Selected Green Chemistry Metrics for Educators

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Beyond Benign Green Chemistry Webinar Series

beyondbenign
green chemistry education

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Overall aim for today

- to highlight **some** important metrics/tools used to teach green chemistry (with connections to industry):
  - mass metrics: atom economy, reaction mass efficiency, E factor, **process mass intensity (PMI)**
  - substance nature/suitability (solvent and reagent usage)
  - profile some educational activities at U of T

Green chemistry is like a good relationship…

…it’s about compromise!

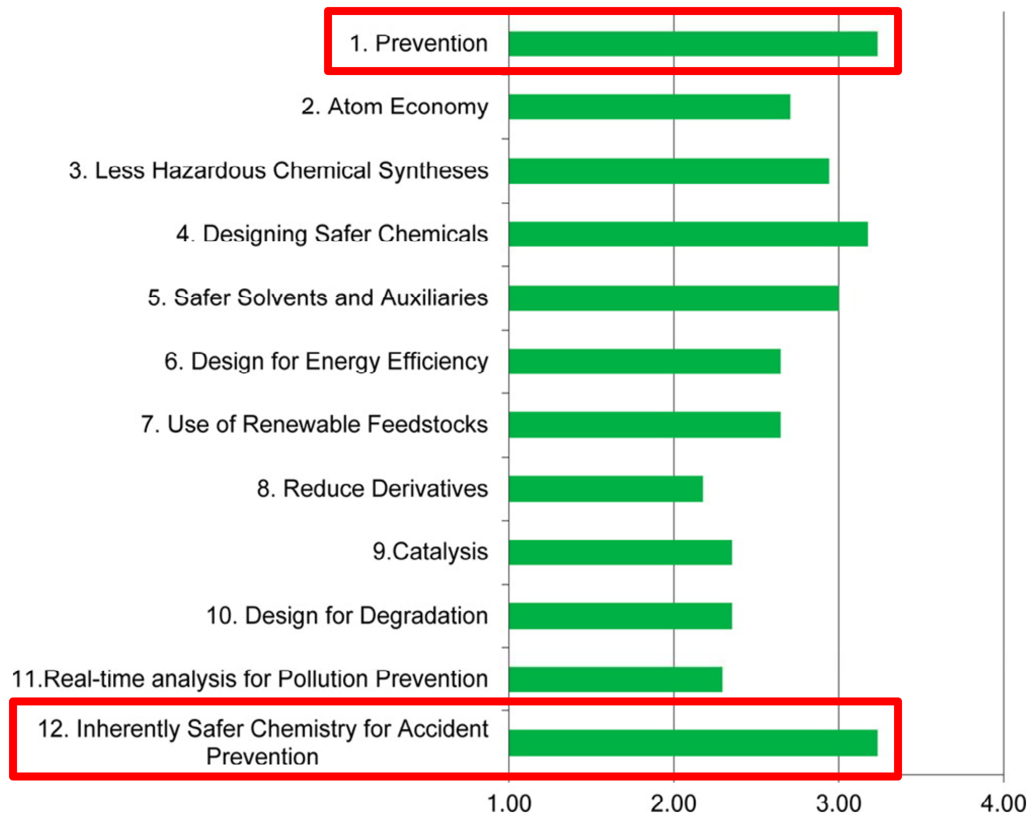
(… and decision-making, and transparency…)

The Twelve Principles…

- ❑ **Prevent waste rather than clean it up**
- ❑ **Incorporate (all) starting materials into desired product**
- ❑ **Use and generate substances possessing little/no toxicity**
- ❑ Design of efficacious products while reducing toxicity
- ❑ **Avoid use of auxiliary substances**
- ❑ Minimize energy requirements
- ❑ **Use renewable raw materials/feedstocks**
- ❑ **Avoid unnecessary derivatization**
- ❑ **Use catalysts**
- ❑ Design products that degrade into innocuous substances
- ❑ Develop analytical methodologies that allow in-process monitoring
- ❑ **Use substances that minimize potential for accidents**

www.epa.gov/research/sciencematters/june2011/principles.htm

Frequency of their application



Average chemical manufacturer responses (*n* = 17) to the survey question:

"In your opinion, how frequently does your company implement the following principles of green chemistry?" on a scale of 1 to 4: (1 = never; 4 = fully implemented)

Giraud, R. J. et al. *ACS Sustainable Chem. Eng.* **2014,** *2*, 2237

Mass metrics

"to measure is to know…"

Lord Kelvin

(importance of "green chemistry metrics")

BUT !

