聲明

永續合成工作坊(4)

“綠色”溶劑與無溶劑反應

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- 溶劑是化學廢棄物的大宗，那些方向有助於改變現況?
- (I)傳統溶劑(藥品)的安全(綠色)考量:
- EHS, LCA, NFPA 704
- (II)傳統溶劑的減量(使用與回收)
- (III)無溶劑反應
- (IV)非傳統溶劑
- (V)尋找綠色溶劑的挑戰

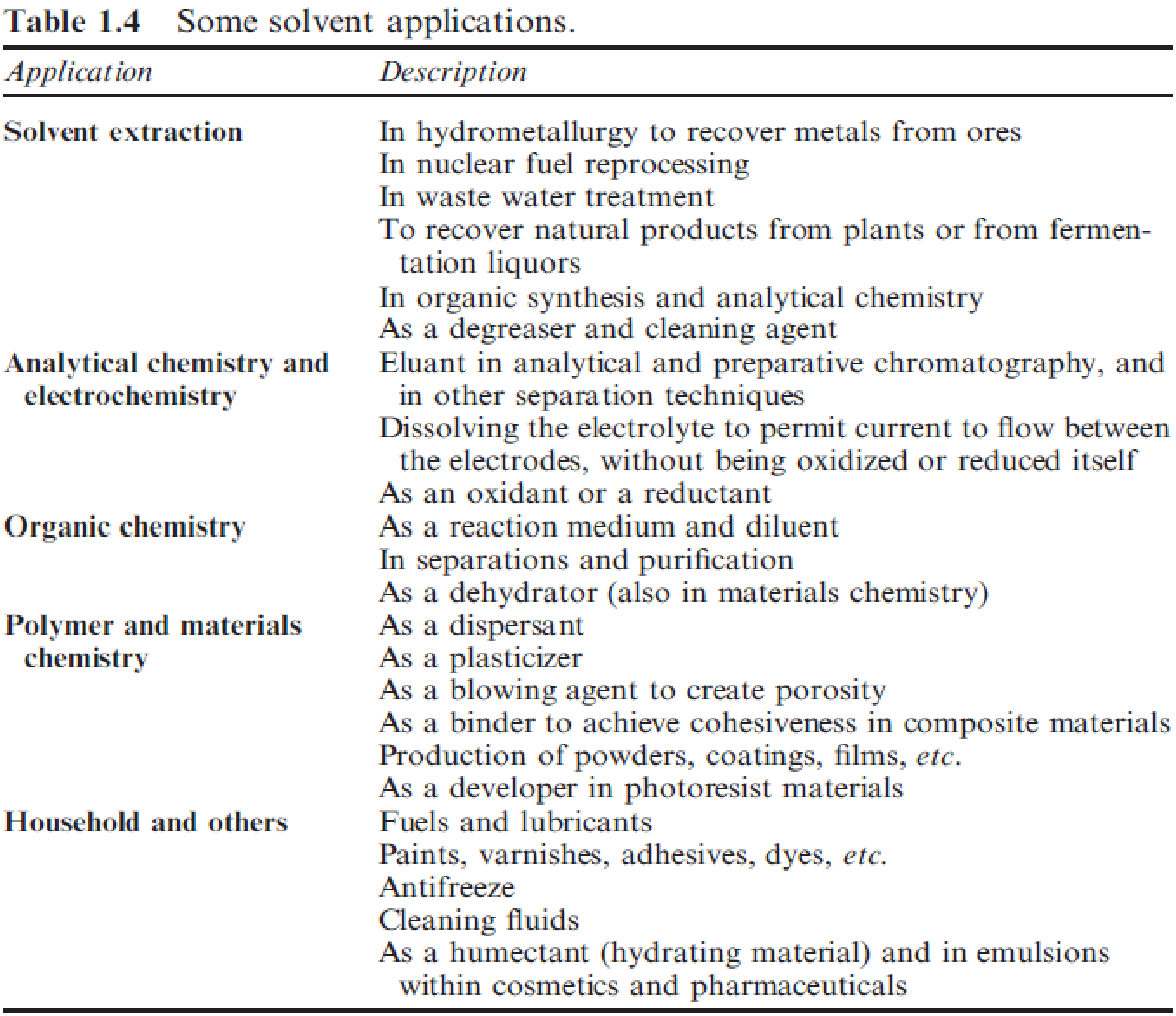


Table 1.4 Some solvent applications.

Application	*Description*
Solvent extraction	In hydrometallurgy to recover metals from ores
	In nuclear fuel reprocessing
	In waste water treatment
	To recover natural products from plants or from fermentation liquors
	In organic synthesis and analytical chemistry
	As a degreaser and cleaning agent
Analytical chemistry and electrochemistry	Eluant in analytical and preparative chromatography, and in other separation techniques
	Dissolving the electrolyte to permit current to flow between the electrodes, without being oxidized or reduced itself
	As an oxidant or a reductant
Organic chemistry	As a reaction medium and diluent
	In separations and purification
	As a dehydrator (also in materials chemistry)
Polymer and materials chemistry	As a dispersant
	As a plasticizer
	As a blowing agent to create porosity
	As a binder to achieve cohesiveness in composite materials
	Production of powders, coatings, films, *etc.*
	As a developer in photoresist materials
Household and others	Fuels and lubricants
	Paints, varnishes, adhesives, dyes, *etc.*
	Antifreeze
	Cleaning fluids
	As a humectant (hydrating material) and in emulsions within cosmetics and pharmaceuticals

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009.

綠色量度

Sheldon E-factor = mass of waste produced/mass of desired product

環境因數

- The E-factor includes all auxiliary materials and takes into account the yields and selectivities of the reactions. However, it does not take into account the toxicities or other environmental hazards of the waste products, nor does it encompass the **energy** used in the process.
- Hence, changing solvents, leading to greater selectivities or more effective separation, can reduce (improve) the E-factor for the reaction. However, using a less toxic solvent or changing related reaction rates has no influence on the E-factor.

Chemical's EHS file

- An Environmental Health and Safety (EHS) tool has been developed to assess the direct environmental risks of a chemical compound. The EHS profile is calculated by considering for the environmental persistency, air hazard, and water hazard; for safety: release potential, fire/explosion risk, and irritation. Any compound is given a score for each of these factors, which are then summed to give an overall EHS profile.

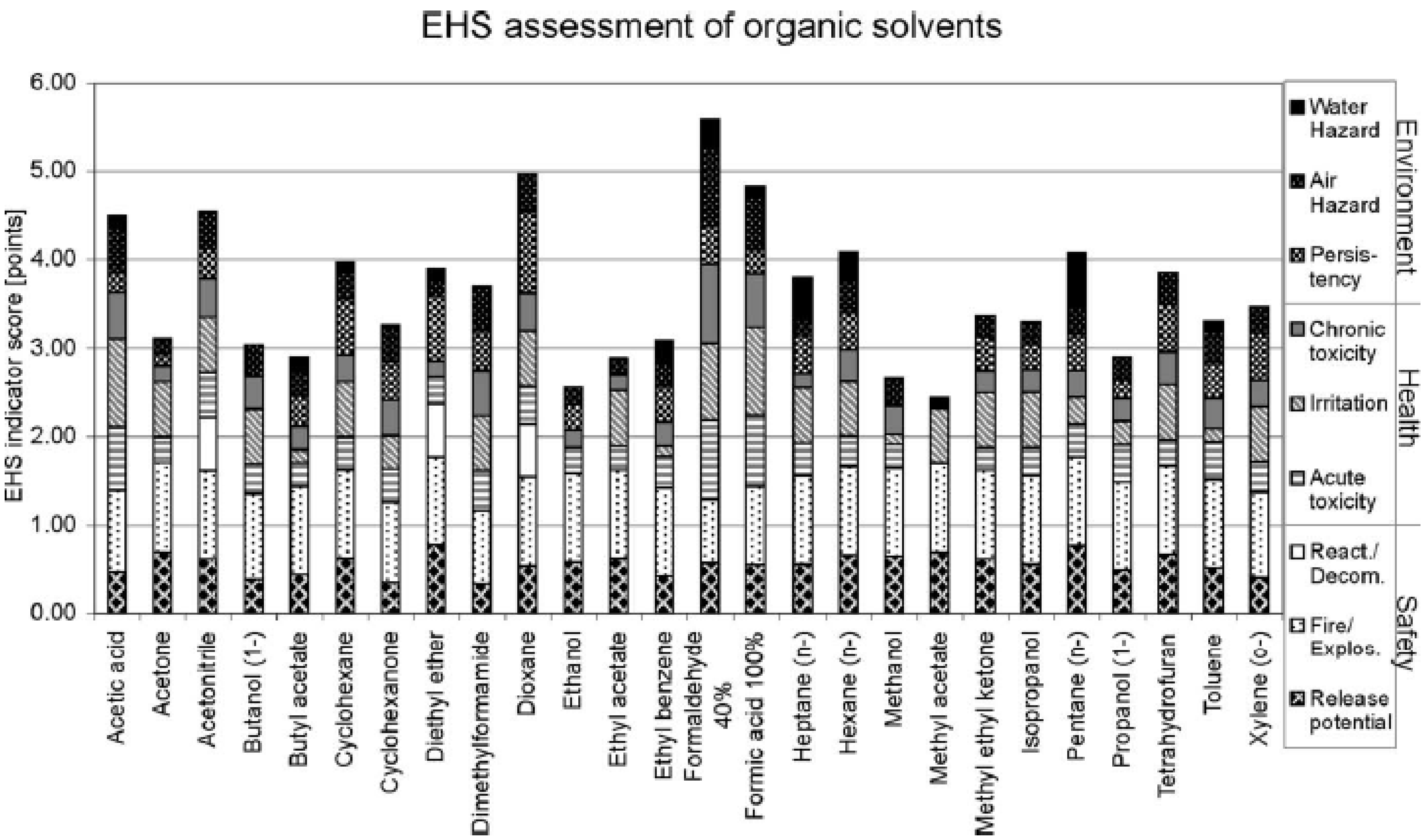


Fig. 2 Results of the EHS method for the 26 pure organic solvents (step (1) in the framework for the assessment of green solvents). The EHS result score is composed of environmental indicators (water and air hazard, persistency), as well as indicators for health (chronic and acute toxicity and irritation)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

Green Chem. 2007, 9, 927-934.

Life Cycle Assessment (LCA)

- The gold standard for the quantification of greeness is the full LCA.
- The LCA seeks to assess the environmental impact of the production and use of a chemical product encompassing all stages of its life from the sourcing of its ingredients through its production, with the inclusion of all auxiliary substances used therein, to its transportation and use, and finally its eventual destination in the environment.

- Full life-cycle assessments
    - Chemists often do not know how the chemicals they use are made
    - Chemists often do not know how their chemistry affects the biosphere

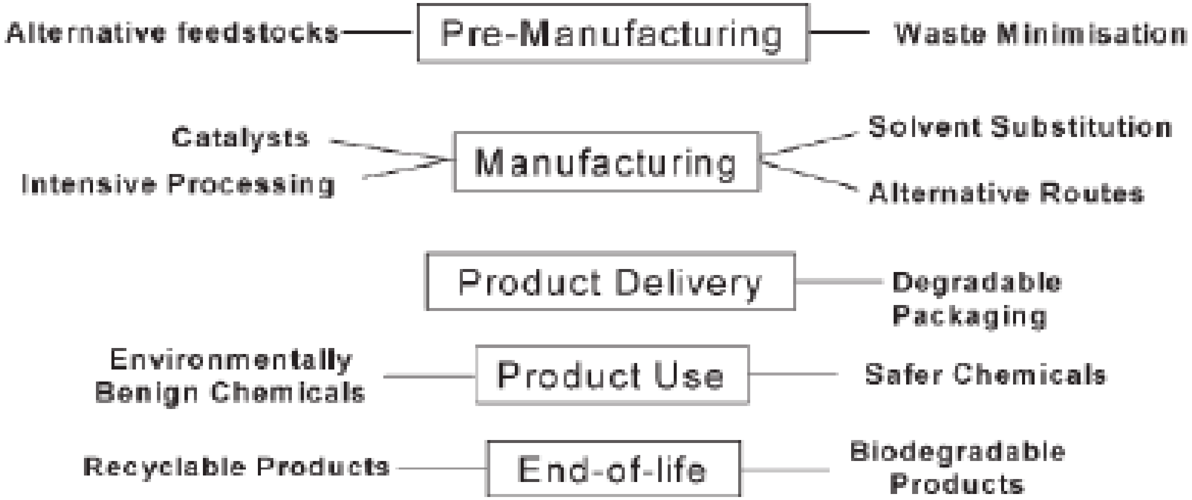
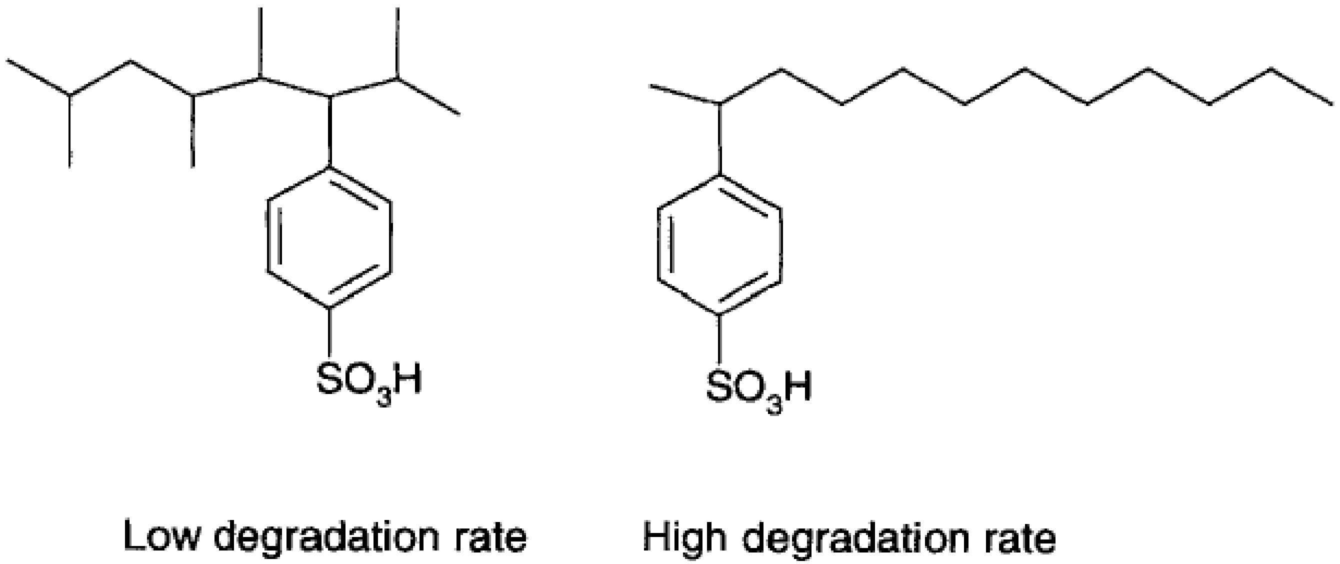


Fig. 3 Green chemistry applied from the cradle to the grave.

"Green Chemistry: Today (and Tomorrow)", J. H. Clark, *Green Chem.* 2006, 8, 17-21.

Long aliphatic chains degrade more readily than branched



Scheme 2.7 *Structure/degradation relationship for alkylbenzene sulfonates*

From: Lancaster, M. “Green Chemistry: An Introductory Text”, RSC, 2002, Chapter 2, p. 46.

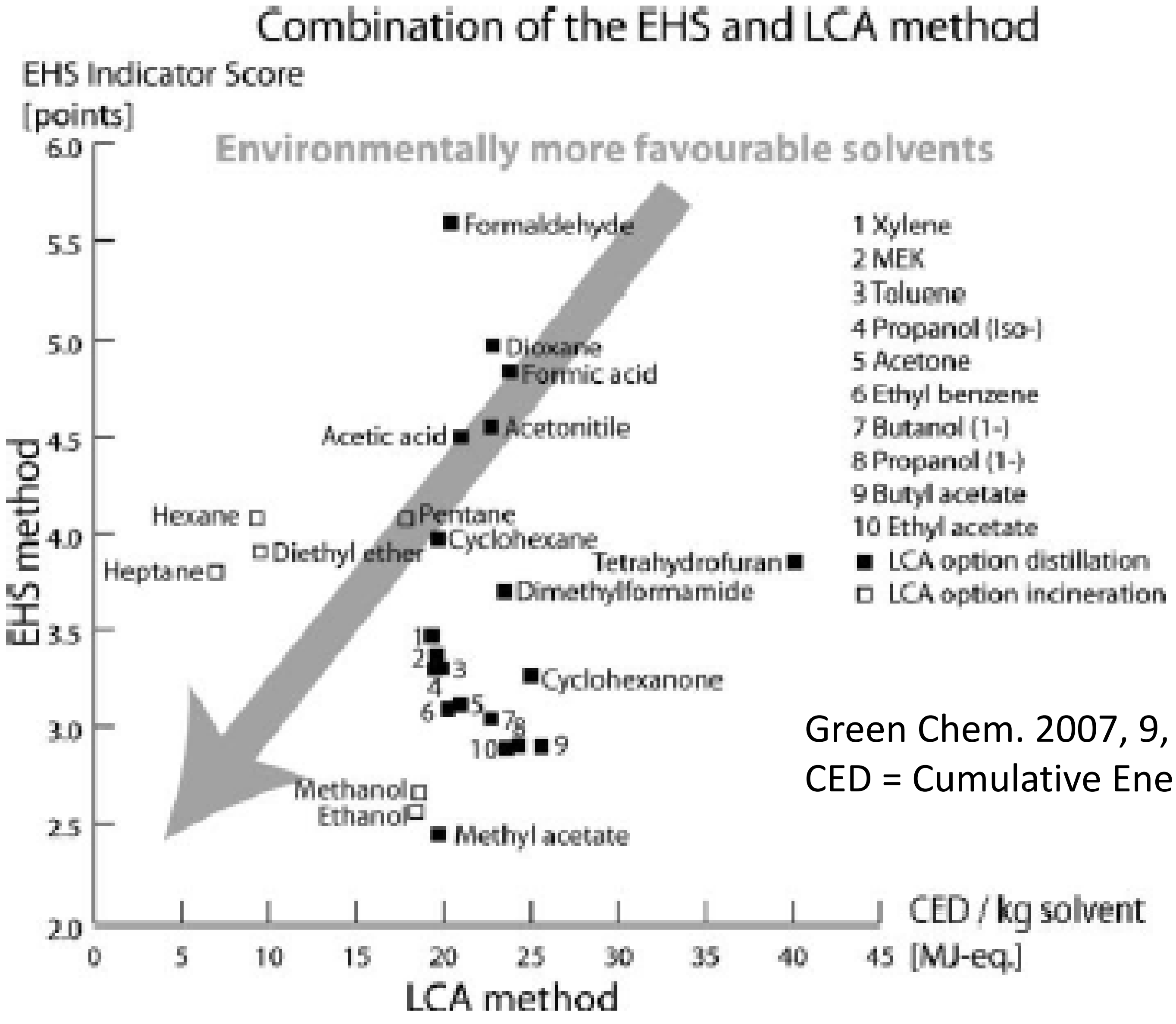
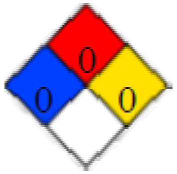
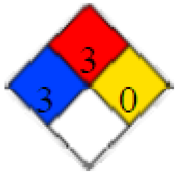
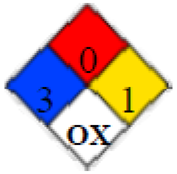
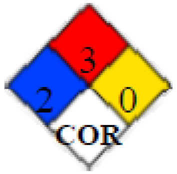
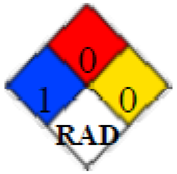
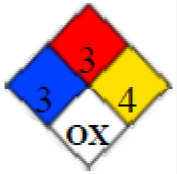


Fig. 4 Environmental assessment of the 26 organic solvents: combination of the EHS method with the LCA method (step (3) of the framework for the assessment of green solvents).

Green Chem. 2007, 9, 927-934.
CED = Cumulative Energy Demand

Safety of Chemicals- NFPA 704

- **NFPA 704**是美國消防協會 (National Fire Protection Association) 制定的危險品緊急處理系統鑒別標準。它提供了一套簡單判斷化學品危害程度的系統，並將其用藍、紅、黃、白四色的警示菱形來表示。
- 警示菱形按顏色分為四部分：藍色表示健康危害性；紅色表示可燃性；黃色表示反應性；白色用於標記化學品的特殊危害性。前三部分根據危害程度被分為0、1、2、3、4，五個等級，用相應數字標識在顏色區域內。

水	甲醇	鉻酸鉀	三乙胺	乙酸鈾醯	三硝基苯酚
					

- **白色／特殊危害性**
- 警示菱形的白色區域可能有以下符號：
- W（有時被寫作W）：與水發生劇烈反應。如：鈣。
- OX（有時被寫作OXY）：氧化劑。如：高錳酸鉀。
- 以上兩個符號是NFPA 704標準中規定的符號，除此之外，化學品廠商有時還使用以下符號標記在白色區域：
- COR：腐蝕性。如：濃硫酸。
  - ACID：強酸。如：鹽酸。
  - ALK：強鹼。如：氫氧化鈉，氫氧化鈣。
- BIO或☣（☣ ）：生物危害性。如：溴化乙錠。
- RAD或☢ ：放射性。如：鈾。
- CRY 或 CRYO：低溫。如：液氮。

Rowan solvent greenness index

(Slater and Savelski)

- Inhalation Toxicity – Threshold Limit Value (TLV)
- Ingestion Toxicity
- Biodegradation
- Aquatic Toxicity
- Carcinogenicity
- Half-Life
- Ozone Depletion
- Global Warming Potential
- Smog Formation
- Acidification
- Soil Adsorption Coefficient
- Bioconcentration Factor

(*Chem. Soc. Rev.* **2012**, *41*, 1452-1461)

Slater and Savelski, Environ. Sci. Health, (A), 2007, 42, 1-11.

II. Reduction of Traditional Solvent Use

- The reduction of the use of auxiliary substances, such as solvents, is important to the green chemistry endeavor that was expressed as one of the 12 Principle of Green Chemistry: Very few auxiliary substances.
- Why?

Traditional Solvent

- Most solvents are volatile organic compounds (VOCs) that can easily disperse in the environment and many show both acute and chronic toxicities.
- Solvents are often used in large quantities. It was previously reported that solvents make up to 35% of all the VOCs, that released into the atmosphere. It was also estimated that 80-90% of the waste generated by the production of a pharmaceutical is the solvent(s) used. The solvent used is responsible for half of the greenhouse gas emission of the process.

How can the reduction of the use of traditional solvents be achieved?

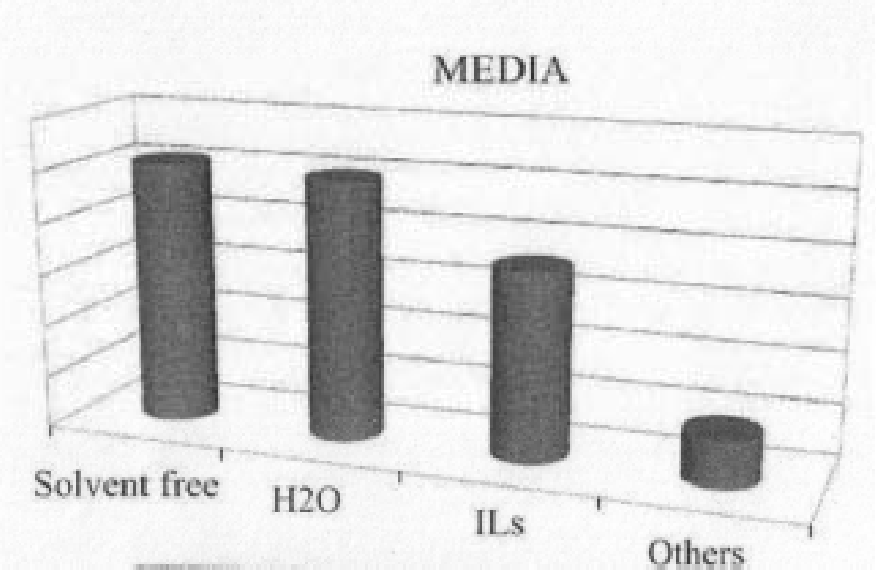
- (1) Solventless synthesis or reactions in the gas phase with solid catalyts.
- (2) Step-economy (i.e., reducing the number of reaction steps). The synthesis of Viagra from an initial discovery chemistry route into the final optimized production route can reduce the solvent use from 1300 to 7 L/Kg.
- (3) Solvent recovery (current about 50-80%*) and recycling
- However, it is not always possible to eliminate solvent use from the synthesis of chemicals.

