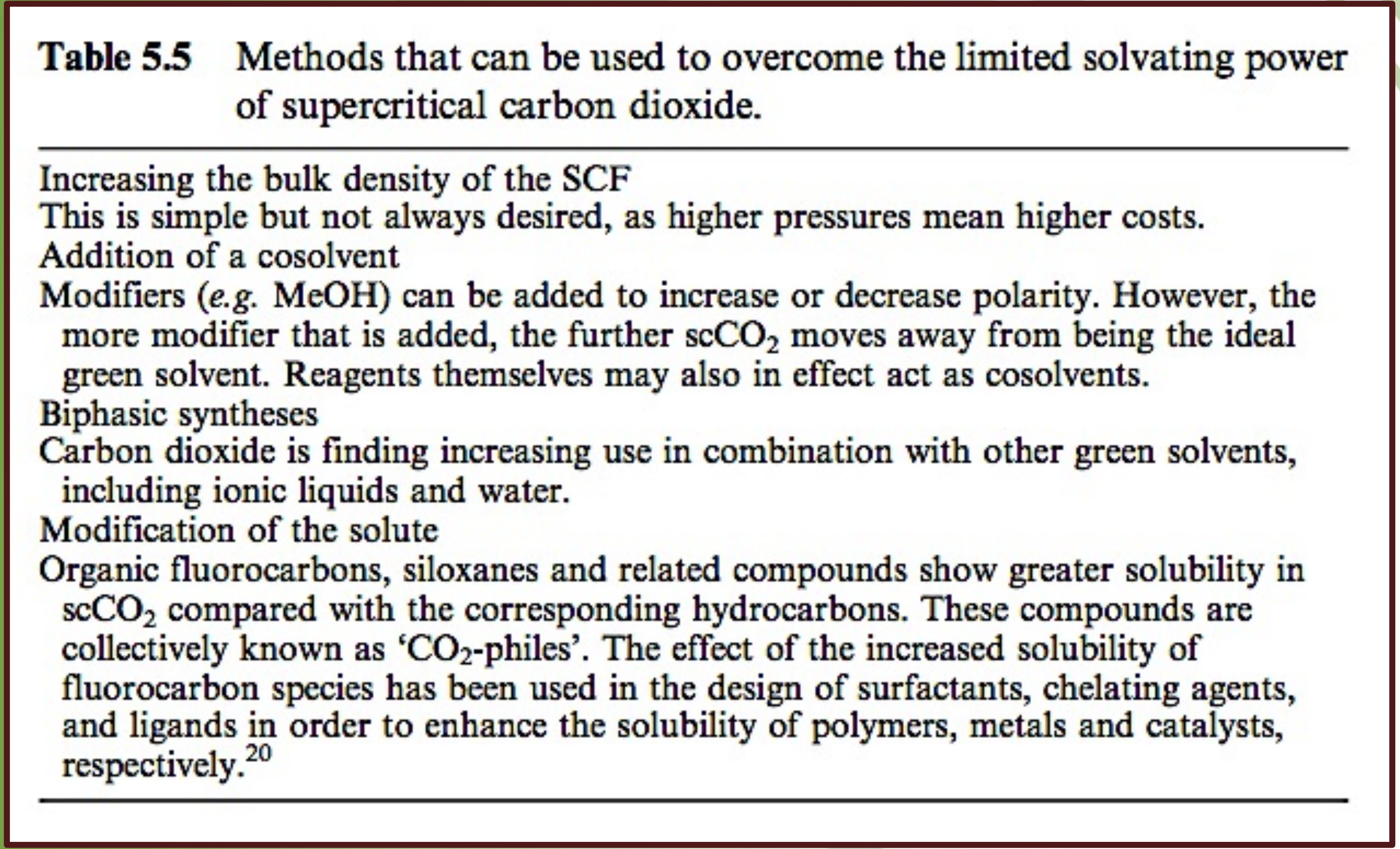


Table 5.5 Methods that can be used to overcome the limited solvating power of supercritical carbon dioxide.

Increasing the bulk density of the SCF

This is simple but not always desired, as higher pressures mean higher costs.

Addition of a cosolvent

Modifiers (*e.g.* MeOH) can be added to increase or decrease polarity. However, the more modifier that is added, the further $scCO_2$ moves away from being the ideal green solvent. Reagents themselves may also in effect act as cosolvents.

Biphasic syntheses

Carbon dioxide is finding increasing use in combination with other green solvents, including ionic liquids and water.

Modification of the solute

Organic fluorocarbons, siloxanes and related compounds show greater solubility in $scCO_2$ compared with the corresponding hydrocarbons. These compounds are collectively known as 'CO_2-philes'. The effect of the increased solubility of fluorocarbon species has been used in the design of surfactants, chelating agents, and ligands in order to enhance the solubility of polymers, metals and catalysts, respectively.[20]

Extraction

Supercritical carbon dioxide is widely used in Supercritical Fluid Extraction (SFE) and Supercritical Fluid Chromatography (SFC)

