

# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**

## Outline:

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  3. H<sub>2</sub> blockers
- V. Conclusion

Excellent reviews that guided this group meeting can be found here:





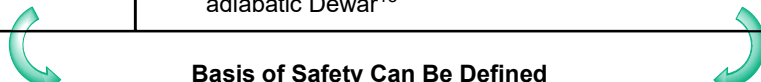
Lee, S.; Robinson, G. In *Process Development: Fine Chemicals from Grams to Kilograms*, 1st ed.; Davies, S. G.; Compton, R. G.; Evans, J.; Gladden, L. F., Eds.; Oxford Chemistry Primers; Oxford University Press: New York, USA, 1995; pp 1–86.

Stitt, E. H.; Simmons, M. J. H. Scale-Up of Chemical Reactions. In *Process Understanding: For Scale-Up and Manufacture of Active Ingredients*; Houson, I., Ed.; Wiley-VCH Verlag & Co. KGaA: Weinheim, Germany, 2011; pp 155–198.

Not covered here:

Scaling chemical reactions in flow  
Recrystallization

## I. Introduction and Background

Desk Screening 	Literature searches Bretherick's handbook of reactive chemical hazards <sup>1</sup> National Fire Protection Association's Manual of Hazardous Chemical Reactions <sup>2</sup> Desktop calculations <sup>3</sup> Hazardous functionalities
Thermal Screening 	Differential Scanning Calorimetry <sup>4</sup> Carius tube <sup>5</sup> Examine thermal stability of individual reaction components Can measure pressure and temperature excursions
Characterize Desired Reaction 	Isothermal calorimetry for data on reaction heats, reaction kinetics, thermodynamics and heat transfer. Mettler-Toledo (RC-1) <sup>6</sup> and others <sup>7-9</sup> Gas evolution rate quantification
Characterize Undesired Reaction 	Adiabatic calorimetry for runaway data ARC, <sup>10</sup> PHI-TEC, <sup>11</sup> APTAC, <sup>12</sup> ARSST, <sup>13</sup> VSP, <sup>14</sup> and adiabatic Dewar <sup>15</sup>
 <b>Basis of Safety Can Be Defined</b>	

**From review:** Butters, M. *et al.* Critical Assessment of Pharmaceutical Processes-A Rationale for Changing the Synthetic Route. *Chem. Rev.* **2006**, *106*, 3002. **1.** Edited by Urben, P. G.; Compiled by Pitt, M. J. *Bretherick's Handbook of Reactive Chemicals*, 6th ed.; Butterworth-Heinemann LTD: Oxford, 1999. **2.** *National Fire Protection Association's Manual of Hazardous Chemical Reactions*, 5th ed.; NFPA: Boston, 1975. **3.** Craven, A. *Inst. Chem. Eng. Symp. Ser.* **1987**, *102*, 97. **4.** Lambert, P.; Amery, G. *Int. Symp. Runaway React.* AIChE: New York, 1989; pp 525. **5.** Dale, D. J. *Org. Process Res. Dev.* **2002**, *6*, 933. **6.** [mettler-toledo.com/quickcal](http://mettler-toledo.com/quickcal). **7.** [helgroup.co.uk/home/reactor-systems/process-scale-up/similar-en.html](http://helgroup.co.uk/home/reactor-systems/process-scale-up/similar-en.html). **8.** [www.setaram.fr/fichiers/produit/drc\\_gb200392941710630.pdf](http://www.setaram.fr/fichiers/produit/drc_gb200392941710630.pdf) **9.** [www.alliedchemicaltech.com/reaction](http://www.alliedchemicaltech.com/reaction). **10.** [www.thermalhazardtechnology.com/products/urc.htm](http://www.thermalhazardtechnology.com/products/urc.htm). **11.** [www.helgroup.co.uk/home/consultancy/reaction-hazards-sp.html](http://www.helgroup.co.uk/home/consultancy/reaction-hazards-sp.html). **12.** [www.tiaxllc.com/technologies/tech\\_tiaxproducts.php](http://www.tiaxllc.com/technologies/tech_tiaxproducts.php). **13.** [www.arsst.com](http://www.arsst.com). **14.** [www.fauske.com/VSP2.asp](http://www.fauske.com/VSP2.asp). **15.** [www.johnmorris.com.au/html/Hel/adiabatic\\_high\\_pressure\\_dewar.htm](http://www.johnmorris.com.au/html/Hel/adiabatic_high_pressure_dewar.htm)

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## 1. Chemical concerns in scaling up

### Synthetic route:

Medicinal Chemistry	Process Chemistry
As versatile as possible	Only one molecule
Only need enough for testing	Need large quantities
Chromatography possible	Crystallization preferred
Cost less of an issue	Cost must be considered
Newer reactions can be tried	Reliable reactions
Supply of reagents easier	Supply is key

Each synthetic route has its own pros and cons. However, the focus of each is entirely different. Where medicinal chemists have to make as many analogues as possible, process chemists are often concerned with a single API.

Toxicity of reagents can often be an issue and must be considered.

Reagents such as cyanide and phosgene require completely different levels of control when scaled up.

Catalytic transformations are often more desirable than their stoichiometric counterparts. This is due to the reduction of stoichiometric byproducts and control of the waste stream.

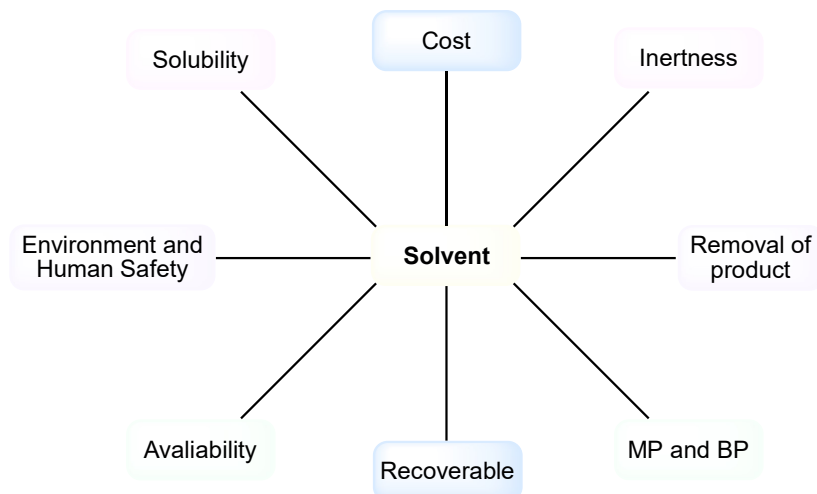
As is often the case, the fewer number of steps, the better. Even if the yield of each step is lower, the overall yield could still be higher than with more higher yielding steps.

9 steps with 85% yield at each step = 23% overall

3 steps with 65% yield at each step = 27% overall

Convergent routes are more desirable as they can lead to more efficient syntheses.

### Solvent:



#### water

Pro: Fulfills most criteria  
Con: Many organics not soluble

#### toluene

Pro: Cheap, available, recoverable  
Con: Can react with halogenation reagents

#### MTBE

Pro: Safe alternative to Et<sub>2</sub>O  
Con: Acids can cleave it

#### methanol

Pro: Cheap, available, recoverable  
Con: Reactive and potentially toxic

#### DCM

Pro: Good solubility, inert  
Con: Very toxic, expensive cleanup

#### acetonitrile

Pro: Good for anhydrous reactions  
Con: Toxic and expensive

#### acetone

Pro: Cheap, low toxicity  
Con: Very reactive

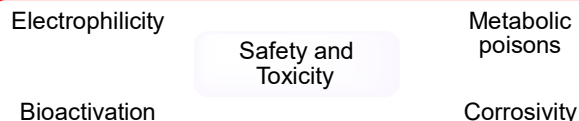
#### ethyl acetate

Pro: Good for extractions  
Con: Can be hydrolyzed

Stitt, E. H.; Simmons, M. J. H. Scale-Up of Chemical Reactions. In *Process Understanding: For Scale-Up and Manufacture of Active Ingredients*; Houson, I., Ed.; Wiley-VCH Verlag & Co. KGaA: Weinheim, Germany, 2011; pp 155-198.

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## Reagents:



Reagent	Typical concentration	Comments
<i>n</i> BuLi	10-30% in PhMe	Pyrophoric, store at 0 °C
<i>n</i> HexLi	25-40% in hexane	Not pyrophoric, store at RT or below
<i>n</i> OctLi	15-40% in hexane	Not pyrophoric, store at RT or below
LDA	1.8 M in THF/heptane	Contains "Mg stabilizer"
LHMDS	1.0 M in THF or hexanes	Also available as a solid
NHMDS	1.0 M in THF; 0.6 M in PhMe	Also available as a solid
KHMDS	0.9 M in THF	Also available as a solid
	0.7 M in PhMe	
NaOH	30-50% aqueous	Phase-Transfer Catalysis (PTC)

## Atom Efficiency

Here is an example of how many concerns can become apparent when merely choosing a methylating reagent, including atom efficiency.

