聲明

永續化學合成(2)

永續化學的非傳統反應方法與溶劑

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永續化學合成

Plechkova and Seddon said: Your work is not green because you choose to call it green and publish it in *Green Chemistry*. Improving a yield, eliminating a toxic reagent, increasing a selectivity, are all admirable, but just a **green attitude**. The term green chemistry has to be applied to a total process, not to an single step. (*Methods and Reagents for Green Chemistry*, **2007**, p. 110)

Thus, a better yield or a higher selectivity at a condition not in line with principles of green chemistry or sustainability will not be regarded to have “green attitude,” either.

反應條件、試劑、溶劑、觸媒等都能盡量配合永續化學十二原則與次原則才是永續化學合成 **(sustainable chemical synthesis)**

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永續化學之反應方法

E-factor is the most important especially from the practical point of view, not only for production, but also for R&D

Alternative activation methods and alternative reaction media are sought for the purpose of reducing:

- Cost
- Energy
- Environmental impact
- Hazards
- Materials
- Non-renewables
- Risk
- Waste

Sustainable chemistry is the design, manufacture, and use of environmentally benign chemical products and processes to prevent pollution, produce less hazardous waste, and reduce environmental and human risks.

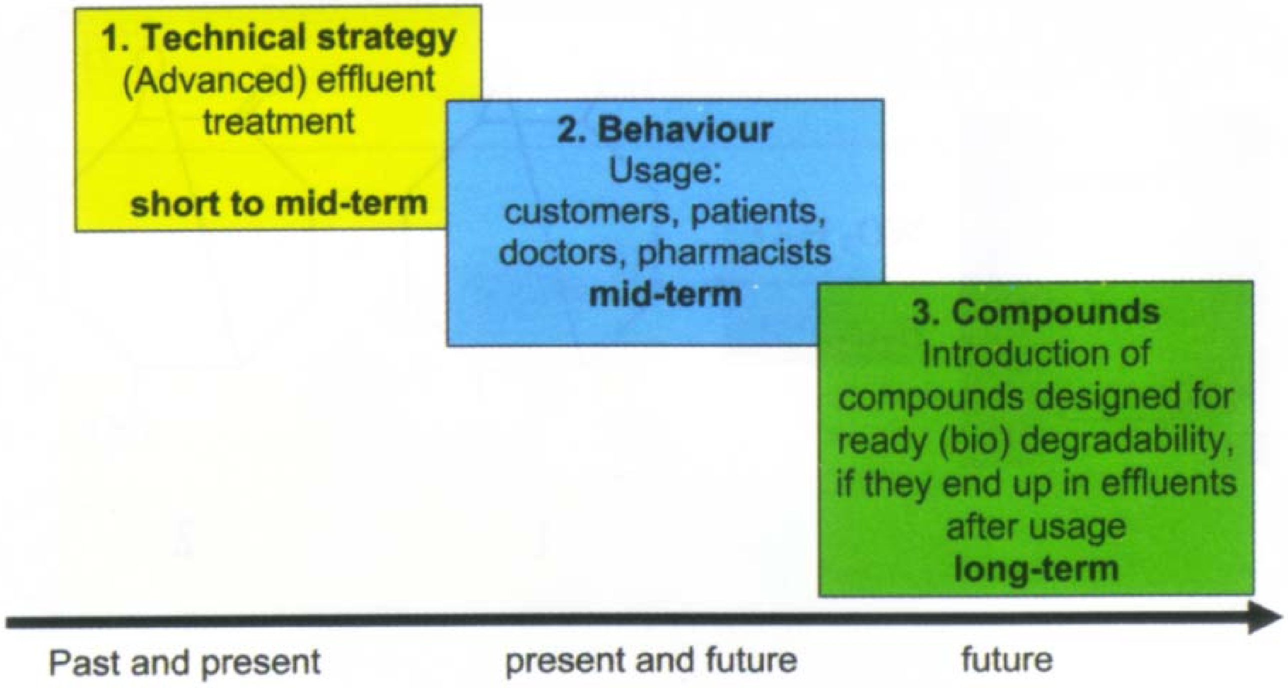
(OECD, 1999)

Sustainable from the very beginning

Example: **Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry**

Klaus Kümmerer *Green Chem*. **2007**, *9*(8), 899

Taking into account the full life cycle of chemicals will lead to a different understanding of the full functionality necessary for a chemical. Examples are presented to underline the feasibility and the economic potential of the approach benign by design.



1. Technical strategy
(Advanced) effluent treatment
short to mid-term

2. Behaviour
Usage:
customers, patients, doctors, pharmacists
mid-term

3. Compounds
Introduction of compounds designed for ready (bio) degradability, if they end up in effluents after usage
long-term

Past and present — present and future — future

Methods for chemical activation

Energy methods	**System requires**
Thermo chemistry	Heating
Photo chemistry	Chromophore, light source
Electro chemistry	Conducting media
Piezo chemistry	High pressure*
Sono chemistry	Ultrasound source
Microwave chemistry	Polar media, microwave source
Mechano chemistry	Solid, mill-grinding

From sustainability point of view, “greener” technologies with high energy and material efficiency are recommended to use.
Examples are ball milling, microwave irradiation, and ultrasound irradiation.
(*Green Chem.* 2008, *10*, 1129-1130, 1131-1141)

* **Chemistry driven by suction** (Ondruschka, *et al. Green Chem*. **2009**, *11*, 1026-1030)

Chu and Bienayme (Ed) *Multicomponent Reactions,* Wiley-VCH, 2005

Chemo-differentiating ABB' multicomponent reactions.
Tejedor, et al., *Chem. Soc. Rev.* **2007**, *36*, 484-491.

Wirth (Ed), *Microreactors in Organic Synthesis and Catalysis*, **Wiley-VCH**, **2008**

Organic Synthesis using Microreactor Technology, Mason, *et al. Chem. Rev*., **2007**, *107,* 2300-2318

Flash Chemistry: Fast Organic Synthesis by using microreactor,Yoshida, *et al. Chem. Eur. J.* **2008**, *14,* 7450-7459

Heterogeneous catalytic synthesis using microreactor technology, Frost and Mutton, *Green Chem*. **2010**, *12*, 1687-1703

Continuous flow multi-step organic synthesis, Webb and Jamison, *Chem. Sci.* **2010**, *1*, 675-680

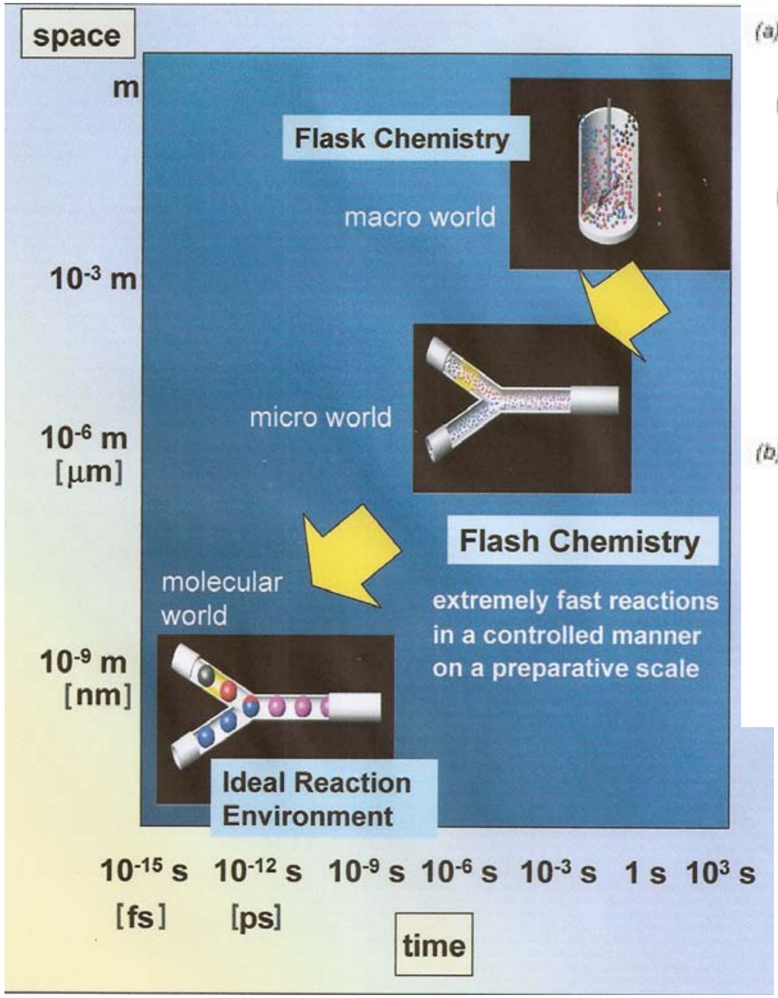
Roesky and Kennepohl (Ed), *Experiments in Green and Sustainable Chemistry*, Wiley-VCH, 2009.

Ballini (Ed), *Eco-Friendly Synthesis of Fine Chemicals*, RSC, 2009

Sustainability through green processing—novel process windows intensify micro and milli process technologies V. Hessel, et al. *Energy Environ. Sci.* 2008, *1*, 467-478.

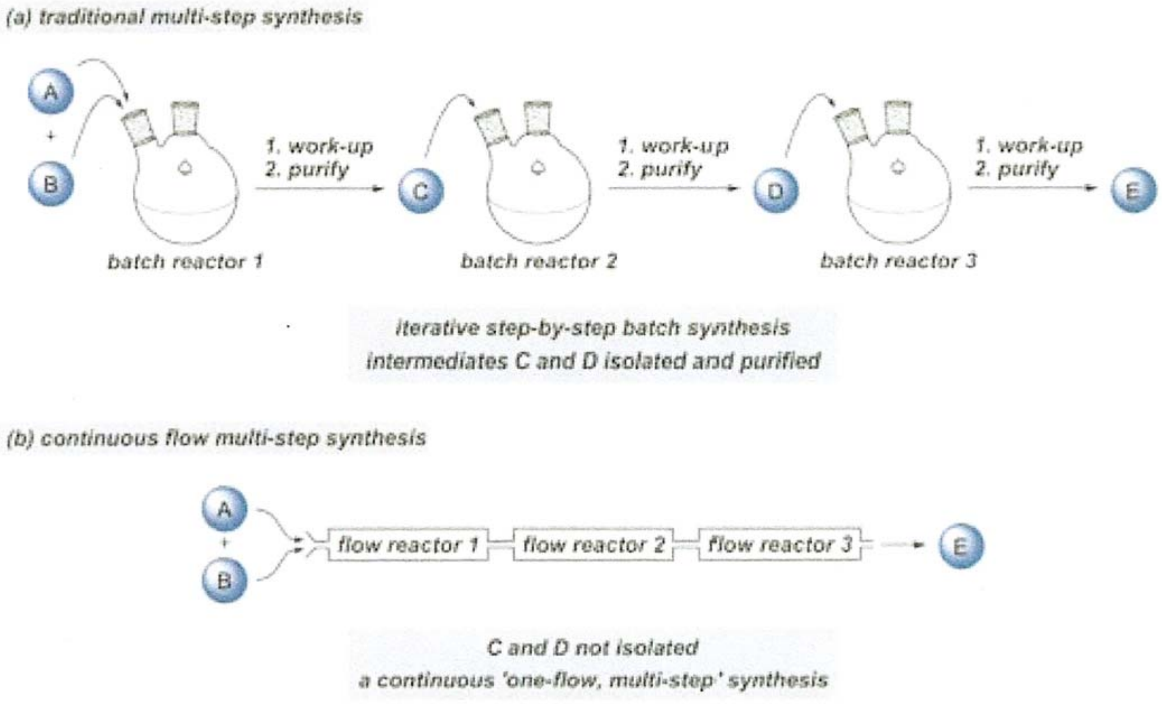
New concepts of synthetic technology

Fast, microreactor



Chem. Eur. J. **2008**, *14, 7450-7459*

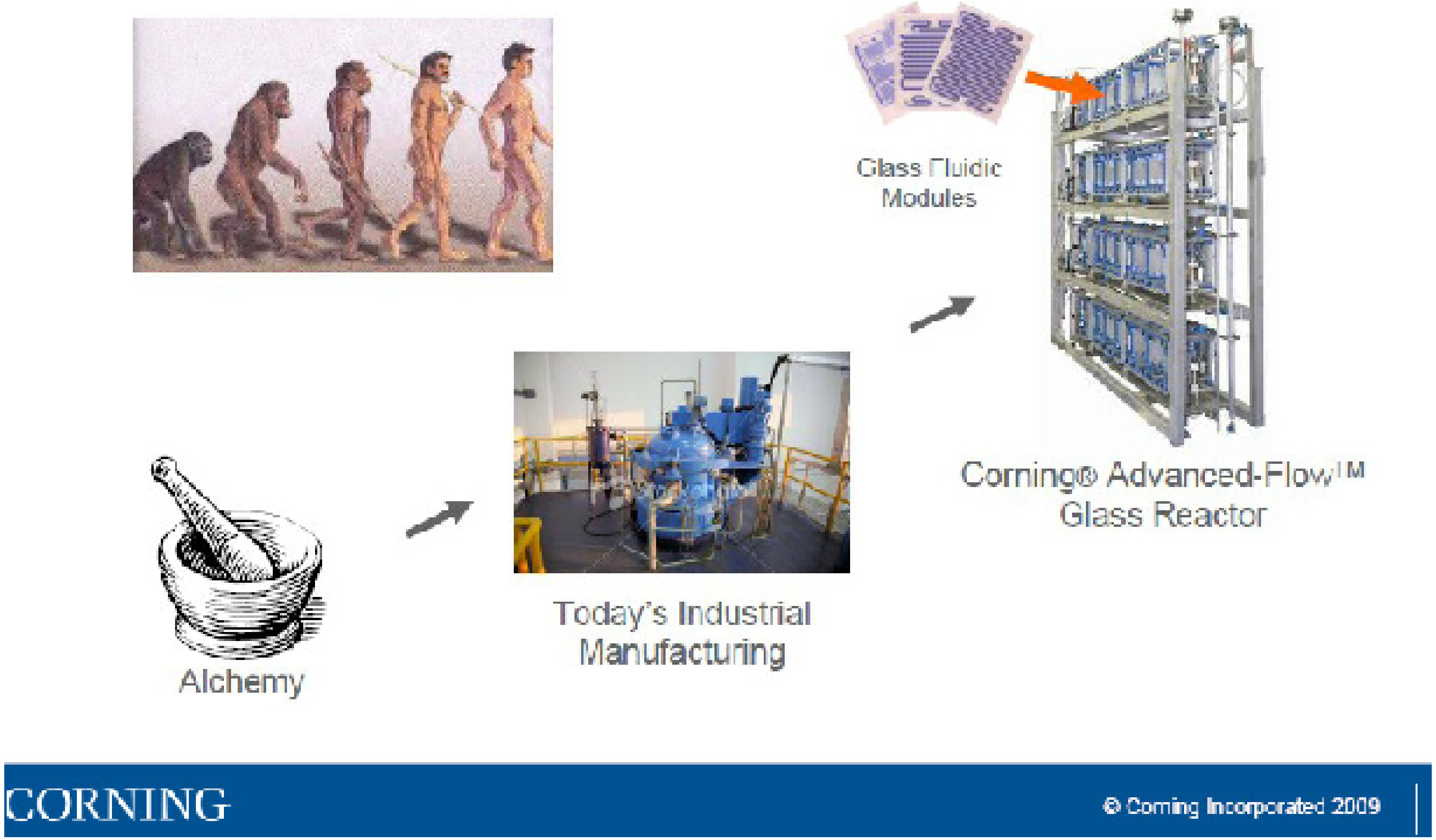
Continuous flow, (microreactor)



Chem. Sci. **2010**, *1*, 675-680

Evolution (Revolution) in Chemical Processing

Corning Advanced-Flow Reactor, announced May, 2009
http://www.corning-cable-systems.org/news_center/news_releases/2009/2009040601.aspx



Glass Fluidic Modules

Corning® Advanced-Flow™ Glass Reactor

Alchemy

Today's Industrial Manufacturing

CORNING

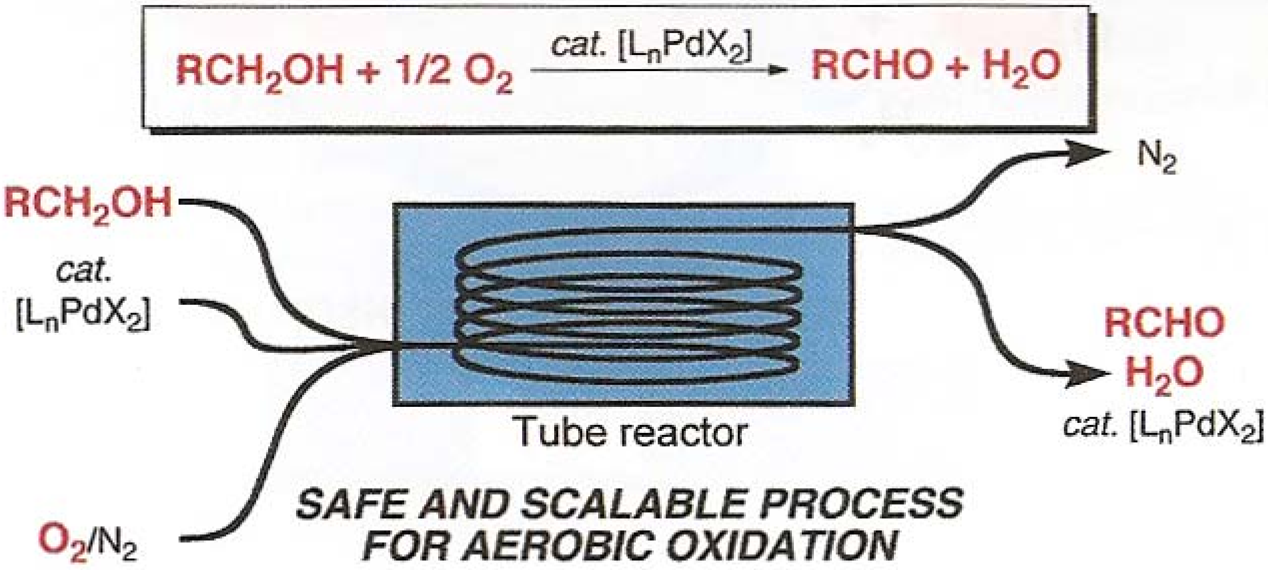
© Corning Incorporated 2009

Georgia Tech to Use Corning Advanced-Flow Reactor in Chemical Synthesis Research since April, 2010

