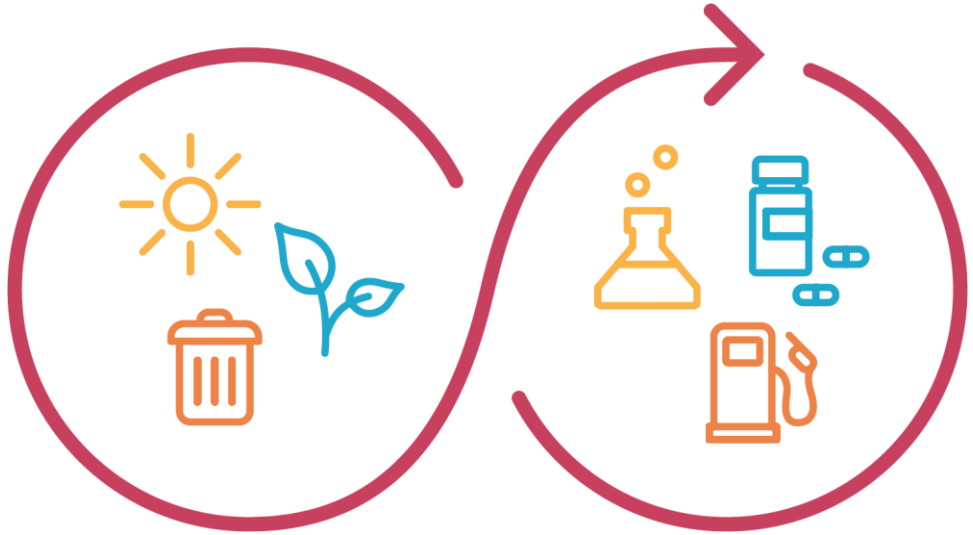
Sustainable drug development and manufacturing

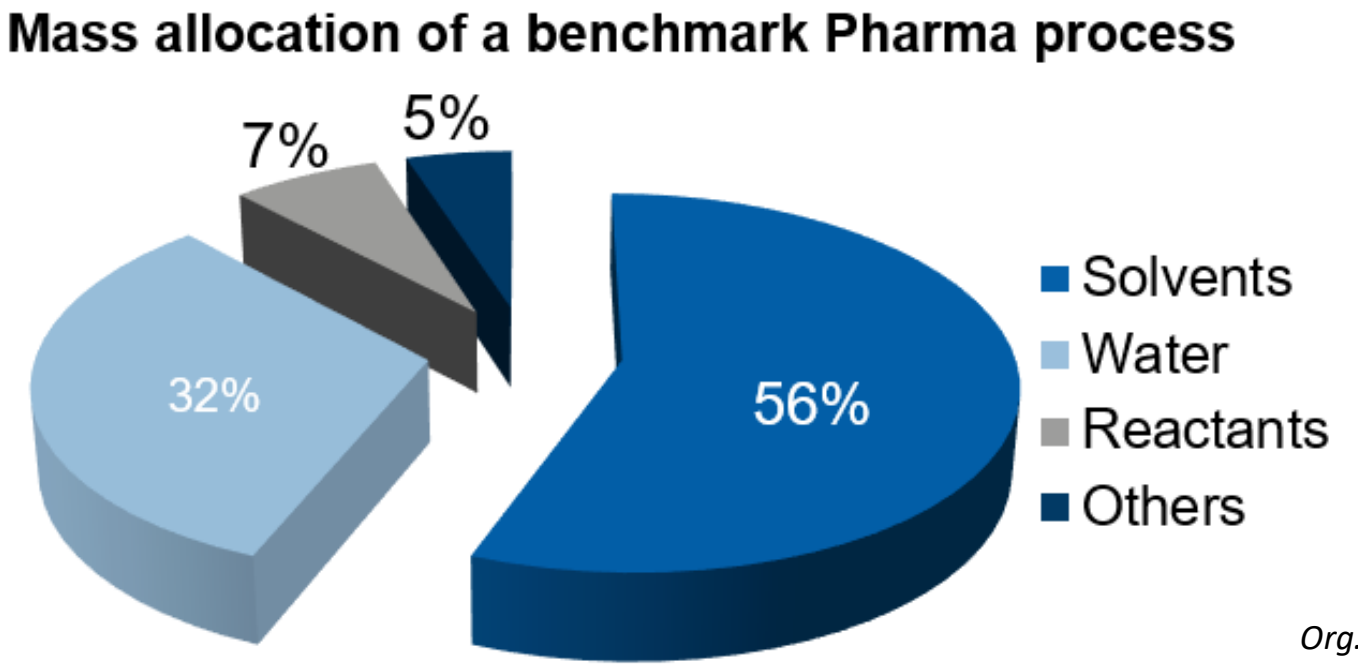


Fabrice Gallou (fabrice.gallou@novartis.com)
Chemical and Analytical Development
Novartis

II – Green Chemistry Tools

- Solvent Guide
- Reagent Guide

The importance of solvents and media

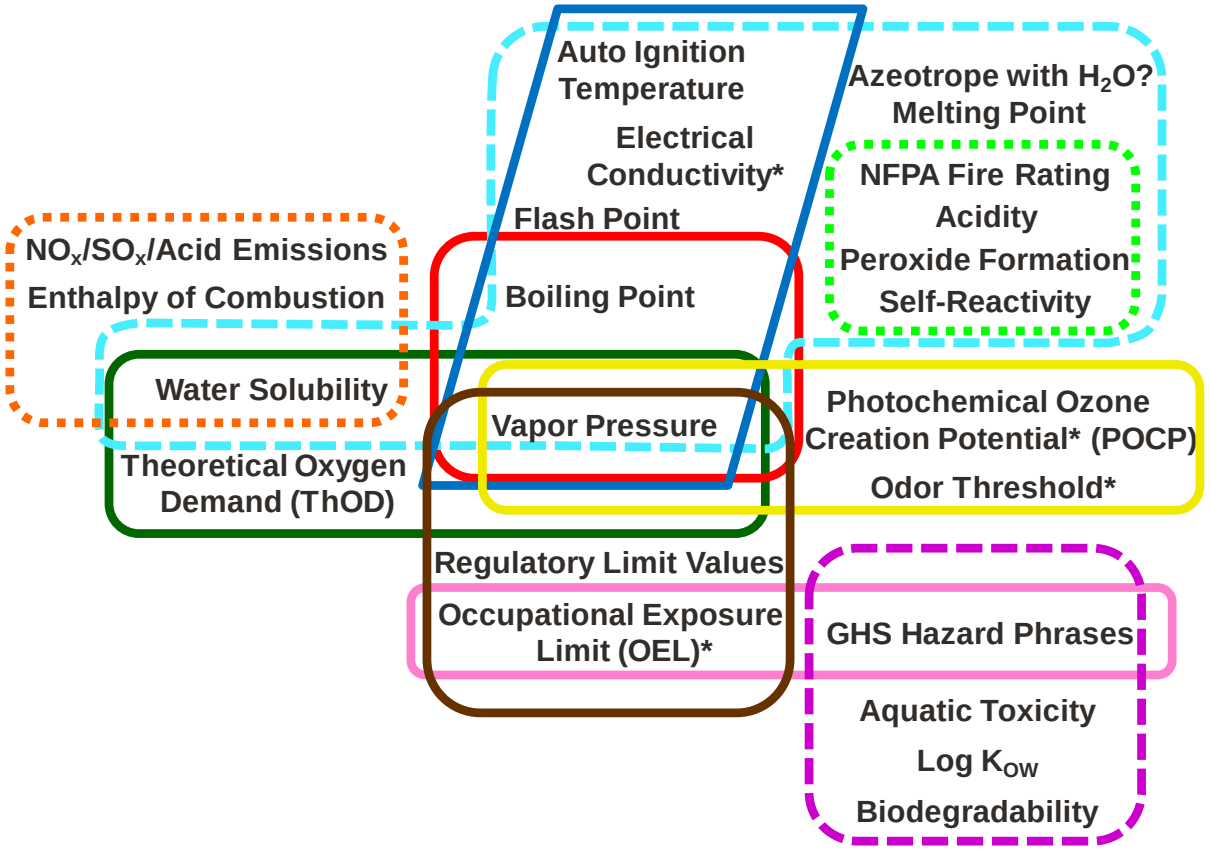


Org. Process Res. Dev. **2015**, *19*, 740.

Solvents (organic and aqueous) contribute to > 80% of overall mass intensity

Reprotoxic polar aprotic NMP, DMF, DMAC under severe pressure from regulatory agencies (*e.g.* REACH)

Solvent Selection Considerations



Key:

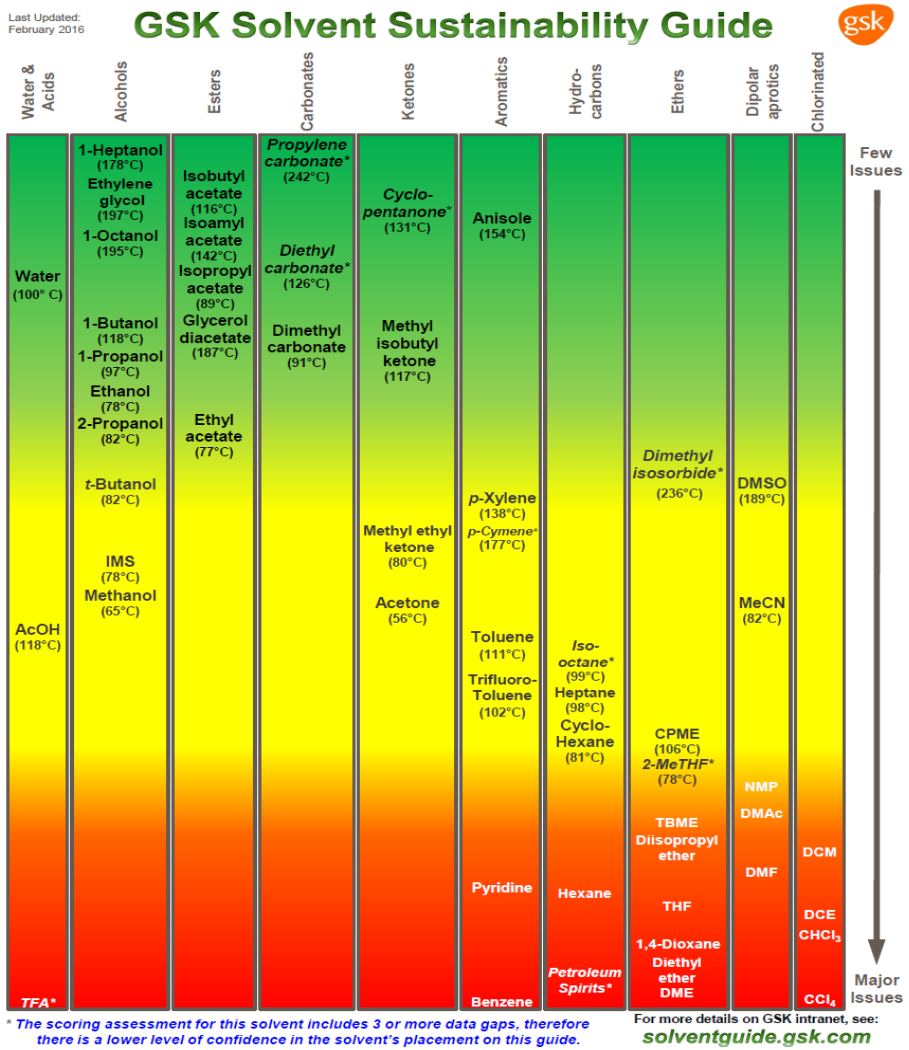
Waste:
- Incineration
- Recycling
- Biotreatment
- VOC Emissions