Reagent	FW	Atom efficiency	Comments/ some uses
Me <sub>2</sub> SO <sub>4</sub>	126.13	12%, 24%	bp 188 °C
MeOTs	186.23	8%	mp 27.5 °C
MeI	141.94	11%	bp 41 °C. Simvastatin
MeBr	94.94	16%	bp 4 °C
MeCl	50.49	30%	bp -24 °C
MeOCO <sub>2</sub> Me	90.08	17%	bp 90 °C
HCHO/H <sub>2</sub>	32.04	47%	Methylation of amines, HCHO toxic.
MeOH/ cat. H <sup>+</sup>	32.04	47%	bp 65 °C. Fischer esterification.
CH <sub>2</sub> N <sub>2</sub>	44.04	34%	bp -23 °C. May be explosive in presence of some impurities. Must be generated prior to use. Reactions performed on scale by specializing contractors.

Anderson, N. G. Reagent Selection. *Practical Process Research & Development*, 1 ed.; Academic Press: Massachusetts, 2000; 53–80.

## 2. Environmental concerns in scaling up

$$\text{Effective mass yield (\%)} = \frac{\text{Mass of products} \times 100}{\text{Mass of non-benign reagents}}$$

Proposed by Hudlicky.

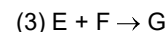
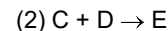
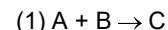
Defined: the percentage of the mass of desired product relative to the mass of all non-benign materials used in its synthesis.

$$\text{E-Factor} = \frac{\text{Total waste (kg)}}{\text{kg product}}$$

Proposed by Roger Sheldon.

Defined: draws attention to the quantity of waste that is produced for a given mass of product.

However, this can be difficult to implement as there can be a lack of clarity on the "total waste" of a process. For example, gases produced that are treated, *i.e.* acid gas scrubbing.



$$\text{Atom economy} = \left( \frac{\text{m.w. of product G}}{\text{m.w. of A} + \text{m.w. of B} + \text{m.w. of D} + \text{m.w. of F}} \right) \times 100$$

Atom economy can be calculated for many different types of reaction sequences. Here is an example of a liner sequence involving three operations. The mass of the final product is divided by the sum of all reagents added and multiplied by 100.

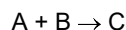
$$\text{Mass intensity (MI)} = \frac{\text{Total mass used in a process or process step (kg)}}{\text{Mass of product (kg)}}$$

Mass intensity takes yield, stoichiometry, solvent, and reagents into account and can give a better overall picture of the reaction when compared to E-Factor.

$$\text{Mass productivity} = \frac{1}{\text{MI}} \times 100$$

Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

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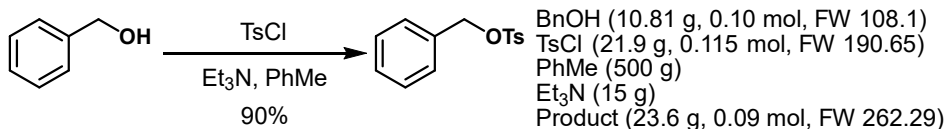
$$\% \text{ Carbon efficiency} = \frac{\text{no. of moles of product} \times \text{no. of carbons in product} \times 100}{(\text{moles of A} \times \text{carbons in A}) + (\text{moles of B} \times \text{carbons in B})}$$

Defined: the percentage of carbon in the reactants that remain in the final product.

$$\text{Reaction mass efficiency} = \left( \frac{\text{mass of product C}}{\text{mass of A} + \text{mass of B}} \right) \times 100$$

Defined: the percentage of mass of the reactants that remain in the product.

As an example:



$$\text{Atom economy} = \left( \frac{262.29}{(108.1 + 190.65)} \right) \times 100 = 87.8\%$$

$$\text{Carbon efficiency} = \left( \frac{(0.09 \times 14)}{(0.1 \times 7) + (0.115 \times 7)} \right) \times 100 = 83.7\%$$

$$\text{Reaction mass efficiency} = \left( \frac{23.6}{10.81 + 21.9} \right) \times 100 = 70.9\%$$

$$\text{Mass intensity} = \frac{(10.81 + 21.9 + 500 + 15)}{23.6} = 23.2 \text{ g/g} = 23.2 \text{ kg/kg}$$

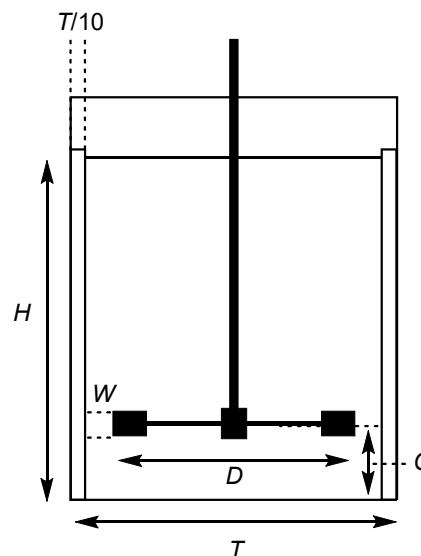
$$\text{Mass productivity} = \frac{1}{\text{MI}} \times 100 = 4.3\%$$

Atom economy < 100% due to HCl generation. Carbon efficiency accounts for 1.15 eq TsCl and 90% yield, as does RME.

Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

## II. Reactors

### 1. Reactor schematic



Stirred tank reactor schematic

$P$  = Power (W)

$N$  = Rotation Rate ( $\text{rev s}^{-1}$ )

$V$  = Volume ( $\text{m}^3$ )

$\mu$  = Fluid dynamic viscosity (Pa. s)

$\rho$  = Fluid density ( $\text{kgm}^{-3}$ )

$D$  = Impeller diameter (m)

$T$  = Tank diameter (m)

$W$  = Impeller width (m)

$H$  = Fill height

$C$  = Impeller clearance from bottom

Longitudinal baffles of width  $T/10$  mounted at  $90^\circ$  round the circumference of the vessel.

Installed to prevent gross rotation of the fluid (*i.e.* vortex formation).

Promotes three-dimensional circulation and mixing.

Typical ratios for the dimensions:

impeller diameter/tank diameter:  $D/T \sim 0.3-0.5$

fill height/tank diameter:  $H/T \sim 1$  for single impeller systems

baffle width/tank diameter:  $\sim 0.1$

impeller clearance/tank diameter:  $C/T \sim 0.2-0.25$

As cleaning efficiency and contamination between batches is a key concern in the pharmaceutical industry, the vessels are usually glass lined and without baffles.

Lee, S.; Robinson, G. In *Process Development: Fine Chemicals from Grams to Kilograms*, 1st ed.; Davies, S. G.; Compton, R. G.; Evans, J.; Gladden, L. F., Eds.; Oxford Chemistry Primers; Oxford University Press: New York, USA, 1995; pp 1–86.

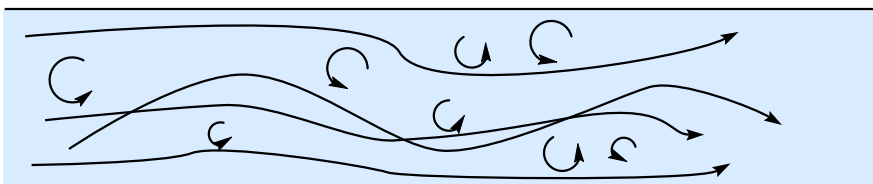
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## 2. Types of flow

Laminar flow: The motion of the fluid molecules always follows the fluid streamlines.



Turbulent flow: dispersion occurs by the action of irregular eddies.



More often than not, turbulent flow is the common form on process scale. This is due to the large scale and close to aqueous viscosities of the solvents.

