A new era for Medicinal Chemistry.
Are we ready for change?

Matthew Campbell-Crawford,

GlaxoSmithKline, Stevenage

Overview

- Pragmatic approach to sustainable chemistry for **chemists**

- GSK solvent selection guide
  - Challenge – a world without chlorinated solvents

- GSK reagent grids

The need for change

- Public image of industry….

Gulf of Mexico oil leak ‘worst US environment disaster‘

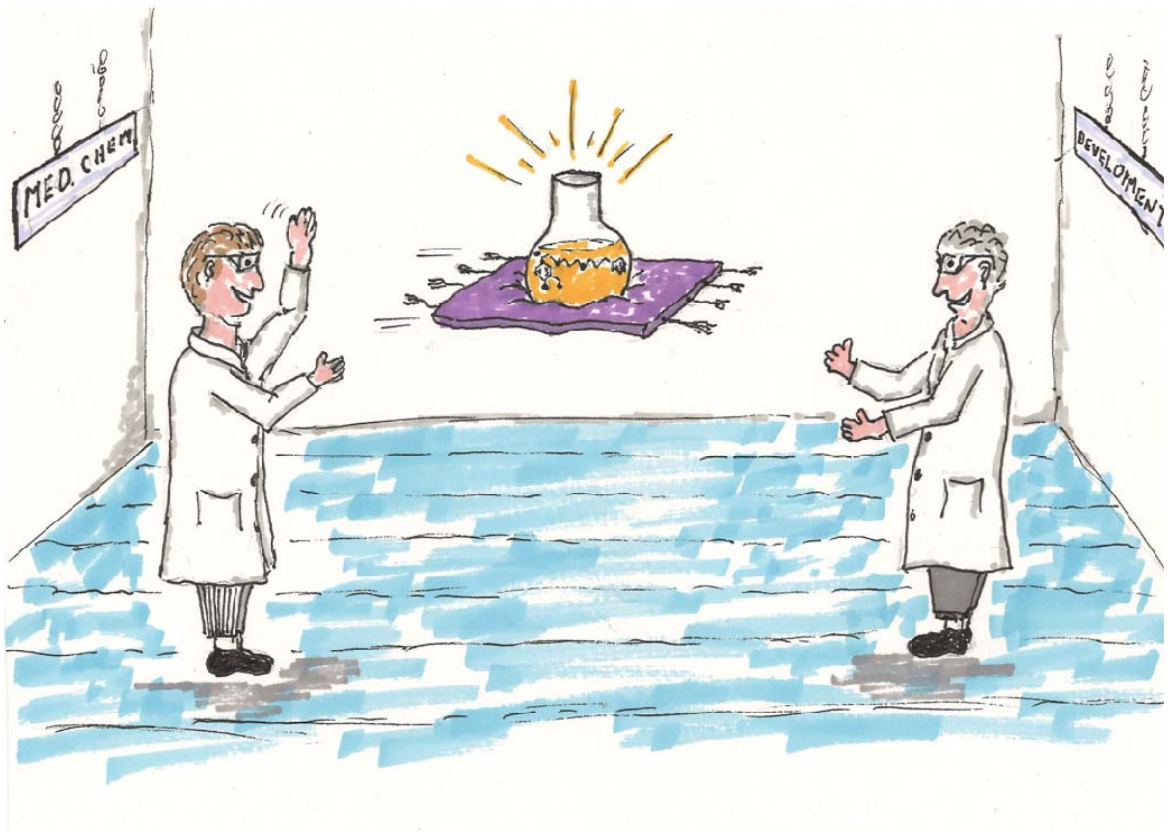
BBC News – 30th May 2010

- Dependence of the present world economy on a dwindling stream of non-renewable natural resources, e.g. Palladium catalysts

- Health and safety of chemists and public

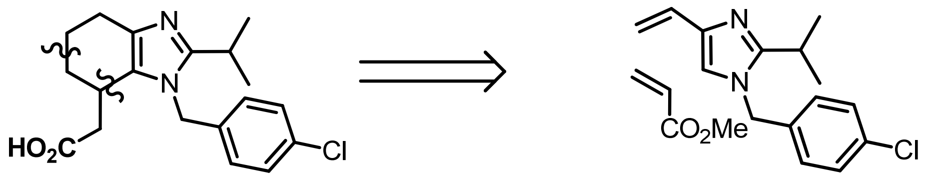
Challenge : What do we embed in our labs?

