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School of Industrial and Information Engineering

Course 096125 (095857)

Introduction to Green and Sustainable Chemistry





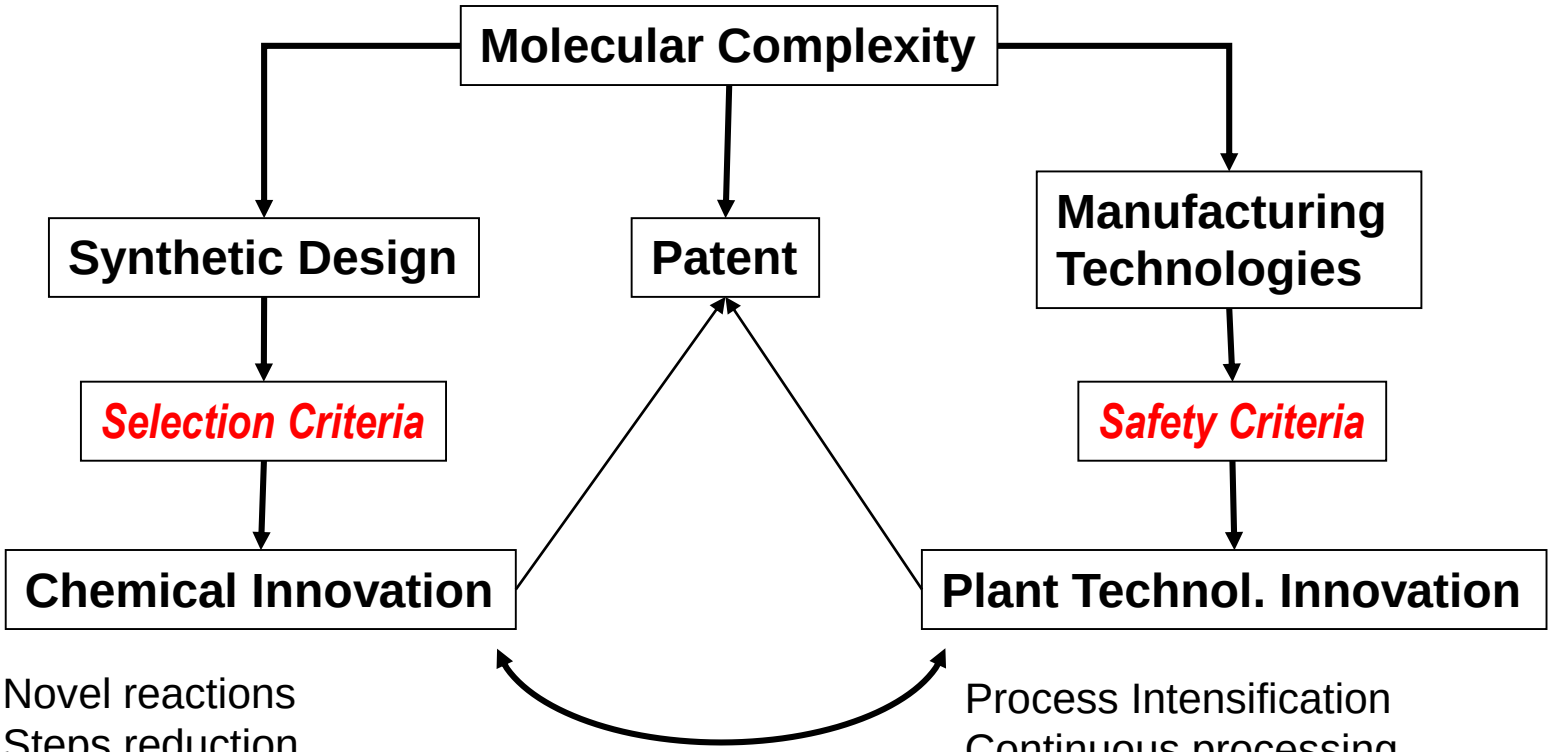
The 12 Principles of GC and GE Applied to Chemical Processes.

Prof. Attilio Citterio

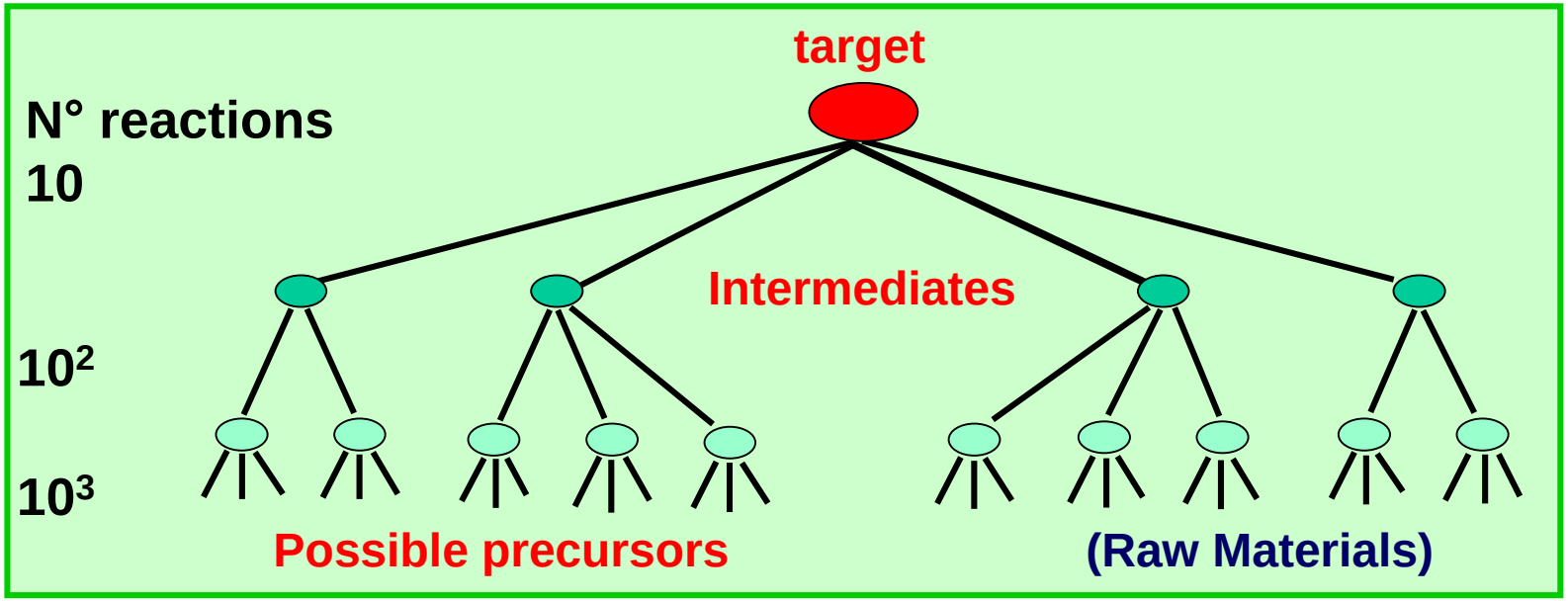
Dipartimento CMIC “Giulio Natta”

https://iscamapweb.chem.polimi.it/citterio/education/course-topics/

Molecular Transformations and Phases of the Research.



Complexity of Chemical Space and Research Phases.

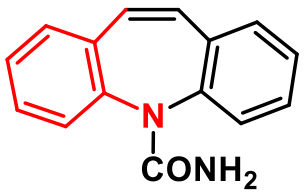


Compounds	15 million
Reactions	several million known

Organic Compounds foreseen with MW < 700 u : 10^{36}

Similarity Research.

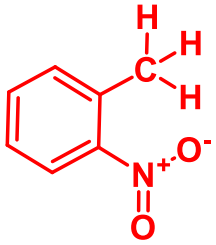
Recognition of structural analogies between the target final molecule and available chemical (analysis by substructures)

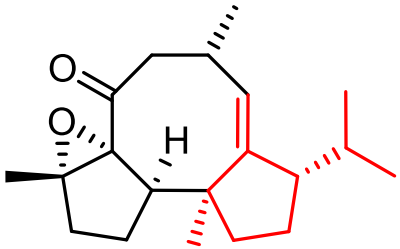


5H-dibenzo[h,f]azepino-5-carboxymide

Product Catalog

1 kg, 98%, $C_7H_7NO_2$

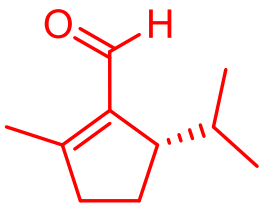




(+) 7,8-epoxy-2-basmen-6-one

Chiron Catalog

10 g, 97%, $C_{10}H_{16}O$



To be Able to Reason Backwards.

Strategy

overall plan to achieve the ultimate synthetic target

intellectual retrosynthetic planning

TRANSFORMS

Target ⟹ **Precursor**

Tactics

means by which plan is implemented

experimental synthetic execution

REACTIONS

Precursor ⟹ **Target**

Definitions.

Retron

Structural unit that signals the application of a particular strategy algorithm during retrosynthetic analysis.

Transform

Imaginary retrosynthetic operation transforming a target molecule into a precursor molecule in a manner such that bond(s) can be reformed (or cleaved) by known or reasonable synthetic reactions.

Strategy Algorithm

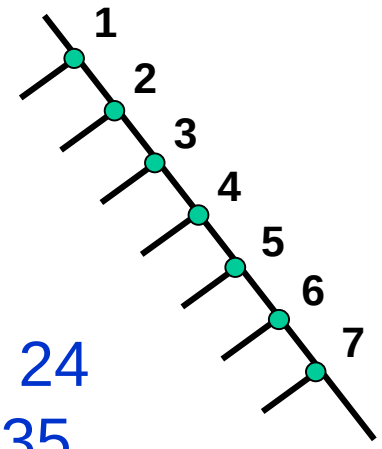
Step-by-step instructions for performing a retrosynthetic operation.

"...even in the earliest stages of the process of simplification of a synthetic problem, the chemist must make use of a particular form of analysis which depends on the interplay between structural features that exist in the target molecule and the types of reactions or synthetic operations available from organic chemistry for the modification or assemblage of structural units. The synthetic chemist has learned by experience to recognize within a target molecule certain units which can be synthesized, modified, or joined by known or conceivable synthetic operations...it is convenient to have a term for such units; the term **"synthon"** is suggested. These are defined as structural units within a molecule which are related to possible synthetic operations... a synthon may be almost as large as the molecule or as small as a single hydrogen; the same atoms within a molecule may be constituents of several overlapping synthons..."

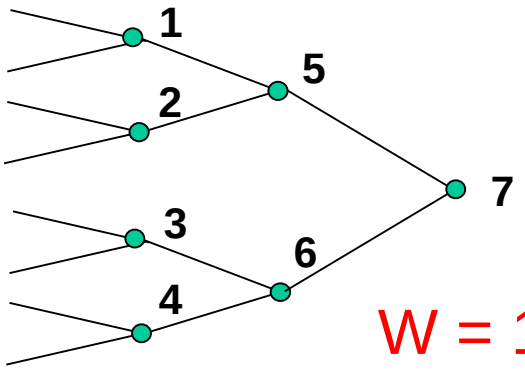
from "General Methods for the Construction of Complex Molecules“ E. J. Corey, Pure Appl. Chem. **1969**, 14, 19

Comparison of Linear and Convergent Syntheses.

7 Steps, 80% yield per step



W = 24
S = 35

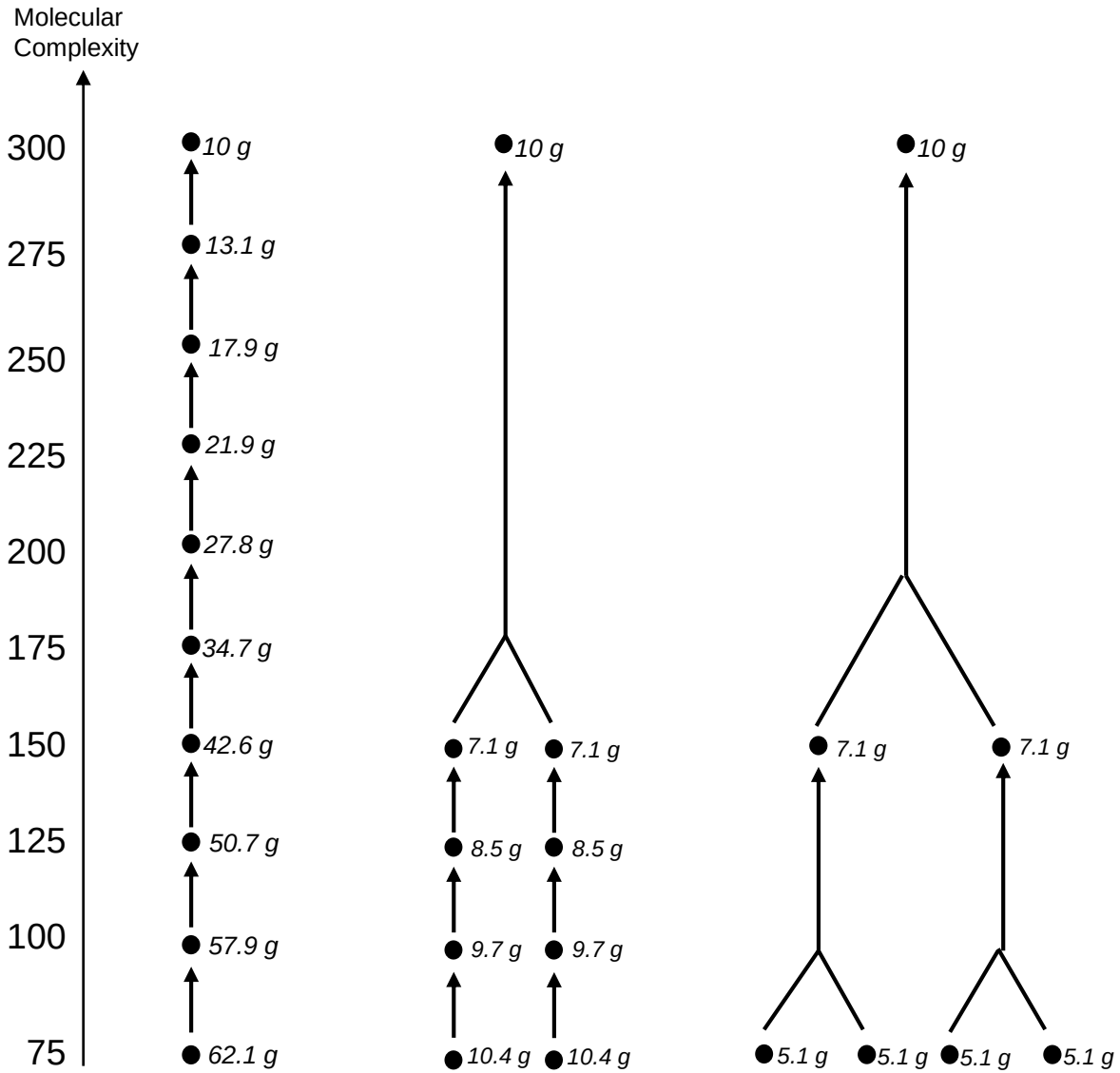


W = 16
S = 24

W = total wt. of all SM
S = sum of steps each SM must pass through

J.S. Hendrickson, *Pure Appl. Chem.*, 1988, 60 (11), 1563.

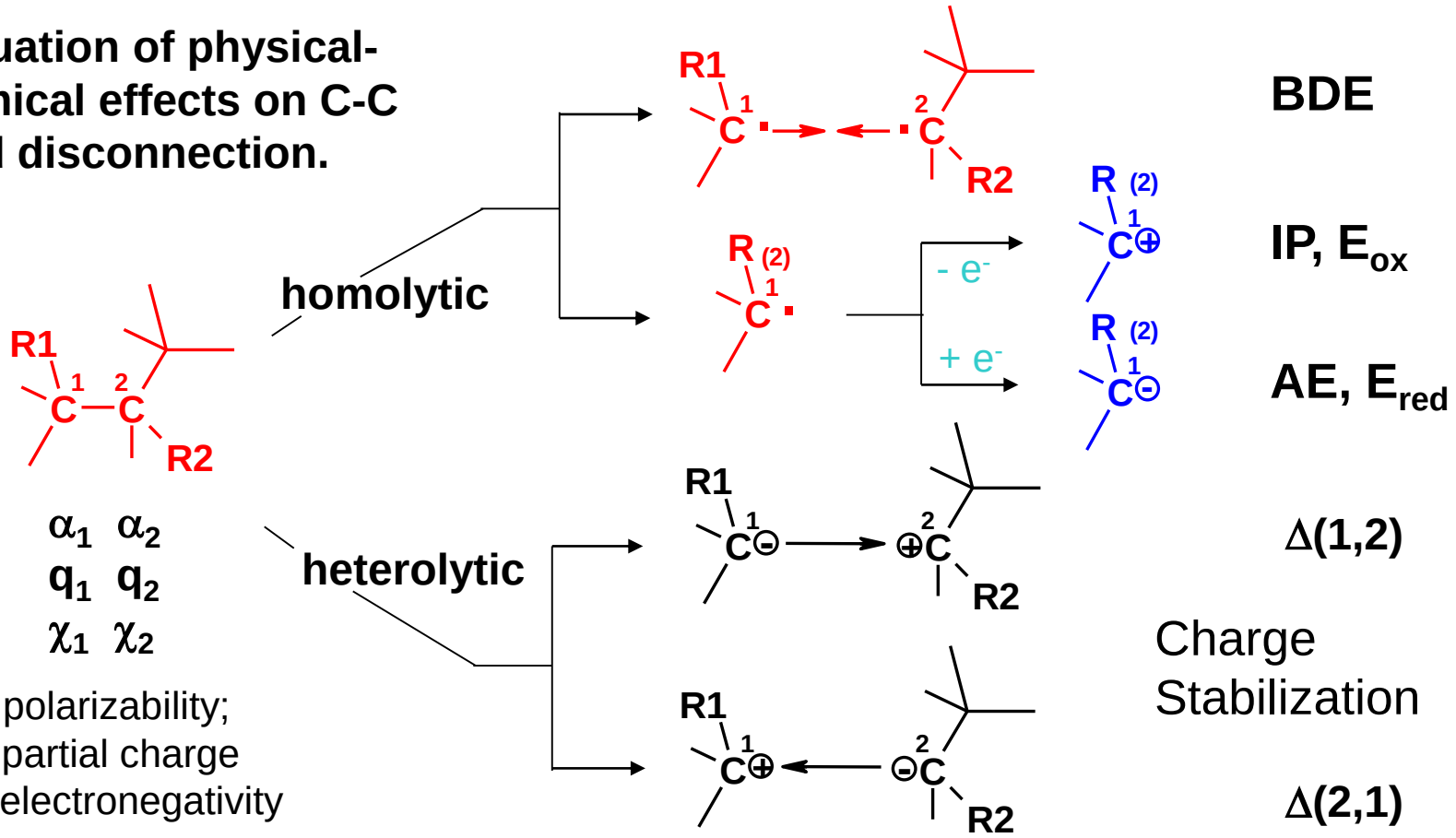
Convergent Strategies are the Most Efficient Strategies for the Assembly of Complex Molecules.



Calculations has been performed on 70% yield per step

Synthesis Strategy – Bond Indices.

Evaluation of physical-chemical effects on C-C bond disconnection.



α_1 α_2
q_1 q_2
χ_1 χ_2

α = polarizability;
q = partial charge
χ = electronegativity

Atom Economy – Solutions.

Positive aspects:

- When possible take in consideration the use of high atom economy reactions (design of synthetic route).
- Consider also other normal reaction parameters, i.e. yield, reaction conditions, stage number, separation facility, by-product nature, solvents, etc. (very important is (yield × AE): 100 × 35 <<< 90 × 85)
- Evaluate the possibility to carry out more reaction stages in one only phase.
- Intensify all the process after developing other measures
- If reactions with low EA must be used, attempt to minimize the effects must be introduced, i.e. a careful choice of catalyst, the reuse in the process or recycle, assuring that all by-products are benign.

Negatives Aspects ……

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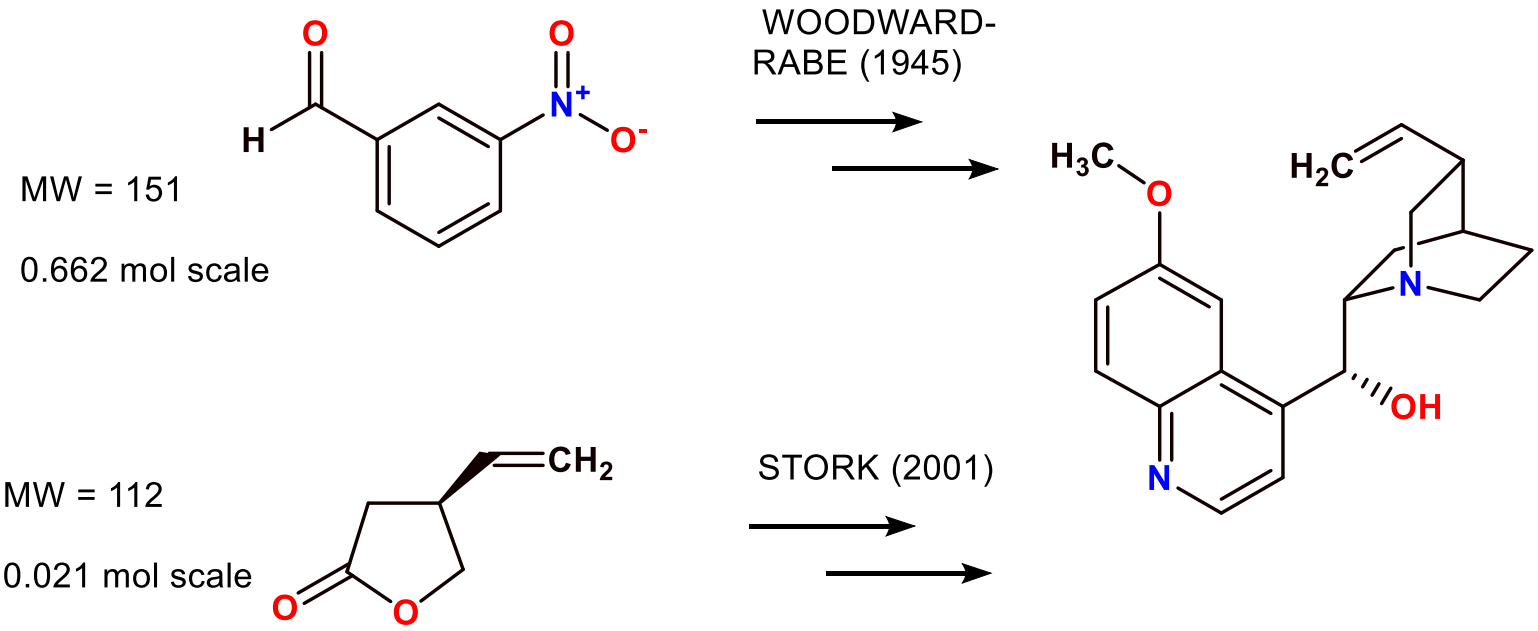
Comparison of Known Reactions.

Quinine Synthesis.

Two multistep alternative routes (after 55 year) from two relevant teams.