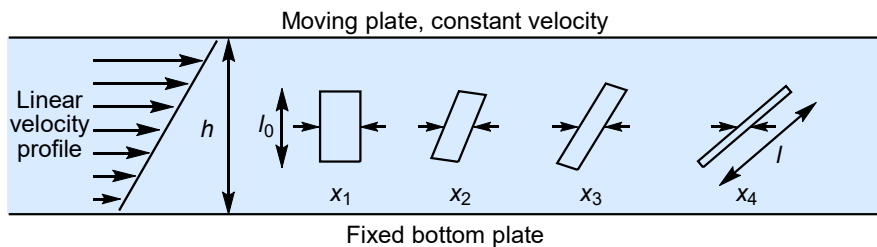
Turbulent flow onset can be determined by the Reynolds number  $Re$ . This is the ratio between inertial and viscous effects in a fluid.

$$Re = \frac{UL}{\nu} = \frac{UL\rho}{\mu}$$

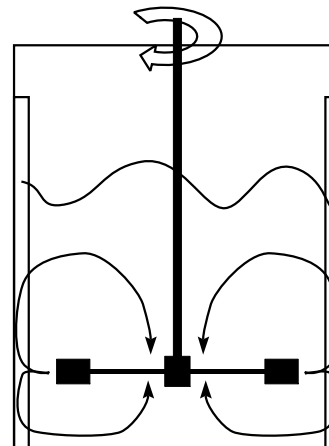
$U$  = characteristic velocity of the flow (m/s)  
 $L$  = characteristic length scale of the flow  
 $\nu$  = kinetic viscosity ( $m^2/s$ )  
 $\mu$  = Fluid dynamic viscosity (Pa. s)  
 $\rho$  = Fluid density ( $kg/m^3$ )

The transition from laminar to turbulent flow occurs at the  $Re_{crit}$ , i.e. inertial effects overcome the viscous effects and cause instabilities in the flow.

Shear flow: the friction between the fluid and the walls causes a disparity in flow rates between the edges and center, causing a stretching of the fluid in the pipe.



## 3. Types of stirring



**Radial Flow**  
 Four flow loops formed.

Generally recommended for gas dispersion as well as single phase operation.

Generated using radial flow impellers (vertical straight or curved blades)

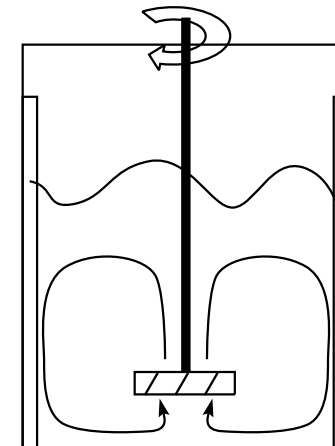
Example: Rushton disk turbine

**Axial Flow: Up-pumping**  
 Two flow loops formed.

Popular for gas-liquid duties, may be applicable for solid-liquid systems

Generated using impeller blades angled against rotation.

Example: Pitched blade turbine

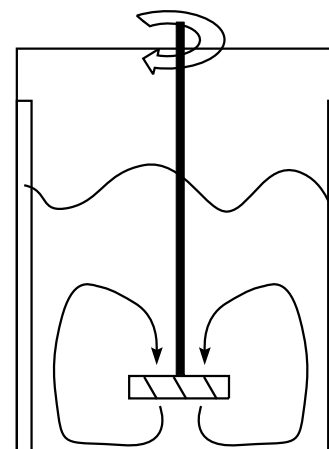


**Axial Flow: Down-pumping**  
 Two flow loops formed.

Used for suspension of solids, i.e. heterogeneous reactions

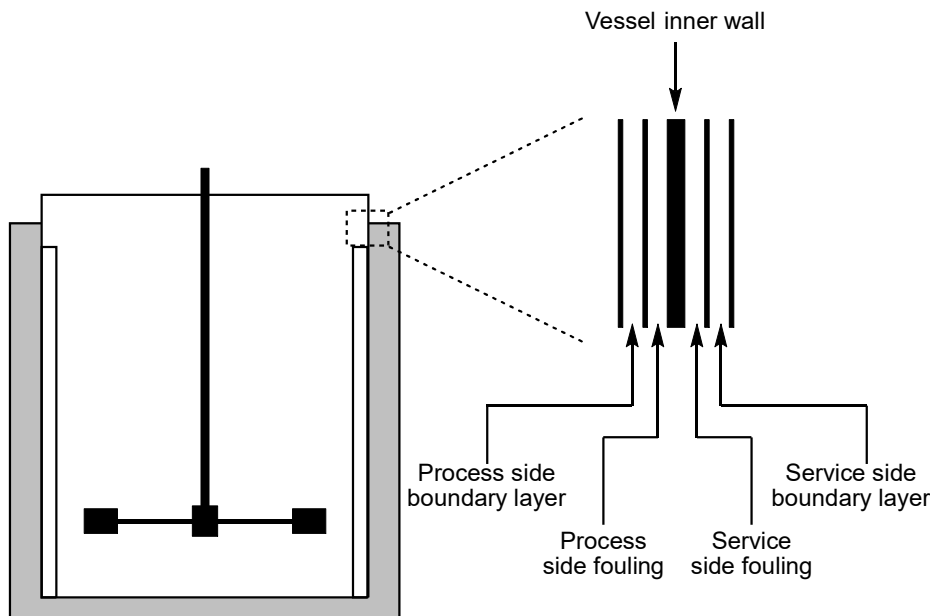
Generated using impeller blades angled with rotation.

Example: Retreat curve impellers



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## 4. Heat transfer



Overall, on process scale, the heat transfer is significantly slower than on laboratory scale. This can lead to selectivity issues if the reaction is particularly sensitive.

Fouling: the accumulation and formation of unwanted materials on the surfaces of processing equipment.

Overall heat transfer ( $U$ ) depends on:

- $h_p$  = process side heat transfer through the boundary layer
- $f_p$  = fouling resistance that results from the formation of any fouling layer
- $x_w$  (thickness) and  $k_w$  (conductivity) of the vessel wall
- $f_s$  = service side fouling layer
- $h_s$  = service side heat transfer through the boundary layer

$$\frac{1}{U} = \frac{1}{h_p} + f_p + \frac{x_w}{k_w} + f_s + \frac{1}{h_s}$$

The heat transfer of the system depends on the largest term on the right-hand side. This is usually  $h_p$ .

## 5. Types of impellers



Rushton disk turbine (RDT)



Concave-blade turbine



Pitched blade turbine (PBT)



Lightnin A310 three blade hydrofoil



Lightnin A<sub>315</sub> four-blade hydrofoil (down-pumping)



Marine propeller



Three-blade retreat curve impeller (RCI)

### III. Reaction types

#### 1. Constant variables

##### Constant Mixing Time (Constant $N$ )

Requires the rotational speed ( $N$ ) to stay constant.

This is applied if the macroscale behavior must stay constant.

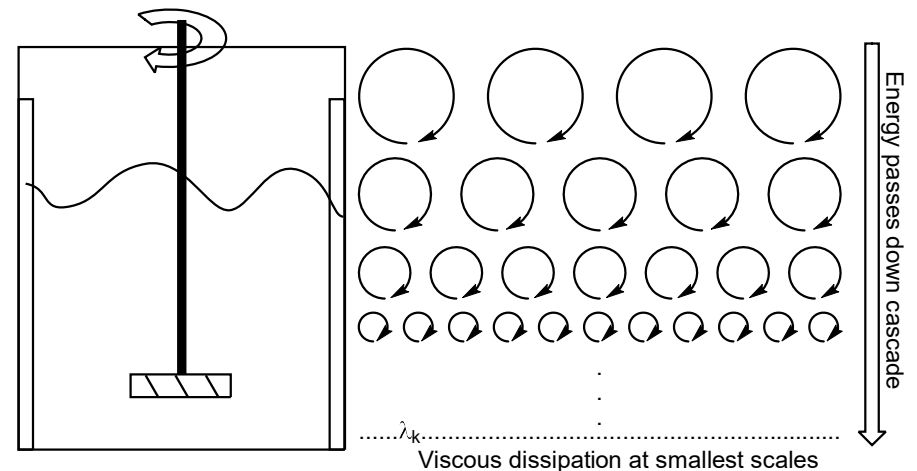
In practice, this can be very difficult, if not impossible, on process scale.

##### "Constant" Turbulent Mixing Behavior (Constant $\epsilon_T$ )

While the turbulent mixing behavior changes with scale, it is assumed that if the average power imparted to the fluid per unit mass is kept constant, then the turbulent mixing behavior can be considered "constant".

This type of constant is used to keep mixing performances on the smallest scale constant. Which can lead to selectivities on large scale remaining constant.

