Green Chemistry:
Teaching & Research

Green Chemistry & Engineering Education
National Academies' Chemical Sciences Roundtable

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Washington, D.C.
United States of America

Teaching is the grindstone on which research skills are sharpened.

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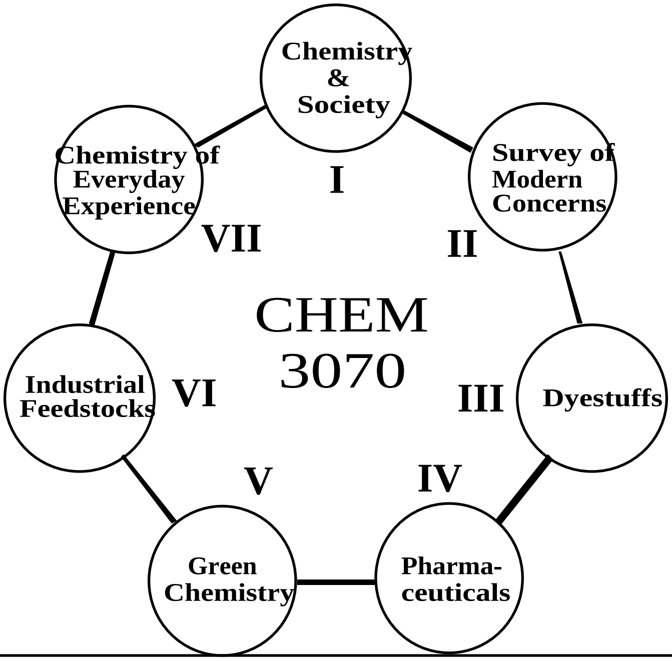
Outline:

Part I Green Chemistry at York (CHEM 3070)
- Course content, teaching strategies and resources
- Sample problems and exercises
- Student feedback

Part II Green Metrics Analysis
- RME master equation and visual depiction
- Synthesis tree analysis
- Material, energy, and cost optimization

CHEM 3070: Industrial and Applied Green Chemistry



CHEM 3070

- I Chemistry & Society
- II Survey of Modern Concerns
- III Dyestuffs
- IV Pharma-ceuticals
- V Green Chemistry
- VI Industrial Feedstocks
- VII Chemistry of Everyday Experience

Resources & Strategies

Resources

- Research journal articles
- Society news magazines
- Patent literature/databases
- Books
- Campus colloquia
- Course website

Strategies

- Inter-disciplinary problems based approach
- Decision making
- Quantitative reasoning and evaluation
- Encourage self-discovery and independent learning

Pre-requisites

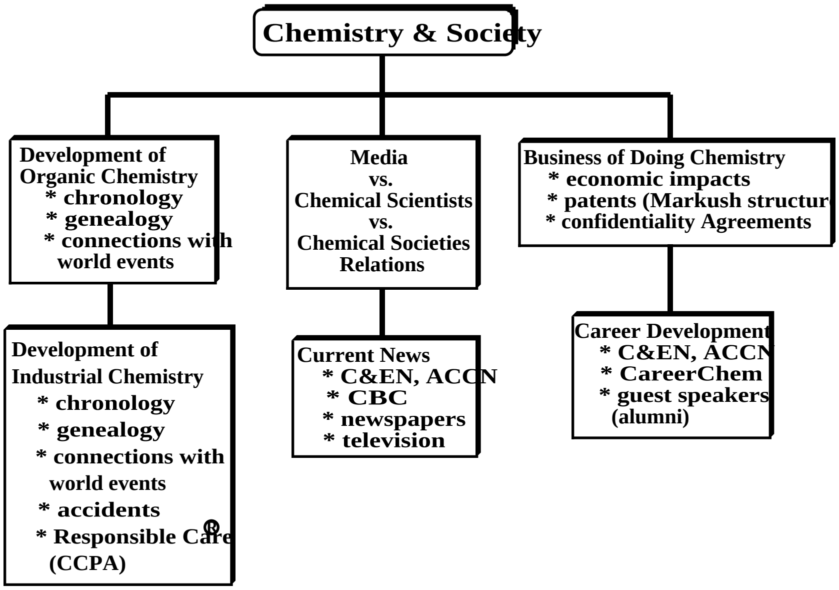
- 2nd year organic chemistry with minimum C grade + brush-up quiz
- Science library resource workshop and quiz

Evaluation

- Biweekly quizzes
- 4 Problem Sets
- 1 Written assignment + oral
- 1 Final Exam (5th problem set)

Written Assignment

- Journalistic style
- Choice of topic
- Rigorous critiquing of synthesis or manufacture of target product or process according to “green” criteria



Chemistry & Society

Development of Organic Chemistry
- chronology
- genealogy
- connections with world events

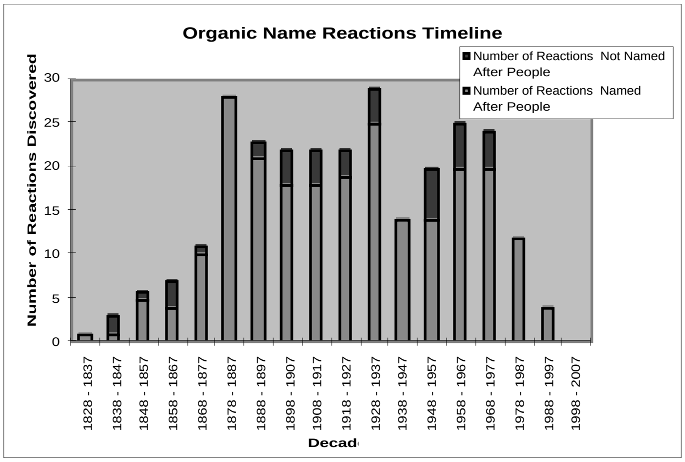
Development of Industrial Chemistry
- chronology
- genealogy
- connections with world events
- accidents
- Responsible Care® (CCPA)

Media vs. Chemical Scientists vs. Chemical Societies Relations

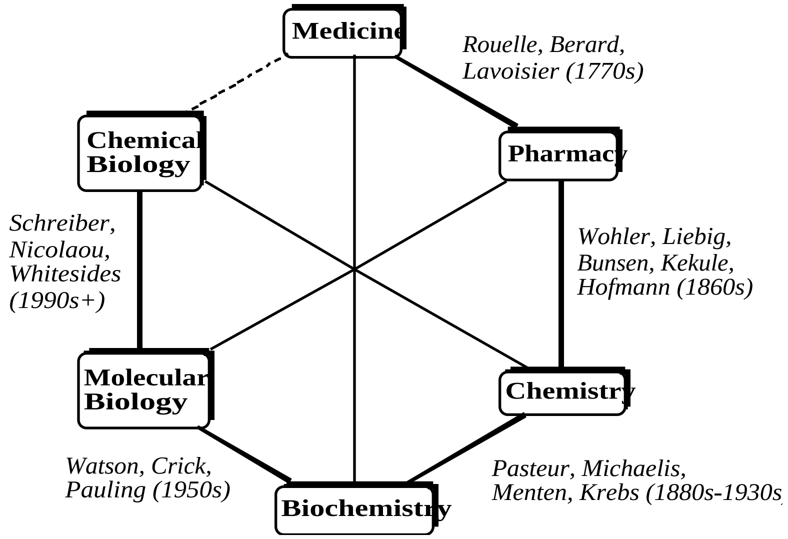
Current News
- C&EN, ACCN
- CBC
- newspapers
- television

Business of Doing Chemistry
- economic impacts
- patents (Markush structur
- confidentiality Agreements

Career Development
- C&EN, ACCN
- CareerChem
- guest speakers (alumni)



Evolution of Chemistry



Medicine

Rouelle, Berard, Lavoisier (1770s)

Pharmacy

Wohler, Liebig, Bunsen, Kekule, Hofmann (1860s)

Chemistry

Pasteur, Michaelis, Menten, Krebs (1880s-1930s

Biochemistry

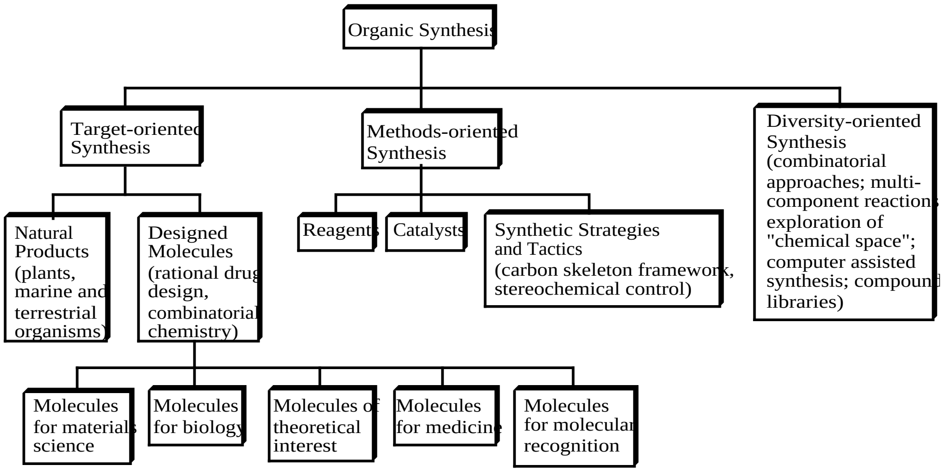
Watson, Crick, Pauling (1950s)