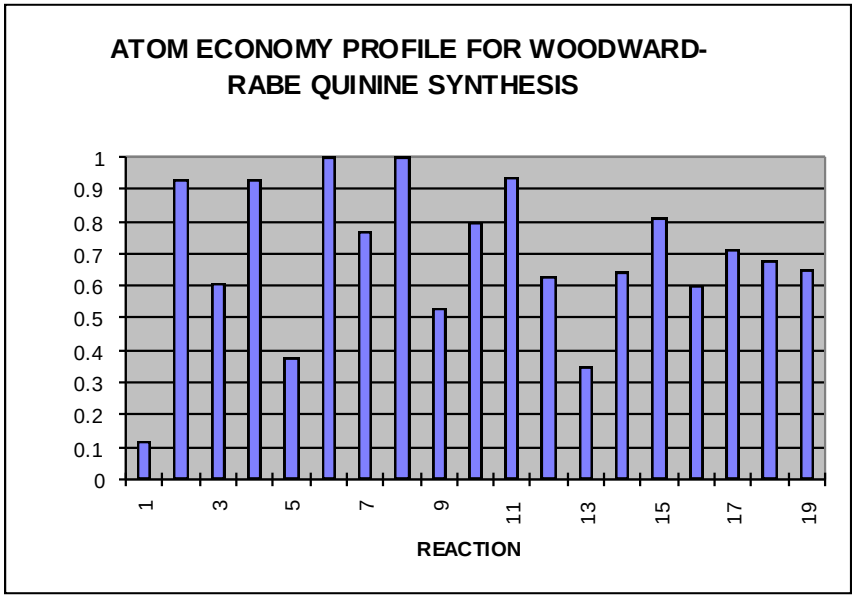
J. Am. Chem. Soc. **1945**, 67, 860

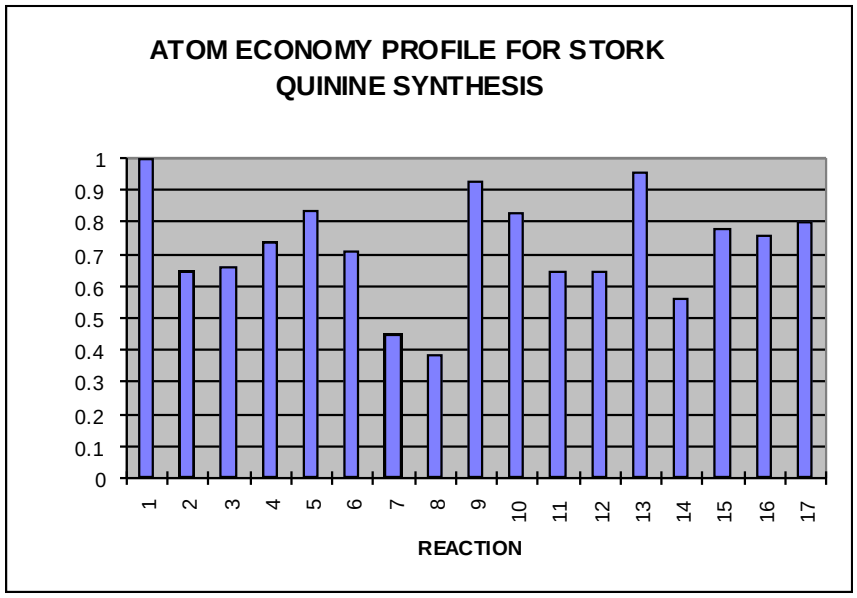
J. Am. Chem. Soc. **2001**, 123, 3239

Comparison Survey.

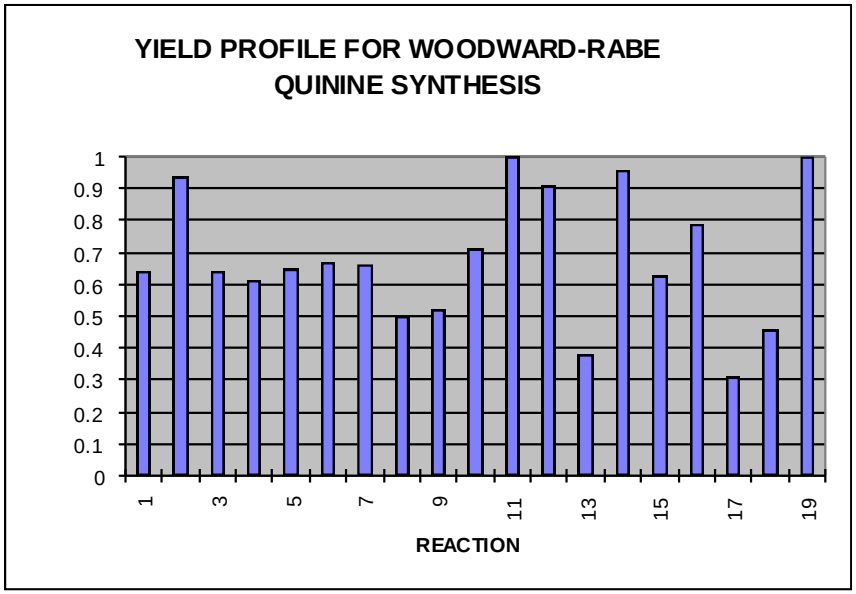
Criterion	Woodward-Rabe synthesis (1945)	Stork synthesis (2001)
Sequence Metrics		
Number of steps	**24**	**17**
Overall yield	**0.029%**	**71%**
% “good” yield reactions ($\varepsilon \geq 75\%$)	**21.1%**	**81.3%**
Average yield per step	**65%**	**86%**
% “golden” AE reactions	**75%**	**81.3%**
Overall AE	**8.0%**	**8.6%**
Overall RME	**0.0039%**	**0.16%**
Waste generated /g quinine, E_m	**25.6 kg/g**	**0,61 kg/g**
Reaction Conditions		
% reactions run at SF $\approx$ 1	**56.2%**	**62.5%**
% reactions run at ambient temperature	**29.2%**	**58.8%**
% catalytic reactions	**37.5%**	**23.5%**

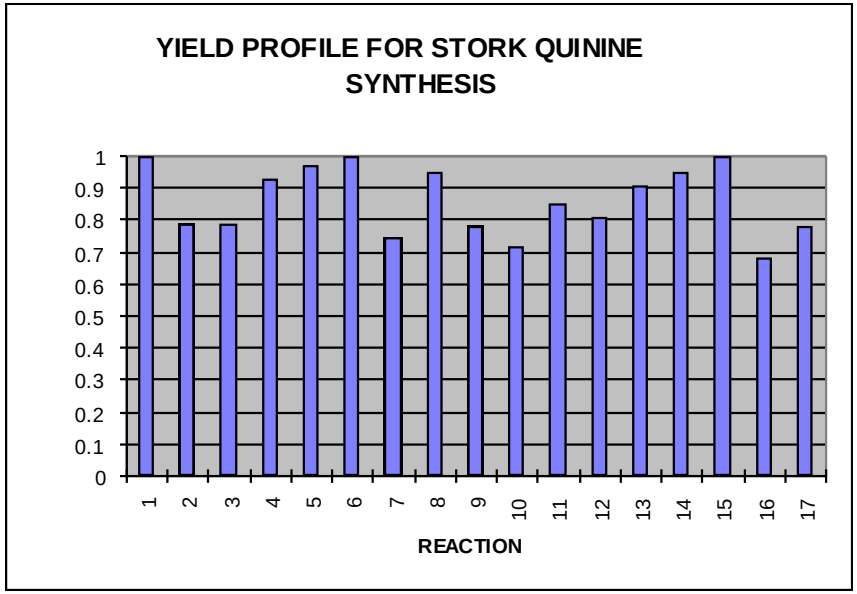
Atom Economy Profile of Alternative Quinine Synthesis.



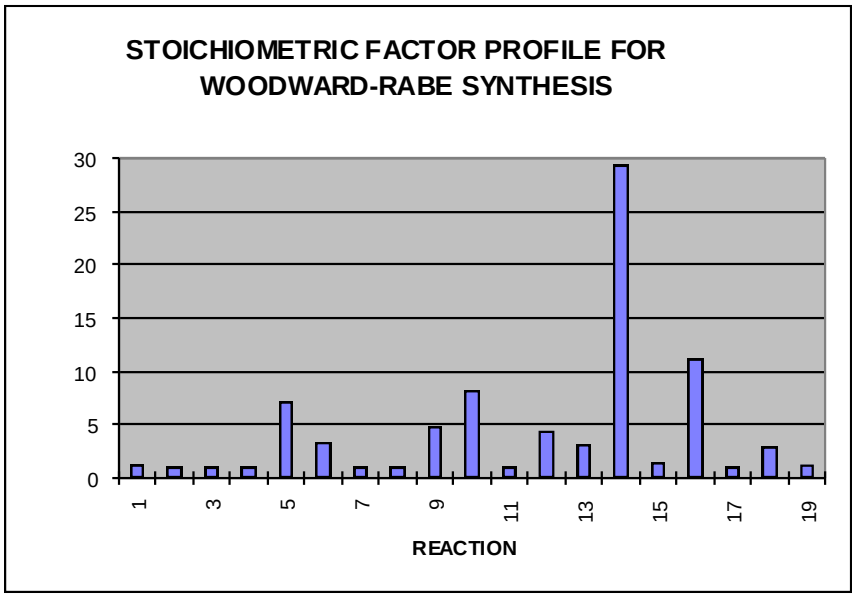


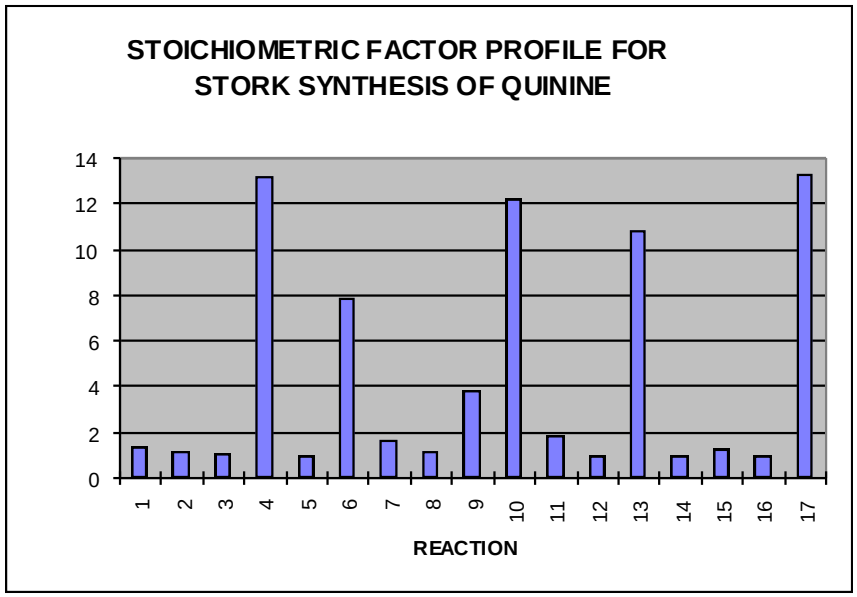
Yield Profile of Quinine Synthesis.



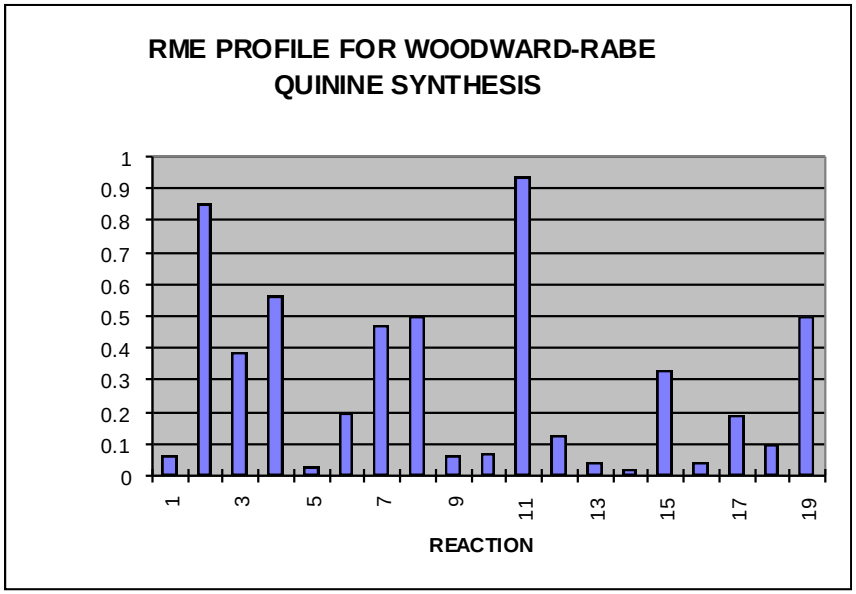


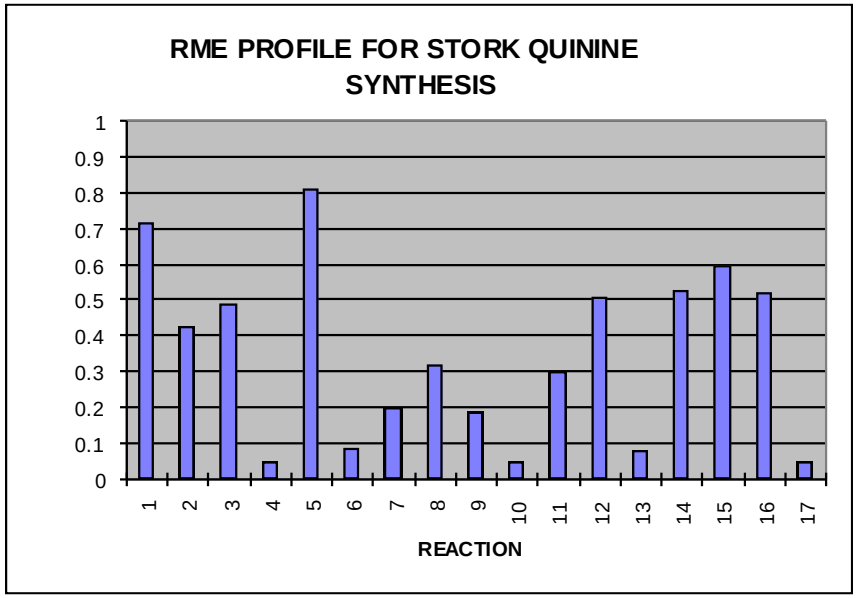
Stoichiometric Factor Profile for Quinine Synthesis.



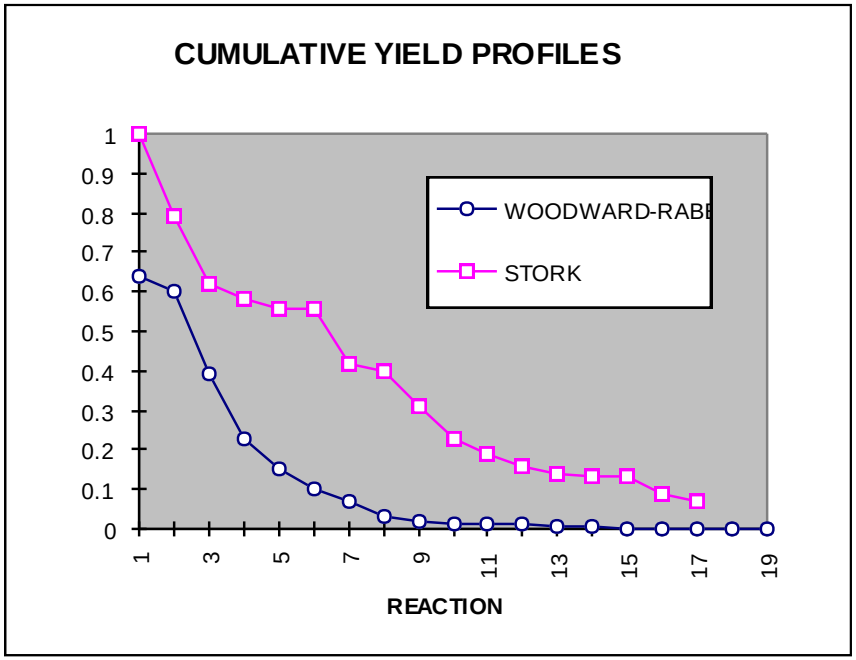


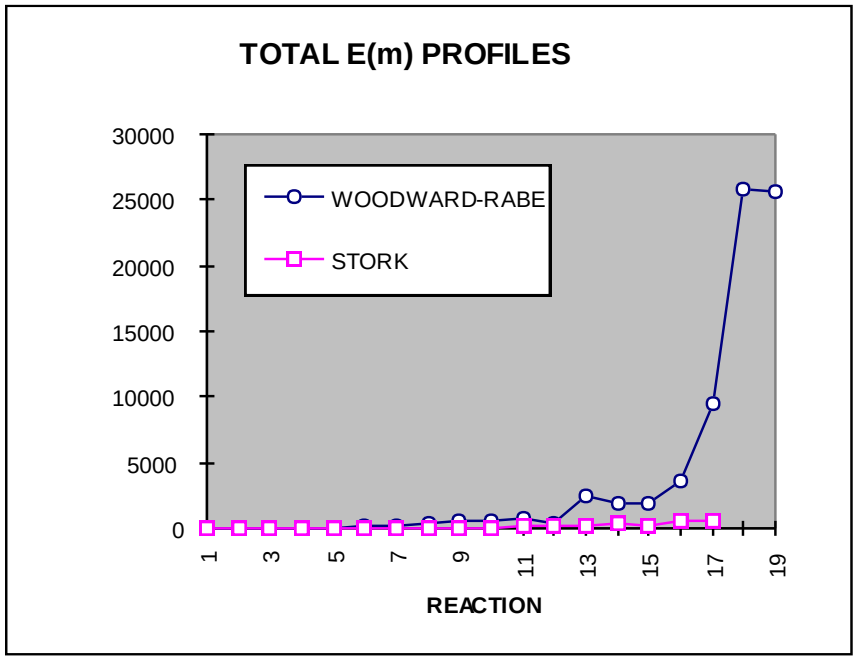
RME Profile for Quinine Synthesis.



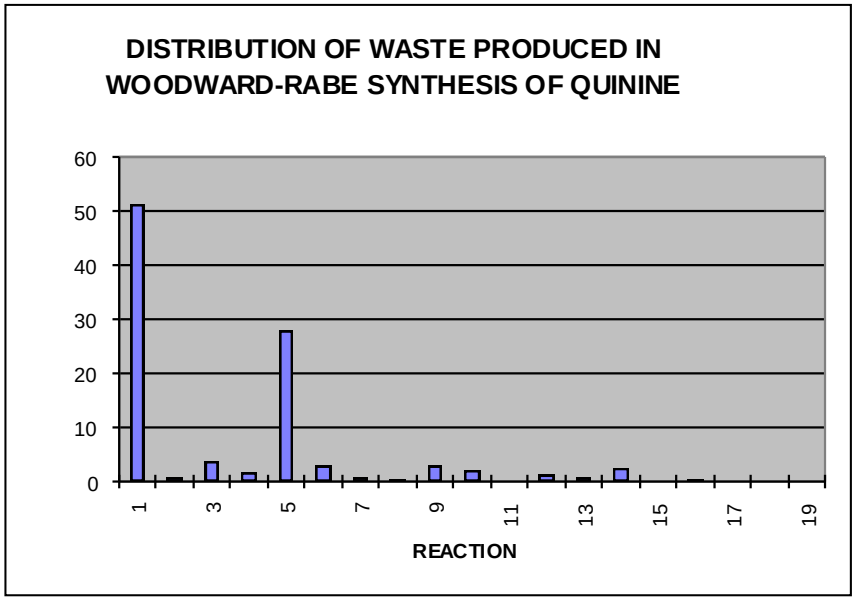


Yield and Total E_m Profiles in the Quinine Synthesis.





Distribution of Waste Produced in Woodward-Rabe Synthesis of Quinine.



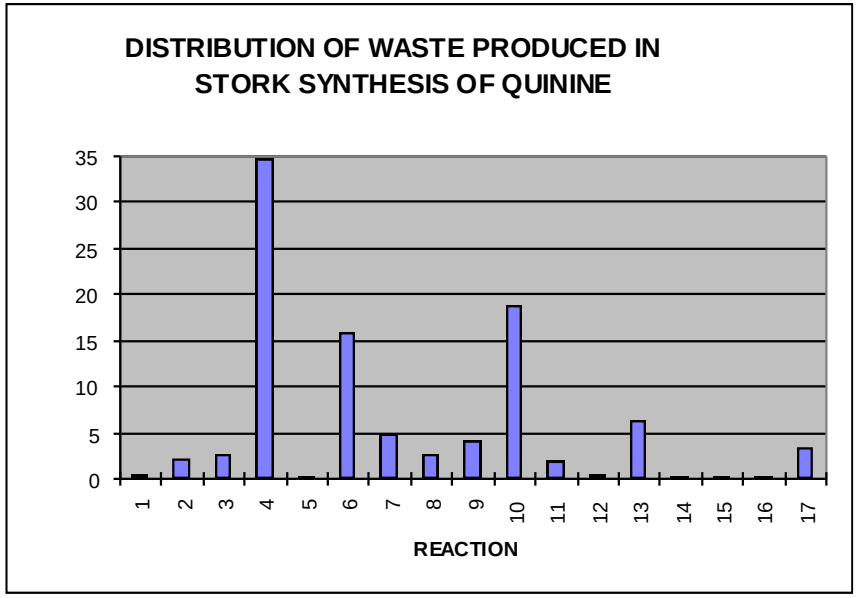
WOODWARD-RABE SYNTHESIS OF QUININE

REACTION TYPE

1 reduction + diazotization + substitution
2 condensation
3 cyclization + ethanol elimination
4 3-CC MCR (HCHO + isoquinoline + piperidine)
5 N-hydroperoxyipiperidinea elimination
6 Aromatic reduction
7 N-acylation
8 Aromatic reduction
9 oxidation of alcohol
10 water elimination + oxidation + ring breaking
11 oxime reduction
12 amine methylation
13 Hofmann elimination + substitution of acyl group by a aminocarboxy group
14 substitution of aminocarboxy group with benzoyl
15 condensation
16 elimination of ethanol + CO_2 + PhCOOH
17 N-bromination
18 cyclization + debromination
19 ketone reduction

The main inputs to waste are due to low yields and low atom economy for step.

Distribution of Waste Produced in Stork Synthesis of Quinine.