#### Kolmogorov length scale

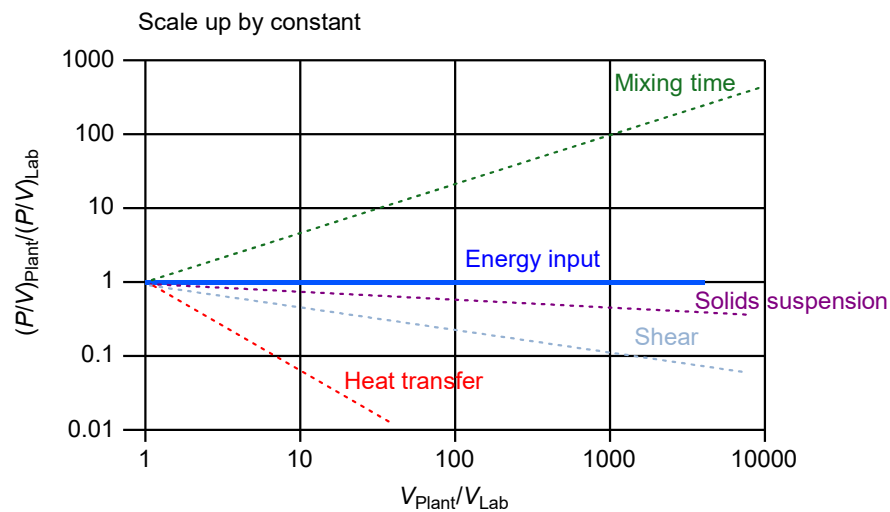


To illustrate, on scale the mixing begins to incorporate the Kolmogorov length scale for energy transfer. This involves large eddies being generated near the impeller and consecutively smaller eddies further away. The energy transfer proceeds without loss of energy between the eddies until the smallest eddies are formed and lose the energy through heat.

Therefore, for constant turbulent mixing behavior, the power supplied to the system must be scaled appropriately.

Beyond the smallest eddies, mixing occurs though diffusion.

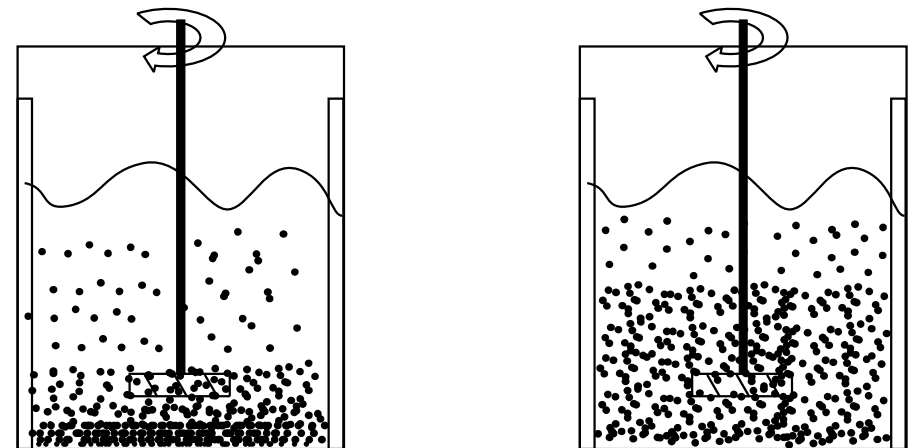
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While on laboratory scale "moving the beaker" is an easy way to ensure adequate mixing of the solid, reactors are significantly larger than flasks and cannot be shaken in a similar manner.

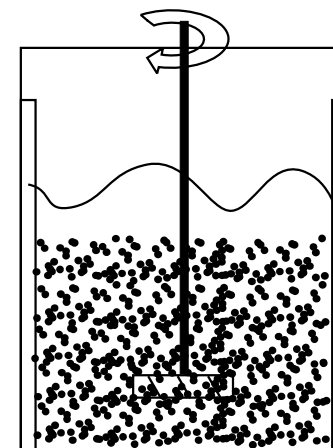
For catalyzed reactions, once the solid is suspended the mass transfer are usually sufficient.

With crystallization occurring in the reaction, mixing can determine: particle size and shape, agglomeration, and morphology.



Solid on bottom

Just suspended



Homogeneous dispersion

## 2. "Fed-Batch" liquid-phase reactions

Often characterized by fast reaction kinetics.

Depending on the rate of addition, the local concentration of the reagent can be quite high, leading to poor selectivities in the reaction.

The location of the reagent addition can also affect selectivity as addition to the surface can often lead to poor and non-homogenous mixing.

This rate can be controlled and slowed by slow liquid subsurface reagent feed.

The fed batch can also control an exotherm in the reaction as the slow addition of the reagent helps prevent runaway.

## 3. Liquid-solid reactions

Three main types:

- i. The solid is a dissolving reagent
- ii. The solid is a catalyst
- iii. The solid is a reaction product (crystallization)

Key design feature is to ensure adequate suspension of the solid

As mentioned before, axial down-pumping stirring is preferred.



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## 4. Gas-liquid reactions

Primarily hydrogenations, oxidation, carbonylation, hydroformylation.

### Gaseous reactant

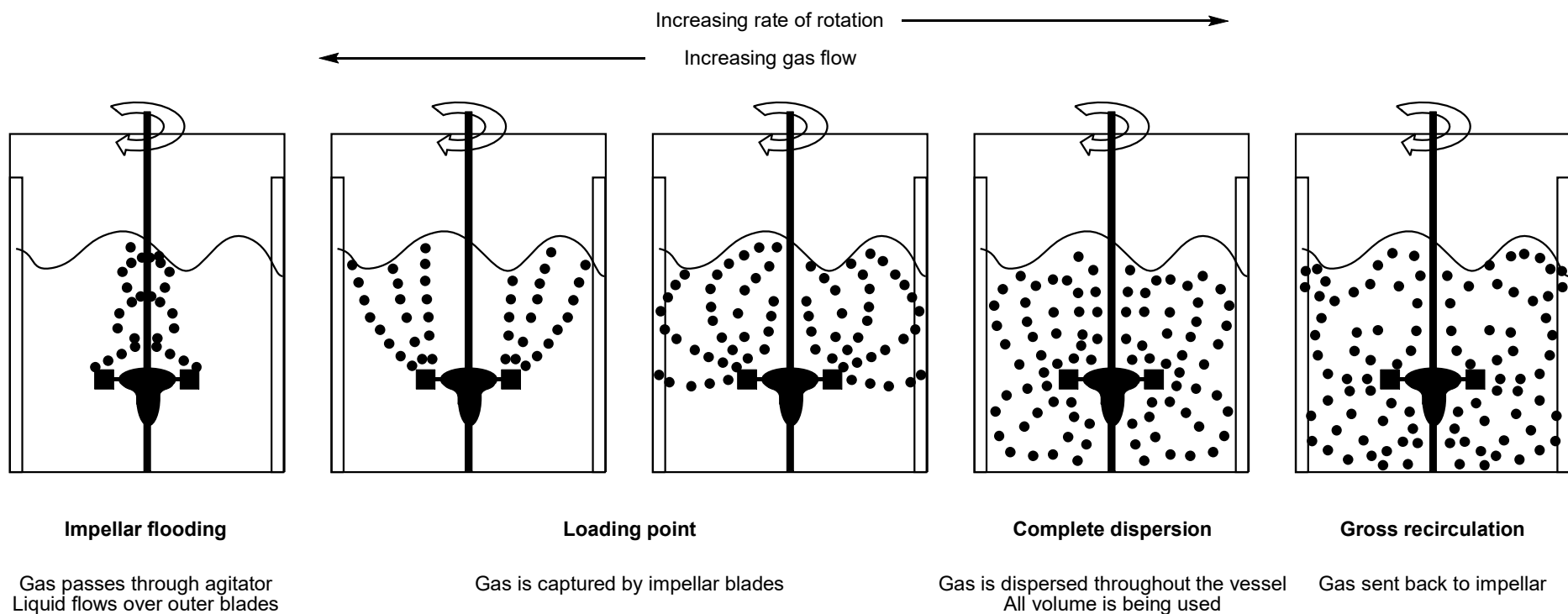
As the scale increases, the gas-liquid mass transfer coefficient decreases.

This means that less gas is dissolved in solution, and is therefore not as available for the catalyst.

This can slow reaction rates, change relative concentration, and adversely affect reaction selectivity.

### Gaseous product

The object is to allow the gaseous product to escape from the liquid phase while having adequate stirring to keep the solid catalyst suspended.



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## IV. Case studies

Lee, S.; Robinson, G. In *Process Development: Fine Chemicals from Grams to Kilograms*, 1st ed.; Davies, S. G.; Compton, R. G.; Evans, J.; Gladden, L. F., Eds.; Oxford Chemistry Primers; Oxford University Press: New York, USA, 1995; pp 1–86.