Extraction

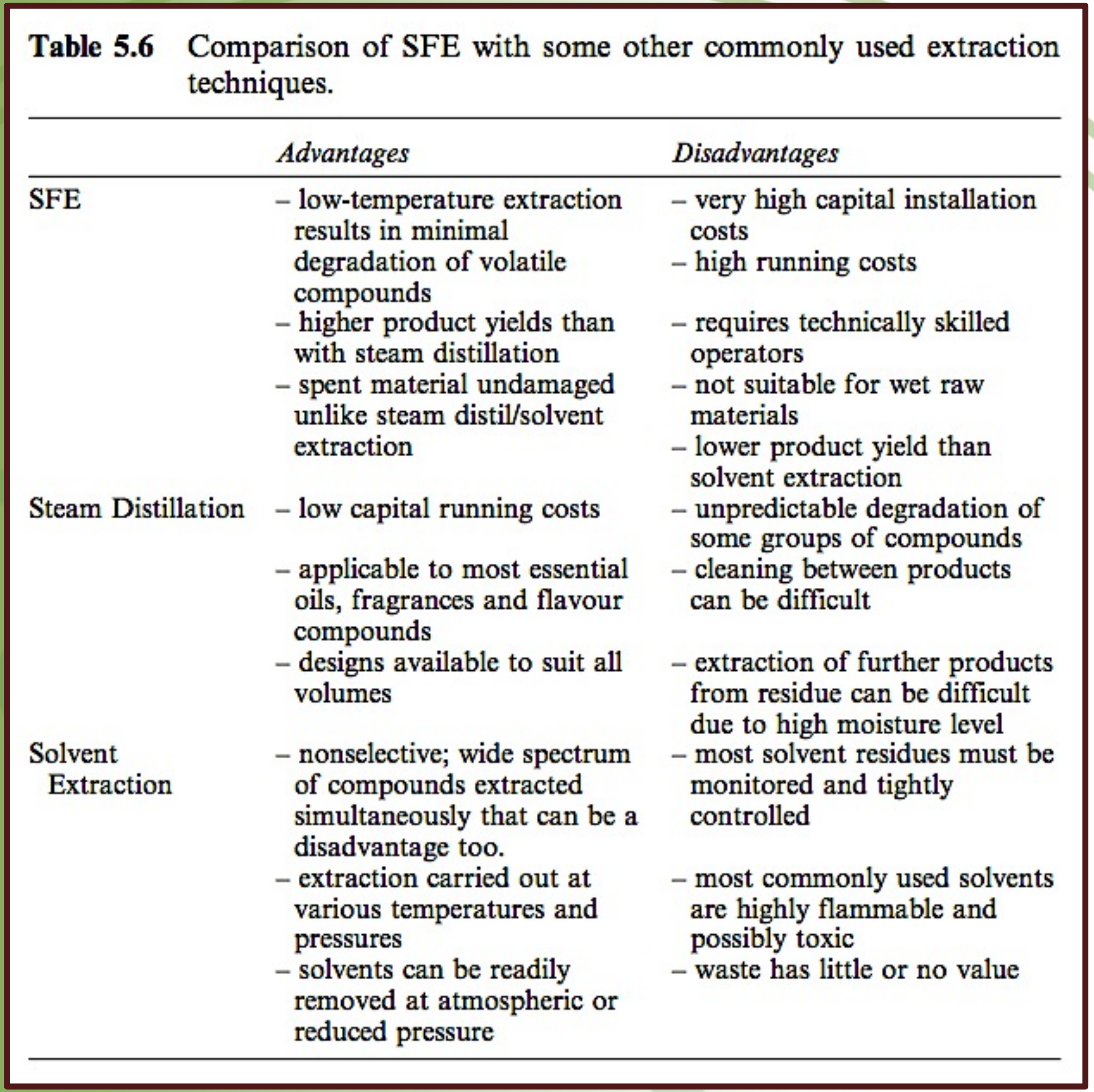


Table 5.6 Comparison of SFE with some other commonly used extraction techniques.

	Advantages	*Disadvantages*
SFE	– low-temperature extraction results in minimal degradation of volatile compounds – higher product yields than with steam distillation – spent material undamaged unlike steam distil/solvent extraction	– very high capital installation costs – high running costs – requires technically skilled operators – not suitable for wet raw materials – lower product yield than solvent extraction
Steam Distillation	– low capital running costs – applicable to most essential oils, fragrances and flavour compounds – designs available to suit all volumes	– unpredictable