- Hypothesis : Try to play our part to reduce the burden on manufacturing by optimising our synthetic routes
- Ensuring <u>**most efficient and benign route**</u> is found

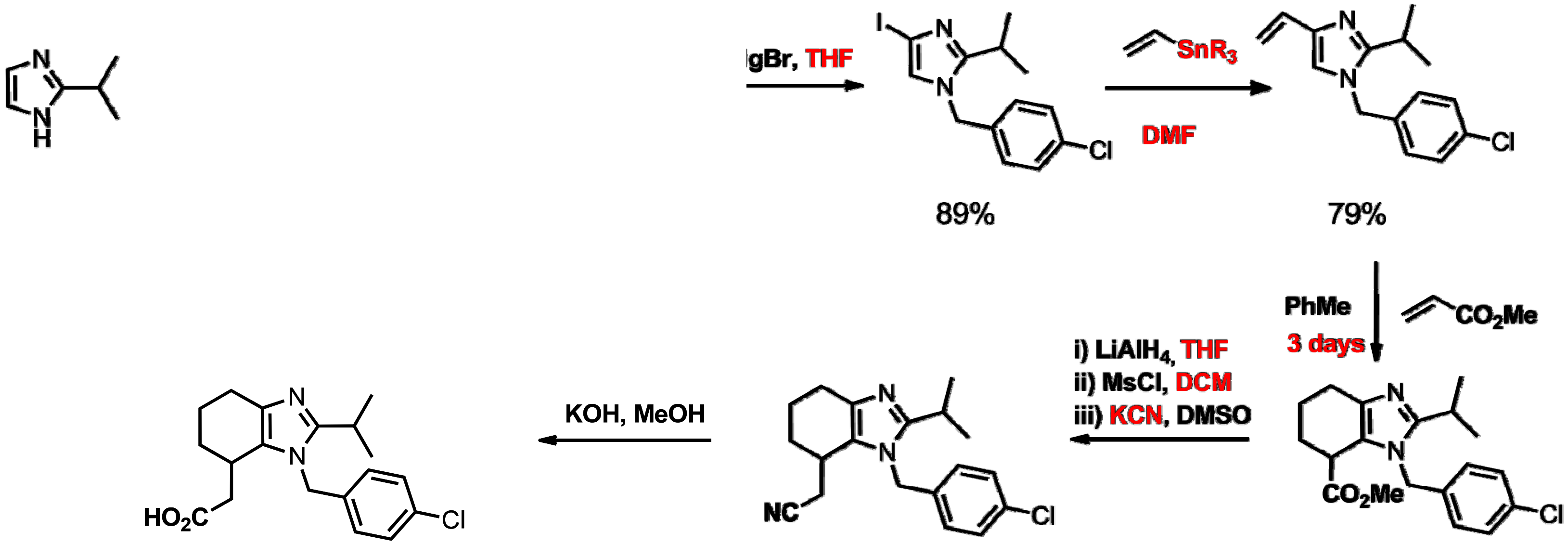


Route with multiple environmental challenges!