Chemists in academia often judge how "good" a reaction is by the % yield obtained

"Yield is everything" mentality: not green chemistry thinking!

$$\% \text{ Yield} = \frac{\text{experimental quantity of desired product}}{\text{theoretical maximum quantity of desired product}} \times 100$$

Well-known mass metric: atom economy (#2) (1)

$$\% \text{ Atom Economy} = \frac{\text{mol. weight of desired product}}{\text{mol. weight of all reactants}} \times 100$$

- useful as can **quickly** judge which reactions are "atom-economical" (or not…)

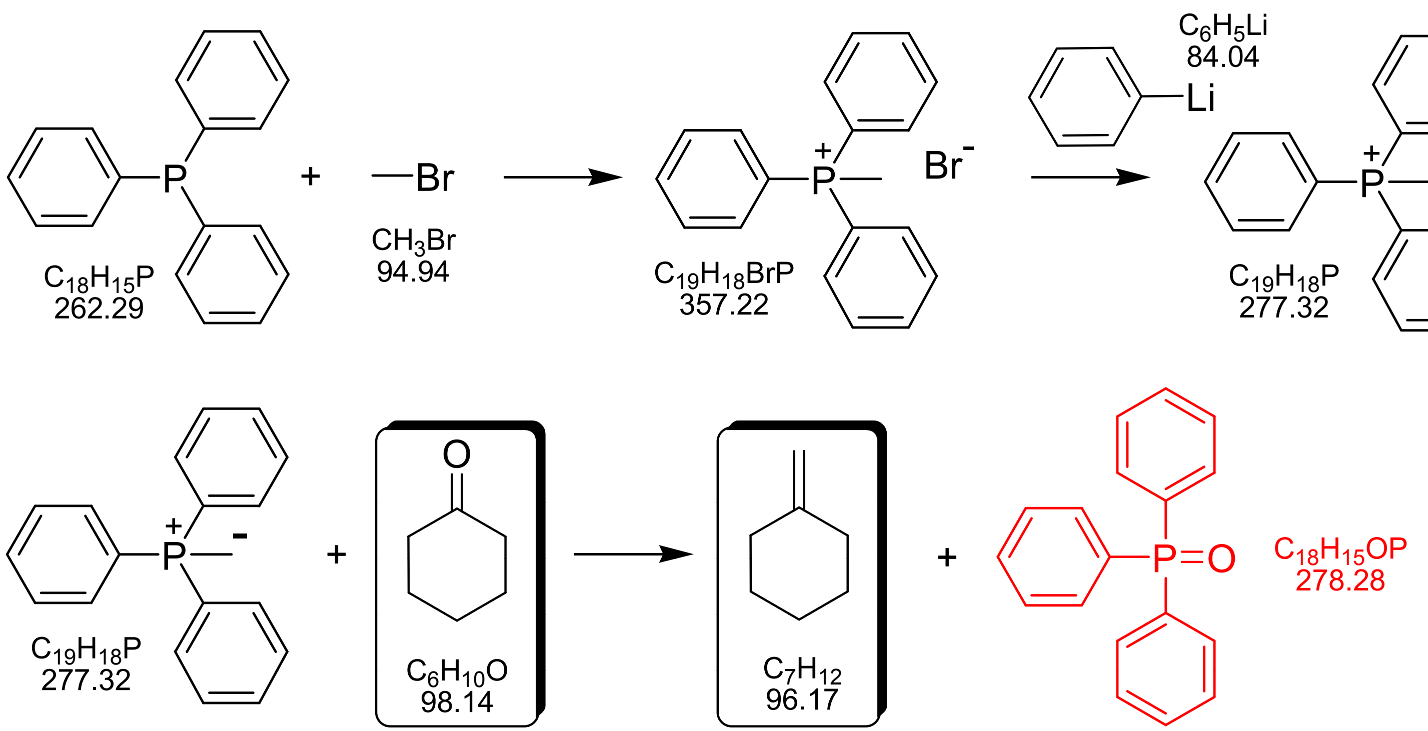
A + **B** ⟶ **C**

A	+	B	→	C	
mol. wt.: 100		mol. wt.: 200		mol. wt.: 300	**100% atom economy**

Trost, B. M. *Science* **1991**, *254*, 1471

Atom economy (2)