Development of safe and scalable continuous-flow methods for palladium-catalyzed aerobic oxidation reactions

A Wisconsin-Lily collaboration

$\mathrm{RR'CHOH} \longrightarrow \mathrm{RR'C{=}O}$

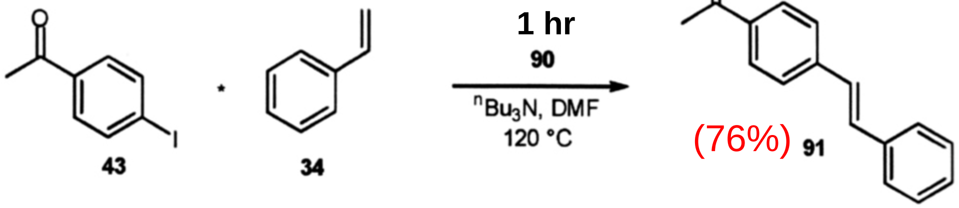


(*Green Chem*. **2010**, *12*, 1180-1186)

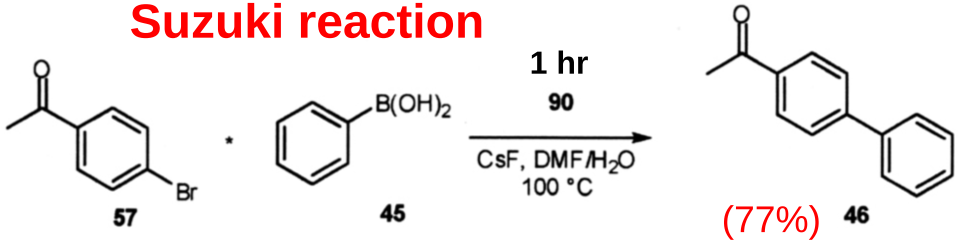
(*C&EN,* Jul. 5, **2010**, p.32)

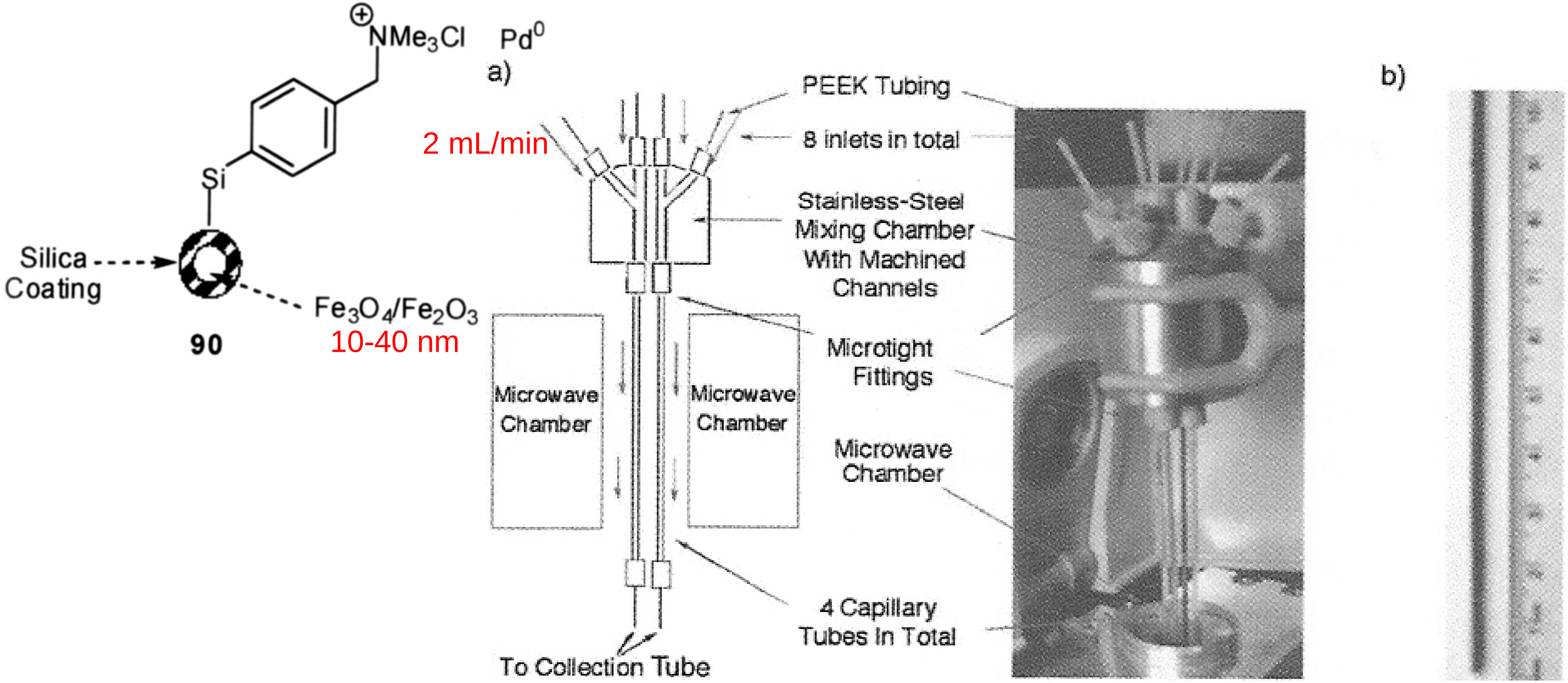
Heterogeneous catalytic synthesis using microreactor

Heck reaction



Suzuki reaction





(*Green Chem*. **2010**, *12*, 1687-1703) a) reactor b) tubing (d/1.150 mm)

Replacement of VOCs

Solvent free or minimum solvent used

Solvent alternatives:

Water

Less-volatile solvents (ethyl lactate(bp 154°), γ -valeralactone (bp 207°))

Other benign solvents (ionic liquids, gas-expansion liquids, fluorous*)

Supercritical and near-critical fluid systems

Recent progresses (organic carbonates, PEG-400, etc)

* They have extremely high global warming potential, 140-24000 times more potent than CO_2.

Green solvents for sustainable organic synthesis (Sheldon, *Green Chem.* **2005**, *7*, 267-278.)

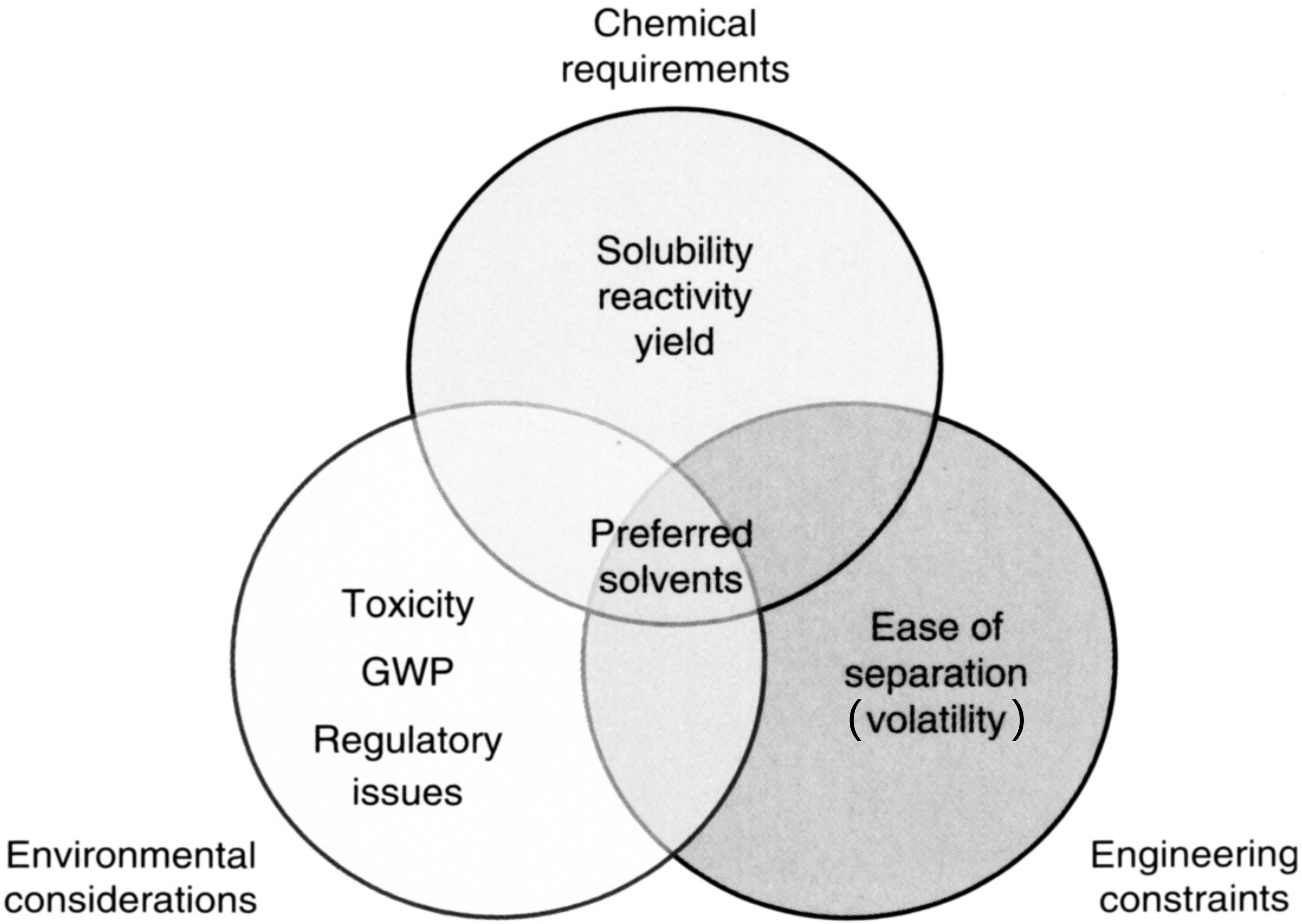
Alternative Solvents: Shades of Green (Clark and Tavener, *Org. Proc. Res. Dev.* **2007**, *11*, 149-155)

Solvents from nature (Horváth, *Green Chem.* **2008**, *10*, 1024-1028.)

Alternative Solvents for Green Chemistry (Kerton, RSC, **2009**)

Eco-Friendly Synthesis of Fine Chemicals (Ballini, Ed. RSC, **2009,** Chapters 1, 4, 5)

Conceptual basis for preferable solvent selection



Lapkin and Constable, *Green Chemistry Metrics*, p.22 (Blackwell, **2008**)

Solvent-free/solid state reactions

K. Tanaka, ***Solvent-free Organic Synthesis,*** **Wiley-VCH, 2003.**

F. Toda (Ed), ***Top. Curr. Chem.*** **2005, Vol. 254 (Organic Solid State Reactions)**

Z. V. Todres, ***Organic Mechanochemistry and its Practical Applications,*** **CRC/Taylor & Francis, 2006.**

P. J. Walsh, ***et al. Chem. Rev.*** **2007,** *107*, **2503-2545.**(solvent-free and highly concentrated reactions)

A. Garay, ***et al. Chem. Soc. Rev.*** **2007,** *36*, 846-855 (metal complexes),

I. G. Georgiev and L. R. MacGillivray ***Chem. Soc. Rev.*** **2007,** *36*, **1239-1248** (metal ion catalyzed reactions).

Chapter 2 in ***Alternative Solvents for Green Chemistry,*** **RSC, 2009**

Chapter 8 in ***Eco-Friendly Synthesis of Fine Chemicals,*** **RSC, 2009**

N. Z. Lyakhov, ***et al.*** *Russ. Chem. Rev.* **2010,** *79*, 189-203(Research by Russians on mechanochemical synthesis)

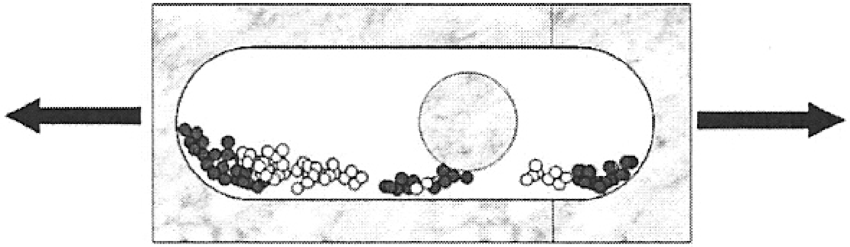
Mixing in Mechanochemistry

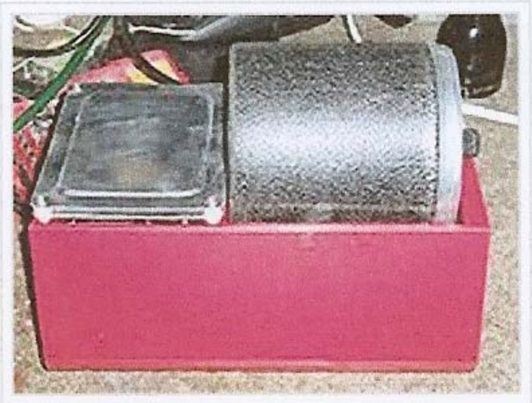
For a solid-state reaction to take place, the reactants have to be vigorously mixed by applying external mechanical energy, and may be called **mechanochemistry**.

Method of mixing might be manual grinding, using a ball mill or a pan mill.

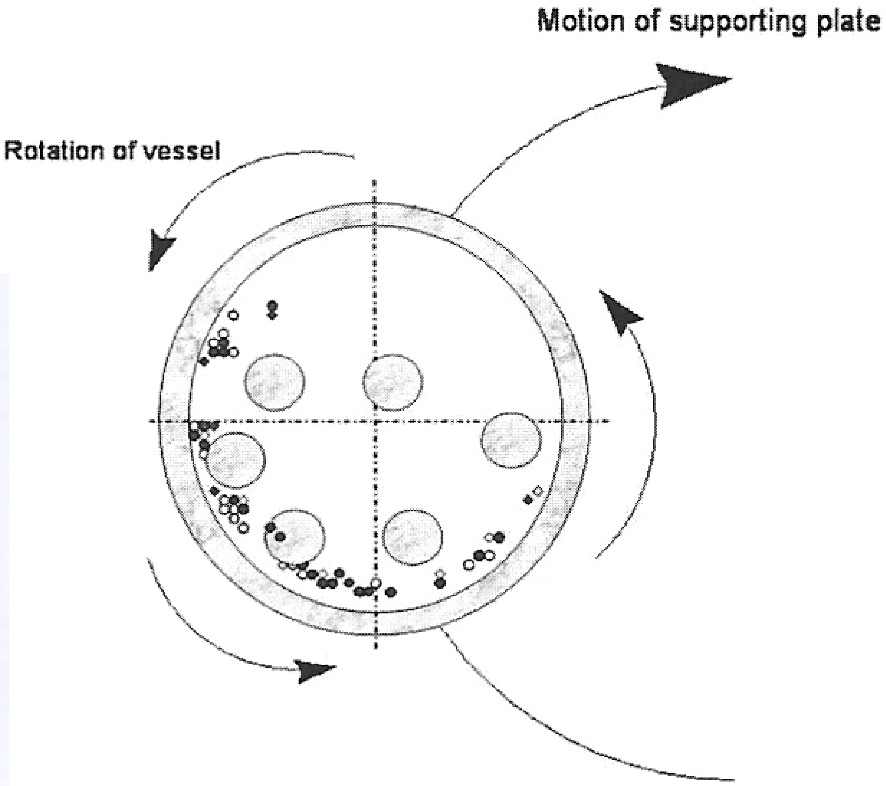
- a shaker mill (vibration)

a planetary mill (rotation)





Bench top ball mill



High speed vibration mill (HSVM)

HSVM at the speed of 3500 rpm was developed by **Komatsu** and coworkers.
A pressure of 10-20000 bar may be generated.