- Target molecule

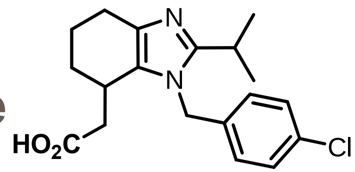


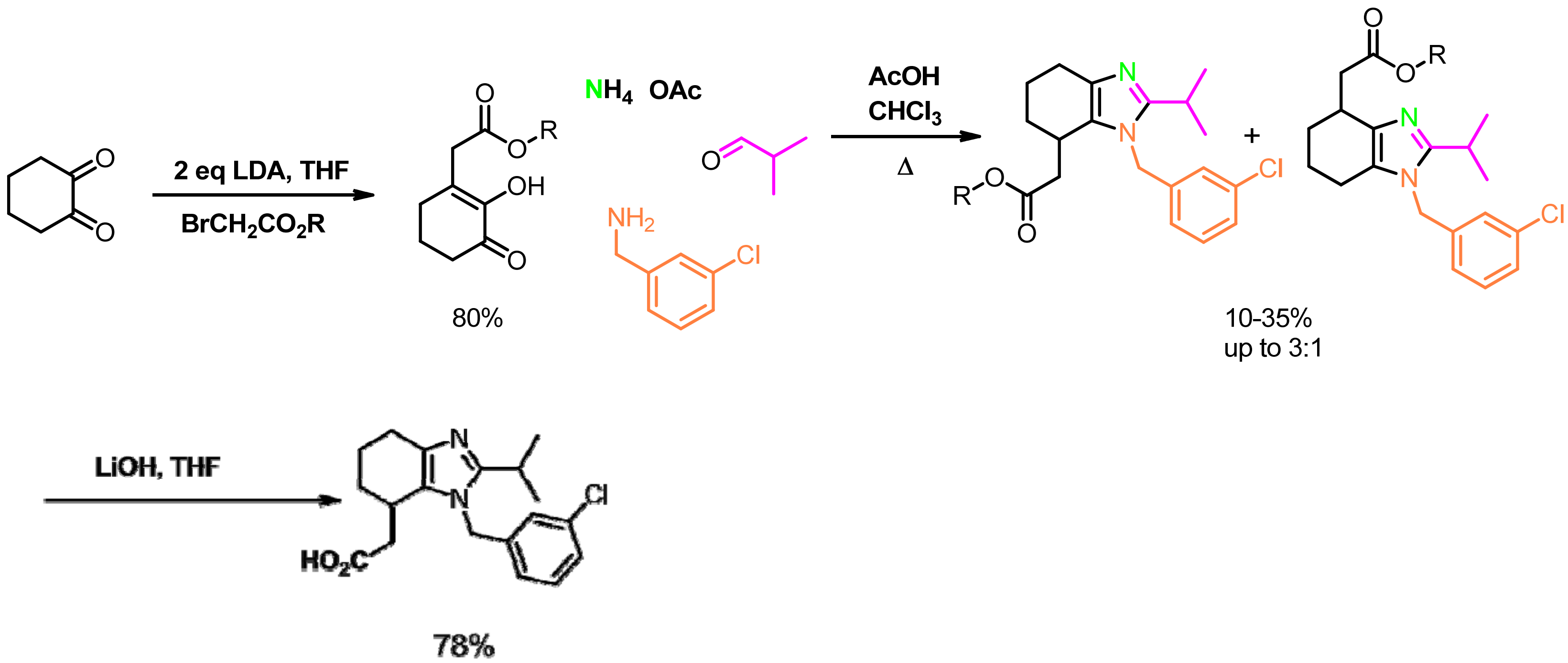
- First synthetic route



- 9 steps
- Overall yield = 2.2%
- Delivery – 6 weeks (1 chemist)

Multi-component reaction - overcomes efficiency challenge





- 3 steps
- Overall yield 6-22%
- Average delivery time : 2 days (1 chemist)
- No use of Sn or KCN

Change in route shows improved efficiency

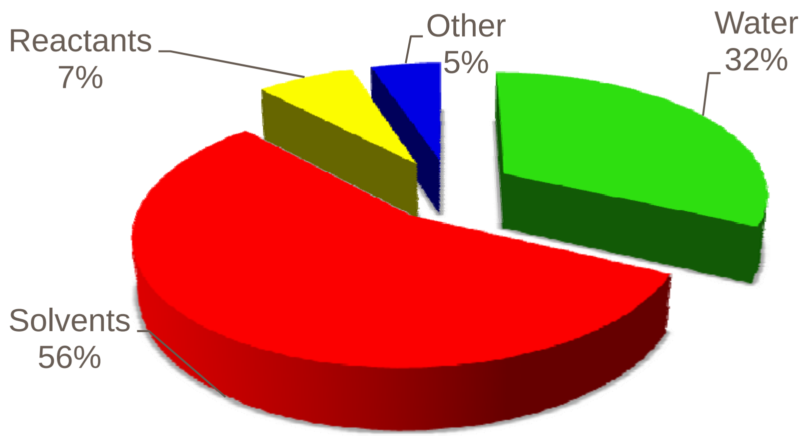
	Old	New	Aspiration
# Steps	9	3	1
# Columns	9	2	0
Average delivery time	6 weeks	2 days	
Typical yield	2%	20%	100 %

$$\text{E-Factor} = \frac{\Sigma \text{ mass of waste (g)}}{\text{mass of product (g)}}$$