STORK SYNTHESIS OF QUININE

REACTION TYPE

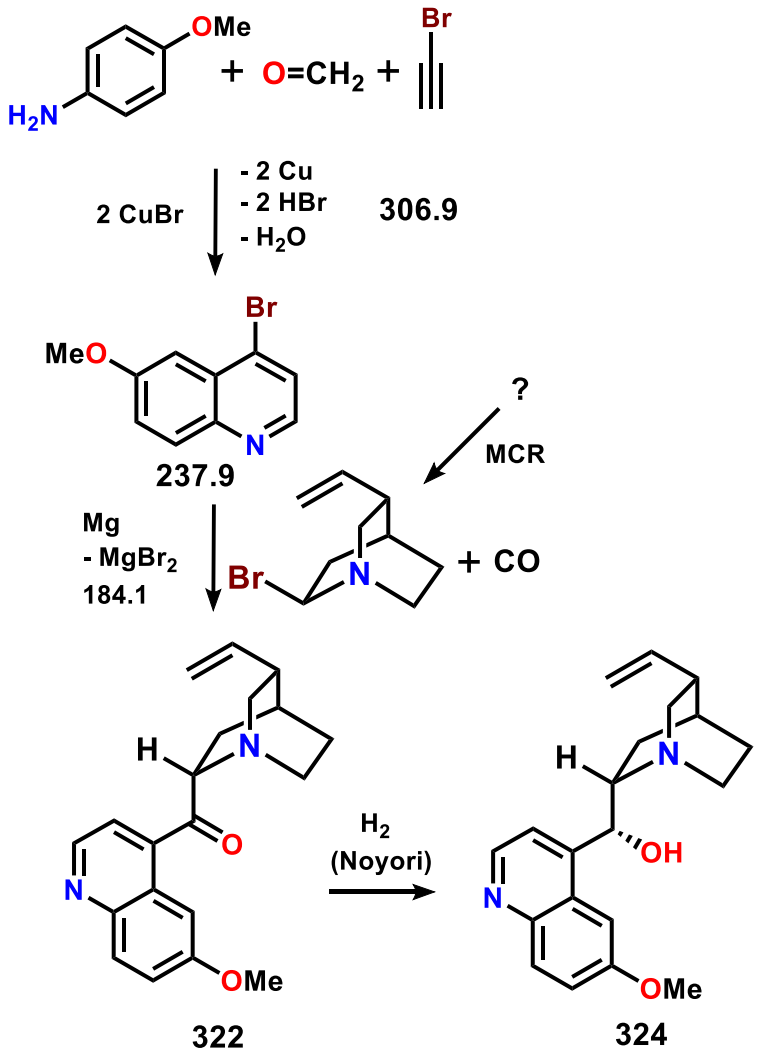
1 ring opening amidation
2 alcohol protection
3 C-alkylation with a protective group
4 elimination (deprotection)
5 cyclization + deamination reduction of lactone to lactol
7 ring opening + Wittig => vinyl ether
8 substitution of OH group with azide group
9 hydration of vinyl ether
10 C-alkylation
11 Swern oxidation of alcohol to ketone
12 cyclization + elimination
13 reduction of imine
14 deprotection
15 mesilation
16 cyclization + elimination of MsOH
17 oxidation of methylene to ketone

The main inputs to waste are due to non-stoichiometric reaction conditions.

Comparison Survey.

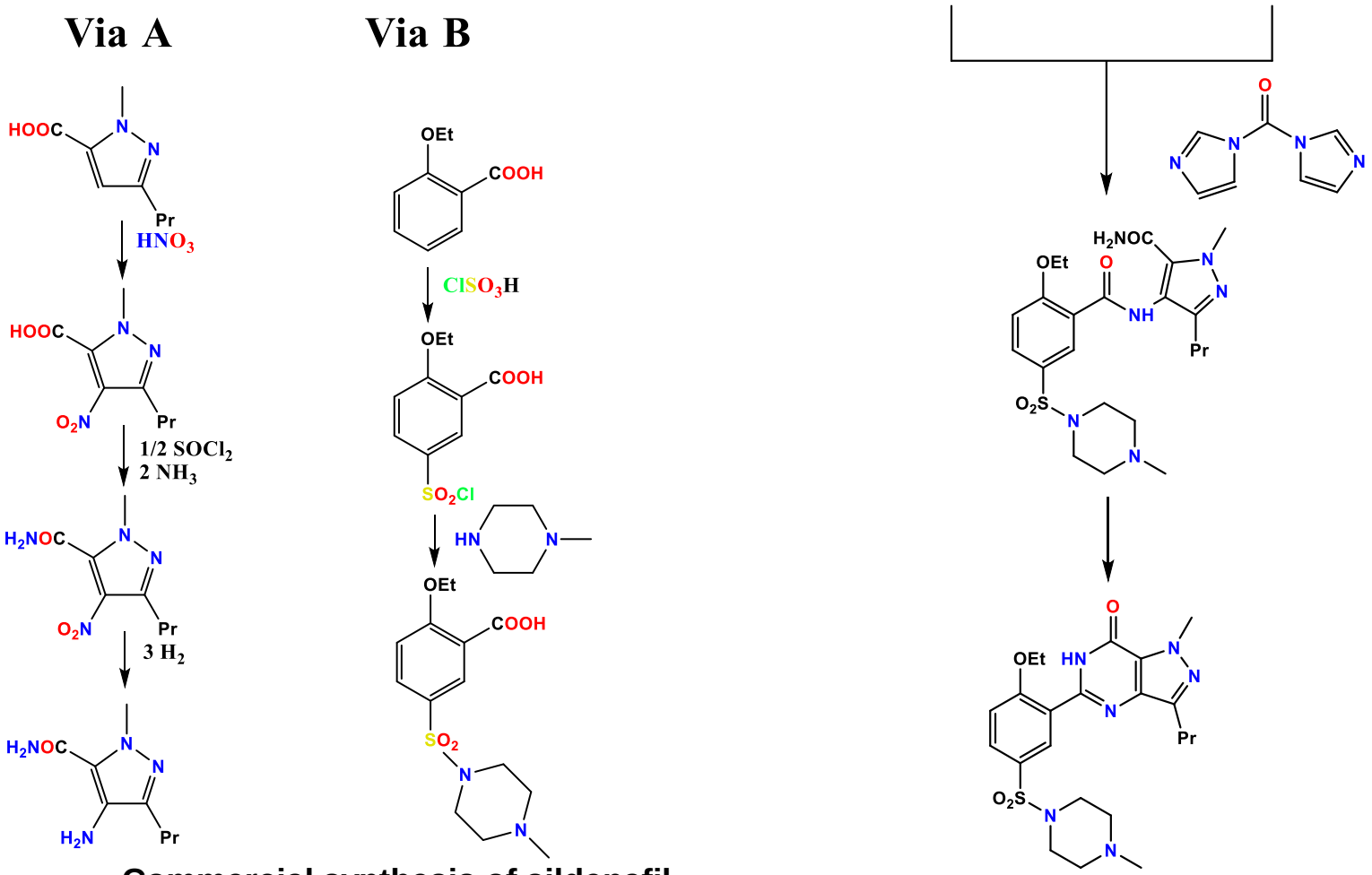
Criterion	Woodward-Rabe synthesis (1945)	Stork synthesis (2001)
Sequence Metrics		
% reactions involving adding and removing protection groups	**0%**	**23.5%**
% redox reactions	**6/24= 25%**	**4/17=23.5%**
% “aufbau” reactions (intermolecular C-C, non C-C bond forming, cond.)	**6/24= 25%**	**6/17=35.3%**
% substitution reactions	**4/24= 16.7%**	**1/17=5.9%**
% MCRs	**1/24=4.2%**	**0%**
% rearrangements	**0%**	**0%**
% eliminations	**6/24=25%**	**6/17=35.3%**
Recycling Potential		
% reactions where byproducts may be recycled back to reagents	**29.2%**	**82.4%**

Application of Nested MCRs to Total Synthesis of Quinine.



Rxn	E	AE
1	1.290	0.437
2	0.572	0.636
3	0	1
Total	**1.515**	**0.398**

Synthesis of Sildenafil (Viagra®).



Commercial synthesis of sildenafil

Dale, D.J.; Dunn, P.J.; Golightly, C.; Hughes, M.L.; Levett, P.C.; Pearce, A.K.; Searle, P.M.; Ward, G.; Wood, A.S. *Org. Proc. Res. Develop.* **2000**, 4, 17.
Dunn, P.J.; Galvin, S.; Hettenbach, K. *Green Chem.* **2004**, 6, 43.

Sildenafil Metrics.

Sequence	Mass of waste (g) $\sum_j \bar{w}_j$	Environmental Impact Factor based on mass, E_m	Reaction Mass Efficiency, RME
Path A	8740.46	5.74	0.15
Path B	6513.72	2.38	0.30
Convergent step	2431.22	0.66	0.60
Forward step	1509.21	0.47	0.68

Total mass of waste for entire process = 19194.61 g

Total mass of sildenafil product collected = 3219.44 g

$$E_m^{total} = \frac{19194.61}{3219.44} = 5.96$$

$$RME_{total} = \frac{1}{E_m^{total}} - 1 = 0.144$$

Overall AE = 0.52 (assuming SF = 1 and $\varepsilon = 1$ for all steps)

Overall E = 0.91 (assuming SF = 1 and $\varepsilon = 1$ for all steps)

Overall yield, ε_{total}

ε_{total} = (overall yield for large scale path)(yield of convergent step)(overall yield for forward steps)

= (0.886)(0.90)(0.902) = 0.72

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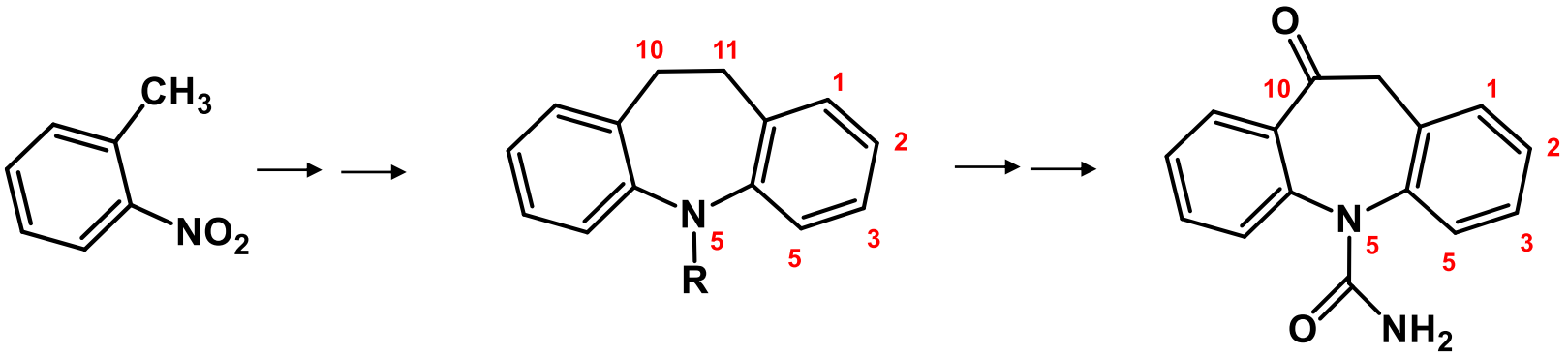
Approaches to New Synthetic Routes.

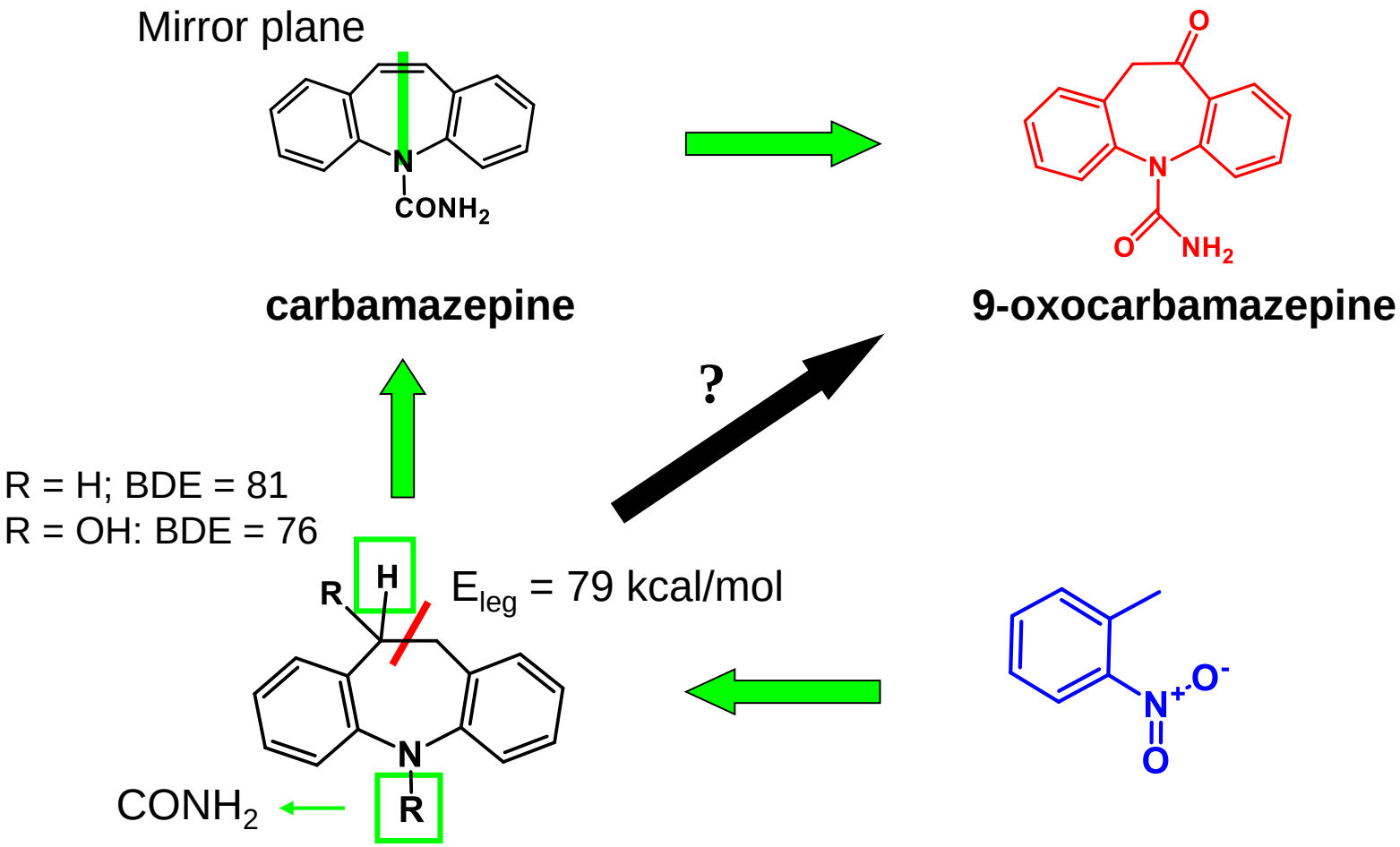
Synthesis of 10-oxo-carbamazepine.



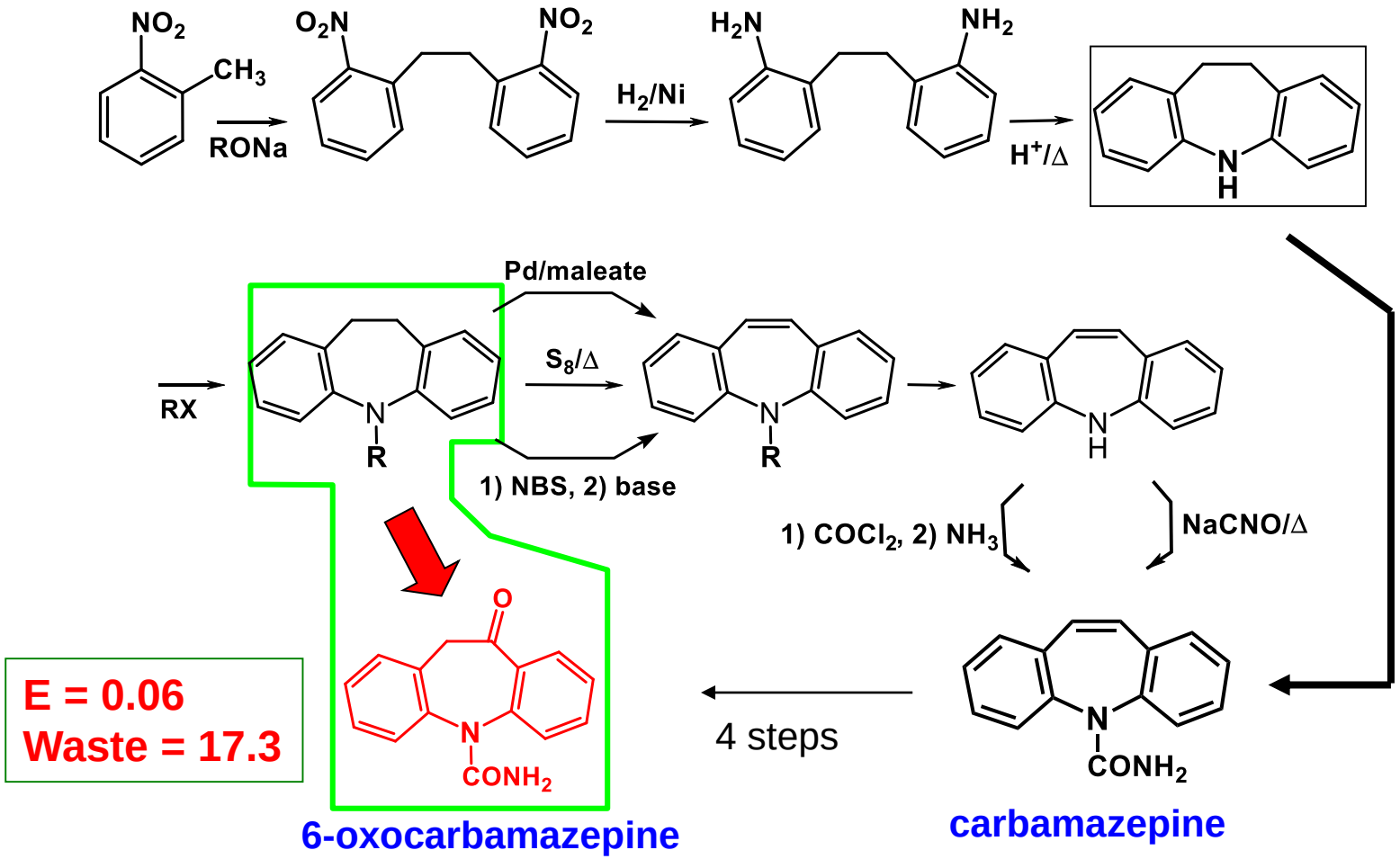
10-Oxo-5-carbamoyl–5H-dibenzo[b,f]azepine

Farchemia, Eur. Pat. Appl. EP 1127877 A2 *(29 Aug 2001)*

Approach to the Synthesis of 5-Carbamoyl–5H-dibenzo[b,f]azepine.



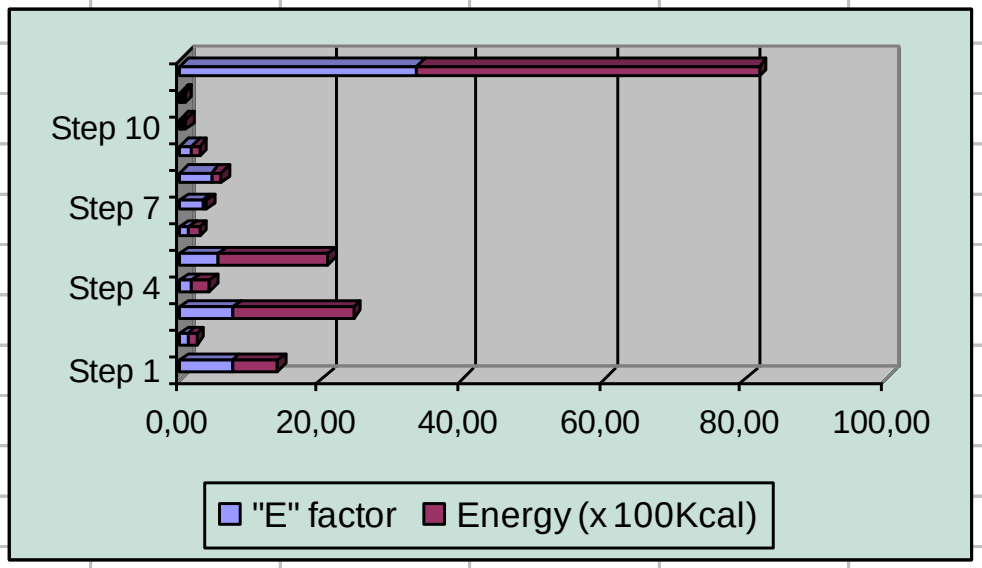
Synthesis of 5H-dibenzo[b,f]azepine Derivatives.



DE Pat.DE-Os 2.011.087; Be Pat.N.597.793; Jp Pat – N. 73.066; Eur.pat.EP 0.028.028

“E” Factor and Energy Balance in the Production of 10-Oxo-5-Carbamoyl–5H-dibenzo[b,f]azepine.

	"E" factor	Energy (x 100Kcal)
Step 1	7,26	6,60
Step 2	0,92	1,38
Step 3	7,48	16,96
Step 4	1,70	2,37
Step 5	5,49	15,30
Step 6	1,25	1,50
Step 7	3,08	0,66
Step 8	4,31	1,57
Step 9	1,65	1,10
Step 10	0,22	0,55
Step 11	0,10	0,40
Total	33,46	48,39



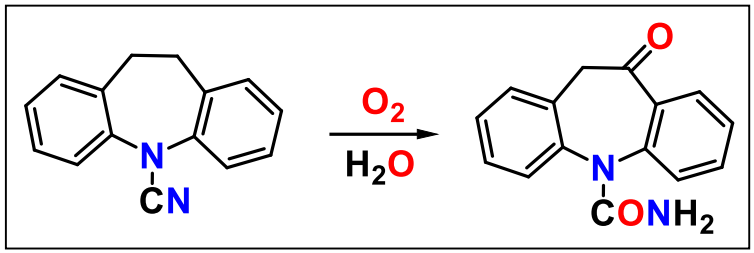
AE from a Strategic Intermediate

5-Cyano-10,11-dihydro-5H-dibenzo[b,f]azepine.