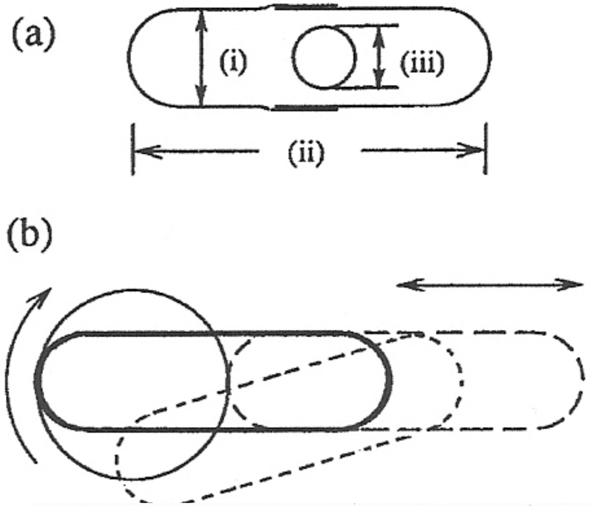
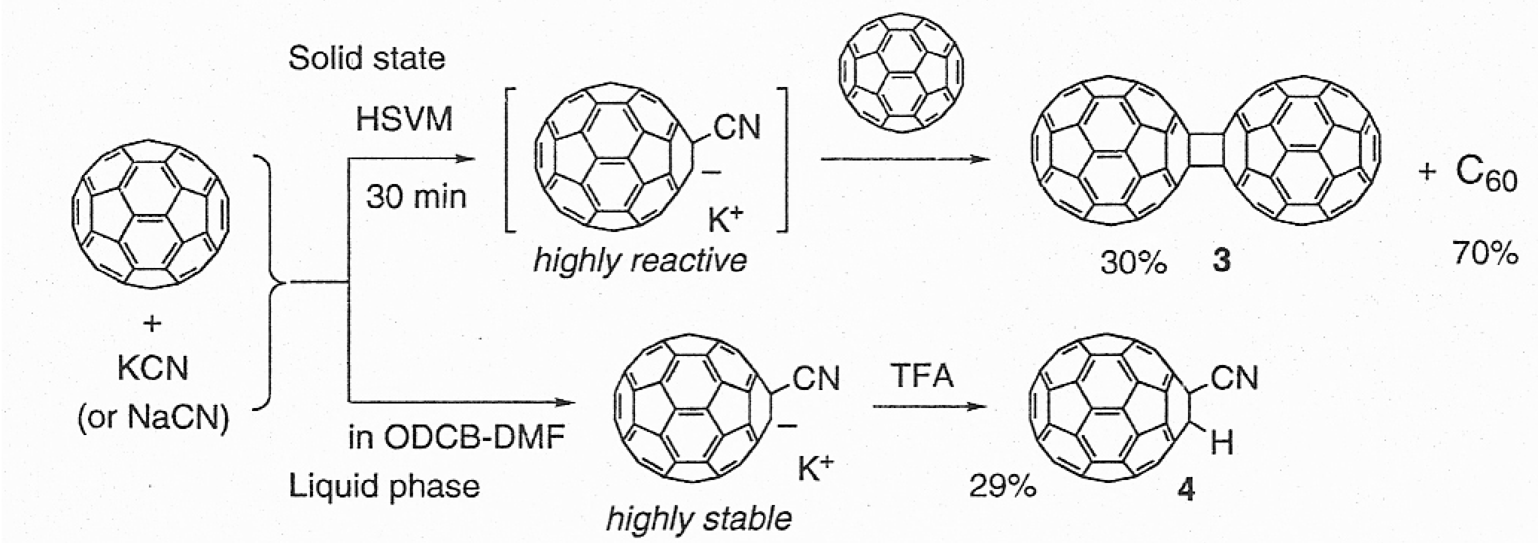


Figure 13. (a) A mixing capsule with a milling ball: (i) inner diameter, 9.0 mm; (ii) inner length, 26 mm; (iii) diameter, 6.0 mm. (b) Schematic representation of the movement of the capsule: one end moves around a circle while the other end moves horizontally.

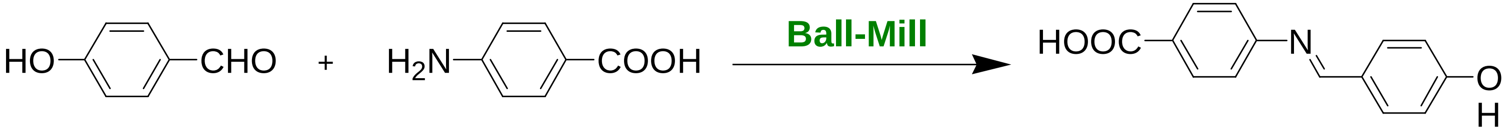
Dimerization of C-60



Komatsu and coworkers (*Top. Curr. Chem*. 2005, *254*, 185-206)

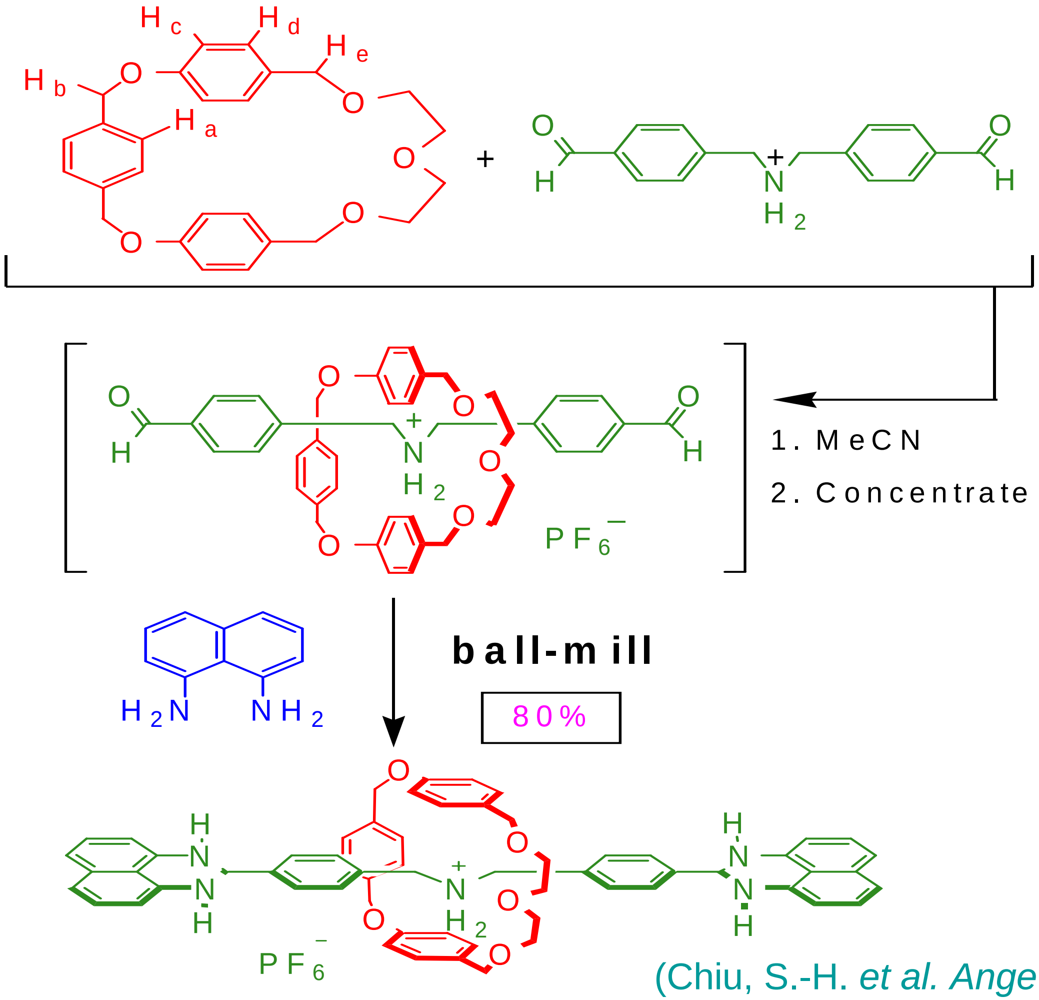
Solid-to-Solid Ball-Milling Process

Imine



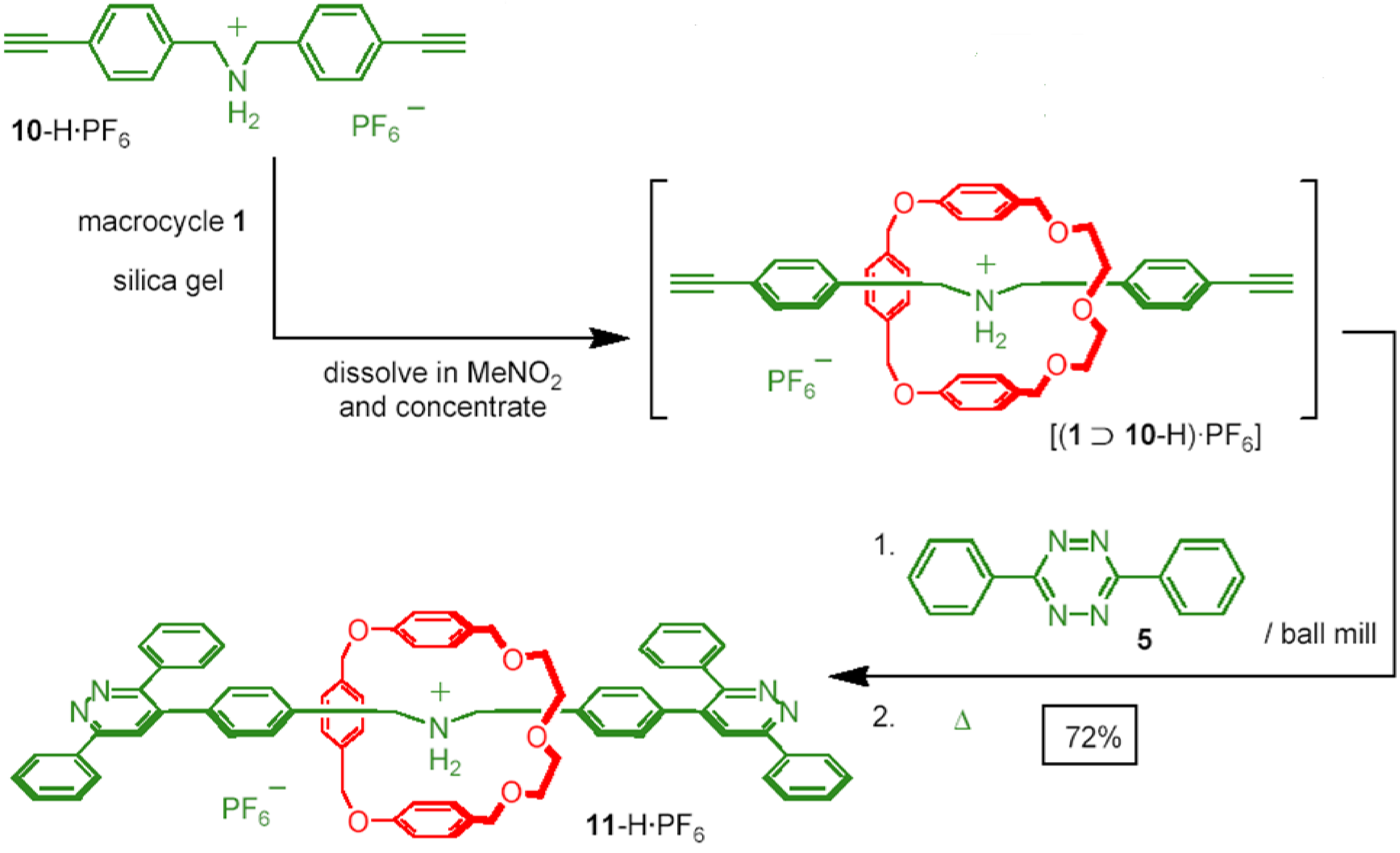
(Kaupp, et al. *Chem. Engin. Sci.* **2002**, *57*, 763)

[2]-Rotaxane



簡單型儀器

(Chiu, S.-H. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 4436-4439)



10-H·PF_6

macrocycle **1**

silica gel

dissolve in $MeNO_2$ and concentrate

[(**1** ⊃ **10**-H)·PF_6]

1. **5** / ball mill

2. Δ

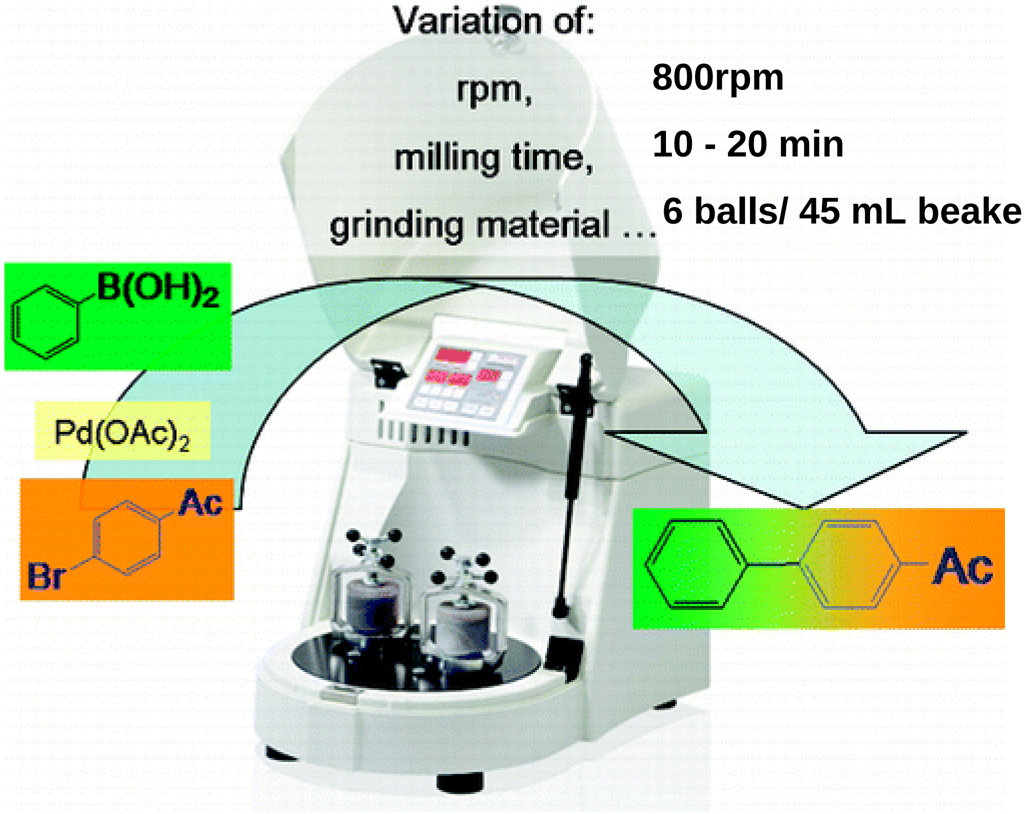
72%

11-H·PF_6

邱勝賢教授等 *Tetrahedron* **2009**, *65*, 2824-2829

The Suzuki–Miyaura Reaction under Mechanochemical Conditions

(Ondruschka, Stolle, *et al*, *Org. Process Res. Dev.*, **2009,** *13,* 44–48)



800rpm

10 - 20 min

6 balls/ 45 mL beaker of same material

As a model for a C–C-coupling procedure a Suzuki–Miyaura reaction has been studied under mechanochemical conditions. Important parameters influencing the yield of the reaction are the revolutions per minute, the milling time, and the material of the milling balls and beakers, as well as the size and number of milling balls.

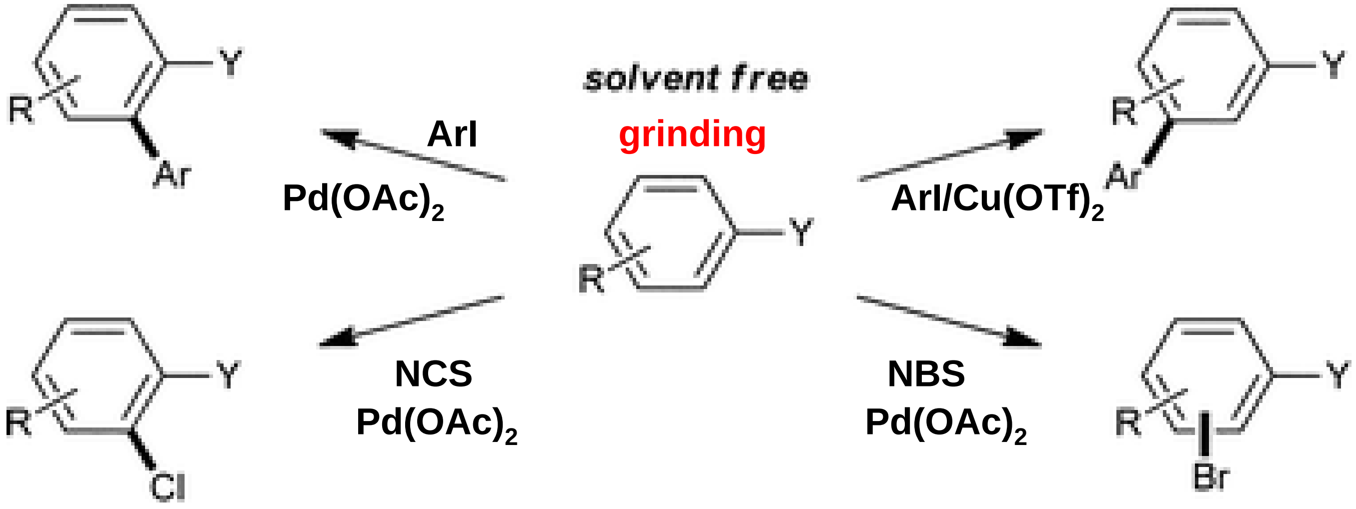
Fast copper-, ligand- and solvent-free Sonogashira coupling

Stolle, Ondruschka, *et al. Green Chem.* **2010**, *12*, 985-991

A protocol for a Pd-catalyzed Sonogashira reaction is presented employing neither copper, solvents nor ligands. Applying DABCO as the base yielded the products after 20 min of ball (agate or ZrO_2) milling with selectivities >95%.