* from: Zhang, W.; Cue, B. W. “Green techniques for organic synthesis and medicinal chemistry”, Wiley, 2012, Chap. 11.
感謝台大化學系劉廣定教授提供

溶劑的回收與處理

- Chemical treatment technologies for **waste-water** recycling—an overview (*RCS Adv*. **2012**, *2*, 6380-6388)
- STEP wastewater treatment: A solar thermal electrochemical process for pollutant oxidation (*ChemSusChem* **2012**, *5*, 2000-2010)
- The importance of **acetonitrile** in the pharmaceutical industry and opportunities for its recovery from waste (*Org. Process Res. Dev*. **2012**, *16*, 612-624)
- Green design alternatives for **isopropanol** recovery in the celecoxib process (*Clean Techn. Environ. Policy* **2012**, *14*, 697-698)
- Pervaporation as a green drying process for **tetrhydrofuran** recovery in pharmaceutical synthesis (*Green Chem. Lett. Rev*. **2012**, *5*, 55-64)

• Solvent-free/solid state reactions



2008 論文相對數量分析
(*Green Chem. Lett. Rev.* **2010**, *3*, 105-113)

Can be applied to solid-solid, solid-liquid, solid-gas, liquid-liquid, and liquid-gas reactions

Recent literatures:

Solid-state dynamic combinatorial chemistry; mechanosynthesis (*Chem. Sci.* **2011**, *2*, *696-700*)

Ball milling in organic synthesis (*Chem. Soc. Rev.* **2011**, *40*, 2317-2329)

Three-component solvent-free synthesis of highly substituted tetrahydroimidazo[1,2-a]pyridines (*RSC Adv.* **2011**, *1*, 596-601)

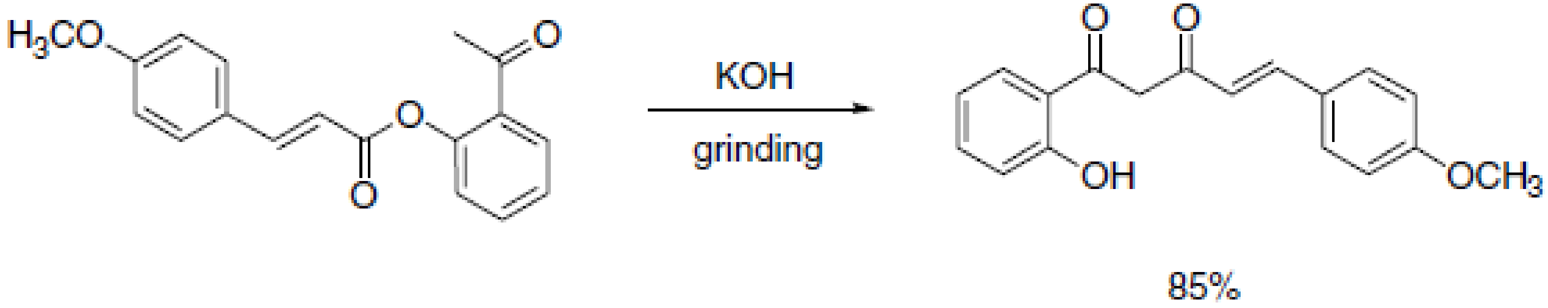
Electrochemical allylation of aldehydes in a solvent-free cavity cell with a graphite powder cathode (*Green Chem.* **2011**,*13*, 1118-1120)

and many more

Cf. 2011 永續合成工作坊---劉廣定教授: 非傳統反應方法與溶劑 p. 15

Chem. Soc. Rev. 2012, 41, 1559-1584.

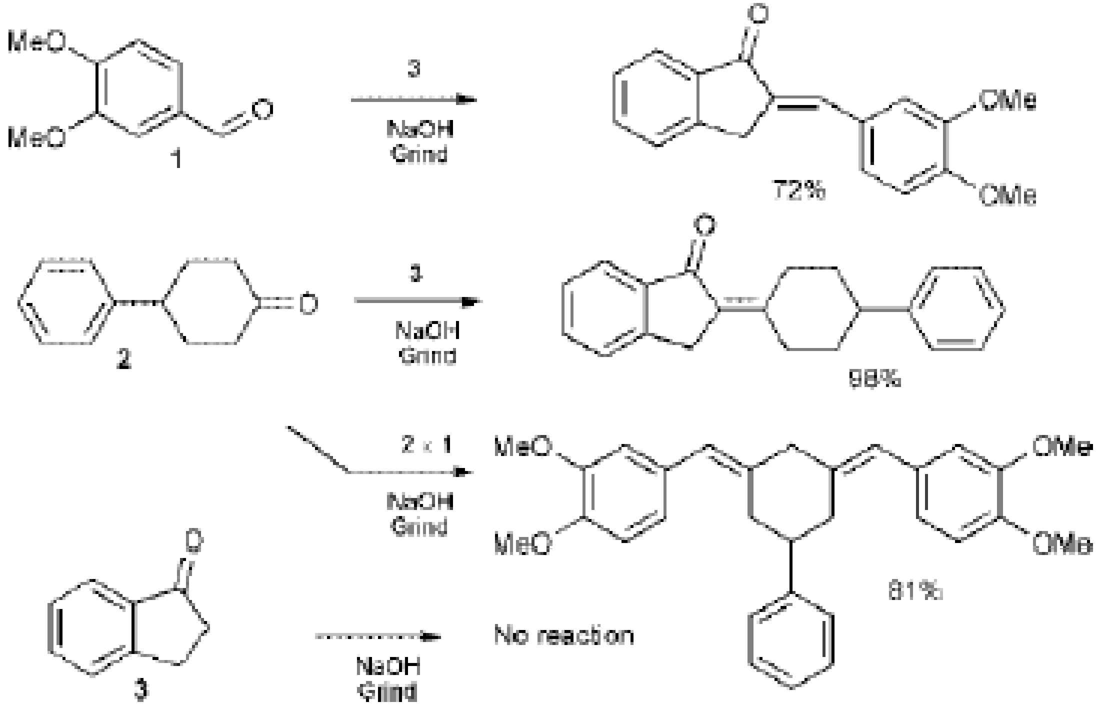
Grinding with a mortar and pestle



Scheme 11.1 *Recent example of a Baker–Venkataraman rearrangement using a mortar and pestle.*

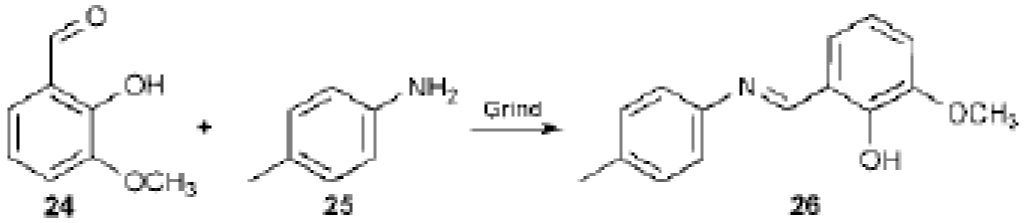
from: Zhang, W.; Cue, B. W. “Green techniques for organic synthesis and medicinal chemistry”, Wiley, 2012, Chap. 11.
感謝台大化學系劉廣定教授提供

Solvent-free Reactions



"Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Versatility"
G. W. V. Cave, C. L. Raston and J. L. Scotta, *Chem. Commun.*, **2001**, 21, 2159-2169.

Solvent-free Reactions



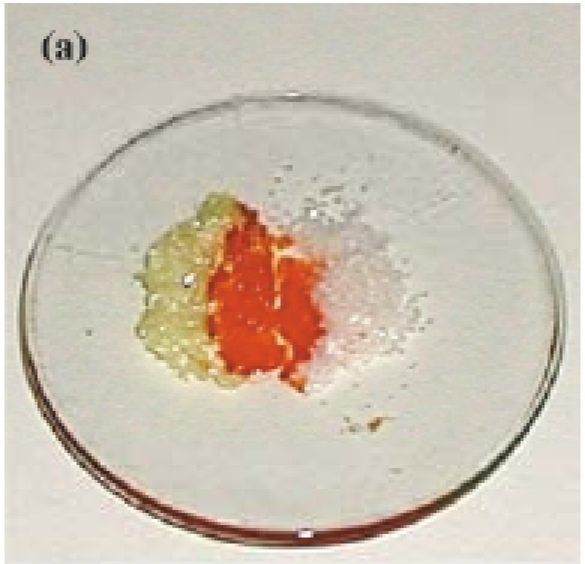
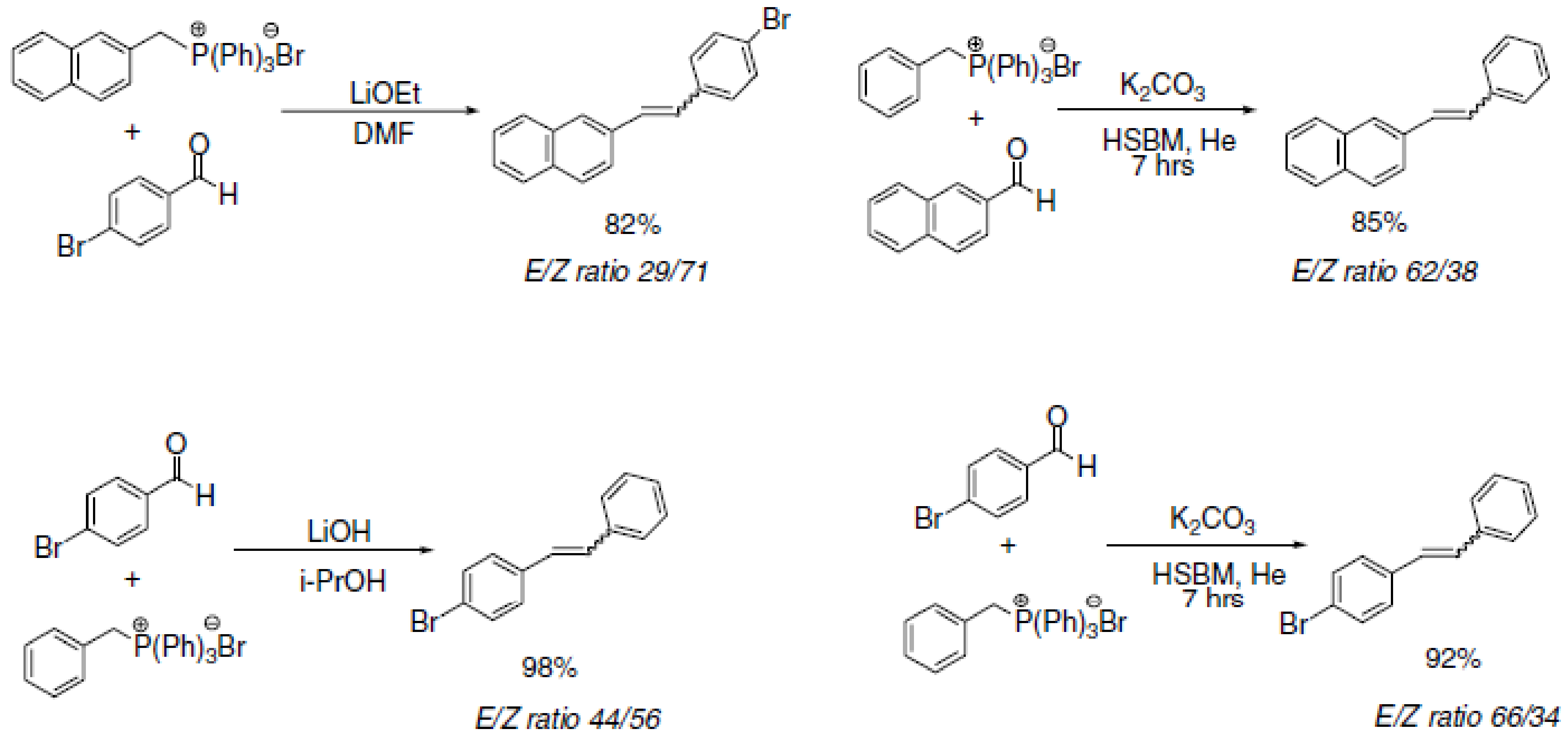


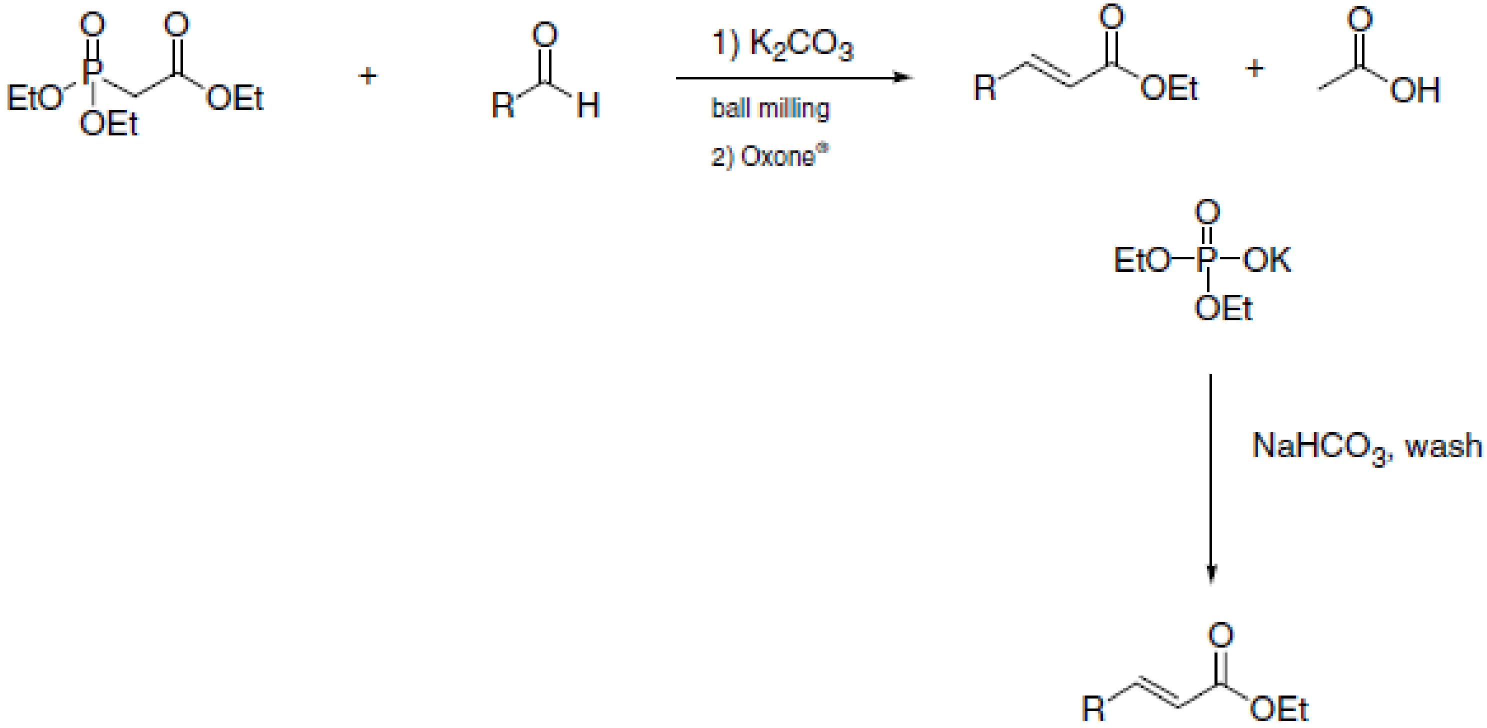
Fig. 7 Photographs of liquid phase formed upon mixing of *o*-vanillin and *p*-toluidine. (a) Pale yellow crystalline *o*-vanillin (left) and white crystalline *p*-toluidine (right) form an orange liquid phase upon contact

"Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Versatility"
G. W. V. Cave, C. L. Raston and J. L. Scotta, *Chem. Commun.*, **2001**, 21, 2159-2169.

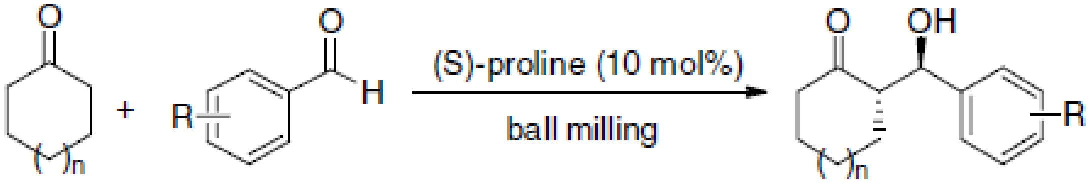
Ball milling



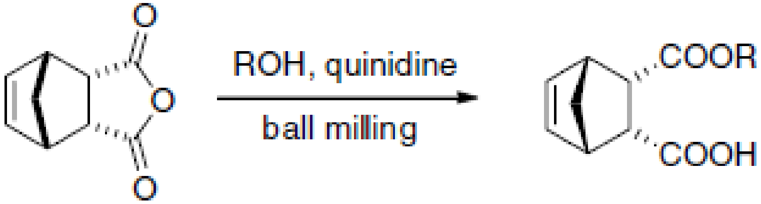
Scheme 11.2 *Wittig reaction under solvent-free ball milling conditions. Using solvent-free ball milling conditions the product has a strong preference for the trans stereoisomer, whereas the cis stereoisomer is preferred in solution.*



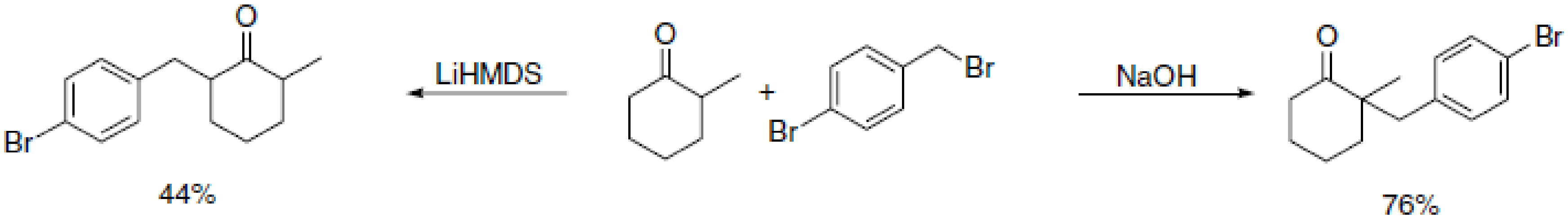
Scheme 11.3 Horner–Wadsworth–Emmons reaction using solvent-free ball milling. Oxone® was added in a second ball milling step to allow for solvent-free isolation of the products.



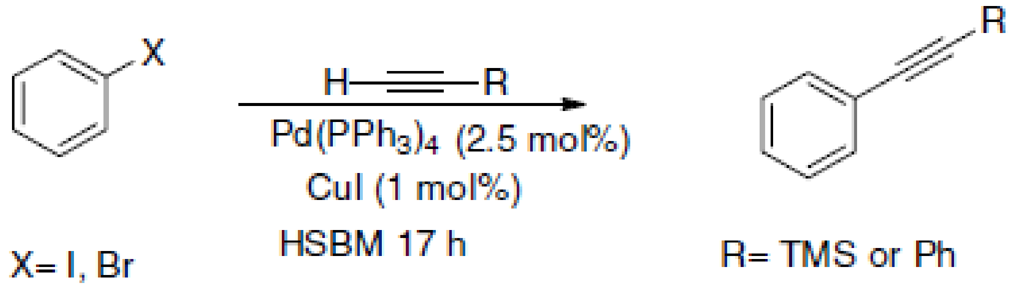
Scheme 11.4 Enantioselective aldol condensation under solvent-free ball milling conditions.



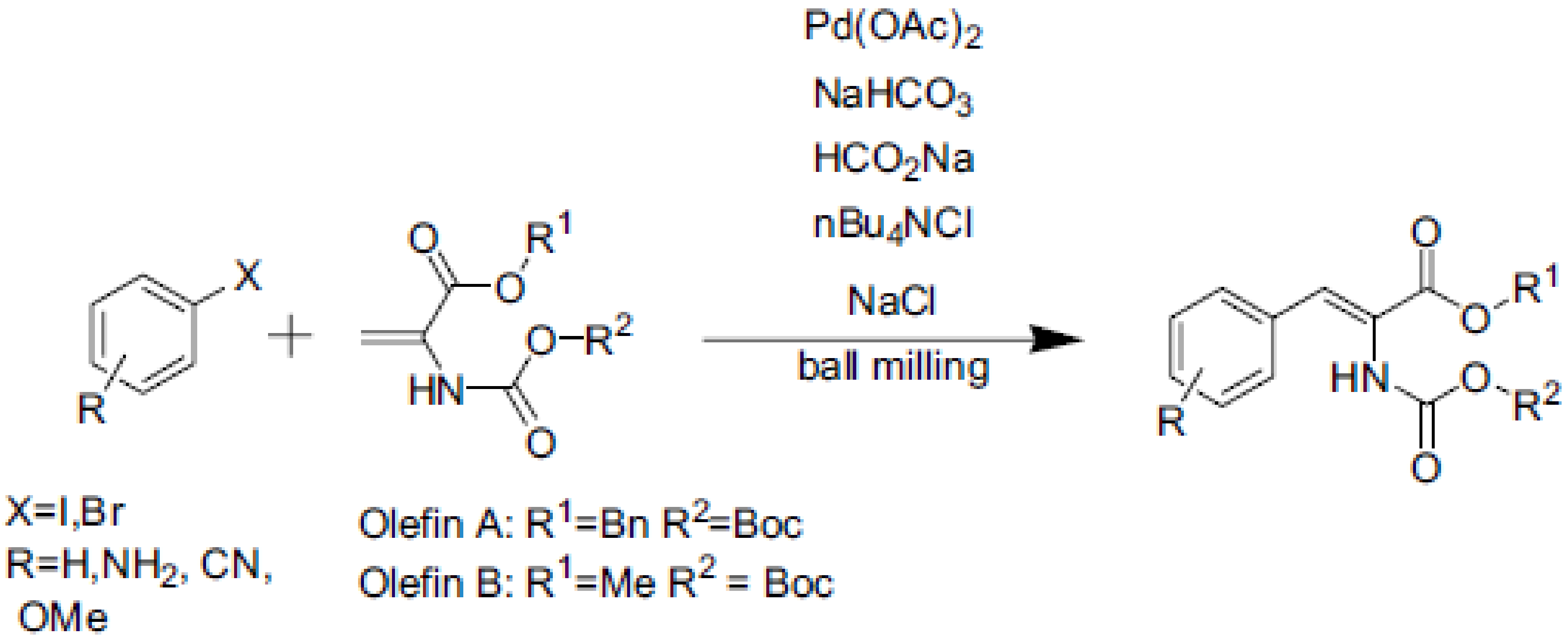
Scheme 11.5 Enantioselective ring opening of cyclic anhydrides under solvent-free ball milling conditions.



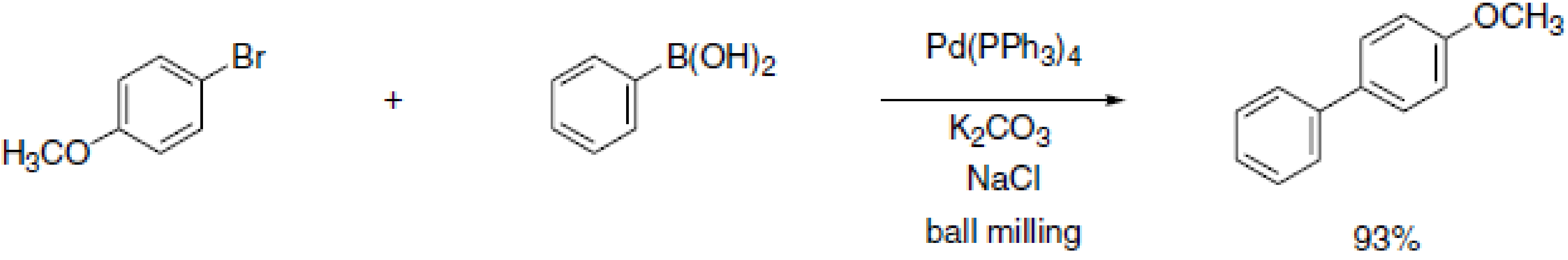
Scheme 11.6 Regioselective formation of the kinetic and thermodynamic enolate under solvent-free ball milling conditions.