Alternative approaches

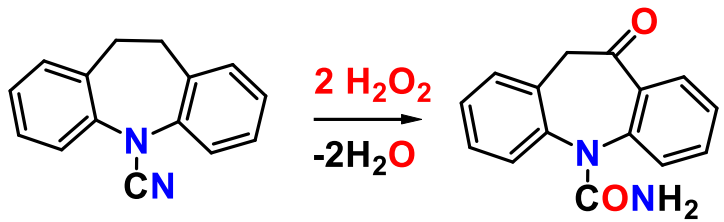
AE % = $(MW_{prod}/ MW_{reag})x100$

a)



a) 100%,

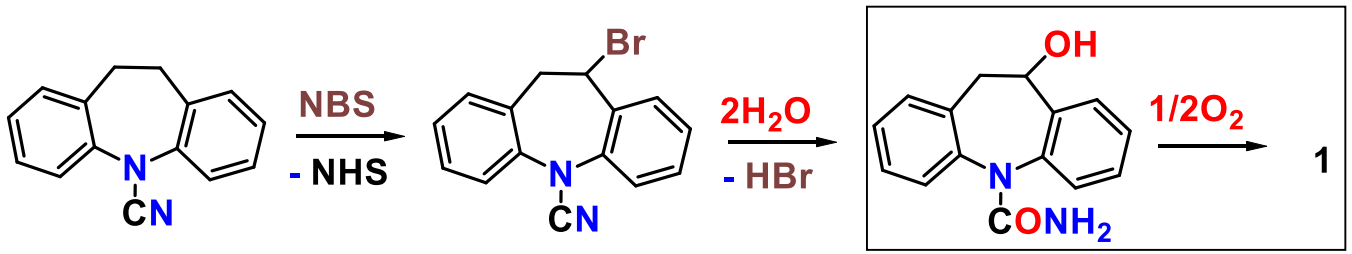
b)



1

b) 87.5%

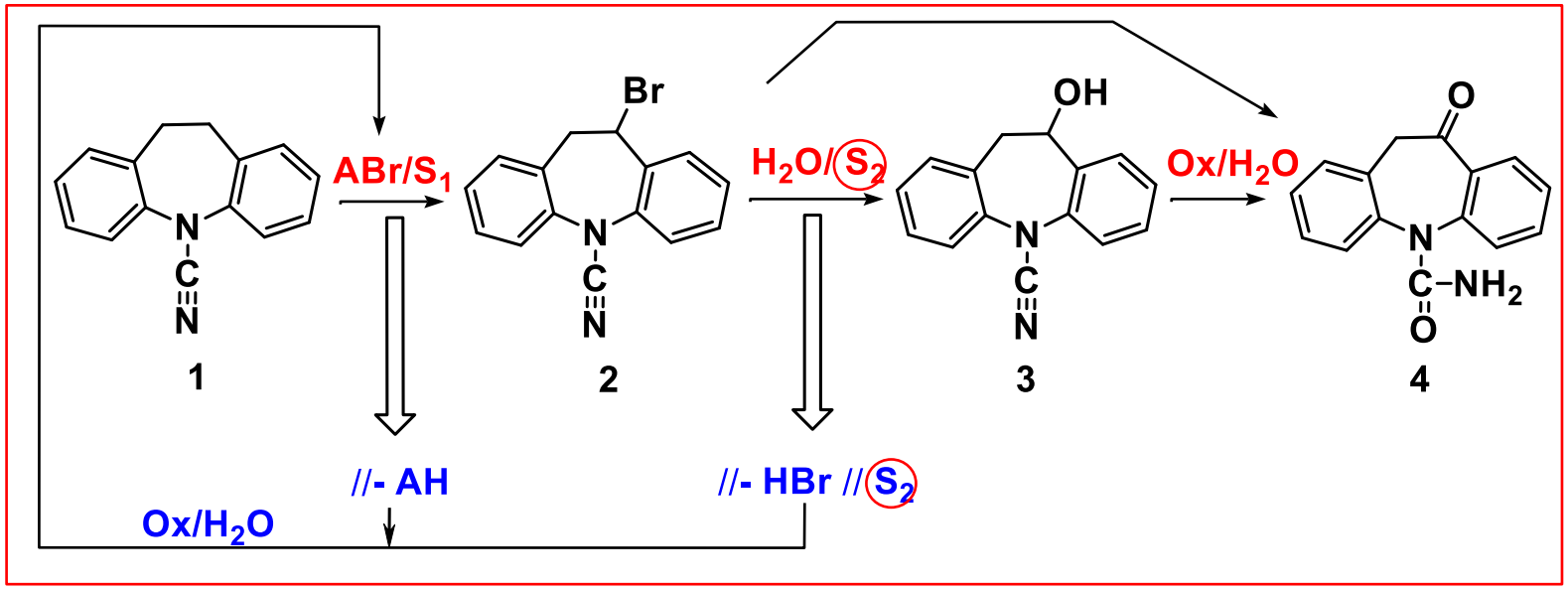
c)



NHS + HBr + 1/2 O_2 ⟶ NBS + H_2O

c) 100%

PEG Assisted Hydrolysis with NBS Recovery.

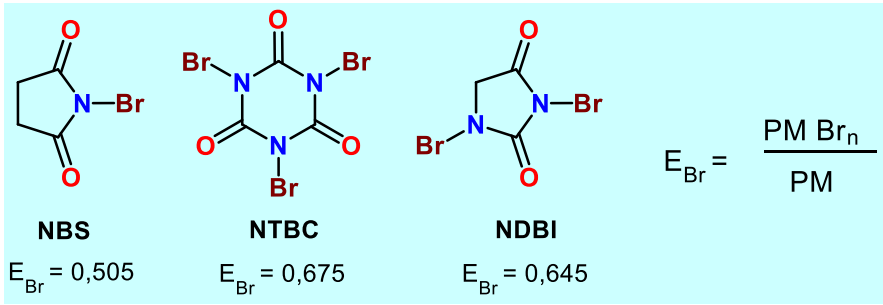


$S_1 = CH_2Cl_2$

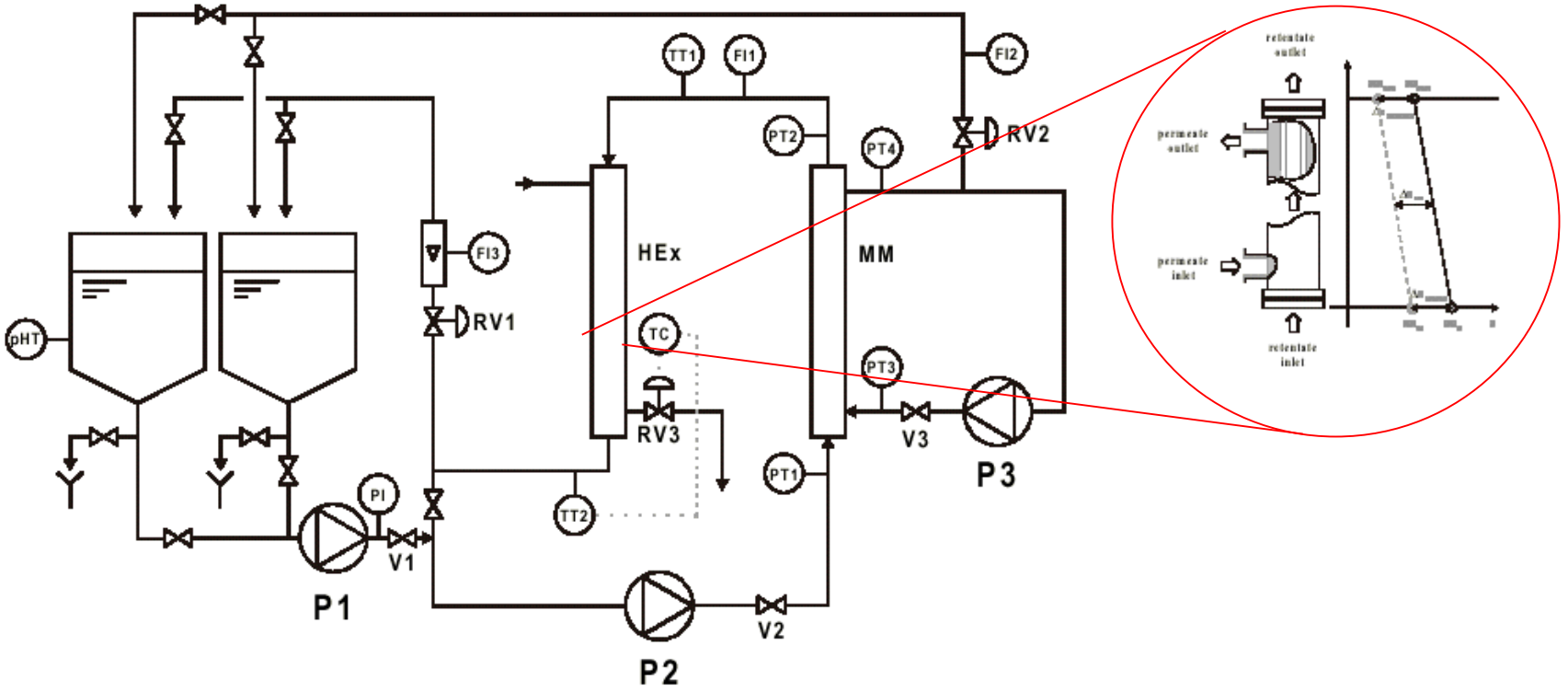
S_2 = PEG 35,000

$HBr, H_2O/NHA//S_2$ - Membrane Separation

Brominating agent



Flow Sheet of Ultra-filtration Pilot Unit in the Recovery Process of HBr/NHA/PEG.



Legend: P1- feed pump, P2- retentate cycling pump, P3-cp. permeate, PI-pressure ind., PT- input retentate pressure sensor, PT2- retentate output, PT3- input permeate, PT4-output permeate, FI 1- retentate flowmeter, FI 2- permeate flowmeter, FI 3- Output retentate flowmeter, TT1-Pt 100 Temp. sensor, RV1e RV2- pressure control valve, TT2- Temp. sensor, TC- Temp. control, RV3- water cooling valve, pHT-pH meter, HEx-heat exchanger, MM- membrane module.

New Synthetic Routes to Produce Cheaper Products.

They need:

- Retrosynthetic analysis either manually or using computerized techniques.
- Knowledge of feedstock and raw materials (price and availability in bulk)
- Knowledge of literature, researching for similar compounds, part-structures, technologies
- Knowledge of plant/manufacturing
- Willingness to speculate
- Willingness to MAKE reaction work

The Shortest Route is the Best?

- Plant occupation minimized, thus benefiting: throughput or lowering capital cost of a new plant.
- Lead time shorter - faster response to orders
- Fewer intermediates - saving on QC, inventory, materials movement
- Less effluent - fewer streams
- Most likely to produce cheap product
- Batch sizes will be smaller or, alternatively, less batches can be prepared on a larger scale.

NB: Count stages from a READILY available (in bulk!) raw material

Overall Yields from a 10-Step Synthetic Route.

Step	60%	70%	80%	85%	90%	95%	97%
1	60	70	80	85	90	95	97
2	36	49	64	78	81	90	94
3	22	34	51	66	73	86	91
4	13	24	41	56	66	81	88
5	8	17	33	48	59	77	86
6	5	12	25	41	53	73	83
7	3	8	21	35	48	70	81
8	2	6	17	30	43	66	78
9	1	4	13	25	39	63	76
10	0,6	2,8	11	21	35	60	74
Raw material for 10 kg of product	1666	357	93	47	28	16	14

Factors Which Could Affect Choice of Synthetic Route.

- ***Raw materials***
  - Are they readily available?
  - Are they available in bulk quantities (kg, tons)?
  - Are they cheap?
  - Is there more than one source?
- ***Likelihood of success***
  - Well-known established reactions?
  - Lots of literature precedent?
  - “Robust” reactions or speculative chemistry?

Factors Which Could Affect Choice of Synthetic Route (2).

- **Number of steps**
  - A short synthesis has many advantages
  - A convergent synthesis will be cheaper than a divergent synthesis with the same number of steps

(J.B. Hendrickson, *Pure App. Chem*., **1988**, *60*(11), 1563)

- **Ease of scale up**
  - Subjective judgement at early stage
  - Do not prejudge apparently difficult procedures
  - Engineering solutions can overcome handling problems for attractive routes
  - However SIMPLEST IS BEST !

Factors Which Could Affect Choice of Synthetic Route (3).

Selectivity

- Selective processes are preferred
- Selectivity can often be vastly improved during development by careful choice of reaction parameters
- Separations, particularly chromatography, are time-consuming and costly

Safety

- The use of highly toxic raw materials or reagents,
- the likelihood of explosion hazards on scale up, may make a route unsafe up to be discharged. Fugitive reactions must be carefully tested in the development stage.

Factors Which Could Affect Choice of Synthetic Route (4).

Environmental

- Effluent and byproduct considerations should be discussed at an early stage.
- A properly managed effluent policy, involving destruction of toxic byproducts or recycling can make other factors outweigh environmental issues.
- Environmental costs and laws are strongly increased. Waste minimization and use of benign reagents and intermediate must be a priority for a successful synthesis in order to reduce risks of final processes.

Although these factors may be taken into account in a research study, it is difficult to quantify the relative importance of each on industrial scale. Decisions, however, are often based on the experience.

Literature.

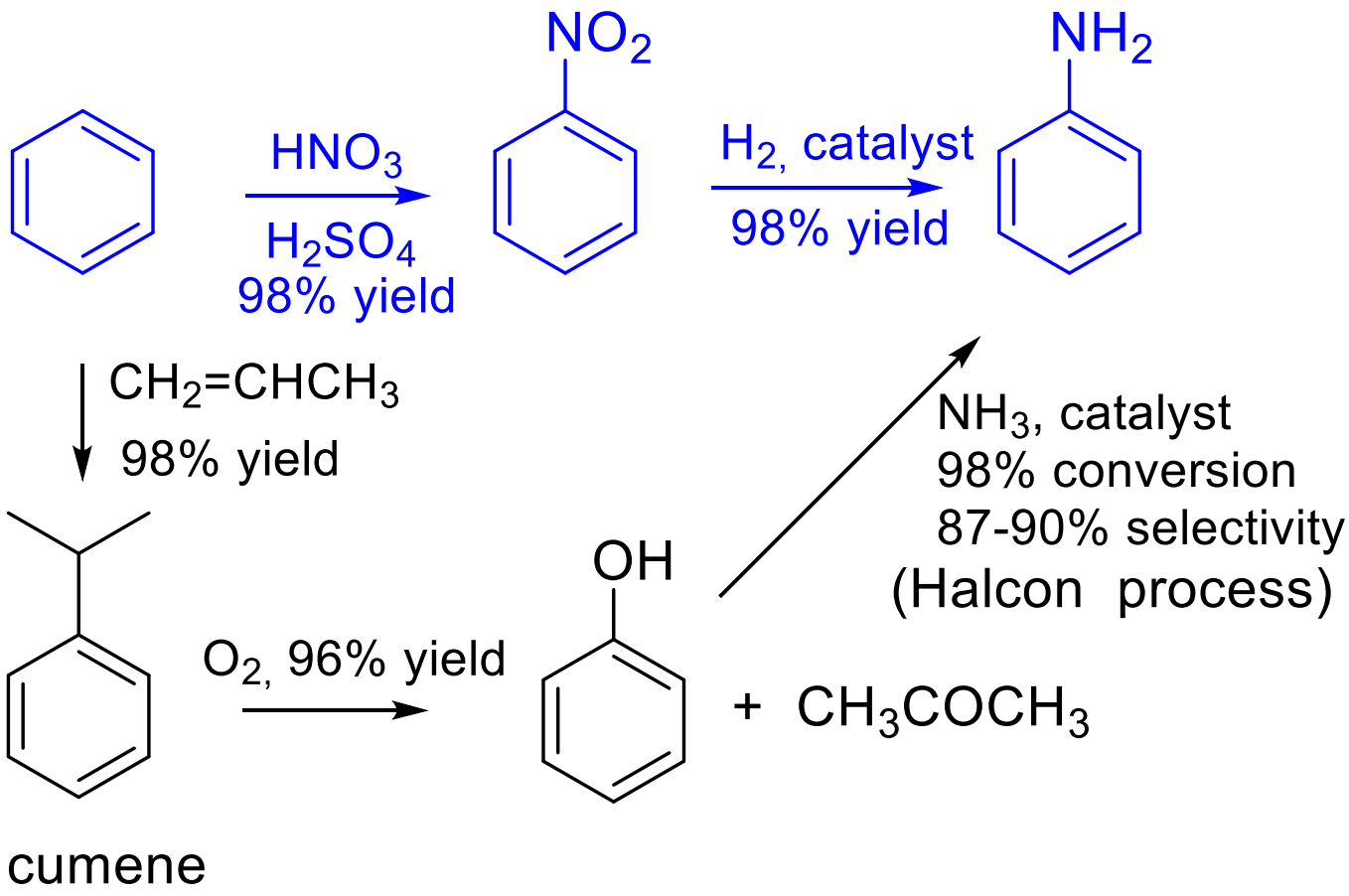
The literature should be scoured for chemistry which is applicable on a large scale

- New cheap reagents, specifically when easily available (oxygen and hydrogen peroxide in oxidation reactions)
- Useful catalysts (heterogeneous catalyst must be used instead of homogeneous, whatsoever possible)
- Reactions which can be carried out in water or under phase-transfer conditions. In any case solvents must be carefully selected
- Use of common bases such as sodium carbonate or triethylamine to effect reactions normally reserved for organolithium reagents
- New technologies (i.e. microreactors, membrane reactors, etc.)

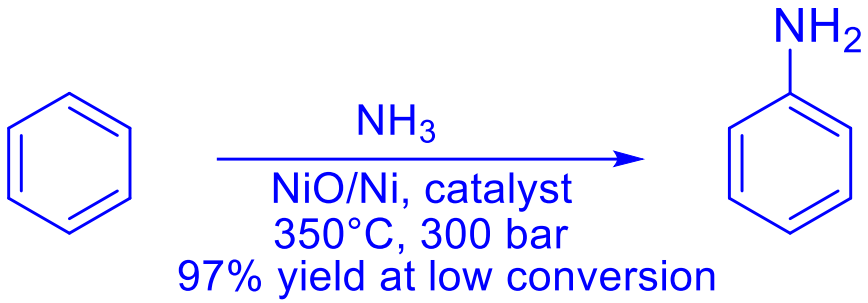
Discovery of New Reactions.

- Sometime it will be useful make a transformation with attractive potentiality but a way to realize the chemistry is unknown.
- New strategies to approach the problem are investigated and support of basic research is required
- Attempts are made to find possible new logics to access to the transformation (research of new reactions)
- **Novel routes are patentable and may extend the product lifetime of say an active substance.**

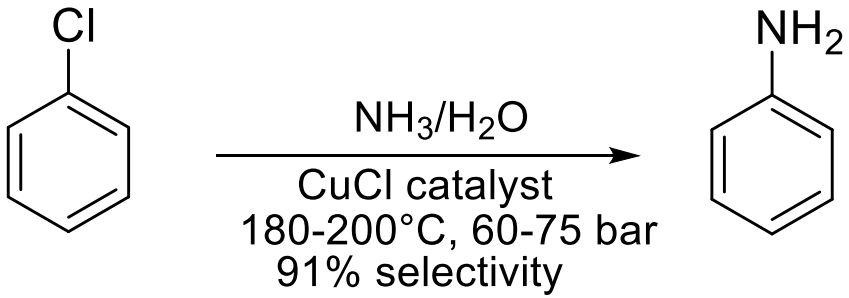
Alternative Routes to Aniline (1).



Alternative Routes to Aniline (2).



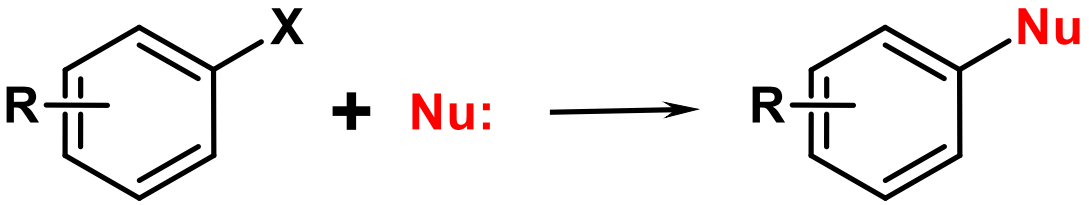
Du Pont process.
Hydrogen generated reduces catalyst, so catalyst regeneration is required



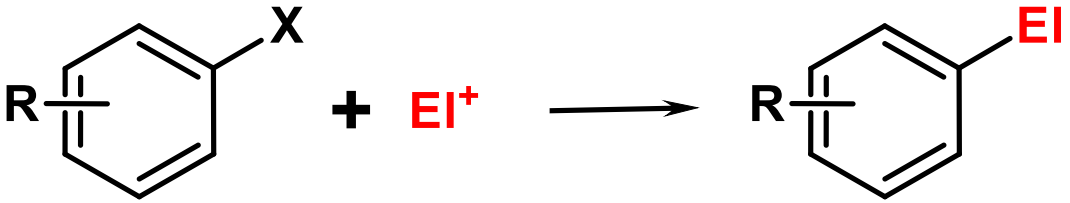
Kanto process.
(also previously operated by Dow, but closed in 1966)

Aromatic Substitutions.

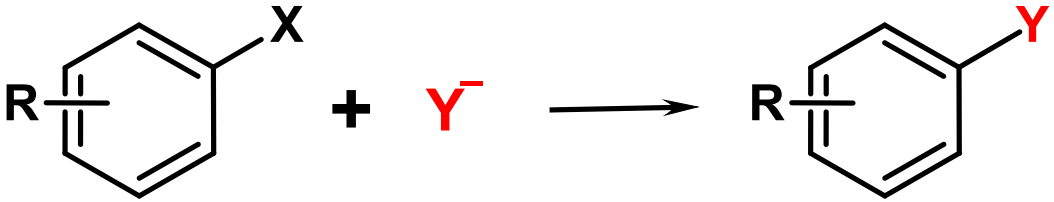
Nucleophilic
(S_NAr)



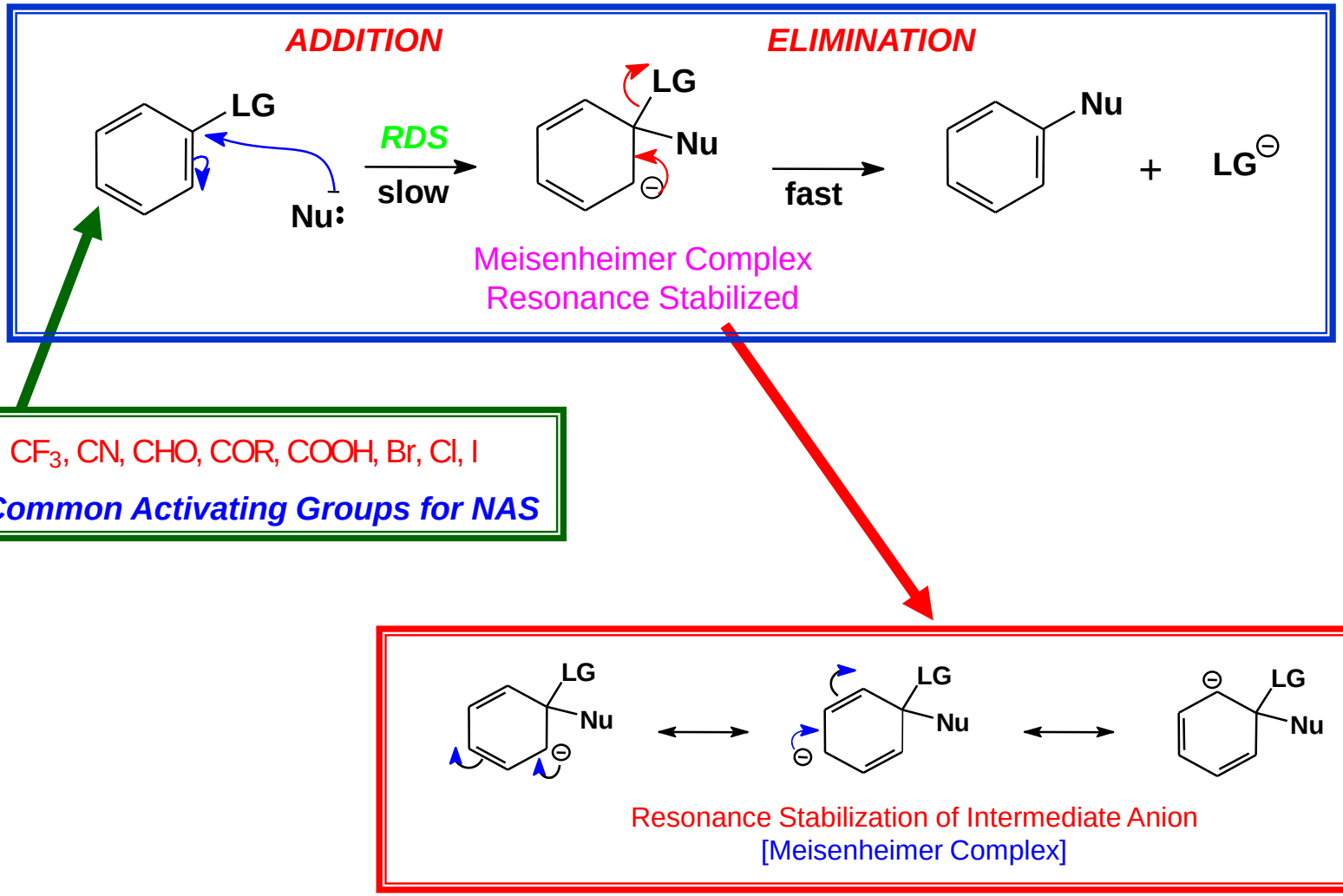
Electrophilic
(S_EAr)



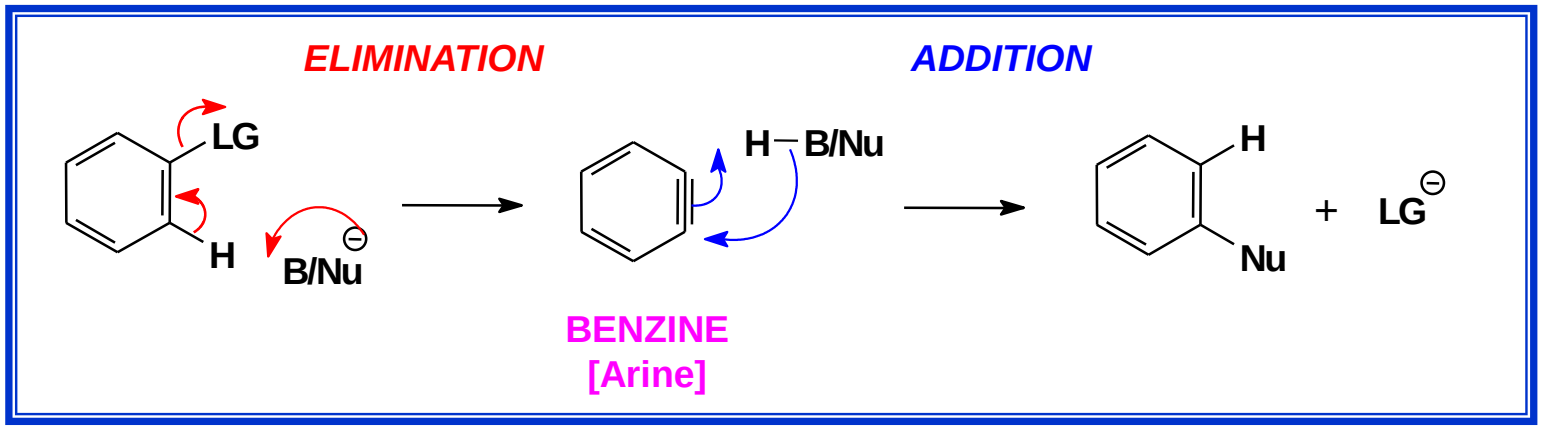
Radical
(S_RAr)



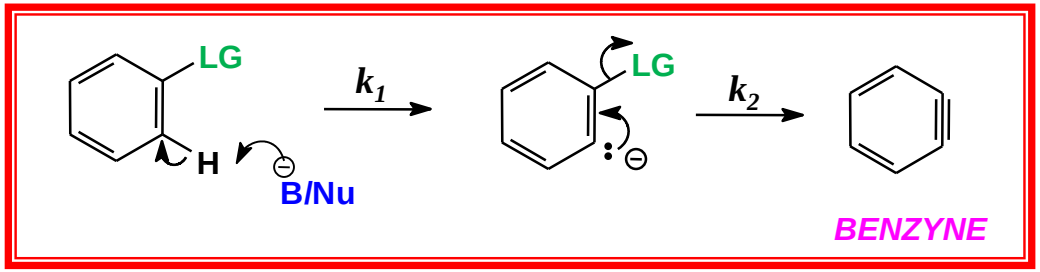
S_NAr Mechanism - Addition/Elimination.