Solvent free catalytic C–H functionalisation

Solvent-free reaction conditions facilitate a range of aromatic C–H functionalisations that traditionally require acidic or disfavoured solvents. These reactions include selective *ortho*- and *meta*-arylation of **aryl carbamates and anilides** and selective halogenation reactions. (40-90 % yield)

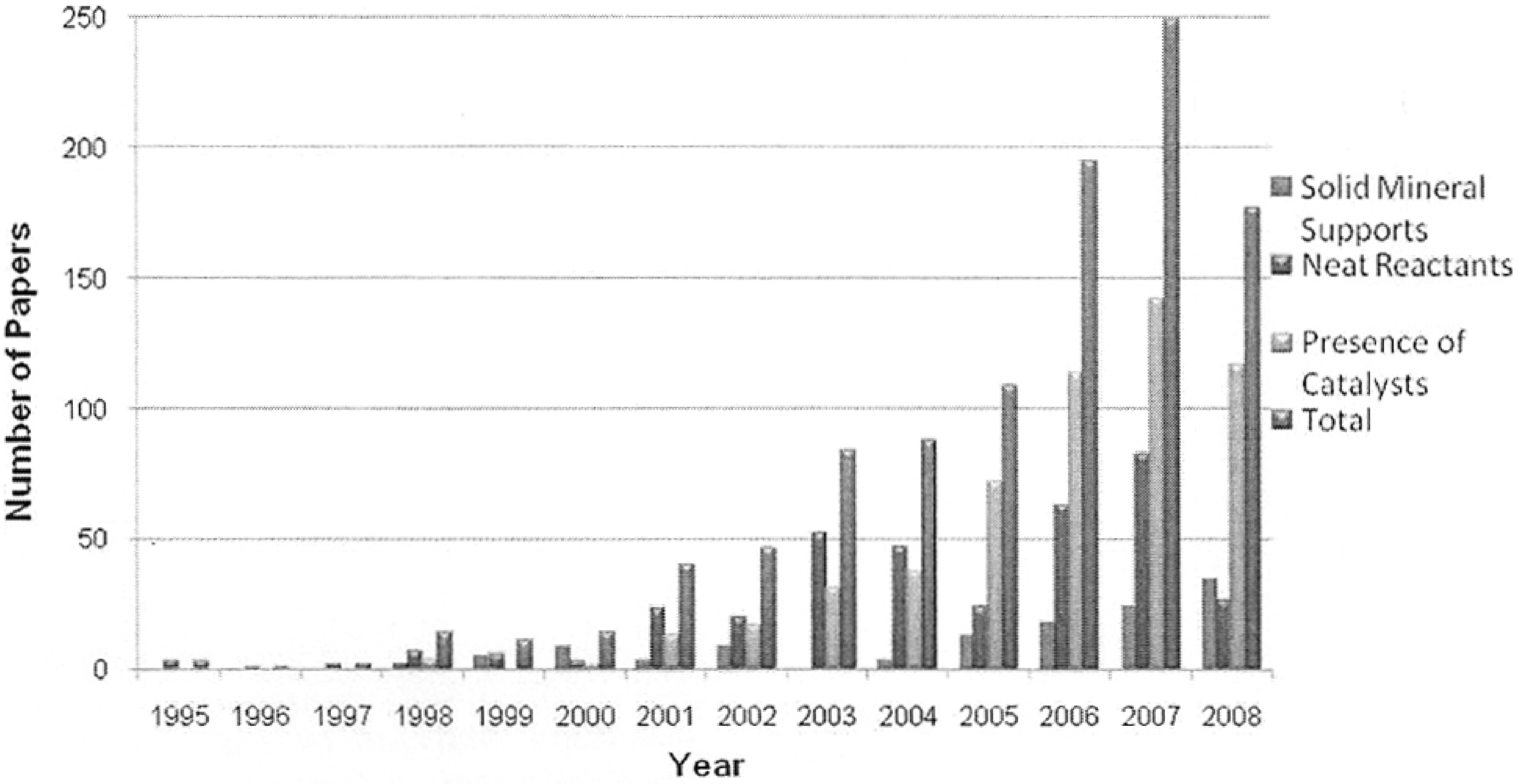


Chem. Commun. **2010**, *46*, 3095 - 3097

Solvent-free Heterocyclic Synthesis

M. A. Martins, et al., *Chem. Rev.* **2009**, *109*, 4140-4182

Distribution of papers dealing with synthesis of heterocyclic compounds under solvent-free condition by year



Heating, microwave irradiation, ultrasound irradiation, and/or grinding

The Use of Microwave Irradiation

COST Chemistry Action D32, starting in 2004

(Co-opération Européenne dans le Recherche Scientifique et Technique, European Co-operation in the Field of Scientific and Technical Research)

Four microwave-based working groups involving collaboration between scientists with different expertise in modern technology:

1. Diversity oriented synthesis under high efficient microwave conditions. (such as, solvent-less, aqueous media, multicomponent reaction, micro-reactor, and alternative reagents)
2. Microwave and high-intensity ultrasound in the synthesis of fine chemicals.
3. Ultrasound and microwave-assisted synthesis of nanometric particles.
4. Development and design of reactors for microwave-assisted chemistry in the laboratory and on the pilot scale.

The objective of COST D32 is to establish a firm EU base in microwave chemistry and to exploit the new opportunities provided by microwave techniques singly or in appropriate combination, for the widest range of applications in modern chemistry.

References:

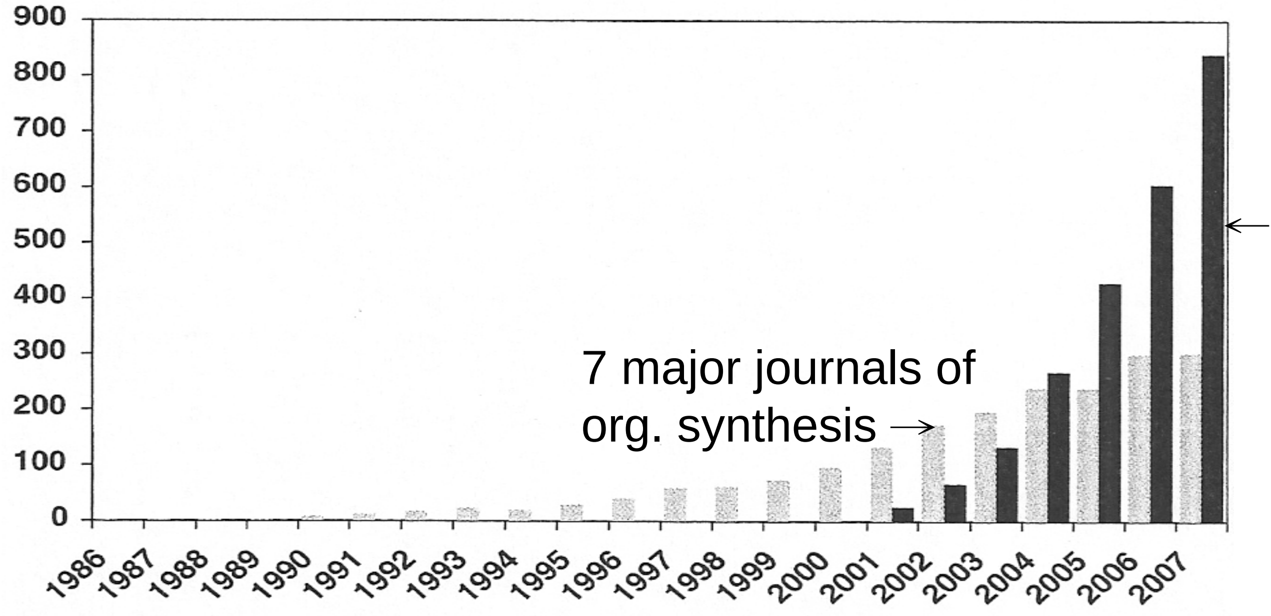
Loupy, Ed. ***Microwaves in Organic Synthesis***, 2nd Edition, 2 Vols, Wiley-VCH , **2006**

Kappe and Stadler, ***Microwaves in Organic and Medicinal Chemistry***, Wiley-VCH, **2005**

Microwave dielectric heating in synthetic organic chemistry, Kappe, ***Chem. Soc. Rev.*** **2008, *37*, 1127-1139**

Kappe, *et al.*, ***Practical Microwave Synthesis for Organic Chemists***, **Wiley-VCH, 2009**

Polshettiwan and Verma, Ed. ***Aqueous Microwave Assisted Chemistry: Synthesis and Catalysis***, **2010**, RSC



7 major journals of org. synthesis →

←50 journals

(Kappe, 2009, p. 4)

Characteristics of microwaves

electromagnetic waves with low energy photon

Microwave-matter interaction

causes movement of molecules (dipolar rotation)
causes movement of ions (ionic conduction)
will be reflected, transmitted or absorbed
volumetric heating throughout an absorbing material

Microwave effects

thermal effects – dipolar polarization
superheating in a mw cavity
non-thermal effects – increasing pre-exponential factor A
decreasing activation energy

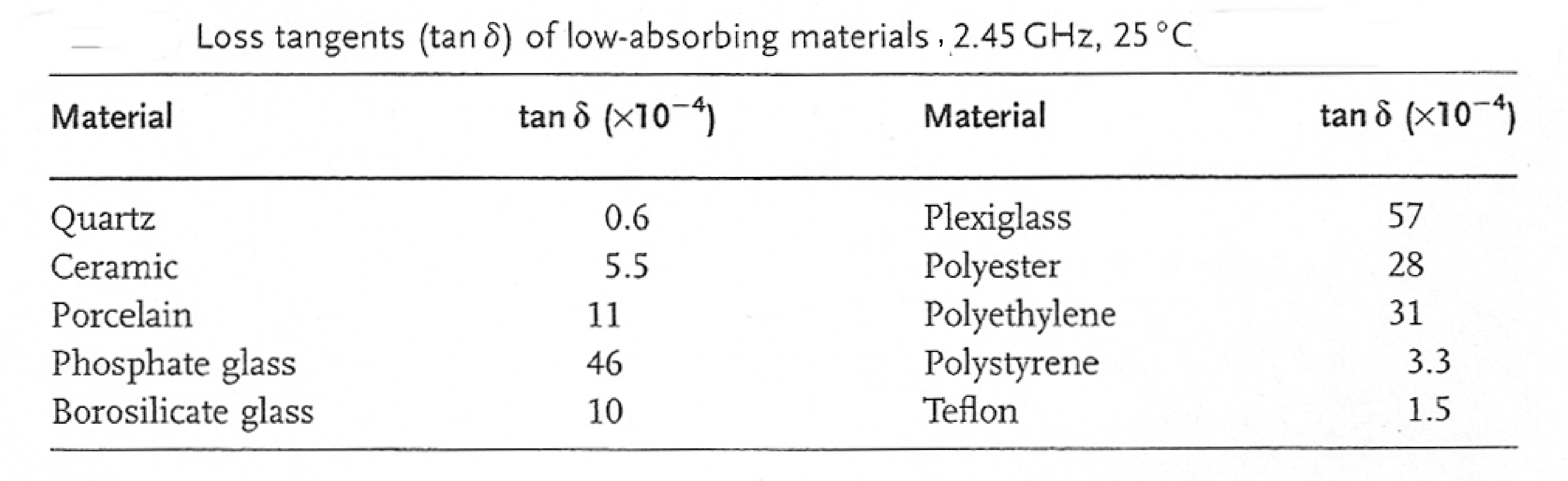
Loss tangents (tan δ of solvents at 2.45 GHz and 20℃)

Solvent	**tan δ**	**Solvent**	**tan δ**
Ethylene glycol	1.350	*N,N*-dimethylformamide	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
Dimethyl sulfoxide	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	Dichloromethane	0.042
1-methyl-2-pyrrolidone (NMP)	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

(Kappe et al., **2009**, p. 15)

Solvents can be classified as high (tan $\delta > 0.5$), medium (tan δ 0.1- 0.5) and low (tan $\delta < 0.1$) microwave absorbing. (tan δ = δ"/ δ')

Absorption of MW by Vessels



Loss tangents (tan δ) of low-absorbing materials, 2.45 GHz, 25 °C

Material	tan δ ($\times 10^{-4}$)	Material	tan δ ($\times 10^{-4}$)
Quartz	0.6	Plexiglass	57
Ceramic	5.5	Polyester	28
Porcelain	11	Polyethylene	31
Phosphate glass	46	Polystyrene	3.3
Borosilicate glass	10	Teflon	1.5

(Kappe et al., **2009**, p. 18)

Microwave vs conventional thermal heating

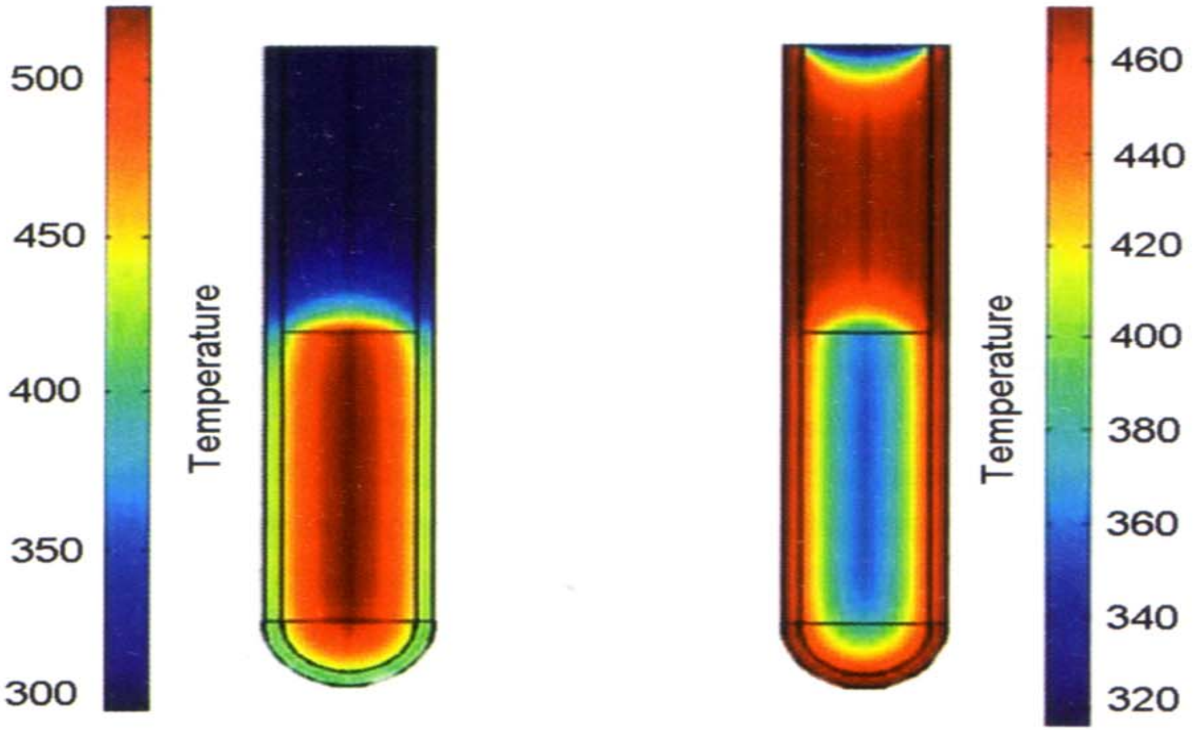


Fig. 2.6 Inverted temperature gradients in microwave versus oil-bath heating [12]. Temperature profiles (finite element modeling) after 1 min as affected by microwave irradiation (left) compared to treatment in an oil bath (right). Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first. Temperature scales in Kelvin. Reproduced with permission from [12].