- some reactions do not fare very well at all… e.g. Wittig:



18% atom economy

- issue: just considers the reaction, **not everything around it**
- **don't have to undertake a reaction to calculate a value**

Much more helpful: Reaction mass efficiency (RME)

$$\% \text{ RME} = \frac{\text{mass product (g)}}{\text{(total input mass - mass recovered materials) (g)}} \times 100$$

- ❑ takes into account **reactant masses** rather than mol. wts.
- ❑ usually does not include “non-reactant materials”
- ❑ can account for recycling (e.g. of a catalyst)
- ❑ actual product yield is factored in **- very important!**
- ❑ **can be calculated for *any* reaction performed in an undergraduate laboratory… students may be surprised!**

Industrial perspective: E (environmental) factor (1)

$$\text{E factor} = \frac{\text{mass adjusted waste (g)}}{\text{mass product (g)}}$$

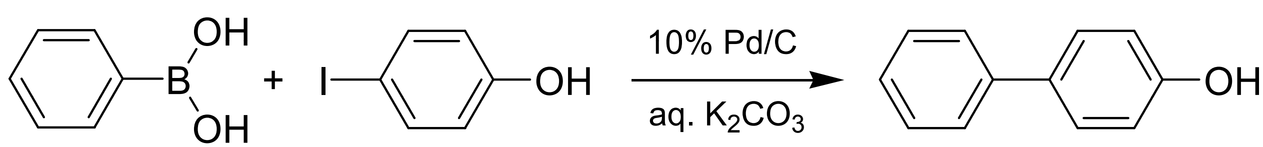
- quick, easy way to assess amount of waste produced
- ideal E factor value = 0
- “adjusted” means can account for recycling
- historical industrial usage (developed 1992)

Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273 (15 years on)

Chemical industry E factor values

Industry segment	Product tonnage	E factor (kg waste/kg product)
Oil refining	$10^6 – 10^8$	< 0.1
Bulk chemicals	$10^4 – 10^6$	< 1-5
Fine chemicals	$10^2 – 10^4$	5-50
Pharmaceuticals	**$10 – 10^3$**	**25-100**

- undergraduate Suzuki reaction performed at U of T:



$$\text{Suzuki E factor} = \frac{49.86\text{ g} - 0.00\text{ g} - 0.115\text{ g}}{0.115\text{ g}} = \mathbf{433\ (!!!)}$$

Aktoudianakis, E. et al. *J. Chem. Educ.* **2008**, *85*, 555
Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273

The gold standard: process mass intensity (PMI)

$$\text{PMI} = \frac{\text{total input mass (kg)}}{\text{mass product (kg)}}$$

- "input mass": reactants, reagents, catalysts, reaction **solvents**, drying agents, workup **solvents**, product purification substances (e.g. column chromatography adsorbents/**solvents**)

- ideal PMI value = 1 (all input mass ends up in product): median industry PMI values of 433 (pre-clinical) and 68 (commercial): GlaxoSmithKline target of 20 in 2015

- **moving away from an emphasis on waste (E factor)**

Jimenez-Gonzalez, C. et al. *Org. Process Res. Dev.* **2011**, *15*, 912
Leahy, D. K. et al. *Org. Process Res. Dev.* **2013**, *17*, 1099