Benzyne Mechanism - Elimination/Addition.

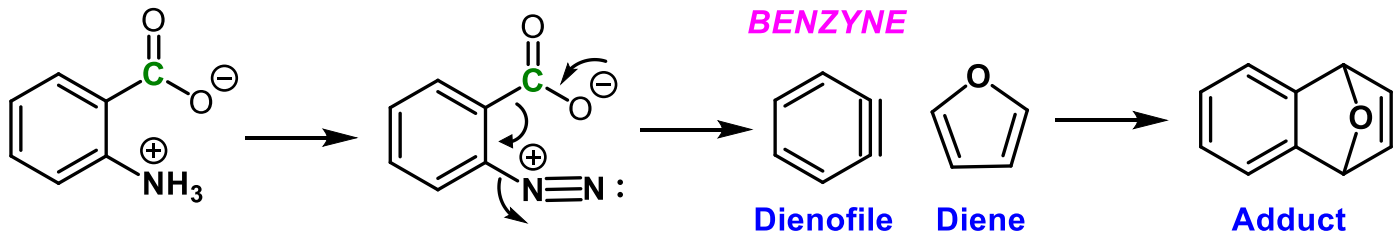


Step Formation of Benzyne

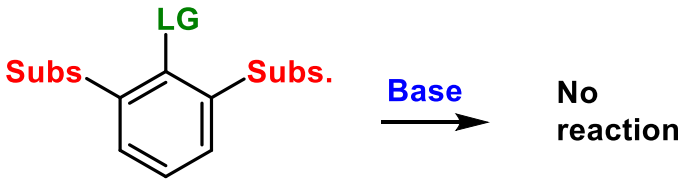


Evidences of Benzyne Mechanism.

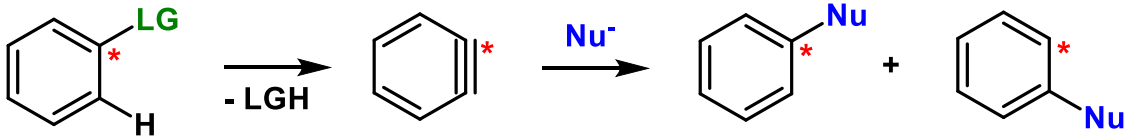
Trapping in Diels/Alder Reaction



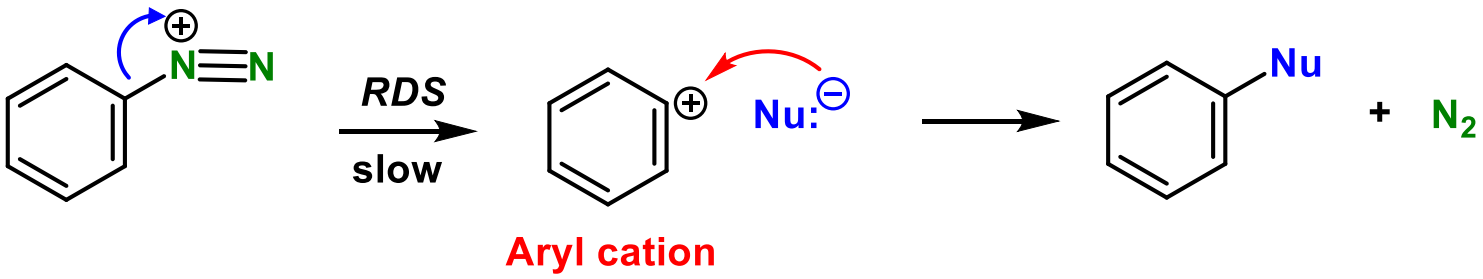
Substrate Change – absence of α–hydrogens



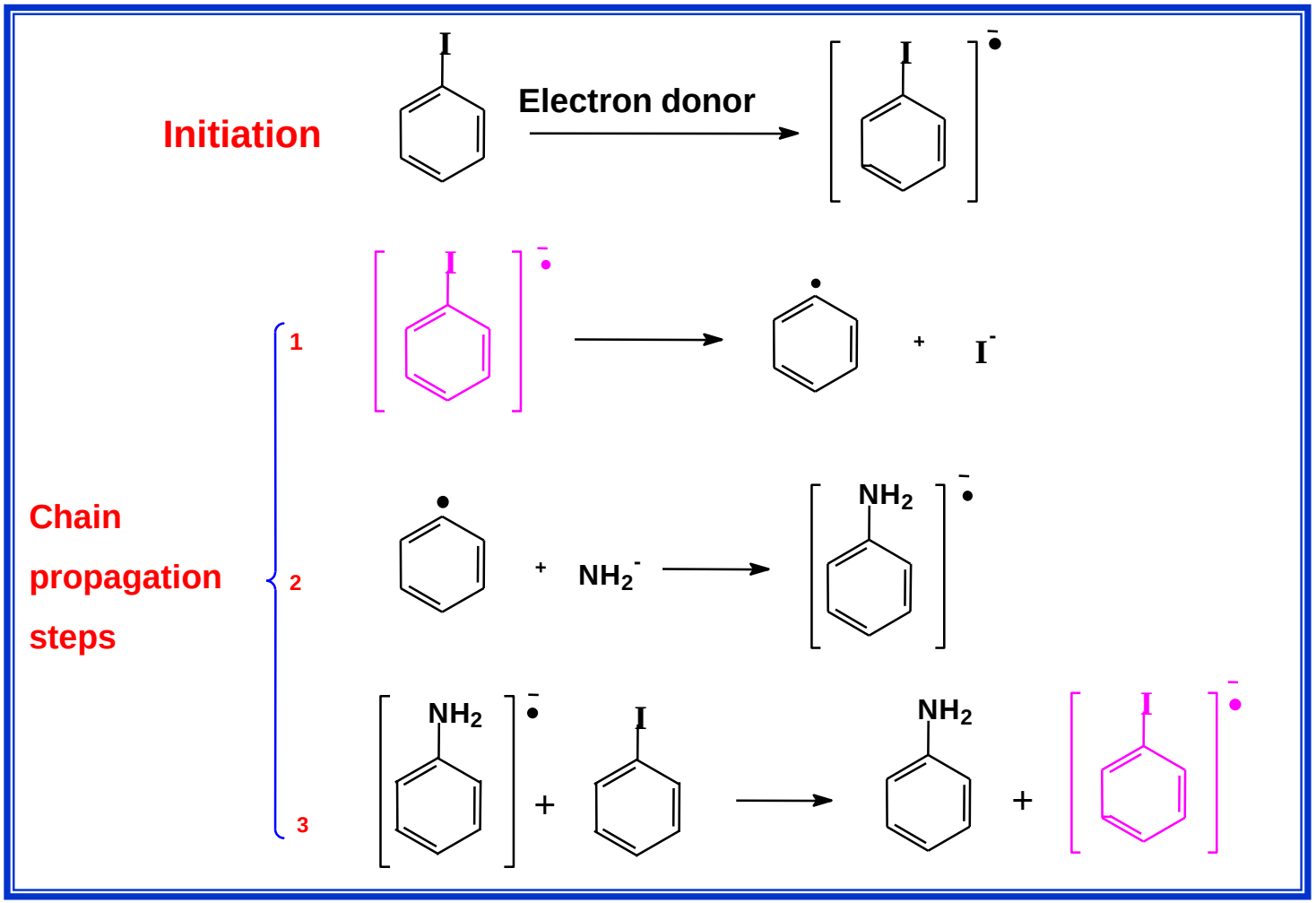
Isotopic Marker



S_N1 Mechanism in Diazonium Salts.

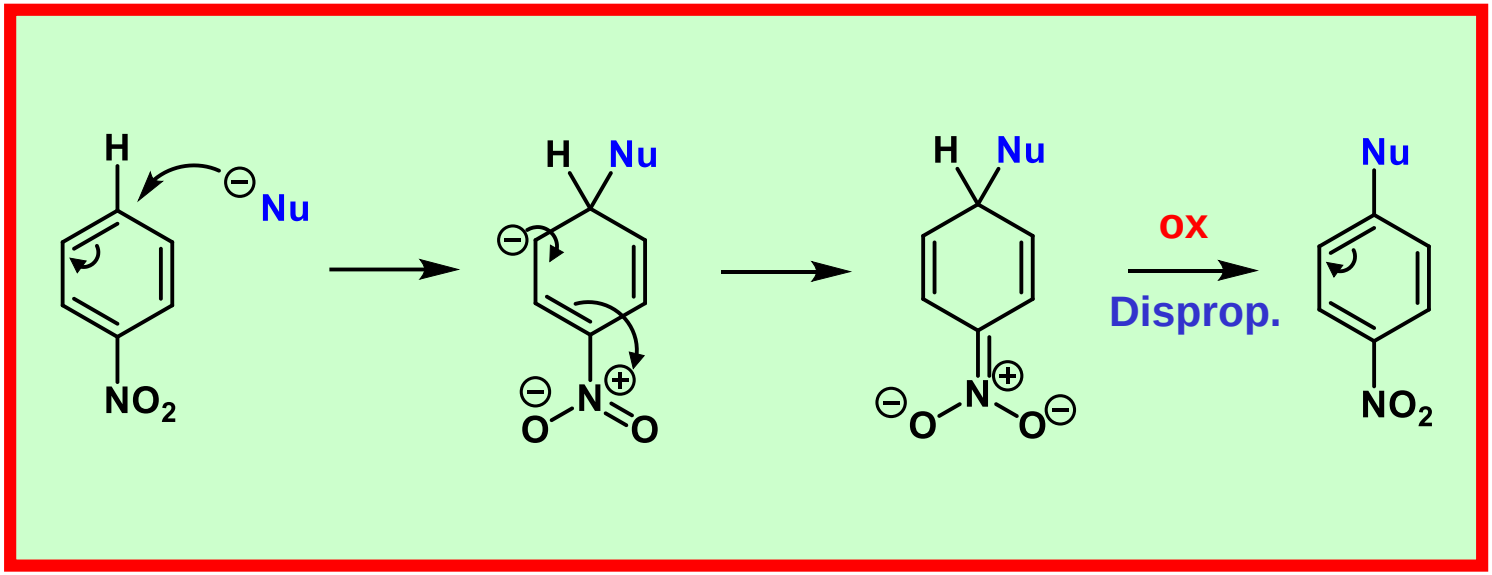


$S_{NR}1$ Mechanism.



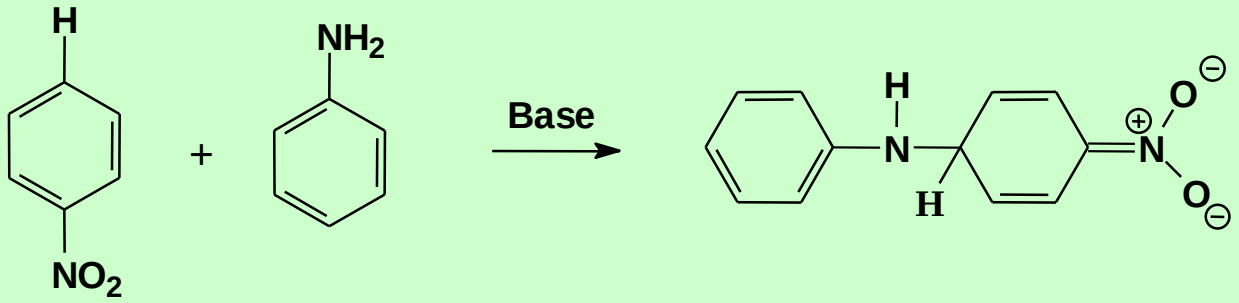
Aromatic Nucleophilic Substitution to Hydrogen (VNC).

General Mechanism



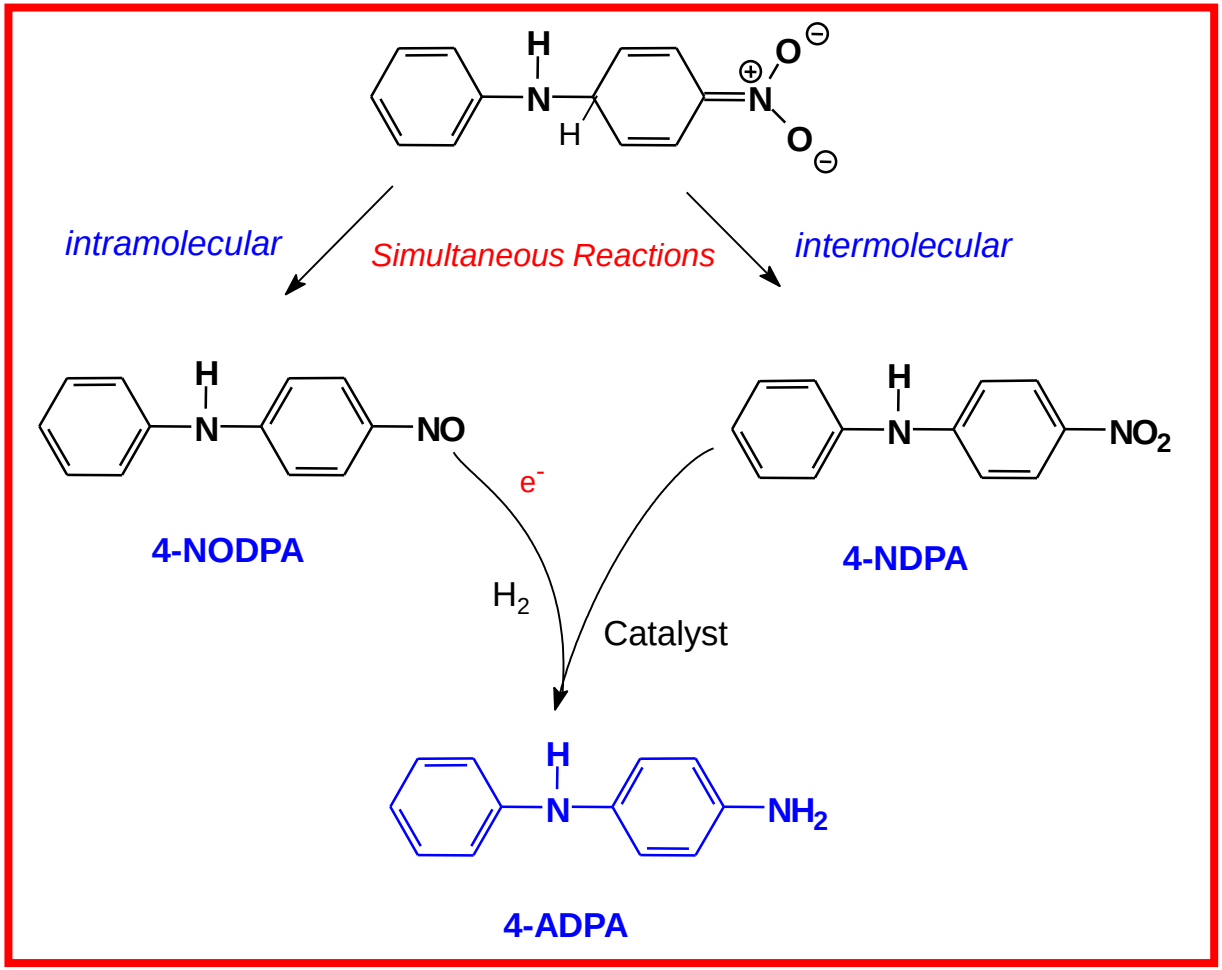
Base Promoted VNC Amination Reaction.

Base promoted coupling reaction

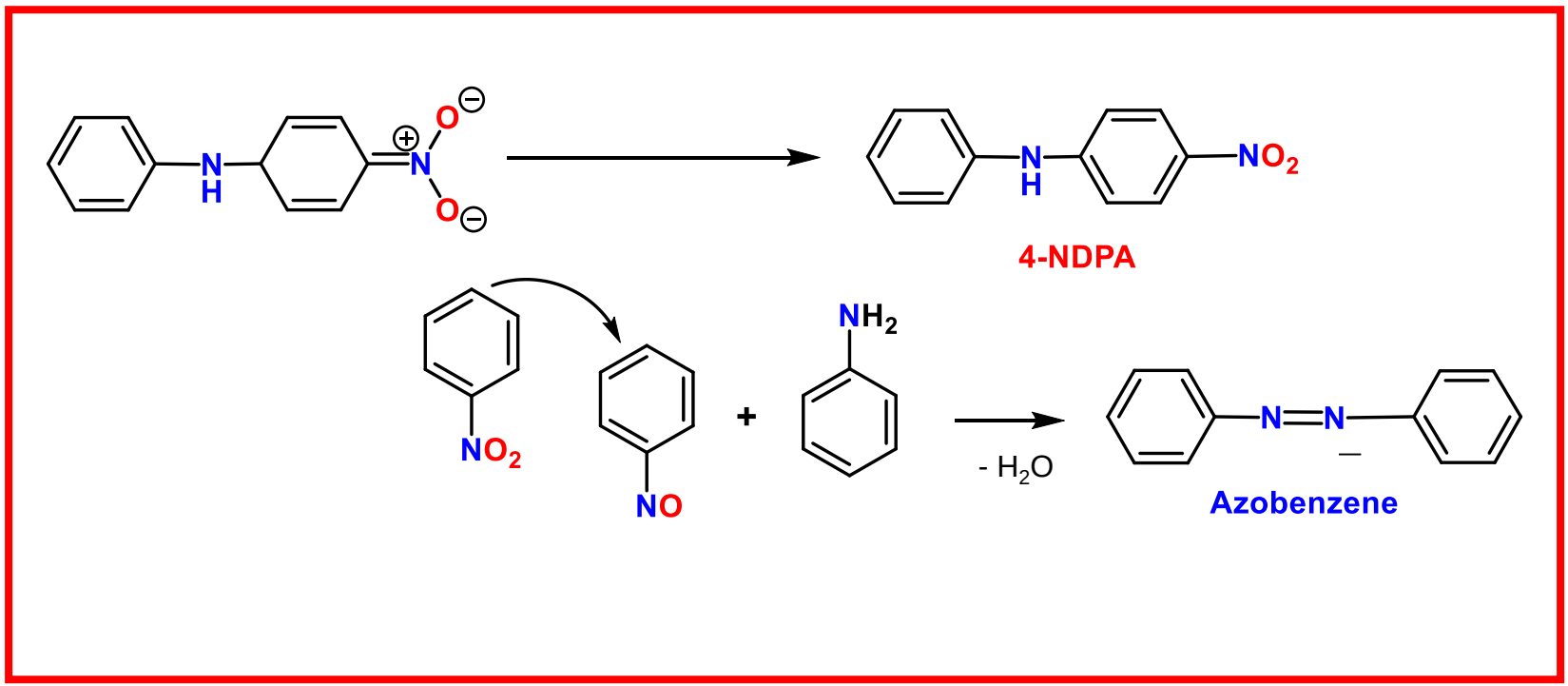


Flexsys - Anaerobic Oxidation to 4-NDPA

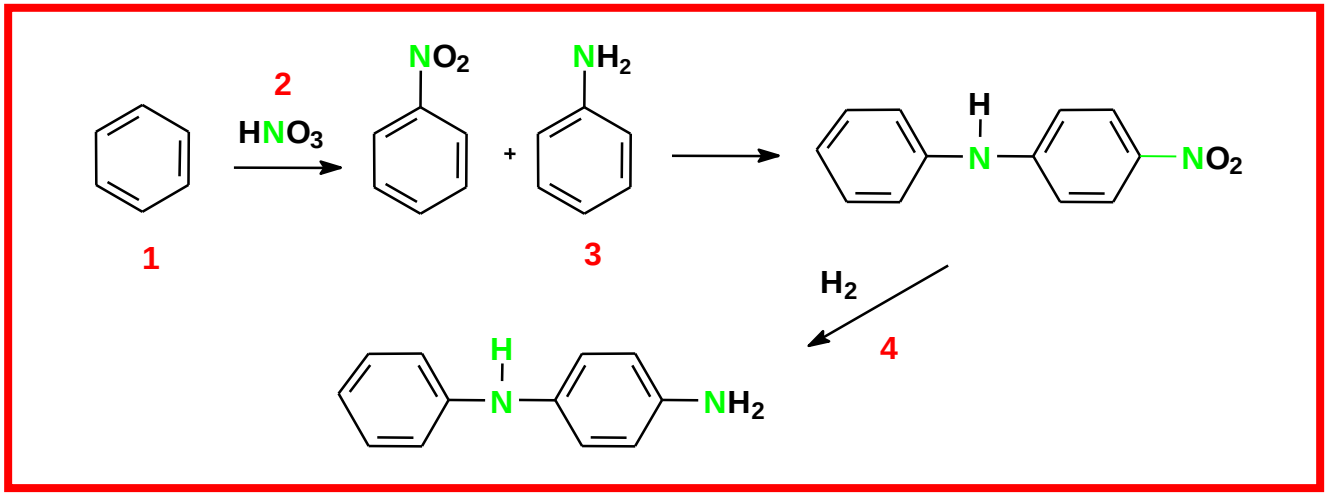
(rubber stabilizer - 130,000 ton/anno).