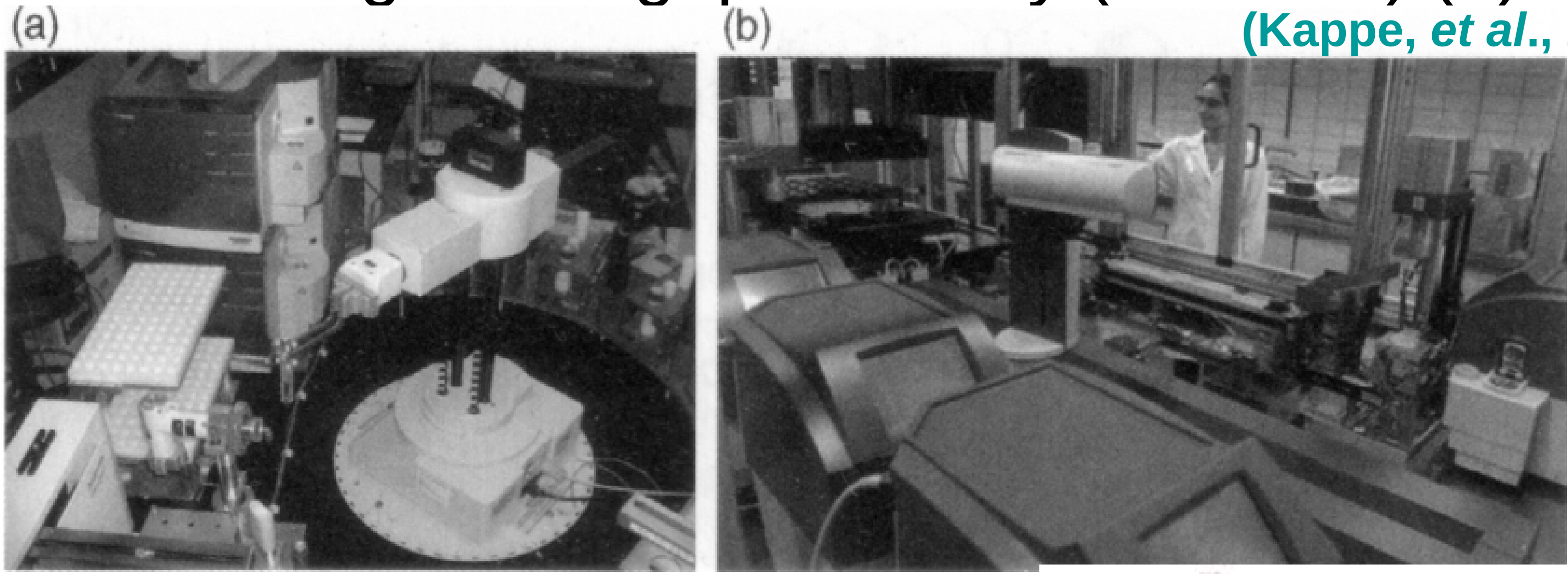
(Kappe and Stadler, p. 10)

Super-heating

Solvent	B.p./ °C)	B.p. MW/°C	Difference
Water	100	105	5
Ethanol	79	103	24
Methanol	65	84	19
Dichloromethane	40	55	15
Tetrahydrofuran	66	81	15
Acetonitrile	81	107	26
Propan-2-ol	82	100	18
Acetone	56	81	25
Ethyl acetate	78	95	17
Dimethylformamide	153	170	17
Diglyme	162	175	13

Robotic facility (Abbott Lab) (a) and high throughput factory (Novartis) (b)

(Kappe, *et al*., 2009, p. 117)

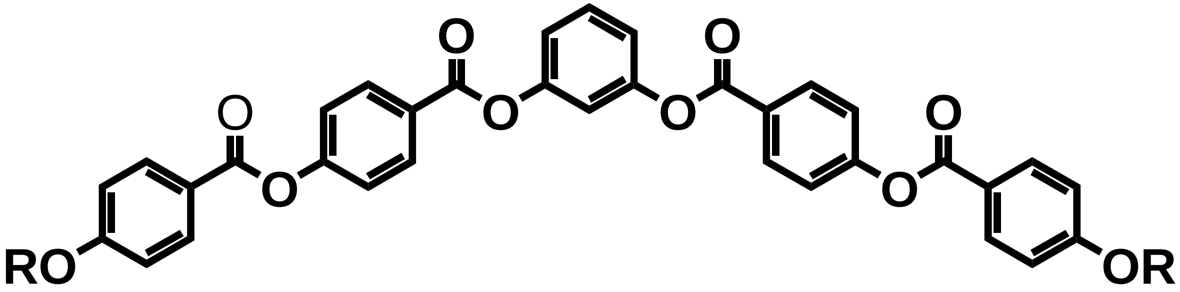


Laboratory scale preparations

簡單型儀器

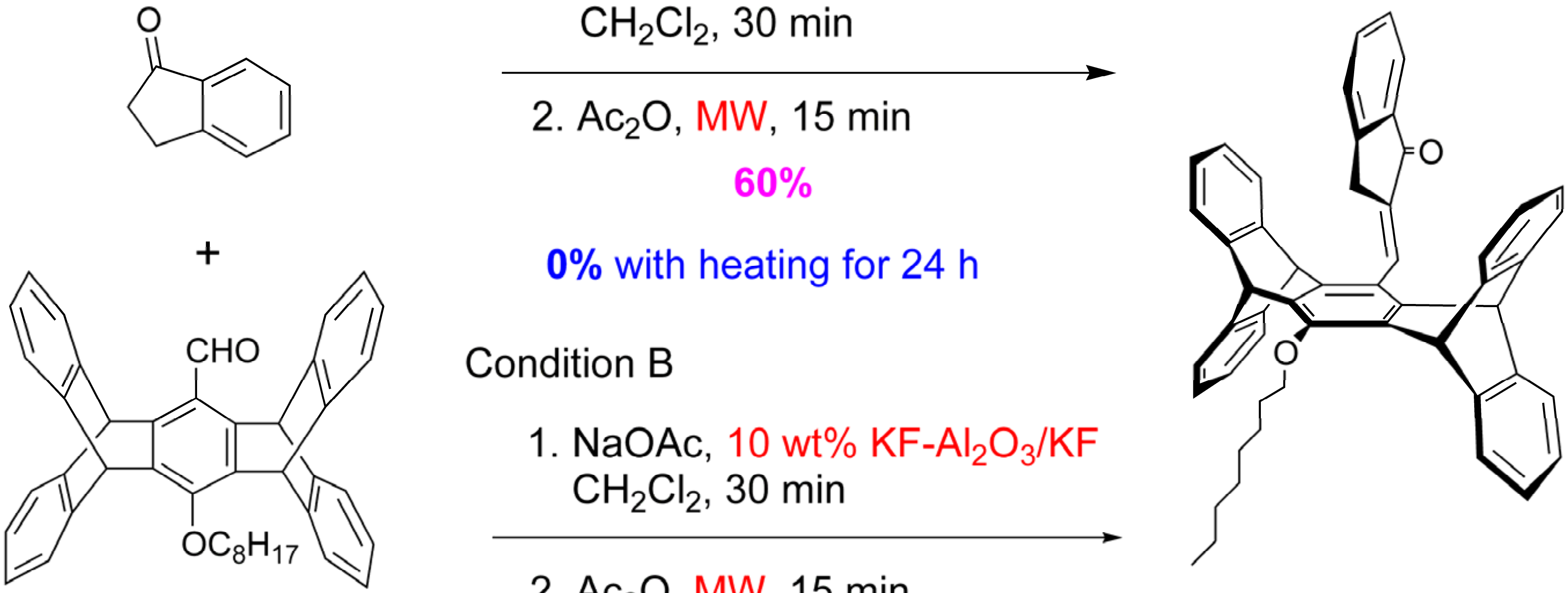
Milestone START System

Microwave-assisted Organic Preparations of banana shape molecules



	MW	Traditional
Yield (6 steps from resorcinol)	33-35%	20-23%
Reaction time	58 min	56hrs
Solvent	34 mL	360 mL
Power (kW/hr)	0.85	2.0

(Liu and coworkers, **2003-2006**)



Condition A

1. NaOAc, Al_2O_3,
   CH_2Cl_2, 30 min

2. Ac_2O, MW, 15 min

60%

0% with heating for 24 h

Condition B

1. NaOAc, 10 wt% $KF\text{-}Al_2O_3/KF$
   CH_2Cl_2, 30 min

2. Ac_2O, MW, 15 min

82%

37% with heating for **16** h

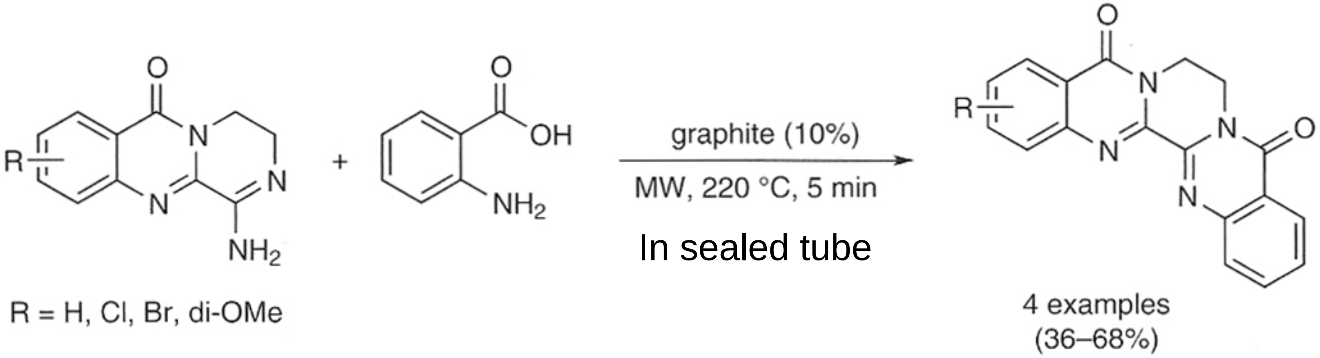
(Yang, J.-S. et al *Chem. Eur. J.* **2010**, *38*, in press).

微波反應法快捷, 節能, 高產率, 省溶劑, 選擇性好.
是極佳之溶液中永續製備方法. 建議試用.

More examples

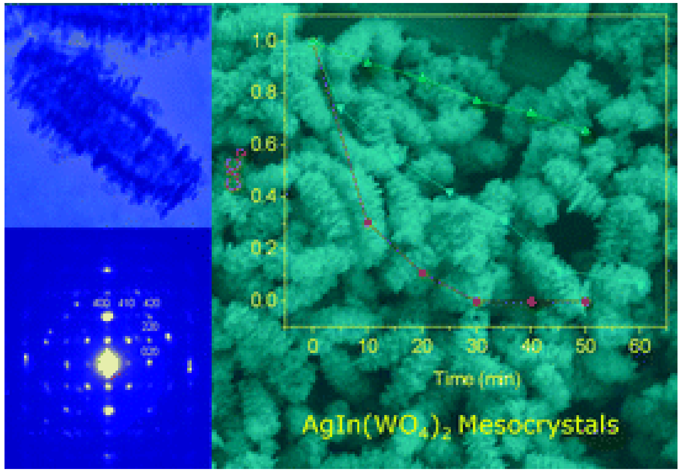
Solventless reaction using graphite as sensitizer

(caution: temperature may be very high, the use of quartz reactor is preferred)



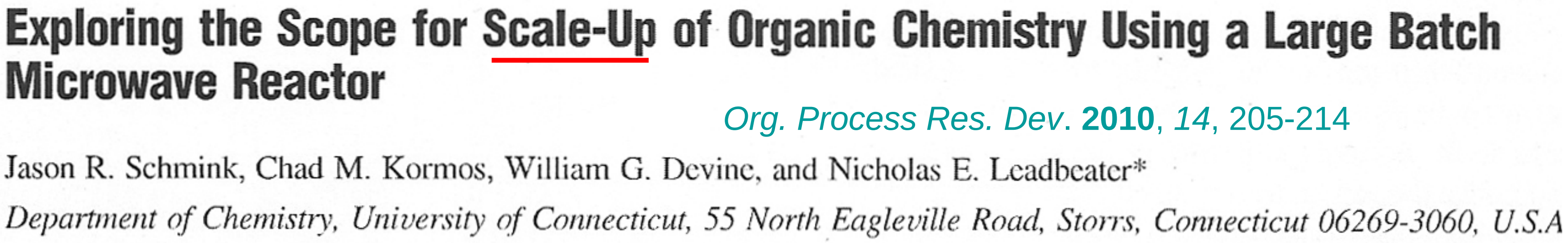
Tetrahedron Lett. **2005**, *46*, 3445-3447

Preparation of microcrystals



A new kind of silver indium tungsten oxide (AgIn(WO$_4$)$_2$) mesocrystals with high hierarchy can be synthesized by a microwave-assisted approach, which shows high and selective photocatalytic activity for the degradation of different organic dyes under UV and visible light irradiation.

Chem. Commun. **2010**, 2277 - 2279

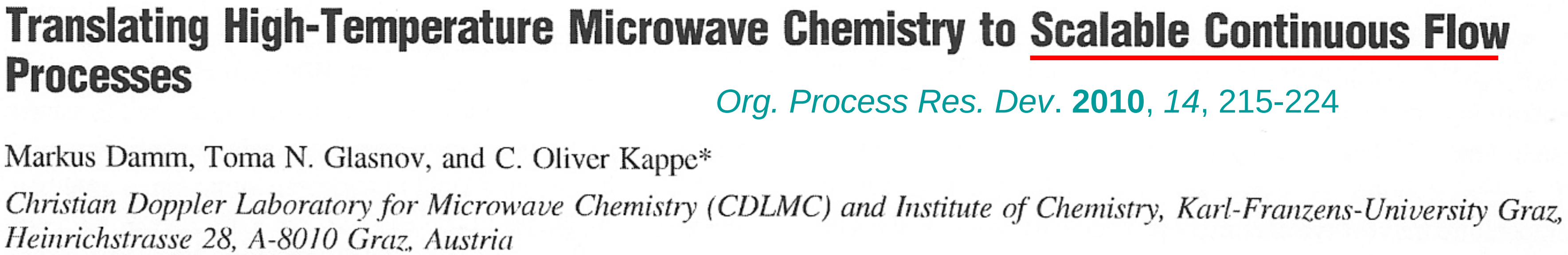


Exploring the Scope for Scale-Up of Organic Chemistry Using a Large Batch Microwave Reactor

Org. Process Res. Dev. **2010**, *14*, 205-214

Jason R. Schmink, Chad M. Kormos, William G. Devine, and Nicholas E. Leadbeater*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269-3060, U.S.A



Translating High-Temperature Microwave Chemistry to Scalable Continuous Flow Processes

Org. Process Res. Dev. **2010**, *14*, 215-224

Markus Damm, Toma N. Glasnov, and C. Oliver Kappe*

Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Flow Processing of Microwave-Assisted (Heterogeneous) Organic Reactions

Org. Process Res. Dev. **2010**, *14*, 251-261

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A Novel Dewar-Like Reactor for Maintaining Constant Heat and Enhancing Product Yields during Microwave-Assisted Organic Syntheses

Org. Process Res. Dev. **2010**, *14*, 1453-1456

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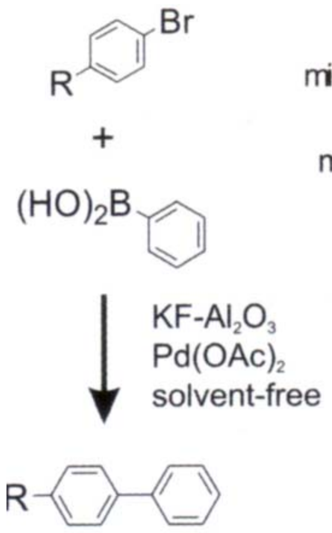
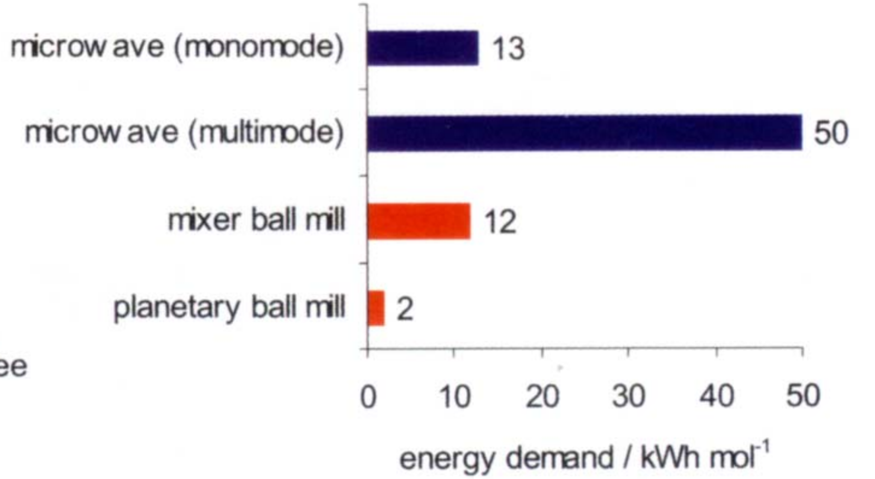
Energetic assessment of Suzuki-Miyaura reactions

Solvent-less $KF-Al_2O_3$-assited Suzuki couplings was used to assess different technologies for greener procedures. Ball-milling is proven to be a more effective tool.