Environment:
- Aquatic Impact
- Air Impact

Health:
- Health Hazards
- Exposure

Safety:
- Flammability & Explosion
- Reactivity

Solvent Selection Guides



New format emphasizes spectrum of green chemistry assessments

Ease of comparison both within a solvent class and across multiple classes

Highlight those solvents with significant data gaps

Reverse side of guide provides more detailed scoring information

Classification	Solvent Name	CAS Number	Composite Colour‡	Boiling Point (°C)	Incineration	Recycling	Biotreatment	VOC Emissions	Aquatic Impact	Air Impact	Health Hazard	Exposure potential	Flammability & Explosion	Reactivity & Stability	Life Cycle Analysis†
Water & Acids	Water	7732-18-5		100	3	2	4	6	10	8	10	9	7	10	10
	Acetic Acid	64-19-7		118	3	5	4	7	8	4	7	5	8	6	8
	*Trifluoroacetic acid**	76-05-1		72	1	5	2	4	4	4	4	3	7	6	
Alcohols	1-Heptanol	111-70-6		178	9	8	10	9	8	4	10	7	9	10	
	Ethylene glycol	107-21-1		197	4	5	5	10	10	8	7	10	10	10	9
	1-Octanol	111-87-5		195	9	7	8	10	5	4	7	10	9	10	
	1-Butanol	71-36-3		118	6	7	5	8	9	3	7	7	8	9	5
	1-Propanol	71-23-8		97	5	3	3	6	10	4	10	7	8	10	7
	Ethanol	64-17-5		78	5	5	3	4	9	5	10	8	6	10	
	2-Propanol	67-63-0		82	5	5	3	5	8	7	10	6	6	8	4
	t-Butanol	75-65-0		82	5	5	3	5	9	7	7	5	6	10	8
	IMS (ethanol, denatured)	64-17-5		78	5	5	3	5	9	5	4	7	6	10	
	Methanol	67-56-1		65	4	7	3	3	10	7	4	6	5	10	9
Esters	Isobutyl acetate	110-19-0		116	7	9	8	6	9	6	10	6	8	10	
	Isoamyl acetate	123-92-2		142	9	9	8	8	4	6	7	8	8	10	
	Isopropyl acetate	108-21-4		89	6	7	5	5	9	5	10	6	6	10	7
	Glycerol diacetate	111-55-7		187	5	6	6	10	6	8	4	8	10	10	
	Ethyl acetate	141-78-6		77	5	6	5	4	9	5	10	7	5	10	6
Carbonates	*Propylene carbonate**	108-32-7		242	4	5	6	10	10	10	10	10	10	10	
	*Diethyl carbonate**	105-58-8		126	7	9	9	7	9	8	4	5	8	10	
	Dimethyl carbonate	616-38-6		91	4	3	5	5	9	7	10	6	6	10	8
Ketones	*Cyclopentanone**	120-92-3		131	8	9	6	7	10	5	7	6	8	10	6
	Methylisobutyl ketone	108-10-1		117	7	8	5	7	9	3	7	6	7	9	2
	Methylethyl ketone	78-93-3		80	5	5	3	4	8	4	10	6	5	9	3
	Acetone	67-64-1		56	5	6	2	2	10	6	10	6	4	9	7
Aromatics	Anisole	100-66-3		154	8	8	8	8	7	6	7	8	7	9	5
	p-Xylene	106-42-3		138	10	9	6	7	5	2	7	7	5	10	7
	*p-Cymene**	99-87-6		177	10	8	7	9	3	2	10	6	6	9	
	Toluene	108-88-3		111	10	7	6	7	7	2	7	6	5	10	7
	Trifluorotoluene	98-08-8		102	4	4	5	6	3	8	10	4	4	10	
	Pyridine	110-86-1		115	3	6	2	7	7	3	4	4	8	9	2
	Benzene	71-43-2		80	9	6	6	4	7	5	1	1	3	10	7
Hydrocarbons	*Isooctane**	540-84-1		99	10	4	5	6	2	5	10	7	3	10	7
	Heptane	142-82-5		98	10	4	5	6	3	5	10	6	3	10	7
	Cyclohexane	110-82-7		81	10	6	5	4	3	5	10	6	2	10	7
	Hexane	110-54-3		69	10	8	4	3	3	5	7	4	2	10	7
	*Petroleum spirits**	8032-32-4		55	6	9	4	2	5	5	1	6	2	10	7
Ethers	*Dimethyl isosorbide**	5306-85-4		236	3	4	5	10	9	6	4	9	9	8	
	Cyclopentyl methyl ether	5614-37-9		106	8	4	5	6	4	3	4	4	6	9	4
	*2-Methyltetrahydrofuran**	96-47-9		78	6	5	3	4	7	4	4	3	4	6	4
	t-Butylmethyl ether	1634-04-4		55	7	8	4	2	7	5	7	4	3	9	8
	Diisopropyl ether	108-20-3		68	9	7	6	3	5	4	10	6	4	3	9
	Tetrahydrofuran	109-99-9		65	5	5	2	3	9	3	7	5	4	6	4
	1,4-Dioxane	123-91-1		102	4	1	3	6	8	4	4	3	4	6	6
	Diethyl ether	60-29-7		35	7	7	3	1	5	3	10	4	2	6	6
	1,2-Dimethoxyethane	110-71-4		85	4	4	3	5	8	7	1	4	4	6	7
Dipolar Aprotics	Dimethyl sulphoxide	67-68-5		189	3	4	4	9	8	6	7	9	9	5	6
	Acetonitrile	75-05-8		82	3	5	1	4	10	8	7	5	6	10	4
	N-Methyl pyrrolidone	872-50-4		202	3	4	3	10	10	6	1	9	9	9	4
	N,N-Dimethyl acetamide	127-19-5		165	3	6	3	9	10	6	1	7	9	9	2
	N,N-Dimethyl formamide	68-12-2		153	3	6	3	8	10	4	1	6	9	9	7
Chlorinated	Dichloromethane	75-09-2		40	2	10	4	1	8	6	7	4	4	10	7
	1,2-Dichloroethane	107-06-2		84	2	7	5	5	9	7	1	2	5	10	7
	Chloroform	67-66-3		61	3	9	5	3	7	5	4	1	5	10	6
	Carbon tetrachloride	56-23-5		77	3	7	5	4	4	1	4	1	4	10	7

GSK Solvent Sustainability Guide

For more details, at GSK internally, see:

solventguide.gsk.com

Column Headings Colour Key

	Waste
	Environment
	Human Health
	Safety

Composite Colour Key

	Few Known Issues
	Some Known Issues
	Major Known Issues

**The scoring assessment for this solvent includes 3 or more data gaps, therefore there is a lower level of confidence in the solvent's placement on this guide.*

†A blank value for Life Cycle Analysis (LCA) indicates that this data is currently not available.

‡The composite colour represents an overall categorization of the holistic sustainability of a solvent, taking all category scores into consideration.

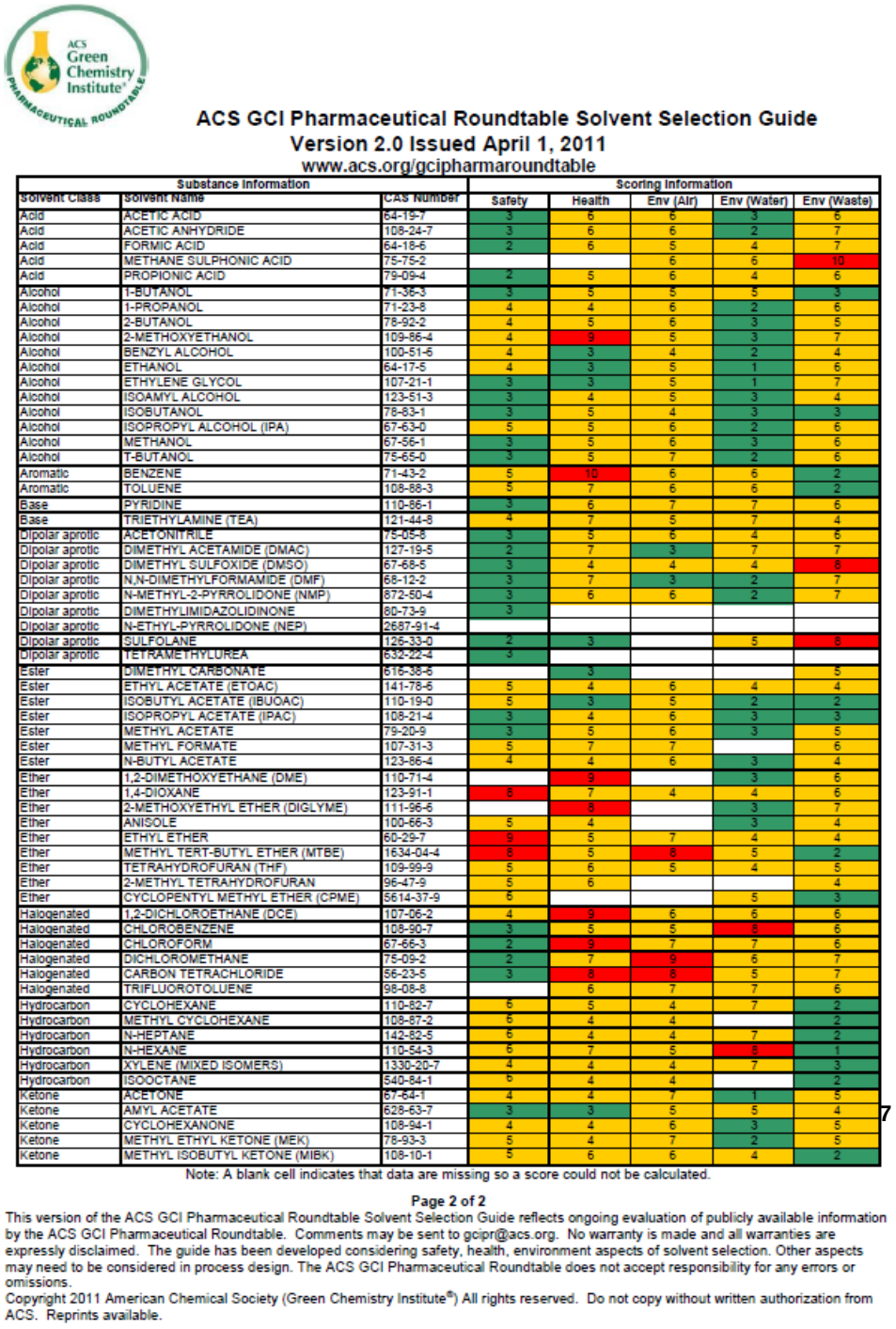
Last Updated: February 3, 2016

ACS Solvent Selection Guide

ACS GCI Pharmaceutical Roundtable guide available free of charge

Considers safety, health and environmental impact of solvents

www.acs.org/gcipharmaroundtable



ACS GCI Pharmaceutical Roundtable Solvent Selection Guide
Version 2.0 Issued April 1, 2011
www.acs.org/gcipharmaroundtable

Substance Information			Scoring Information				
Solvent Class	Solvent Name	CAS Number	Safety	Health	Env (Air)	Env (Water)	Env (Waste)
Acid	ACETIC ACID	64-19-7	3	6	6	3	6
Acid	ACETIC ANHYDRIDE	108-24-7	3	6	6	2	7
Acid	FORMIC ACID	64-18-6	2	6	5	4	7
Acid	METHANE SULPHONIC ACID	75-75-2			6	6	10
Acid	PROPIONIC ACID	79-09-4	2	5	6	4	6
Alcohol	1-BUTANOL	71-36-3	3	5	5	5	3
Alcohol	1-PROPANOL	71-23-8	4	4	6	2	6
Alcohol	2-BUTANOL	78-92-2	4	5	6	3	5
Alcohol	2-METHOXYETHANOL	109-86-4	4	9	5	3	7
Alcohol	BENZYL ALCOHOL	100-51-6	4	3	4	2	4
Alcohol	ETHANOL	64-17-5	4	3	5	1	6
Alcohol	ETHYLENE GLYCOL	107-21-1	3	3	5	1	7
Alcohol	ISOAMYL ALCOHOL	123-51-3	3	4	5	3	4
Alcohol	ISOBUTANOL	78-83-1	3	5	4	3	3
Alcohol	ISOPROPYL ALCOHOL (IPA)	67-63-0	5	5	6	2	6
Alcohol	METHANOL	67-56-1	3	5	6	3	6
Alcohol	T-BUTANOL	75-65-0	3	5	7	2	6
Aromatic	BENZENE	71-43-2	5	10	6	6	2
Aromatic	TOLUENE	108-88-3	5	7	6	6	2
Base	PYRIDINE	110-86-1	3	6	7	7	6
Base	TRIETHYLAMINE (TEA)	121-44-8	4	7	5	7	4
Dipolar aprotic	ACETONITRILE	75-05-8	3	5	6	4	6
Dipolar aprotic	DIMETHYL ACETAMIDE (DMAC)	127-19-5	2	7	3	7	7
Dipolar aprotic	DIMETHYL SULFOXIDE (DMSO)	67-68-5	3	4	4	4	8
Dipolar aprotic	N,N-DIMETHYLFORMAMIDE (DMF)	68-12-2	3	7	3	2	7
Dipolar aprotic	N-METHYL-2-PYRROLIDONE (NMP)	872-50-4	3	6	6	2	7
Dipolar aprotic	DIMETHYLIMIDAZOLIDINONE	80-73-9	3				
Dipolar aprotic	N-ETHYL-PYRROLIDONE (NEP)	2687-91-4					
Dipolar aprotic	SULFOLANE	126-33-0	2	3		5	8
Dipolar aprotic	TETRAMETHYLUREA	632-22-4	3				
Ester	DIMETHYL CARBONATE	616-38-6		3			5
Ester	ETHYL ACETATE (ETOAC)	141-78-6	5	4	6	4	4
Ester	ISOBUTYL ACETATE (IBUOAC)	110-19-0	5	3	5	2	2
Ester	ISOPROPYL ACETATE (IPAC)	108-21-4	3	4	6	3	3
Ester	METHYL ACETATE	79-20-9	3	5	6	3	5
Ester	METHYL FORMATE	107-31-3	5	7	7		6
Ester	N-BUTYL ACETATE	123-86-4	4	4	6	3	4
Ether	1,2-DIMETHOXYETHANE (DME)	110-71-4		9		3	6
Ether	1,4-DIOXANE	123-91-1	8	7	4	4	6
Ether	2-METHOXYETHYL ETHER (DIGLYME)	111-96-6		8		3	7
Ether	ANISOLE	100-66-3	5	4		3	4
Ether	ETHYL ETHER	60-29-7	9	5	7	4	4
Ether	METHYL TERT-BUTYL ETHER (MTBE)	1634-04-4	8	5	8	5	2
Ether	TETRAHYDROFURAN (THF)	109-99-9	5	6	5	4	5
Ether	2-METHYL TETRAHYDROFURAN	96-47-9	5	6			4
Ether	CYCLOPENTYL METHYL ETHER (CPME)	5614-37-9	6			5	3
Halogenated	1,2-DICHLOROETHANE (DCE)	107-06-2	4	9	6	6	6
Halogenated	CHLOROBENZENE	108-90-7	3	5	5	8	6
Halogenated	CHLOROFORM	67-66-3	2	9	7	7	6
Halogenated	DICHLOROMETHANE	75-09-2	2	7	9	6	7
Halogenated	CARBON TETRACHLORIDE	56-23-5	3	8	8	5	7
Halogenated	TRIFLUOROTOLUENE	98-08-8		6	7	7	6
Hydrocarbon	CYCLOHEXANE	110-82-7	6	5	4	7	2
Hydrocarbon	METHYL CYCLOHEXANE	108-87-2	6	4	4		2
Hydrocarbon	N-HEPTANE	142-82-5	6	4	4	7	2
Hydrocarbon	N-HEXANE	110-54-3	6	7	5	8	1
Hydrocarbon	XYLENE (MIXED ISOMERS)	1330-20-7	4	4	4	7	3
Hydrocarbon	ISOOCTANE	540-84-1	6	4	4		2
Ketone	ACETONE	67-64-1	4	4	7	1	5
Ketone	AMYL ACETATE	628-63-7	3	3	5	5	4
Ketone	CYCLOHEXANONE	108-94-1	4	4	6	3	5
Ketone	METHYL ETHYL KETONE (MEK)	78-93-3	5	4	7	2	5
Ketone	METHYL ISOBUTYL KETONE (MIBK)	108-10-1	5	6	6	4	2

Note: A blank cell indicates that data are missing so a score could not be calculated.