Efficiency measure	Old	New	Aspiration
E-factor	177000	845	0

Sheldon, R.A. Chem. Ind. (London). 1992, **903**

90% of all reaction material is discarded!



Composition by mass of types of material used to manufacture an API
American Chemical Society Green Chemistry Institute
Pharmaceutical Roundtable Benchmarking 2006 & 2008

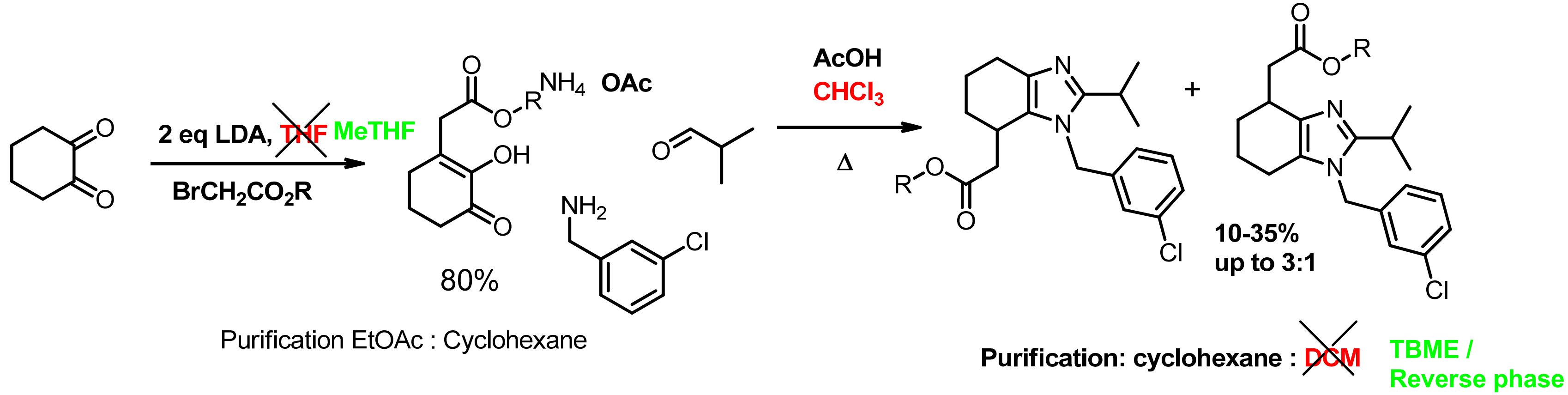
Org. Process Res. Dev., 2007, ***11***, 133–137

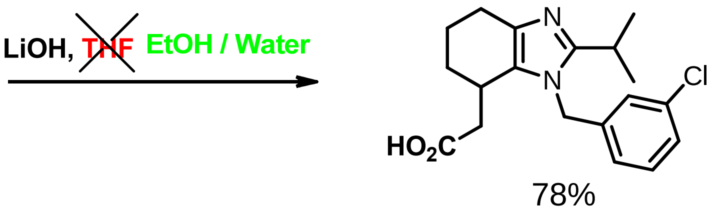
	Few issues (bp°C)	Some issues (bp°C)	*Major* issues
Chlorinated	….before using chlorinated solvents, have you considered TBME, isopropyl acetate, ethyl acetate or 2-Methyl THF?		Dichloromethane ** Carbon tetrachloride ** Chloroform ** 1,2-Dichloroethane **
Greenest Option	**Water** (100°C)		
Alcohols	**1-Butanol** (118°C) **2-Butanol** (100°C)	**Ethanol/IMS** (78°C) **t-Butanol** (82°C) **Methanol** (65°C) **1-Propanol** (97°C) **2-Propanol** (82°C)	2-Methoxyethanol **
Esters	**t-Butyl acetate** (95°C) **Isopropyl acetate** (89°C) **Propyl acetate** (102°C)	**Ethyl acetate** (77°C) **Methyl acetate** (57°C)	
Ethers		**t-Butyl methyl ether** (55°C) **2-Methyl THF** (78°C)	1,4-Dioxane ** 1,2-Dimethoxyethane ** Tetrahydrofuran