Molecular Biology

Schreiber, Nicolaou, Whitesides (1990s+)

Chemical Biology

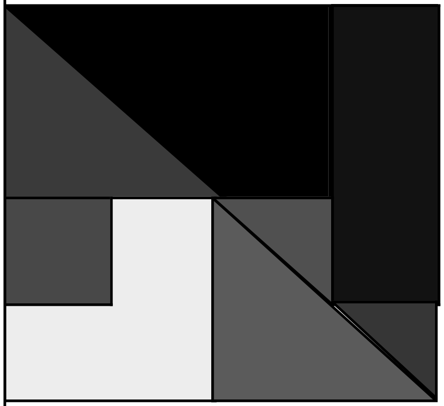
Evolution of Paradigms in Organic Synthesis



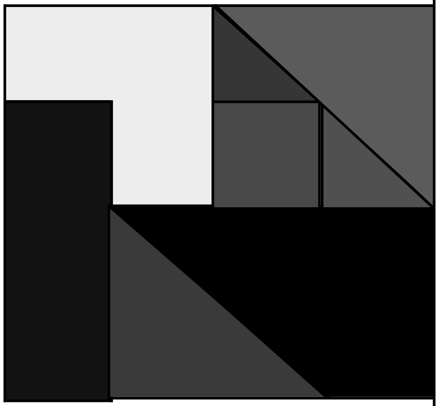
Organic Synthesis

- Target-oriented Synthesis
  - Natural Products (plants, marine and terrestrial organisms)
  - Designed Molecules (rational drug design, combinatorial chemistry)
    - Molecules for materials science
    - Molecules for biology
    - Molecules of theoretical interest
    - Molecules for medicine
    - Molecules for molecular recognition
- Methods-oriented Synthesis
  - Reagents
  - Catalysts
  - Synthetic Strategies and Tactics (carbon skeleton framework, stereochemical control)
- Diversity-oriented Synthesis (combinatorial approaches; multi-component reactions; exploration of "chemical space"; computer assisted synthesis; compound libraries)

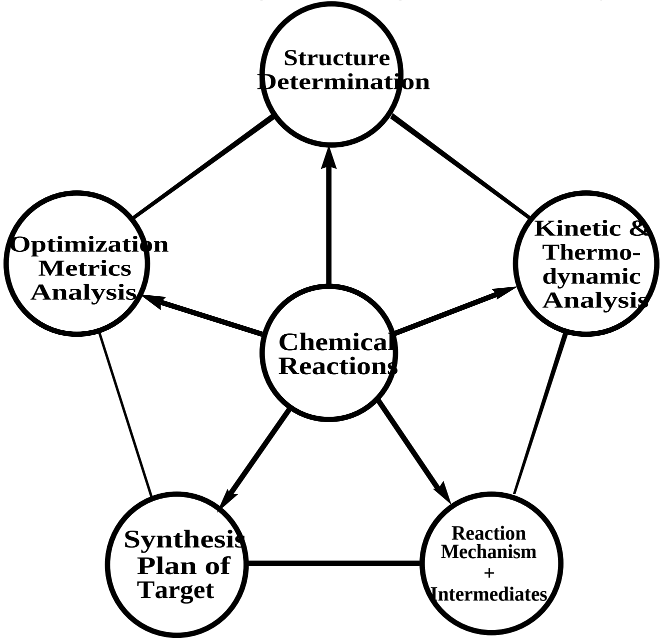
Synthesis Plan #1



Synthesis Plan #2



Concept Paradigms in (Organic) Chemistry



Structure Determination

Optimization Metrics Analysis

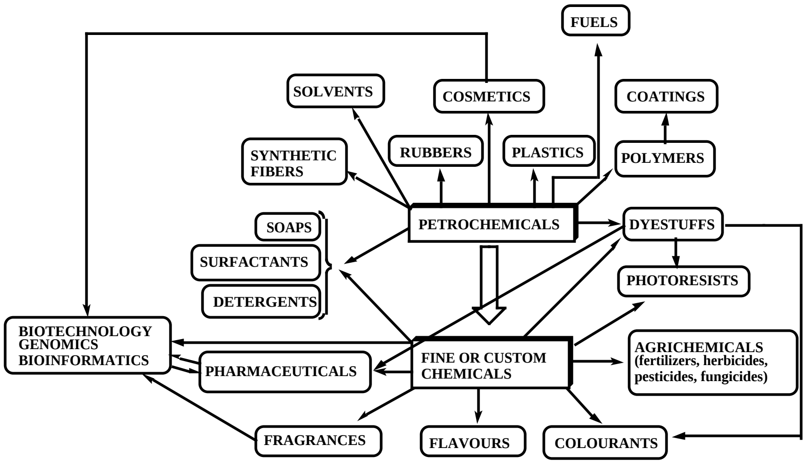
Kinetic & Thermo- dynamic Analysis

Chemical Reactions

Synthesis Plan of Target

Reaction Mechanism + Intermediates

Interconnections Between Chemical Industry Sectors



FUELS

SOLVENTS

COSMETICS

COATINGS

SYNTHETIC FIBERS

RUBBERS

PLASTICS

POLYMERS

SOAPS

SURFACTANTS

DETERGENTS

PETROCHEMICALS

DYESTUFFS

PHOTORESISTS

BIOTECHNOLOGY
GENOMICS
BIOINFORMATICS

PHARMACEUTICALS

FINE OR CUSTOM CHEMICALS

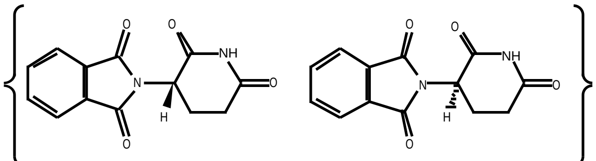
AGRICHEMICALS (fertilizers, herbicides, pesticides, fungicides)

FRAGRANCES

FLAVOURS

COLOURANTS

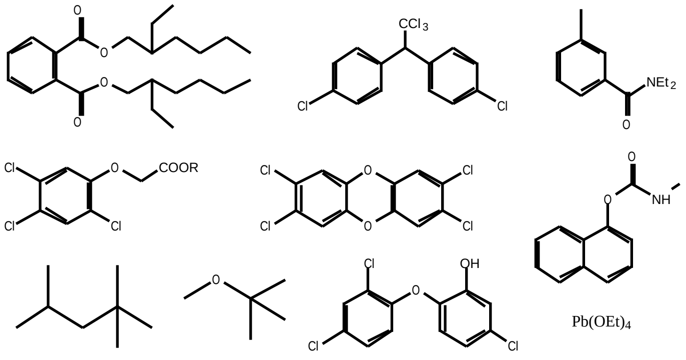
Survey of Modern Concerns



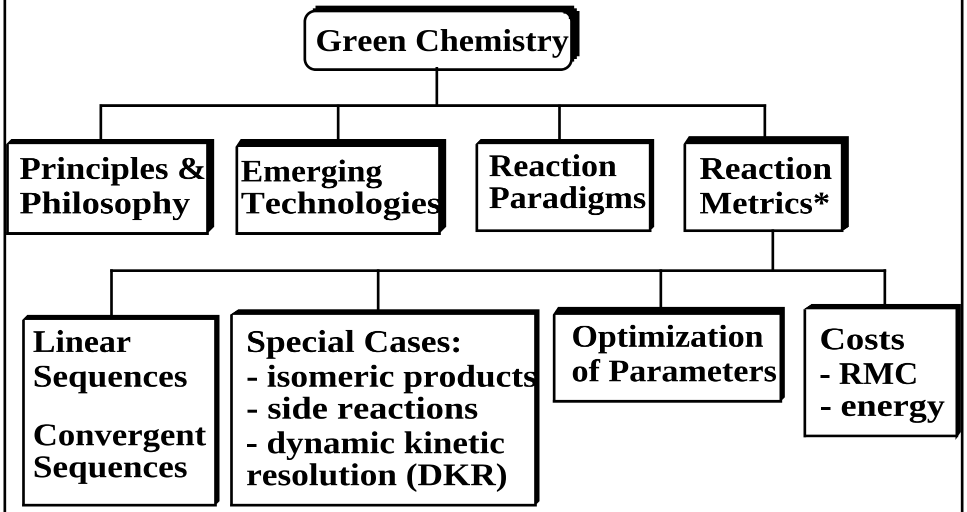
(S)-thalidomide (R)-thalidomide

chirality

chemical
function
property



$Pb(OEt)_4$



Green Chemistry

Principles & Philosophy

Emerging Technologies

Reaction Paradigms

Reaction Metrics*

Linear Sequences

Convergent Sequences

Special Cases:
- isomeric products
- side reactions
- dynamic kinetic resolution (DKR)