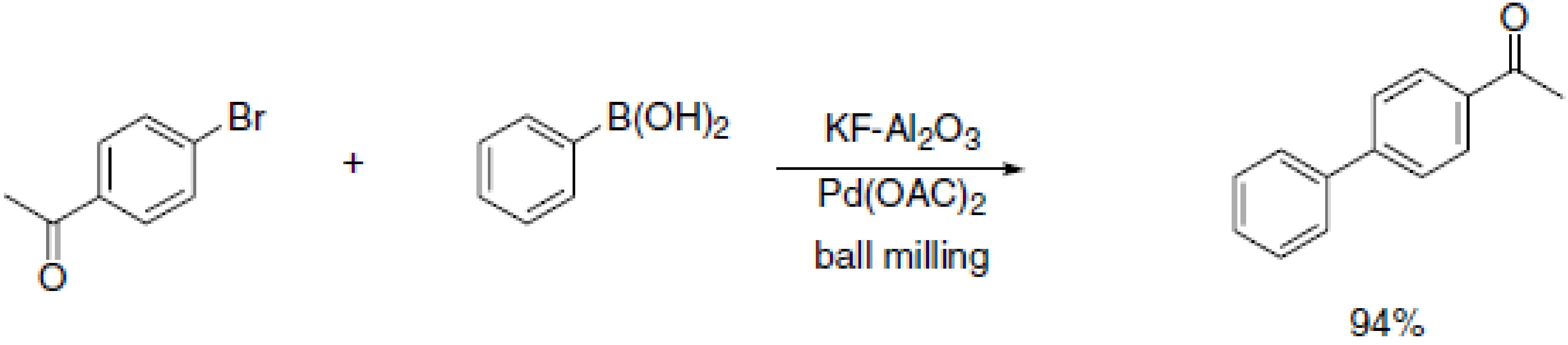
Scheme 11.7 *Sonogashira reaction under solvent-free high speed ball milling conditions.*



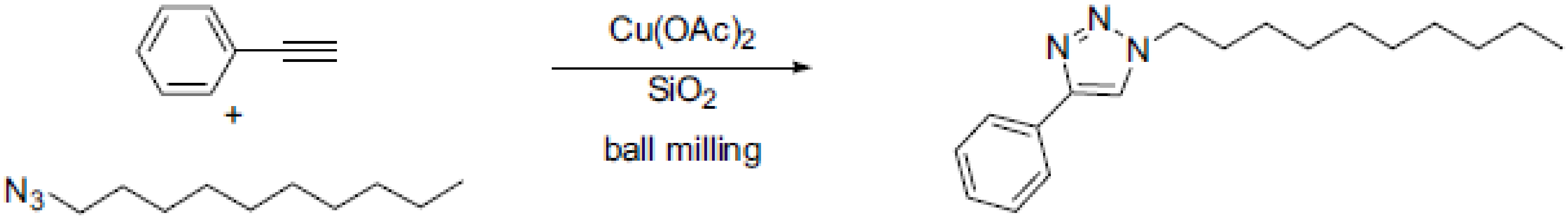
Scheme 11.10 *Example of the ball milled Heck reaction.*



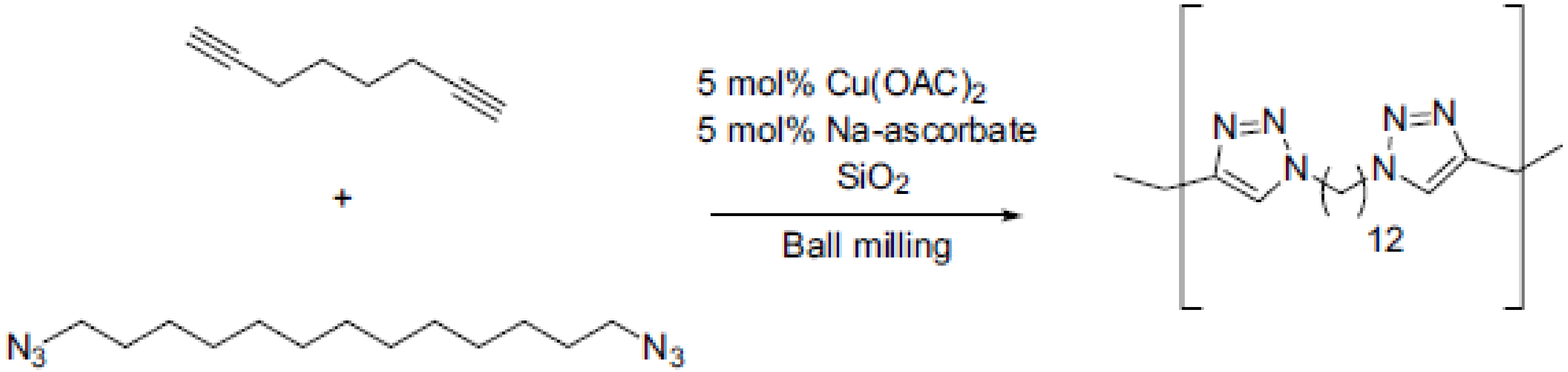
Scheme 11.12 *Suzuki reaction using potassium carbonate and sodium chloride.*



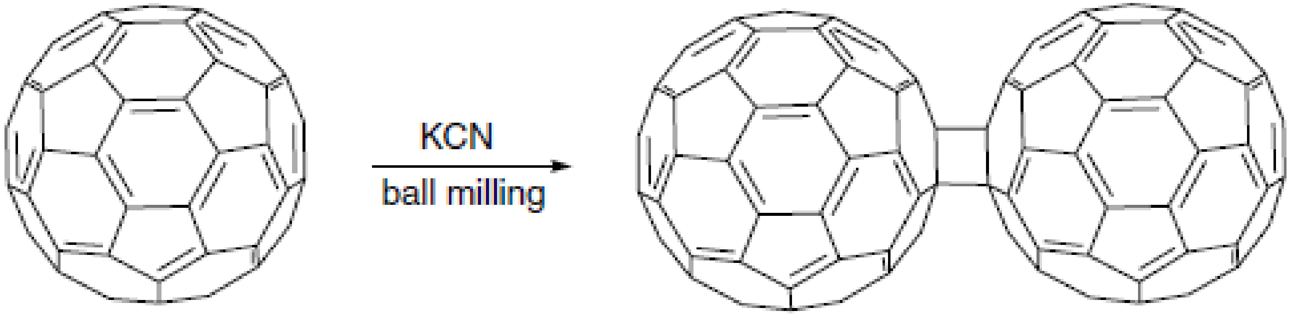
Scheme 11.13 *Suzuki reaction in the presence of KF-Al_2O_3.*



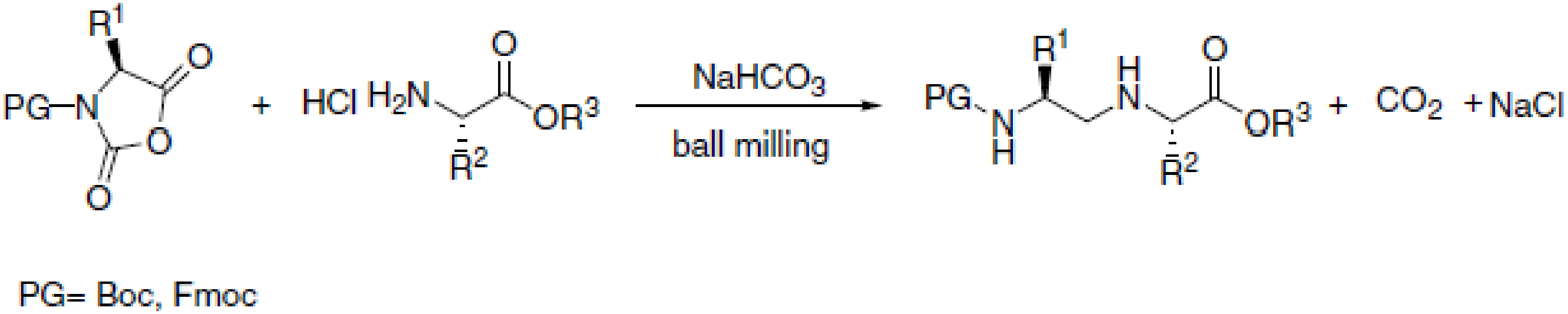
Scheme 11.14 *"Click" chemistry under solvent-free ball milling conditions.*



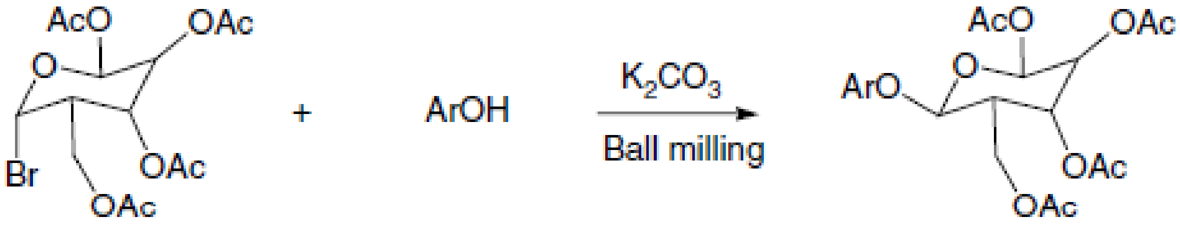
Scheme 11.15 *Polymeric materials made using solvent-free click chemistry.*



Scheme 11.16 Formation of a novel fullerene dimer under solvent-free ball milling conditions.



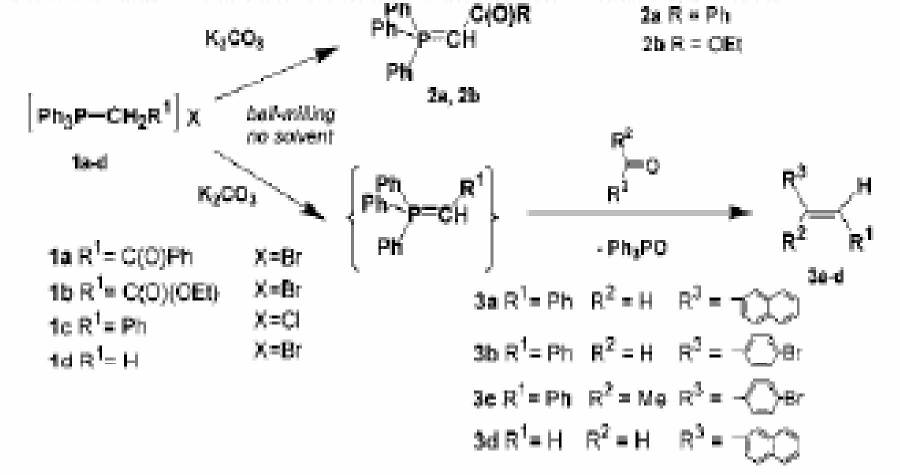
Scheme 11.17 Solvent-free synthesis of peptides using ball milling.



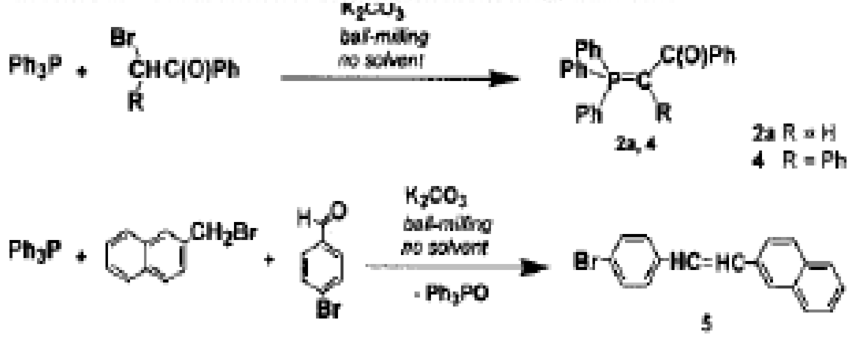
Scheme 11.18 Glycoside derivatives made under solvent-free ball milling conditions.

Solvent-free Reactions

Scheme 1. Mechanochemical Generation of Phosphoranes



Scheme 2. "One-Pot" Mechanochemical Synthesis



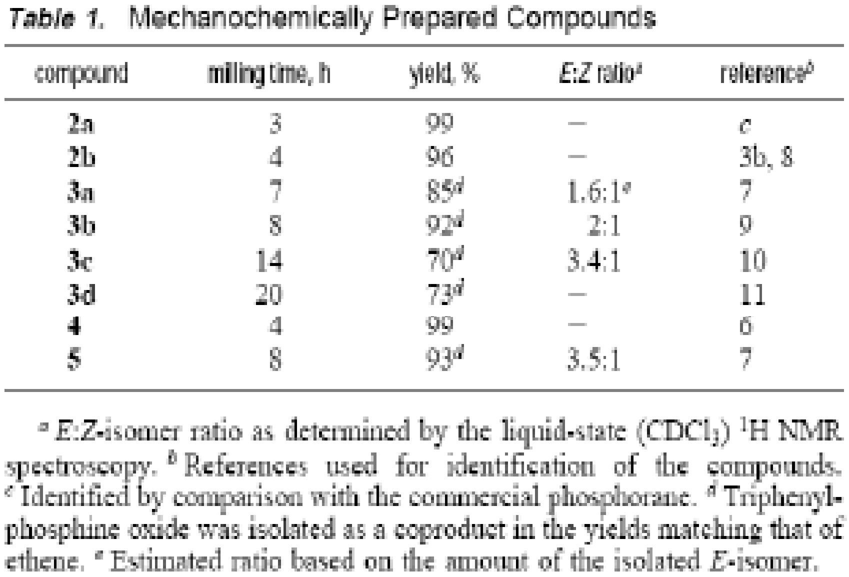


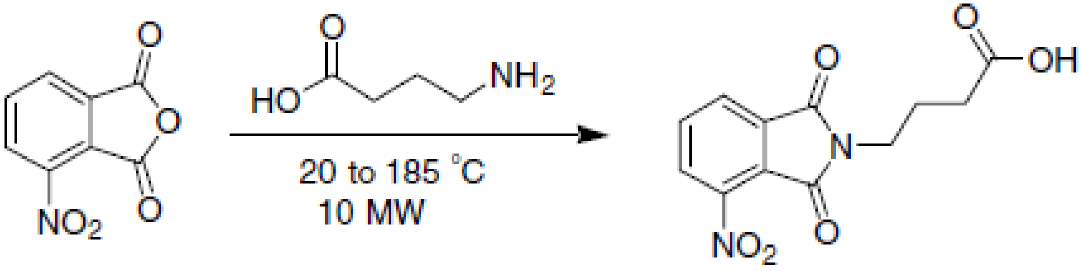
Table 1. Mechanochemically Prepared Compounds

compound	milling time, h	yield, %	E:Z ratio[a]	reference[b]
2a	3	99	–	c
2b	4	96	–	3b, 8
3a	7	85[d]	1.6:1[e]	7
3b	8	92[d]	2:1	9
3c	14	70[d]	3.4:1	10
3d	20	73[d]	–	11
4	4	99	–	6
5	8	93[d]	3.5:1	7

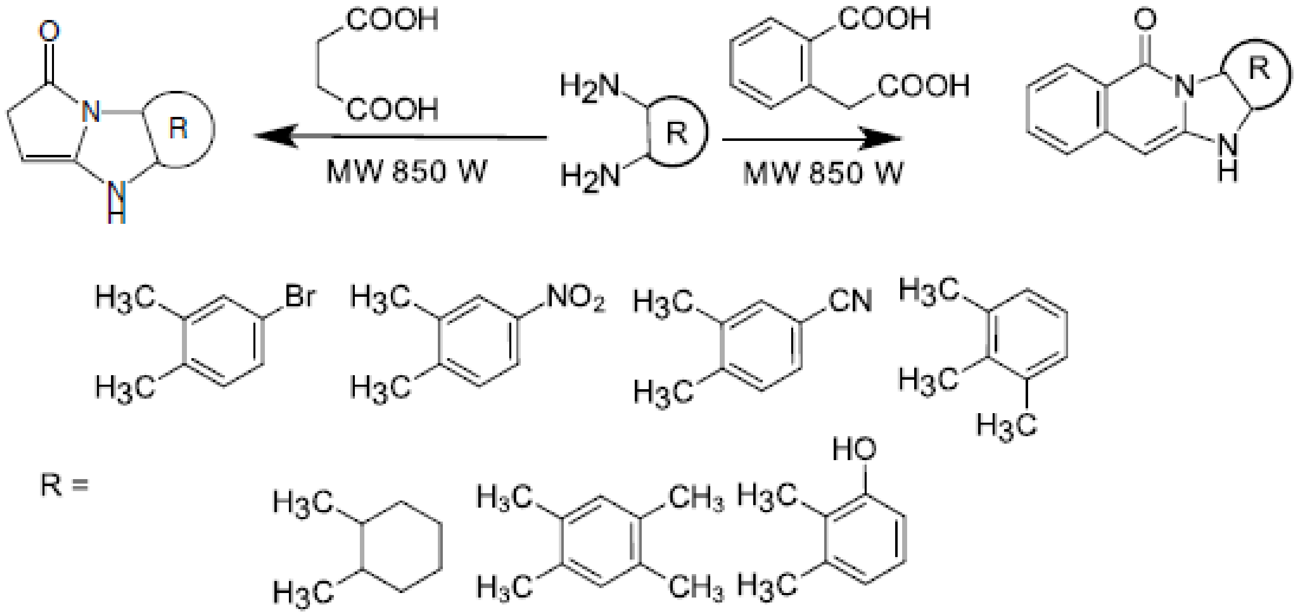
[a] E:Z-isomer ratio as determined by the liquid-state ($CDCl_3$) ^1H NMR spectroscopy. [b] References used for identification of the compounds. [c] Identified by comparison with the commercial phosphorane. [d] Triphenylphosphine oxide was isolated as a coproduct in the yields matching that of ethene. [e] Estimated ratio based on the amount of the isolated E-isomer.

"Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-Free Wittig Reaction"
Balema V. P., Wiench J. W., Pruski M. and Pecharsky V. K., *J. Am. Chem. Soc.*, **2002**, 124, 6244-6245.

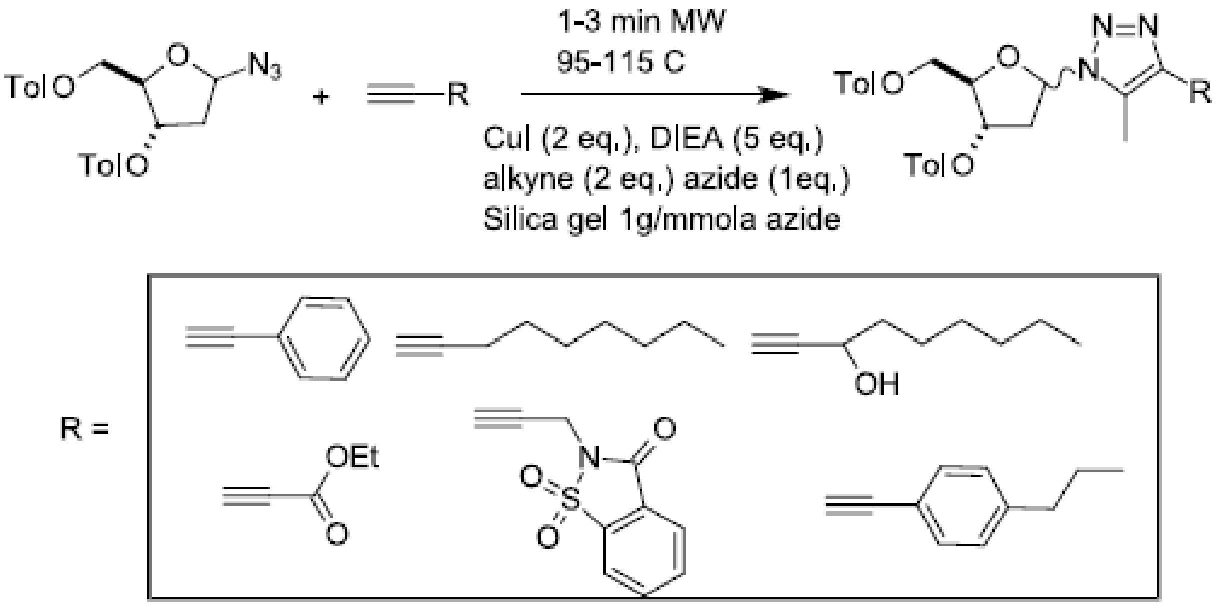
Microwave



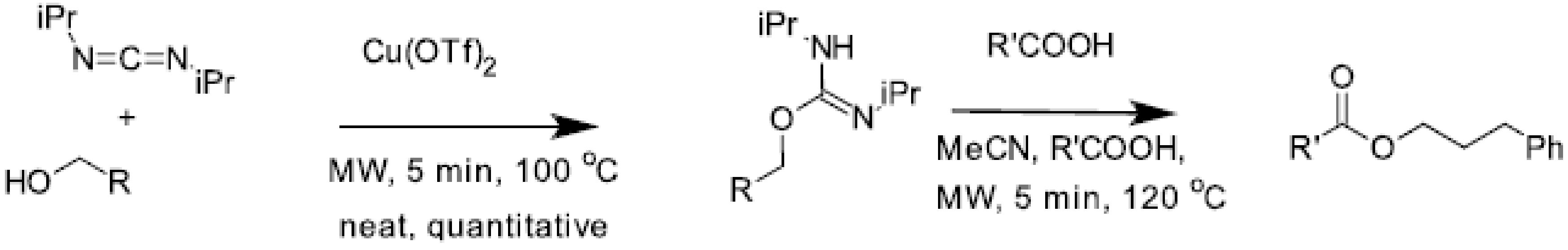
Scheme 11.19 *Conversion of a phthalic anhydride derivative to the phthalmide group.*



Scheme 11.20 *Solvent-free generation of benzimidazole derivatives that have anticancer and anti-inflammatory activity.*

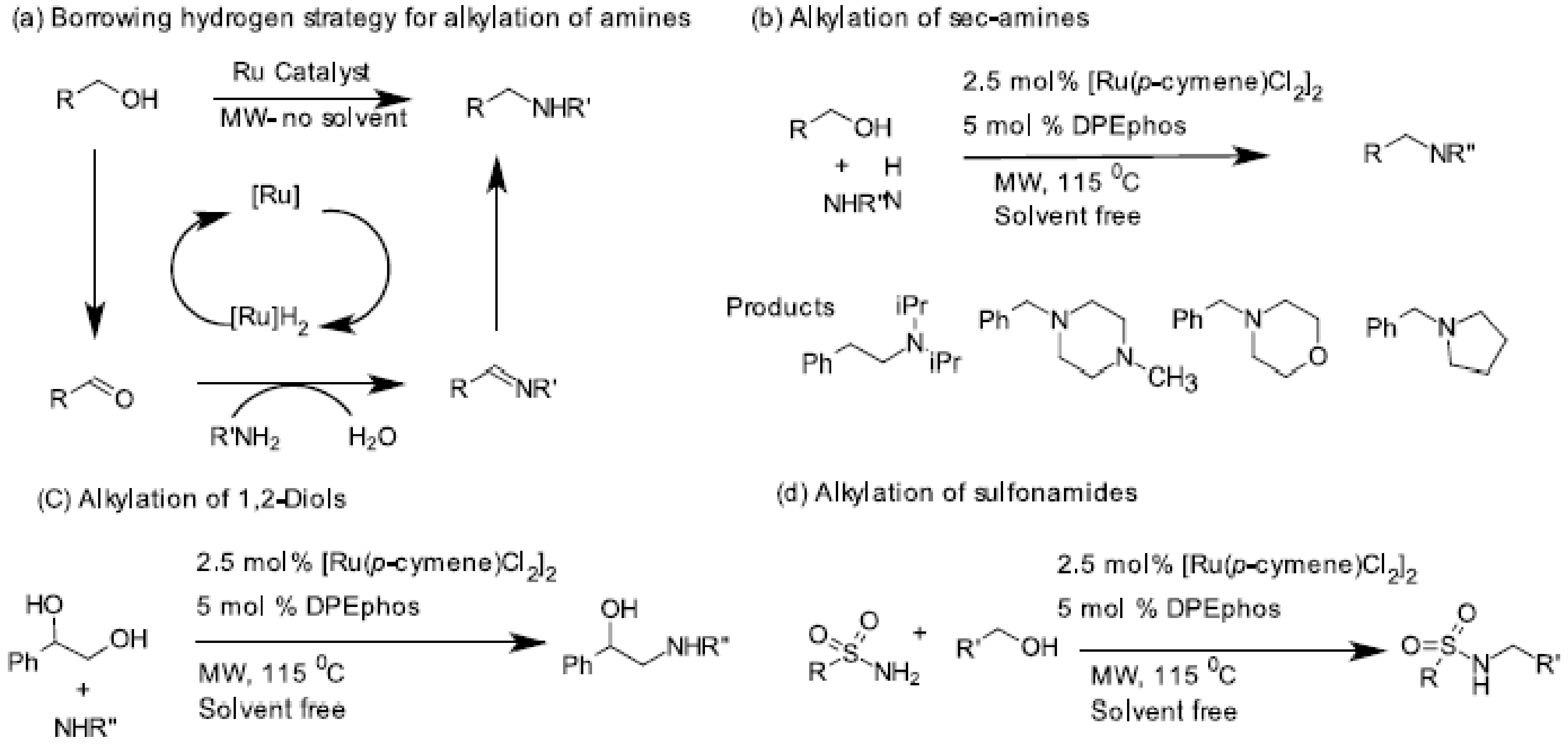


Scheme 11.21 *Solvent-free conditions dramatically enhanced the 1,3-dipolar cycloaddition between azido-2'-deoxyribose and terminal alkynes.*