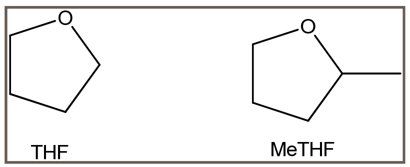
Green Chem., 2011, ***13,*** 854-856

Improving the greenness of the reaction by using green solvents

- Medicinal chemistry route



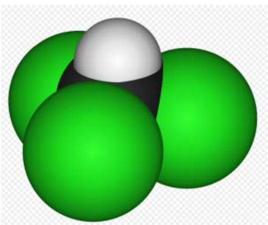


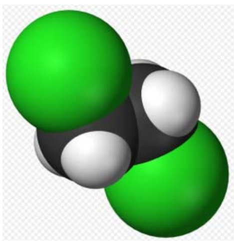


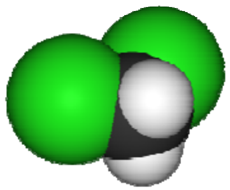
Selected Solvents	Typical yield	Ratio
THF	0 – 5%	N/A
MeTHF	0 – 5%	N/A
DCM	15 – 35%	Up to 2 : 1
$CHCl_3$	10 – 35%	Up to 3 : 1

Challenge : Can we go chlorinated free?

- Challenge – 6 weeks without using **ANY** chlorinated solvent
  - Reaction solvents
  - Work up
  - Purification
  - $CDCl_3$ for NMR

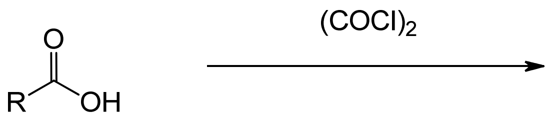




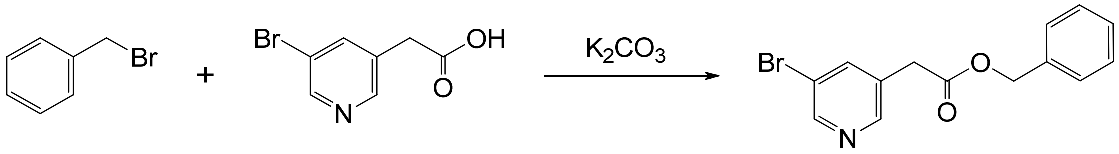


Challenge : Can we go chlorinated free?

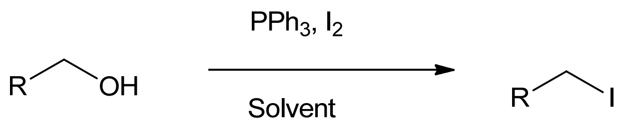
- Reaction solvents



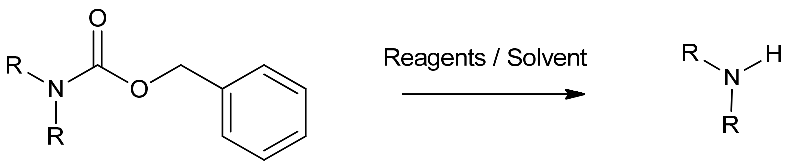
DCM 81%
MeTHF 85%



DCM 98%
MeTHF 97%



DCM 86%
MeTHF 78%



BBr_3 / $CHCl_3$ 92%
TMSI / EtOAc 72%

- Reaction / work - ups

DCM → MeTHF

It is possible to find alternatives to chlorinated solvents!