Optimization of Parameters

Costs
- RMC
- energy

Green Chemistry

Founded Green Chemistry Institute
http://www.chemistry.org/greenchemistryinstitute/

Joseph Breen Green Chemistry Awards
http://www.chemistry.org/greenchemistryinstitute/awards.html#breen

Green Chemistry Network (Canada)
http://www.greenchemistry.ca

12 Principles of Green Chemistry
(Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998

1. **Prevention**
2. **Atom economy**
3. **Less hazardous chemical syntheses**
4. **Designing safer chemicals**
5. **Safer solvents and auxiliaries**
6. **Design for energy efficiency**
7. **Use of renewable feedstocks**
8. **Reduce derivatives**
9. **Catalysis**
10. **Design for degradation**
11. **Real-time analysis for pollution prevention**
12. **Inherently safer chemistry for accident prevention**

Green Chemistry Paradigms

REACTION MEDIUM

- **Ionic Liquids**
- **Water**
- **Supercritical CO_2**
- **Solvent Free (solid supports)**

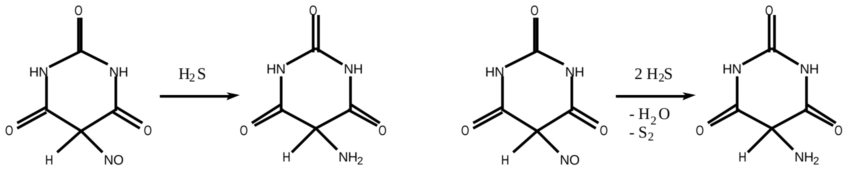
REACTION METHOD OR STRATEGY

- **Ultrasound (Sonochemistry)**
- **Microwave Irradiatio**
- **Grindstone chemistry**
- **Biocatalysis using Enzymes**
- **Organic Synthesis by Multi-component Approach**
- **Microstructured reactors**
- **Renewable feedstocks as starting materials**

Evolution of Depiction of Organic Reactions

Baeyer, A. *Ann. Chem.* **1863**, 127, 199

$$N_3C_4O_4H_3 + 2\,H_2S = N_2C_4O_3H_3(NH_2) + H_2O + S_2$$



Old Paradigm

- Balanced chemical equations
- Functional group identification tests
- Structure determination by melting point derivatives, index of refraction, degradation to known compounds
- Purification by distillation, recrystallization

Modern Paradigm

- Juxtaposition of substrate and product structures only in chemical equations
- Structure determination by spectroscopic methods, total synthesis
- Purification by chromatographic methods

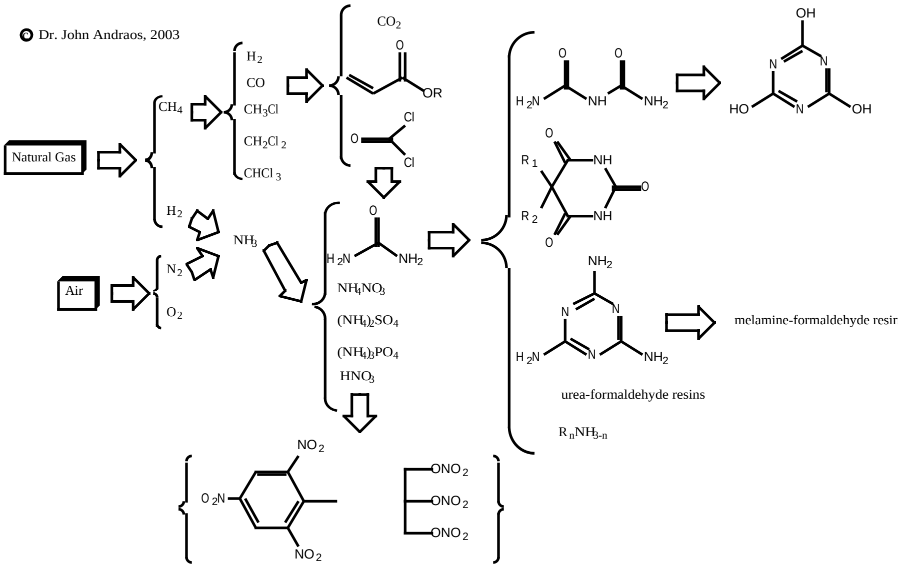
Evaluation of a Chemical Reaction

Economic feasibility based on raw material costs and availability
Technical feasibility based on energy demands
Potential for unwanted side, runaway, and hazardous reactions
Environmental impact of all materials used
Quantification of reaction metrics:

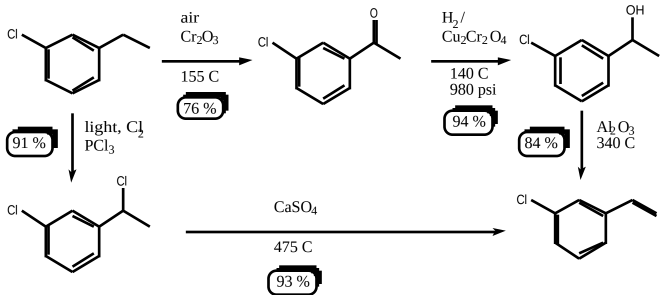
- % conversion of substrate to product
- % yield of product based on conversion of limiting reagent
- atom economy (Trost AE)
- reaction mass efficiency (RME)
- environmental impact factor (Sheldon E)
- stoichiometric factor (SF)
- process energy metric
- solvent recovery metric

Toxicity parameters for all materials used (LD50)

Industrial Feedstock Trees


© Dr. John Andraos, 2003

Sample Problem #1



Two industrial routes to *m*-chlorostyrene from *m*-chloroethylbenzene are shown.

(a) Account for all byproducts and identify catalysts in each step.

(b) For each route write out a set of balanced chemical equations for the transformations.

(c) For each route determine the overall yield, overall RME, and overall mass of waste per kg of *m*-chlorostyrene product. Assume each step in both routes is run under stoichiometric conditions.

(d) Determine the raw material costs (RMC) to produce 1 kg of *m*-chlorostyrene from each route using the market values for various starting materials given in the table below.

(e) Identify byproducts that may pose toxicity concerns and those that pose hazards upon scale-up.

(f) Identify recycling potential of waste products.

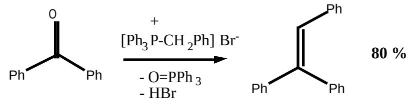
(g) Identify processes that may pose equipment corrosion problems.

(h) Identify reactions that are energy demanding (high temperature / high pressure).

Taking all factors together decide which route is better economically and environmentally.

Sample Problem #2

The Wittig reaction produces triphenylphosphine oxide as a waste byproduct.



Given the three recycling reactions shown below that convert O=PPh$_3$ back to PPh$_3$, assess which option is best according to the combined RME values for the Wittig and recycling reactions.

(1) $O{=}PPh_3 + H_2O + HSiCl_3 \longrightarrow PPh_3 + 3\,HCl + SiO_2$ **90 %**

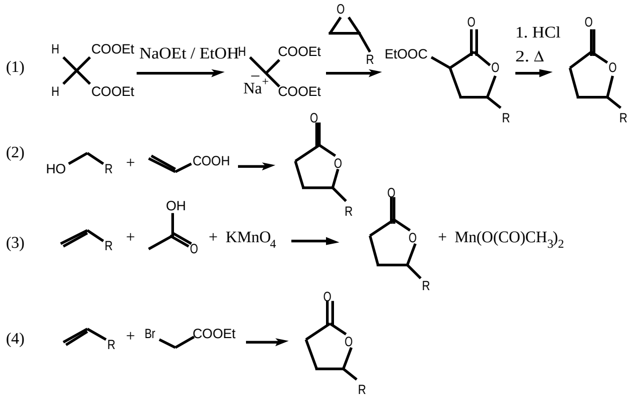
(2) $O{=}PPh_3 + O{=}CCl_2 + 2/3\,Al \longrightarrow PPh_3 + 2/3\,AlCl_3 + CO_2$ **90 %**

(3) $O{=}PPh_3 + HCl + 1/4\,Ti(i\text{-}OPr)_4 \longrightarrow PPh_3 + H_2O + O{=}C(CH_3)_2 + 1/4\,TiCl_4$ **90 %**

Sample Problem #3

Four different routes to a generalized γ-lactone are given. For each route provide an overall balanced chemical equation and determine values for AE(min) and E(max). If the RME for each route is to be above a threshold value of $\alpha = 0.5$ determine the range of permissible reaction yield values when AE = AE(min) and the probability of achieving such a threshold in each case.