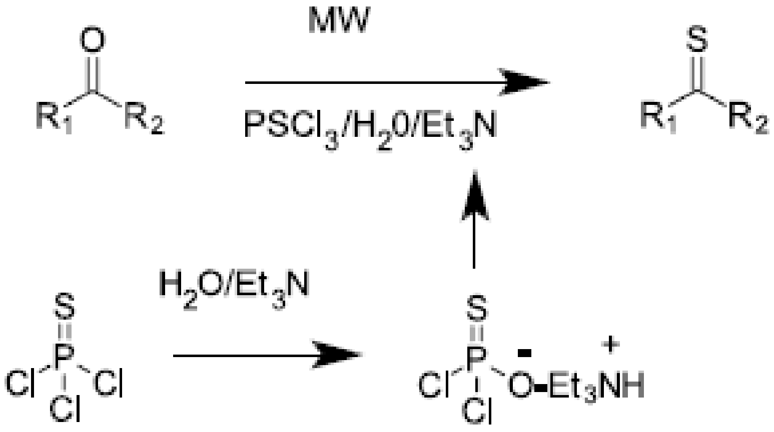


R = Primary alcohols R' = aliphatic and aromatic acids

Scheme 11.24 *Microwave assisted ester formation using O-alkylisoureas under neat solvent-free conditions.*



Scheme 11.25 *(a–d) Example of C—N bond formation from alcohols and amines using microwave irradiation.*



Scheme 11.29 *Solvent-free microwave assisted synthetic route to a variety of thiocarbonyl compounds.*

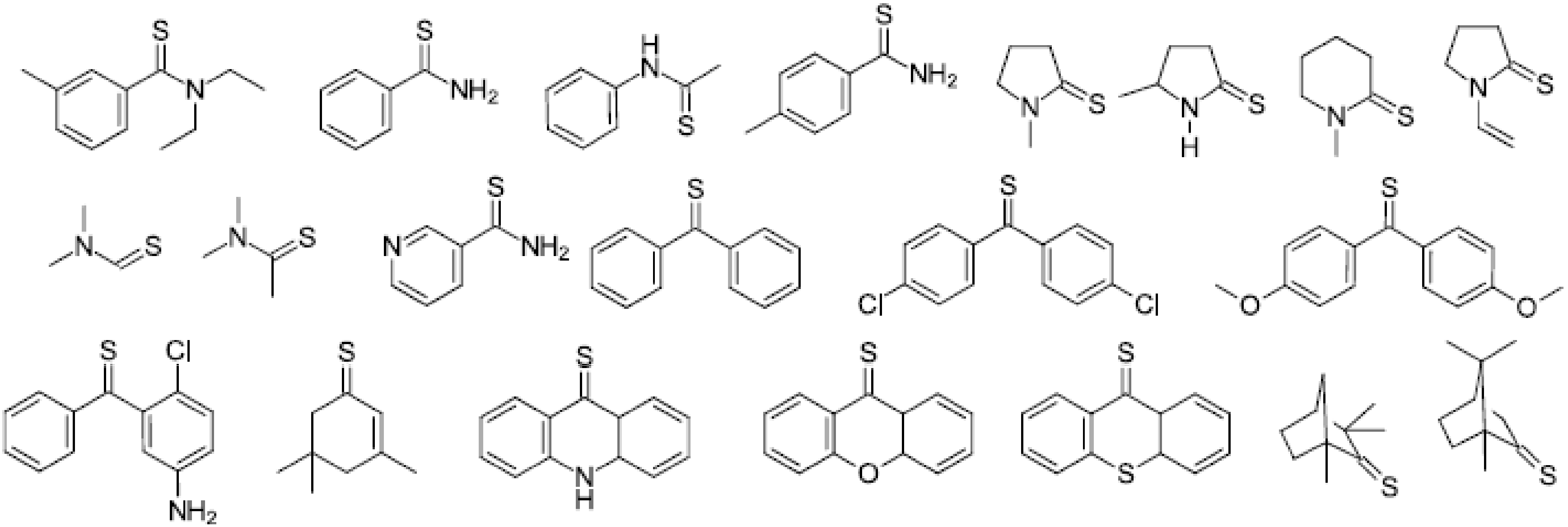
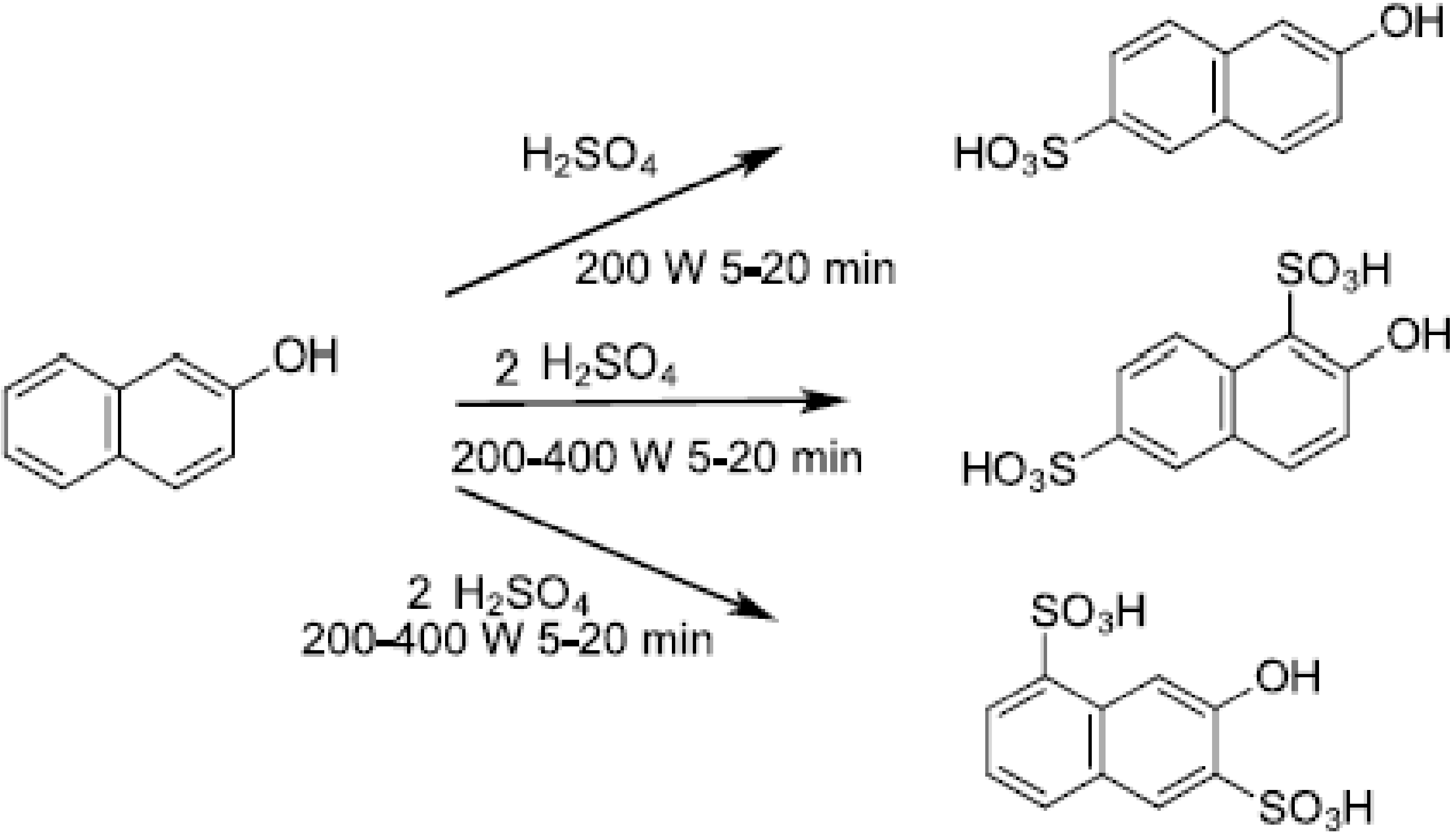
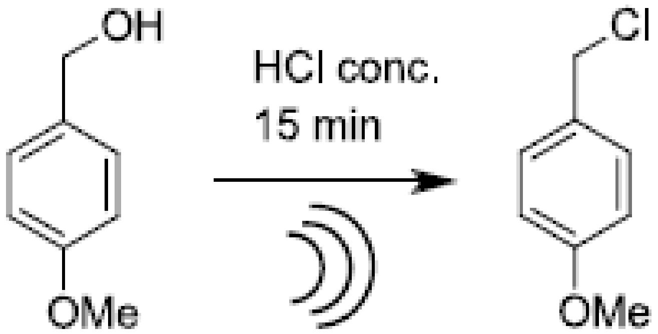


Figure 11.5 *A variety of thiocarbonyl compounds such as thioamides, thioketones, thioxanthanes, and thioacridones.*

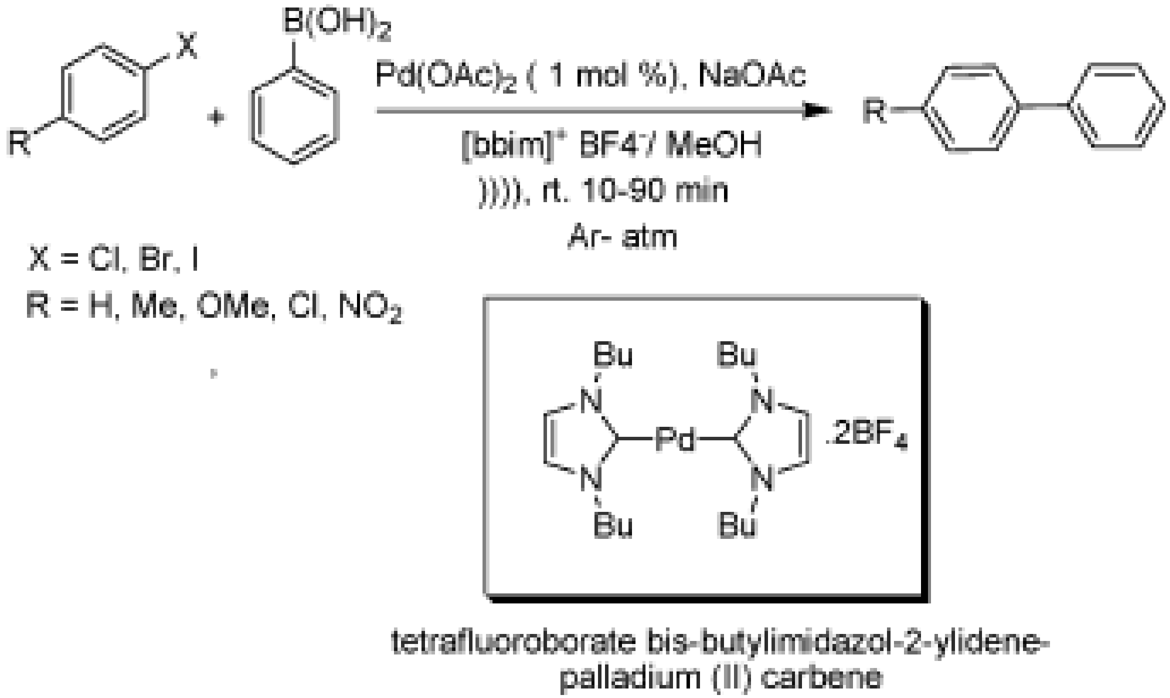


Scheme 11.31 *Microwave assisted synthesis of Schaeffer's acid.*

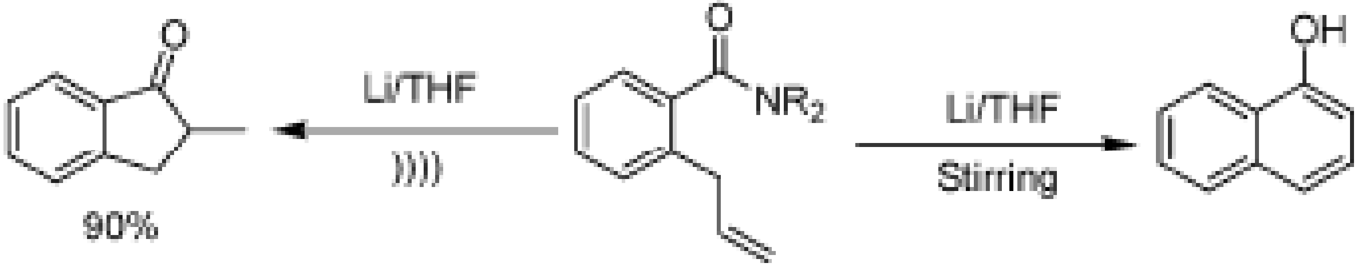
Sonochemical Synthesis



Scheme 11.36 *Rapid preparation of 4-methylbenzyl chloride using ultrasound.*



Scheme 48 Ultrasound-assisted Suzuki reaction.



Scheme 70 Synthesis of indanone under sonochemical conditions.

From: Chem. Soc. Rev. 2012, 41, 1559-1584.

III. “Green” Solvent Selection

- To choose solvent(s) that will lead to the lowest possible negative environmental impacts for a synthetic process.
- There is no such thing as a green solvent. The greenness of a solvent can only be considered in the context of the process in which it is being used.

Water- A “green” solvent?

- Advantage: the most environmentally benign solvent in terms of its direct impact in the environment.
- Disadvantage: Its high heat of vaporization can lead to excess energy demands if it is removed from a product by evaporation, which in turn leads to the production of CO_2, hence it may be better to use a less apparently green solvent from which the desired product can be more easily produced.

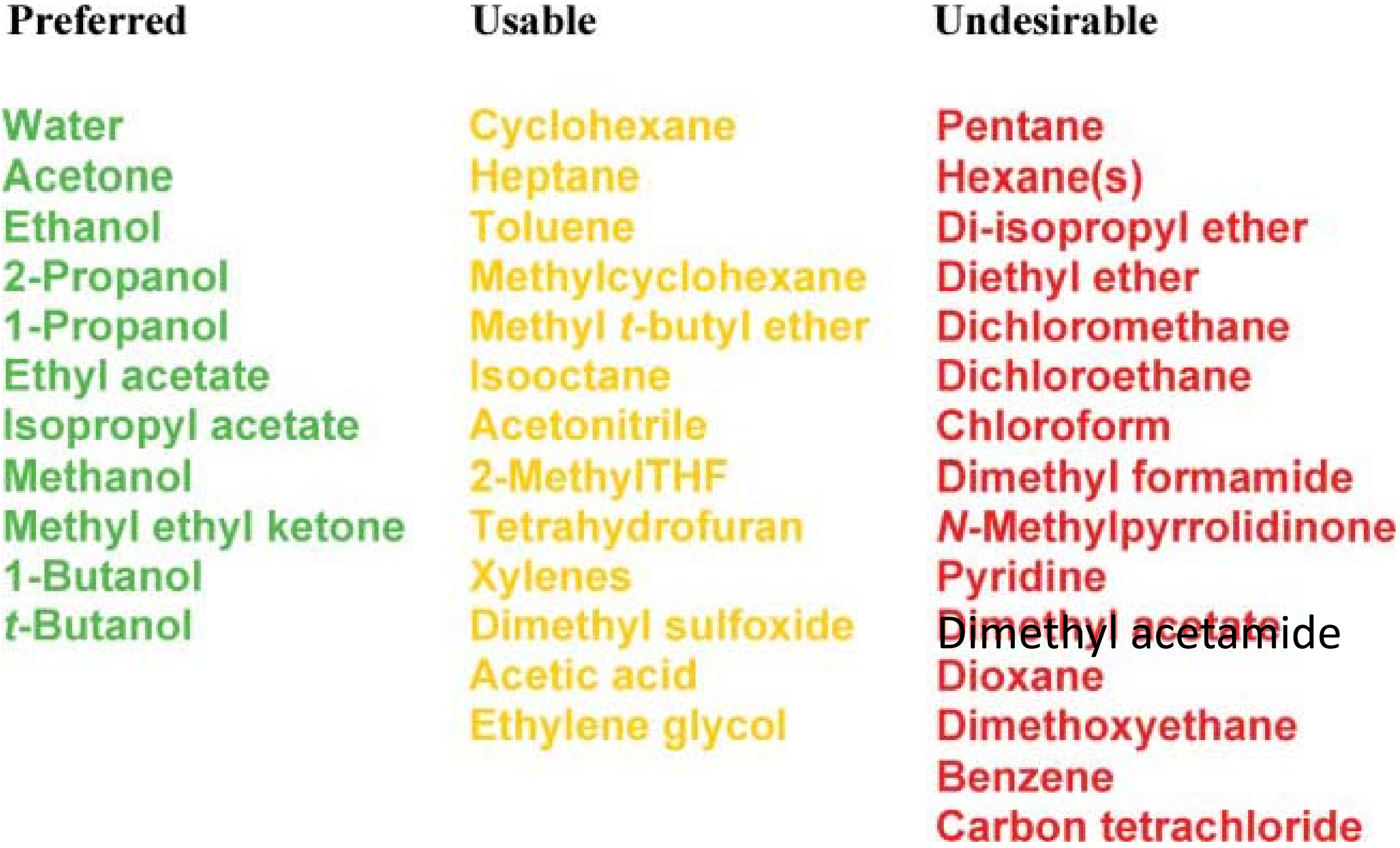
Selection of Solvents

- It affects yields, selectivities, and the rate of reactions.
- The careful selection of the solvent can greatly reduce the wastefulness and the energy use of a synthetic process.

Solvent Selection

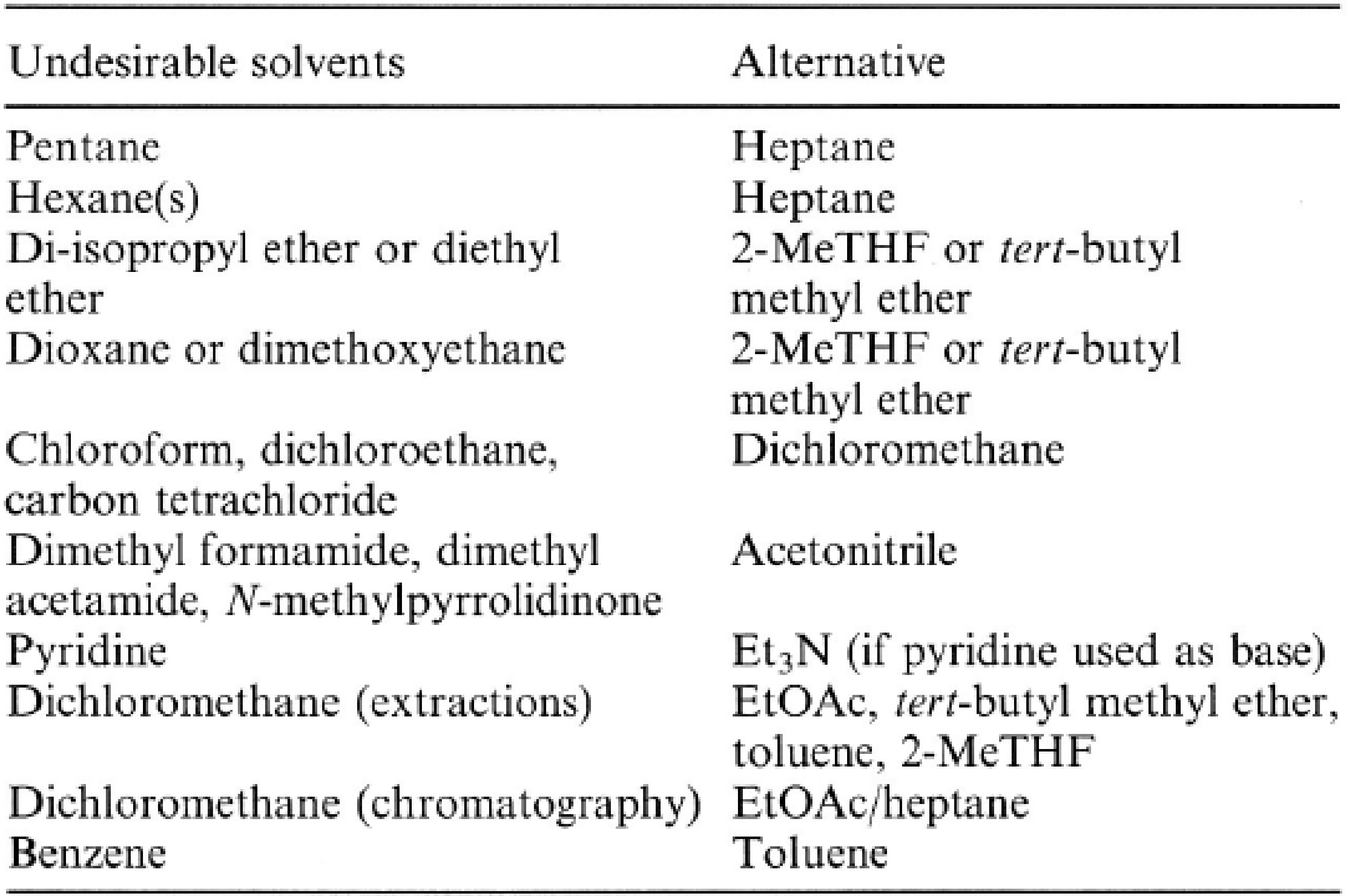
- Environmental Health and Safety (EHS)
- Life Cycle Assessment (LCA)
- National Fire Protection Association (NFPA 704)
- Pfizer “traffic light” system-very simple to use
- Alternative Solvents to replace CH_2Cl_2

The Pfizer “traffic light” solvent preference, based on worker safety, process safety, and environmental and regulatory considerations (Green Chem. 2008, 10, 31-36.)



Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl *t*-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MethylTHF	Dimethyl formamide
Methyl ethyl ketone	Tetrahydrofuran	*N*-Methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethyl acetamide
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Pfizer’s solvent replacement table

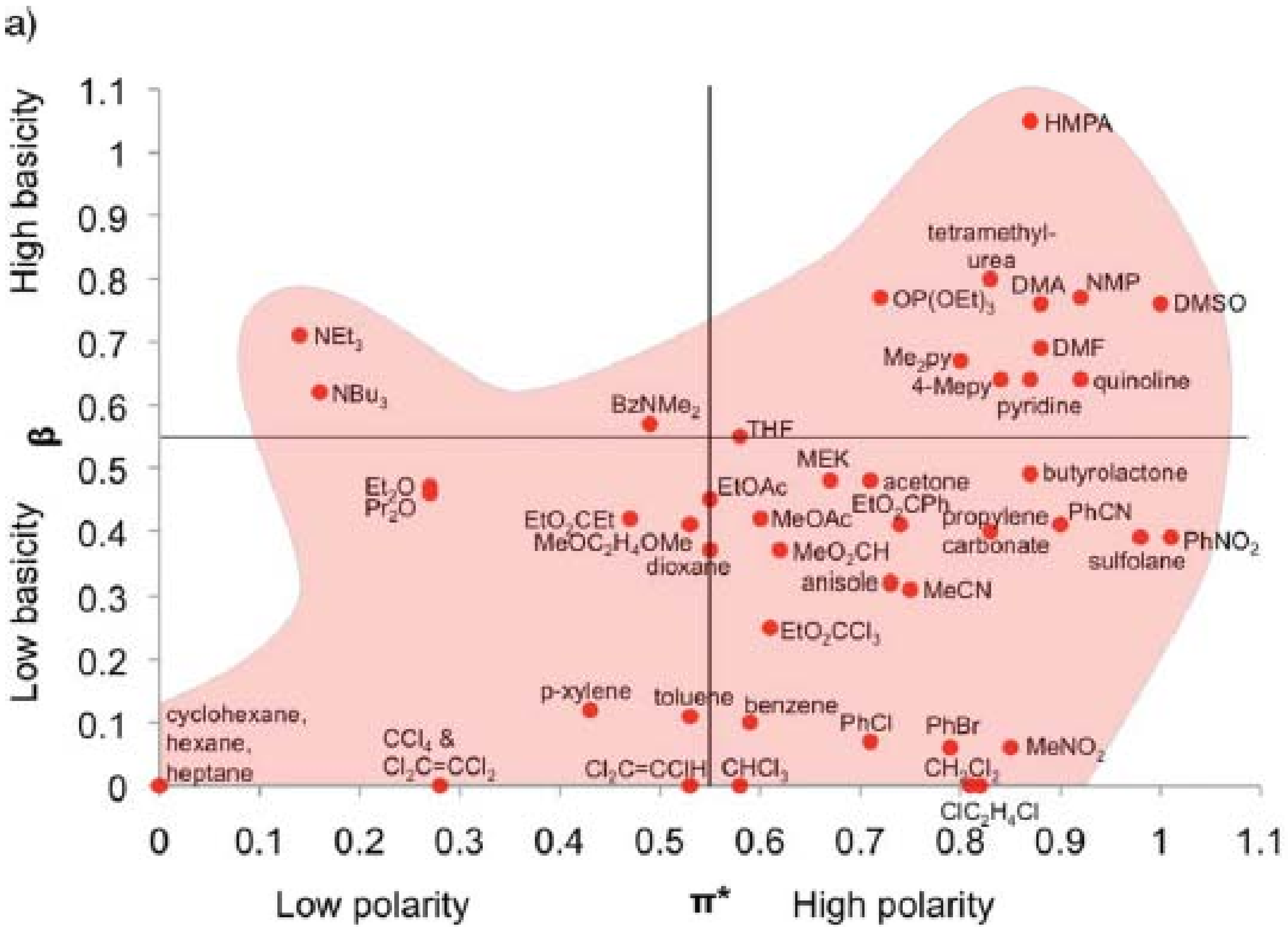


Undesirable solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-MeTHF or *tert*-butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or *tert*-butyl methyl ether
Chloroform, dichloroethane, carbon tetrachloride	Dichloromethane
Dimethyl formamide, dimethyl acetamide,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

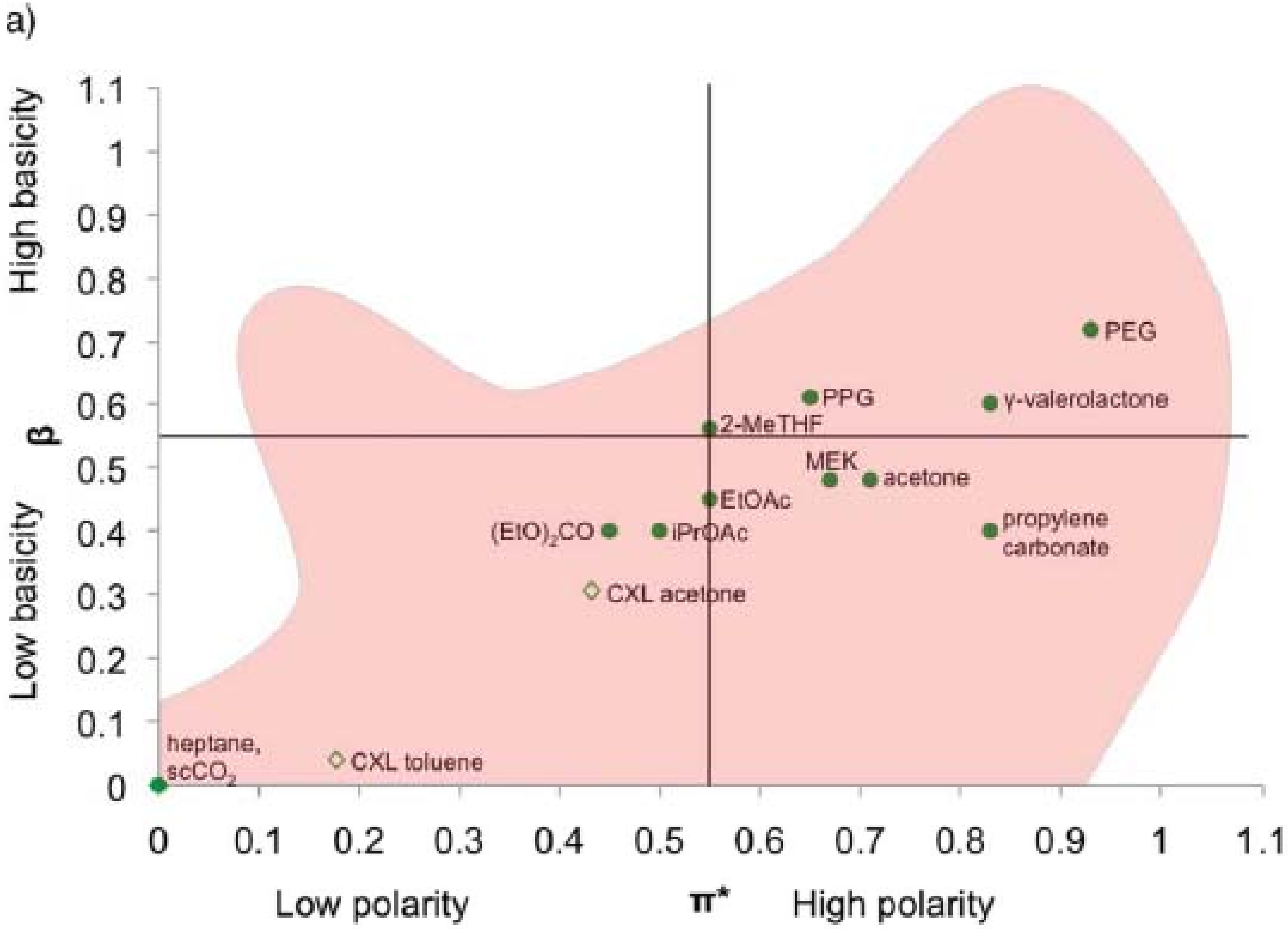
Traditional vs. Greener Solvents

- Green Chem. 2011, 11, 1391-1398.
- Greener solvents are available as replacements for non-green traditional solvents of any kind.
- Kamlet-Taft plots for solvents are shown. In such plots, solvents are identified by π^* (a measure of their polarity and polarizability), α (a measure of their acidity or hydrogen-bond donating ability), and β (a measure of their basicity or hydrogen-bond accepting ability) values.
- Unfortunately, currently identified greener solvents are not sufficient.

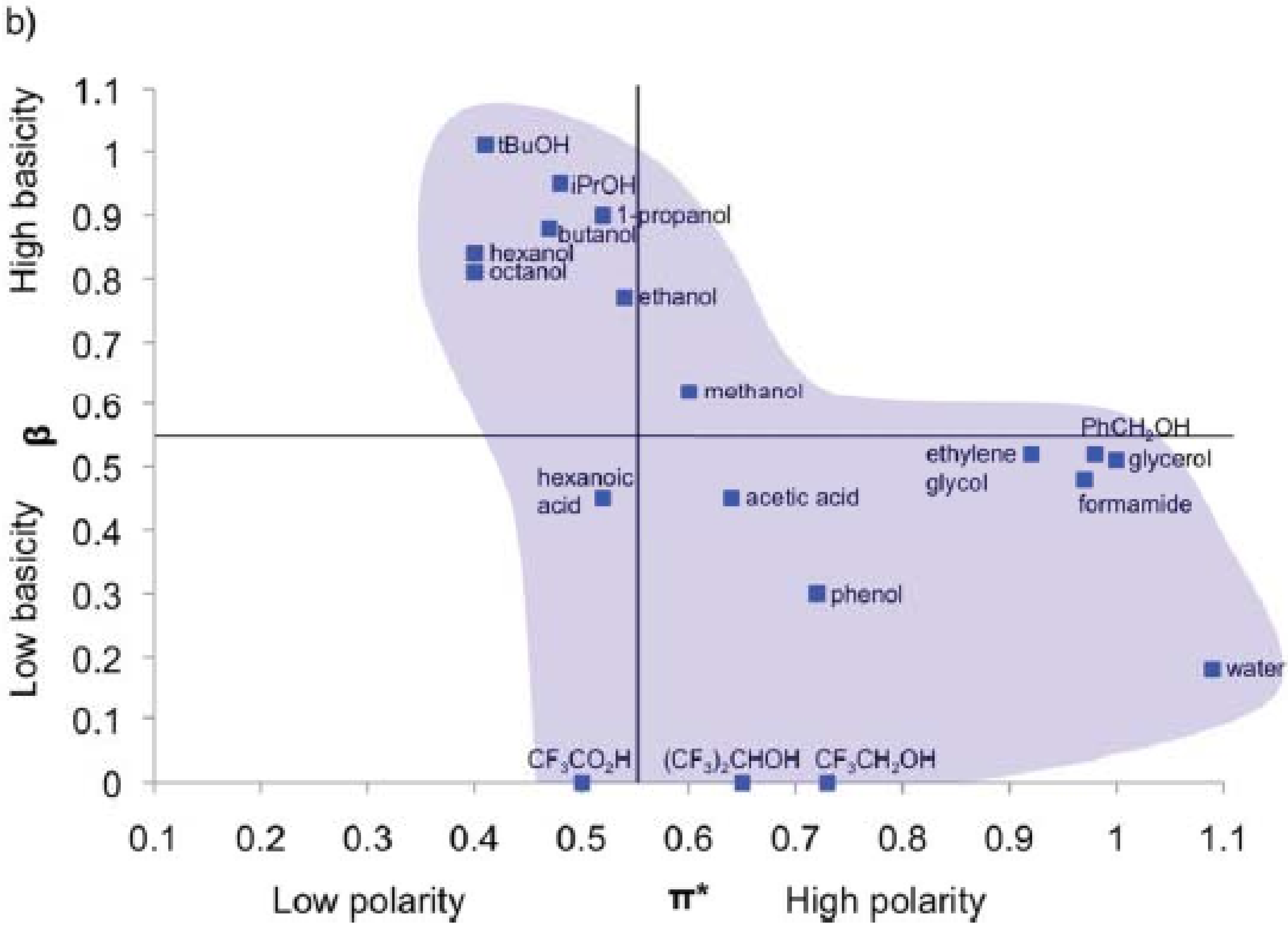
Traditional aprotic solvent with $\alpha < 0.5$



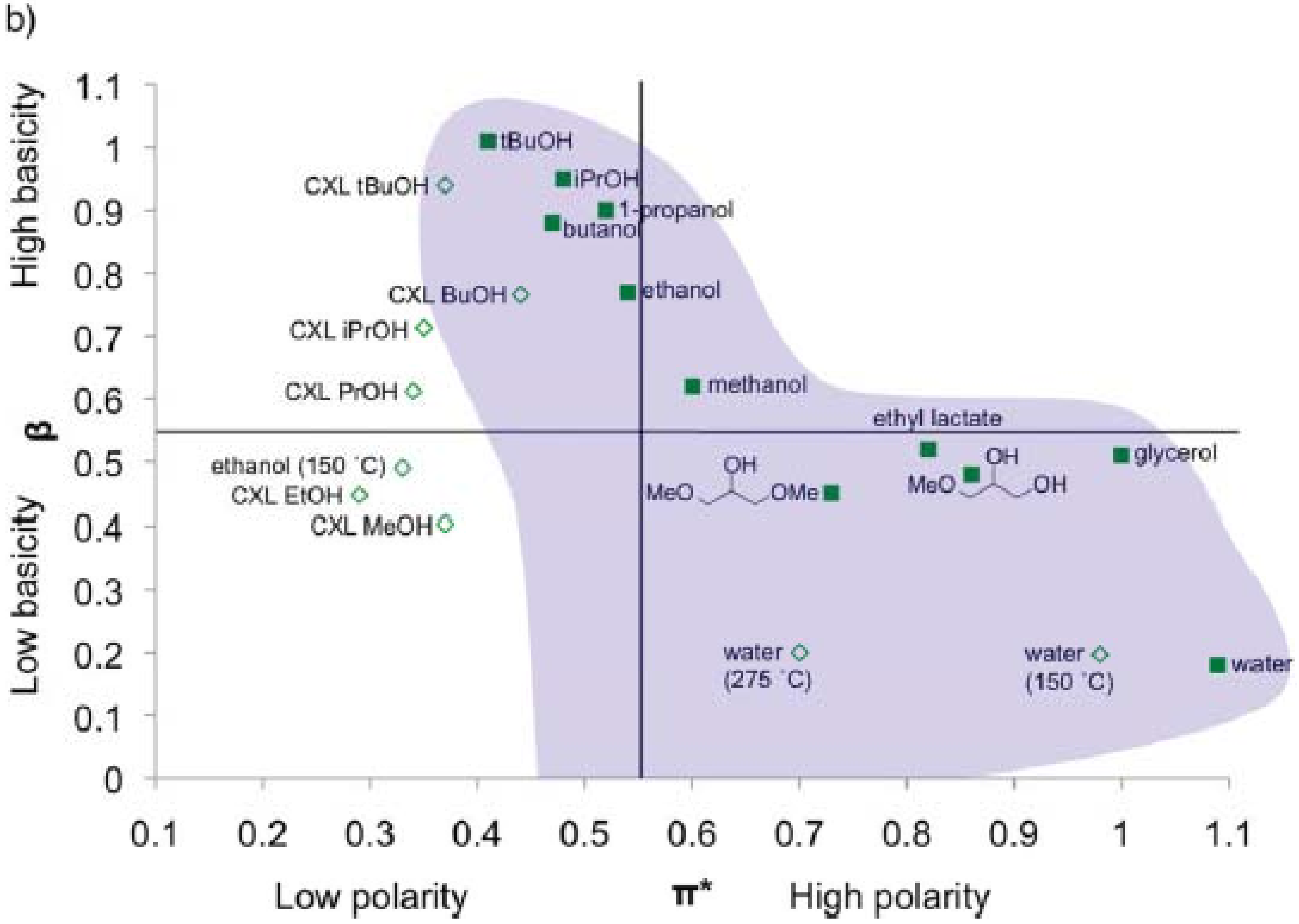
Greener aprotic solvents with $\alpha < 0.5$

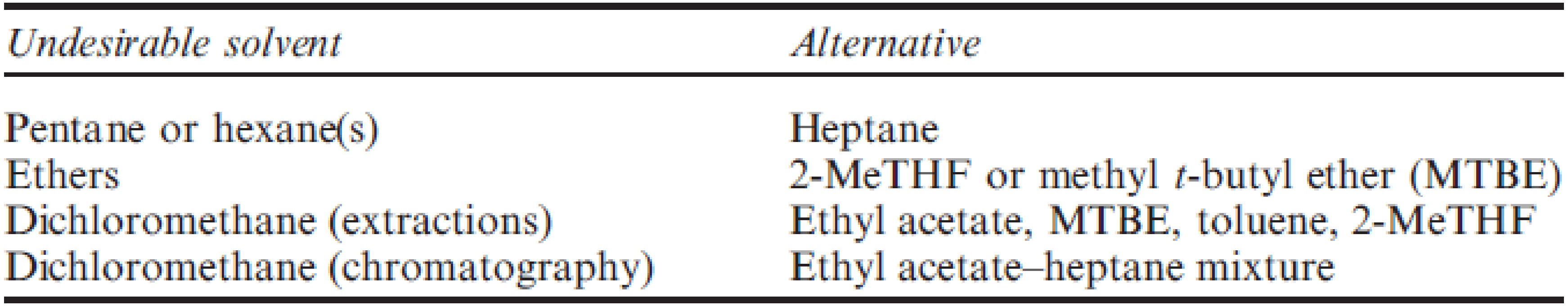


Traditional protic solvent with $\alpha > 0.5$



Greener protic solvents with $\alpha > 0.5$

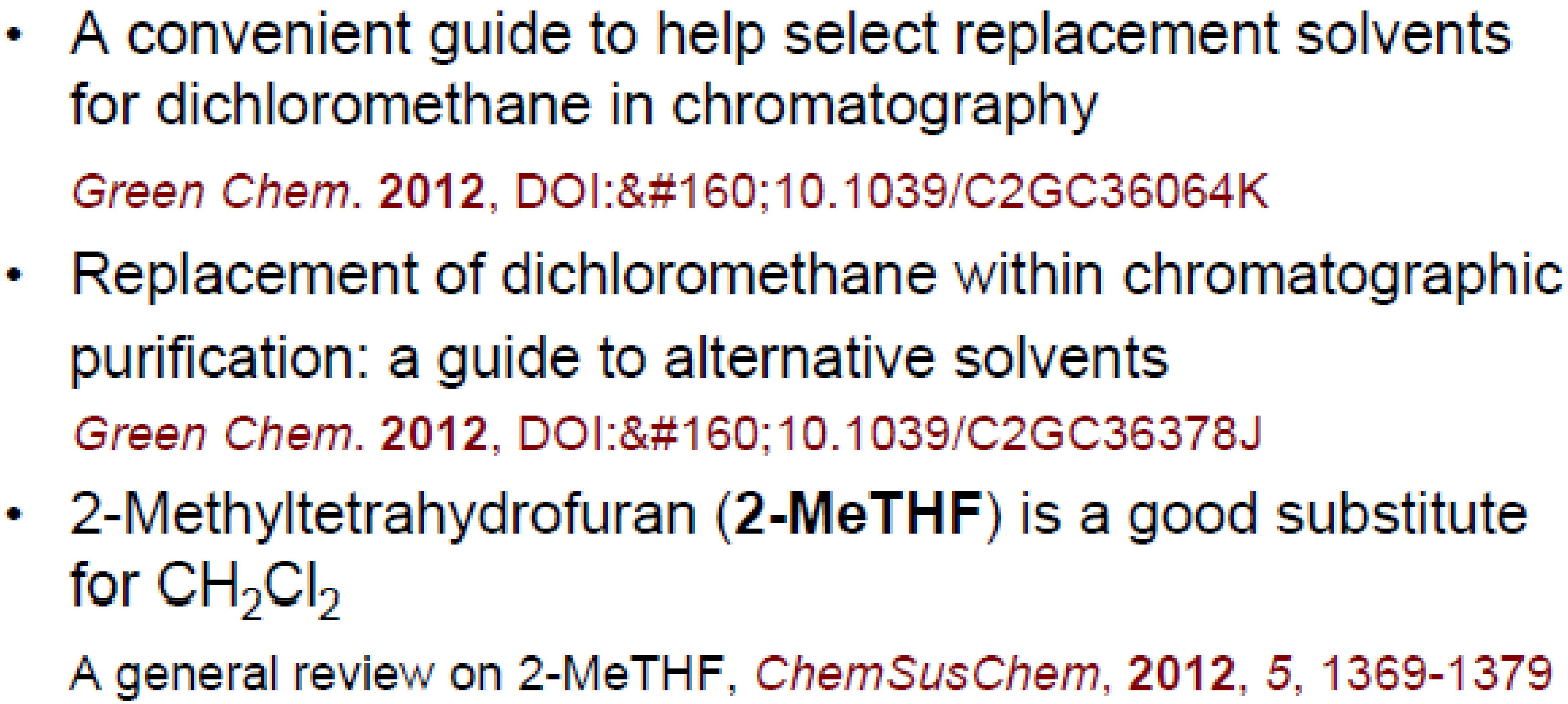




Undesirable solvent	*Alternative*
Pentane or hexane(s)	Heptane
Ethers	2-MeTHF or methyl *t*-butyl ether (MTBE)
Dichloromethane (extractions)	Ethyl acetate, MTBE, toluene, 2-MeTHF
Dichloromethane (chromatography)	Ethyl acetate–heptane mixture

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 14.

Alternative Solvents to replace CH_2Cl_2



- A convenient guide to help select replacement solvents for dichloromethane in chromatography

  Green Chem. **2012**, DOI: 10.1039/C2GC36064K

- Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents

  Green Chem. **2012**, DOI: 10.1039/C2GC36378J

- 2-Methyltetrahydrofuran (**2-MeTHF**) is a good substitute for CH_2Cl_2

  A general review on 2-MeTHF, *ChemSusChem*, **2012**, *5*, 1369-1379

IV. Non-Traditional Solvents

- Recently, a number of solvents have been proposed as the greener replacements for traditional VOC solvents. However, there are usually insufficient LCA or EHS data available. The solvents should be used with caution.
- In response to this, Clark and Tavener made a semi-quantitative analysis of some of these. In their method, water, supercritical CO_2 (sc-CO_2) and solvents derived from renewable sources scored well, whereas ionic liquids and fluorous solvents scored less well.
- Org. Proc. Res. Dev. 2007, 11, 149-155.