Page 2 of 2

This version of the ACS GCI Pharmaceutical Roundtable Solvent Selection Guide reflects ongoing evaluation of publicly available information by the ACS GCI Pharmaceutical Roundtable. Comments may be sent to gcipr@acs.org. No warranty is made and all warranties are expressly disclaimed. The guide has been developed considering safety, health, environment aspects of solvent selection. Other aspects may need to be considered in process design. The ACS GCI Pharmaceutical Roundtable does not accept responsibility for any errors or omissions.

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NOVARTIS | Reimagining Medicine

Comparison of Different Guides

Ranking	Solvents
Recommended	Water, EtOH, iPrOH, nBuOH, AcOEt, AcOiPr, AcOnBu, PhOMe, sulfolane
Recommended or Problematic ?	MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, AcOMe, AcOH, Ac_2O
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylene, chlorobenzene, acetonitrile, DMPU, DMSO
Problematic or Hazardous ?	THF, MTBE, cyclohexane, DCM, formic acid, pyridine
Hazardous	iPr_2O, dioxane, DME, pentane, hexane, DMF, DMA, NMP, TEA, methoxyethanol
Highly hazardous	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane

67% convergence (AZ, ACS GCI, GSK, Pfizer, Sanofi)

The divergences reflect the different weighing of criteria

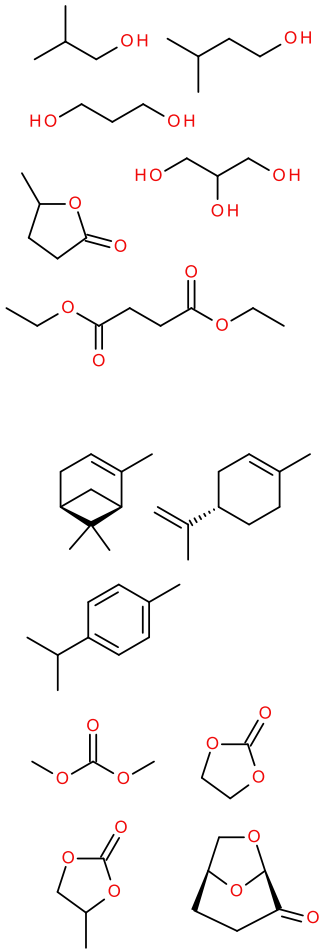
CHEM21

efpia

imi
Innovative Medicines Initiative

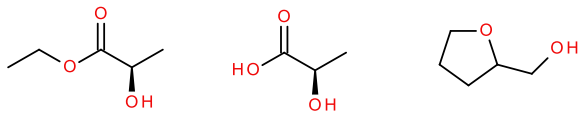
D. Prat, J. Hayler, A. Wells, *Green Chem*. **2014**, *16*, 4546

Chem21 Solvent Guide

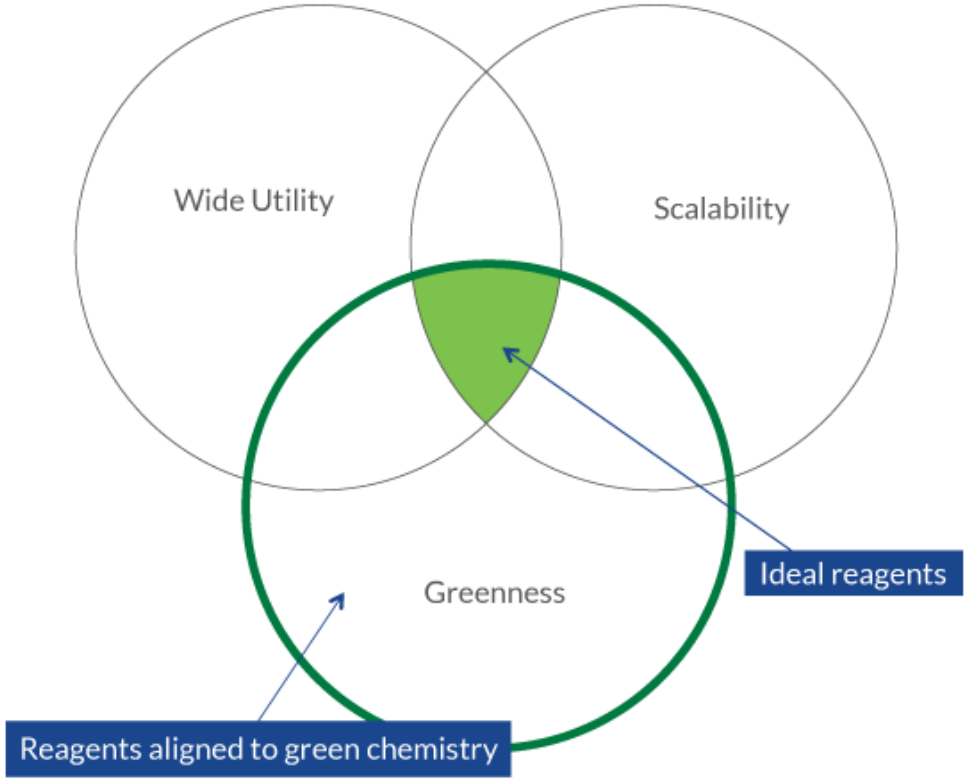


Ranking of bio-derived solvents

Family	Solvent	BP (°C)	FP (°C)	Worst H3xx	H4xx	Safety score#	Health score	Env. score	Ranking by default
Alcohols	*i*-Butanol	107	28	H318	none	3	4	3	Recommended
	i-Amyl alcohol	131	43	H315	none	3	2	3	Recommended
	1, 3-Propane diol	214	>100	none	none	1	1	7	Problematic
	Glycerol	290	177	none	none	1	1	7	Problematic
Esters	*i*-Butyl acetate	115	22	H336	none	4	2	3	Recommended
	i-Amyl acetate	142	25	none	none	3	1	5	Recommended
	Glycol diacetate	186	82	none	none	1	1	5	Recommended
	γ-Valerolactone	207	100	n.a.	n.a.	1	5	7	Problematic
	Diethyl succinate	218	91	n.a.	n.a.	1	5	7	Problematic
Hydrocarbons	D-Limonene	175	49	H304	H400	4	2	7	Problematic
	Turpentine	166	38	H302	H411	4	2	7	Problematic
	p-Cymene	177	27	n.a.	n.a.	4	5	5	Problematic
Aprotic polar	Dimethyl carbonate	90	16	none	none	4	1	3	Recommended
	Ethylene carbonate	248	143	H302	none	1	2	7	Problematic
	Propylene carbonate	242	132	H319	none	1	2	7	Problematic
	Cyrene	203	61	H319	n.a.	1	2	7	Problematic
Miscellaneous	Ethyl lactate	155	47	H318	none	3	4	5	Problematic
	Lactic acid	230	113	H318	none	1	4	7	Problematic
	TH-Furfuryl alcohol	178	75	H360	none	1	9	5	Hazardous



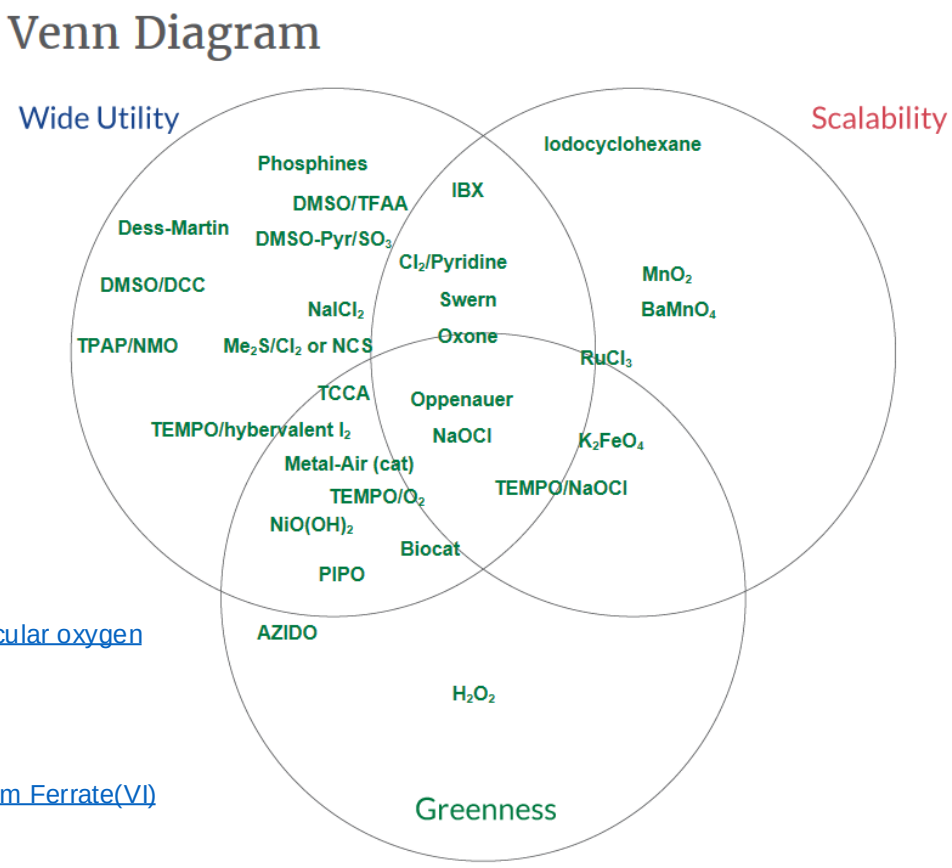
Reagent Guides



- Judicious reagent selection for a given chemical transformation represents a key decision, which is influenced by a variety of different factors depending on what stage it is made in the drug development process.
- From a Green Chemistry perspective, it is important to introduce the greenest possible reagent as early as possible in the discovery/development process with the assessment of greenness taking into account factors including worker safety, ecotoxicity and atom economy.

Reagent Guides

List of Reagents
Full Review
[NiO_2 oxidation of alcohols]
[MnO_2 oxidations in organic chemistry]
[Hypervalent Iodine reagents – general overview]
[IBX 2-Iodoxybenzenesulfonic Acid]
[Dess Martin Periodate]
[$NaIO_2$ A simple system for the oxidation of alcohols]
[PDC Pyridium dichromate oxidations]
[PCC Review on Cr(VI) oxidation]
[Oppenauer oxidation: An Integrated Approach]
[DMSO –Oxalyl Chloride, Swern oxidation]
[DMSO/DCC Pfitzner-Moffat (also TFAA activation)]
[DMSO – Pyridine-SO_3 (Parikh-Doering)]
[DMSO activation in Pseudo-Swern reaction]
[Me_2S/NCS Corey - Kim oxidation]
[NaOCl bleach oxidation]
[TCA Trichloroisocyanuric Acid: A Safe and Efficient Oxidant]
[TPAP/NMO (tetrapropylammonium perruthenate)]
[*TEMPO (General overview)*]
[TEMPO-Bleach]
[TEMPO –air –catalyst]
[TEMPO-hypervalent iodine]
[Air-Metal catalyst transition-metal catalyzed reactions using molecular oxygen]
[Activated H_2O_2 hydrogen peroxide]
[Biocatalysis biocatalytic methods for oxidation]
Light touch overview
[$BaMnO_4$ oxidation of primary and secondary alcohols]
[Potassium Ferrate A Novel Oxidizing Reagent Based on Potassium Ferrate(VI)]
[Oxidation with Chlorine /Pyridine complexes]
[$RuCl_3$]
[PIPO- Polymer immobilised TEMPO]
[Ce Cerium(IV) ammonium nitrate]
[Aqueous oxone]
[AZIDO (TEMPO variants)]



Oxidation to aldehydes and keto

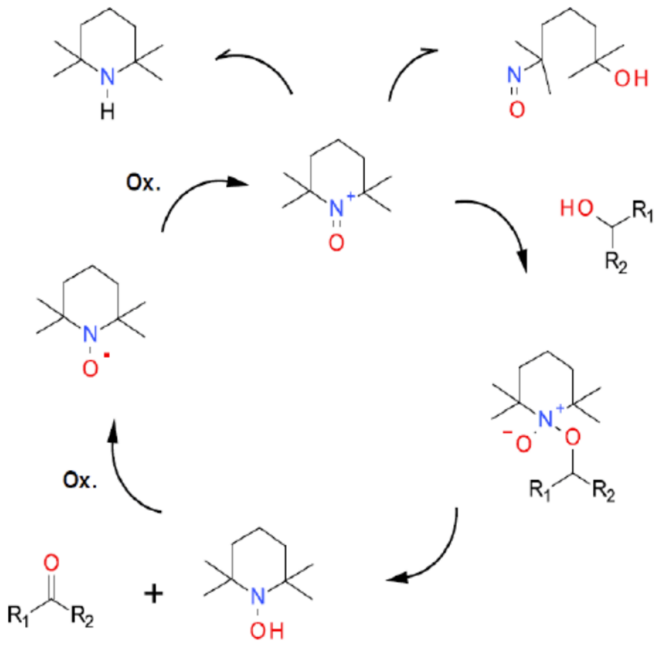
reagentguides.com

Reagent Guides

TEMPO-Bleach oxidation

Mechanism + Description

As previous for TEMPO NaOCl is often used as a co-oxidant which generates NaCl as a by-product.
NaBr or borates are often added as a promoter.