Note for multi-step sequences assume the reaction yield refers to the combined steps.



Student Feedback & Comments

"This course promotes thinking on real-live practical chemical problems rather than mindlessly memorizing facts and spilling the beans on an exam. Biweekly quizzes kept us on the ball."

"I enjoyed the course because the instructor allowed his students to experience the material with a positive feeling even though the industry is quite negative at times."

"I liked that we were introduced to the chemical literature."

"The course gives a good sense of the type of work you'll be involved in as a chemist."

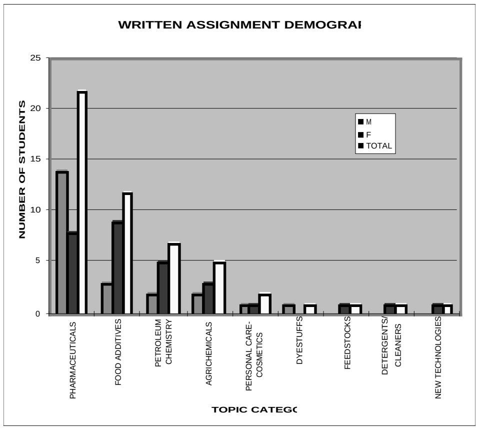
"I liked reading material about current issues in chemistry. This is the only way students can make the transition from school to work."

"I had a better appreciation of chemistry after learning about how the subject evolved."

"I was motivated to learn chemistry by this course. I liked the exercise of coming up with as many synthetic routes as possible to a given compound. My negative feelings about the subject disappeared!"

"This course provided a good insight of the "real world" of chemistry. It introduced a number of topics that are important to chemistry but never mentioned in other courses. We were introduced to chemical industries and what they are all about. The instructor encouraged us to attend public lectures to get a better sense of the chemistry that is evolving. He got back to us the very next lecture and answered any questions that he was unable to answer in the last lecture. I learned more about organic chemistry in this class than from previous chemistry courses. I also learned a lot more about the chemical industry."

Student Interests



Part II

Green Metrics Analysis

RME master equation and visual depiction
Synthesis tree analysis
Material, energy, and cost optimization

Reaction Mass Efficiency Master Equation

Andraos, J. *Org. Proc. Res. Develop.* **2005**, *9*, 149; 404

$$RME = (\varepsilon)(AE)\left(\frac{1}{SF}\right)(MRP) = (\varepsilon)(AE)\left(\frac{1}{SF}\right)\left(\frac{1}{1+\frac{\varepsilon(AE)[c+s+\omega]}{(SF)(m_P)}}\right)$$

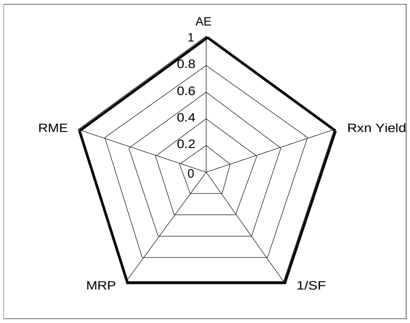
Parameters:

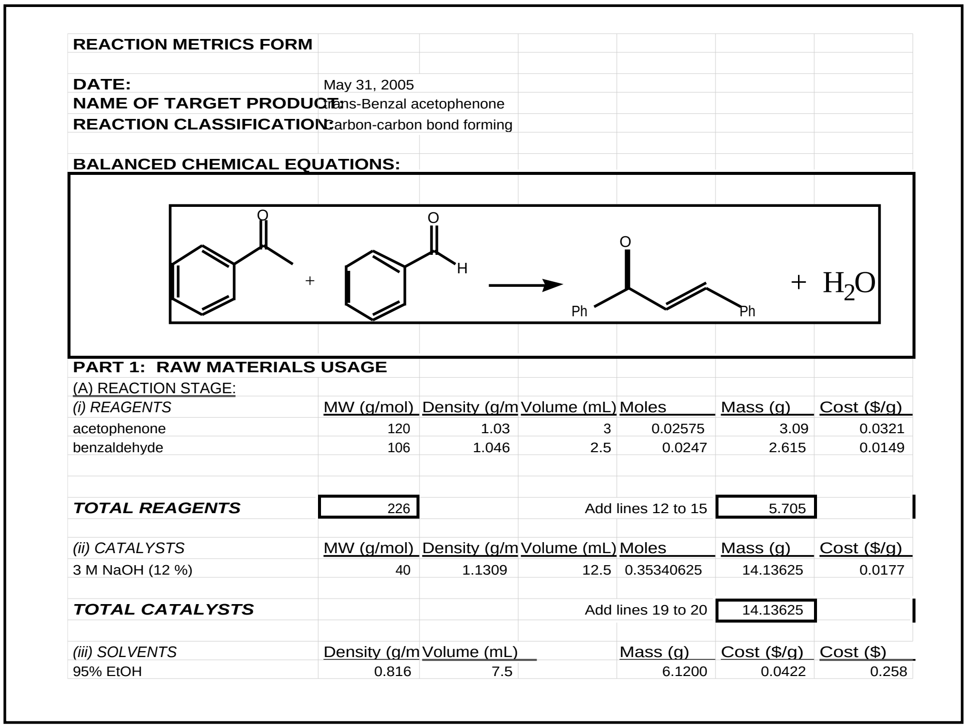
ε	reaction yield
AE	atom economy
SF	stoichiometric factor; SF =1 implies no excess reagents SF > 1 implies excess reagents used
MRP	materials recovery parameter

Recall: Lavoisier's law of conservation of mass for balanced chemical reaction/equation.

The Pentagon

The "Green" Pentagon





REACTION METRICS FORM

DATE: May 31, 2005
NAME OF TARGET PRODUCT: trans-Benzal acetophenone
REACTION CLASSIFICATION: Carbon-carbon bond forming

BALANCED CHEMICAL EQUATIONS:

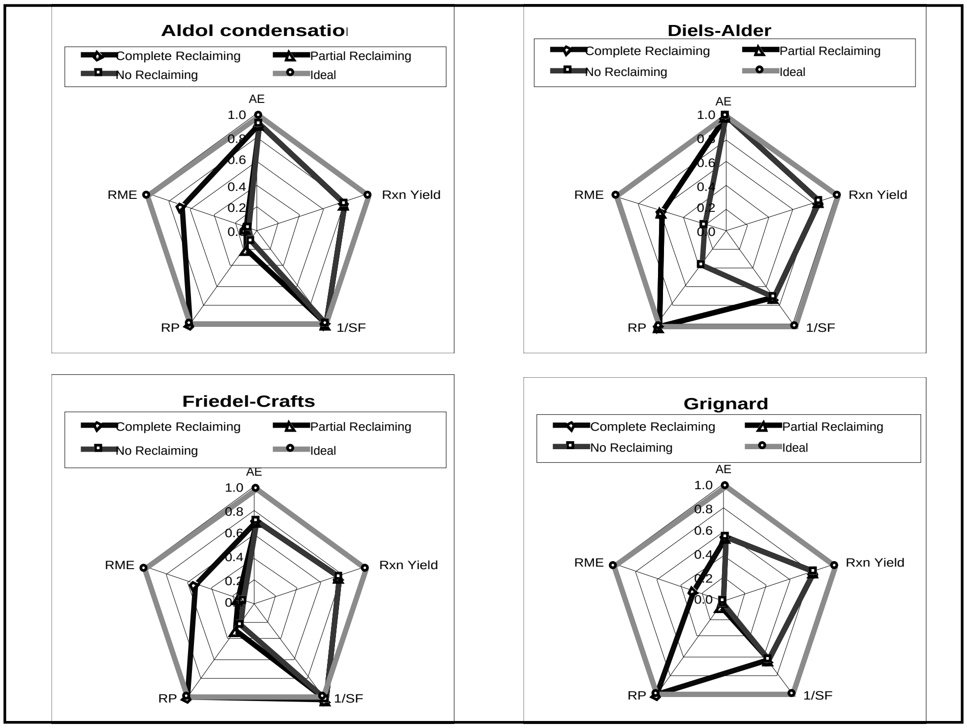
PART 1: RAW MATERIALS USAGE

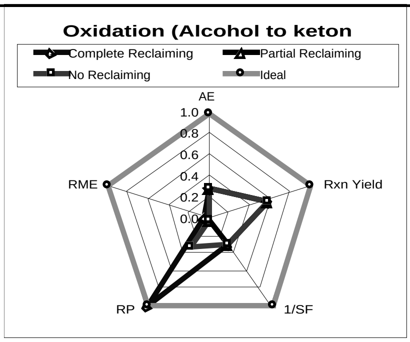
(A) REACTION STAGE:

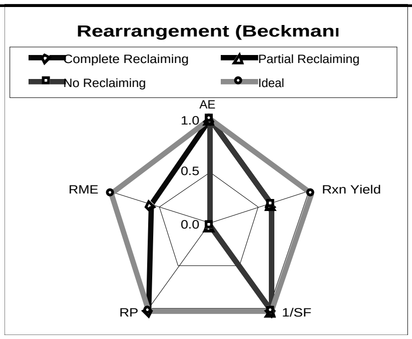
(i) REAGENTS	MW (g/mol)	Density (g/m	Volume (mL)	Moles	Mass (g)	Cost ($/g)
acetophenone	120	1.03	3	0.02575	3.09	0.0321
benzaldehyde	106	1.046	2.5	0.0247	2.615	0.0149
TOTAL REAGENTS	226			Add lines 12 to 15	5.705	

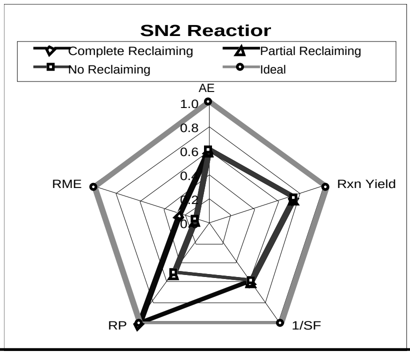
(ii) CATALYSTS	MW (g/mol)	Density (g/m	Volume (mL)	Moles	Mass (g)	Cost ($/g)
3 M NaOH (12 %)	40	1.1309	12.5	0.35340625	14.13625	0.0177
TOTAL CATALYSTS				Add lines 19 to 20	14.13625	

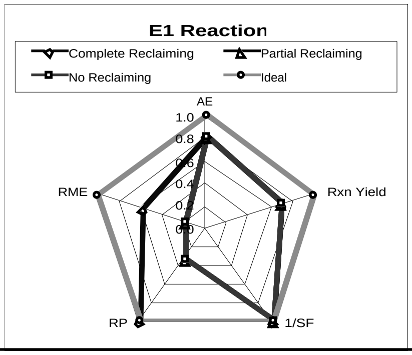
(iii) SOLVENTS	Density (g/m	Volume (mL)		Mass (g)	Cost ($/g)	Cost ($)
95% EtOH	0.816	7.5		6.1200	0.0422	0.258







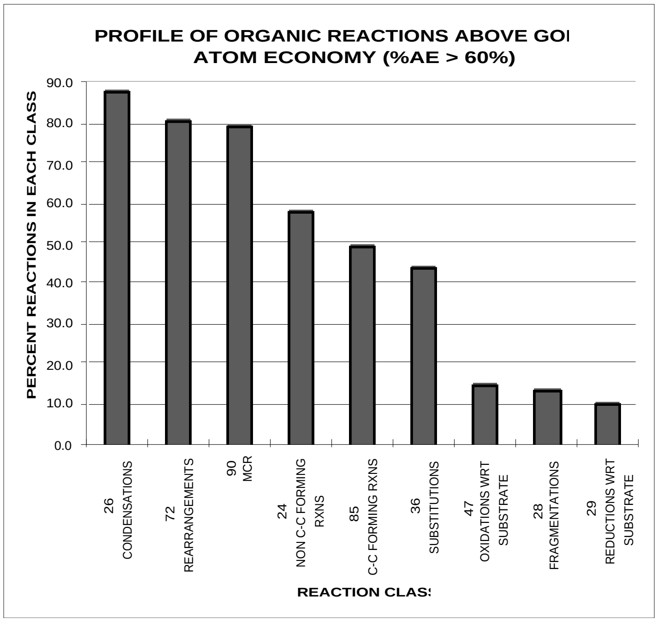


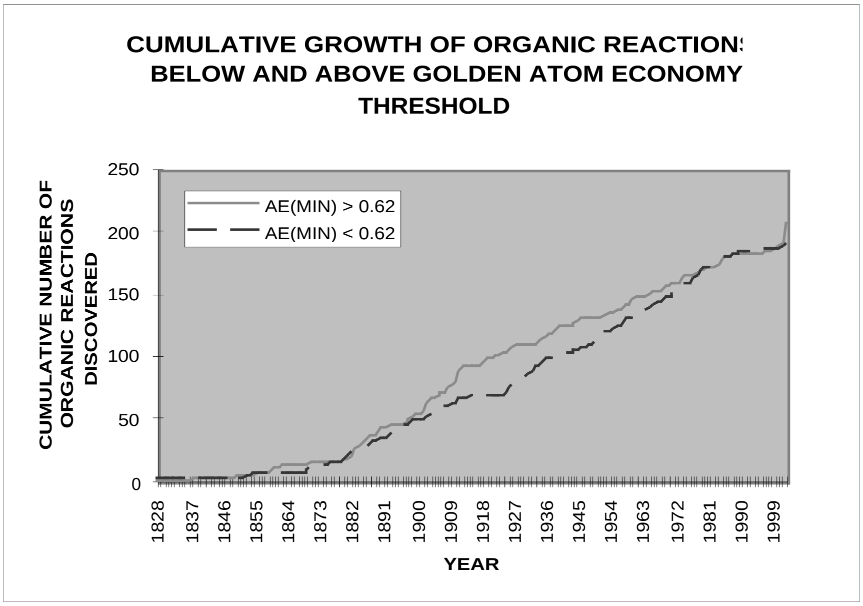


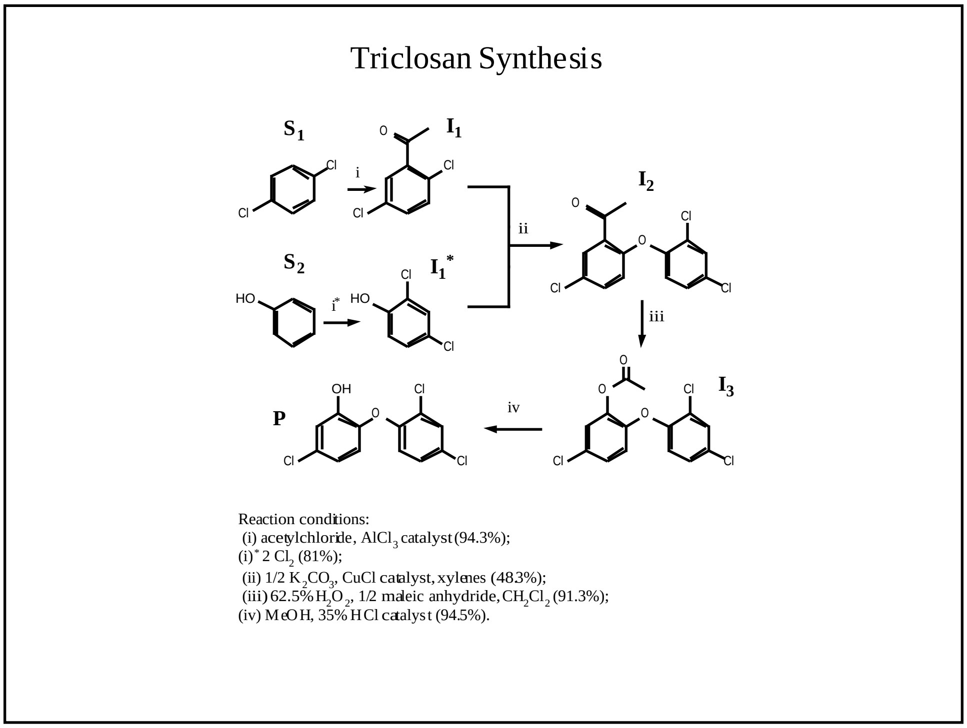
Atom Economy/Reaction Mass Efficiency - E-factor Connecting Relationships

$$AE = \frac{1}{1 + E_{mw}} \qquad RME = \frac{1}{1 + E_m}$$

Criteria for “green” reactions:
(1) AE $\geq$ 61.8 % so that AE > E_{mw}
(2) RME $\geq$ 61.8 % so that RME > E_m
(3) Reaction solvents and all post-reaction materials used in work-up and purification stages **must** be reclaimed and/or eliminated.