degradation of some groups of compounds – cleaning between products can be difficult – extraction of further products from residue can be difficult due to high moisture level
Solvent Extraction	– nonselective; wide spectrum of compounds extracted simultaneously that can be a disadvantage too. – extraction carried out at various temperatures and pressures – solvents can be readily removed at atmospheric or reduced pressure	– most solvent residues must be monitored and tightly controlled – most commonly used solvents are highly flammable and possibly toxic – waste has little or no value

Chemical Synthesis

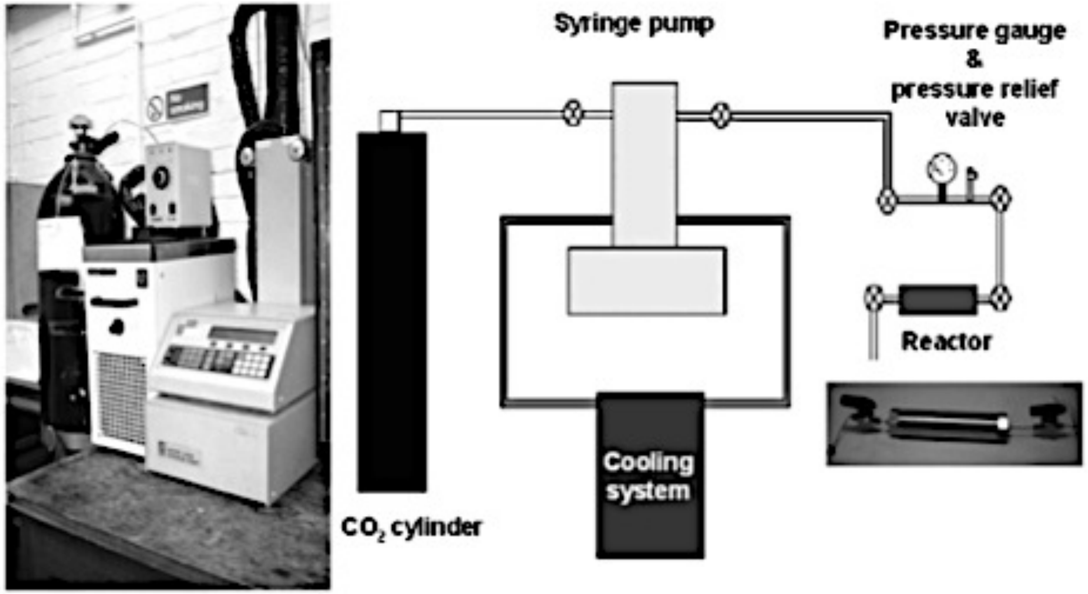
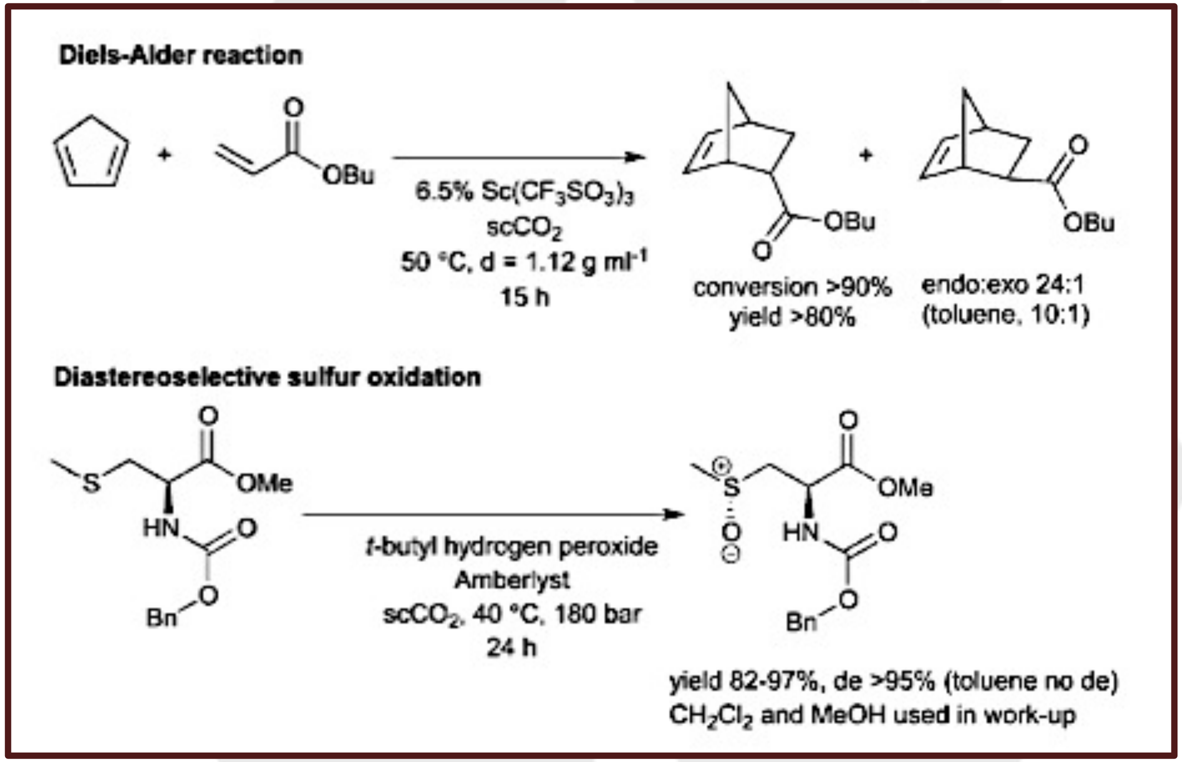
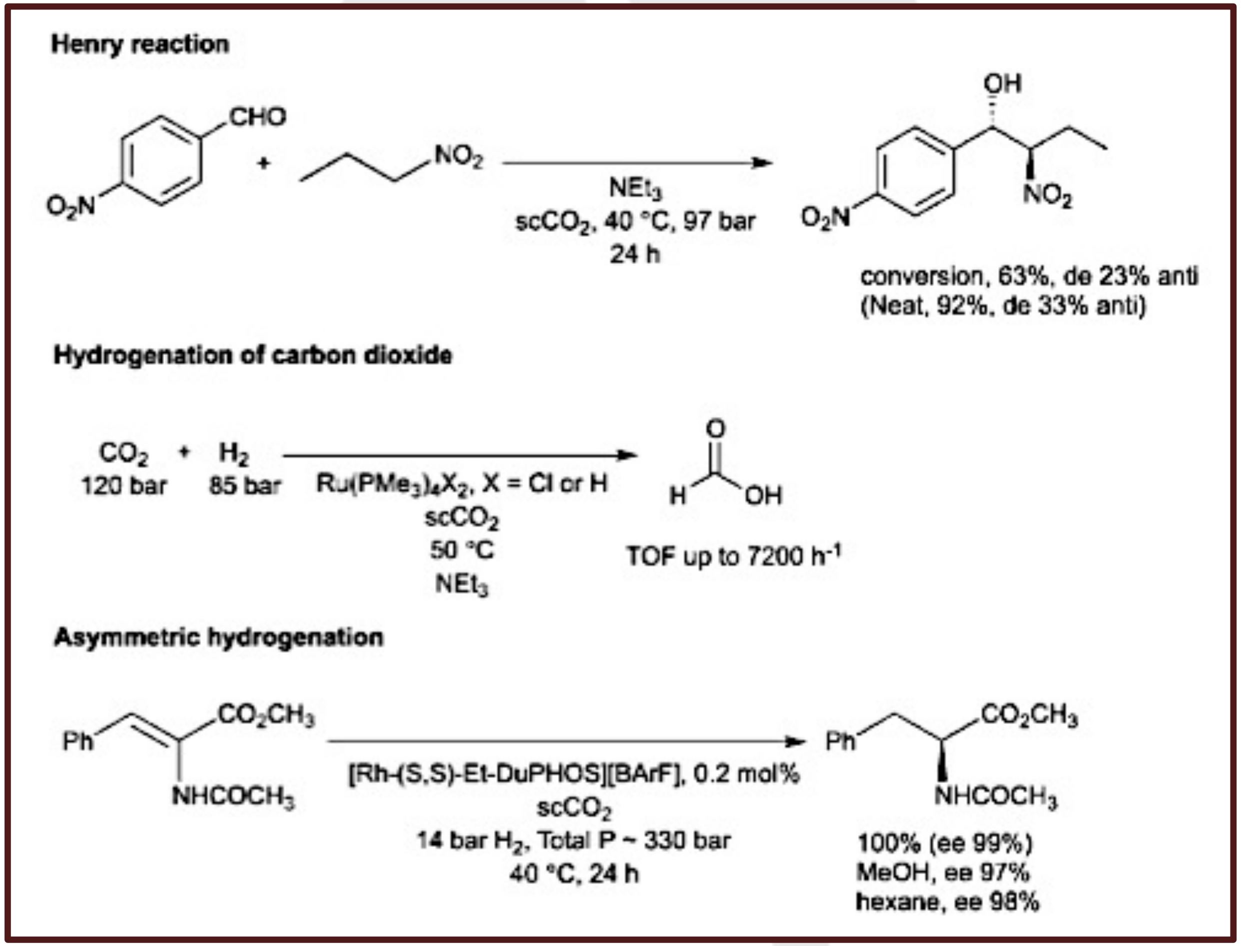