Pharmaceutical industry perspective

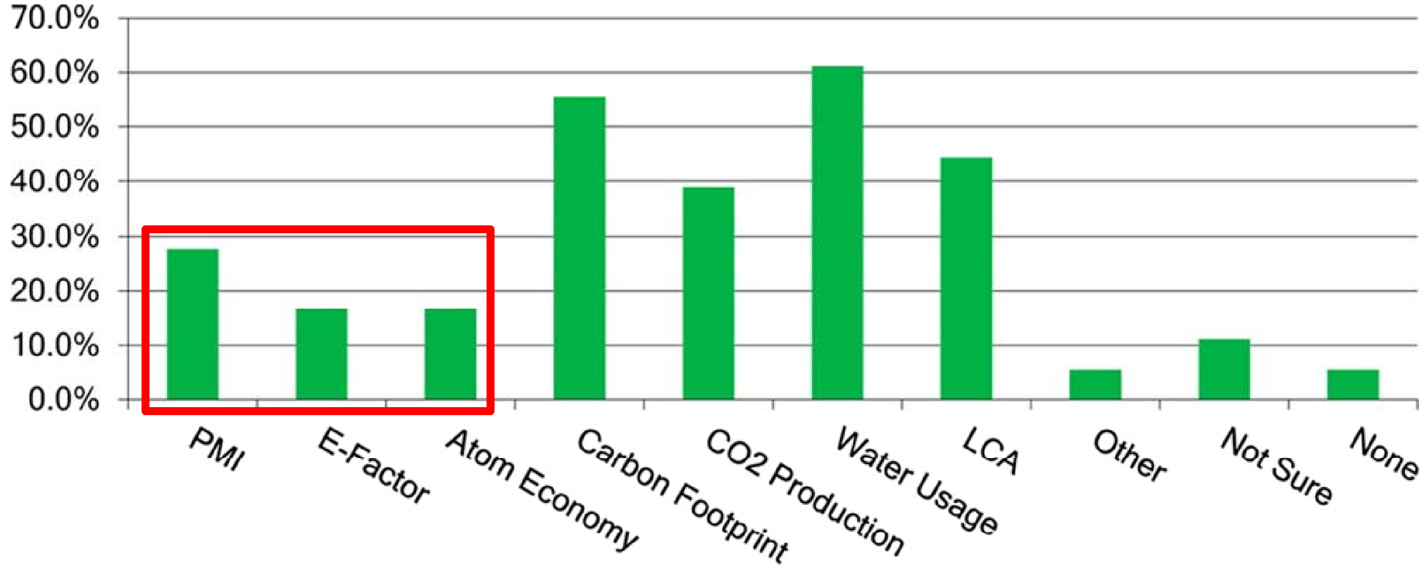
- ACS GCI Pharmaceutical Roundtable has chosen **PMI** as the key metric for evaluating progress towards more sustainable manufacturing

"to truly integrate green chemistry and engineering into chemical processes, one has to look at the inputs instead of the outputs"

"focusing on reducing waste helps companies to reduce costs, but focusing on efficiency also enables innovation to create additional value"

acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html
Jimenez-Gonzalez, C. et al. *Org. Process Res. Dev.* **2011**, *15*, 912

Industry metric use



Chemical manufacturer responses (n = 18) to the survey question:

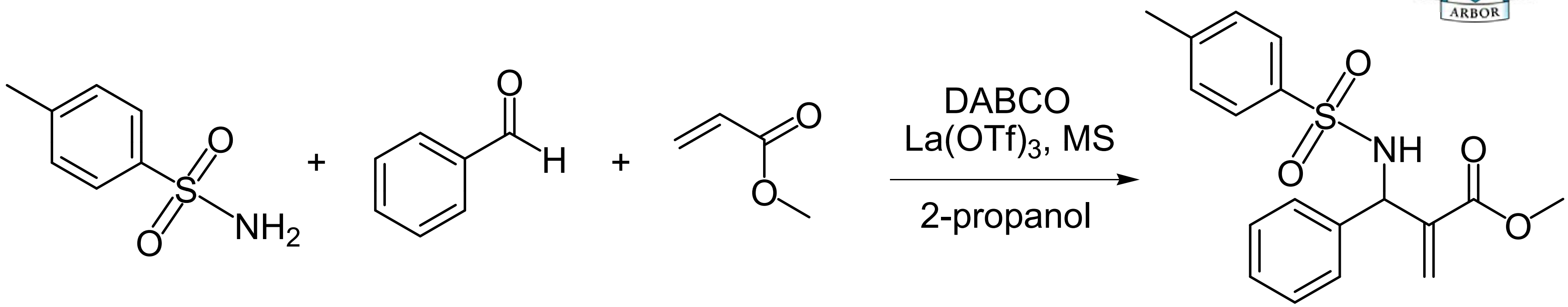
"What green chemistry and engineering related metrics does your company use? Select all that apply"

PMI = process mass intensity = (mass of raw materials)/(mass of final product)
E factor = (mass of waste)/(mass of final product)
LCA = life cycle assessment

Giraud, R. J. et al. *ACS Sustainable Chem. Eng.* **2014,** *2,* 2237

A “green” literature reaction?

aza-Baylis-Hillman:



- two catalysts & greener solvent option (alcohol)
- multi-component reaction: **atom economy = 95%**
- reaction yield = 80% **(reaction mass efficiency = 76%)**
- energy-efficient reaction conditions (stir at r.t.)