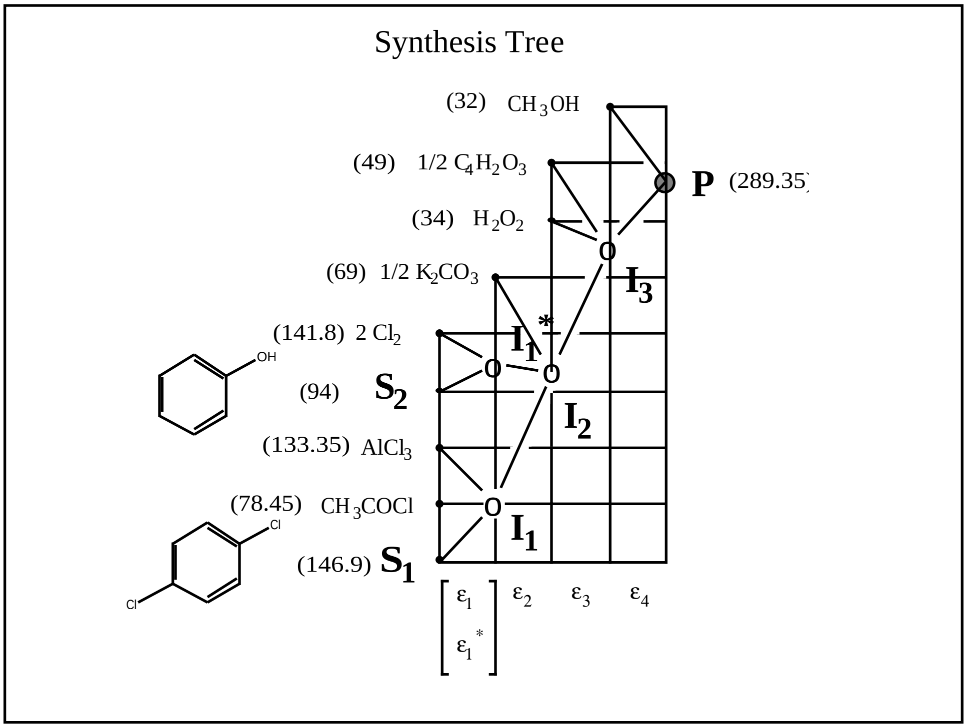

PROFILE OF ORGANIC REACTIONS ABOVE GOI
ATOM ECONOMY (%AE > 60%)
PERCENT REACTIONS IN EACH CLASS
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
26 CONDENSATIONS
72 REARRANGEMENTS
90 MCR
24 NON C-C FORMING RXNS
85 C-C FORMING RXNS
36 SUBSTITUTIONS
47 OXIDATIONS WRT SUBSTRATE
28 FRAGMENTATIONS
29 REDUCTIONS WRT SUBSTRATE
REACTION CLAS


CUMULATIVE GROWTH OF ORGANIC REACTION
BELOW AND ABOVE GOLDEN ATOM ECONOMY
THRESHOLD
CUMULATIVE NUMBER OF ORGANIC REACTIONS DISCOVERED
250
200
150
100
50
0
AE(MIN) > 0.62
AE(MIN) < 0.62
1828
1837
1846
1855
1864
1873
1882
1891
1900
1909
1918
1927
1936
1945
1954
1963
1972
1981
1990
1999
YEAR



Triclosan Synthesis

Reaction conditions:
(i) acetylchloride, $AlCl_3$ catalyst (94.3%);
(i)* 2 Cl_2 (81%);
(ii) 1/2 K_2CO_3, CuCl catalyst, xylenes (48.3%);
(iii) 62.5% H_2O_2, 1/2 maleic anhydride, CH_2Cl_2 (91.3%);
(iv) MeOH, 35% HCl catalyst (94.5%).



Synthesis Tree

Kernel RME function

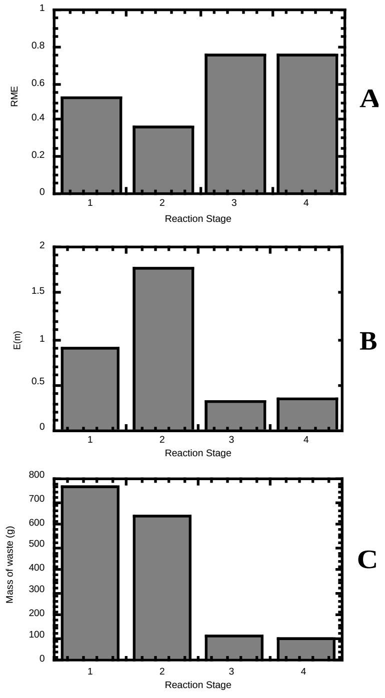
$$RME = \frac{289.35\,x}{S}$$

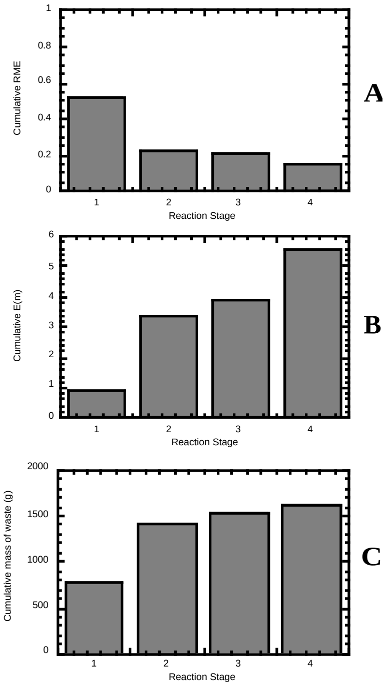
$$S = x\left[\frac{32}{\varepsilon_4} + \frac{49+34}{\varepsilon_3\varepsilon_4} + \frac{69}{\varepsilon_2\varepsilon_3\varepsilon_4} + \frac{133.35+78.45+146.9}{\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4} + \frac{94+141.8}{\varepsilon_1^*\varepsilon_2\varepsilon_3\varepsilon_4}\right]$$

$$= x\left[\frac{32}{\varepsilon_4} + \frac{83}{\varepsilon_3\varepsilon_4} + \frac{69}{\varepsilon_2\varepsilon_3\varepsilon_4} + \frac{358.7}{\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4} + \frac{235.8}{\varepsilon_1^*\varepsilon_2\varepsilon_3\varepsilon_4}\right]$$

RME = 0.1517 (about 15 %), $E_m = 5.59$

AE = 0.3717 (about 37 %), $E_{mw} = 1.69$



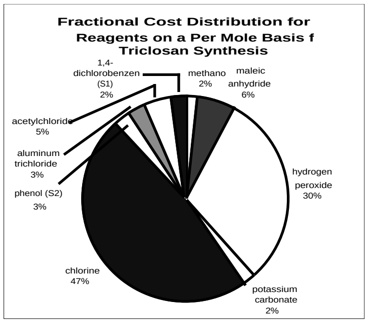


Kernel RMC function

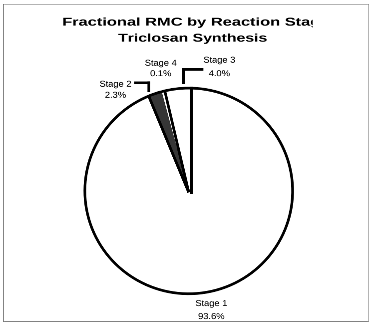
$$RMC = x\left[\frac{32\$_{MeOH}}{\varepsilon_4} + \frac{49\$_{MA} + 34\$_{H_2O_2}}{\varepsilon_3\varepsilon_4} + \frac{69\$_{K_2CO_3}}{\varepsilon_2\varepsilon_3\varepsilon_4} + \frac{141.8\$_{Cl_2} + 94\$_{PhOH}}{\varepsilon_1{}^{*}\varepsilon_2\varepsilon_3\varepsilon_4} + \right.$$

$$\left. + \frac{133.35\$_{AlCl_3} + 78.45\$_{AC} + 146.9\$_{1,4-DCB}}{\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4}\right]$$

RMC = \$ 333.61 per mole = \$1.15 per gram

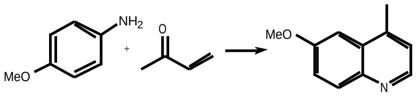


A



B

6-Methoxylepidine Synthesis



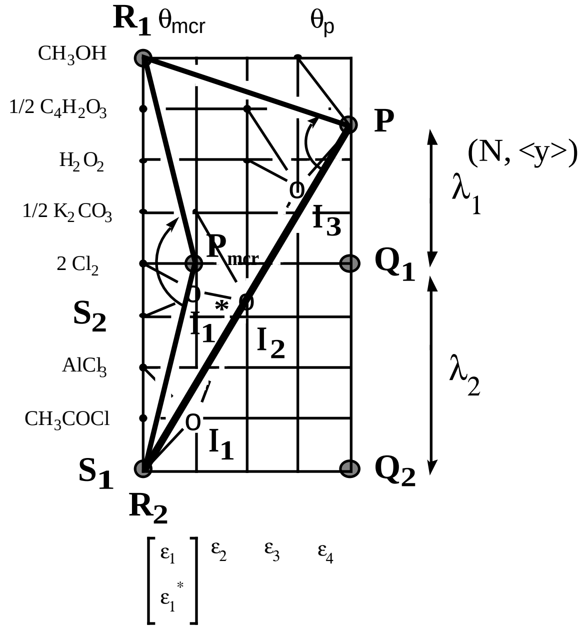
	Method	**Yield (%)**	**Atom Economy (%)**	**Kernel RME (%)**	**Kernel RMC ($/gram)**
A	$FeCl_3$, $ZnCl_2$	52	46	24	0.62
B	$InCl_3$ microwaves	83	42	35	8.22

A: *J.Am.Chem.Soc.* **1945**, 67, 86
B: *Tetrahedron Lett*. **2003**, 59, 813

For method B to be cost competitive with method A, price of metal halide must not exceed $ 55 per mole.