General Comments

A common terminal oxidant is bleach (NaOCl) which is often employed with a Bromide or borate co-catalyst. Reactions in water of bi-phasic reactions are often helped by the addition of a phase transfer catalyst

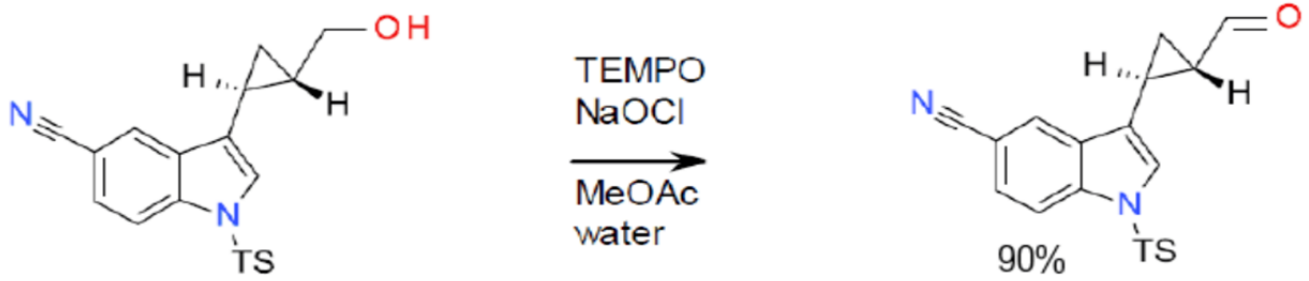
Key References

Org. Process Res. Dev., 2005, 9 (5), 577–582 - Production of Aldehydes by Continuous Bleach Oxidation of Alcohols Catalyzed by 4-Hydroxy-TEMPO
Org. Process Res. Dev., 2008, 12 (2), 322–338– Discussion of optimisation to prevent racemisation (50 L scale)
Org. Process Res. Dev., 2010, 14 (2), 441–458 - DOE and robustness studies on TEMPO stage statin oxd'n (2000 L scale)
Org. Process Res. Dev., 2010, 14 (1), 142–151 - Use of NaI to prevent chlorination of heteroaromatic (50 L scale)

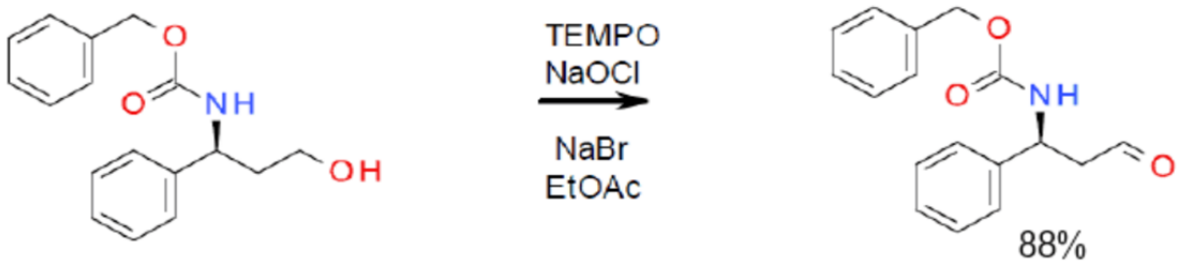
Reagent Guides

reagentguides.com

Relevant Scale up examples



Org. Process Res. Dev., 2008, 12 (2), 168–177 – 100 L oxd'n in MeOAc or THF



Org. Process Res. Dev., 2008, 12 (6), 1104–1113– 2000 L prep of Maraviroc intermediate

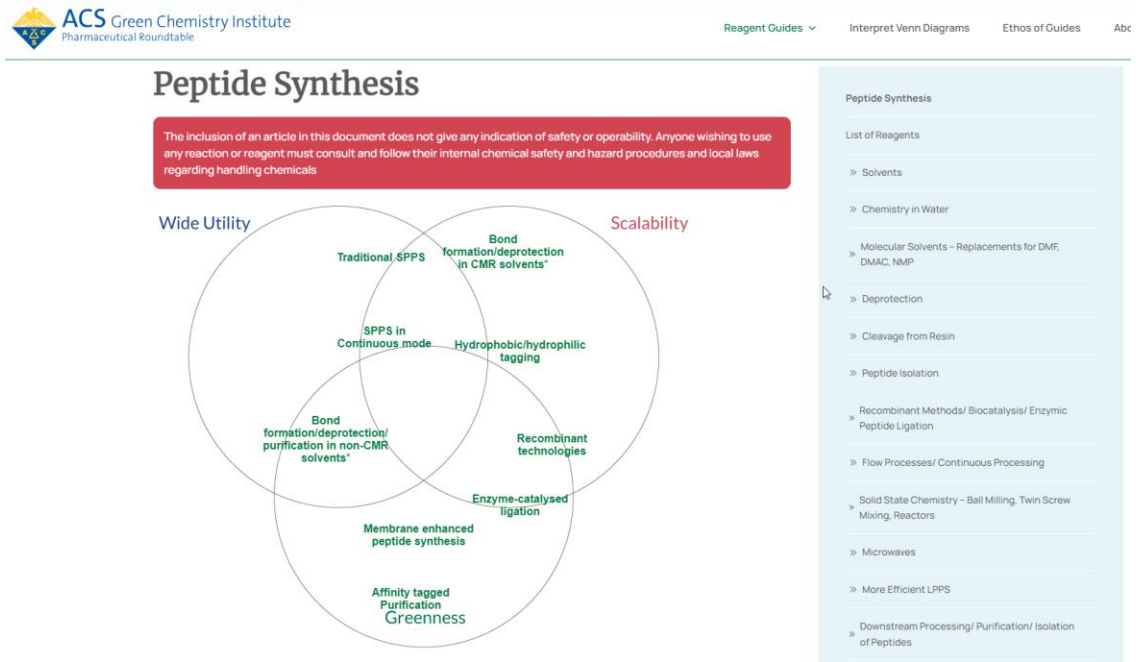
Reagent Guides

ACS Green Chemistry Institute on LinkedIn: The ACS GCIPR has recently published a new reagent guide on peptide...

The ACS GCIPR has recently published a new reagent guide on peptide synthesis. The reagent guides use Venn diagrams to provide an easy comparison of the...

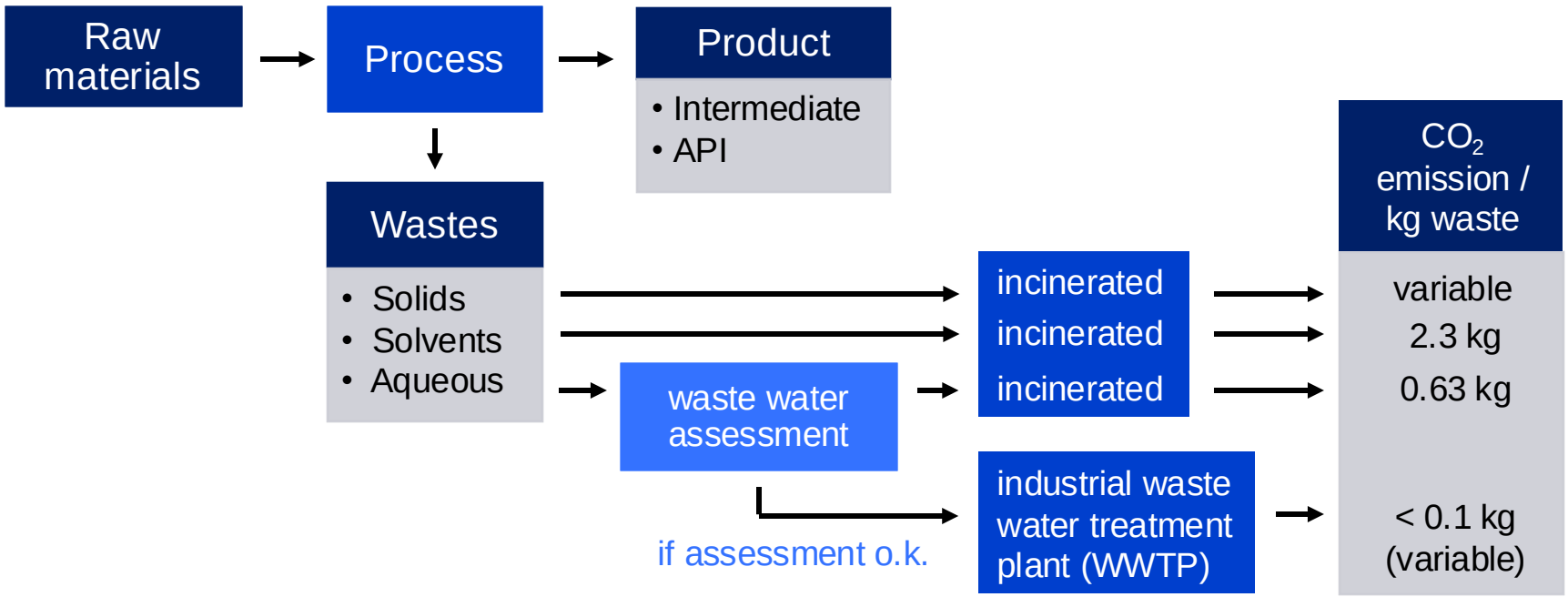
www.linkedin.com

[Peptide Synthesis – WordPress (acsgcipr.org)]

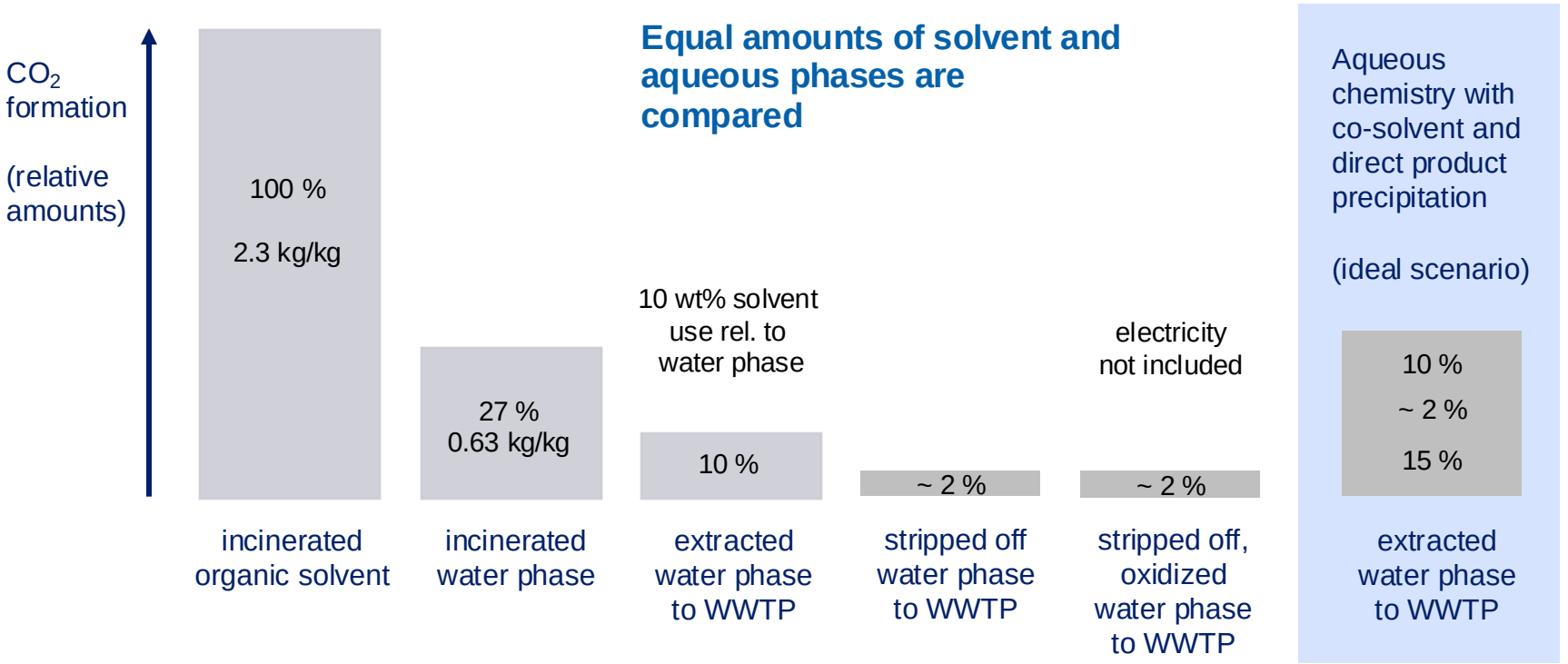


III. Waste water from chemical processes

Waste streams from conventional chemical processes

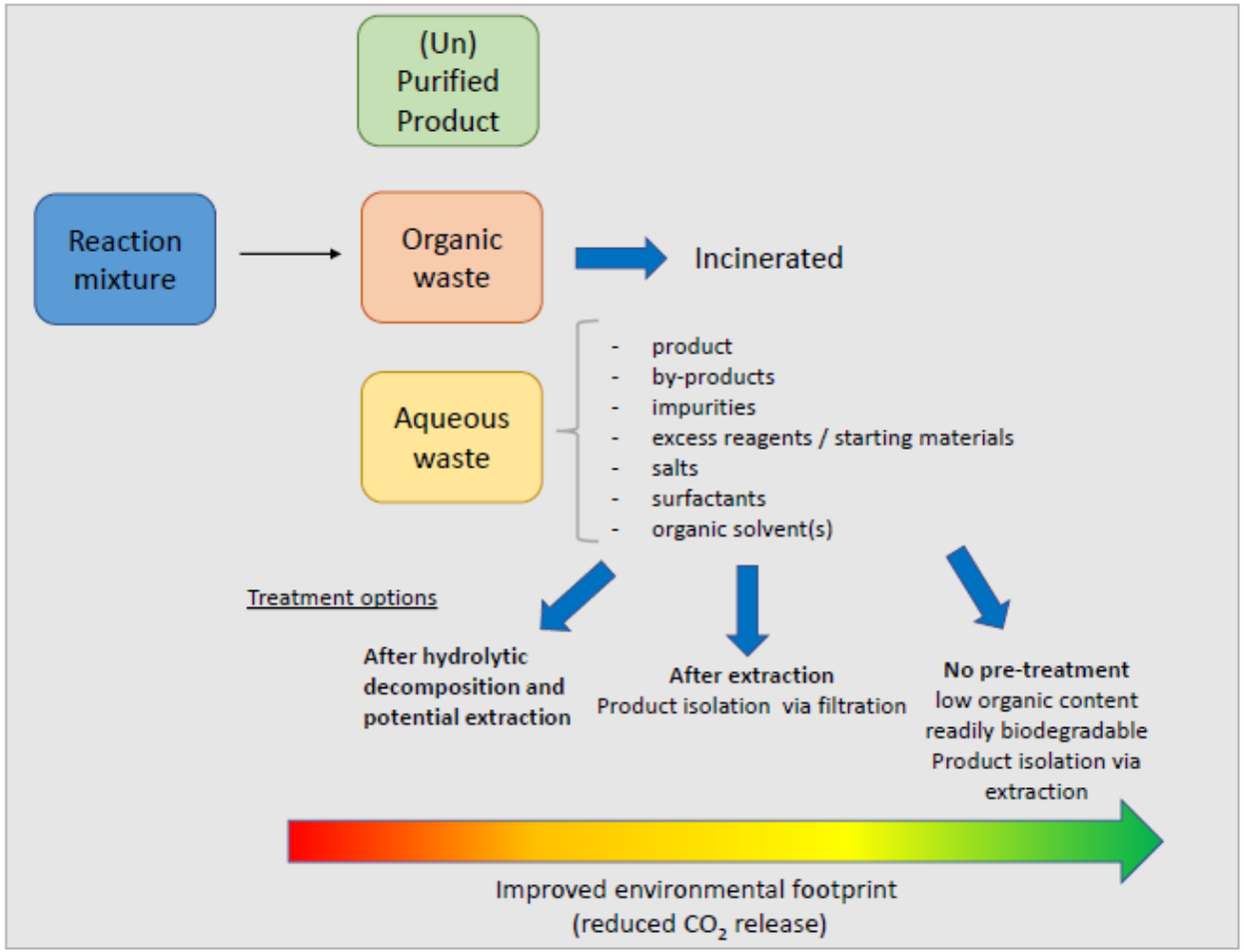


CO_2 formation from liquid waste disposals



Waste streams from conventional chemical processes

Why water-based chemistry can be disruptive



Org. Proc. Res. Dev. **2021**, *25*, 900.