Figure 5.5 Schematic diagram of typical $scCO_2$ lab set-up for reactions. Inset left, cylinder, circulating chilling unit and syringe pump. Inset right, typical pressure vessel.

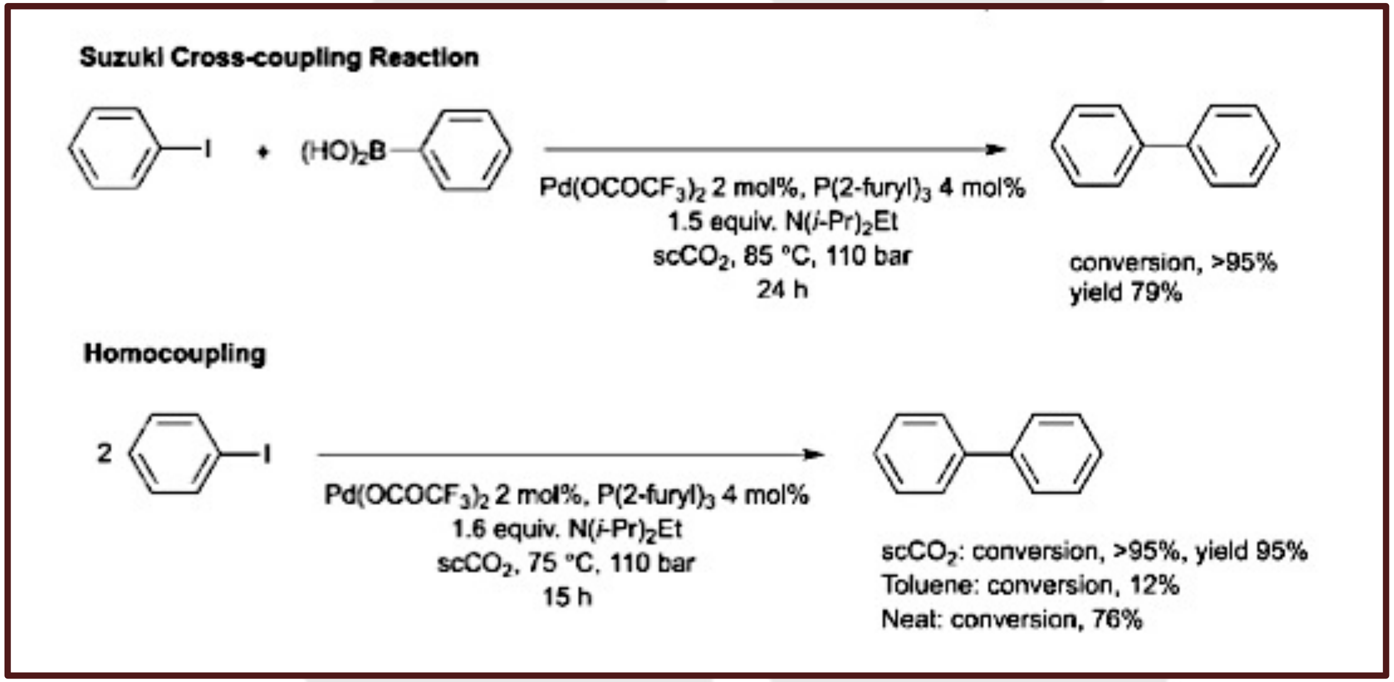
Chemical Synthesis



Chemical Synthesis



Chemical Synthesis



Chemical Synthesis

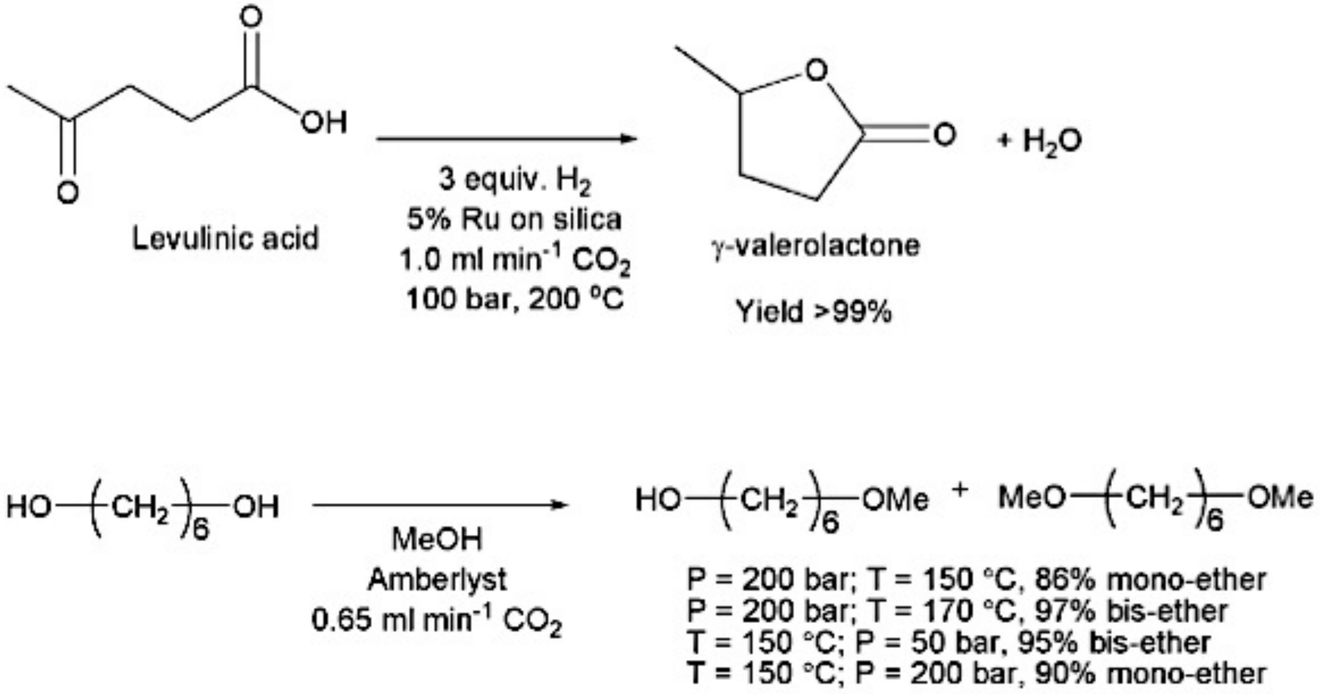


Figure 5.7 Reactions performed in $scCO_2$ using heterogeneous catalysts.

Chemical Synthesis

Biphasic Carbon Dioxide–Aqueous and Carbon Dioxide–Ionic Liquid Systems

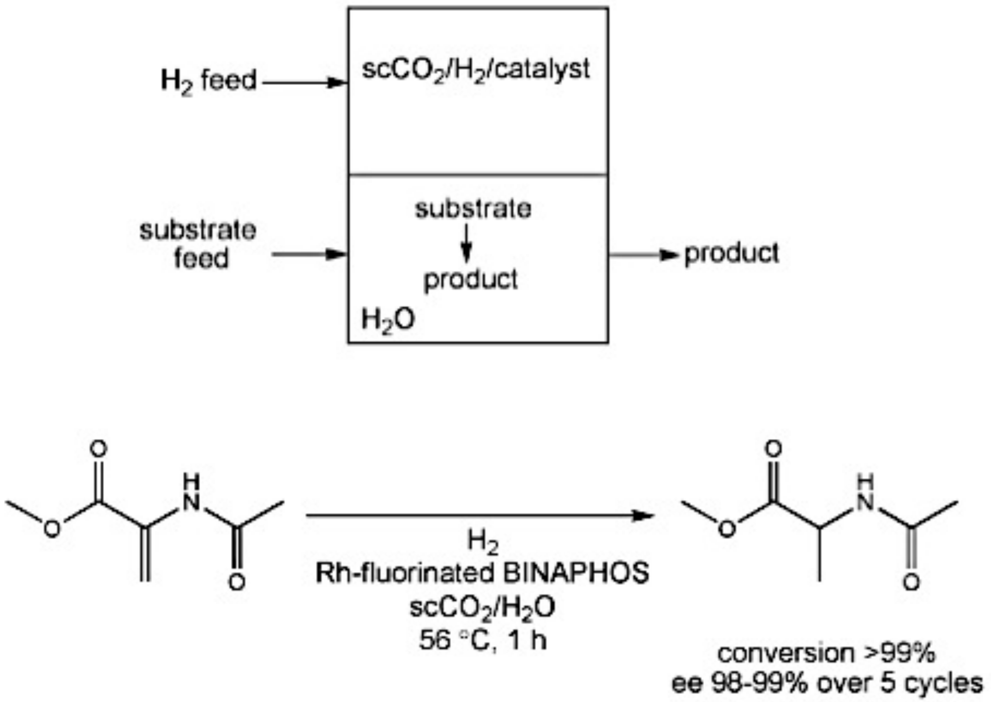


Figure 5.8 Inverted scCO$_2$–aqueous biphasic enantioselective hydrogenation reaction.

Chemical Synthesis

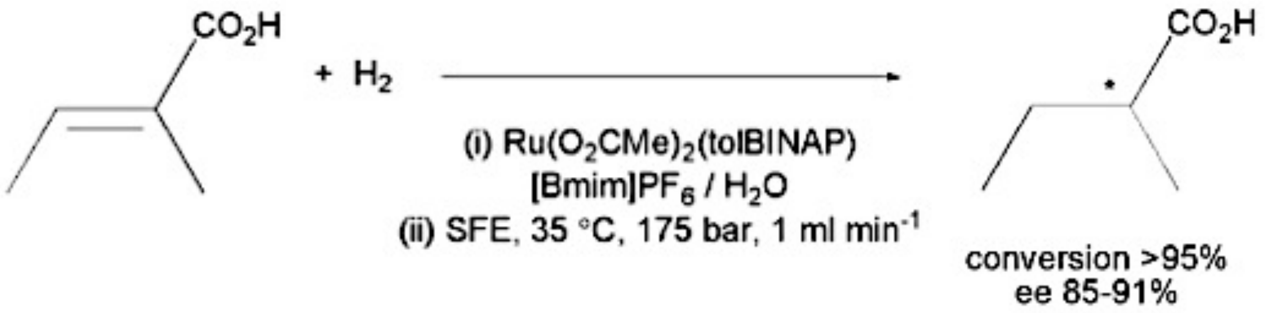


Figure 5.9 Hydrogenation in a biphasic ionic liquid-$scCO_2$ system.