Flexsys - Anaerobic Oxidation to 4-NDPA.



Atom Efficiency in VNC Reaction.



Reagent Formula	Reagent MW	Used Atoms	Weight	Unused Atoms	Weight
1 C_6H_6	78	6 C, 4 H	76	2 H	2
2 HNO_3	63	1 N	14	1 H, 3 O	49
3 C_6H_7N	93	6 C, 6 H, N	92	1 H	1
4 H_2	2	2 H	2	----------	0
TOTAL	236	12C, 12 h, 2 n	184	4H, 3O	52

Benefits of VNS Flexys Approach.

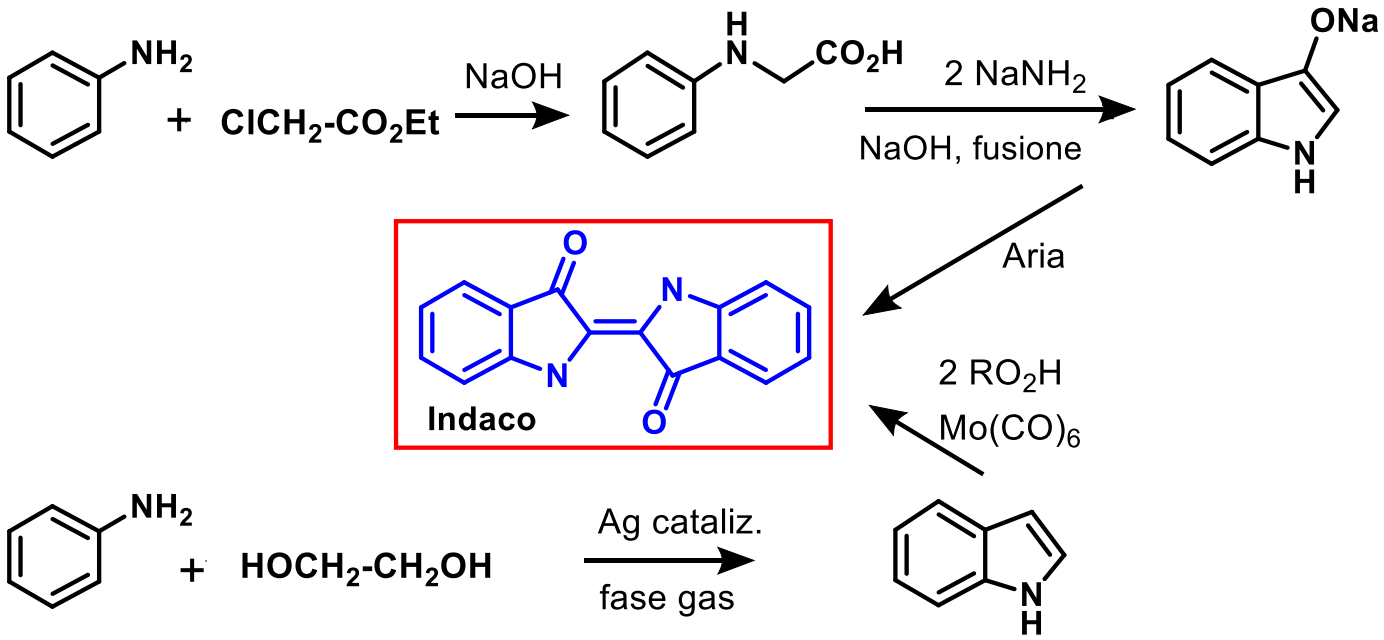
- ***Reduction of waste generation***
  - elimination of
  - 74% of organic wastes
  - 99% of inorganic wastes
- ***Elimination of chlorine use***
- ***Water reduction in wastes***
  - saving higher than 97%
- ***Elimination of xylene use*** (a SARA chemical)
- ***Improvement of process safety***
  - Lower reaction temperature
- ***Lower costs***

Development and Scale up of a Synthesis.

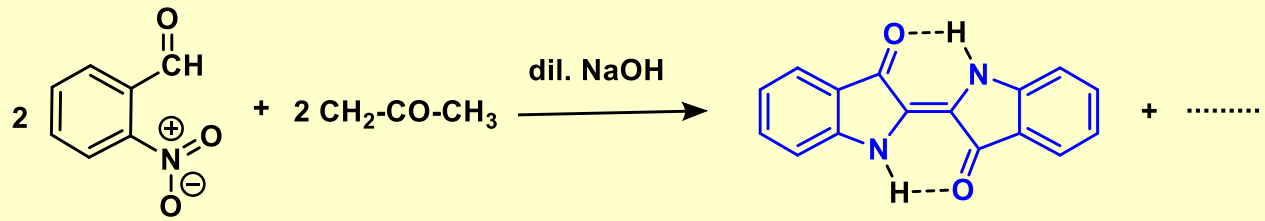
PROCESS RESEARCH

- New Synthetic Routes
- Some Initial Optimization
- Yield improvement
- Possible scale up to large laboratory equipment (up to 20L), then pilot plant translation
- Optimization by design of experiments
- Lower changes of route/intermediates
- More cheap reagents
- More eco-compatible reagents
- Improve yield/productivity
- Application of Statistical Methods (i.e. FED/Simplex)
- Process Analytical Technology (PAT)

Alternative Routes to Indigo.



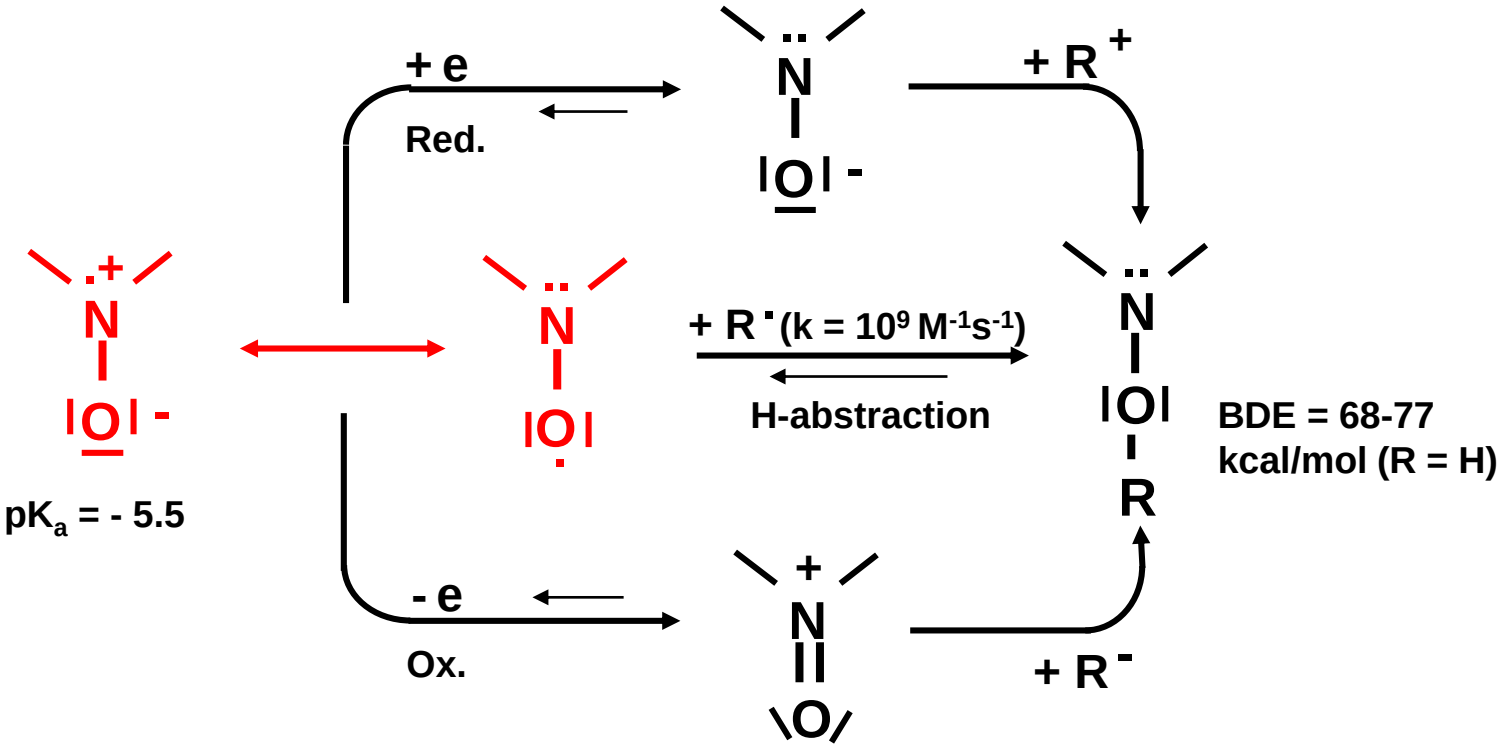
BAEYER-DREWSON INDACO SYNTHESIS



3-nitrobenzaldehyde

(2E)-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene)-1,2-dihydro-3H-indol-3-one

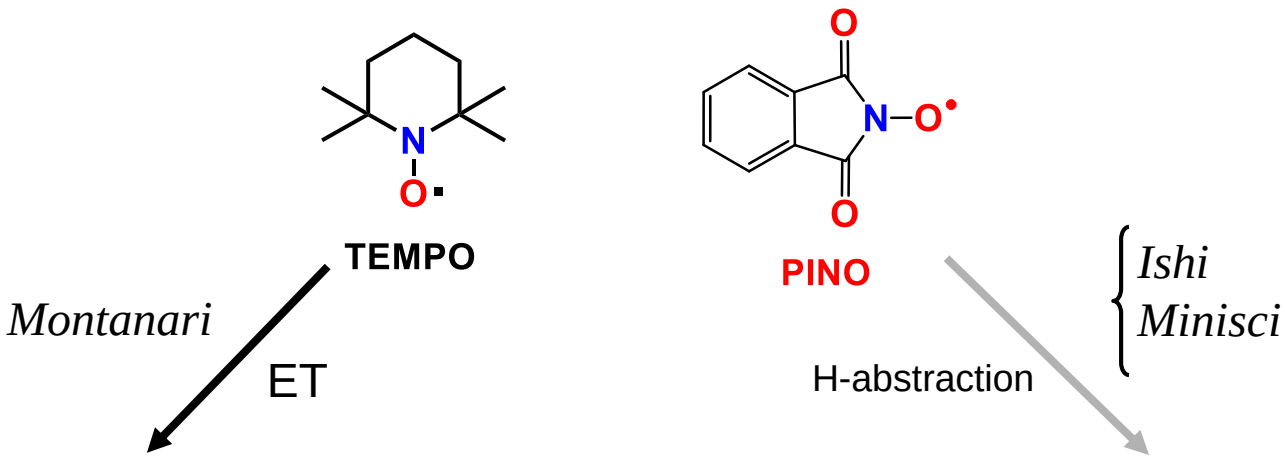
Oxidations through Nitroxide Radicals: $R_2NO^{\bullet}$ Chemistry.

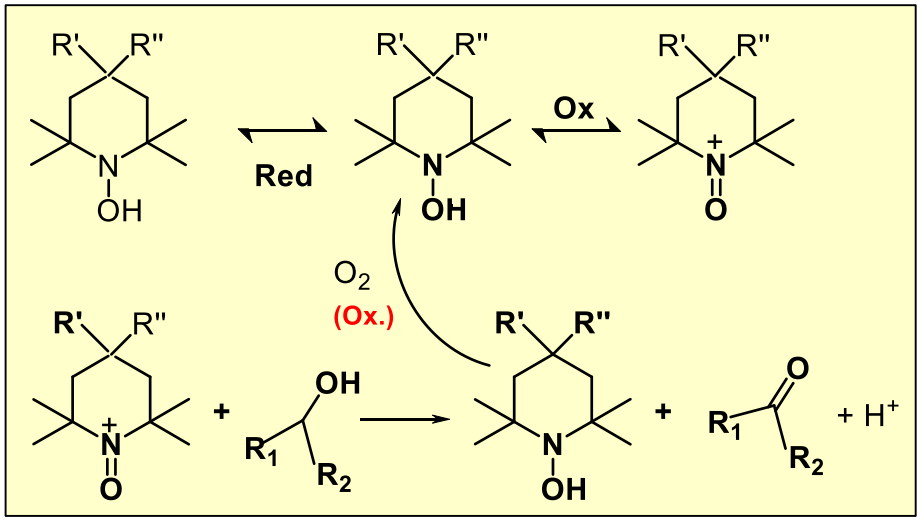


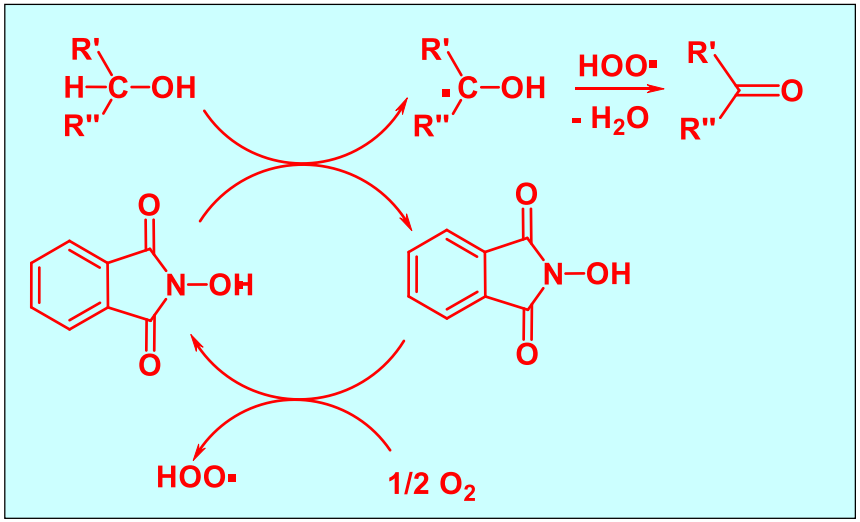
Nitroxide	$E_{1/2}$	$E_{1/2}$ (V) (H_2O)
Di t-Bu	0.187	0.657
TEMPO	0.203	0.728
4-OH-TEMPO	0.224	0.813

Nitroxide	$E_{1/2}$ (V)
4-O-TEMPO	0.301
Fremy Salt	0.901
Succinimide-N-oxyl	1.112

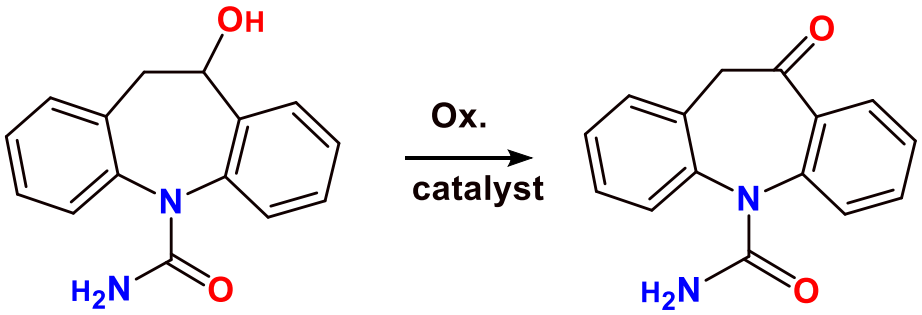
Catalysis by Nitroxide Radicals in the Oxidation of Alcohols with O_2.





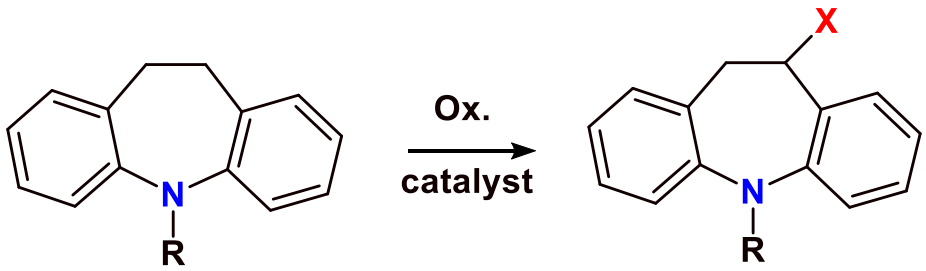


Oxidation of 10-Hydroxycarbamazepine.



Catalytic System	T (°C)	Oxidant	Solvent	Yield (%)
Time (2%)	0-30	NaClO (1.1) pH 8.2	H_2O/AcOEt	85-93
Time (2%)	0-70	O_2	"	12-25
PINO (5%) /Co(0.5%)	70	O_2	AN	36
PINO (5%) /Keggin-V(2%)	70	O_2	AN	29
PINO (5%)/Keggin Cu(2%)	70	O_2	$H_2O/CF_3C_6H_5$	64

Oxidation of 10,11-Dihydro Derivative.

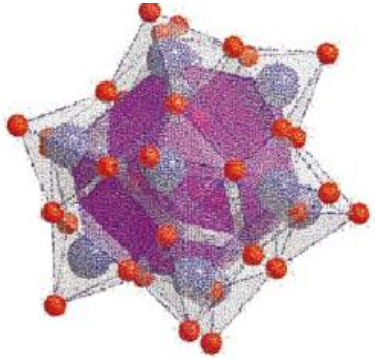


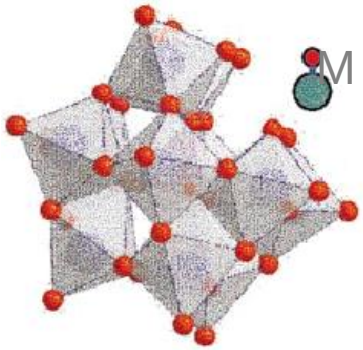
X = OH, O, …
R = CN

Catalytic System	T (°C)	Oxidant	Solvent	Yield (%)	
Time (2%)	0-70	NaClO	H_2O/AcOEt	0	
Time (2%)	0-70	O_2	"	3-5	
PINO (5%) /Co (0.5%)	70	O_2	AN	11 (O)	Ishi
PINO (5%) /Keggin (2%)	70	O_2	AN	16 (OH) 12(O)	Minisci*
PINO (5%)/ Keggin Cu^{2+} (2%)	70	O_2	$H_2O/CF_3C_6H_5$	10 (OH) 31(O)	

*Minisci, F. et al., Eur. Pat. 12658 (1999)

Keggin Systems for Alkylaromatic Oxidation with Molecular Oxygen.

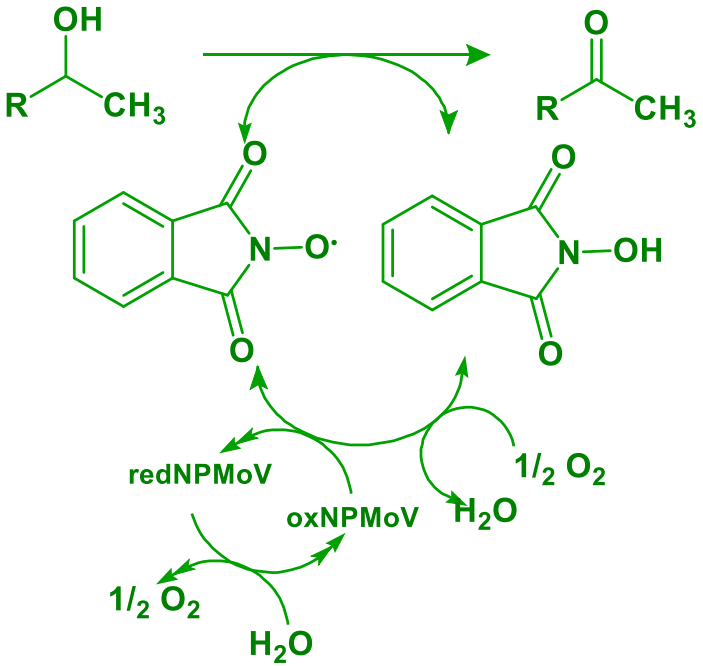




Defective Keggin
(insertion of metal cations)

Keggin

$H_4PVMo_{11}O_{40}$

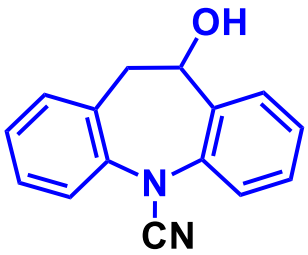


Peculiarity:

- Heterogeneous
- Work by electron and ligand transfer
- Direct and indirect mechanism

Catalytic System Selection: Combinatorial Analysis.

Steel Reactor
a 8x12 1ml vials
P_{max} = 20 bar



	0.5 Cu^{II}	1.0 Cu^{II}	0.5 Fe^{II}	1.0 Fe^{II}	0.5 Fe^{III}	0.5 Mn^{II}	1.0 Mn^{II}	0.5 Co^{II}	1.0 Co^{II}	0.5/0.5 Cu^{II}/Fe^{II}	0,5/0,5 Co^{II}/Fe^{II}
V_1	V_1/Cu^{II}	V_1/Cu^{II}	V_1/Fe^{II}	V_1/Fe^{II}	V_1/Fe^{III}	V_1/Mn^{II}	V_1/Mn^{II}	V_1/Co^{II}	V_1/Co^{II}	$V_1/Cu^{II}/Fe^{II}$	$V_1/Co^{II}/Fe^{II}$
V_2	V_2/Cu^{II}	V_2/Cu^{II}	V_2/Fe^{II}	V_2/Fe^{II}	V_2/Fe^{III}	V_2/Mn^{II}	V_2/Mn^{II}	V_2/Co^{II}	V_2/Co^{II}	$V_2/Cu^{II}/Fe^{II}$	$V_2/Co^{II}/Fe^{II}$
V_3	V_3/Cu^{II}	V_3/Cu^{II}	V_3/Fe^{II}	V_3/Fe^{II}	V_3/Fe^{III}	V_3/Mn^{II}	V_3/Mn^{II}	V_3/Co^{II}	V_3/Co^{II}	$V_3/Cu^{II}/Fe^{II}$	$V_3/Co^{II}/Fe^{II}$
V_1/N	$V_1/N/Cu^{II}$	$V_1/N/Cu^{II}$	$V_1/N/Fe^{II}$	$V_1/N/Fe^{II}$	$V_1/N/Fe^{III}$	$V_1/N/Mn^{II}$	$V_1/N/Mn^{II}$	$V_1/N/Co^{II}$	$V_1/N/Co^{II}$	$V_1/N/Cu^{II}/Fe^{II}$	$V_1/N/Co^{II}/Fe^{II}$
V_2/N	$V_2/N/Cu^{II}$	$V_2/N/Cu^{II}$	$V_2/N/Fe^{II}$	$V_2/N/Fe^{II}$	$V_2/N/Fe^{III}$	$V_2/N/Mn^{II}$	$V_2/N/Mn^{II}$	$V_2/N/Co^{II}$	$V_2/N/Co^{II}$	$V_2/N/Cu^{II}/Fe^{II}$	$V_2/N/Co^{II}/Fe^{II}$
V_3/N	$V_3/N/Cu^{II}$	$V_3/N/Cu^{II}$	$V_3/N/Fe^{II}$	$V_3/N/Fe^{II}$	$V_3/N/Fe^{III}$	$V_3/N/Mn^{II}$	$V_3/N/Mn^{II}$	$V_3/N/Co^{II}$	$V_3/N/Co^{II}$	$V_3/N/Cu^{II}/Fe^{II}$	$V_3/N/Co^{II}/Fe^{II}$
VD_1	VD_1/Cu^{II}	VD_1/Cu^{II}	VD_1/Fe^{II}	VD_1/Fe^{II}	$VD_1//Fe^{III}$	VD_1/Mn^{II}	VD_1/Mn^{II}	VD_1/Co^{II}	VD_1/Co^{II}	$VD_1/Cu^{II}/Fe^{II}$	$VD_1/Co^{II}/Fe^{II}$
VD_1/N	$VD_1/N/Cu^{II}$	$VD_1/N/Cu^{II}$	$VD_1/N/Fe^{II}$	$VD_1/N/Fe^{II}$	$VD_1/N/Fe^{III}$	$VD_1/N/Mn^{II}$	$VD_1/N/Mn^{II}$	$VD_1/N/Co^{II}$	$VD_1/N/Co^{II}$	$VD_1/N/Cu^{II}/Fe^{II}$	$VD_1/N/Co^{II}/Fe^{II}$

Optimization of Catalytic System.