Substituting solvents by water

Water as (reaction) solvent relates to Green Chemistry Principles

- **3. Less Hazardous Synthesis**
- **5. Benign Solvents & Auxiliaries**
- **12. Inherently Benign Chemistry for Accident Prevention**

Substituting solvents by water

Water as (reaction) solvent relates to Green Chemistry Principles

3. Less Hazardous Synthesis

5. Benign Solvents & Auxiliaries

12. Inherently Benign Chemistry for Accident Prevention

"Performing a reaction in water is green because no/little solvent is used"

"Biocatalysis is green because it uses water as solvent"

Substituting solvents by water

Water as (reaction) solvent relates to Green Chemistry Principles

3. Less Hazardous Synthesis

5. Benign Solvents & Auxiliaries

12. Inherently Benign Chemistry for Accident Prevention

"Performing a reaction in water is green because no/little solvent is used"

"Biocatalysis is green because it uses water as solvent"

This may be true ... if the spent water is **acceptable for the WWTP**, and not incinerated.

Residues of	Reactants Reagents Product Co-solvent Solvent from work-up By-products	• need to be **degradable** in the WWTP (= not persistent) • the remains after the WWTP need to be **unproblematic in the environment,** particularly - **of low toxicity** towards several organisms - do not promote algae growth

Biodegradability of organic compounds

Breakdown of organic matter by microorganisms, mainly by bacteria

Goal: complete transformation down to CO_2, H_2O, NH_4^+, NO_3^-, N_2, SO_2, sulfate, sulfide, phosphate

Enzymatic reactions
Hydrolysis
N-dealkylation
Nitrile hydration
C-oxidation
N- and S-oxidation
+ other reactions

Ready biodegradability Tests, OECD 301 A to F

- Test substance + aqueous medium + activated sludge from WWTP + air, stirred at r.t. for up to 28 d
- Six test principles. Biodegradation calculated based on DOC decrease, CO_2 production or O_2 uptake
- Precise criteria → clear outcome

Zahn-Wellens/EMPA Test, OECD 302 B

- Setup as above. DOC determination in time intervals.
- Biodegradation [%] = 100 x $DOC_{eliminated}$ / $DOC_{initial}$

DOC = Dissolved Organic Carbon

OECD = Organization for Economic Co-operation and Development

Biodegradability *vs.* compound structure

Breakdown of organic matter by microorganisms, mainly by bacteria

Goal: complete transformation down to CO_2, H_2O, NH_4^+, NO_3^-, N_2, SO_2, sulfate, sulfide, phosphate

	Biodegradable	Moderately degradable	Sparingly / non-degradable
Aliphatic	*prim- & sec*-alcohols aldehydes ketones carboxylic acids esters *prim- & sec*-amines amides	*tert*-alcohols nitriles alkenes nitro alkanes	ethers hydrocarbons halogen compounds *tert*-amines quaternary amines
Aromatic	anilines (no/few substituents) imidazole	anilines (substituted ones) phenols (*bacteriotoxic*) nitro aromatics	hydrocarbons biaryls halogen compounds

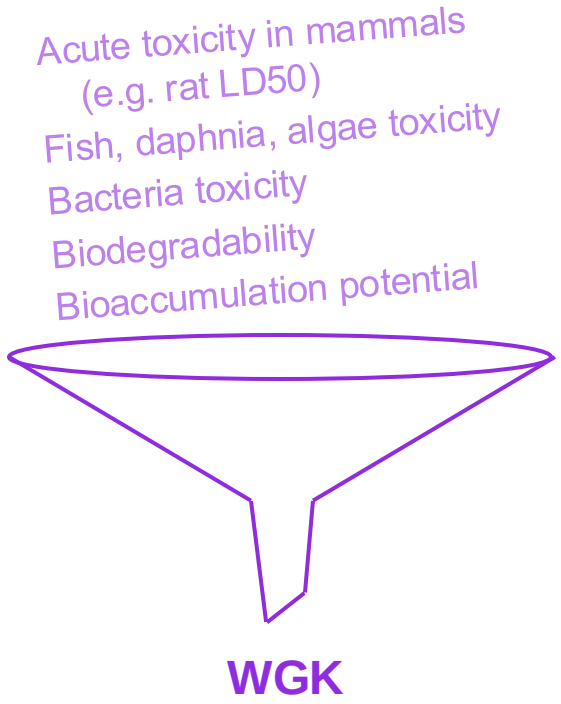
Biodegradability falls with increasing:

- degree of branching and chain length
- number of substituents

Water hazard classes - *Wassergefährdungsklassen (WGK)*

WGK

-	not water endangering	*nicht wassergefährdend*
1	slightly hazardous to water	*schwach wassergefährdend*
2	hazardous to water	*wassergefährdend*
3	highly hazardous to water	*stark wassergefährdend*

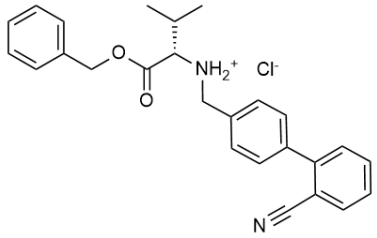


- System of the German environmental authorities (*Umweltbundesamt*)
  '*Verordnung über Anlagen zum Umgang mit wassergefährdenden Stoffen (AwSV)*'
- List of compounds: 'Rigoletto' data base (public domain)
- Novartis Pharma Data Set (NPDS) → KSO data base

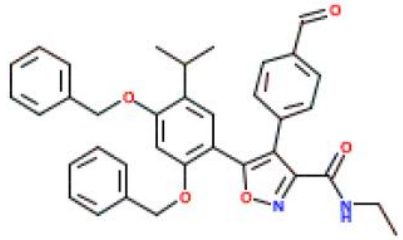
Water hazard classes - Pharma compounds

All examples not ‘readily biodegradable’

intermediates



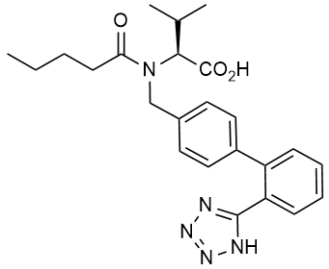
WGK 2
Biodegradation: 10 %



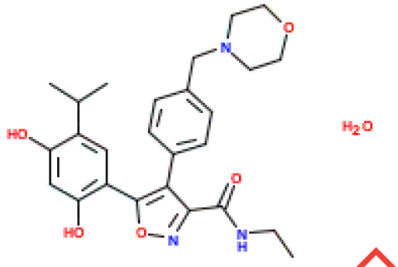
WGK 1
Biodegradation: 3 - 12 %

WGK 2
Biodegradation: 16 %

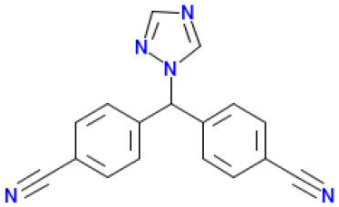
drug substances



WGK 1
Biodegradation: 0 %



WGK 3
Biodegradation: 0 %



WGK 3
Biodegradation: 1 %

Regulatory framework

Switzerland (Basel)	China (Changshu)
Waters Protection Act (WPA) *Gewässerschutzgesetz (GSchG)* Waters protection ordinance → general and specific goals *Gewässerschutzverordnung (GSchV)*	Law of the People's Republic of China on Prevention and Control of Water Pollution
Novartis Corporate HSE GL 7 'Waste Management', GL 15 'Pharmaceuticals in the Environment', GN 15.3	
Disposal permission of local authorities (BS / BL)	
HSE CH Guidance Note 004.3.1 'Wastewater Disposal and Water Protection Installations' Waste water management system (surveillance, assessment, inventory, reporting)	SOP-7017963 'Environmental management' - SNPT emission/discharge limits for waste water - Wastewater management procedures
Waste water assessment → Waste water card (AWK) *Abwasserkarte (AWK)* DERA Info File 3020 'Poorly degradable substances'	Wastewater Register WP-7005368 Waste Water File FRM-7026109 → WW assessment Process waste water classification tree

Information resources

Biodegradability test methods	
Biodegradability of compounds	• Novartis KSO data base, MSDS, ECHA website
Water hazard class (WGK)	• Novartis KSO (NPDS, section 'Regulatory') • Supplier MSDS • Rigoletto data base (also in English) https://webrigoletto.uba.de/rigoletto/public/welcome.do • GESTIS data base (also in English): http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index.jsp (section 'Regulations' / *'Vorschriften'*)
$logP_{ow}$ **Solubility in water**	• Novartis KSO, GESTIS data base, MSDS, ECHA website, solvent selection guides

Summary and Conclusions

Chemists and engineers have enormous control over manufacturing processes by selection of synthetic routes.

The Design Principles of Sustainable Green Chemistry are guidelines. Use of metrics is imperative!

The incorporation of catalysis, biocatalysis, continuous flow, nanofiltration, etc. can dramatically improve processes in terms of waste generation.

Solvent and reagent selection guides, coupled with metrics and life cycle analysis, can help make routes more sustainable.

Green chemistry is a triple win: cost-effective, better for the environment, and safer for the employees.

Take home messages

Be curious about environmental and physical properties of the compounds

All input materials and their resulting by-products determine the quality of the waste water

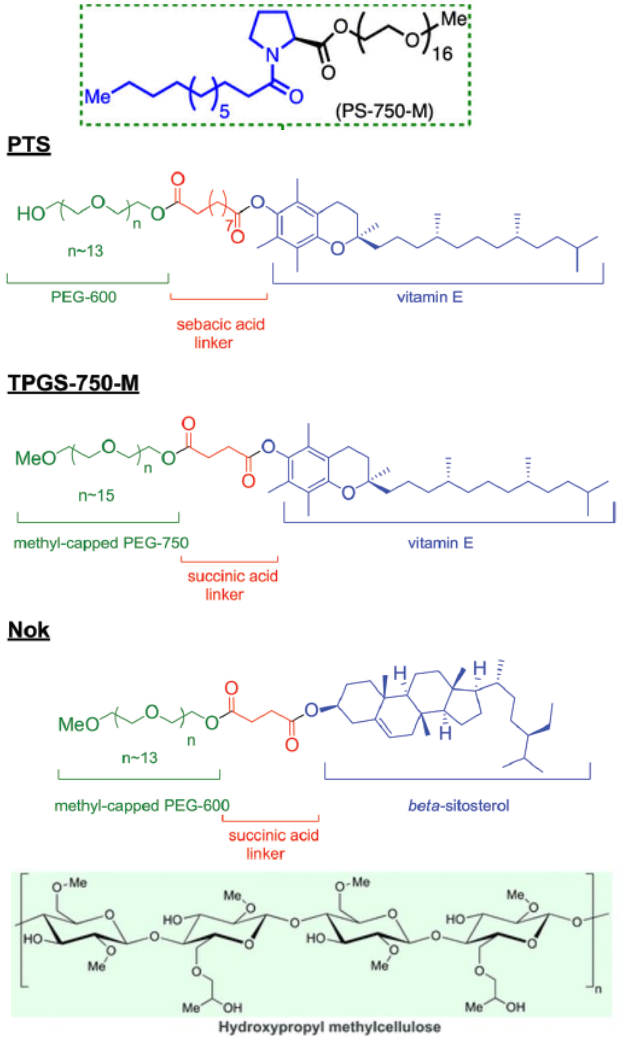
Early collection of information will enable data-driven decisions