Chemical Synthesis

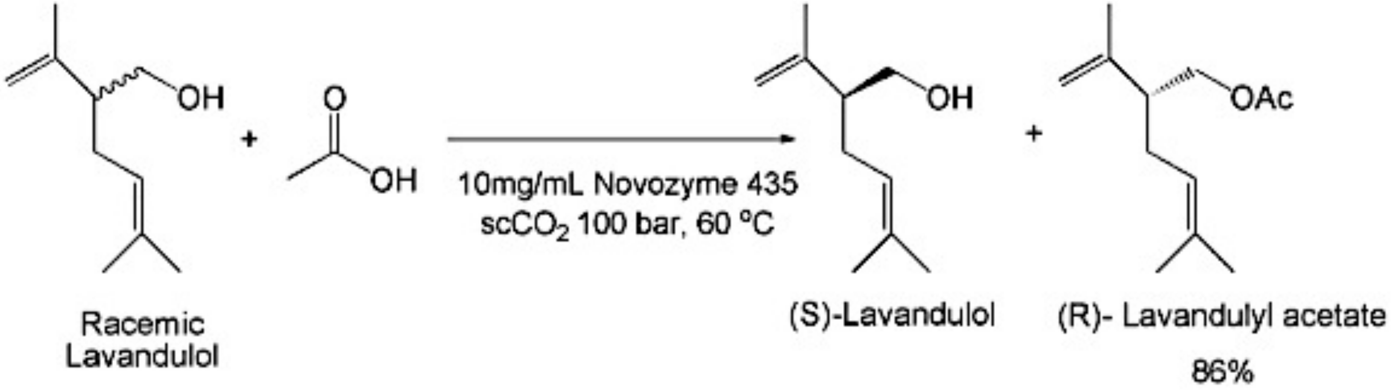


Figure 5.10 Biocatalytic esterification of biosourced chemicals.

Materials Synthesis and Modification

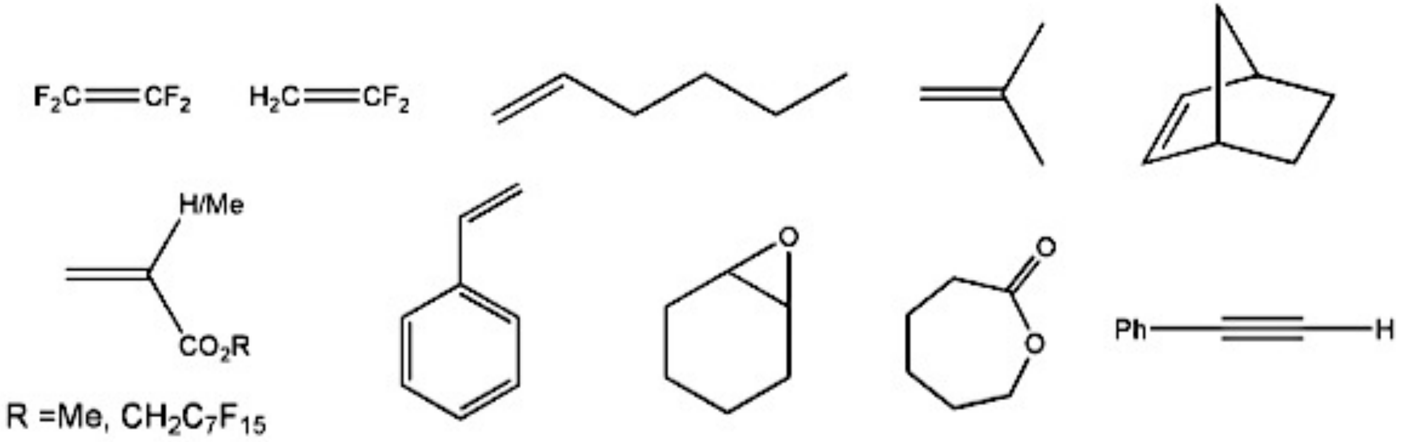


Figure 5.11 Selection of monomers polymerised in $scCO_2$.

SUPERCRITICAL FLUIDS

Supercritical Water and Near-Critical Water

Introduction

A wide and increasing range of synthetic reactions have been performed in near-critical (around 275 °C, 60 bar) and supercritical water (around 400 °C, 200 bar).

The solvent properties of near-critical water (NCW) are similar to a polar organic solvent such as acetone.

Introduction

As K_w increases with temperature, $[H_3O^+]$ and $[OH^-]$ concentrations are high compared to room temperature, and therefore, this leads to many of the interesting properties of NCW and SCW.

NCW is less corrosive than SCW and requires lower temperatures and pressures. Therefore, research using NCW has grown recently, especially in extractions and microwave-assisted syntheses.

Extraction

Supercritical water is rarely used in the extraction of natural products due to its corrosive nature and tendency to degrade (oxidize) organic compounds.

NCW, and even room-temperature pressurized water, have excellent properties for natural product extraction.

Extraction

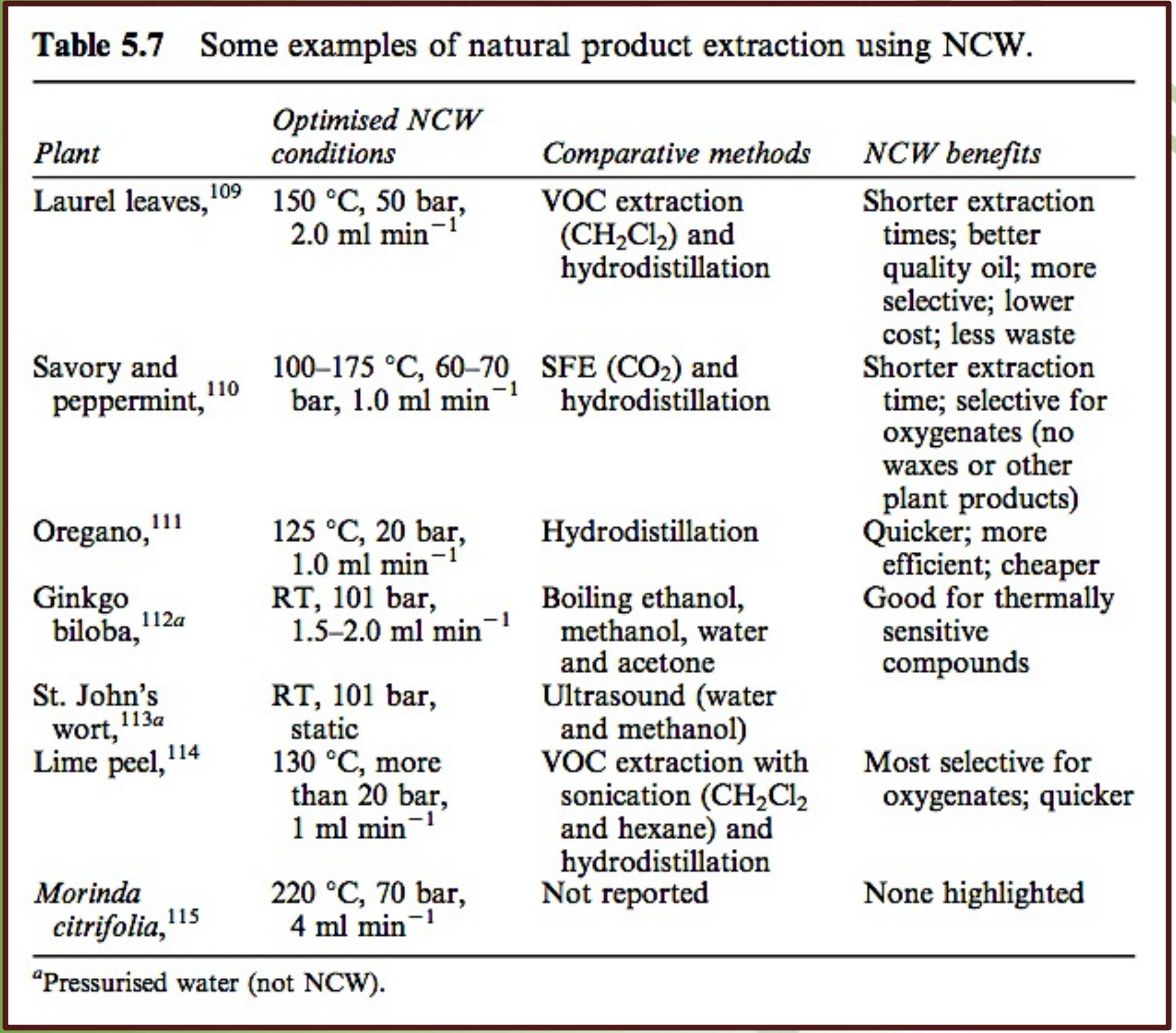


Table 5.7 Some examples of natural product extraction using NCW.