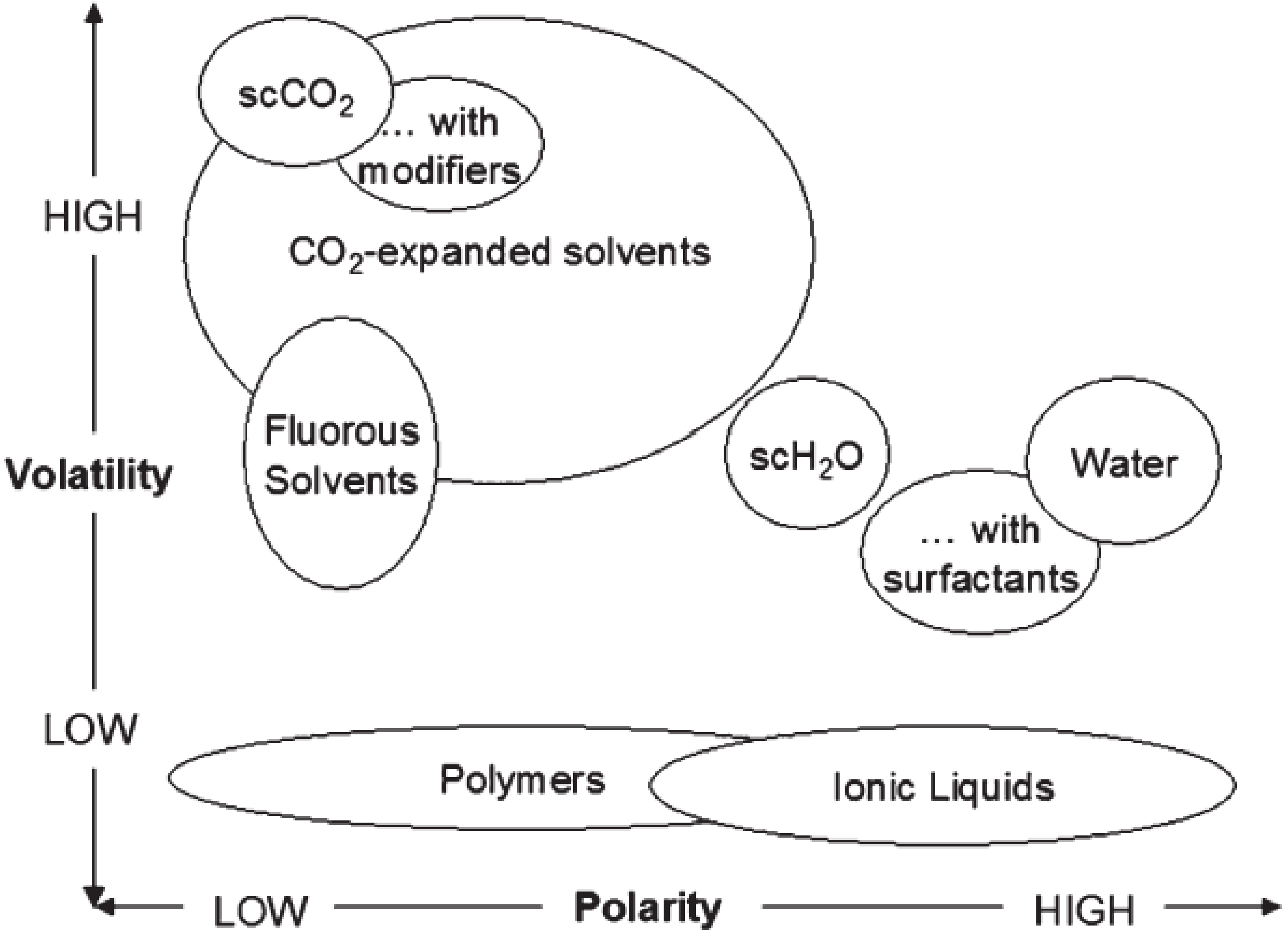
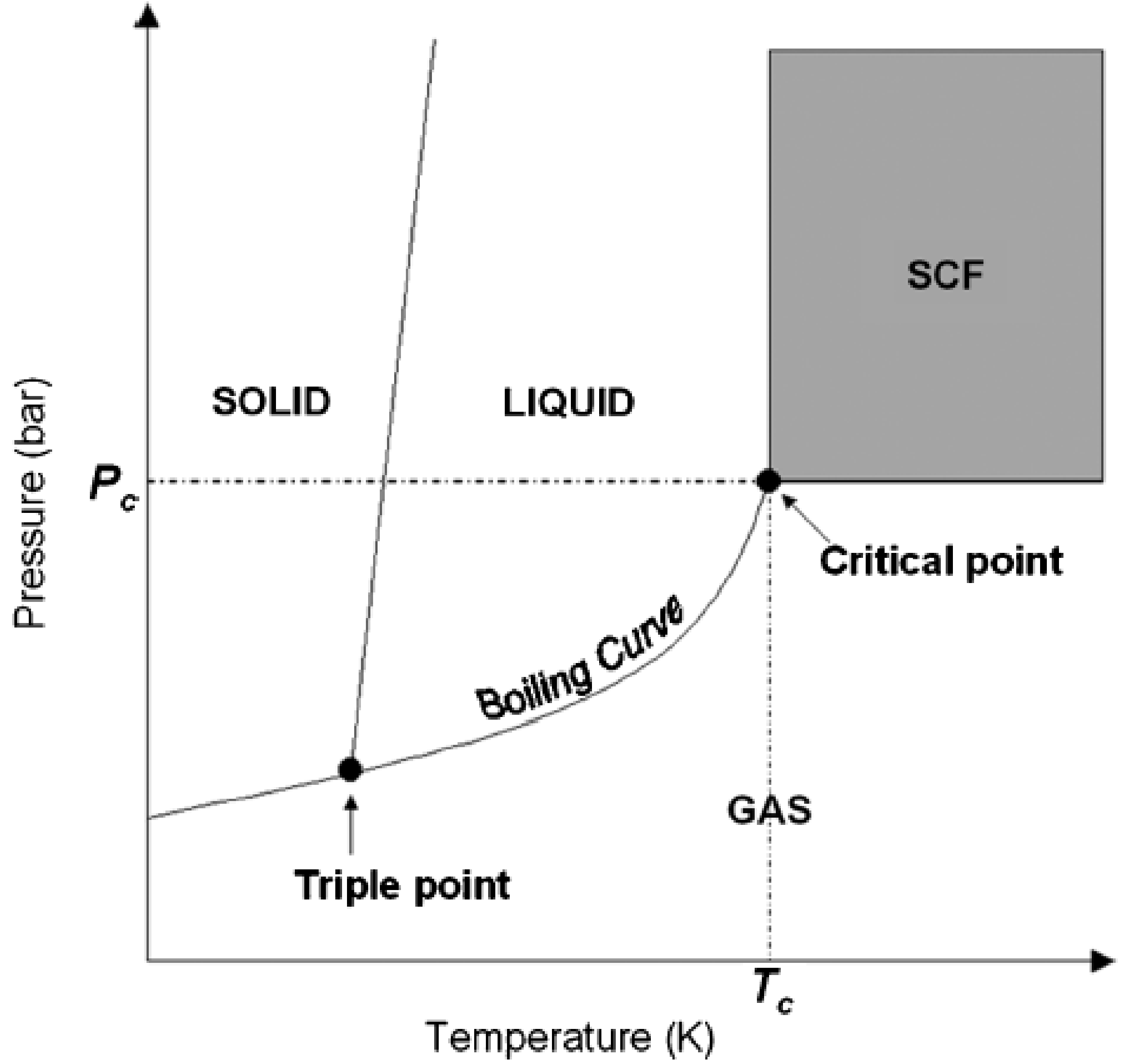


Figure 1.7 Typical polarity and volatility characteristics of alternative reaction media. [Reprinted with modifications and permission from *Org. Proc. Dev.*, 2007, **11**, 149–155. Copyright 2007 American Chemical Society.]

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 17.



Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 69.

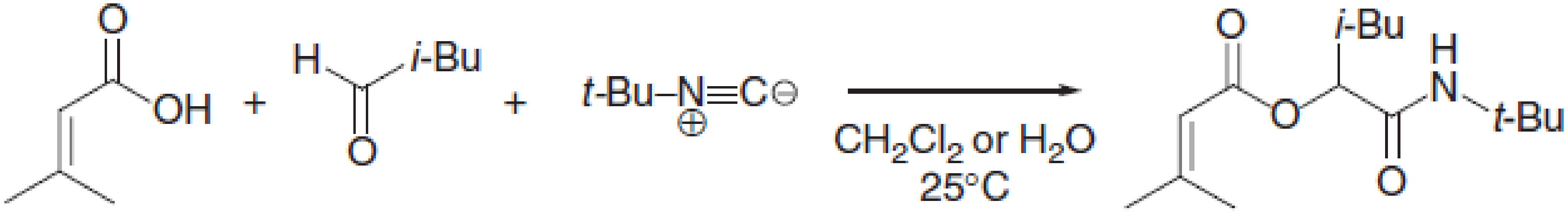
IV-(1a) Water

- The most abundant molecule on Earth.
- A polar solvent
- Hydrogen-bonding interactions involved
- Reactive toward electrophilic and nucleophilic reagents----thus limiting the range of reagents in water as the reaction medium
- However, the advent of green chemistry has led to a renaissance of interest in the use of water as a solvent of synthesis. Also, the solvent for most biocatalytic chemical syntheses. Water's advantages as a solvent: abundant, nontoxic, not harmful to health, and nonflammable. But, once it is contaminated, difficult and energy intensive to purify. Thus, the high heat capacity makes water a good heat sink for exothermic reactions, but difficult to increase temperature for water.

IV-(1b) Influence of Water on Organic Reactions

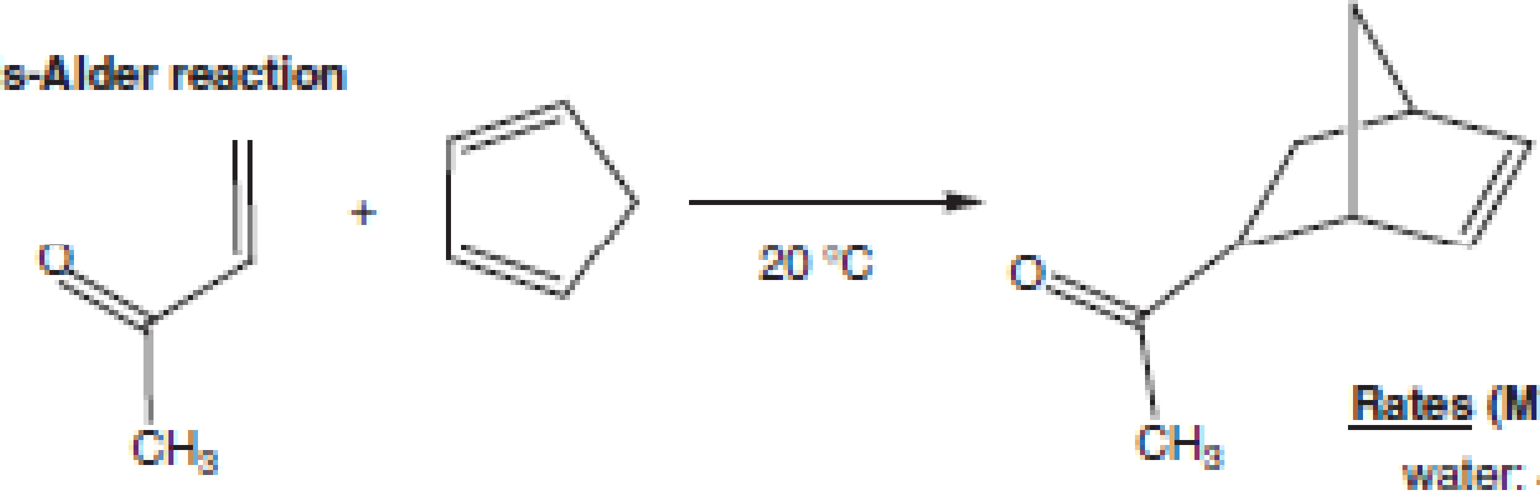
- The discoveries by Breslow and co-workers in the 1980s that using water as the solvent for Diels-Alder cycloaddition reaction could lead to both rate and selevitity enhancements raise the interest in water as a solvent for synthesis. (For example: Simon, M.-O.; Li, C.-J. Chem. Soc. Rev. 2012, 41, 1415-1427.)
- However, apart from the inherent reactivity of water, the other problem that can most often limit the use of water as a solvent is the poor solubility of many potential solutes, which has led to a number of techniques to deal with it. For example, (1) tagging the reactants with some hydrophilic group to increase its solubilty---untagging, not green! (2) Simple ionization with acids or bases---lower eco-efficiencies. (3) Organic co-solvents or solubilizin auxiliary agents---need further purification to produce waste stream.

Passerini Reaction



CH_2Cl_2, 18 h, 45%
H_2O, 3.5 h, 95%
2.5 M LiCl aq., 0.3 h, 95%

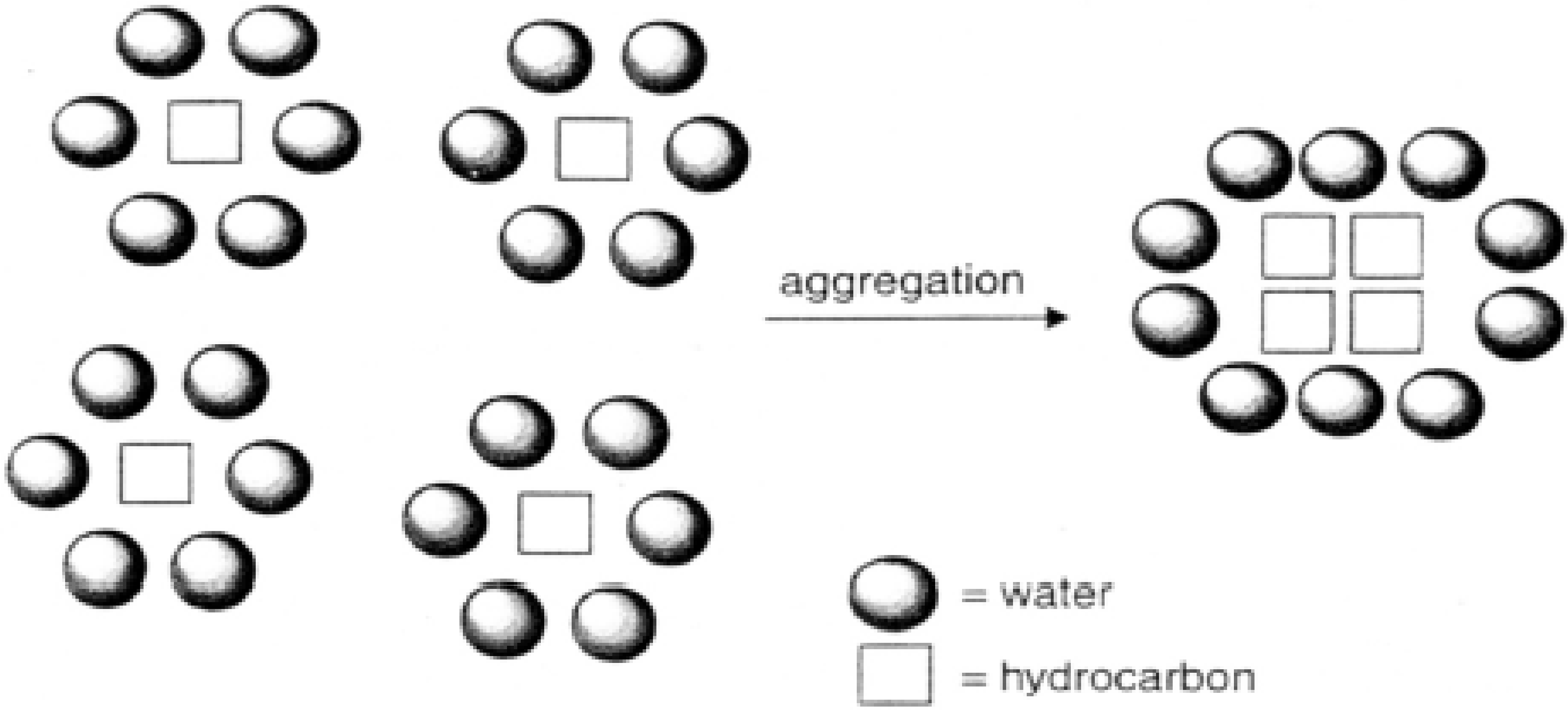
Diels-Alder reaction



Rates ($M^{-1}s^{-1}$)
water: 4400
LiCl (4.86M): 10800
β-cyclodextrin (10mM): 10900
MeOH: 75.5
isooctane: 5.94

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 52, 53.

Hydrophobic Effects



IV-(1c) High-Temperature and Supercritical Water (Sc-H_2O)

- Once water is heated under pressure to above its boiling point, dramatic changes in its physicochemical properties occur. Nonpolar materials are soluble and salts are insoluble in water.
- Benzene is completely miscible with water at 305 ^{o}C, whereas it has a solubility of only 500 ppm under ambient conditions.

Near-Critical Water

- Water becomes supercritical (i.e., no distinct liquid and gas phases) above 374 ^{o}C and 218 bar. Physicochemical property depends on temperature. Near-critical water with T around 200 ^{o}C is also used as the reaction medium.

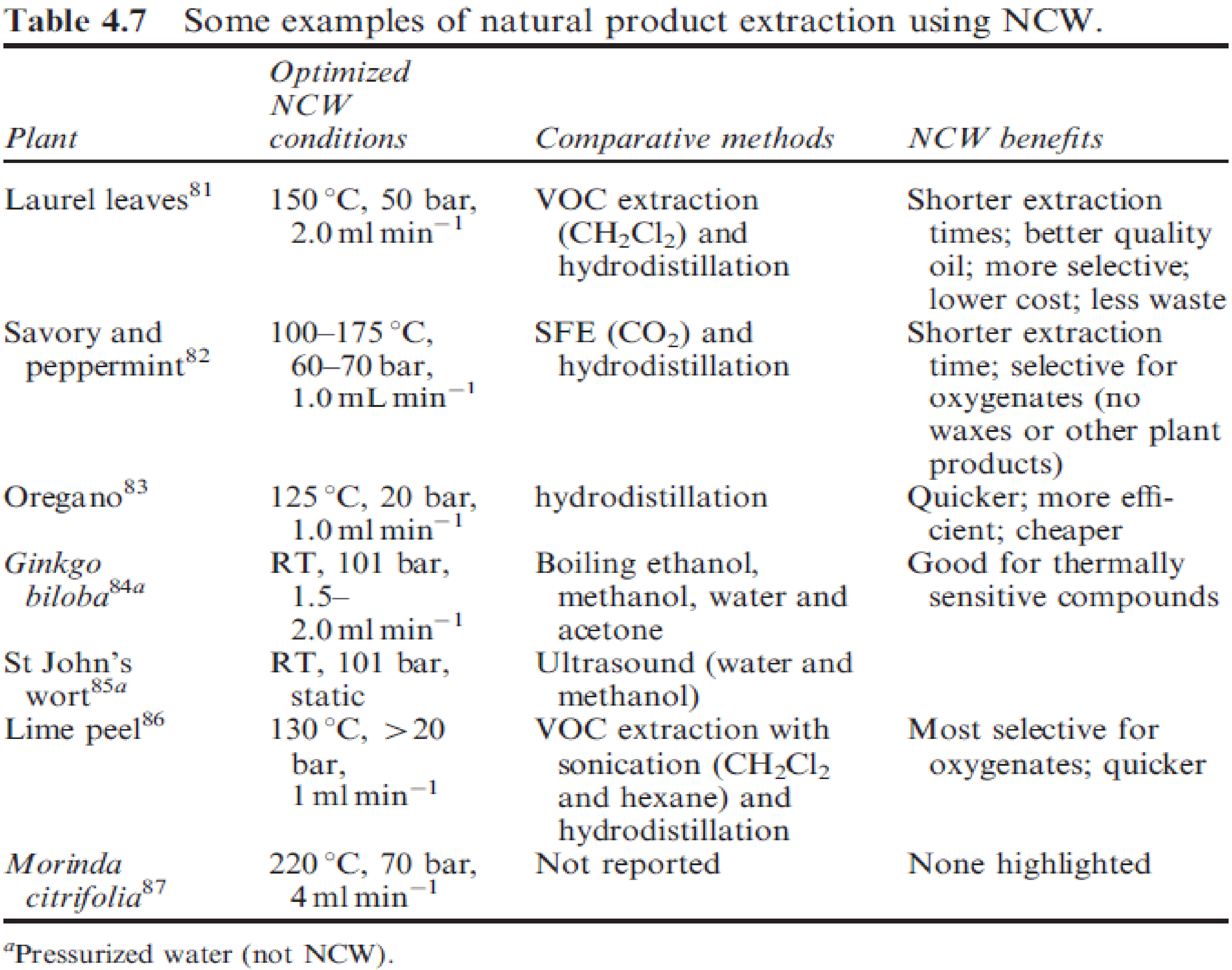


Table 4.7 Some examples of natural product extraction using NCW.

Plant	*Optimized NCW conditions*	*Comparative methods*	*NCW benefits*
Laurel leaves[81]	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[82]	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[83]	125 °C, 20 bar, 1.0 ml min^{-1}	hydrodistillation	Quicker; more efficient; cheaper
Ginkgo biloba[84a]	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[85a]	RT, 101 bar, static	Ultrasound (water and methanol)	
Lime peel[86]	130 °C, >20 bar, 1 ml min^{-1}	VOC extraction with sonication (CH_2Cl_2 and hexane) and hydrodistillation	Most selective for oxygenates; quicker
Morinda citrifolia[87]	220 °C, 70 bar, 4 ml min^{-1}	Not reported	None highlighted

[a] Pressurized water (not NCW).

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 85.

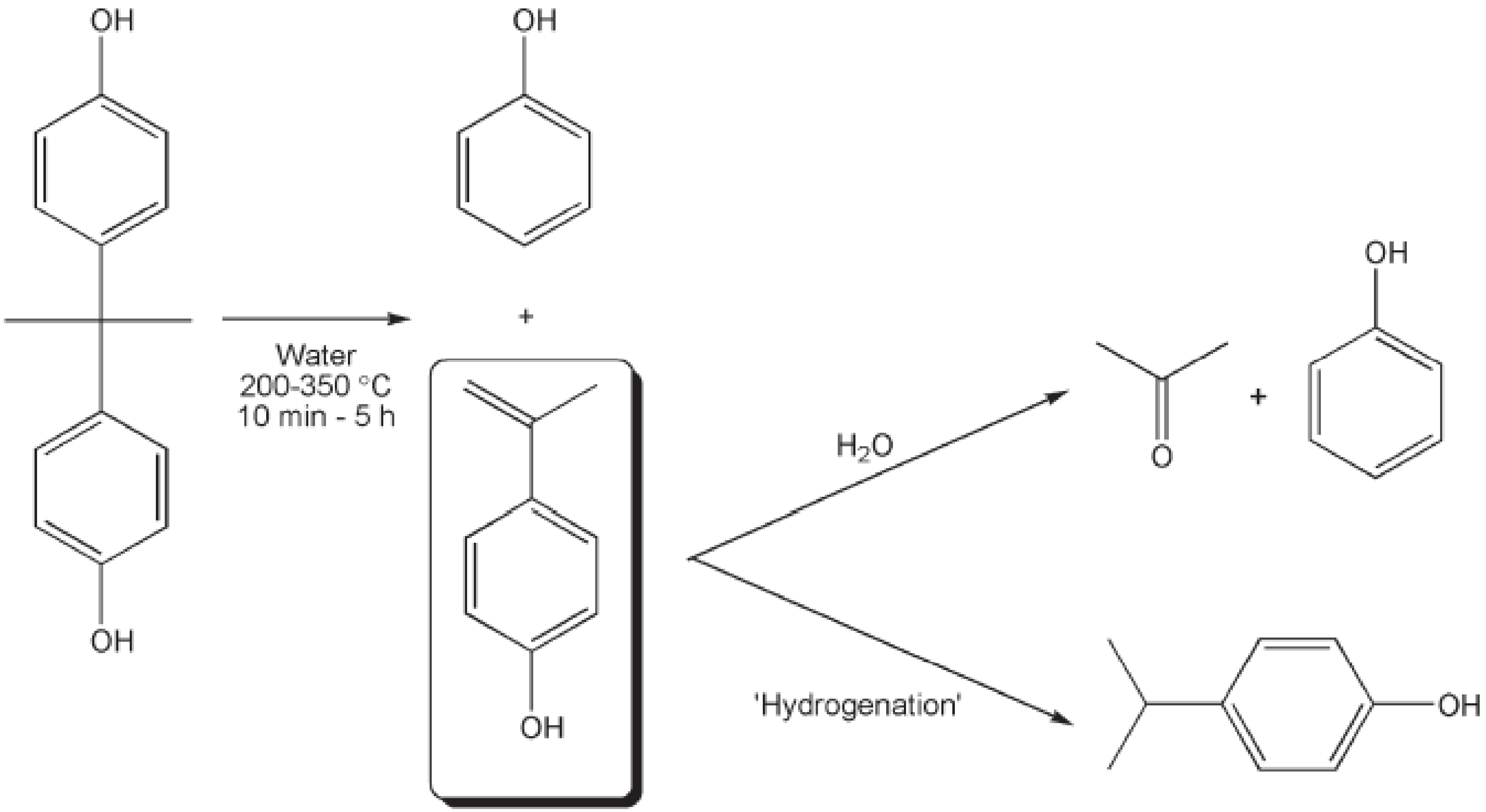
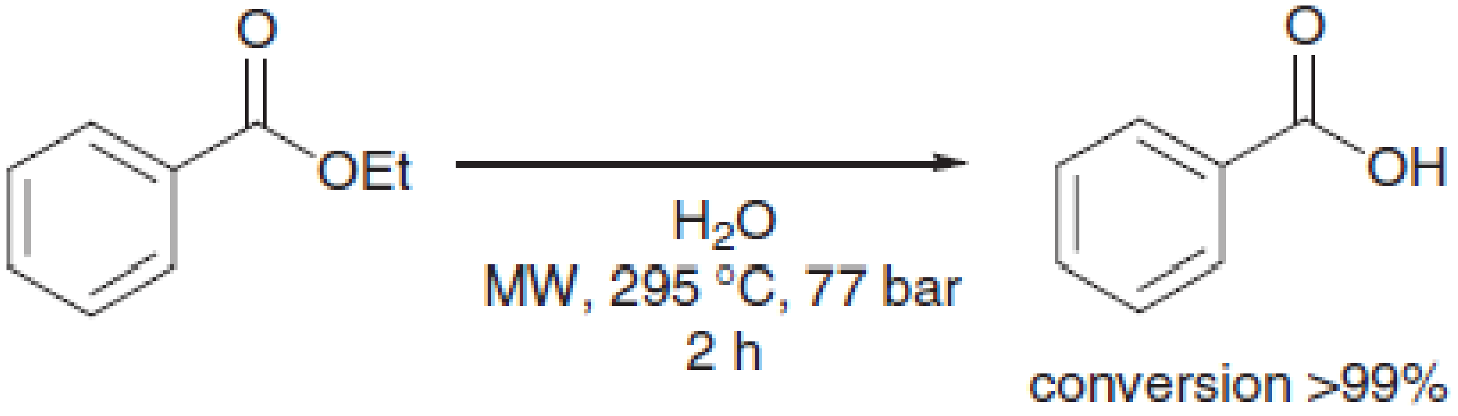


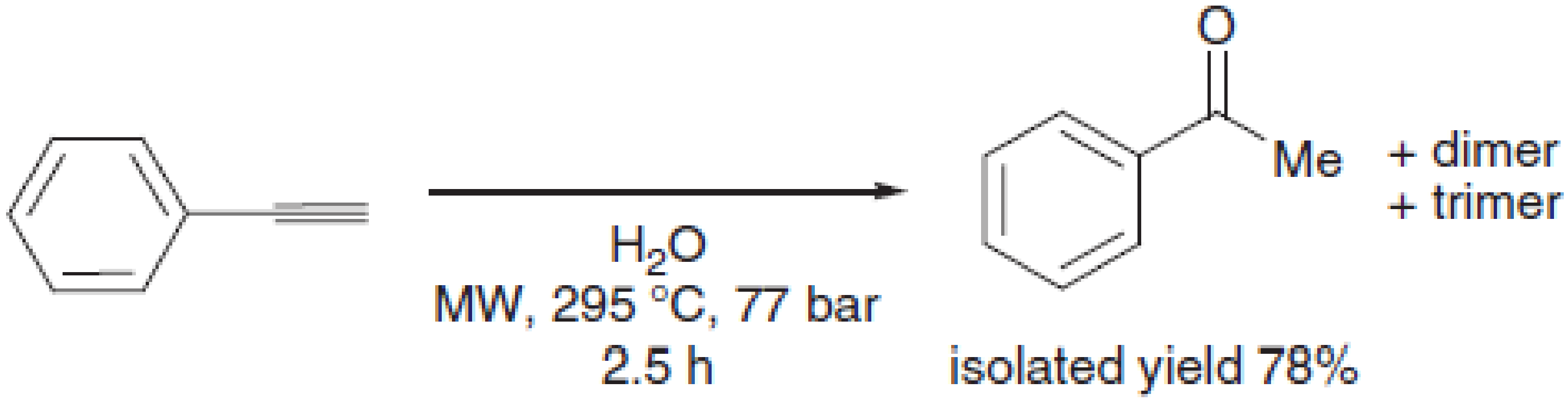
Figure 3.18 *p*-Isopropenylphenol synthesis via bisphenol A decomposition in NCW.