Strive for simplicity and robustness if a pre-treatment is needed

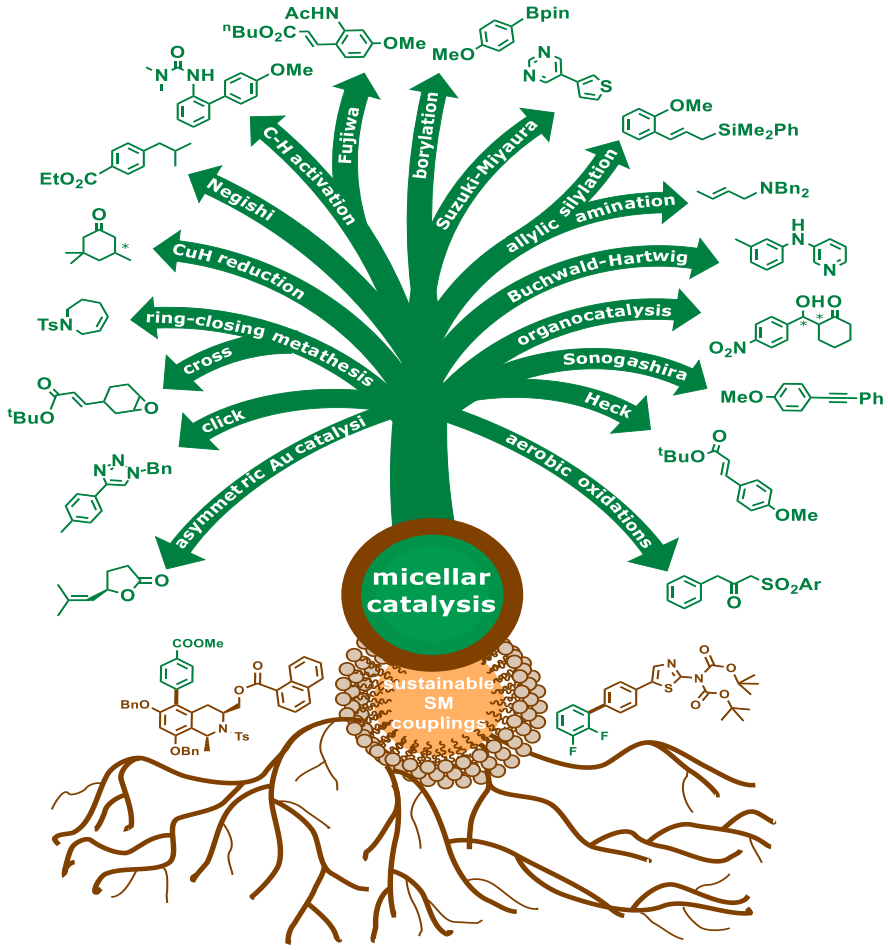
IV. Impact of technologies

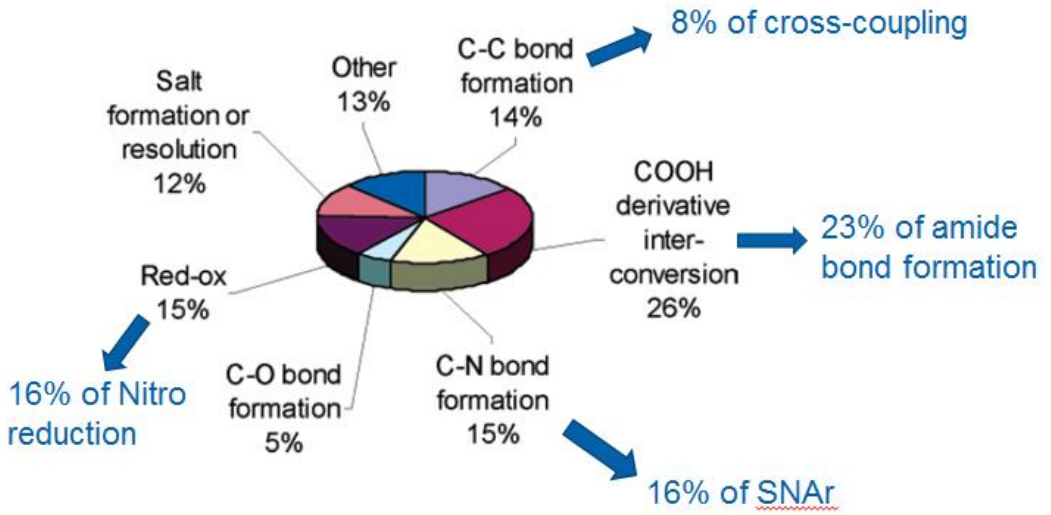
Use of surfactants to enable chemistry in water

- Surfactants are known for their remarkable physical properties as solubilizers.
- Use of versatile nonionic surfactants – Lipshutz and Handa, Abbvie, Takeda, Novartis
- Development of a variety of transformations mediated in water
- No safety or environmental baggage – “benign-by-design”



Surfactant applied to a broad range of transformations

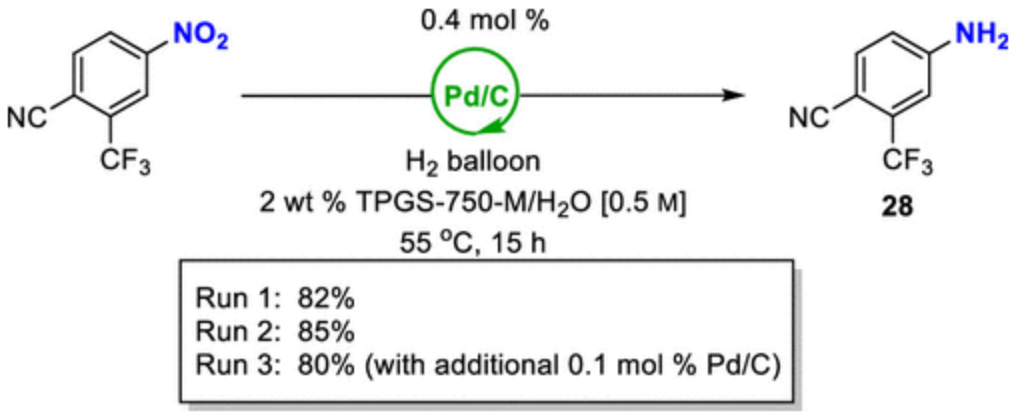




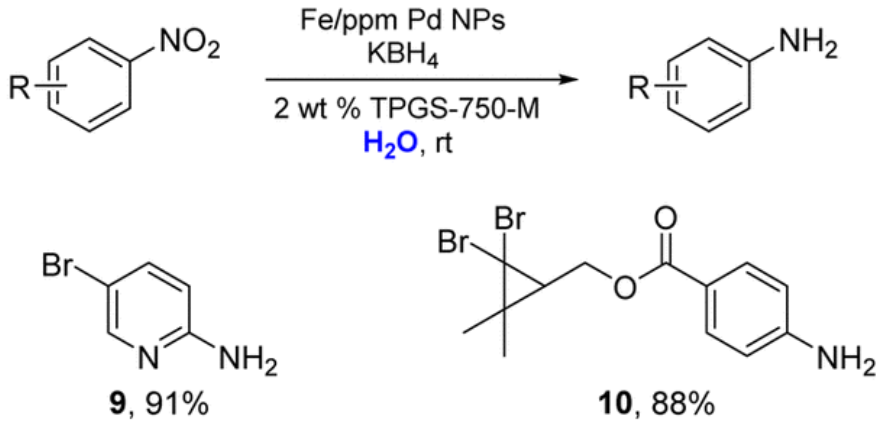
The Roundtable recently triggered a new collaborative working group of chemistry in water. Roundtable member companies meet to share best practices and advance the reaction, work-up, and isolation technology required for running water-based synthetic organic reactions.

Nitro Reduction

Cheap and very efficient options



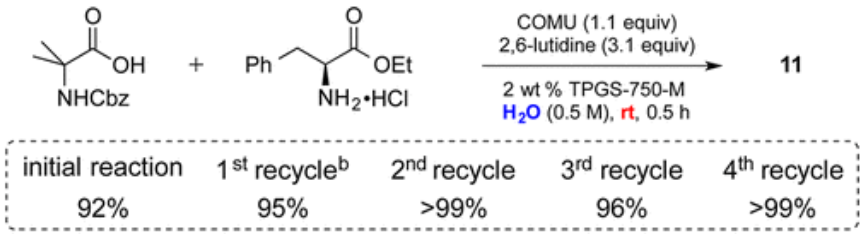
Org. Lett. **2021**, *23*, 8114.



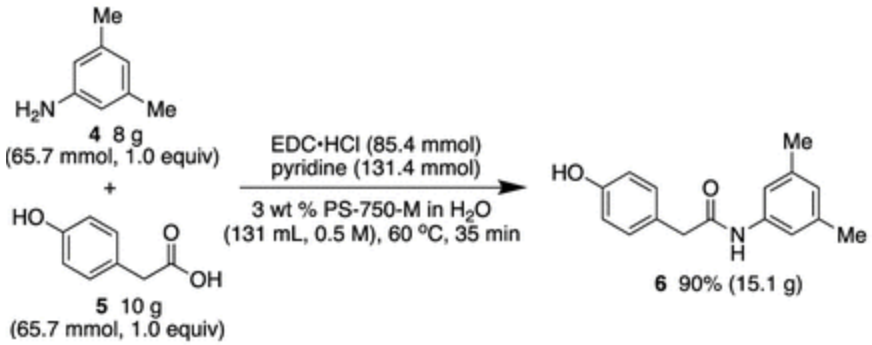
Org. Proc. Res. Dev. **2017**, *21*, 247.

Amidation

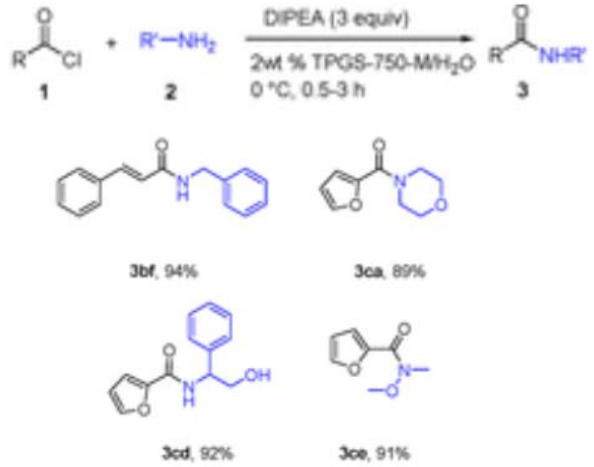
A toolbox of options



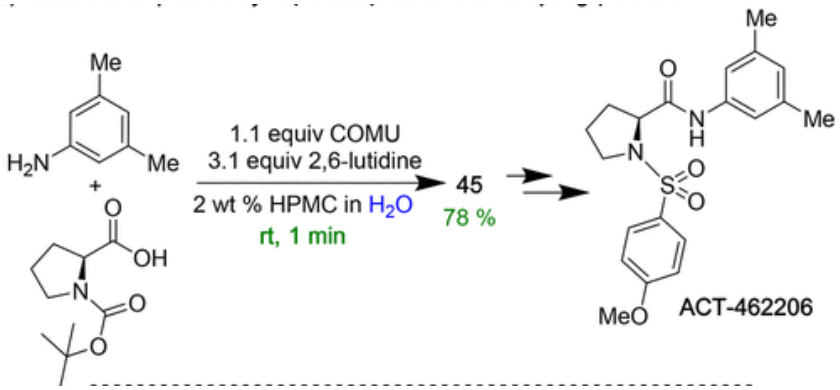
Org. Lett. **2015**, *17*, 3968.



Org. Process Res. Dev. **2021**, *25*, 1960.



_*Org. Process Res. Dev.* **2020**, *24*, 1543.

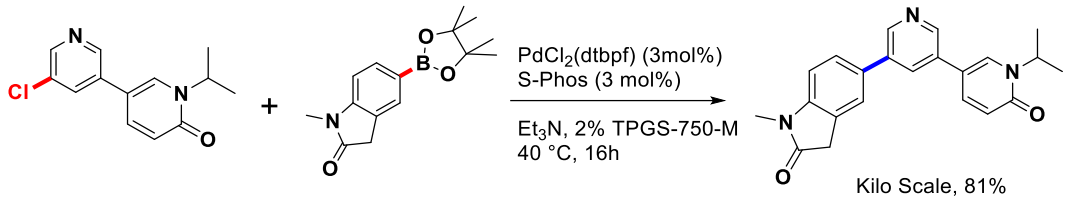


ACS Sustainable Chem. Eng. **2020**, *8*, 12612.

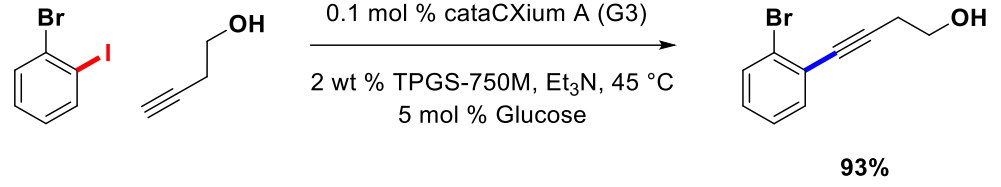
Cross-Couplings

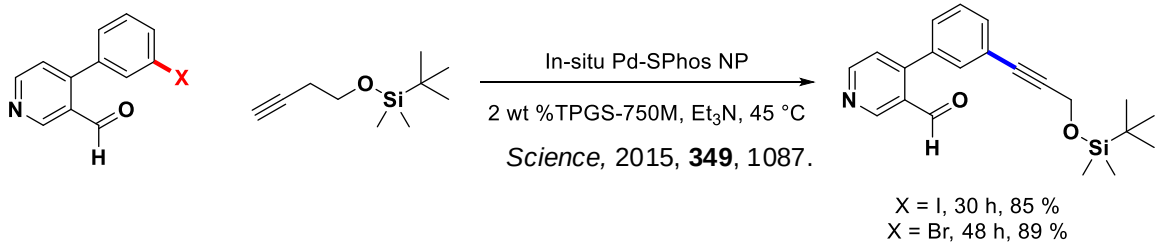
Well established transformation

- **Suzuki-Miyaura:**
  - Applied on Kg-Scale
  - Robust and efficient
  - Mild reaction conditions avoid degradation
  - Improved stoichiometry