Plant	*Optimised NCW conditions*	*Comparative methods*	*NCW benefits*
Laurel leaves,[109]	150 °C, 50 bar, 2.0 ml min^{-1}	VOC extraction (CH_2Cl_2) and hydrodistillation	Shorter extraction times; better quality oil; more selective; lower cost; less waste
Savory and peppermint,[110]	100–175 °C, 60–70 bar, 1.0 ml min^{-1}	SFE (CO_2) and hydrodistillation	Shorter extraction time; selective for oxygenates (no waxes or other plant products)
Oregano,[111]	125 °C, 20 bar, 1.0 ml min^{-1}	Hydrodistillation	Quicker; more efficient; cheaper
Ginkgo biloba,[112a]	RT, 101 bar, 1.5–2.0 ml min^{-1}	Boiling ethanol, methanol, water and acetone	Good for thermally sensitive compounds
St. John's wort,[113a]	RT, 101 bar, static	Ultrasound (water and methanol)	
Lime peel,[114]	130 °C, more than 20 bar, 1 ml min^{-1}	VOC extraction with sonication (CH_2Cl_2 and hexane) and hydrodistillation	Most selective for oxygenates; quicker
Morinda citrifolia,[115]	220 °C, 70 bar, 4 ml min^{-1}	Not reported	None highlighted

[a] Pressurised water (not NCW).

Chemical Synthesis

As organic molecules show an increase in solubility in water as its temperature rises, chemical transformations performed in NCW are becoming more common

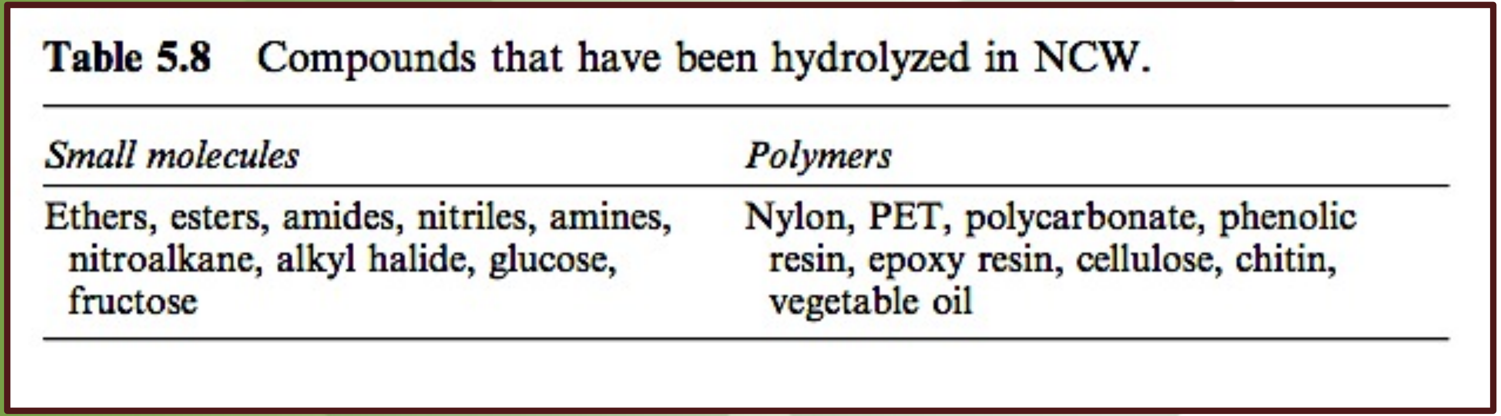


Table 5.8 Compounds that have been hydrolyzed in NCW.

Small molecules	*Polymers*
Ethers, esters, amides, nitriles, amines, nitroalkane, alkyl halide, glucose, fructose	Nylon, PET, polycarbonate, phenolic resin, epoxy resin, cellulose, chitin, vegetable oil