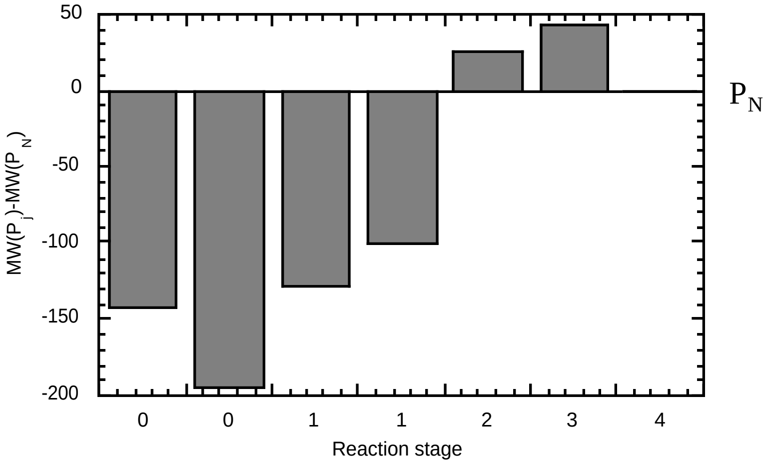
$FeCl_3$	**$ 21**
$ZnCl_2$	**$ 12**
$InCl_3$	**$ 1147**

Synthesis Tree Parameters



P (4, 6.781)
N = 4
M = 5
I = 9
$\delta = 0.503$
$\beta = 0.695$
$\rho_{rel} = 1.70$

μ_1 = - 99.54 g/mol/reaction stage



Fractions of Total Energy Input

$$\Phi_{product} = FTE = \frac{\sum_{j}^{M} (RME)_j \Psi_j}{\sum_{j}^{M} \Psi_j}$$

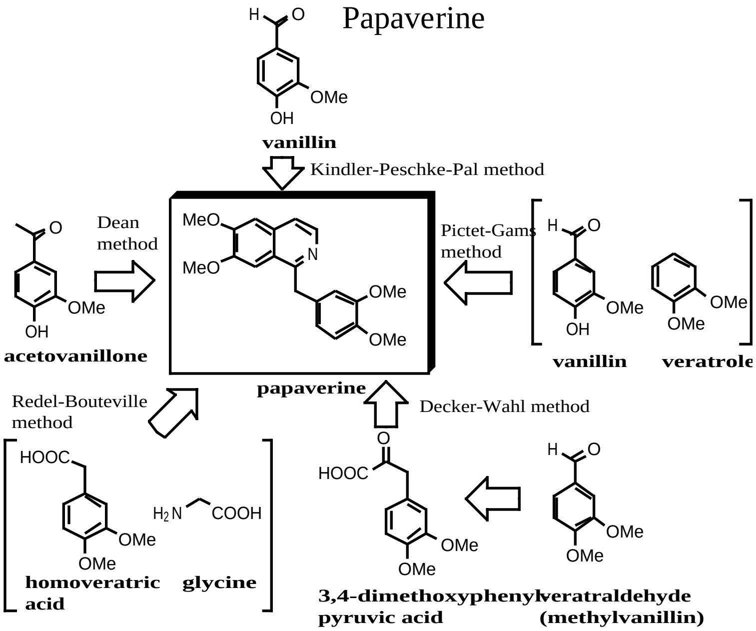
$$\Phi_{waste} = \frac{\sum_{j}^{M} \left[1 - (RME)_j\right] \Psi_j}{\sum_{j}^{M} \Psi_j}$$