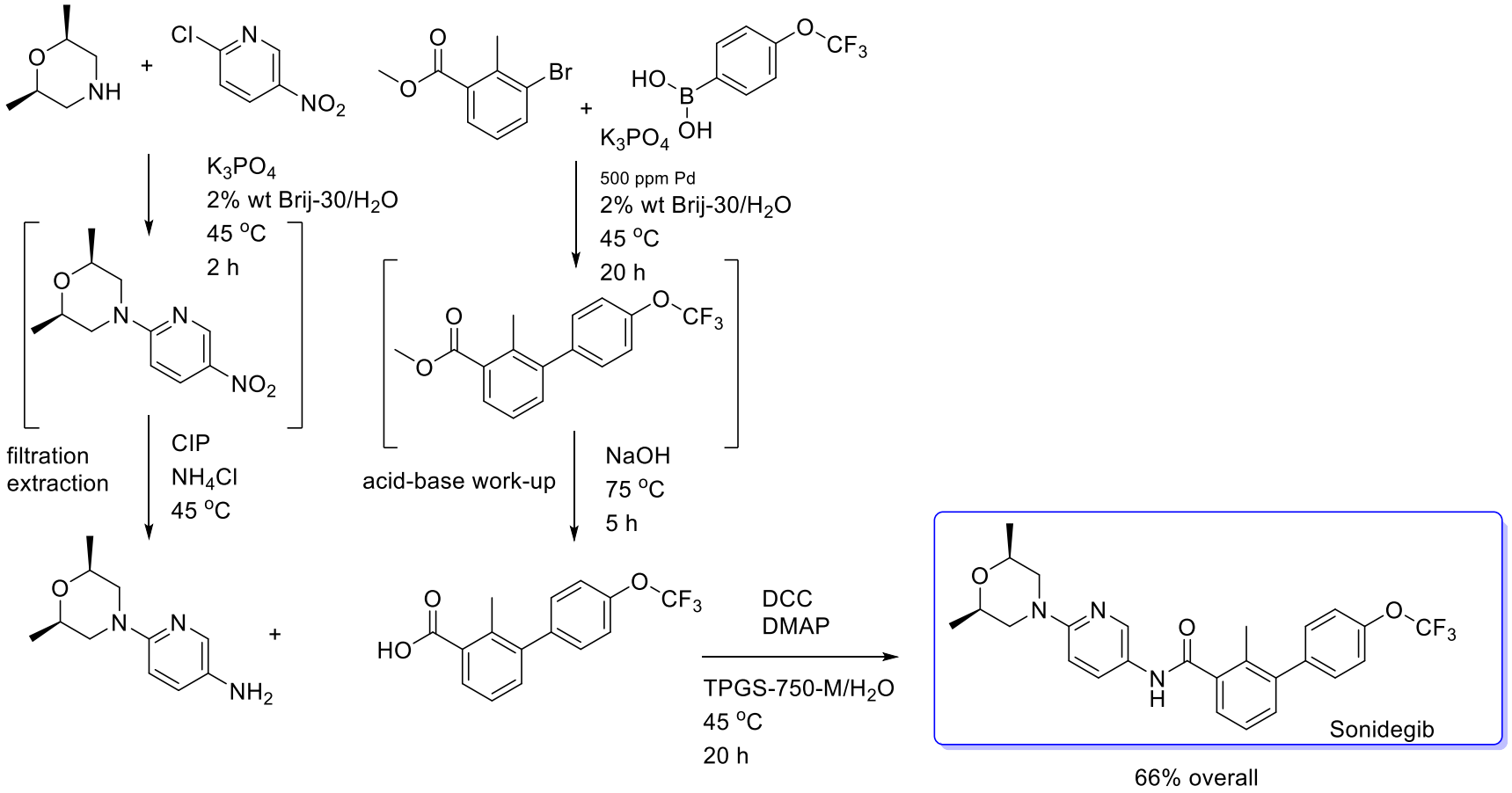
- **Sonogashira:**
  - Copper free reaction
  - Very low catalyst loading
  - Fe-NPs with ppm level of Pd
  - Mild reaction conditions





Tandem reactions

All transformations run in 2% TPGS-750-M in water

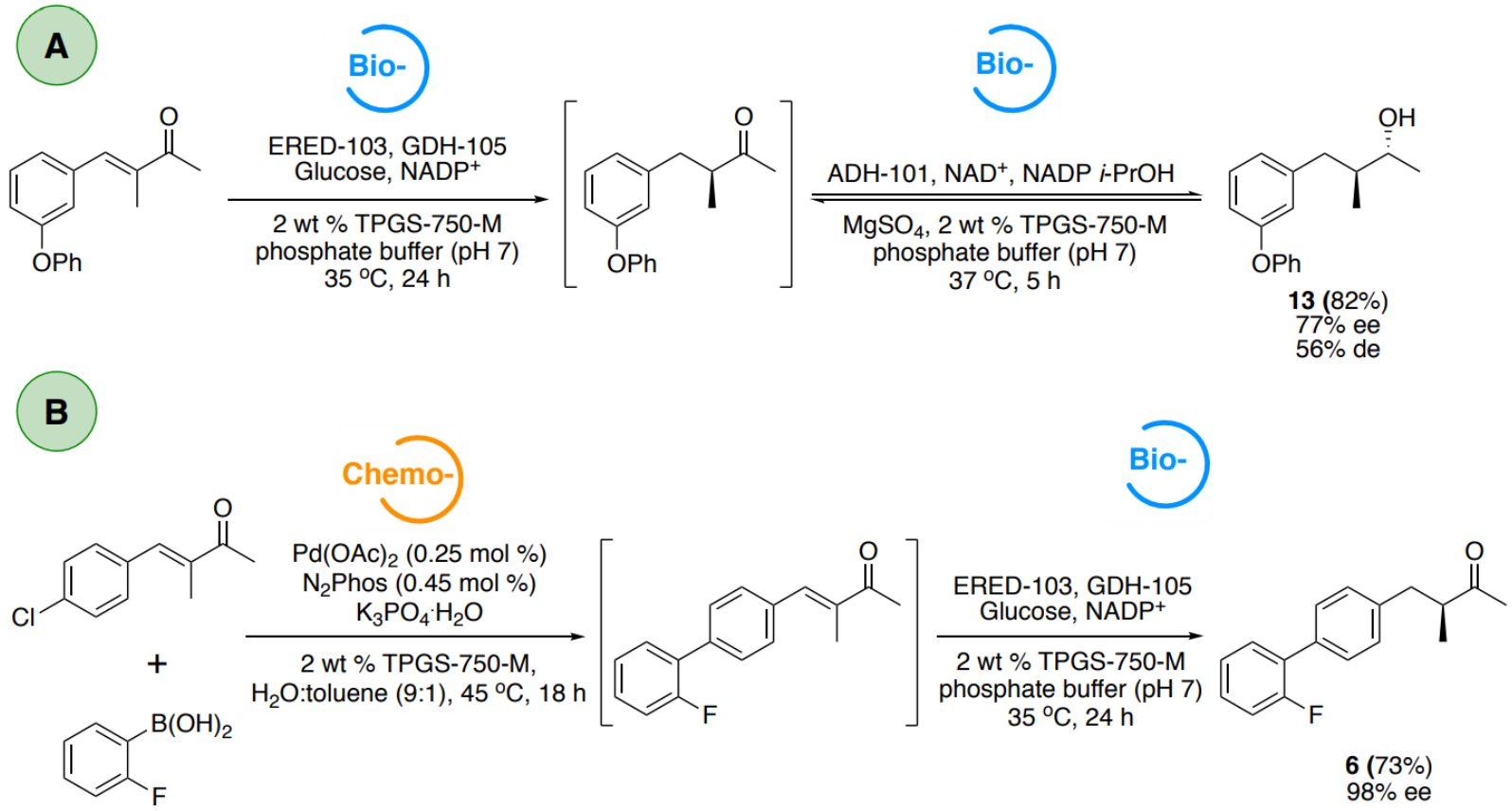


66% overall

Chem. Sci. **2019**, *10*, 3481–3485.

Tandem reactions

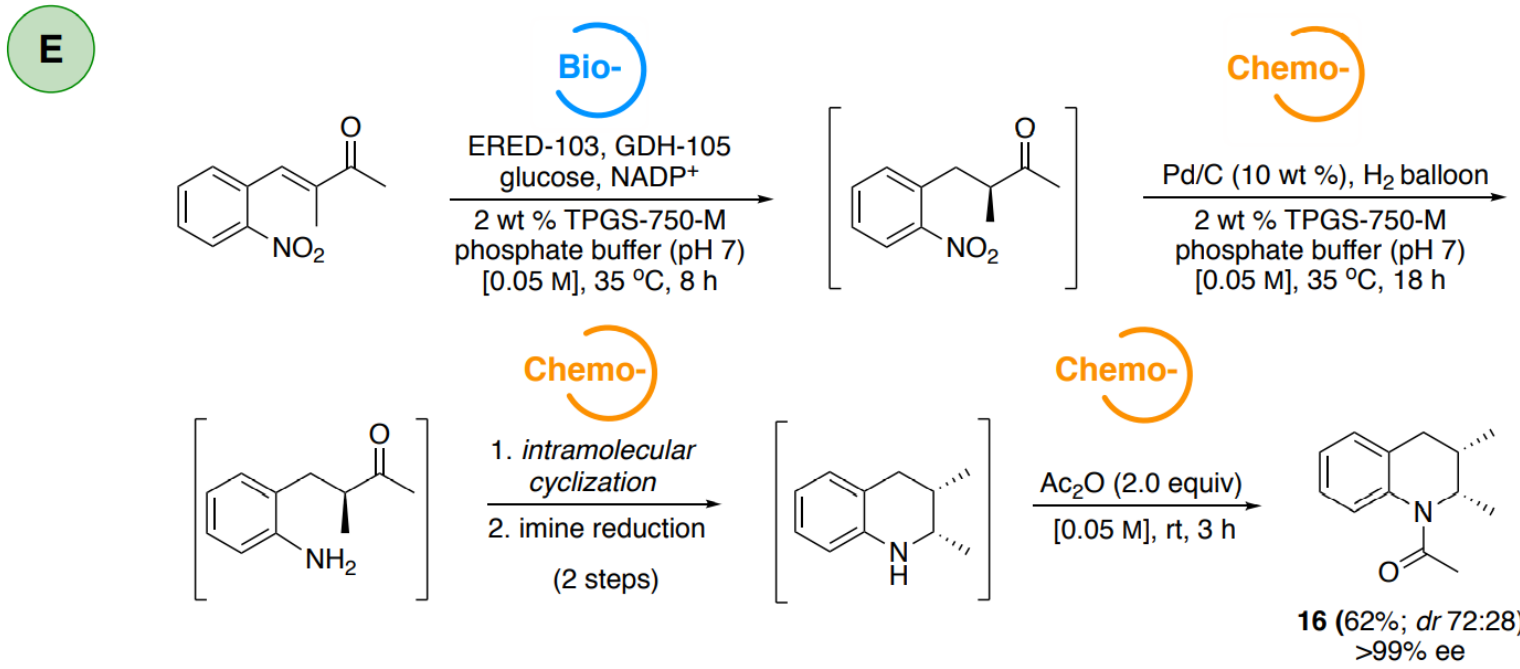
Sequences of Chemo-/Bio-catalysis



Chem. Comm. **2021**, *57*, 11847.

Tandem reactions

Sequences of Chemo-/Bio-catalysis



Chem. Comm. **2021**, *57*, 11847.

Tandem reactions

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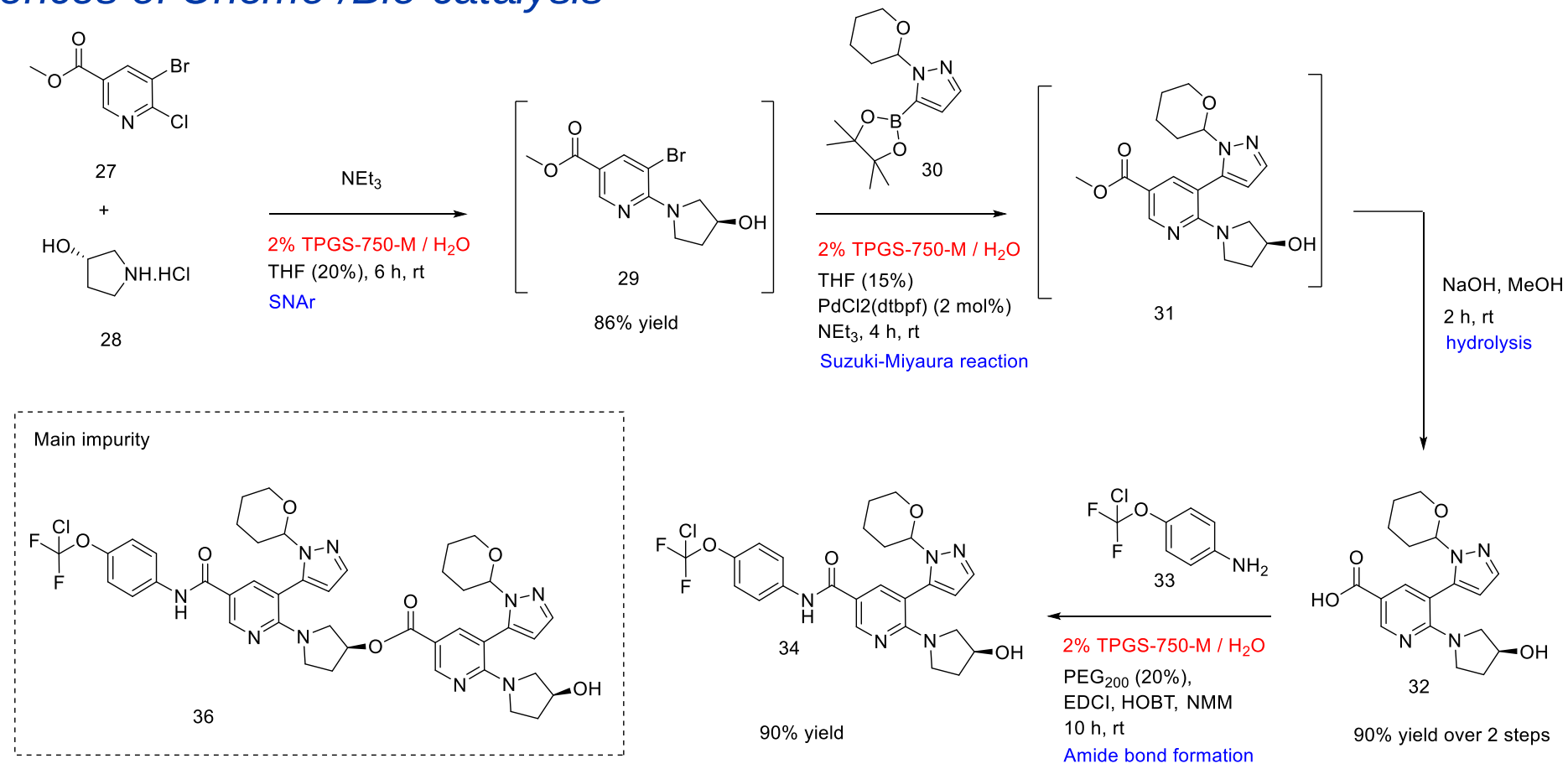
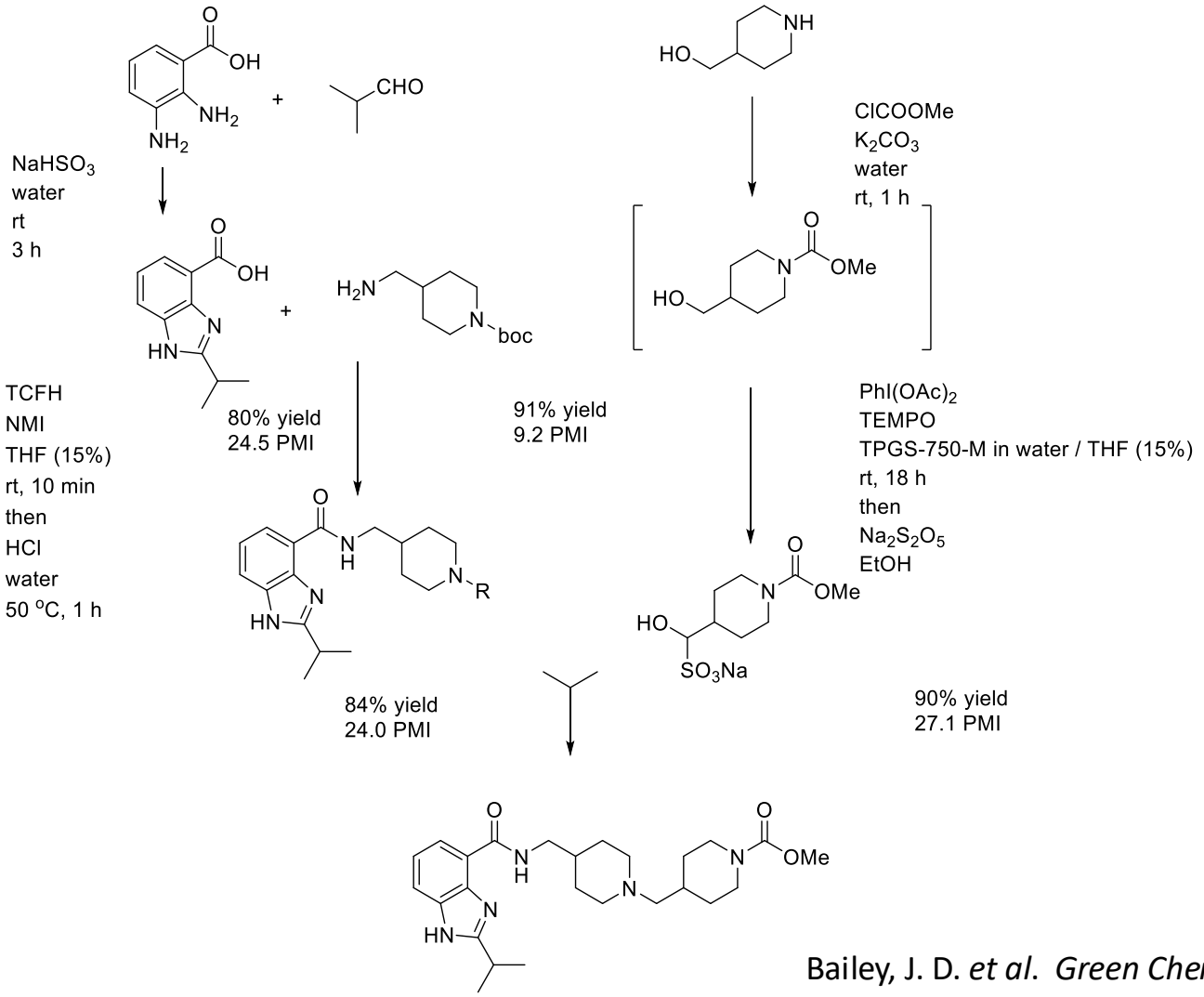