Balan, D. et al. *J. Org. Chem.* **2001**, *66*, 6498-6501

Student procedure (makes 1.0 g of product)

reaction:

In a 25-mL Erlenmeyer flask capped with a rubber septum, combine a magnetic stirring bar, *p*-toluenesulfonamide (855 mg, 5 mmol), DABCO (0.75 mmol), $La(OTf)_3 \cdot H_2O$ (0.1 mmol), molecular sieves (900 mg) and 2-propanol (2 mL). Add benzaldehyde (5 mmol) and finally methyl acrylate (5 mmol). Proceed to stir the reaction solution for 90 minutes. Afterwards, place the flask in your equipment locker until the second laboratory period.

workup:

During the second period, remove your reaction flask from your drawer. Remove the molecular sieves and any undissolved solid material by performing a gravity filtration, washing the filter paper twice with 5 mL of 2-propanol and collecting the filtrate in a 100 mL round-bottomed flask. Proceed to remove the solvent by placing the filtered solution under vacuum on a rotary evaporator. Add methanol (25 mL) and 1 M sulfuric acid (10 mL), and stir at room temperature for 60 min. Afterwards, remove the methanol under vacuum on a rotary evaporator **(NOT the sulfuric acid)**. Dilute the remaining acidic solution with 50 mL of water, transfer it to a 250 mL separatory funnel and extract with dichloromethane (3 × 30 mL). Wash the combined organic layers successively with 50 mL saturated aqueous $NaHCO_3$, 50 mL NaOH (1M) and finally 50 mL saturated aqueous NaCl. Dry the washed organic layer with $MgSO_4$ and gravity filter the solution into a pre-weighed 250-mL round-bottomed flask. Rinse the drying agent on the filter paper with a small amount of dichloromethane. Place the dried organic layer under vacuum on a rotary evaporator to remove the solvent. Weigh the liquid product and obtain an IR spectrum (neat) and ^1H NMR spectrum ($CDCl_3$ solvent). Submit the remaining product for inspection in a small vial.

"Student reaction mass inventory"

reaction:

Mass (g)	Substance
0.855	*p*-toluenesulfonamide
0.084	DABCO
0.059	$La(OTf)_3 \cdot H_2O$
0.527	benzaldehyde
0.43	methyl acrylate
9.4	isopropanol
10	aq. sulfuric acid

workup:

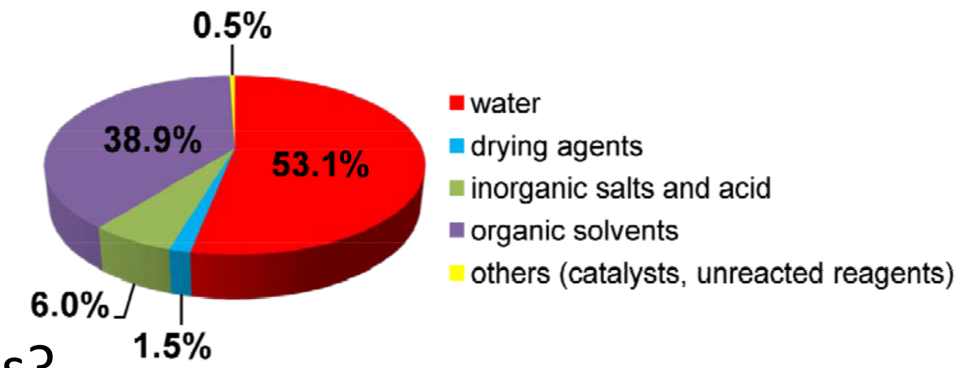
Mass (g)	Substance
50	aq. sodium hydroxide
50	aq. sodium bicarbonate
50	aq. sodium chloride
50	water
119.7	dichloromethane
19.8	methanol
TOTAL: 360.9 g	

the devil is in here!

this ignores masses of molecular sieves and $MgSO_4$ used for drying…

Student reflections: reducing the PMI (around 361!)