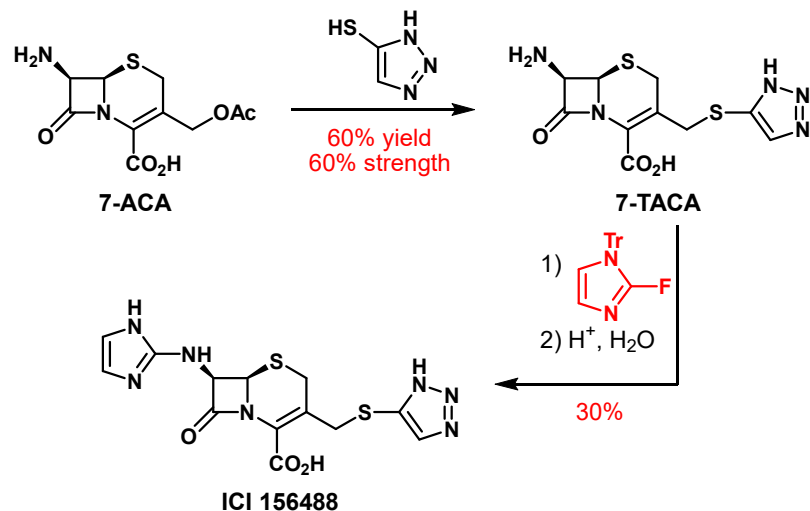
Imperial Chemical Industries

### 1. Cephalosporins

Overall lessons learned:

- 1)  $\beta$ -lactams are unstable to heat and pH
- 2) Determination of product purity
  - Single peak by HPLC does not mean full purity
  - UV inactive compounds can still be present
- 3) Crystallinity in the API is highly beneficial
  - $\beta$ -lactam products are often amorphous
  - Chromatography helps, but is hard to obtain >98% purity

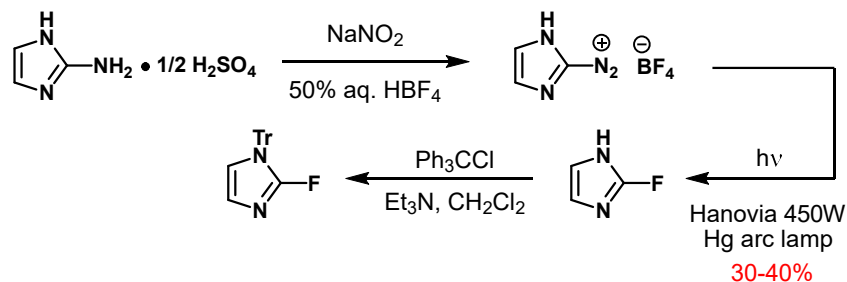
### Research route



Comments:

- 7-ACA was made by semisynthesis that ICI was not set up for and would need to be purchased (£200/kg)
- While 7-TACA crashed out of the reaction in 60% weight yield, the actual purity (strength) was only 60% due to UV inactive impurities such as polymers
- The 30% yield to the API was not acceptable, and the 2-fluoroimidazole was not easy to synthesize

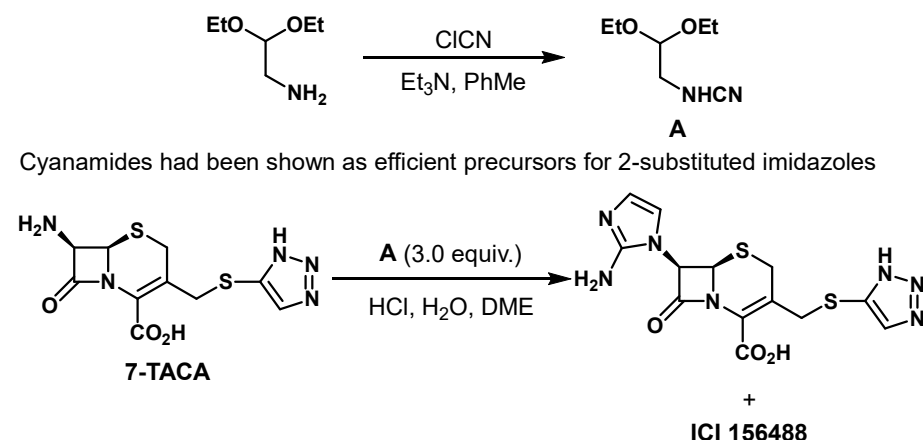
## Synthesis of 2-fluoroimidazole



Comments:

- The diazonium salt tended to trimerize during the photochemical reaction
- The yield for the photochemical step fell from 30-40%, to 10% on 100 g scale
- The output of the product was low, about 2% w/v concentration

## The cyanamide route

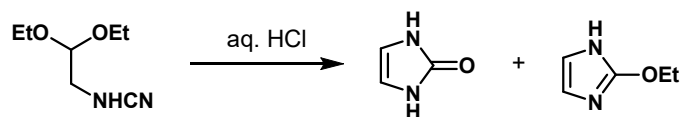


Cyanamides had been shown as efficient precursors for 2-substituted imidazoles

Comments:

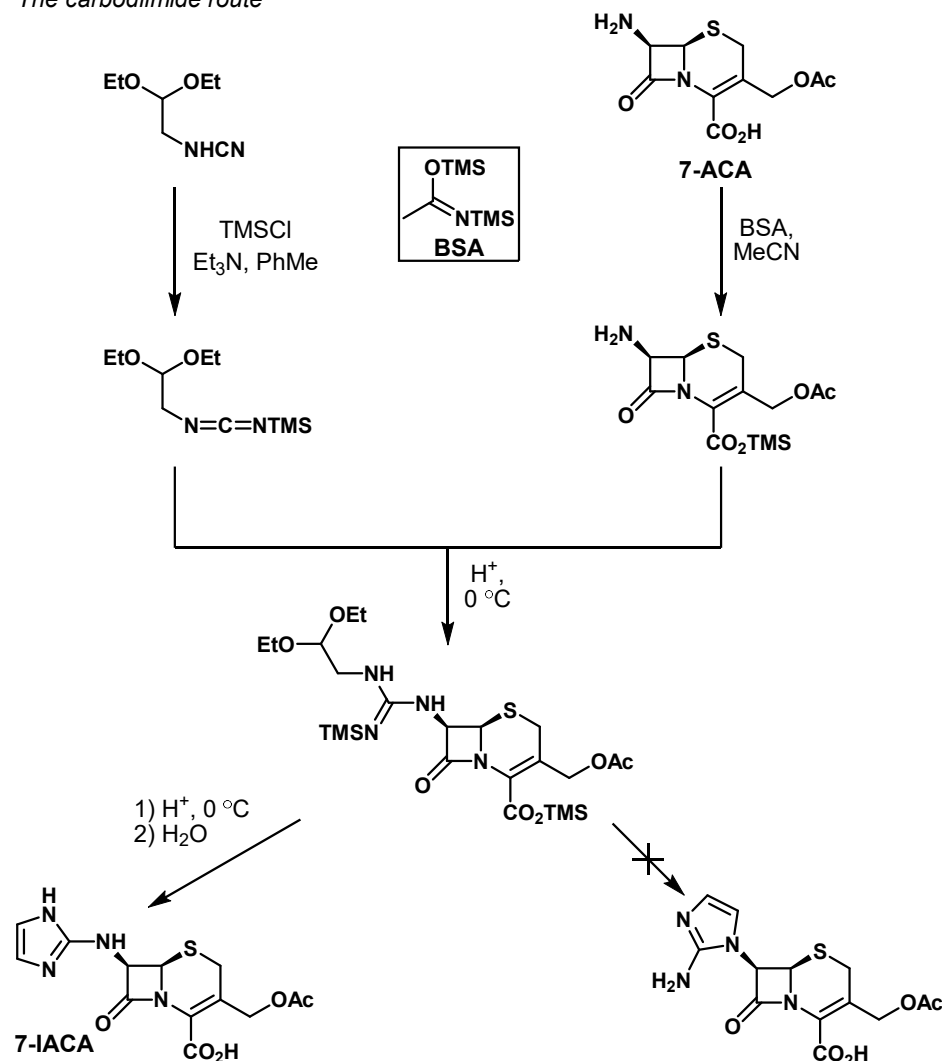
- 20% yield of a mixture of ICI 156488 (major) and its byproduct (shown)
- Employed to synthesize 150 g of ICI 156488, yield fell to <10% on scale
- Chromatography required to fully purify the API

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Furthermore, the cyanamide was unstable under reaction conditions and could not be addressed on scale.