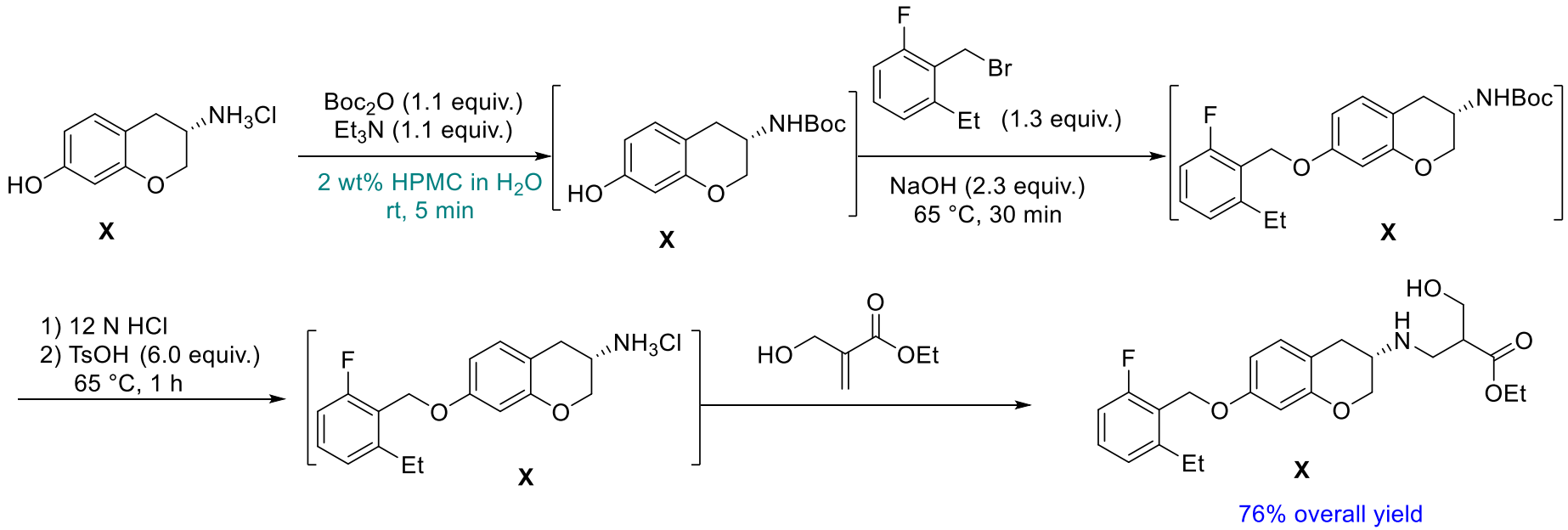
Nat. Rev. Chem. **2018**, *2*, 306–327.

Tandem reactions



Bailey, J. D. *et al*. *Green Chem*. **2021**, *23*,788–795.

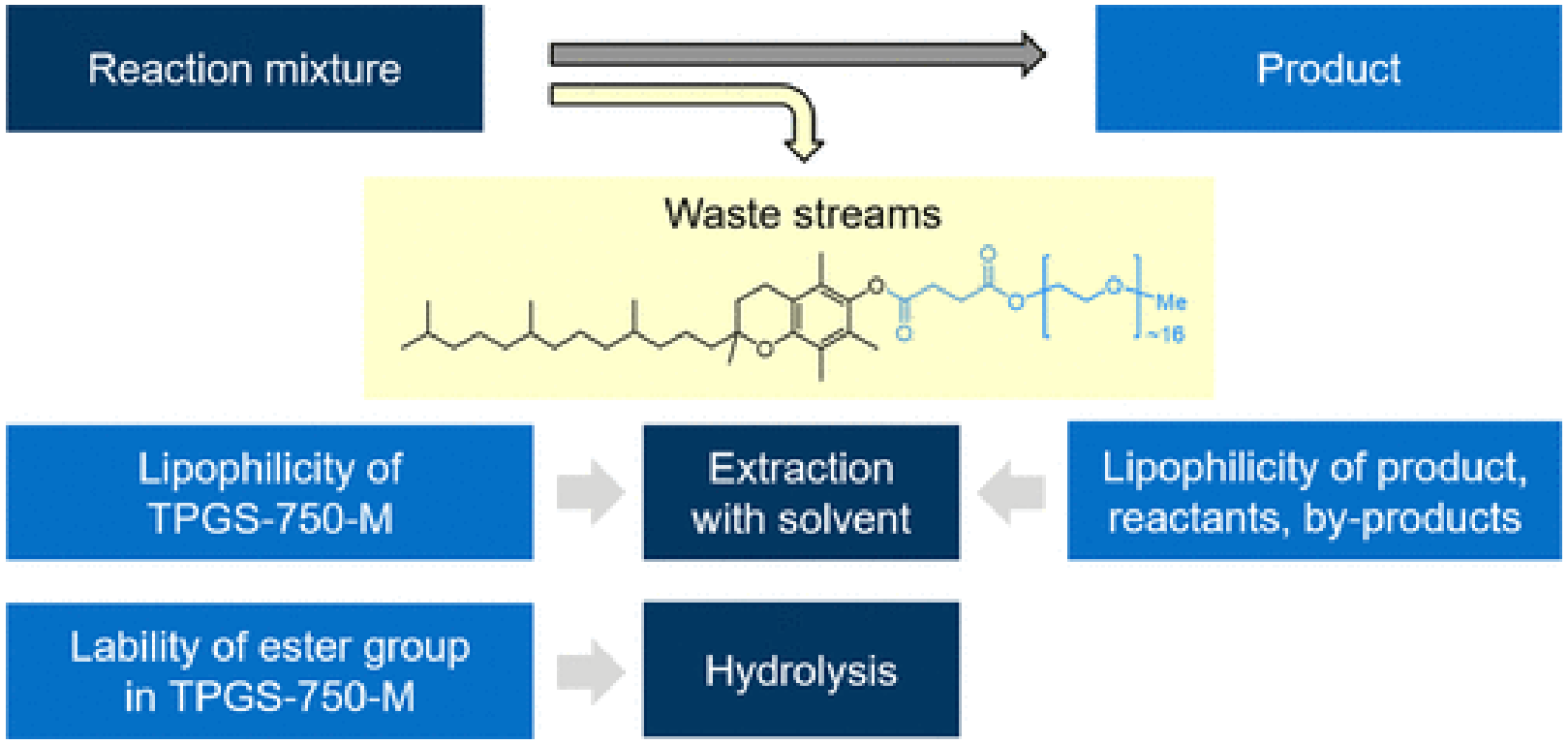
Tandem reactions



Braje, W. M. & Handa, S. *ACS Sustainable Chem. Eng*. **2020**, *8*, 12612−12617.

Waste water concept

Strategies to Tackle the Waste Water from α-Tocopherol-Derived Surfactant Chemistry



Org. Proc. Res. Dev. **2021**, *25*, 900.

Opportunities

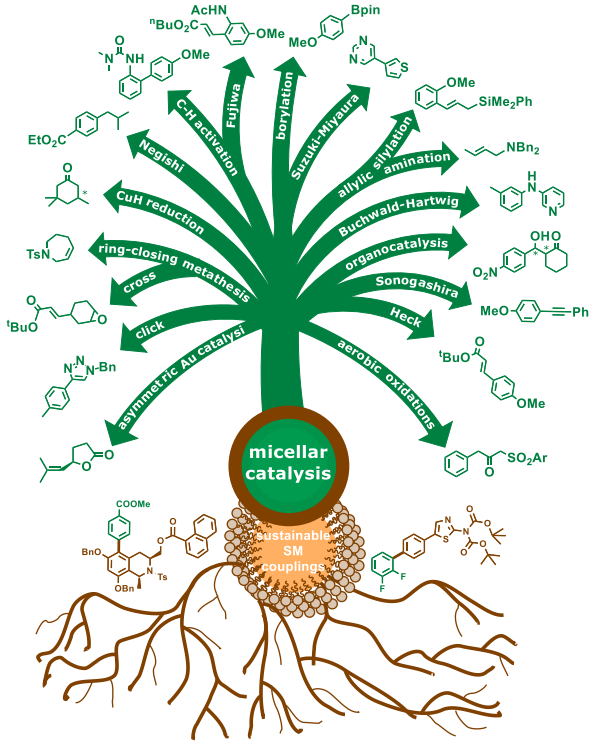
Some biases and unknown facts

- Chemistry with surfactants in water requires **as much or even less water than traditional transformations** due to high concentration
- **Contamination of water waste equivalent** whether traditional or surfactant in water process is being used
- Standard process in surfactant water can be as simple as running the reaction, filtering and drying
- **No capital investment** required, no special equipment !
- Technology mostly driven by physical properties of various components of the system Limited understanding of mechanisms and appreciation

Take home message

A powerful alternative to classical polar aprotic solvents still at its enfancy

- Sustainable alternative for reprotoxic polar aprotic solvents demonstrated with significant advantages
- Ever-growing toolbox and understanding
- Next generation of reagents/catalytic systems tailor-made to the medium
- New rules remain to be discovered and exploited



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The incorporation of catalysis, biocatalysis, continuous flow, nanofiltration, etc. can dramatically improve processes in terms of waste generation.

Solvent and reagent selection guides, coupled with metrics and life cycle analysis, can help make routes more sustainable.

Green chemistry is a triple win: cost-effective, better for the environment, and safer for the employees.

Some important tools

- **Proper design of syntheses and processes is the essence of sustainability !**
  - Strong correlation cost and environmental footprint

- **Solvent selection**

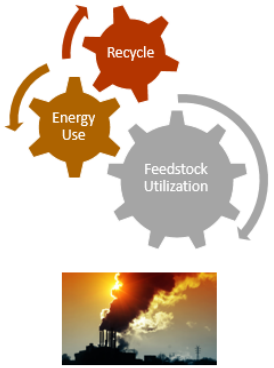
http://learning.chem21.eu/

  - Considers safety, health and environmental impact of solvents
  - Make the right solvent choice – there are alternatives !

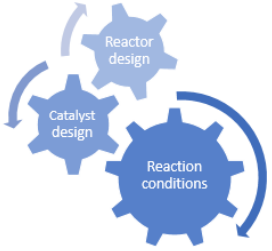
Reagents guide

https://reagents.acsgcipr.org/

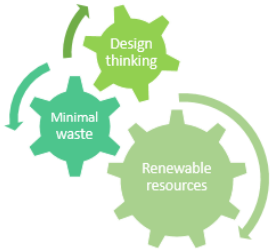
  - The greenest conditions for common transformations (*Green Chem*. **2013**, *15*, 1542-1549)



Reduced global warming potential



Sustainably improved economy



Green chemistry

Thanks to the all, questions?

xxx