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 64.

Hydrolysis of ethyl benzoate



Hydration of phenylacetylene



Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 88.

IV-(1d) Reactions “On Water”

- Although solubility is usually required for efficient reactions, the “on water” reactions, described by Sharpless and co-workers, do take place with substantial rate acceleration when insoluble reactants are stirred in aqueous suspension. (Angew. Chem. Int. Ed. 2005, 44, 3275-9)

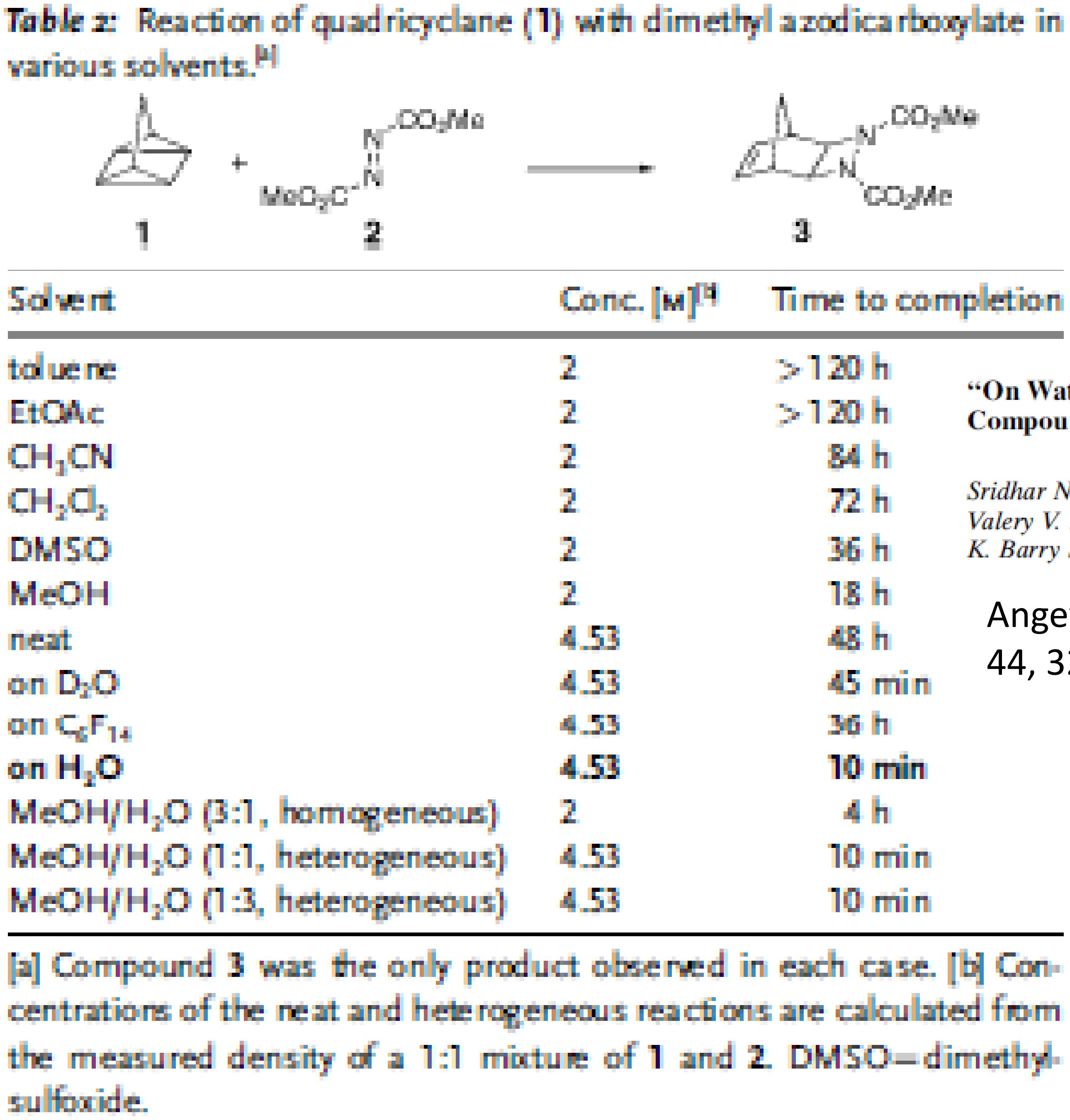
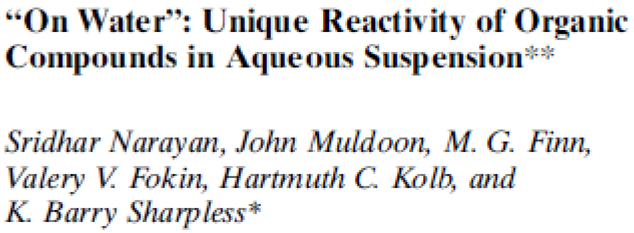


Table 2: Reaction of quadricyclane (1) with dimethyl azodicarboxylate in various solvents.[a]

Solvent	Conc. [M][b]	Time to completion
toluene	2	>120 h
EtOAc	2	>120 h
CH_3CN	2	84 h
CH_2Cl_2	2	72 h
DMSO	2	36 h
MeOH	2	18 h
neat	4.53	48 h
on D_2O	4.53	45 min
on C_6F_{14}	4.53	36 h
on H_2O	**4.53**	**10 min**
MeOH/H_2O (3:1, homogeneous)	2	4 h
MeOH/H_2O (1:1, heterogeneous)	4.53	10 min
MeOH/H_2O (1:3, heterogeneous)	4.53	10 min

[a] Compound 3 was the only product observed in each case. [b] Concentrations of the neat and heterogeneous reactions are calculated from the measured density of a 1:1 mixture of 1 and 2. DMSO = dimethylsulfoxide.



"On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension**

*Sridhar Narayan, John Muldoon, M. G. Finn, Valery V. Fokin, Hartmuth C. Kolb, and K. Barry Sharpless**

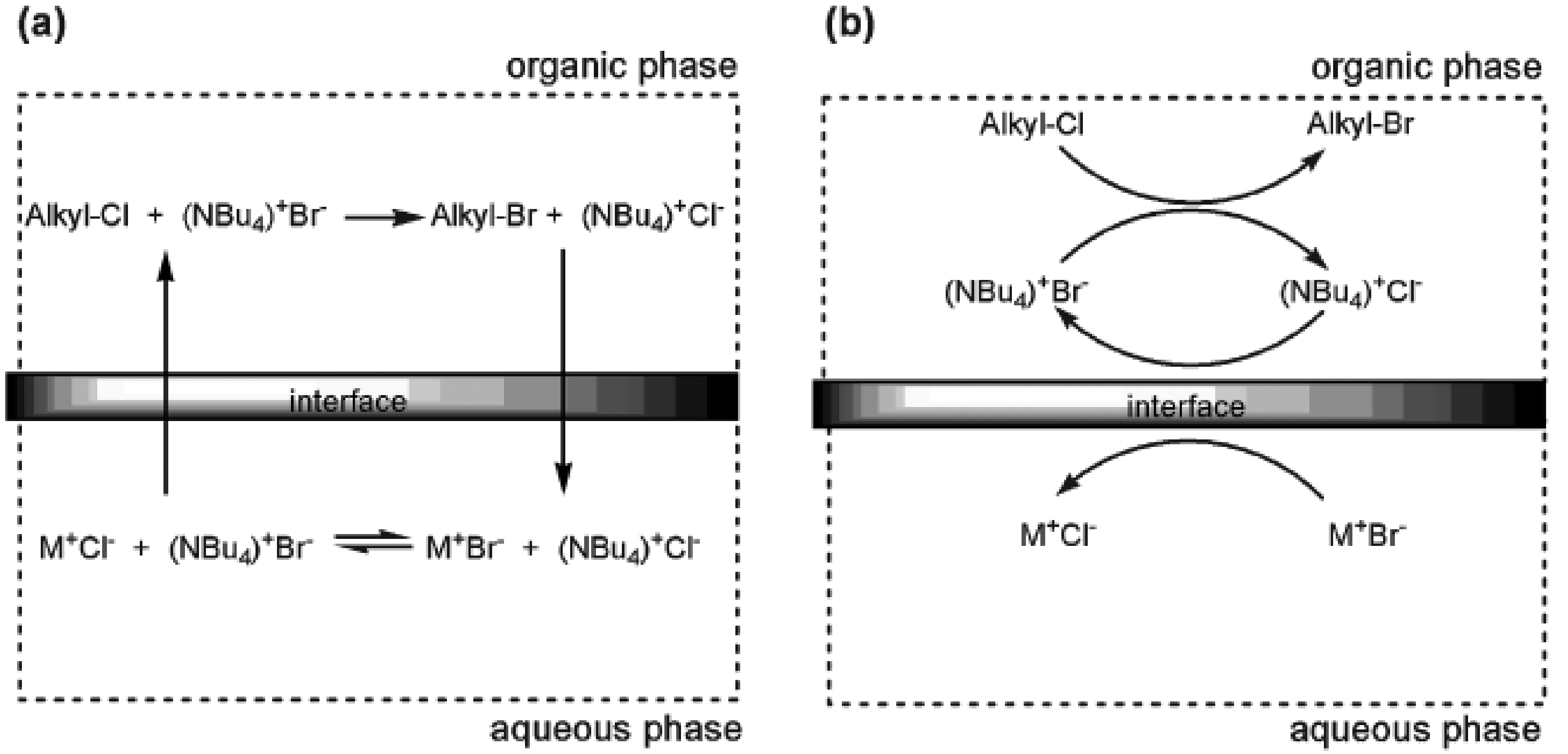
Angew. Chem. Int. Ed. 2005, 44, 3275-9.

IV-(1e) Phase-Transfer Catalysis

- Phase-transfer catalysis (PTC) is a well-established technique, applying in over 600 industrial processes in the fine chemicals and pharmaceuticals industries, with advantages: increased rate of reaction and product specificity, low energy requirements, use of inexpensive, nontoxic, recoverable solvents, use of inexpensive catalysts and bases.
- PTC is not widely applied in the bulk chemicals industry, because of the costs associated with the need to treat both the organic and aqueous effluents from the processes.

Types and Outcomes of PTCs

- A number of different types of PTC are available commercially. The most common PTCs are quaternary ammonium salts. These and the related phosphonium salts operate by formation of lipophilic ion pairs. The neutral PTCs, crown ethers and polyethylene glycols (PEGs) , bind specifically to the metal cation of the salt, making the salt more soluble in the organic phase.
- The outcomes of PTC reactions arise from a combination of the nature of the anion, the nature of the quaternary onium cation (or neutral PTC), and the effects of the organic solvent. The optimum cation for one anion may not be the same as for another anion, and vice versa.



Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 48.

The organic phase in PTCs

- The first requirement of the organic phase of an aqueous PTC system is that it forms a second phase under the reaction conditions. This limits the number of liquids that can be used and most reports in the literature use alkanes, chlorocarbons, or aromatics. These are all solvents of environmental concern and there is a need to develop suitable alternatives.

PTC oxidation reactions

- Oxidation are particularly problematic with regard to green chemistry. The traditional stoichiometric metal-containing oxidants, e.g. $KMnO_4$ and $K_2Cr_2O_7$, generate large amounts of metal wastes. Chlorine-containing oxidants also produce environmentally hazardous wastes. Nitric acid forms nitrogen oxides, particularly N_2O, which is a potent ozone-depleting agent and greenhouse gas. Although the use of PTC with these reactants may allow more effective reaction conditions, it does not remove these problems.
- With the advent of green chemistry, there has been a great deal of interest in the use of aqueous H_2O_2 as an oxidant. O_2 is potentially the greenest oxidant, but its use is hampered by its poor controllability and particularly the danger of combustion.

H_2O_2 as a green oxidant

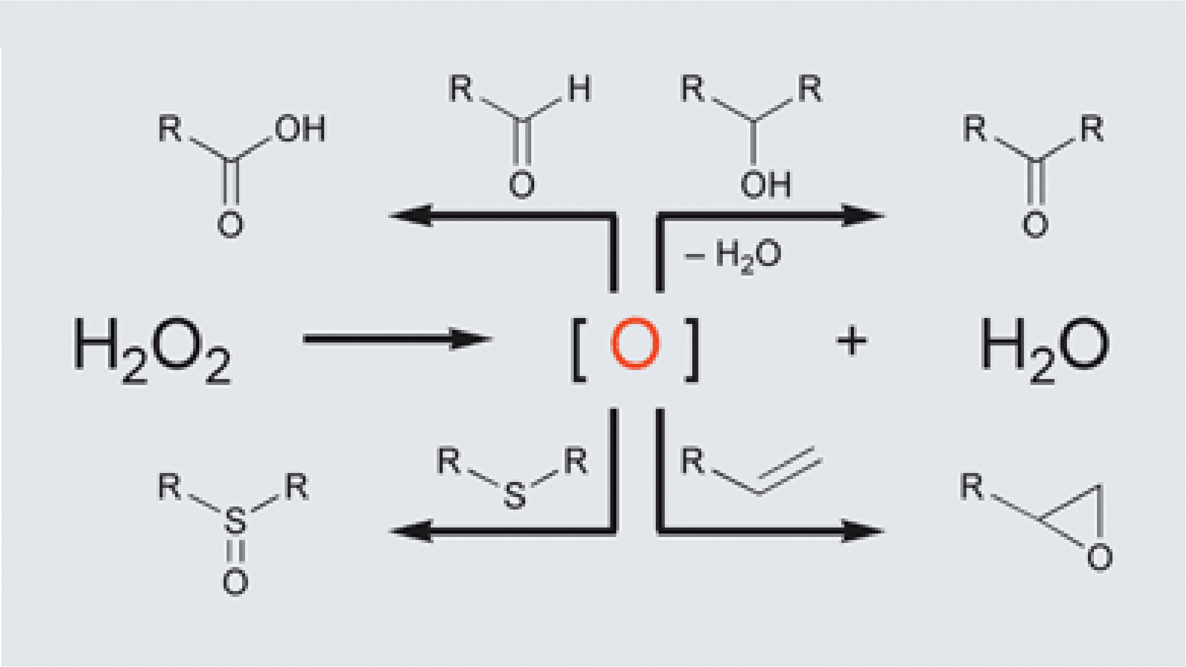
- Since the only by-product of its use is water, H_2O_2 offers a practical alternative as a green oxidant. H_2O_2 is produced as aqueous solutions with concentrations ranging from 0.35 to 0.70 g/g. Although it is a better controlled oxidant than many others, care must still be exercised to avoid its highly exothermic decomposition. Consequently, lower concentrations of H_2O_2 are preferred, typically $\leqq$ 30%.

PTCs using H_2O_2 as an oxidant

- In most reactions, a catalyst is required for H_2O_2 to achieve good yields and rates of PTCs. Venturello et al, used a PTC system, $Na_2WO_4/H_2O_2\text{-}H_2O/H_3PO_4/[CH_3(n\text{-}C_8H_{17})_3NCl/1,2\text{-}$dichloroethane or benzene for epoxidation of alkenes with $\leqq$ 10% H_2O_2. (J. Org. Chem. 1983, 48, 3831.) They noted that both the tungstate and the phosphate were required and the pH of the aqueous phase was controlled to < 2. Noyori et al, used a PTC system for alcohol oxidation, $Na_2WO_4/H_2O_2\text{-}[CH_3(n\text{-}C_8H_{17})_3NHSO_4$ with the reactant/product (2-octanol/2-octanone) acting as the organic phase and 30% H_2O_2. (J. Am. Chem. Soc. 1997, 119, 12386.)

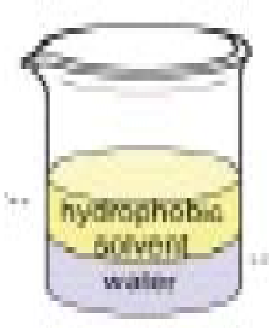
Green Oxidation with aqueous H_2O_2

Chem. Commun. 2003, 1977-1986.



IV-(1f) Aqueous Biphasic Catalysis

- Aqueous/organic biphasic catalysis is conceptually simple and different from PTC. The reactants and products are soluble in the organic phase but largely insoluble in the aqueous phase, whereas the **catalyst is insoluble in the organic phase** but **soluble in the aqueous phase**. The reactants are contacted with the catalyst by rapid stirring of the reaction mixture, so that the reaction can occur at a satisfactory rate. The reaction itself occurs in the interfacial region and not by transfer into one or the other bulk phases. At the end of the reaction the stirring is stopped, so that the products can be separated from the catalyst solution, which can be recycled. This methodology gives **the advantages associated with both homogeneous and heterogeneous catalysis**.



Hydroformylation of alkenes using Aqueous Biphasic Catalysis

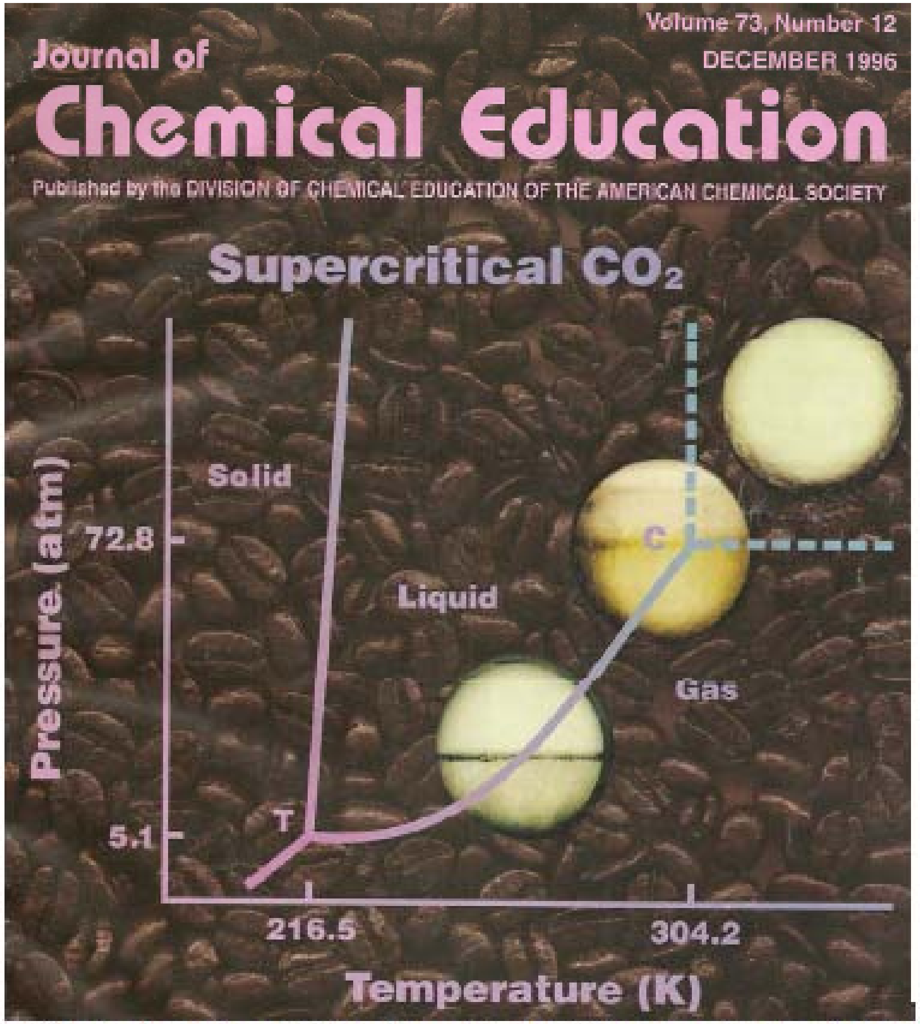
- $RCH{=}CH_2$ + CO + H_2 forms RCH_2CH_2CHO and $RCH(CHO)CH_3$.
- The Wilkinson's hydroformylation catalyst, $[RhH(CO)(PPh_3)_3]$, was made water soluble by changing the phosphine ligands, $[RhH(CO)(m\text{-}SO_3NaC_6H_4)_3P)]$, hence allowing biphasic technology. The outcome has better environmental performance with an E-factor of 0.04-0.1, vs. that of 0.6-0.9 when $[CoH(CO)_4]$ was previously used. (Cornils, B. et al, Multiphase Homogeneous Catalysis, Wiley-VCH, 2005.)
- Limit: It works well only for light olefins, such as propene, because the light olefins have sufficient solubility in the aqueous layer.