R = H, Me, OMe, COMe, NO_2

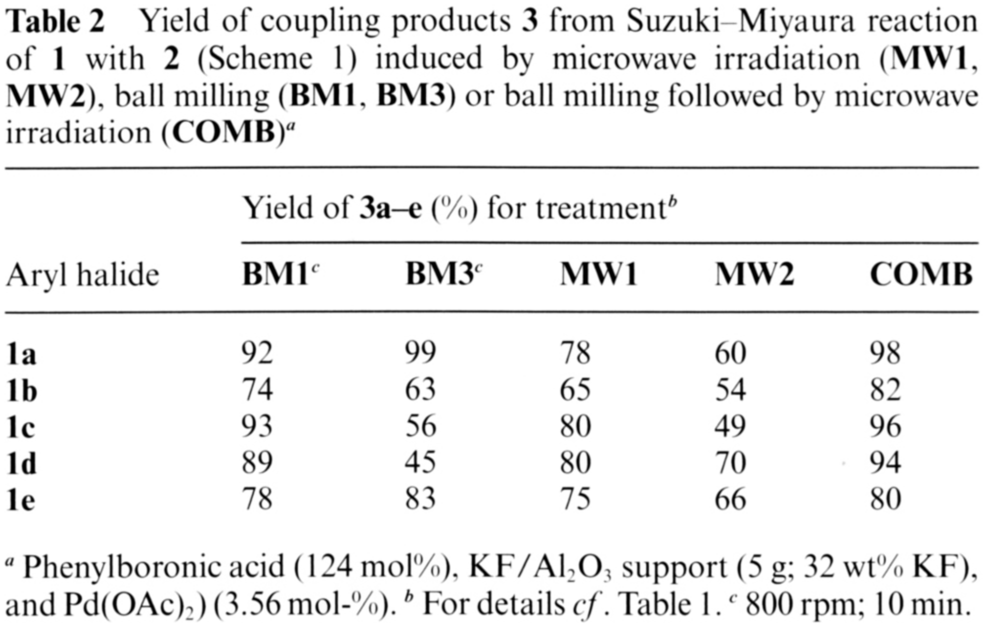


Table 2 Yield of coupling products **3** from Suzuki–Miyaura reaction of **1** with **2** (Scheme 1) induced by microwave irradiation (**MW1**, **MW2**), ball milling (**BM1**, **BM3**) or ball milling followed by microwave irradiation (**COMB**)[a]

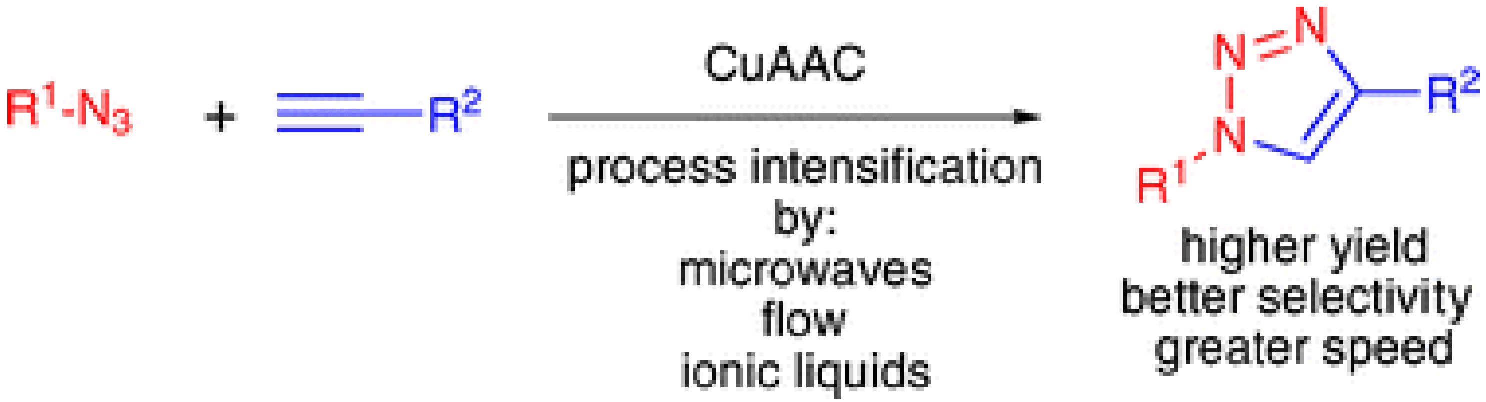
	Yield of **3a–e** (%) for treatment[b]				
Aryl halide	**BM1**[c]	**BM3**[c]	**MW1**	**MW2**	**COMB**
1a	92	99	78	60	98
1b	74	63	65	54	82
1c	93	56	80	49	96
1d	89	45	80	70	94
1e	78	83	75	66	80

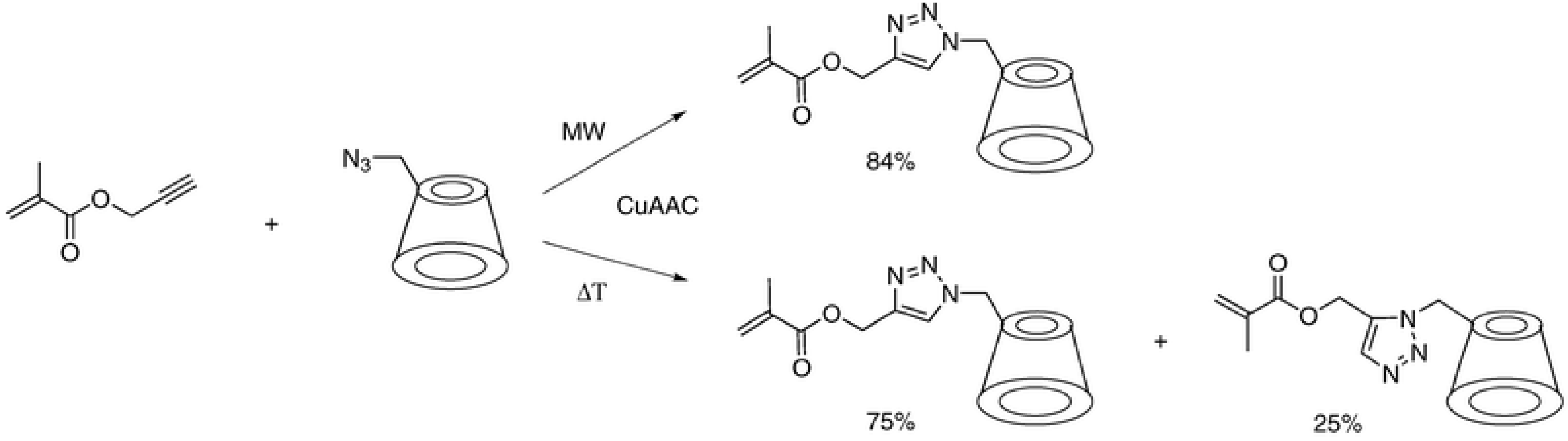
[a] Phenylboronic acid (124 mol%), KF/Al_2O_3 support (5 g; 32 wt% KF), and $Pd(OAc)_2$) (3.56 mol-%). [b] For details *cf*. Table 1. [c] 800 rpm; 10 min.

(Ondruschka, Stolle, *et al. Green Chem*. **2009**, *11*, 1894-1899)

Click chemistry under non-classical reaction conditions

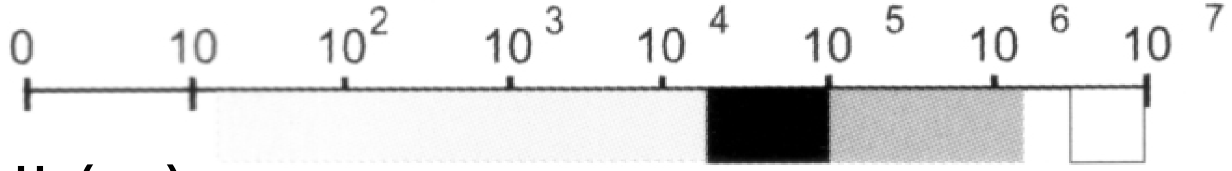
Kappe and Van der Eycken, *Chem. Soc. Rev*. **2010**, *39*, 1280 - 1290





Sonochemistry

Sound frequencies



Hz (cps)

| → **Ultrasound (supersound)**

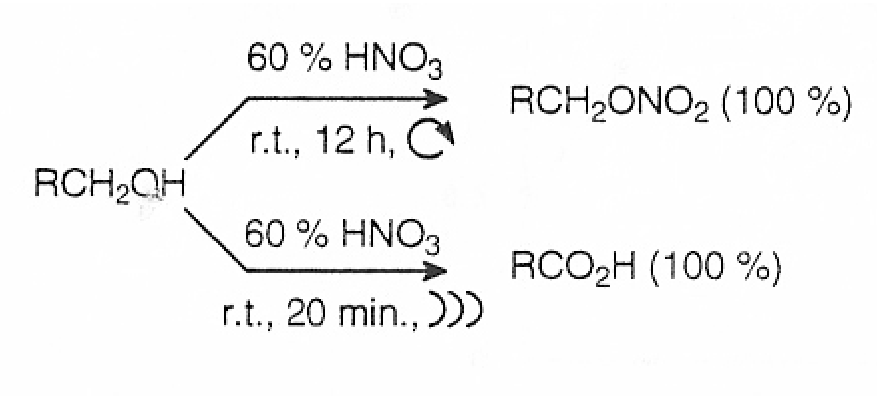
Human hearing	░	20Hz - 20kHz	(Normally, 16Hz to 16kHz)
Conventional power ultrasound	■	20kHz - 100kHz	**high input power** (1-1000 W/cm^2) **(Destructive)**
Extended range for sonochemistry	■▒	20kHz —2MHz	
Diagnostic ultrasound	□	5MHz - 10MHz	**Low input power** (mW/cm^2) **(Non-invasive)**

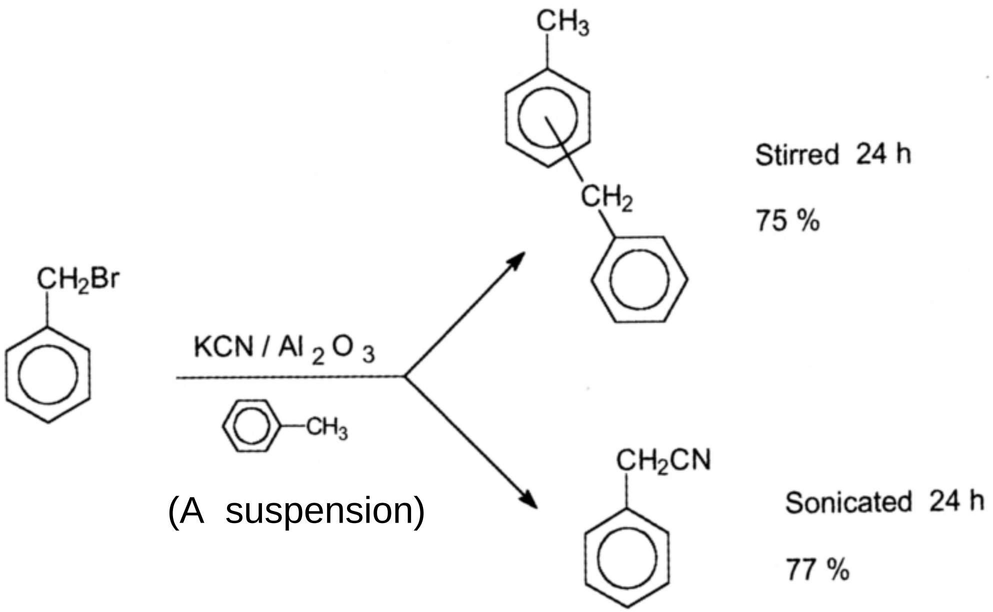
Used for cleaning, chemical reactions, plastic welding, etc.

Mason, *Practical Sonochemistry: User's Guide to…*, 2nd Ed, E. Horwood, 2001
Mason and Lorimer, *Applied Sonochemistry*, Wiley-VCH, 2002
***Ultrasonic Sonochemistry*, (**Elsevier, 1993-)

Sonochemical switching of pathways

For **true** sonochemical reactions (homogeneous or heterogeneous), formation of radical or radical-ion will be favored by ultrasound. But **false** sonochemical reactions (heterogeneous) are influenced by physical and mechanical properties of sonication (ultrasound agitation). Examples are:





Sonochemical decomposition pathway of water into radicals

$H_2O \longrightarrow H\cdot + \cdot OH + \text{etc.}$

Ultrasonic activation of Heck type reactions in the presence of Aliquat-336

- Without phosphine and base, Pd catalysts such as $PdCl_2$, $Pd(OAc)_2$ and $PdCl_2(PhCN)_2$ in water/DMF mixtures with Aliquat-336 proved to be excellent catalytic systems for Heck reactions involving several aryl bromides with styrene and acrylic compounds. Yields are remarkably improved under ultrasonic irradiation (40-60% to 84-91%)

$$\mathrm{ArBr} + \mathrm{H_2C{=}CH\text{-}EWG} \longrightarrow \mathrm{Ar\text{-}CH{=}CH\text{-}EWG}.$$

(*Ultrasonic Sonochem*. **2010**, *18*, 23-27)

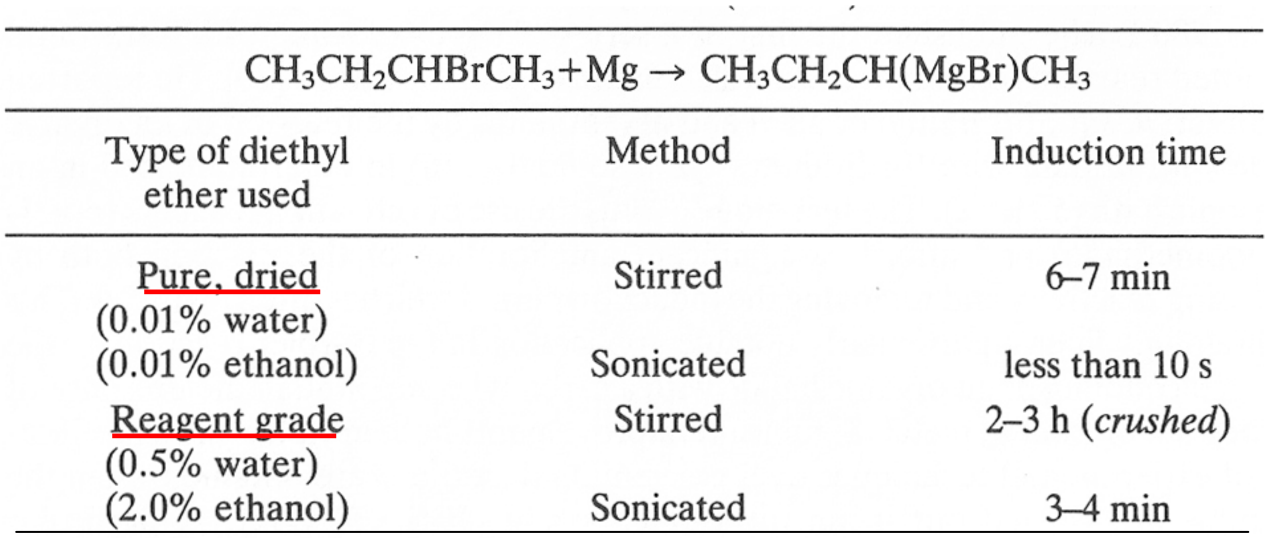
Cleaner with timer and heater **ultrasound horn**

Less expensive **more effective**

Heterogeneous reactions in a cleaning bath

Formation of Grignard reagents

(Mason and Lorimer, p. 98)

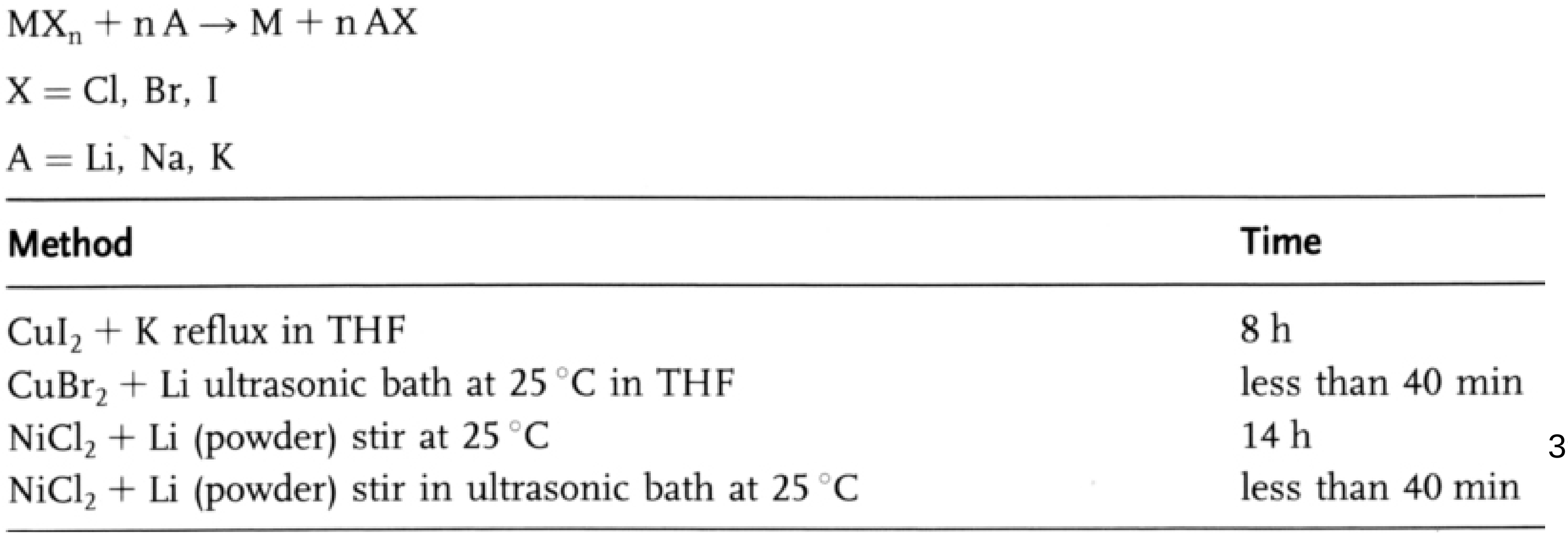


$$CH_3CH_2CHBrCH_3 + Mg \rightarrow CH_3CH_2CH(MgBr)CH_3$$

Type of diethyl ether used	Method	Induction time
Pure, dried (0.01% water) (0.01% ethanol)	Stirred	6–7 min
	Sonicated	less than 10 s
Reagent grade (0.5% water) (2.0% ethanol)	Stirred	2–3 h (*crushed*)
	Sonicated	3–4 min

Generation of metal (Cu, Ni, etc.) powders

(Mason and Lorimer, p. 95)



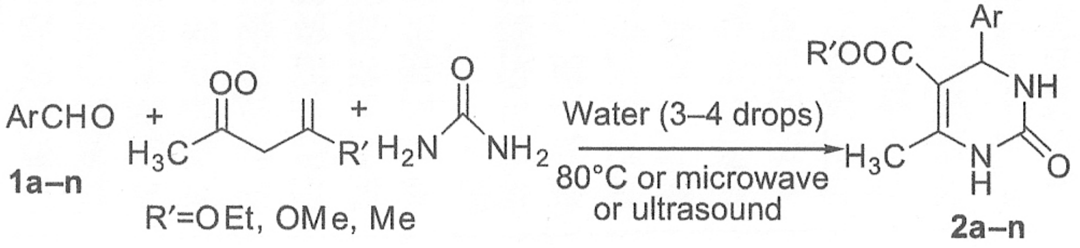
$$MX_n + n\,A \rightarrow M + n\,AX$$

$X = Cl, Br, I$

$A = Li, Na, K$

Method	**Time**
CuI_2 + K reflux in THF	8 h
$CuBr_2$ + Li ultrasonic bath at 25 °C in THF	less than 40 min
$NiCl_2$ + Li (powder) stir at 25 °C	14 h
$NiCl_2$ + Li (powder) stir in ultrasonic bath at 25 °C	less than 40 min