Chemical Synthesis

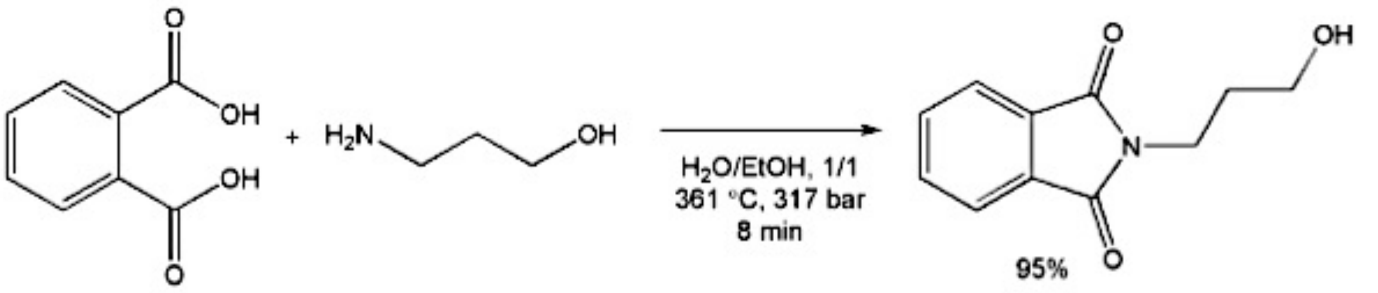
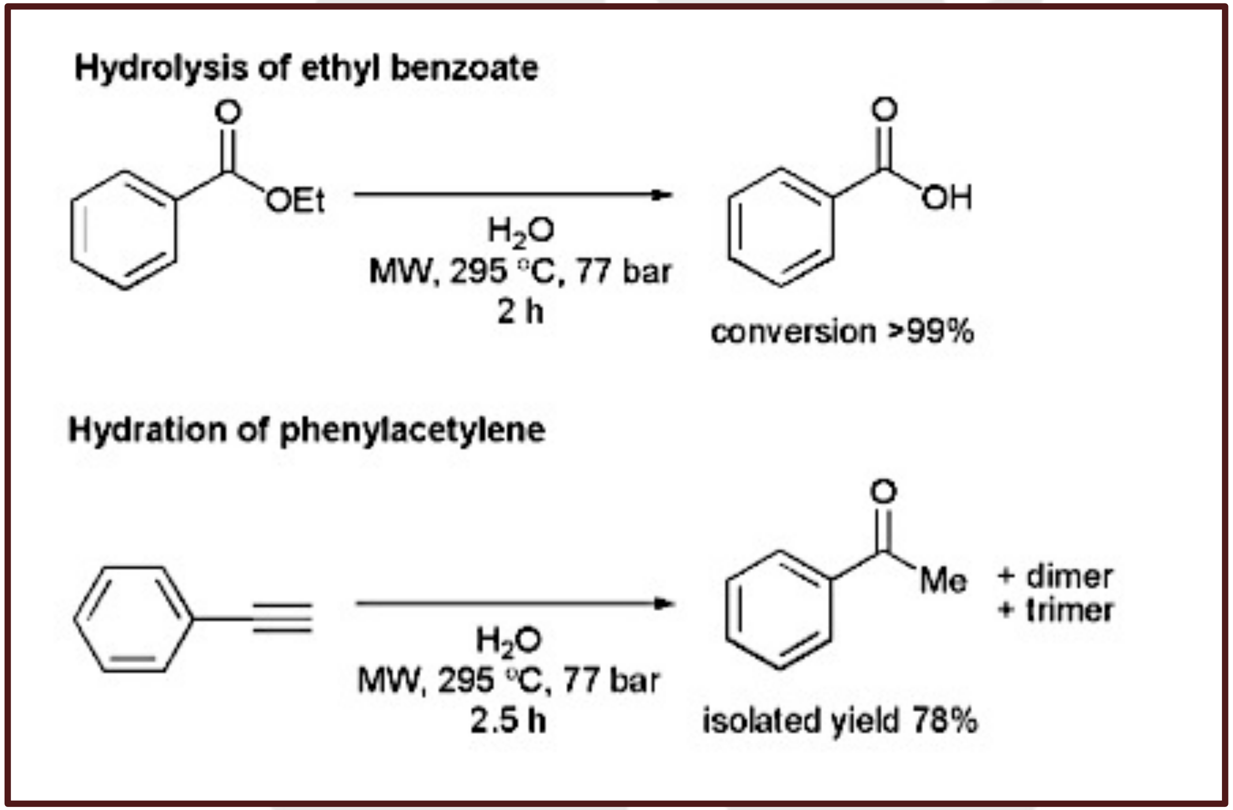
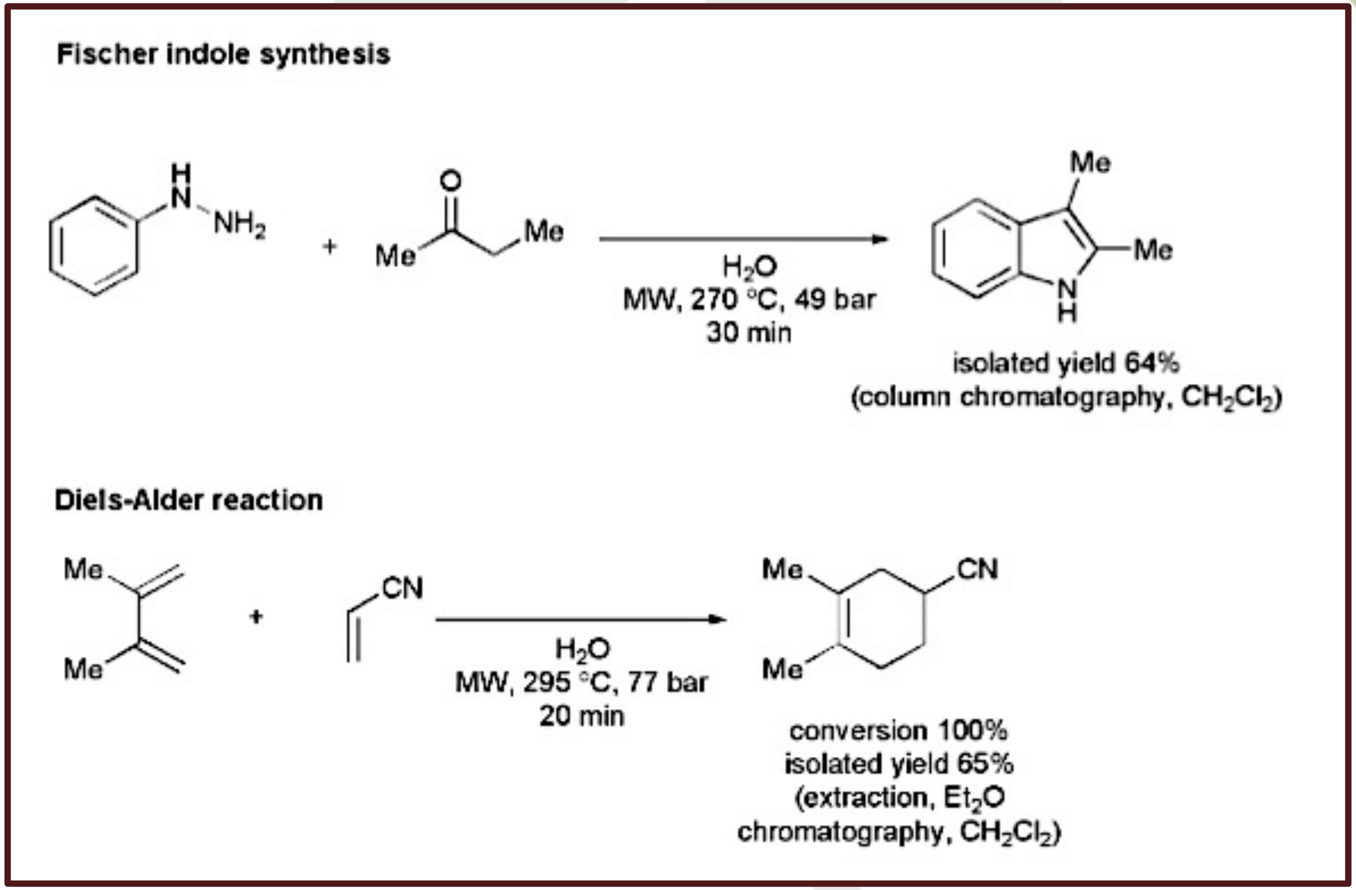


Figure 5.12 Phthalimide synthesis in a high-pressure and -temperature ethanol–water mixture.