- ❑ use a recyclable extraction solvent (although may introduce an energy cost)…



- ❑ reduce aqueous washes
- ❑ recycling of aqueous washes?

NOT…

- ❑ recycling catalysts or other unreacted reaction components!

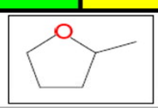
"Yield is everything" mentality: this does not encourage sustainability – don't forget the workup!

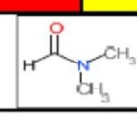
Gómez-Biagi et al. *J. Chem. Educ.* **2015**, *92*, **DOI:** 10.1021/acs.jchemed.5b00249

The nature of process substances used (1)

- industrial solvent and reagent selection guides have been published: aim to "rank greenness"

- Sanofi solvent guide sets up ID cards: overall ranking, H, S & E hazards, ICH limit, physical properties, cost, **substitution advice**

METHYL-THF 2-Methyl tetrahydrofurane			DANGER		
CAS : 96-47-9			SDS (SEDDA) : FR10910		
Recom-mended	ICH limit: n. a.	Guide 709-2 : n. a.	OEB V2	SHB 4	EHB 3
		C5H10O	Other constraints : peroxides, cost		
		MW: 86,13	BP: 79°C	MP: -137°C	FP: -11°C
Sol in water : 140 g/L		d : 0,854	Resistivity : dissipative		Cost : 18
Biodeg. : low		Sustain. : Hydrogenation or furfural			AIT = 270°C
Advice : the most advisable ether. Due to its cost, recycling is recommended.					

DIMETHYLFORMAMIDE DMF					
CAS : 68-12-2			SDS (SEDDA) : FR00185		
Substitution requested	ICH limit : 880 ppm	Guide 709-2 : list B	OEB V4G2 Sk CMR	SHB 2	EHB 1
		C3H7NO	Other constraints : CMR (R1B)		
		MW: 73,10	BP: 153°C	MP: - 61°C	FP: 58°C
Miscible with water		d : 0,944	Resistivity : dissipative		Cost : 3
Biodeg. : > 90%		Sustain. : synthesis from dimethylamine			
Advice : CMR solvent, use it only if there is no alternative such as acetontrile, ureas or sulfolane					

Prat, D. et al. *Org. Process Res. Dev.* **2013**, *17*, 1517

Prat, D. et al. *Green Chem.* **2014**, *16*, 4546 **(survey of different guides, 51 solvents)**

The nature of process substances used (2)

- reagent selection guides: examples from Pfizer, GlaxoSmithKline

- GSK approach: reagents scored for a particular reaction by H, S & E risks, atom economy, stoichiometry, workup, **LCA**

GSK Reagent Selection Guide – Alkene Reduction

Few Issues	Some Issues	Major Issues
H_2, Pd/C	HCO_2Na, Pd/C	Li, 4,4′-Di-*t*-butylbiphenyl
H_2, Ru/C	$NaBH_4$, Pd/C	Li, NH_3
H_2, $Pd(OH)_2$/C	HCO_2NH_4, Pd/C	H_2, Raney Ni
H_2, Pt/C	Li, *n*-Propylamine, Ethylenediamine	Cyclohexene, Pd/C
H_2, Rh/C	H_2, $Rh(PPh_3)_3Cl$	HI, Red phosphorus
H_2, Crabtree's catalyst	Et_3SiH, TFA	Hydrazine, *N*-Ethylriboflavin
H_2, PtO_2	Et_3SiH, Pd/C	
	HCO_2NEt_3H, Pd/C	
	Stabilized sodium	

Adams, J. P. et al. *Green Chem.* **2013**, *15*, 1542

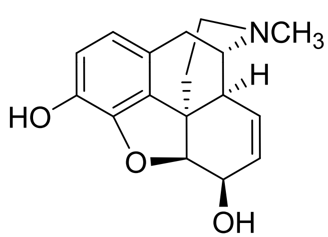
Henderson, R. K. et al. *Green Chem.* **2015**, *17*, 945 **(acid/base selection guide)**