Synthesis of 3,4-dihydropyrimidinones under solvent-free conditions. Comparison of conventional heating, microwave and ultrasound irradiation



2a, Ar=Ph, R′=OEt
2b, Ar=4-$CH_3C_6H_4$, R′=OEt
2c, Ar=4-$CH_3OC_6H_4$, R′=OEt
2d, Ar=4-$NO_2C_6H_4$, R′=OEt
2e, Ar=4-ClC_6H_4, R′=OEt
2f, Ar=2-ClC_6H_4, R′=OEt

		Conventional[b]		Microwave[c]	Ultrasound[d]	
Entry	Product 2	*t* (min)	Yield[e]	Yield[e]	*t* (min)	Yield[e]
1	2a	45	92	98	30	96
2	2b	45	94	96	30	95
3	2c	50	90	96	35	92
4	2d	60	89	97	40	92
5	2e	65	90	96	40	94
6	2f	60	90	95	40	94
7	2g	55	80	88	35	85
8	2h	60	80	90	35	90
9	2i	75	92	90	50	82
10	2j	55	90	92	40	90
11	2k	60	92	95	35	94
12	2l	65	92	89	40	86
13	2m	60	90	90	35	87
14	2n	75	90	92	40	90

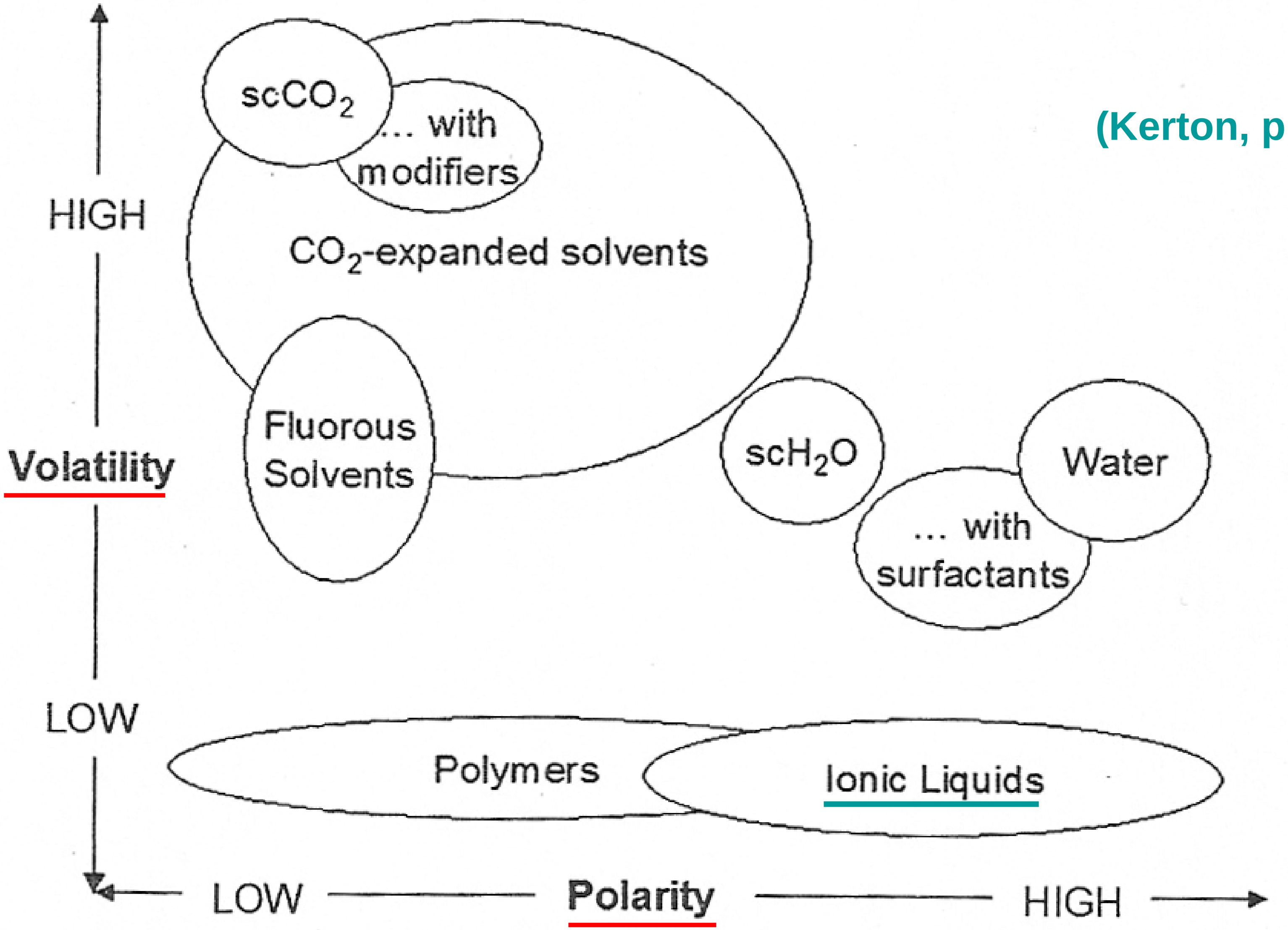
[a] Reaction conditions: aldehyde (2 mmol); urea (2 mmol); β-dicarbonyl compound (2 mmol); and water (3–4 drops).
[b] Heating at 80°C.
[c] Microwave irradiation (750 W, reaction time 2 min).
[d] Ultrasound irradiation (25 kHz).
[e] Isolated yields.

Green Chem. Lett. Rev. **2010**, *3*, 23-26.

Alternative solvents

Polarity and volatility characteristics

(Kerton, p. 17)



Ionic liquids in Synthesis

Ionic Liquids in Organic Synthesis, Ed. by Malhotra, ACS Symposium Series 950, **2006**

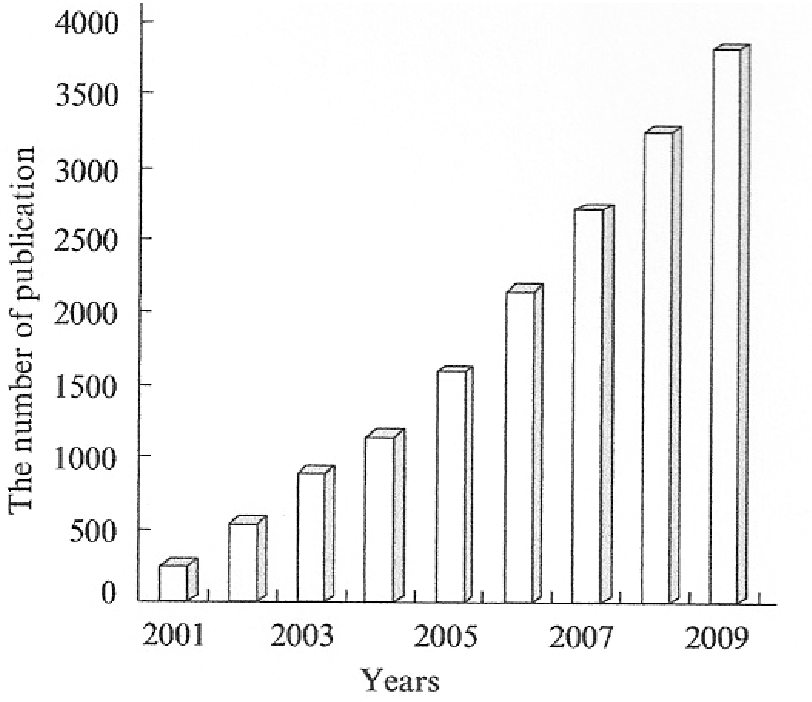
Ionic Liquids in Synthesis, 2nd, Completely Revised and Enlarged Edn., 2 Vols, Ed by Wasserscheid and Welton, Wiley-VCH, **2008**

Alternative Solvents for Green Chemistry, *by* Kerton, RSC, Chapter 6, **2009**

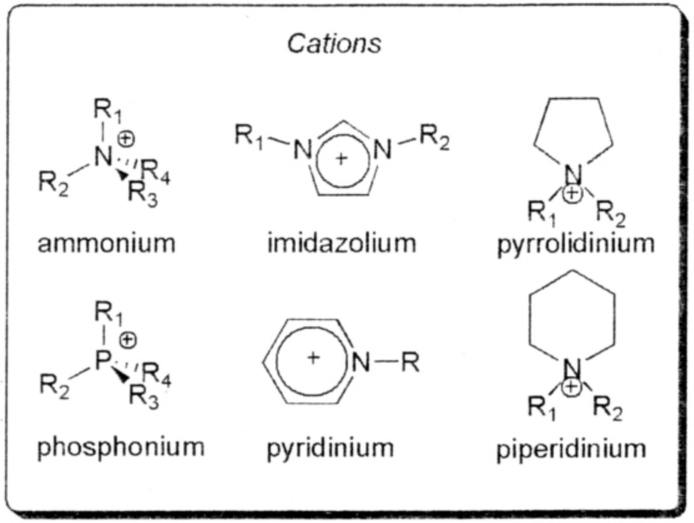
Chem. Rev. **2007**, *107*, 2615-2665 (Catalysis in Ionic Liquids)

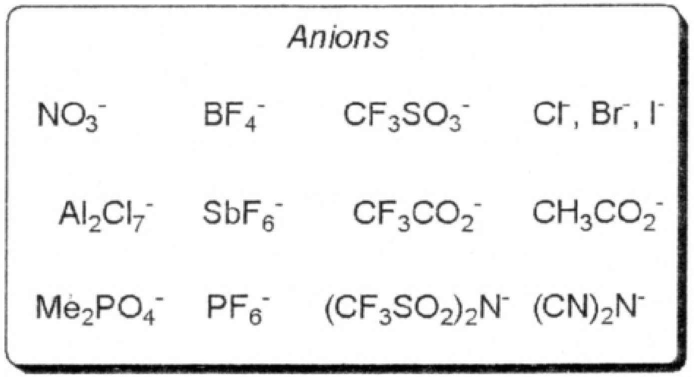
Russ. Chem. Rev. **2010**, *79*, 543-583 (Reactions of carbon acids and 1,3-dipoles)

Russ. Chem. Rev. **2010**, *79*, 463-477 (Synthesis of nanoobjects)



Room temperature ionic liquids




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

$R = (CH_2)_nCH_3$, n = 1, 3, 5, …

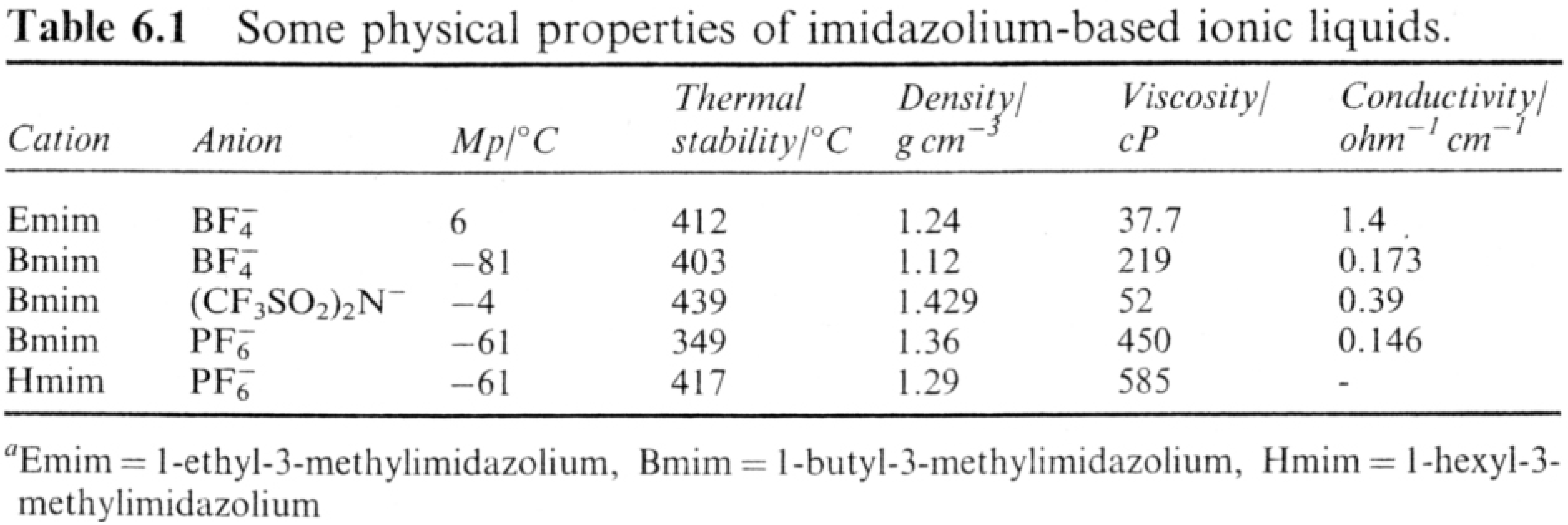


Table 6.1 Some physical properties of imidazolium-based ionic liquids.

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, p. 119)

Properties

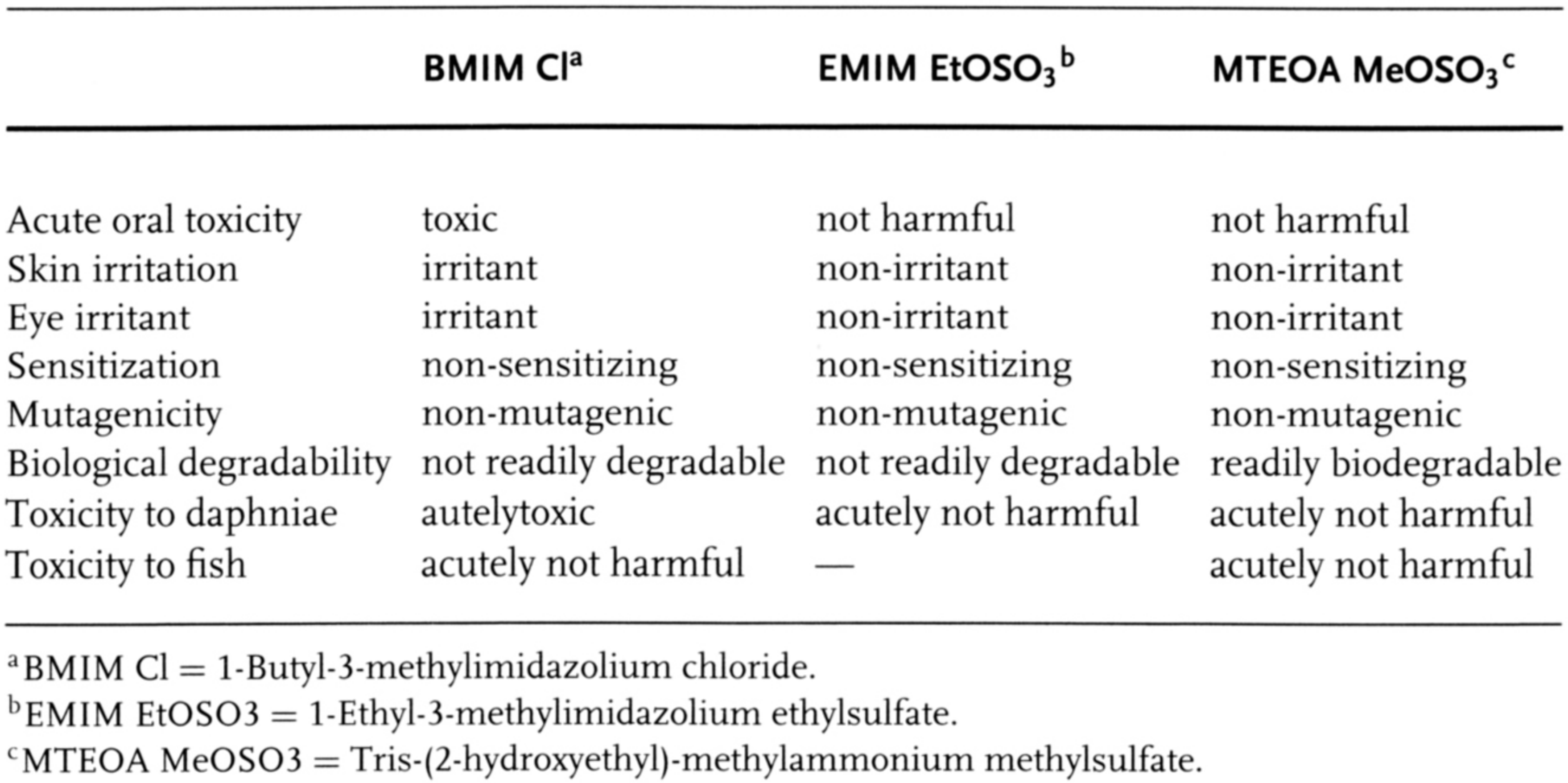
- Liquid range of 300°C (−96–+200°C) (It is distillable)
- Excellent solvents for organic, inorganic, and polymeric materials
- Acidic compositions are superacids ($\mathrm{p}K_\mathrm{a} \approx -20$)
- Some are very water sensitive and must be used in a dry box; others are hydrophobic and air stable
- Thermally stable under conditions up to 200°C
- *Now* — easy to buy and simple to prepare
- *No* measurable vapor pressure at room temperature
- Nonflammable (but some are explosive!)
- Exhibit Brønsted, Lewis, Franklin, and “super” acidity
- *Highly* solvating—therefore low volumes used, thus process intensification
- Catalysts as well as solvents
- Highly selective reactions
- *New chemistry*

Some are corrosive, and some are harmful

Mostly non-biodegradable

Costly

Some safety data



	BMIM Cl[a]	EMIM $EtOSO_3$[b]	MTEOA $MeOSO_3$[c]
Acute oral toxicity	toxic	not harmful	not harmful
Skin irritation	irritant	non-irritant	non-irritant
Eye irritant	irritant	non-irritant	non-irritant
Sensitization	non-sensitizing	non-sensitizing	non-sensitizing
Mutagenicity	non-mutagenic	non-mutagenic	non-mutagenic
Biological degradability	not readily degradable	not readily degradable	readily biodegradable
Toxicity to daphniae	autelytoxic	acutely not harmful	acutely not harmful
Toxicity to fish	acutely not harmful	—	acutely not harmful

[a] BMIM Cl = 1-Butyl-3-methylimidazolium chloride.