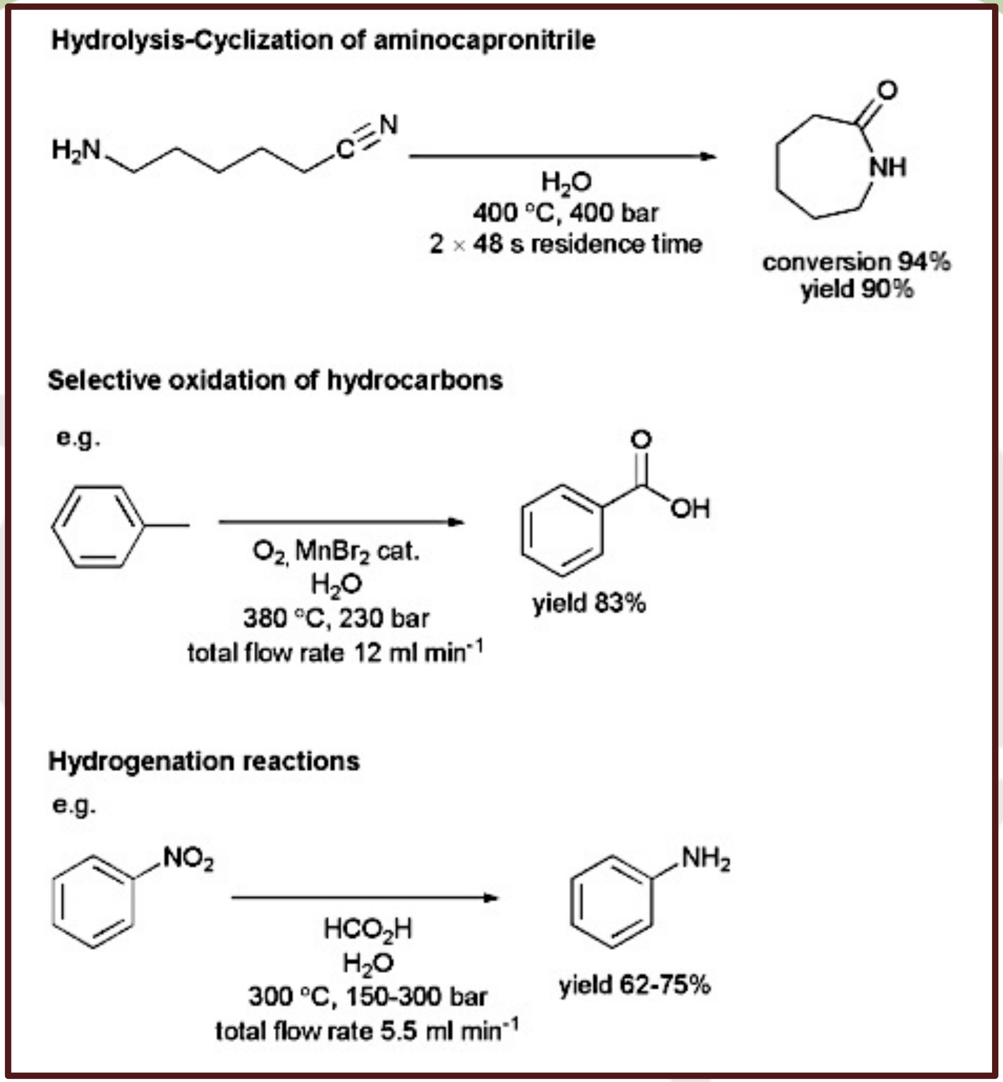
Chemical Synthesis



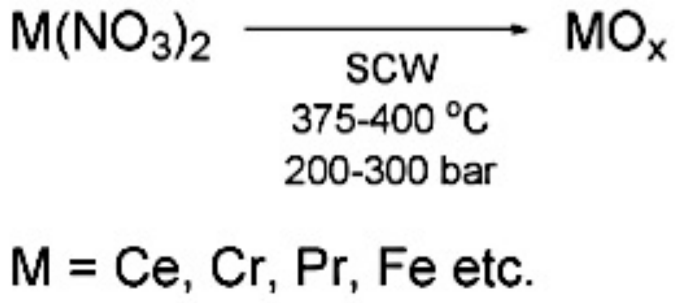
Chemical Synthesis



Chemical Synthesis



Materials Synthesis



$$M(NO_3)_2 \xrightarrow[\substack{\text{375-400 °C} \\ \text{200-300 bar}}]{\text{SCW}} MO_x$$

M = Ce, Cr, Pr, Fe etc.

Figure 5.15 Typical synthesis of metal oxides in SCW.

Supercritical Water Oxidation (SCWO)

SCW is an excellent medium for the total oxidation of unwanted and hazardous organic compounds such as those that need to be removed from wastewater and process streams

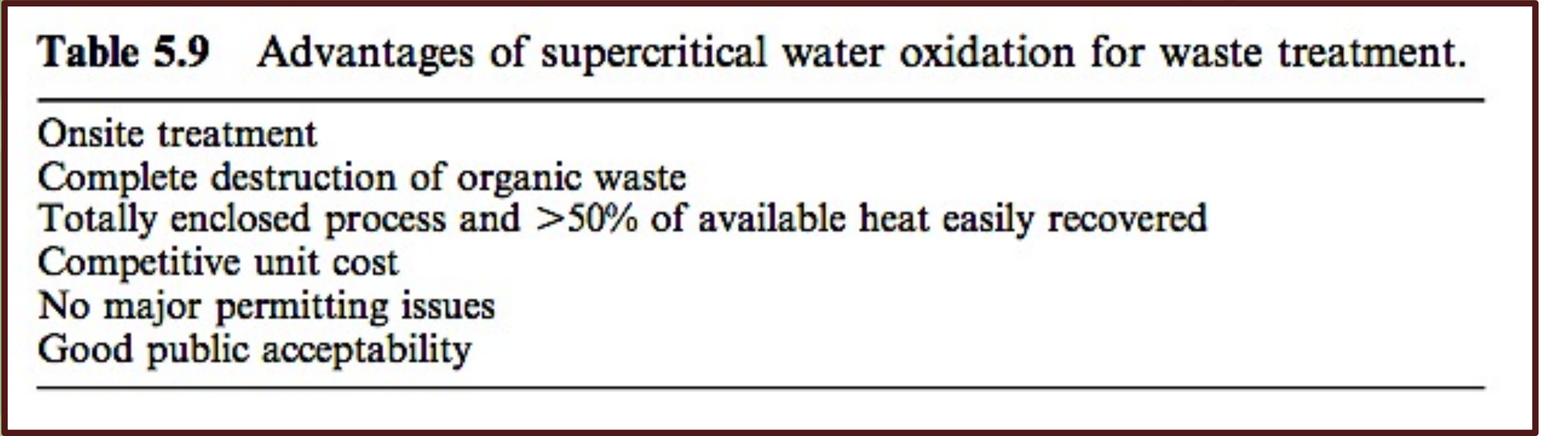


Table 5.9 Advantages of supercritical water oxidation for waste treatment.

Onsite treatment
Complete destruction of organic waste
Totally enclosed process and >50% of available heat easily recovered
Competitive unit cost
No major permitting issues
Good public acceptability

SUPERCRITICAL FLUIDS

Supercritical Alcohols

Introduction

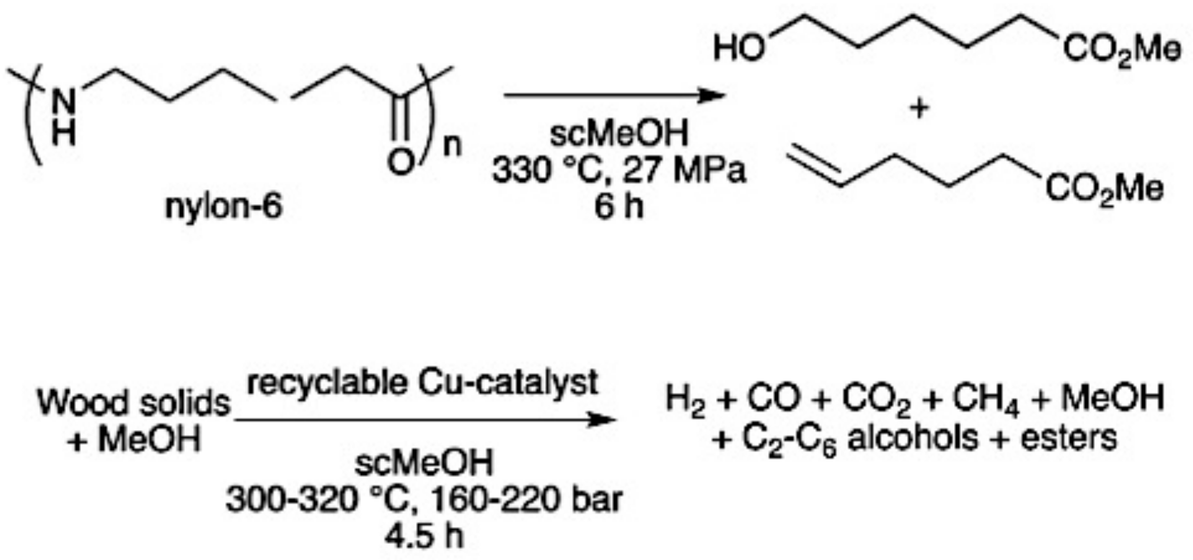


Figure 5.16 Depolymerisation of nylon-6 and conversion of cellulose into fuels in scMeOH.