*The carbodiimide route*



Comments:

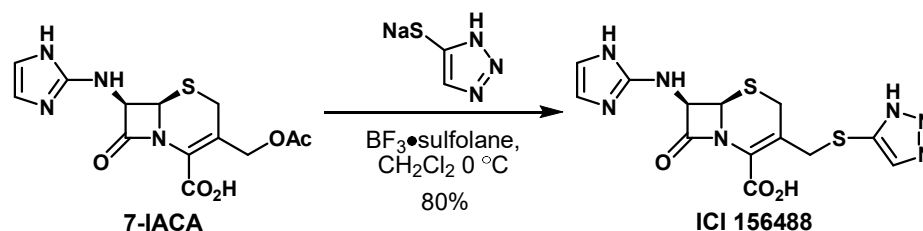
– At first, trifluoromethanesulfonic acid was used in the guanidine formation step, but it was found that sulfuric acid could effect the reaction as efficiently

– For cyclization, HCl caused the buildup of a gum. This was avoided by using  $\text{BF}_3 \cdot \text{HOAc}$

– Passing the compound through a resin column gave crystalline 7-IACA in 50% yield. 7-IACA was much easier to crystallize than 7-TACA.

*C-3' substitution*

It was apparent from the literature that the most efficient way to introduce the mercapto heterocycle to produce the API was by employing a  $\text{BF}_3$  catalyst.



Comments:

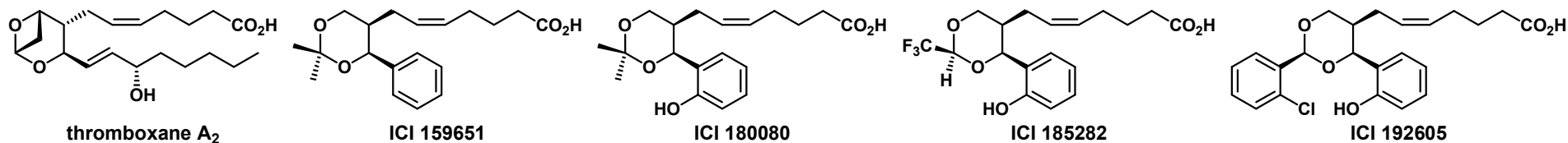
– The sulfolane complex of  $\text{BF}_3$  was preferred to the etherate as diethyl ether is highly flammable and would not be suitable for large-scale production

– Purification of the API was accomplished by passing through a resin column and recrystallization from the triethylamine salt

– The free thiol of the mercaptotriazole was found to be explosive, but the sodium salt was found to be stable.

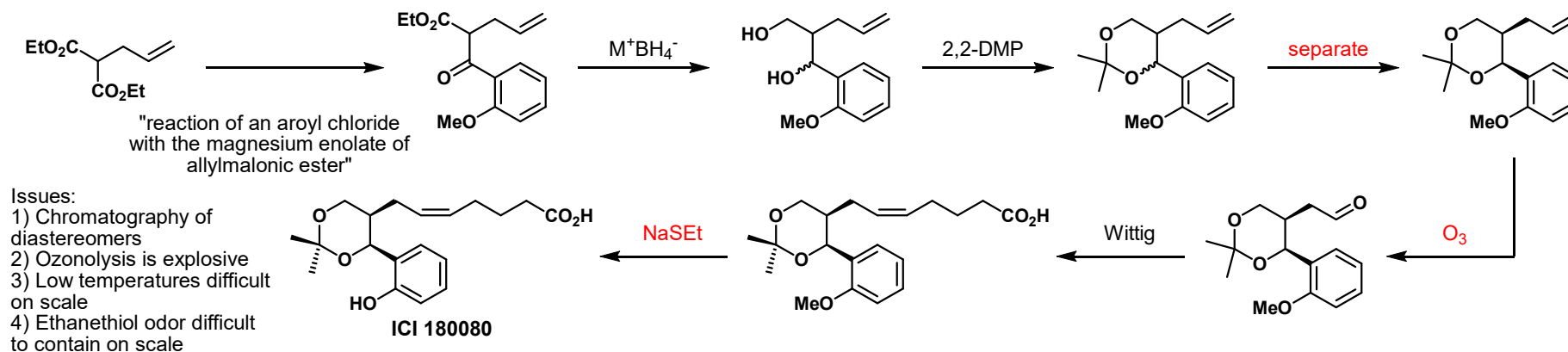
# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**

## 2. Thromboxane antagonists

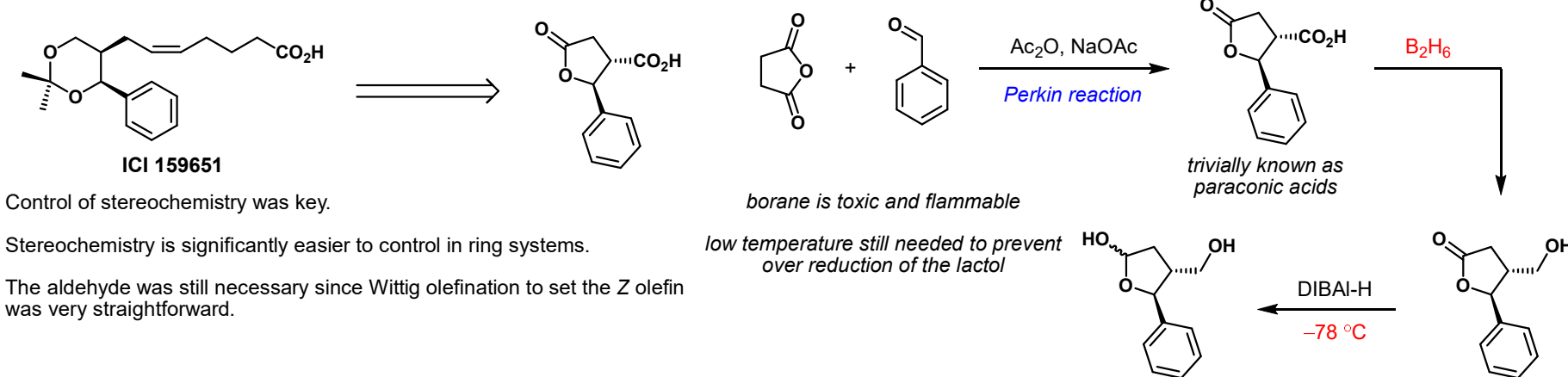


Thromboxane causes bronchoconstriction, aggregation of blood platelets, and vasoconstriction. This has implications for the treatment of asthma. Key stereochemical features: 1) *cis* relation of the side chains, 2) *Z*-olefin in the side chain, 3) *cis* substituent on the acetal, 4) single enantiomer desired.

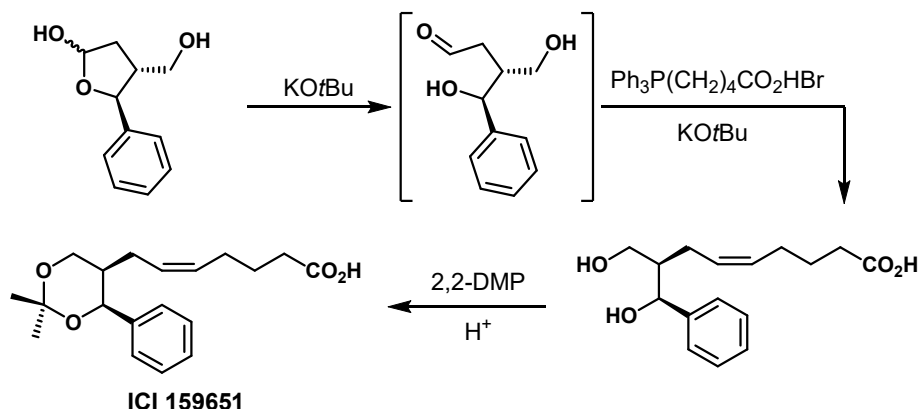
### Research route



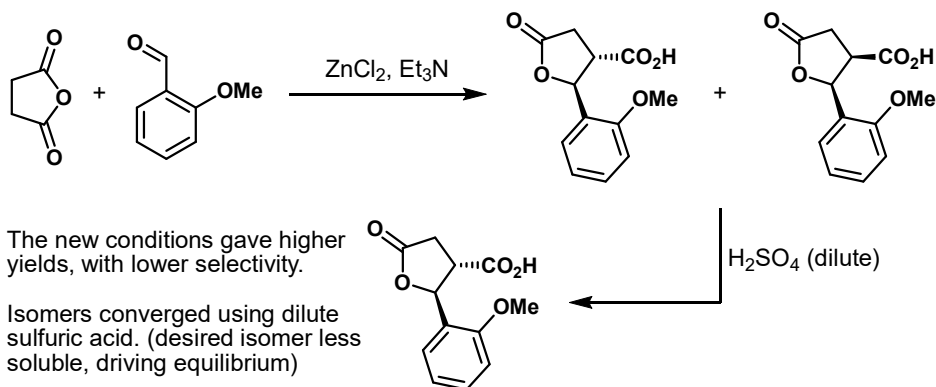
### Removing the need for chromatographic separation of diastereomers