[b] EMIM EtOSO3 = 1-Ethyl-3-methylimidazolium ethylsulfate.

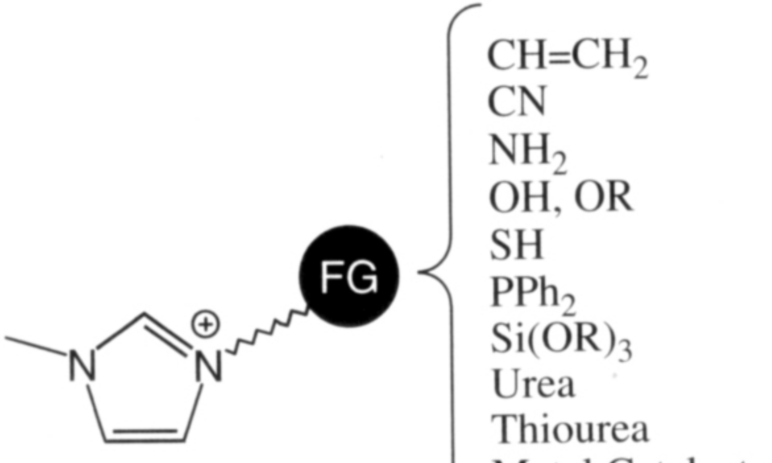
[c] MTEOA MeOSO3 = Tris-(2-hydroxyethyl)-methylammonium methylsulfate.

Ionic Liquids in Synthesis (Vol. 2), p. 683

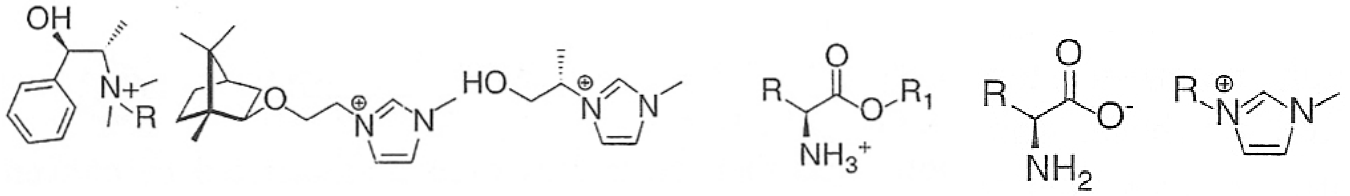
Task-specific ionic liquids

(Ballini (Ed), *Eco-Friendly Synthesis of Fine Chemicals*, Chapter 4, RSC, **2009**)

Functionalized ionic liquid cations

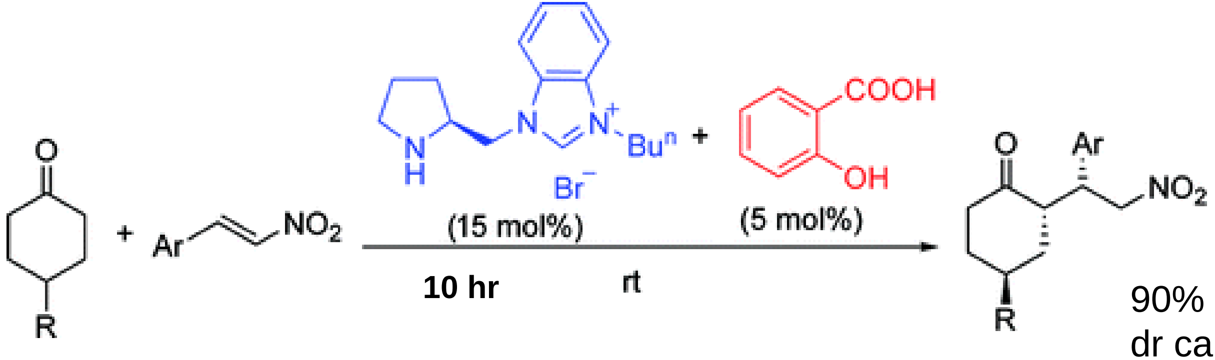


Novel chiral ionic liquids



etc.

Example:



90% yield; 97-99% ee
dr ca. 6:1

JOC **2007**, *72*, 9350-9352

Applications

Friedel-Crafts reactions
Coupling reactions
Oxidation
Reduction
Sulfonation
Nitration
Halogenation
Diazotization
Diels-Alder reaction
Aldol condensation
Formation of Coordination compounds

Formation of inorganic oxides
Oligomerization
Polymerization
Bio-catalytic reactions
N- and O-alkylations
Chiral hydrogenation
Nanoscale process
and many more

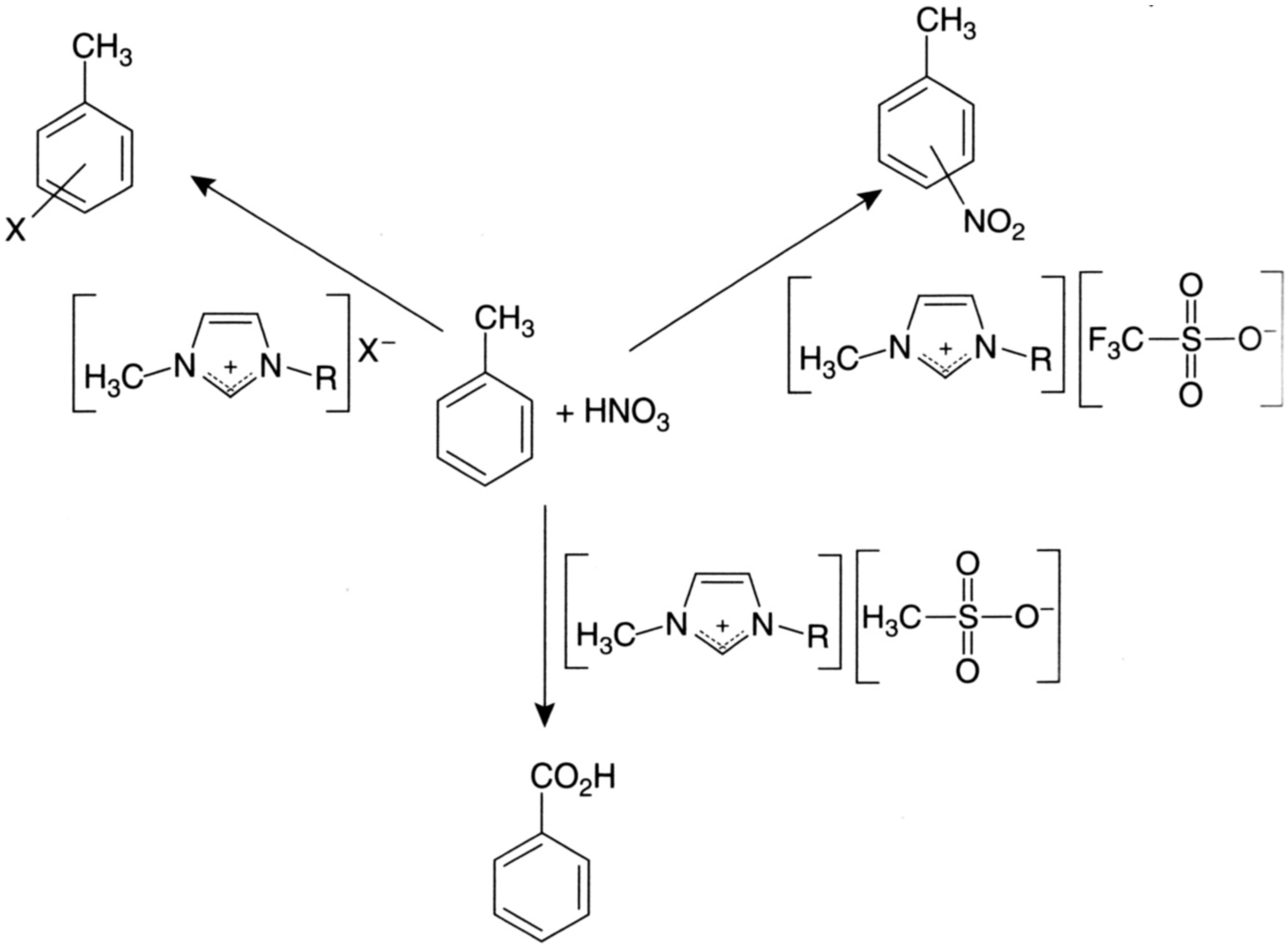


Figure 5.8 The reactions between toluene and nitric acid in (a) a halide-based ionic liquid, (b) a triflate-based ionic liquid, and (c) a mesylate-based ionic liquid.

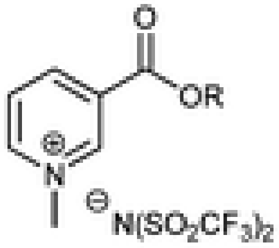
(*Methods and Reagents for Green Chemistry,* p. 119, Wiley, **2007**)

Sonogashira coupling in biodegradable ionic liquids derived from nicotinic acid

Harjani, et al., *Green Chem.*, **2010**, *12*, 650 – 655

The biodegradable (68-72% in 28 days) ionic liquids, 3-butoxycarbonyl-1-methylpyridinium bis(trifluoromethanesulfonyl)imides (**1a–d**), have been evaluated as solvents for copper- and phosphine-free Sonogashira coupling reactions. The stability of these ionic liquids toward basic conditions was analysed.

(72-93% isolated yield)



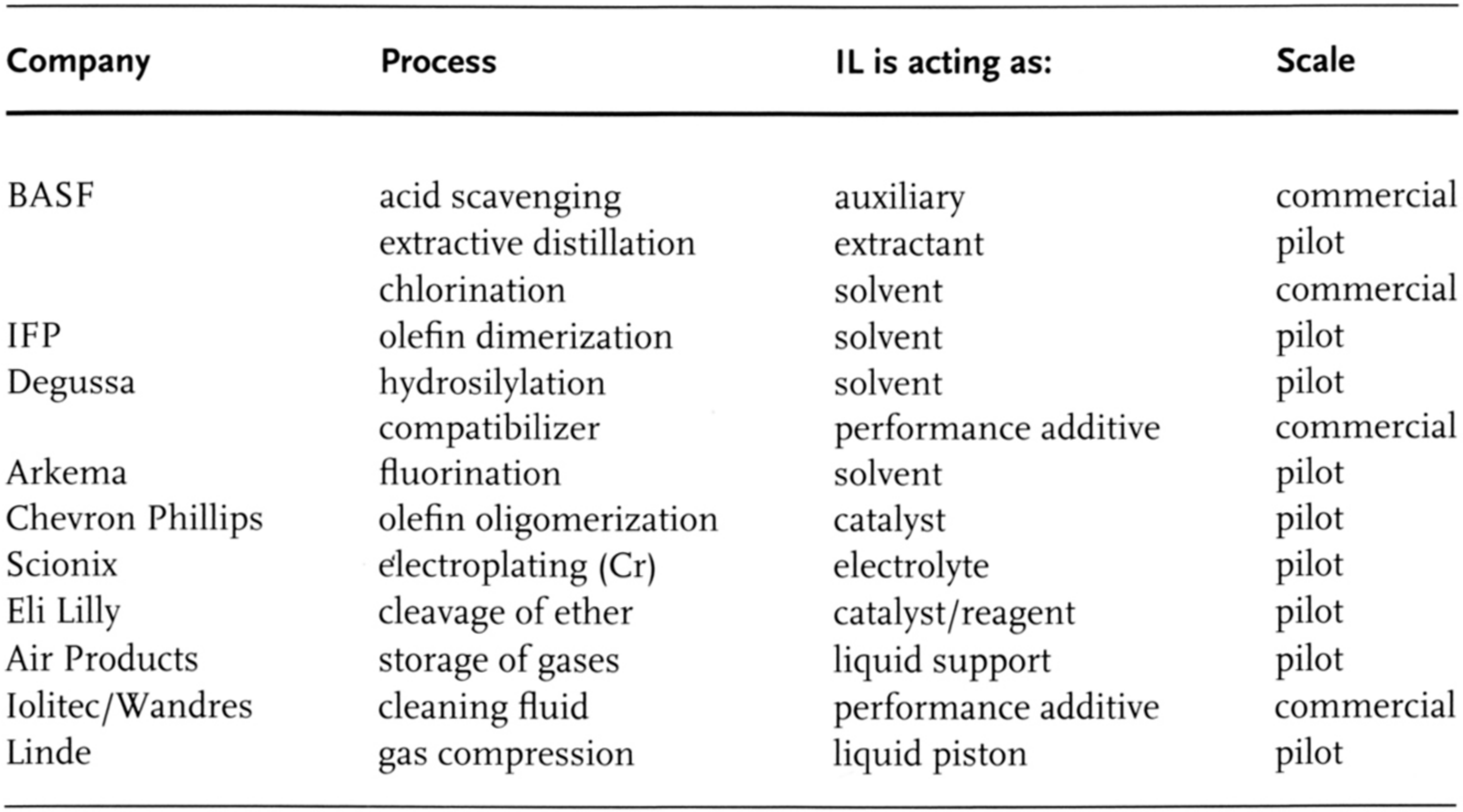
1a-d

(R = *n*-Bu, *iso*-Bu, *sec*-Bu and *tert*-Bu, respectively)

Biodegradation studies of ionic liquids

Coleman and Gathergood, *Chem. Soc. Rev.*, **2010**, *39*, 600 - 637
Ranke, *et al*., *Chem. Rev*. **2007**, *107*, 2183-2206 (biodegradable or nontoxic)
Harjani, *et al*, *Green Chem*. **2009**, *11*, 821-829

Large scale preparations using IL

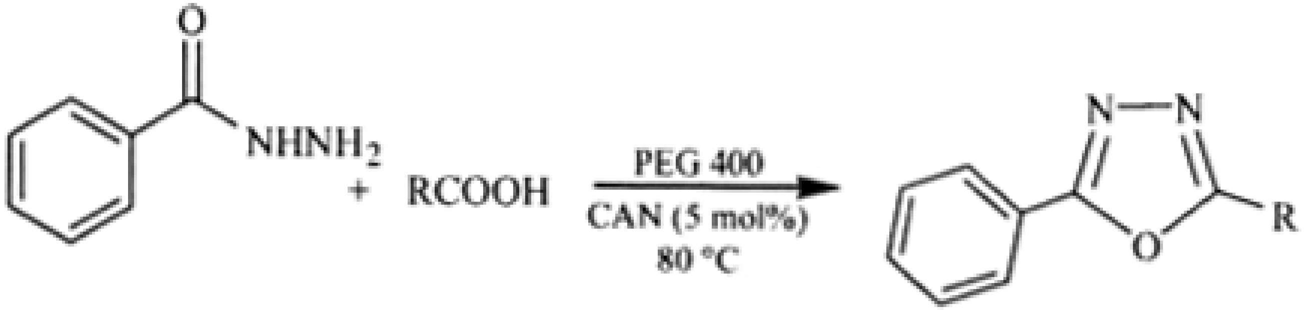


Company	Process	IL is acting as:	Scale
BASF	acid scavenging	auxiliary	commercial
	extractive distillation	extractant	pilot
	chlorination	solvent	commercial
IFP	olefin dimerization	solvent	pilot
Degussa	hydrosilylation	solvent	pilot
	compatibilizer	performance additive	commercial
Arkema	fluorination	solvent	pilot
Chevron Phillips	olefin oligomerization	catalyst	pilot
Scionix	electroplating (Cr)	electrolyte	pilot
Eli Lilly	cleavage of ether	catalyst/reagent	pilot
Air Products	storage of gases	liquid support	pilot
Iolitec/Wandres	cleaning fluid	performance additive	commercial
Linde	gas compression	liquid piston	pilot

Ionic Liquids in Synthesis (Vol. 2), p. 665

Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles catalyzed by CAN in PEG

(Kidwai, et al., *Green Chem. Lett. Rev*. **2010**, *3*, 55-59)



PEG was found the better solvent (faster and higher yield) than acetonitrile, ethanol and toluene. With 5 mole% of catalyst the reaction was done in 5 hr. The mixture was cooled in dry ice-acetone bath to precipitate PEG, and extracted with ether (PEG being insoluble). Isolation yield was 97-98%. The PEG (2% loss) could be reused for at least three times.

唯永續化學能使化學永續

Sustainability of chemistry can only be achieved by sustainable chemistry

歡迎討論

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