	0,5 Cu^{II}	1,0 Cu^{II}	0,5 Fe^{II}	1,0 Fe^{II}	0,5 Fe^{III}	0,5 Mn^{II}	1,0 Mn^{II}	0,5 Co^{II}	1,0 Co^{II}	0,5/0,5 Cu^{II}/Fe^{II}	0,5/0,5 Co^{II}/Fe^{II}
V_1											
V_2											
V_3											
V_1/N											
V_2/N											
V_3/N											
VD_1											
VD_1/N											

P = 1 bar

	0,5 Cu^{II}	1,0 Cu^{II}	0,5 Fe^{II}	1,0 Fe^{II}	0,5 Fe^{III}	0,5 Mn^{II}	1,0 Mn^{II}	0,5 Co^{II}	1,0 Co^{II}	0,5/0,5 Cu^{II}/Fe^{II}	0,5/0,5 Co^{II}/Fe^{II}
V_1											
V_2											
V_3											
V_1/N											
V_2/N											
V_3/N											
VD_1											
VD_1/N											

P = 3 bar

- **Yield < 20%**
- **20% < Yield < 40%**
- **40% < Yield < 60%**
- **60% < Yield < 80%**
- **Yield > 80%**

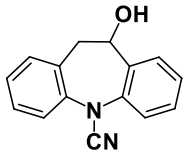
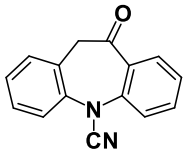
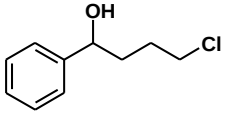
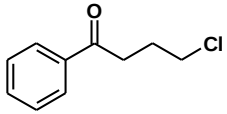
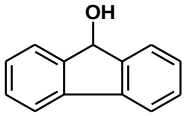
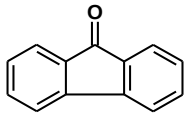
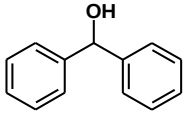
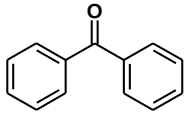
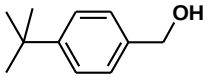
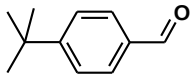
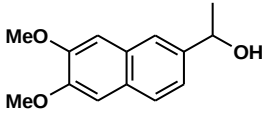
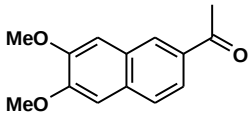
Co-catalyst Fe/Cu,Co

- **Defective Keggin are more active than the intact in the presence of transition metal ions**
- **Bimetallic systems Cu(II)/Fe(II) e Co(II)/Fe(II) afford the best yield(> 80%)**

Development of Catalytic System in Autoclave via Chemometrics.

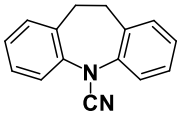
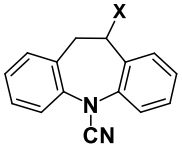
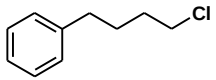
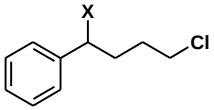
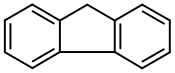
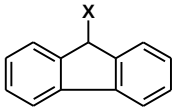
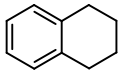
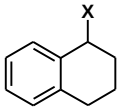
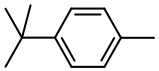
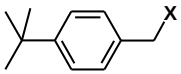
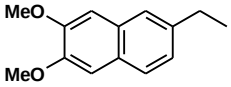
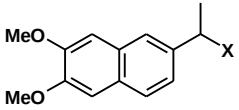
Run	VD_1	$Cu(NO_3)_2$	$Fe(SO_4)_2$	NHPI	T(°C)	[Ar]	Yield(%)
1	-	-	-	-	-	-	65
2	+	-	-	-	-	-	66
3	-	+	-	-	-	-	69
4	-	-	+	-	-	-	60
5	-	-	-	+	-	-	75
6	-	-	-	-	+	-	71
7	+	+	-	-	-	-	86
8	+	-	-	+	+	-	91
9	+	+	+	-	-	-	66
10	+	+	+	+	-	-	81
11	+	+	+	+	+	-	88
12	+	+	+	+	+	+	73

Oxidation of Benzylic Alcohols by O_2 Catalyzed by defective NHPI/Keggin(V).

Run	Alcohol	Product	Yield (%)	Time (h)
1			91	8
2			92	12
3			93	9
4			88	10
5			68	8
6			91	6

a reaction condition: 30°C, 1 atm O2, Cat. [Fe/Cu (2:1)] 1 %, CH3CN. The yield are based on the isolated material of >95% purity b GC–MS yield.

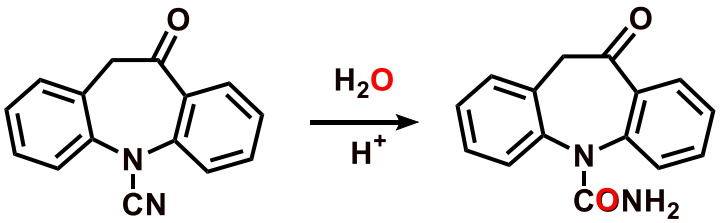
Oxidation of Benzylic Methylene by O_2 Catalyzed by NHPI/ Defective Keggin(V).

Run[a]	Aromatic	Product	Yield%[b] (X)	Time (h)
1			15(OH) 60(O)	8
2			19(OH) 68(O)	12
3			11(OH) 82(O)	9
4			12(OH) 64(O)	8
5			16(OH) 12(O)[c]	8
6			3(OH) 38(O)	8

[a] reaction conditions: 50°C, 1 atm O_2, Cat. [Fe/Cu (2:1)] 2 %, NHPI 2%, CH_3CN. [B] Yield were determined by GC-MS; for runs 1 and 2 are on isolated product with >95% purity. [c] 44% of corresponding acid; 84% a 24 h.

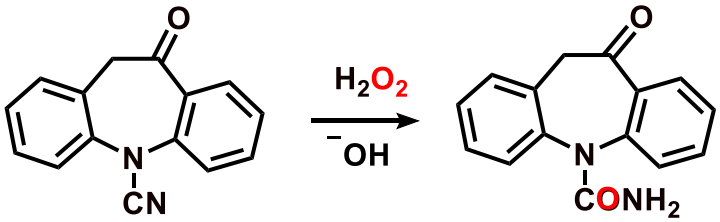
Conversion CN → $CONH_2$.

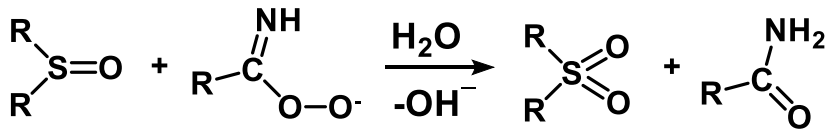
A)



Conditions	Yield %	AE%
H_2SO_4 (sol. 30%) RT	95	20
Amberlist 15 (12 h)	91	88

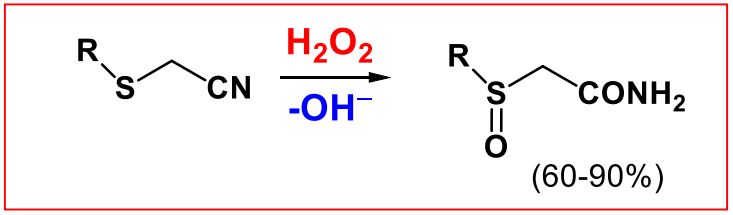
B)





Resa %	AE%
96	55(75)

RT, 0.7 h, 3% K_2CO_3



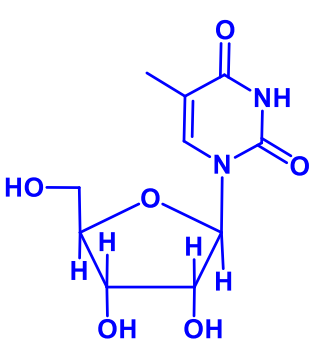
Reduce Derivatives





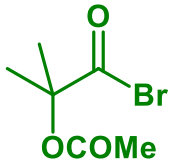
Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized avoided if possible, because such steps require additional reagents and can generate waste.

Homolytic Reduction of 1,2-diols to Alkenes.



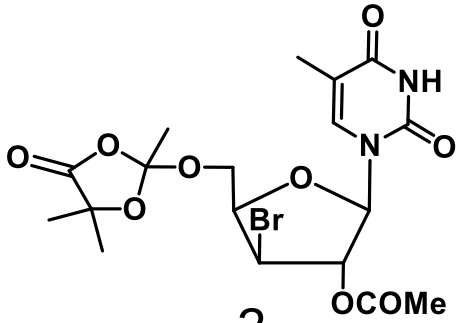
1

2.5



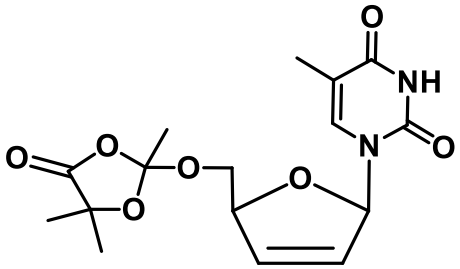
MeCN/4h

55 %



2

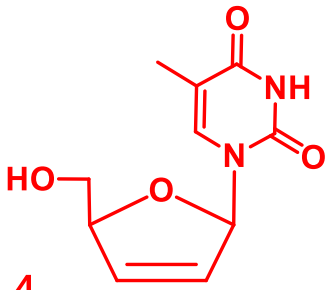
80 % Zn/MeCN/AcOH
25°C/8 h



3

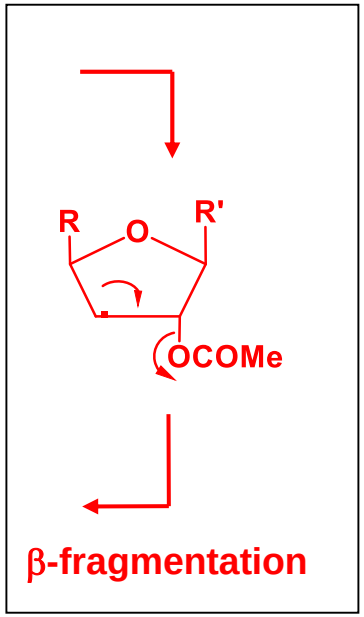
KOH/MeOH
20°C/5 h

93 %



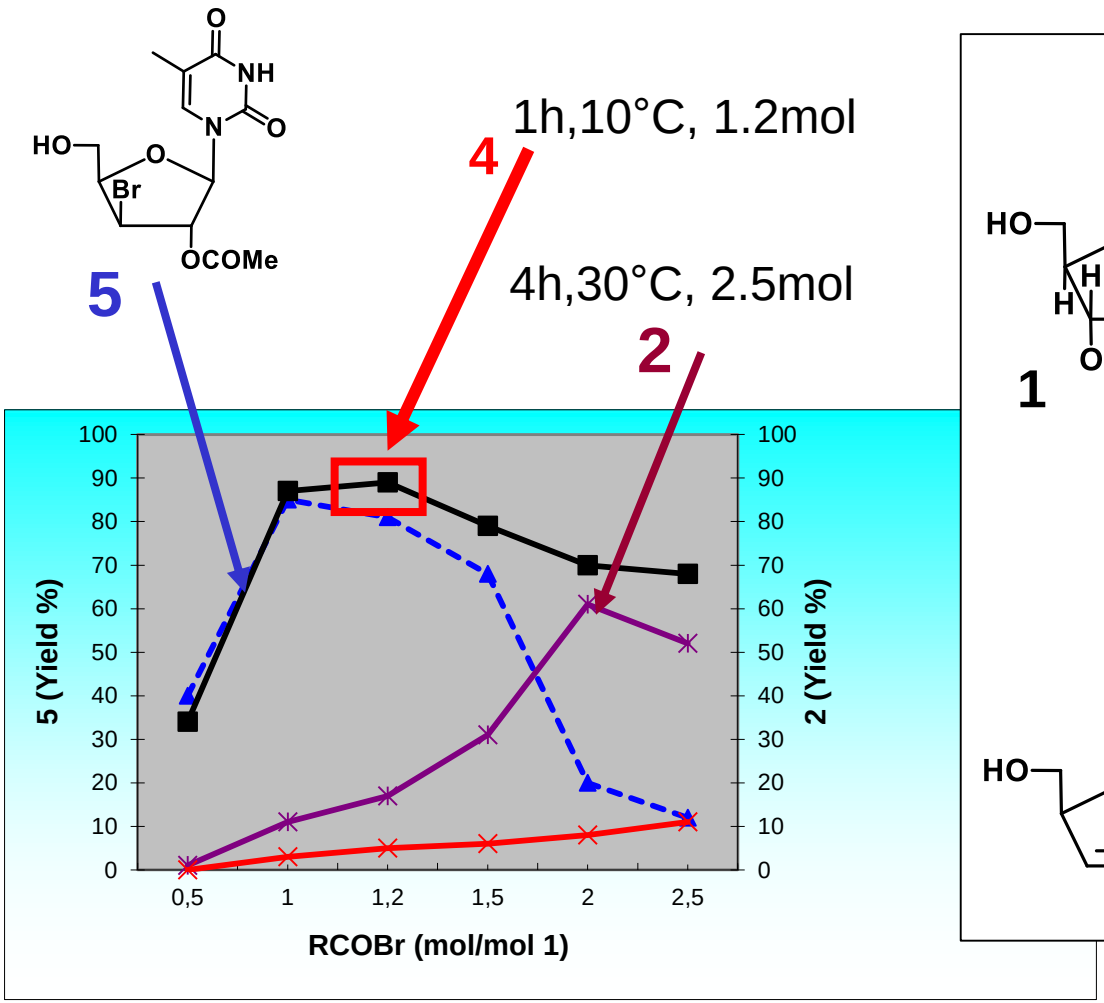
4

One step?



Overall yield = 41 %
E Factor = 18

One step Synthesis: Relevance of Kinetic Data.



1

1,2

MeCN/H_2O(5%)(0.7 h, 10°C)
Zn/$TiCl_3$/AcOH (1.5 h, 10°C)

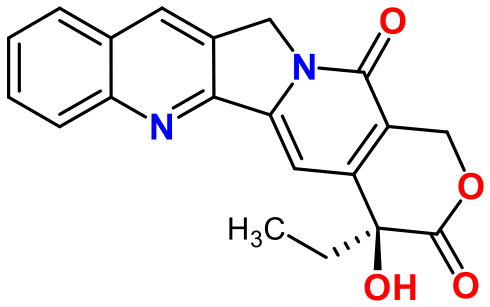
4

total yield 89%
E Factor = 4.2

Compact Synthesis
(reduce the number of steps).

The number of steps must be limited through a careful molecular design and with the aid of all chemical knowledge.

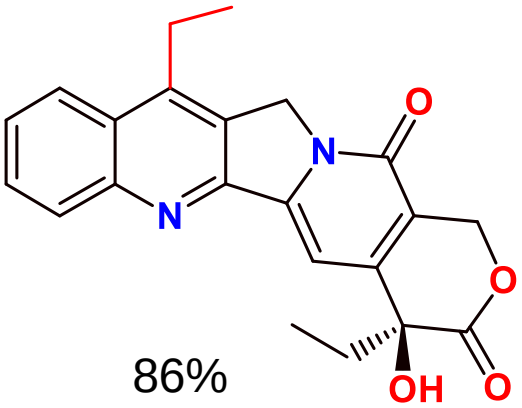
Synthesis of Camptothecin Derivatives by Homolytic Heteroaromatic Substitution.



Camptothecin

$EtCOCO_2H$
$S_2O_8^{2-}/Ag^+$

H_2SO_4 23%,
$C_6H_5CH_3$



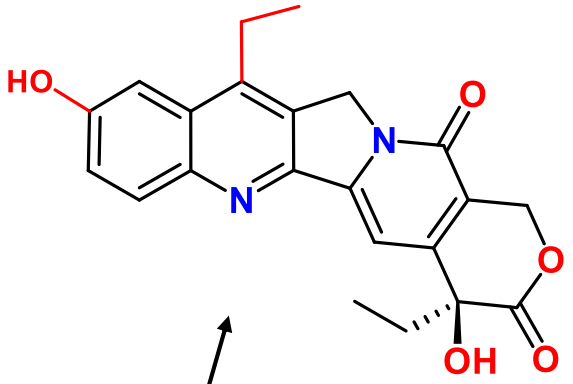
86%

$H_2O_2/h\nu$

H_2SO_4 23%

76%

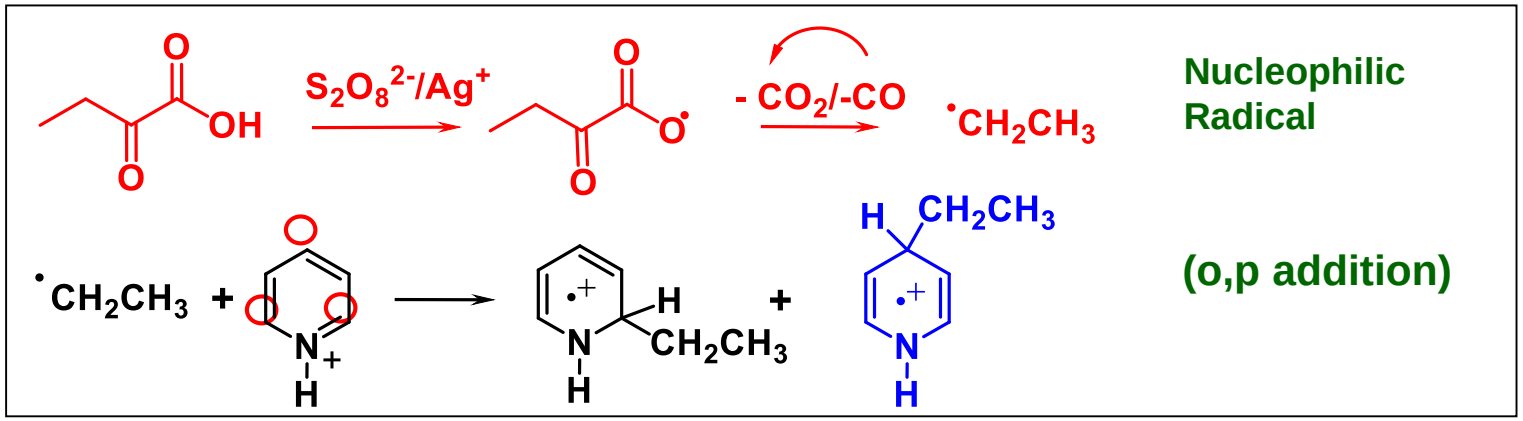
E = 6.1



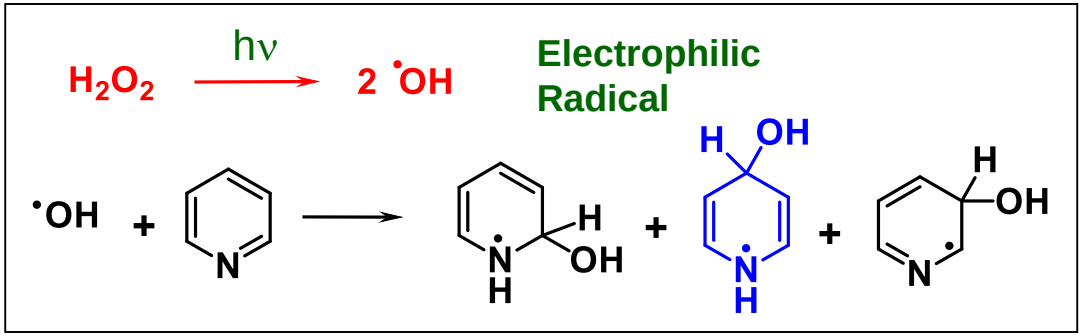
4-Ethyl-6-hydroxy Camptothecin

(reported yield: 3%
12 step sequence
- Patent JP 72132.01)
E = 62!

Heteroaromatic Substitution by Ethyl and Hydroxy Radicals.



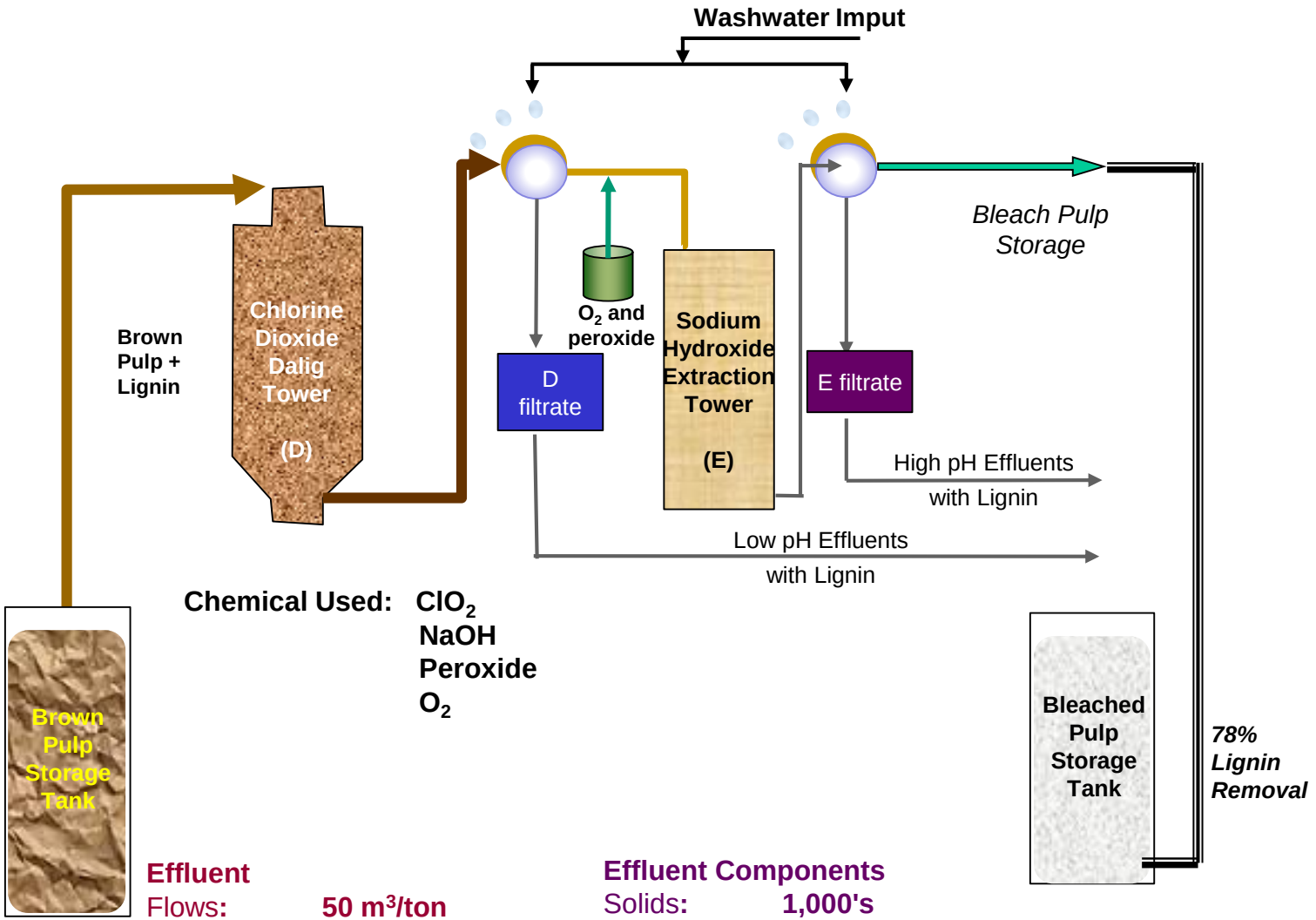
Conditions: a 0,8 M $K_2S_2O_8$ solution is added in 3 h to a biphasic system [23% H_2SO_4 solution, containing 2-ketobutiric acid and $AgNO_3$ (1 mol %), and toluene], stirred at 1600 rpm at 45°C.