Building these guides into a third-year assignment

worth 20% of final course grade

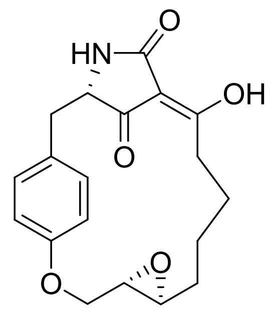
three molecules = three different assignments

pharmaceutical



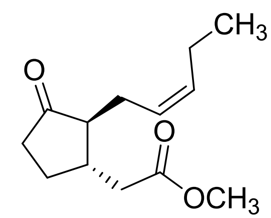
(+)-morphine

agrochemical



nor-macrocidin A

fragrance



(+)-methyl jasmonate

PART 1: introduction (6 marks)

PART 2: green solvent analysis (12 marks)

PART 3: green reagent analysis (20 marks)

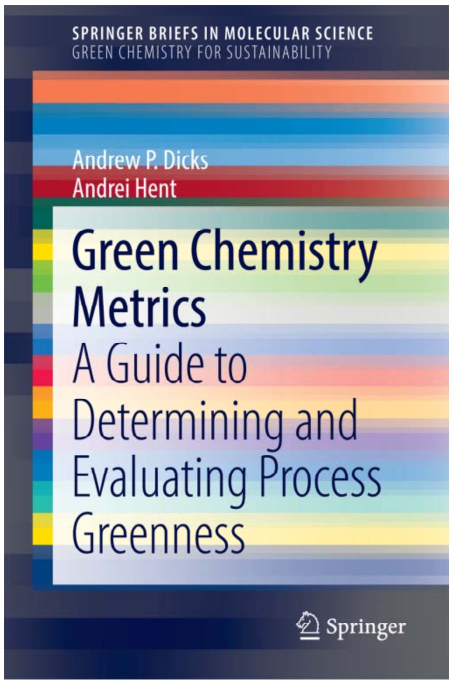
PART 4: green chemistry discussion question (12 marks): mechanism and green metrics

Summary

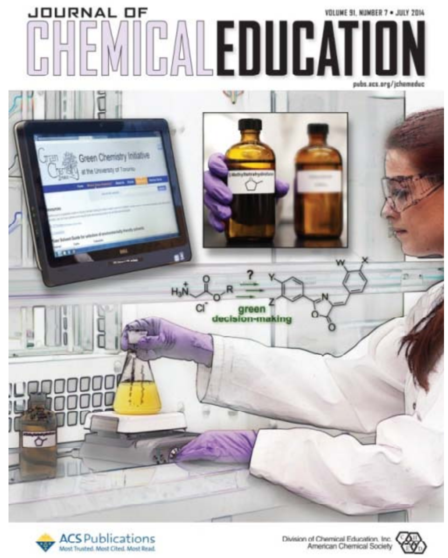
"…too many chemists are not counting chemicals…"

(importance of "green chemistry metrics")

Some (hopefully!) useful resources

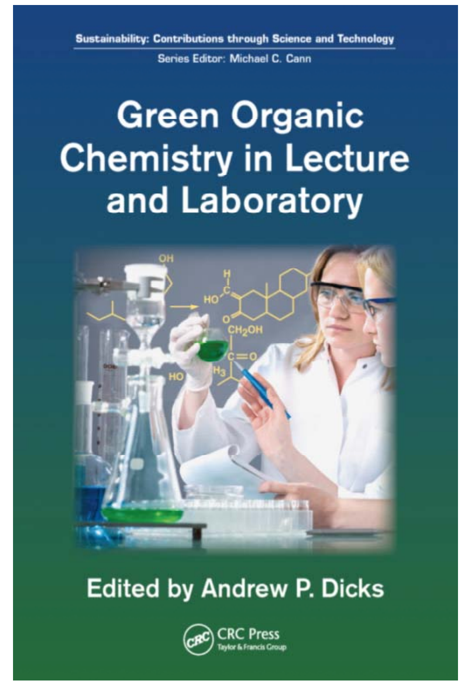


Springer, 2014
(Andrei Hent)



***JCE* cover, July 2014**

"Green chemistry decision-making in an upper-level undergraduate organic laboratory"



Taylor & Francis, 2012

Edgar, L. J. E. et al. *J. Chem. Educ.* **2014**, *91*, 1040