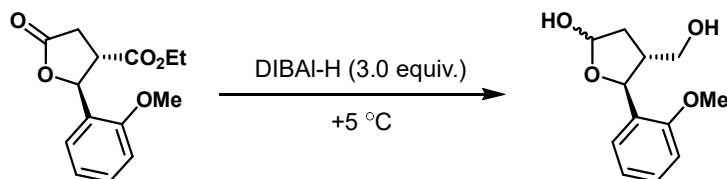
# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**



Scaling the paraconic acid synthesis



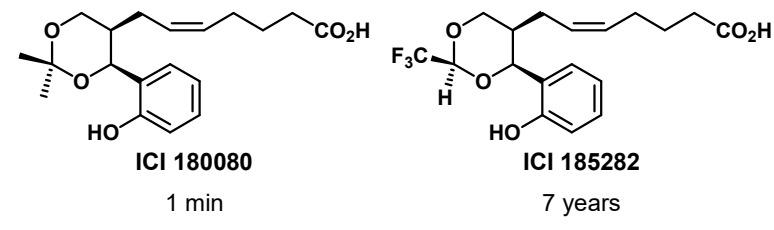
Solving the reduction to the lactol



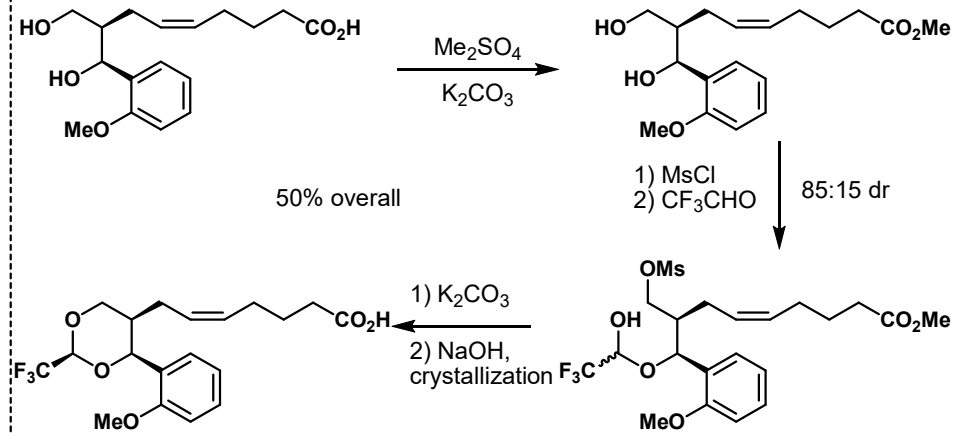
Leveraging the lower inherent reactivity of the lactone ester versus the acyclic one led to selective reduction to the lactol.

Inert atmosphere prevented any issues with DIBAL-H flammability.

Dioxane ring formation

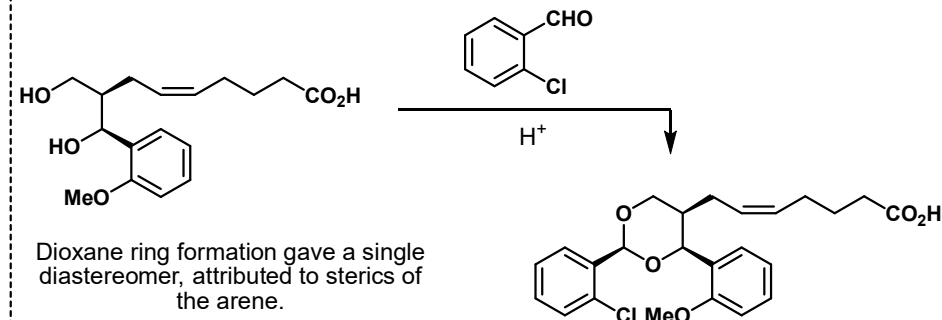


Attempts to form the trifluoromethyl acetal under acidic conditions led to scrambling at the benzylic position.



Diastereomers could be separated by crystallization after saponification of the ester.

Process was telescoped from the starting acid, as only the acids were crystalline.



# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**

## Demethylation

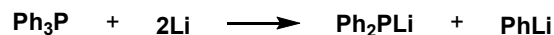
With NaSEt, several side reactivities were observed, such as dechlorination of the precursor for ICI 192605.

Ethanethiol was also not ideal as the smell needed to be contained.

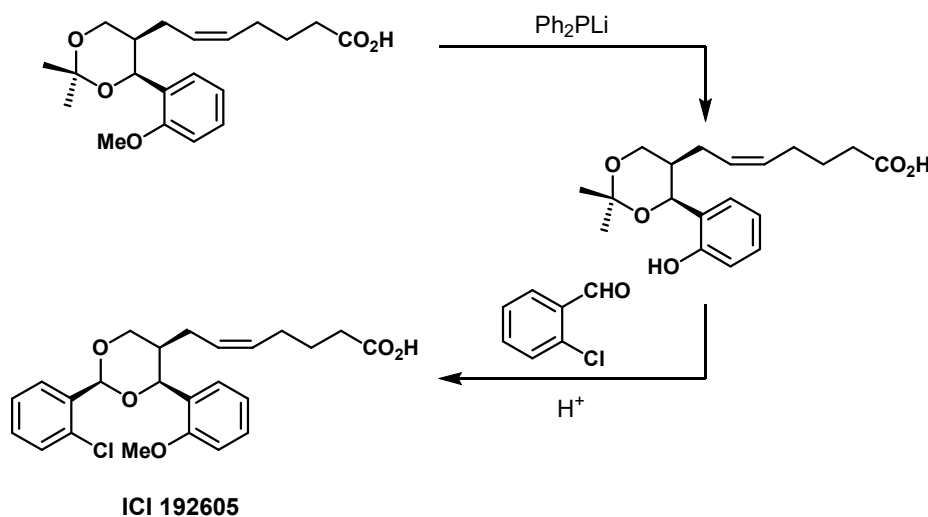
Other deprotection reagents tested ( $\text{BBr}_3$ , LiI, TMSI), but they either did not work or caused decomposition.



Lithium diphenylphosphide proved highly selective, and could be easily made on small scale using BuLi.



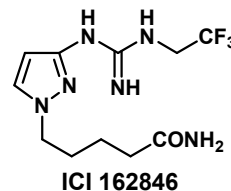
On scale, triphenylphosphine could be converted to the reagent by first reacting with 2 equivalents of lithium and then reaction of the PhLi with *t*-butyl chloride.



Solved problems:

- 1) *cis* stereochemistry in the dioxane
- 2) *cis* stereochemistry for the acetal (achieved by crystallization)
- 3) Demethylation that did not require NaSEt
- 4) Synthesis made enantioselective by resolution of paraconic acid

## 3. H<sub>2</sub> blockers



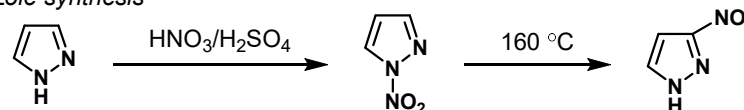
H<sub>2</sub> blockers block the H<sub>2</sub> receptor in the stomach lining to suppress the release of HCl.

Lower pH in the stomach due to the over release of HCl can lead to ulcers.

The pathogen that causes stomach ulcers in the majority of cases has since been identified as *Helicobacter pylori*

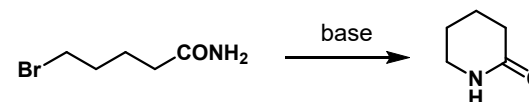
### Research route

#### Pyrazole synthesis

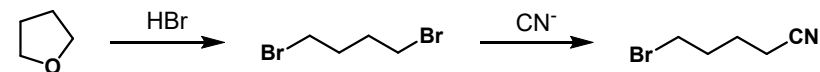


"Nitropyrazoles were subsequently shown to be violent explosives!"

#### 4-carboxamidobutyl moiety synthesis

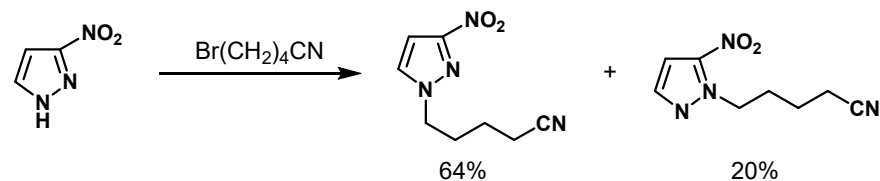


Attempts to alkylate the 3-nitropyrazole directly with 4-bromobutanamide led to cyclization to the piperidone.