Reagent (Toxic) Substitution: More Benign Synthesis.

When possible, inherently safer syntheses must be designed which use or produce chemicals less toxic to man and environment.

Comparison of Lignin Removal from Wood: Traditional Method.



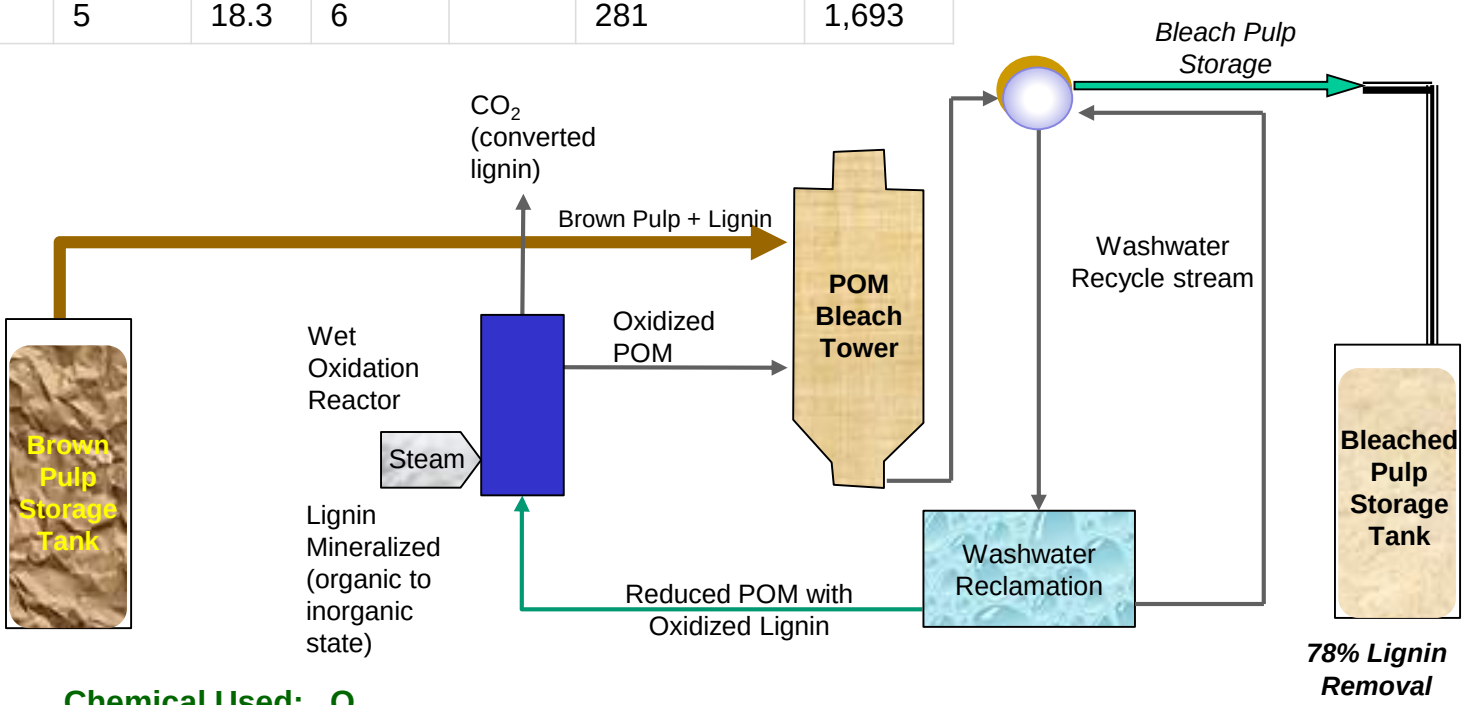
Effluent
Flows: **50 m^3/ton**
Composition: AOX, Organics

Effluent Components
Solids: **1,000's**
Color: Coffee/Tea
Treatment: 1°, 2°, 3°

Comparison of Lignin Removal from Wood: Alternative "Green" Method.

	Process Stream Inputs						Energy Inputs	
	NaOH	O_2	H_2SO_4	ClO_2	H2O2	POM	Electricity (kW-hr/MT)	Steam (kg/MT)
POM		137				0.27	277	2,858
DEop	24	5	5	18.3	6		281	1,693

1000 kg of Bleached Pulp



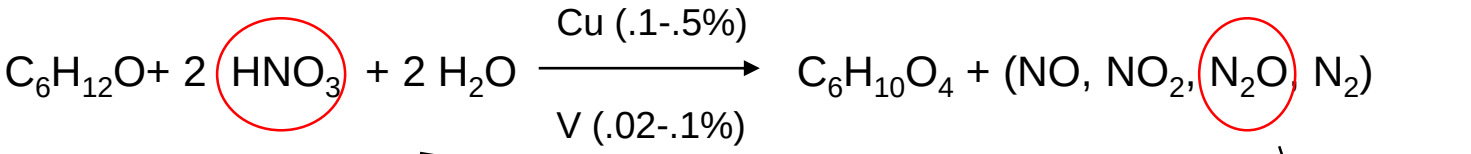
Chemical Used: O_2
POM

Effluent
Flows: **0.2 m³/ton**
Composition: Evaporation condensate, mainly ethanol

Effluent Components
Solids: **0**
Color: clear
Treatment: none

Adipic Acid Synthesis
Traditional vs. New.

Traditional Route - from cyclohexanol/cyclohexanone



92-96% Yield of Adipic Acid

hazardous

global warming
ozone depletion

- Carbon - 100%
- Oxygen - 4/9 x 100 = 44.4%
- Hydrogen - 10/18 x 100 = 55.6%
- Nitrogen - 0%

Product Mass = (6 C)(12) + (10 H)(1) + (4 O)(16) = 146 g

Reactant Mass = (6 C)(12) + (18 H)(1) + (9 O)(16) + (2 N)(14) = 262 g

Mass Efficiency = 146/262 x 100 = 55.7%

Davis and Kemp, 1991, Adipic Acid, in Kirk-Othmer Encyclopedia of Chemical Technology, V. 1, 466 - 493

Adipic Acid Synthesis
Traditional vs. New.

New Route - from cyclohexene

$$C_6H_{10} + 4\ H_2O_2 \xrightarrow[[CH_3(n\text{-}C_8H_{17})_3N]HSO_4\ (1\%)]{Na_2WO_4 \cdot 2H_2O\ (1\%)} C_6H_{10}O_4 + 4\ H_2O$$

90% Yield of Adipic Acid

- Carbon - 100%
- Oxygen - 4/8 x 100 = 50%
- Hydrogen - 10/18 x 100 = 55.6%

Product Mass = (6 C)(12) + (10 H)(1) + (4 O)(16) = 146 g

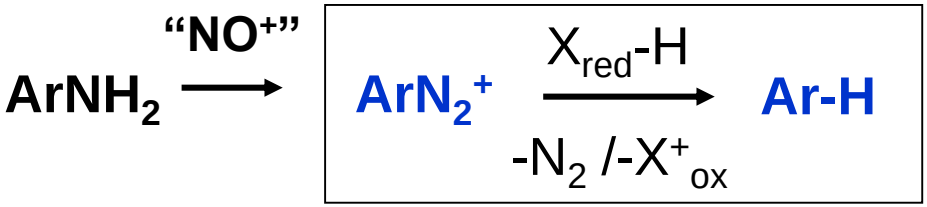
Reactant Mass = (6 C)(12) + (18 H)(1) + (8 O)(16) = 218 g

Mass Efficiency = 146/218 x 100 = 67%

Sato, et al. 1998, A "green" route to adipic acid:…, Science, V. 281, 11 Sept. 1646 - 1647

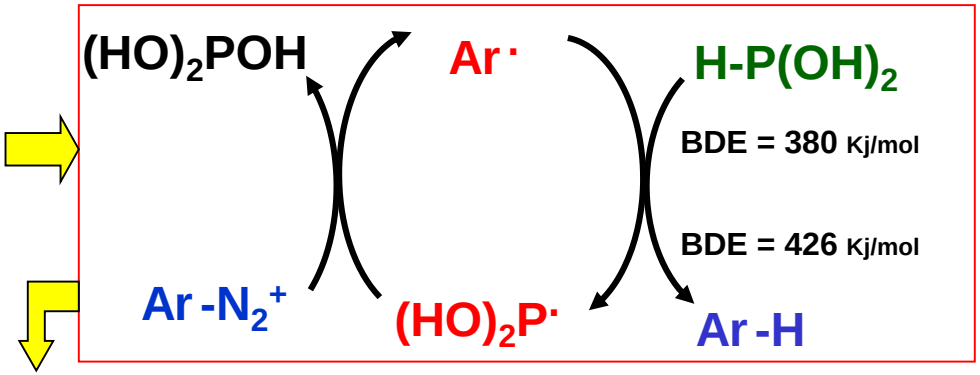
Redox Chain Radical Reaction: Hydrodediazoniation of Arendiazonium Salts.

N aromatic substitution by H



Reducing agents :

- H_3PO_2 (Kharasch 1950) used in excess (7-10)
- H-donor solvents (R-C(-H)Y- [Y = O, N,])
- RSH, R_2PH
- Hydroquinone, etc.



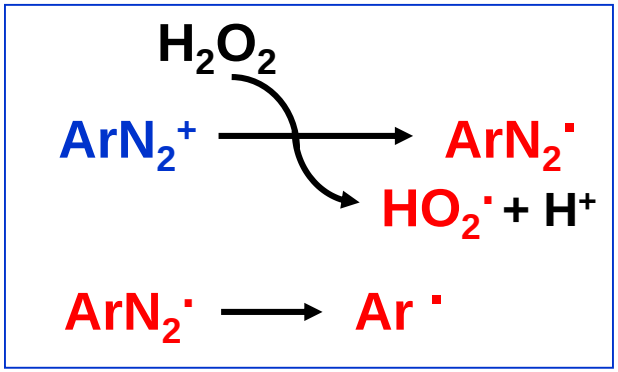
Problems:

1) High E factors and toxic reagents

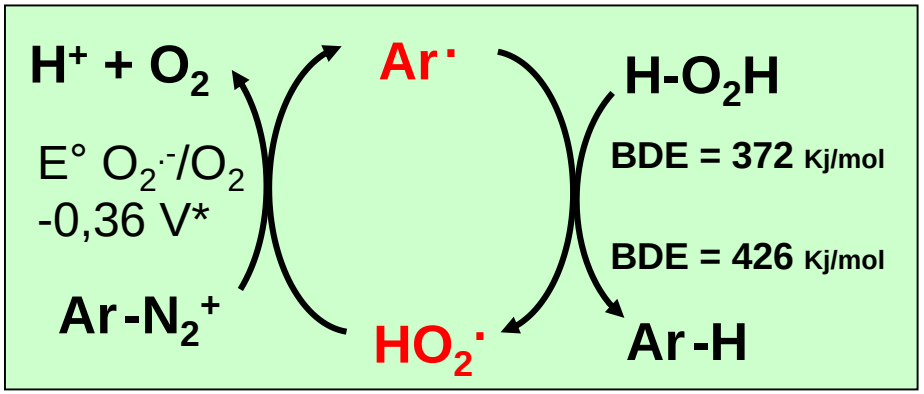
2) Safety, owing inefficient initiation

H_2O_2 as Homolytic Reducing Agent of Arendiazonium Salts.

$$ArN_2^+X^- + HOO\text{-}H \longrightarrow Ar\text{-}H + N_2 + HX + O_2$$



BDE Ar-N_2· = ~46 kJ/mol



E° ArN_2^+/ArN_2· = + 0,1-0.6 V vs SCE

Conditions: T = 30-50°C, H_2O pH = 3-5, H_2O_2 15-60% (5-10 mol), Arendiazonium salt added in 2-4 h .
(In case: biphasic system with an hydrocarbon solvent)

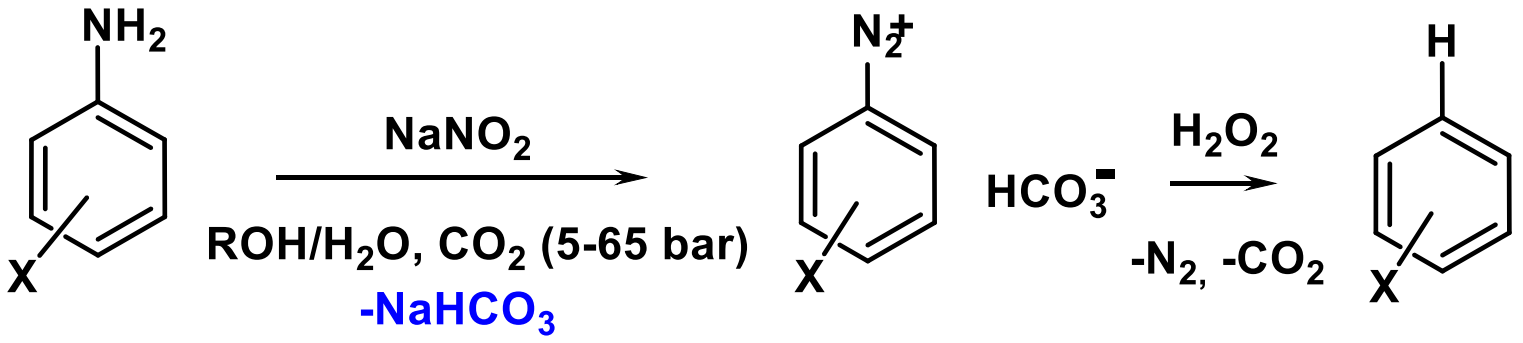
Salt Free Hydrodediazonation.

Classical methods of arenediazonium salts generates as by-products large amounts of sals (E factor = 4-7).

The Bayer approach can overcome this limit:

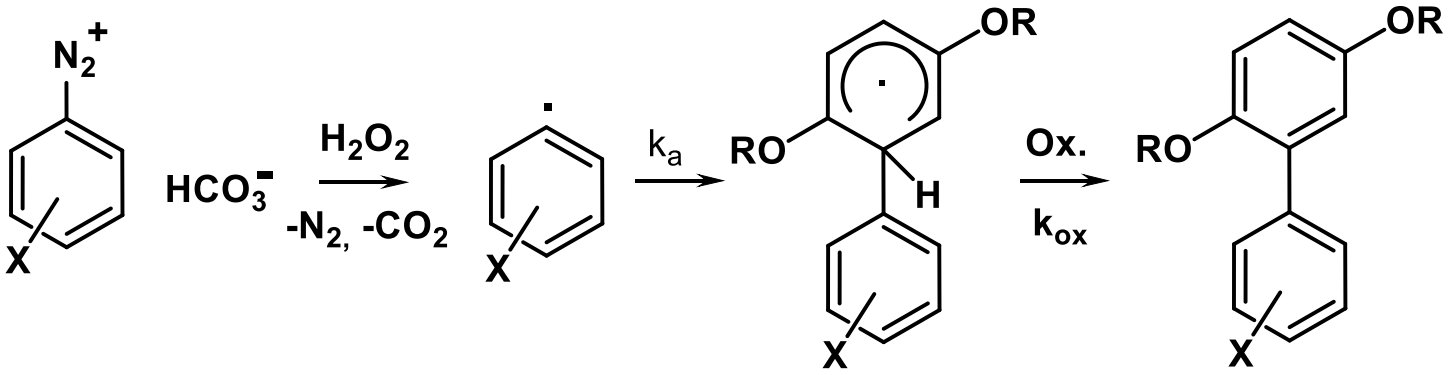
$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \quad (pK_{a\,H_2CO_3} = 3.3 \sim pK_{a\,HNO_2})$$

Combined with the hydro-dediazoniation by H_2O_2 a more benign process can be obtained (AE% = 70-80):



50-95 %

H_2O_2 as Initiator of Arenediazonium Salt Decomposition.



50-95 %

(1% H_2O_2 steady state)

Safer Alternatives to Chemicals grouped by their functional-use class.

- Chemicals are marked as a green circle, green half-circle, yellow triangle, or grey square.*
- This list includes many of the chemicals evaluated through the Safer Choice Program. It does not include confidential chemicals. There may be chemicals not included in this list that are also safer.

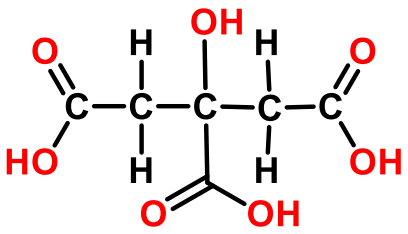
- Antimicrobial Actives
- Chelating Agents
- Colorants
- Defoamers
- Enzymes and Enzyme Stabilizers
- Fragrances
- Oxidants and Oxidant Stabilizers
- Polymers
- Preservatives and Antioxidants
- Processing Aids and Additives
- Solvents
- Specialized Industrial Chemicals
- Surfactants
- Uncategorized

United States Environmental Protection Agency

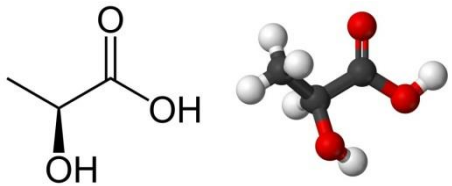
Antimicrobial actives.

Evaluated chemicals that are acceptable for use in DfE/OPP pilot products

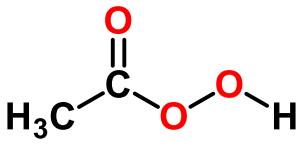
Common Name	CAS Registry Number
Citric acid, anhydrous ($C_6H_8O_7$)	77-92-9
Ethanol (C_2H_5OH)	64-17-5
Hydrogen peroxide (H_2O_2)	7722-84-1
Isopropanol ($(CH_3)_2CHOH$)	67-63-0
L-Lactic acid ($CH_3CH(OH)COOH$)	79-33-4
Peracetic acid (CH_3COOOH)	79-21-0



Citric acid



Lactic Acid



Peracetic acid

Chelating Agents

Evaluated chemicals that meet Criteria for Chelating and Sequestering Agents	
Common Name	**CAS Registry Number**
2-Butenedioic acid (2Z)-, ammonium salt (1:?), homopolymer, hydrolyzed, sodium salts	181828-06-8
Alanine, N,N-bis(carboxymethyl)-, sodium salt (1:3)	164462-16-2
Aspartic acid, N-(1,2-dicarboxyethyl)-, tetrasodium salt	144538-83-0
Citric acid, anhydrous	77-92-9
D-Gluconic acid	526-95-4
D-glycero-D-gulo-Heptonic acid, calcium salt (2:1)	17140-60-2
D-glycero-D-gulo-Heptonic acid, monosodium salt	13007-85-7
Dipotassium hydrogen citrate	3609-96-9
L-Lactic acid	79-33-4
Monosodium D-glucoheptonate	31138-65-5
N,N'-Ethylenediamine disuccinic acid	20846-91-7
Potassium citrate, anhydrous	866-84-2
Potassium citrate, monohydrate	6100-05-6
Sodium citrate, anhydrous	68-04-2
Sodium citrate, dihydrate	6132-04-3
Sodium ethylene diamine disuccinate	178949-82-1
Sodium gluconate	527-07-1
Tetrasodium N,N-bis(carboxylatomethyl)-L-glutamate	51981-21-6

Specialized Industrial Chemicals.

These chemicals are only eligible for use in specialized industrial products and are qualified based on Safer Choice Criteria for Specialized Industrial Products (see also Section 4.6 of the Safer Choice Standard)

Common Name	CAS Registry Number
1H-Imidazole-1-ethanol, 2-(heptadecenyl)-4,5-dihydro-	27136-73-8
Amphoteric fluorinated surfactant	34455-29-3
(T-4)-,	452080-64-7
(T4)-ether	452080-67-0
Ethanolamine	141-43-5
Fatty acids, C16-18 and C18-unsatd., methyl esters	67762-38-3
Fatty acids, soya, Me esters	68919-53-9
Halogenated aliphatic acid	27619-97-2
Soybean oil, methyl esters	67784-80-9
Tri-2-Butoxyethyl phosphate	78-51-3
Triethanolamine	102-71-6

Enzymes and Enzymes Stabilizers.

Evaluated chemicals that meet Safer Choice Criteria for Enzymes and Stabilizers

Common Name	CAS Registry Number
1,2-Propanediol	57-55-6
Alpha-amylase	9000-90-2
Amylase	9000-92-4
Amylase bacterial	9000-85-5
Borax (*Only allowed as a protease stabilizer.)	1303-96-4
Boron sodium oxide (*Only as protease stabilizer)	1330-43-4
Calcium chloride, anhydrous	10043-52-4
Calcium chloride, dihydrate	10035-04-8
Calcium formate	544-17-2
Cellulase	9012-54-8
DL-Methionine	59-51-8
Hydratase, phosphoenolpyruvate	9014-08-8
Mannase, endo-1,4-beta-	37288-54-3
Orthoboric acid (*Only as a protease stabilizer.)	10043-35-3
Polygalacturonase	9032-75-1
Proteinase	9001-92-7
Rizolipase	9001-62-1
Sodium formate	141-53-7
Subtilisins	9014-01-1

Polybrominated Compounds.

Concern exist that certain polybrominated diphenyl ethers (PBDEs) are persistent, bioaccumulative, and toxic to both humans and the environment. This concern extends to decaBDE, which breaks down into other PBDE congeners. Various PBDEs have been studied for ecotoxicity in mammals, birds, fish, and invertebrates. In some cases, current levels of PBDE exposure for wildlife may be at or near adverse effect levels. Human exposure to decaBDE can occur through occupations that manufacture flame retardants or products that contain flame retardants, as well as in recycling operations. Consumer exposure to decaBDE is possible because decaBDE can be released from products in the home and become a component in household dust.

In December 2009, the largest commercial producers and suppliers of decaBDE in the United States agreed to phase out use of the chemical by the end of 2013 and the decision was respected.

Seek for a benign substitution is actually actively pursued.