Ψ_j = energy input for jth reaction

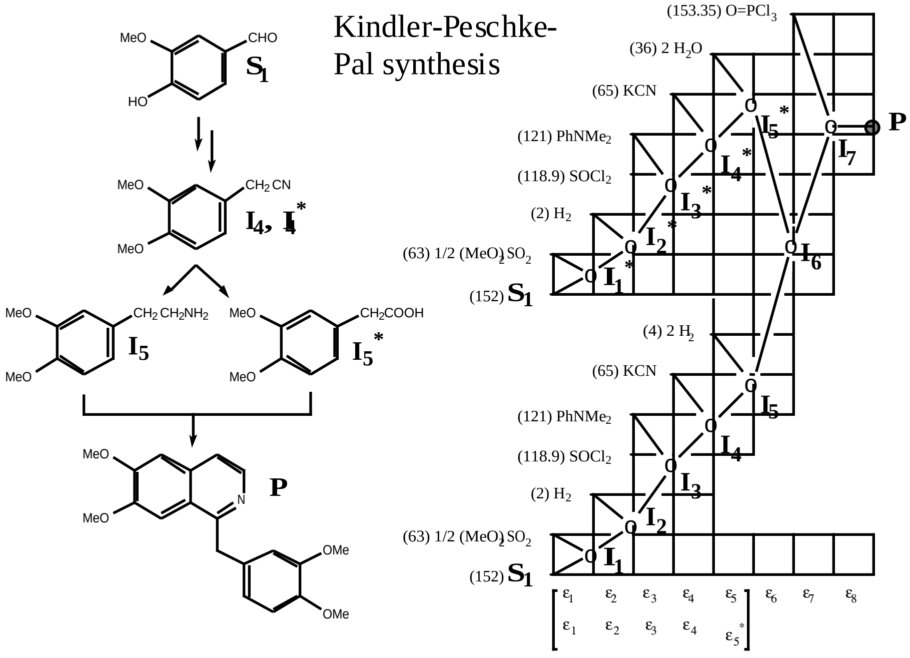
M = number of reactions

$(RME)_j$ = reaction mass efficiency for jth reaction

Papaverine

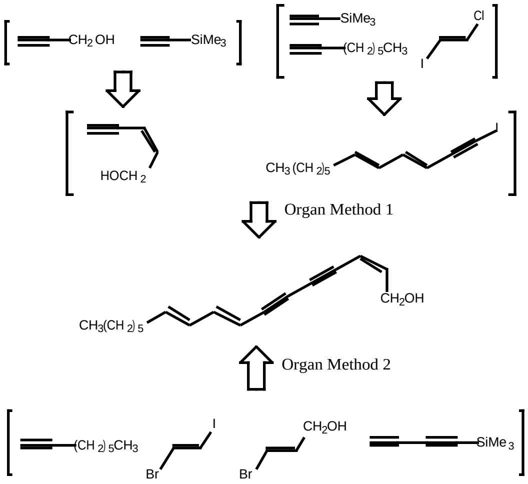


Kindler-Peschke-Pal synthesis

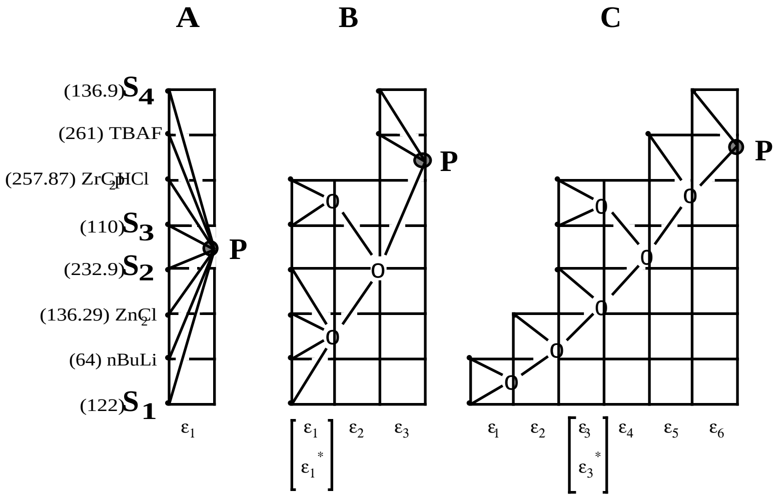


	Pictet Gams	**Decker Wahl**	**Redel Bouteville**	**Kindler Peschke Pal**	**Dean**
Kernel Reaction Metrics					
AE (%)	13.6	19.7	**31.7**	27.4	19.9
E_{mw}	6.37	4.03	2.15	2.65	4.03
RME (%)	0.52	2.8	4.0	**15.1**	8.0
E_m	191.12	35.37	23.75	5.63	11.57
$\varepsilon_{pseudo-overall}$ (%) ($\varepsilon_{overall}$)	3.8	13.8 (10.6)	12.7 (7.6)	**55.0**	40.0
Number of reaction inputs, *I*	18	20 (13)	**11**	15	12 (8)
Number of reaction steps, *M*	11	12 (9)	**8**	13	10 (8)
Number of reaction stages, *N*	8	9 (9)	8	8	8 (8)
μ_1 (g per mole per reaction stage)	- 163.57	- 83.10 (+ 86.40)	- 54.06	**– 218.9**	-151.56 (-151.56)
RMC^a ($ CAD per gram)	29.04	4.72	8.17	**0.45**	22.05
Tree Parameters					
Degree of convergence, δ	0.443	0.425 (0.360)	0.359	**0.450**	0.392 (0.308)
Relative rate of convergence, ρ_{rel}	**0.227**	0.207 (0.199)	0.218	0.200	0.204 (0.186)
Asymmetry, β	0.813	0.861 (0.791)	0.746	**0.604**	0.630 (0.490)

Bupleurynol Synthesis

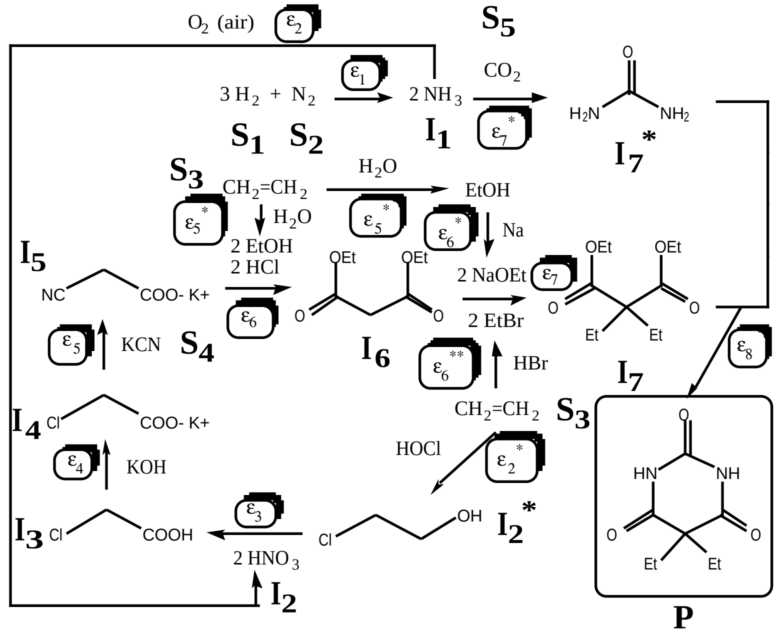


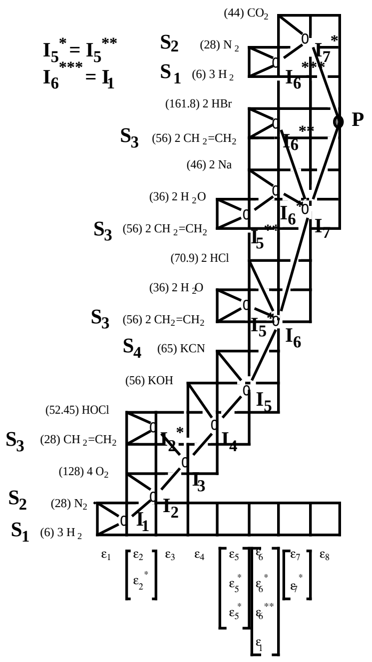
Organ, M.G. *et al.* Org. Lett. **2004**, *6*, 2913



A	B	C
$\delta = 1$	$\delta = 0.59$	$\delta = 0.37$
$\beta = 0$	$\beta = 0.57$	$\beta = 0.67$
$\rho_{rel} = 1$	$\rho_{rel} = 0.52$	$\rho_{rel} = 0.28$

Veronal





$N = 8$

$M = 15$

$I = 14$

$\delta = 0.530$

$\beta = 0.591$

$\rho_{rel} = 0.199$

$\mu_1 = -286$

$$(RME)_{overall} = \frac{184}{S}$$

$$S = \frac{44}{\varepsilon_7^{*}\varepsilon_8} + (28+6)\left(\frac{1}{\varepsilon_1\varepsilon_7^{*}\varepsilon_8} + \frac{3/2}{\varepsilon_1\varepsilon_2\ldots\varepsilon_8}\right) + \frac{161.8}{\varepsilon_6^{**}\varepsilon_7\varepsilon_8}$$

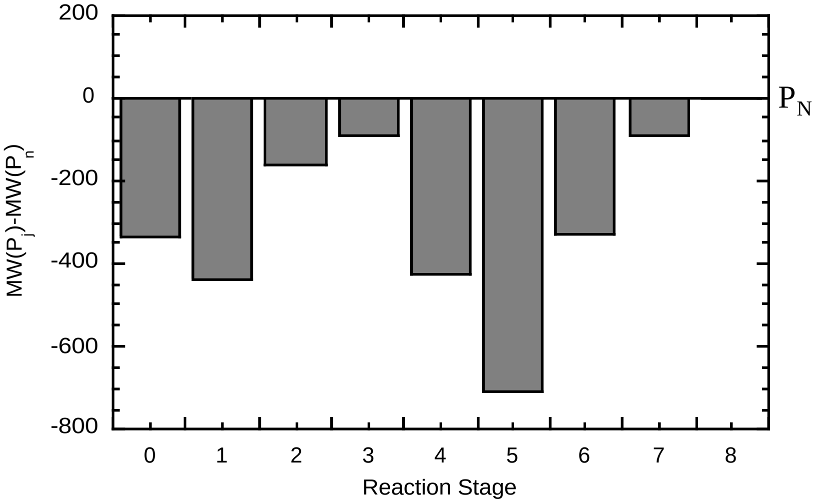
$$+\frac{28}{\varepsilon_7\varepsilon_8}\left(\frac{2}{\varepsilon_6^{**}} + \frac{2}{\varepsilon_5^{*}\varepsilon_6^{*}} + \frac{2}{\varepsilon_5^{*}\varepsilon_6} + \frac{1}{\varepsilon_2^{*}\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6}\right)$$

$$+\frac{46}{\varepsilon_6^{*}\varepsilon_7\varepsilon_8} + \frac{36}{\varepsilon_5^{*}\varepsilon_7\varepsilon_8}\left(\frac{1}{\varepsilon_6^{*}} + \frac{1}{\varepsilon_6}\right) + \frac{70.9}{\varepsilon_6\varepsilon_7\varepsilon_8} + \frac{65}{\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8} + \frac{56}{\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8} + \frac{52.45}{\varepsilon_2^{*}\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8}$$

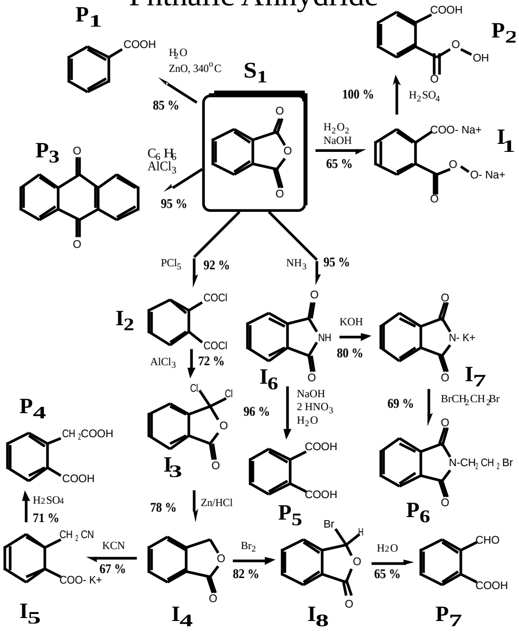
$$+\frac{168}{\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\varepsilon_6\varepsilon_7\varepsilon_8}$$

RME = 0.083 (about 8 %) $E_m = 11.09$

AE = 0.1809 (about 18 %) $E_{mw} = 4.53$



Phthalic Anhydride



Acknowledgements:

2002

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