- Purification
  - Loading

DCM → MeTHF
Florisil™

  - Eluting

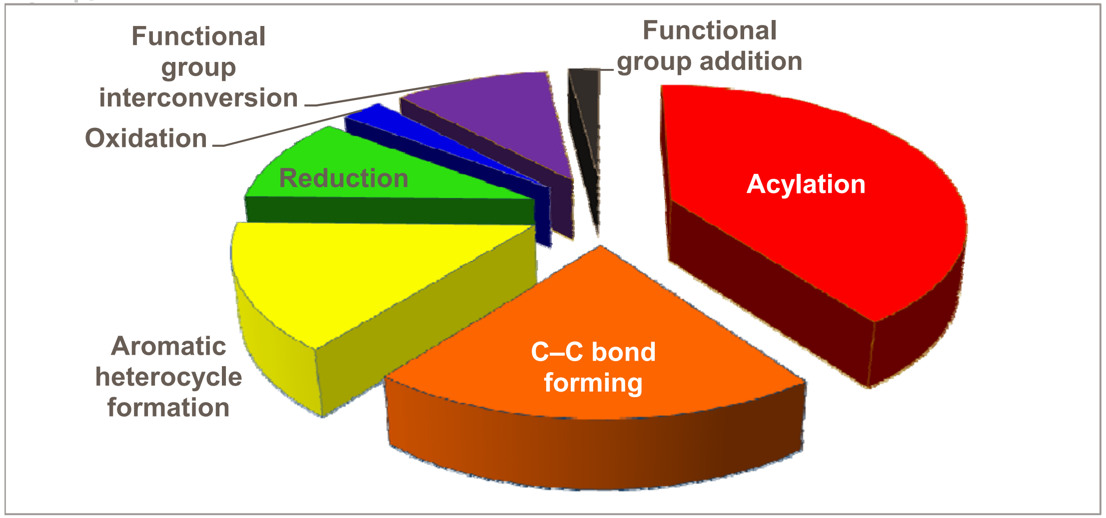
DCM / MeOH → TBME:MeOH; or EtOH:EtOAc; or reverse phase

- NMR

$CDCl_3$ → d_6-DMSO
d_6-Acetone

Green Chem., 2012, 14, 3016

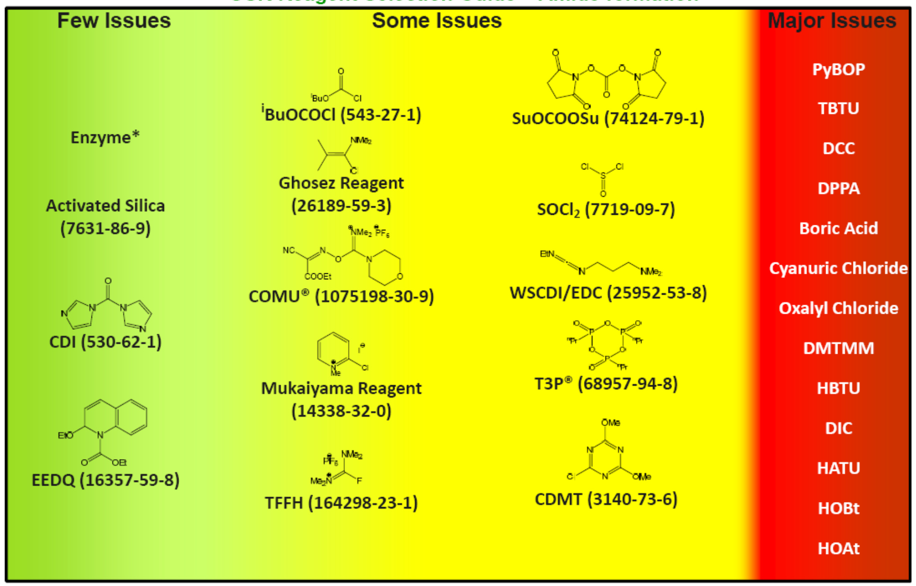
What's the next logical step? Reagent grids