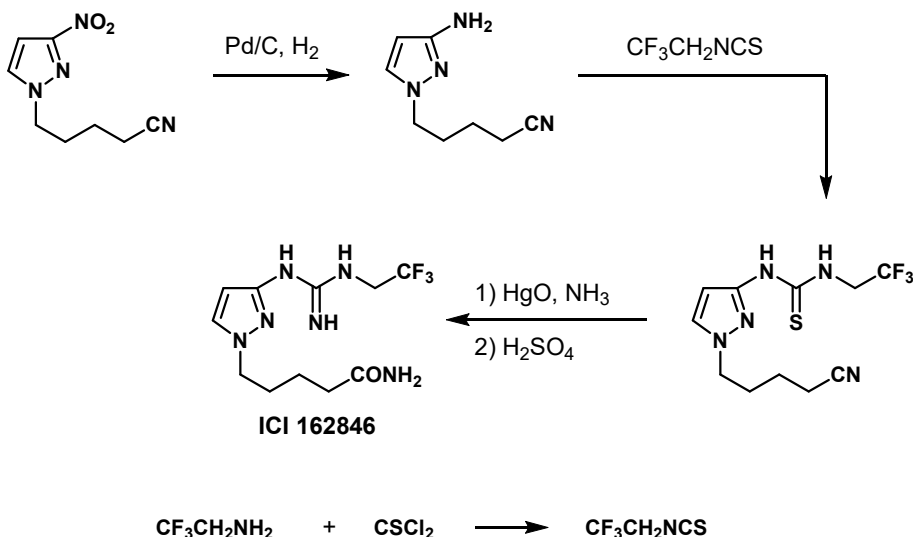
0.6 equivalents of the cyanide anion led to optimal conversion as more equivalents would give statistical mixtures of starting material, mono-, and di-alkylated compounds.

The unreacted 1,4-dibromobutane could be recovered by distillation.



# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**

Completion of the synthesis

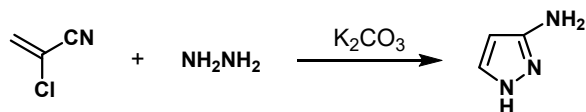


Manufacturing difficulties:

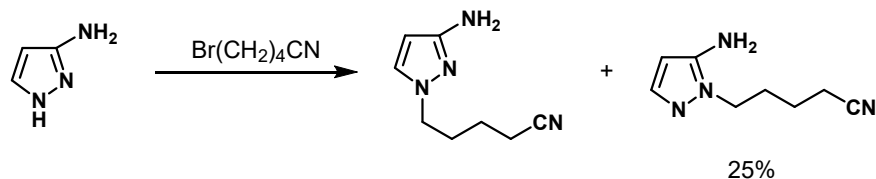
- The explosive nature of the nitropyrazoles would be prohibitive on scale
- Thiophosgene, trifluoroethylamine, trifluoromethylisothiocyanate, and mercuric oxide were highly undesirable due to toxicity concerns

Manufacturing route

Avoiding nitropyrazoles



Despite its toxicity, hydrazine could react with 2-chloroacrylonitrile to give 3-aminopyrazole on scale. Furthermore, as an oil, the pyrazole product could be telescoped to the next step.



Even though there were three possible sites for alkylation with 5-bromovaleronitrile, the predominant product was the desired.

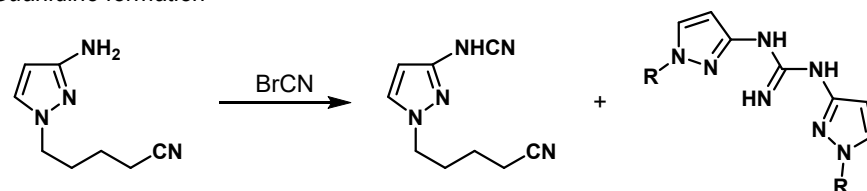
This product could then be purified as the tosylate salt to completely remove all impurities.

Production of trifluoroethylamine

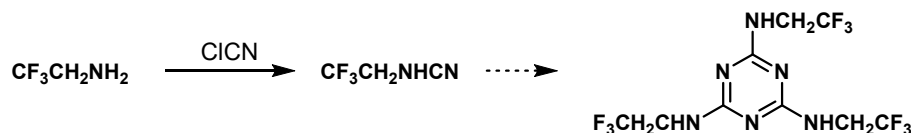
Despite its toxicity, low boiling point (36 °C), and sparse availability from commercial sources, trifluoroethylamine was still needed in large quantities.



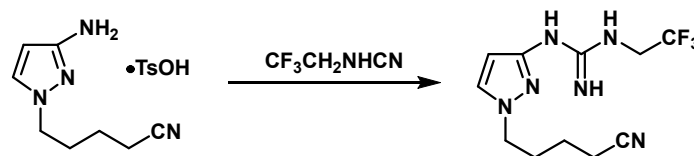
Guanidine formation



Cyanamides had been shown to be excellent precursors to guanidines. However, the 3-aminopyrazole also formed a significant amount of the dimer byproduct.



However, due to the weaker nucleophilicity of trifluoroethylamine, the trifluoroethylcyanamide could be formed selectively. Yet, if not stored properly, the cyanamide would trimerize to the triazine.

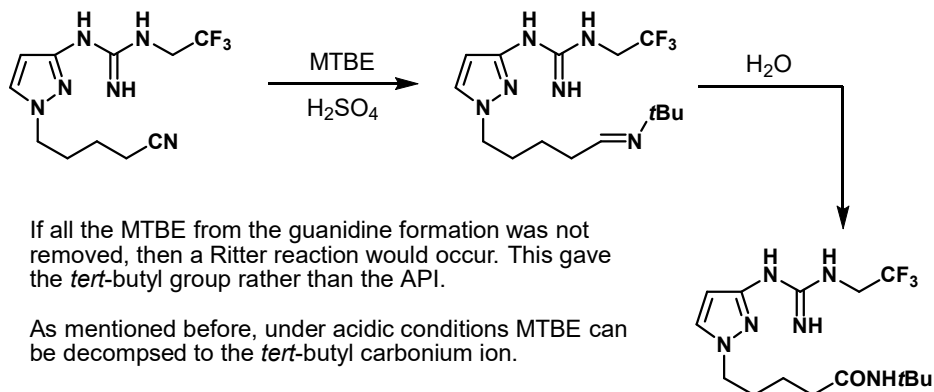
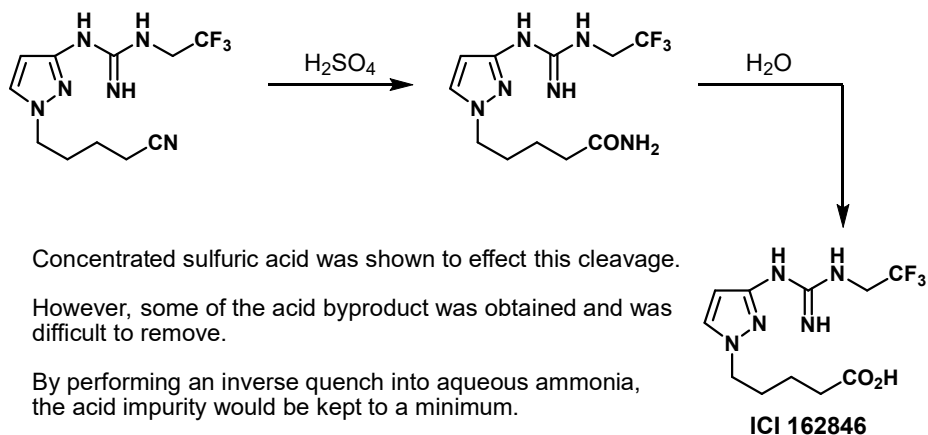


Conveniently, the tosylate salt provided the acid necessary to mediate the guanidine formation.

Purification could be achieved by forming the salt with carbonic acid as all impurities in the reaction were not basic enough to form this salt.

# Sarlah Group **Scaling Chemical Reactions: From Grams to Kilograms Part 1**

## Nitrile hydrolysis



## Accomplishments

- 1) The explosive nitropyrazole, thiophosgene, and mercury were avoided
- 2) Facile and scalable synthesis of trifluoroethylamine and 5-bromovaleronitrile
- 3) Efficient and convergent

## V. Conclusion

In conclusion, many factors go into scaling chemical reactions. This presentation merely scrapes the surface of all the concerns that must be addressed when running reactions on scale.

The restrictions placed on the chemistry that can be run on scale can make for some very creative workarounds.