IV-(2a) Supercritical CO_2

- An accessible critical point of 31 ^{o}C and 74 bar.
- Nontoxic, nonflammable
- Easy removable: by depressurization
- Miscible with H_2 and O_2
- Its polarity can be tuned by <u>changing T and P</u>
- Replacement for VOCs in extraction processes, e.g., Decaffeinated Coffee

唯有永續化學
能使化學永續

$ScCO_2$ “老” 技術



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Supercritical CO_2

化工技術

1998年10月號／第67期

超臨界流體技術　專輯　　談駿嵩主編

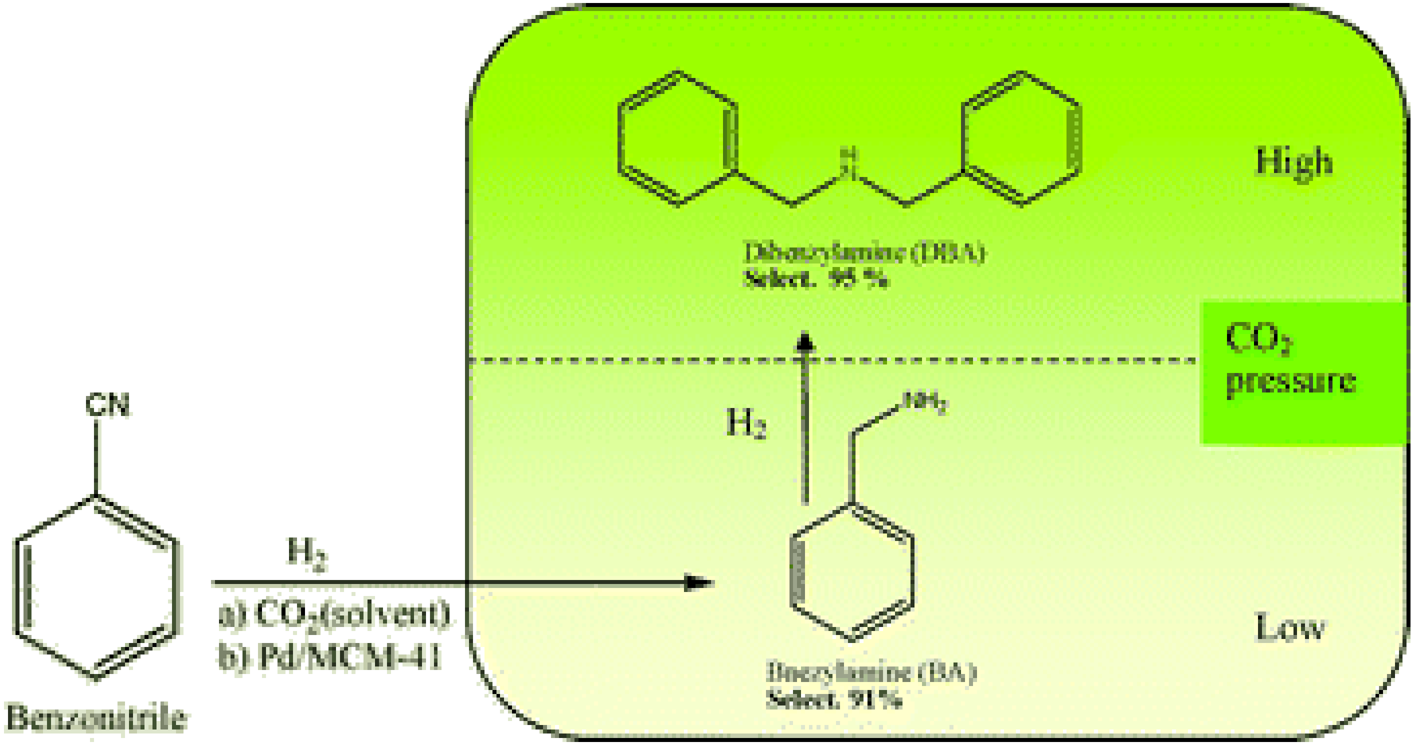
Chemical reactions in supercritical carbon dioxide
C. M. Wai, *J. Chem. Educ.* **1996**, *75*, 1641-1645

劉廣定教授: 永續化學溶劑, p. 36

Hydrogenation of nitrile in supercritical carbon dioxide: a tunable approach to amine selectivity

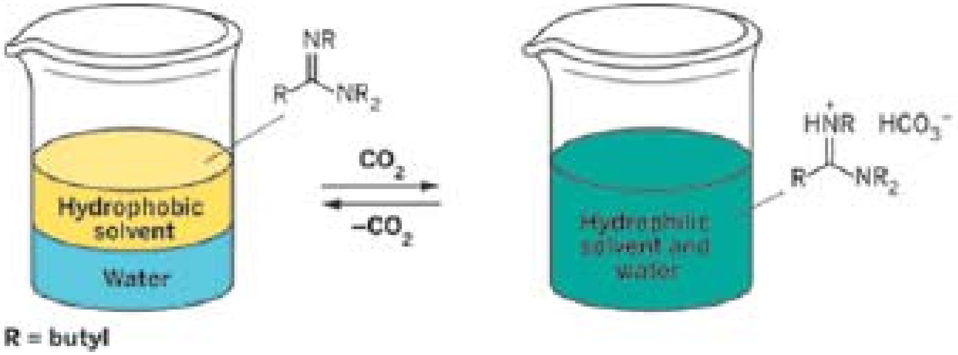
Green Chem. 2010, 12, 87-93.

- Simply tuning the CO_2 pressure changes the product selectivity from benzylamine to dibenzylamine.

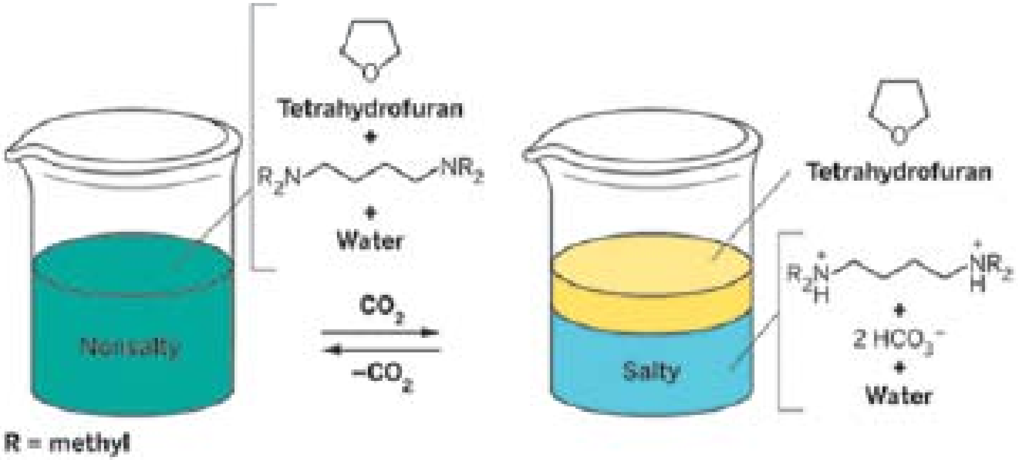


IV-(2b) Switchable Water: Aqueous Solutions of Switchable Ionic Strength

Mercer and Jessop, *ChemSusChem* **2010**, *3*, 467-470



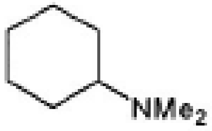
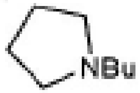
Switchable hydrophilicity solvent



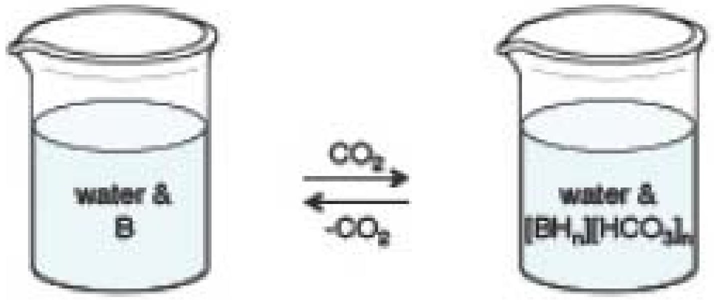
Switchable water

Tertiary amine and polyamines having switchable hydrophilicity

Jessop, *et al.* *Green Chem.* **2011**, *13*, 619-623; **2012**, *14*, 832-839

NEt_3	Me_2NBu	Et_2NBu	Pr_2NMe			$Me_2NC_6H_{13}$	
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1.2	1.6	1.7	1.9	1.7	2.1	2.5	2.4

SWITCHABLE WATER



- low ionic strength
- low osmotic pressure
- good solvent for polar organics

- high ionic strength
- high osmotic pressure
- poor solvent for polar organics

Green Chem. 2011, 13, 1391. Canada, 2007, 1830 tonnes hexane (a known neurotoxin) emissions from oilseed processing to air, 41% more than those from petroleum and related industries.

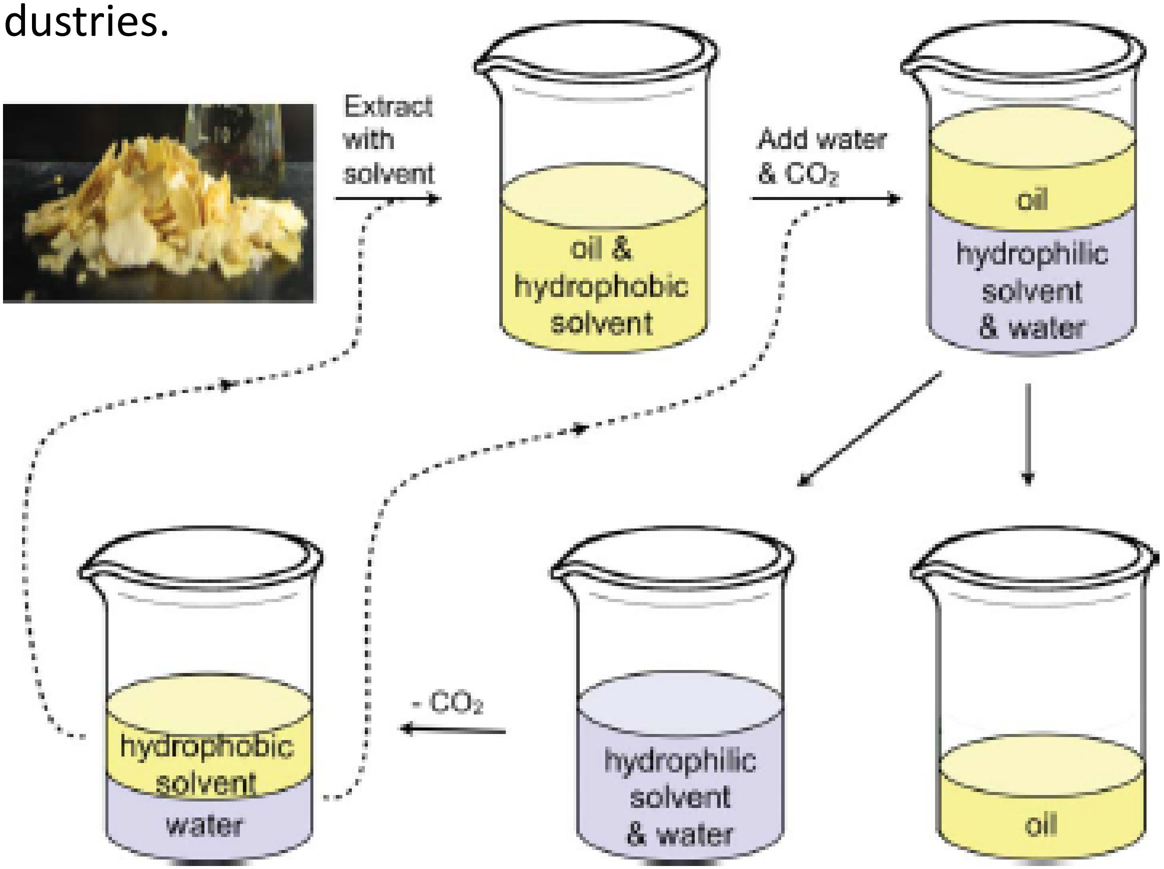
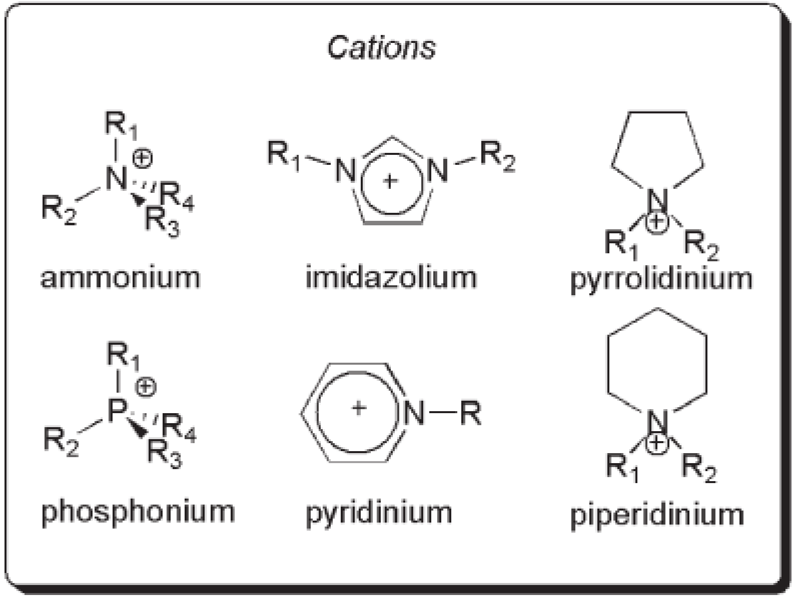


Fig. 11 The process by which an SHS can be used to extract soybean oil from soybean flakes without a distillation step. The extraction is performed with the solvent in its hydrophobic form, after which the addition of carbonated water converts the SHS to its hydrophilic form. Later removal of the CO_2 switches the SHS back to its hydrophobic form. The dashed lines indicate the recycling of the solvent and the aqueous phase.[43,44]

IV-(3) Room-Temperature Ionic Liquids (RTILs) and Low-Melting Eutectic Mixtures



Anions

NO_3^- BF_4^- $CF_3SO_3^-$ Cl^-, Br^-, I^-

$Al_2Cl_7^-$ SbF_6^- $CF_3CO_2^-$ $CH_3CO_2^-$

$Me_2PO_4^-$ PF_6^- $(CF_3SO_2)_2N^-$ $(CN)_2N^-$

Table 6.1 Some physical properties of imidazolium-based ionic liquids.[4a]

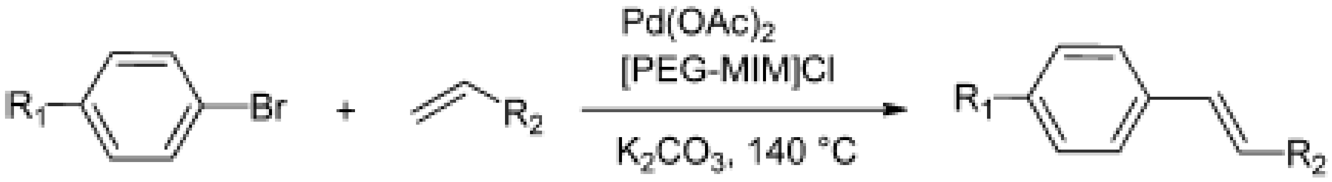
Cation	*Anion*	*Mp/°C*	*Thermal stability/°C*	*Density/ g cm^{-3}*	*Viscosity/ cP*	*Conductivity/ ohm^{-1} cm^{-1}*
Emim	BF_4^-	6	412	1.24	37.7	1.4
Bmim	BF_4^-	−81	403	1.12	219	0.173
Bmim	$(CF_3SO_2)_2N^-$	−4	439	1.429	52	0.39
Bmim	PF_6^-	−61	349	1.36	450	0.146
Hmim	PF_6^-	−61	417	1.29	585	-

[a] Emim = 1-ethyl-3-methylimidazolium, Bmim = 1-butyl-3-methylimidazolium, Hmim = 1-hexyl-3-methylimidazolium

Kerton, F. M. Alternative Solvents for Green Chemistry, RSC, 2009, p. 119.

Ether- and alcohol-functionalized task-specific ionic liquids: attractive properties and applications

- Chem. Soc. Rev. 2012, 41, 4030-66**.**
- The tunable solvent properties of ether- and hydroxylfunctionalized ILs have enabled their unique performance in a number of organic reactions. The primary role of these specialized ILs in organic reactions generally falls into one of three categories: reaction solvent, catalyst, and support for the catalyst or reactant.



Low melting mixtures in organic synthesis – an alternative to ionic liquids?

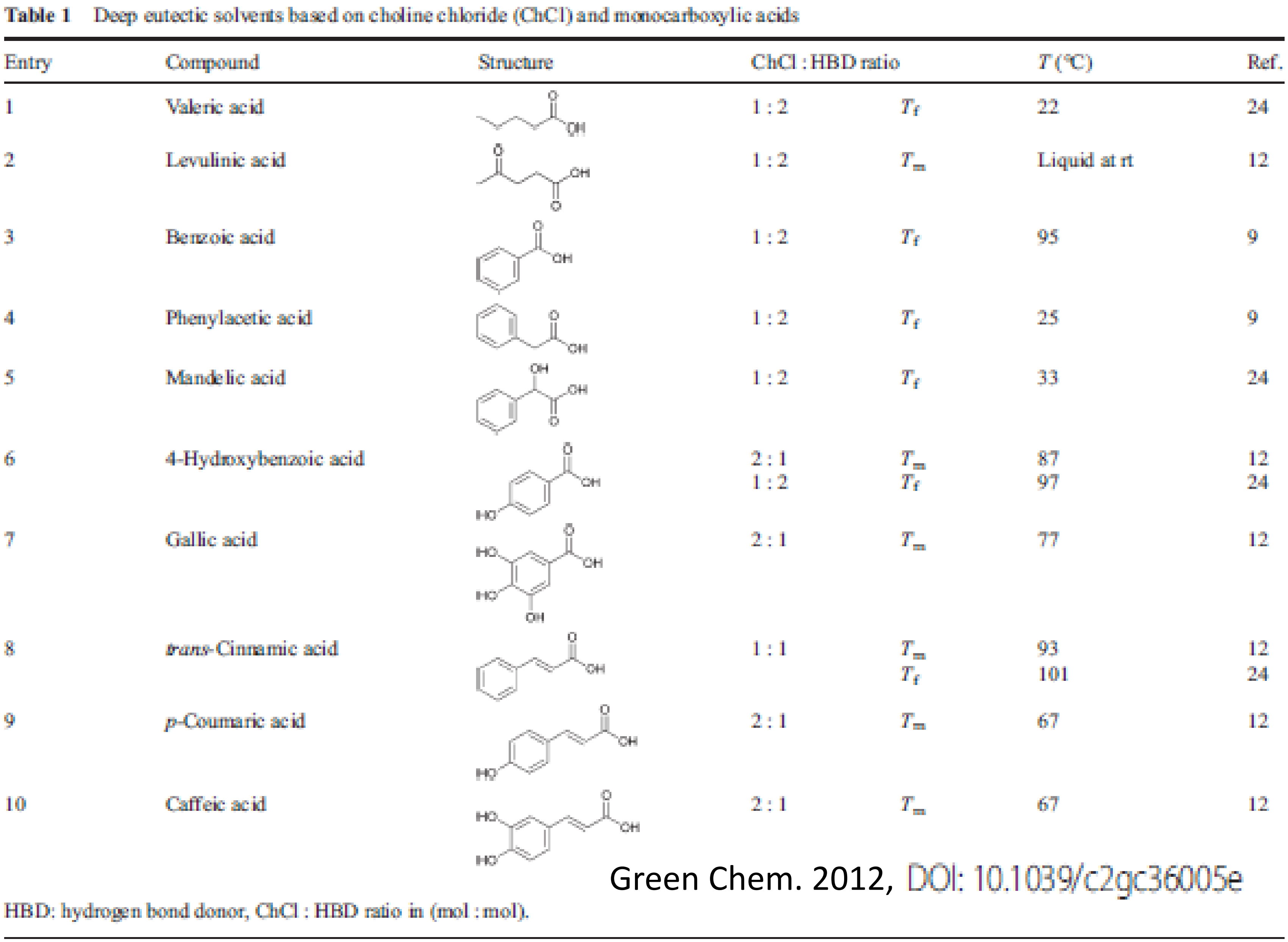


Table 1 Deep eutectic solvents based on choline chloride (ChCl) and monocarboxylic acids

Entry	Compound	Structure	ChCl : HBD ratio		T (°C)	Ref.
1	Valeric acid		1 : 2	T_f	22	24
2	Levulinic acid		1 : 2	T_m	Liquid at rt	12
3	Benzoic acid		1 : 2	T_f	95	9
4	Phenylacetic acid		1 : 2	T_f	25	9
5	Mandelic acid		1 : 2	T_f	33	24
6	4-Hydroxybenzoic acid		2 : 1 1 : 2	T_m T_f	87 97	12 24
7	Gallic acid		2 : 1	T_m	77	12
8	*trans*-Cinnamic acid		1 : 1	T_m T_f	93 101	12 24
9	*p*-Coumaric acid		2 : 1	T_m	67	12
10	Caffeic acid		2 : 1	T_m	67	12

HBD: hydrogen bond donor, ChCl : HBD ratio in (mol : mol).

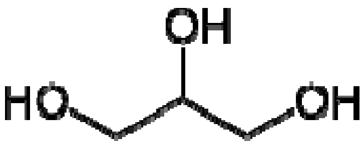
Green Chem. 2012, DOI: 10.1039/c2gc36005e

IV-(4) Liquid Polymers

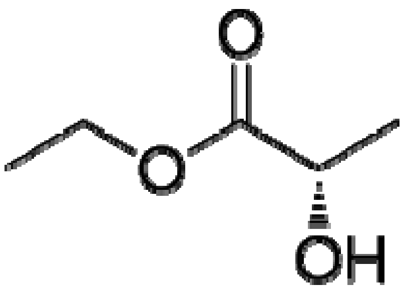
- Polyethylene Glycols (PEGs) are a range of water-soluble liquid polymers that are cheap and readily available. They have low vapor pressures and their mammalian toxicities are well known; they are even approved for human consumption. Hence, they have generated some interest as potential green solvents. They are usually named by their average molecular mass, e.g. PEG-300 has a molecular mass of 300.
- The rate the Diels-Alder cycloaddition of 2,3-dimethyl-1,3-butadiene with nitrosobenzene in PEG-300 has been shown to just over twice that of the same reaction in MeOH or CH_2Cl_2. (Chem. Eng. Commun. 2003, 190, 431.)

IV-(5) Biomass-Derived Solvents

- Concerns over the longevity of crude oil reserves and the desire to produce chemicals in a way that is carbon nature are leading both academia and industry to look to biomass as the source of chemicals and fuels for the future, produced in the integrated biorefinery. Some liquids produced in this way become important solvents in a biomass-based economy.



Glycerol and its Derivatives. Crude glycerol is a by-product of the synthesis of biodiesel via the transesterification of plant oils and has been suggested to be a green solvent. It is biodegradable and nontoxic. Pure glycerol has a high boiling point of 290 ^{o}C. It is more viscous than most common traditional solvents. Several reactions including Pd-catalyzed Heck and Suzuki CC couplings were conducted in glycerol. (Environ. Chem. Lett. 2007, 5, 67.)



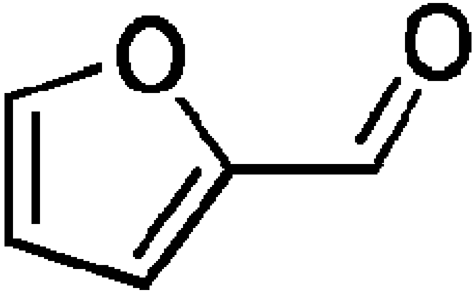
- **Ethyl Lactate** is produced through the esterification of lactic acid with ethanol, both of which are biomass derived. It is a colorless, nonvolatile liquid (bp 154 ^{o}C). It has a similar polarity to short-chain alcohols such as MeOH or 1-propanol. It has low toxicity and safe for human consumption. However, the hydrolytic instability toward acids or bases may place limits on the useful range of chemistries. Some applications were known, such as the extraction of food-grade lycophene from dried tomato powder. (J. Agric. Food Chem. 2009, 57, 1051.)

Fatty Acid Esters

- Biodiesel (生質柴油)is a plant oil-derived alternative to petroleum-derived diesel fuel. It is made up of methyl or ethyl fatty acids esters with variable chain lengths, depending on the sources. It is biodegradable and nontoxic and has been suggested as a potential solvent to aid the clean-up of oil spills in the environment. A study shows that the solvation power of biodiesels depend on the fatty-acid chain length with shorter chains having greater solvation power. (Ind. Eng. Chem. Res. 2004, 43, 7928.)

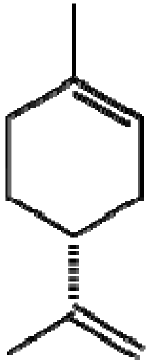
2-Methyltetrahydrofuran
(2-Me-THF)

- It is a biomass-derived, environmentally friendly and safe solvent. It is produced from furfural (2-furaldehyde), a natural pentose produced from agricultural waste. It is currently marked as a direct replacement of THF.



糠醛（呋喃甲醛，英文：*furfural*）是一種工業用化學製品，可由各種農副產品中萃取，包括玉米穗軸、燕麥與小麥的麥麩和鋸木屑。*furfural*這個字取自於拉丁字的*furfur*，意思是麥麩，因爲這是糠醛取得的來源。

Limonene檸烯、檸檬油精



Biodegradable limonene can be extracted from citrus peel as a by-product of fruit juice production. It is widely used for its fragrance in domestic cleaning products. Although classified as a VOC, it does not contribute to depletion of the ozone layer, due to its rapid oxidation to CO_2 and H_2O. It is a nonpolar solvent and has been suggested as a replacement for alkanes in the extraction of edible oils or for recycling polystyrene into fibers. However, the presence of the reactive C=C bond in limonene may limit its applications as a solvent.

V. Challenges in searching for “green” solvents

- (1) Green with satisfactory properties (basic or acidic, polar or non-polar, protic or aprotic, volatile, flammable, …)
- (2) LCA assessment of a green solvent- environmental effects of its synthesis, use, and disposal (LCA)
- (3) Polar and aprotic-enough polarity to dissolve organic substrates and ionic (catalysts) reagents; easy to separate after extraction to water
- (4) To find ways to remove solvents without distillation- membrane-based processes such as nanofilration and switchable hydrophilicity solvents (SHS)

Green Chem. 2011, 13, 1391.