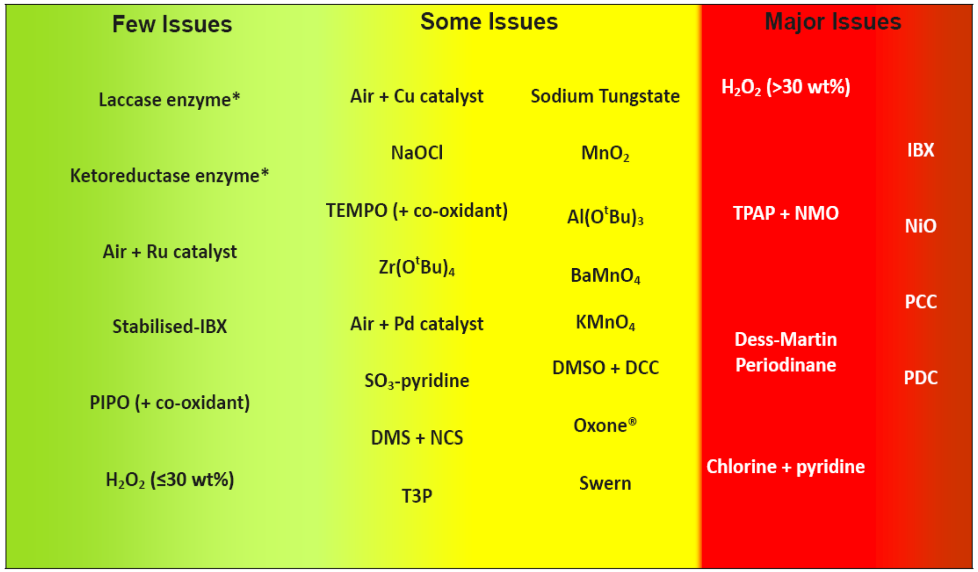
Composition of different classes of over 7000 reactions carried out across a number of pharmaceutical companies

S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, **2011**, *54*, 3451–3479

GSK Reagent Selection Guide – Amide formation



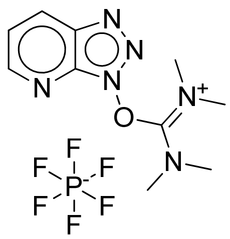
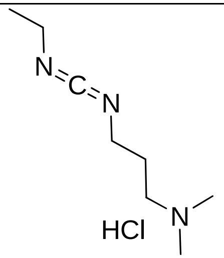
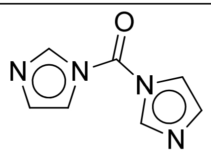
GSK Reagent Selection Guide – Oxidation to aldehydes and ketones



H.Sneddon *et. al.* Green Chemistry *in press* **DOI:** 10.1039/C3GC40225H

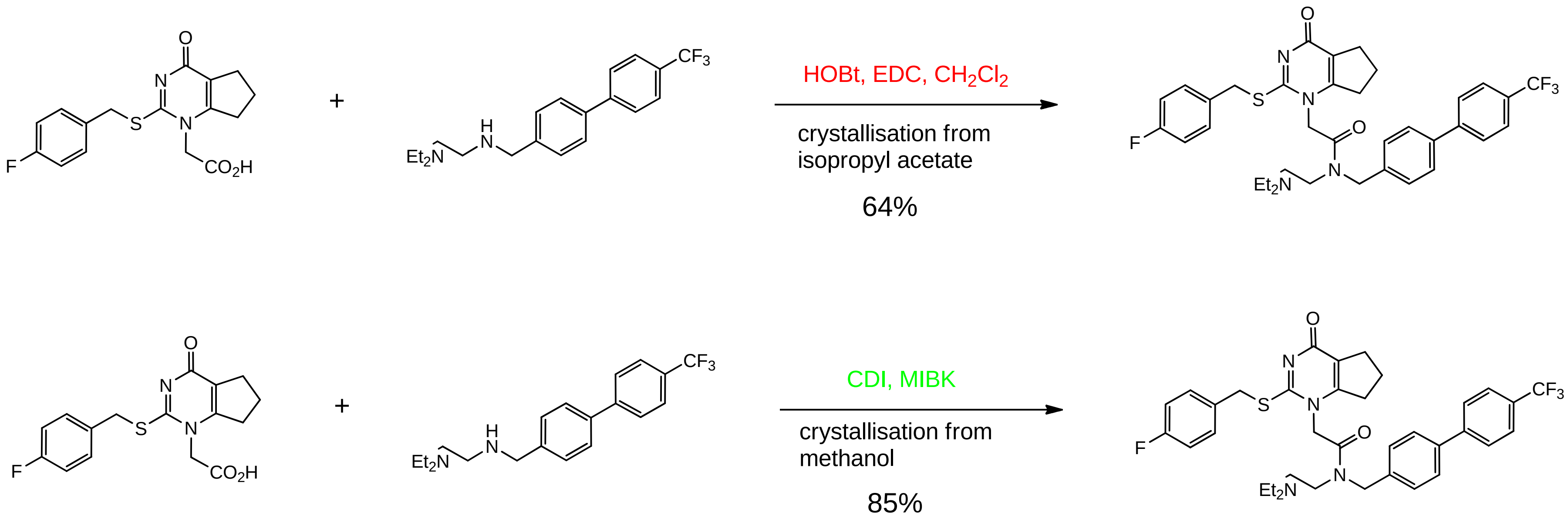
Factors to determine sustainability

- Reagent **<u>&</u>** by-products – safety, R/S phrases, work up procedures etc

Name	Structure	Overall Score
HATU		3
EDC		7
CDI		8

H. Sneddon *et. al.* Green Chemistry *in press* **DOI:** 10.1039/C3GC40225H

Encouraging greener reagent use by first intent



- If we can ensure we use the best route first time, it will help downstream

Summary

- Pragmatic approach to sustainable chemistry for **chemists**
- GSK solvent selection guide
- Survived going chlorinated solvent free

DCM → Ethyl acetate, Isopropyl acetate, MeTHF

- GSK reagent grids

HATU, EDC/HOBt → CDI, T3P®

Acknowledgements

Medicinal Chemistry

Simon Macdonald

Simon Peace

John Pritchard

Graham Inglis

Juliet Simpson

Jo Redmond

Aoife Maxwell

Ian Campbell

Steve Keeling

Green chemistry

Helen Sneddon

John Hayler

Catriona Oare

Matthew Walker

Gail Fisher

James Sherwood

Environment and Sustainability

Centre of Excellence

Richard Henderson

Jim Hagen

Conchita Jimenez-Gonzalez

University of Strathclyde / GlaxoSmithKline

PhD programme

Dr Vipul Patel

Dr Harry Kelly

Dr Pan Procopiou

Professor W. Kerr

Professor J. Percy

And I will leave you with…

Manufacturing have the footprint but it originated in research

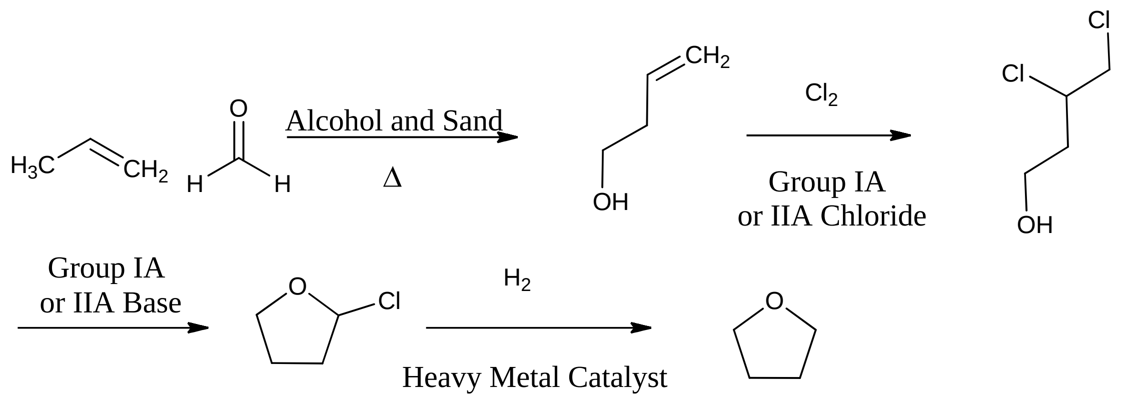
GlaxoSmithKline

University of Strathclyde Glasgow

gsk GlaxoSmithKline

Back up slide – synthesis of THF vs 2MeTHF

- Synthesis of THF



- Synthesis of 2MeTHF