HOW GREEN IS MY CHEMISTRY- AN R&D PERSPECTIVE

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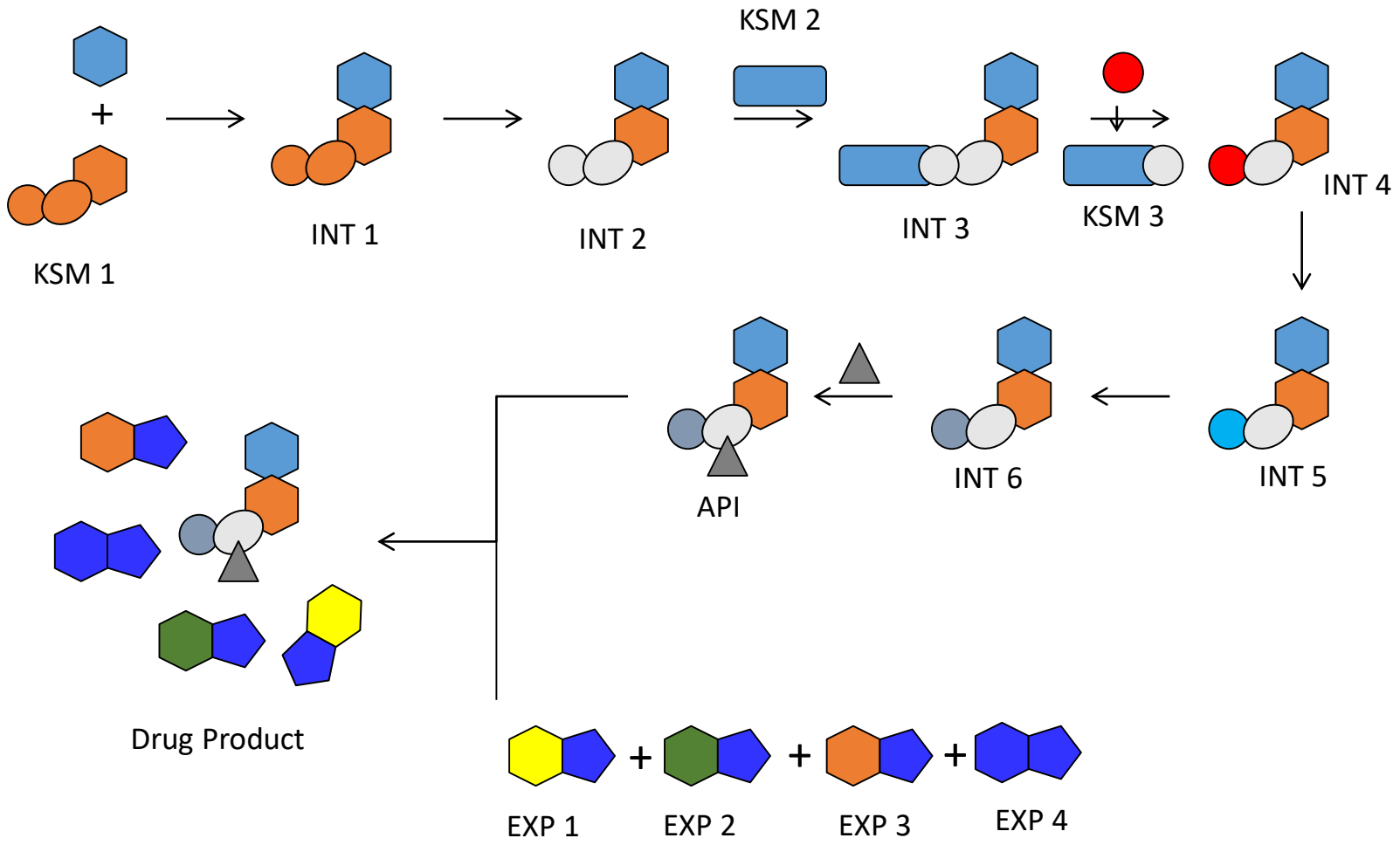
Troikaa
Imagine . Innovate

Indian Pharmaceutical Industry

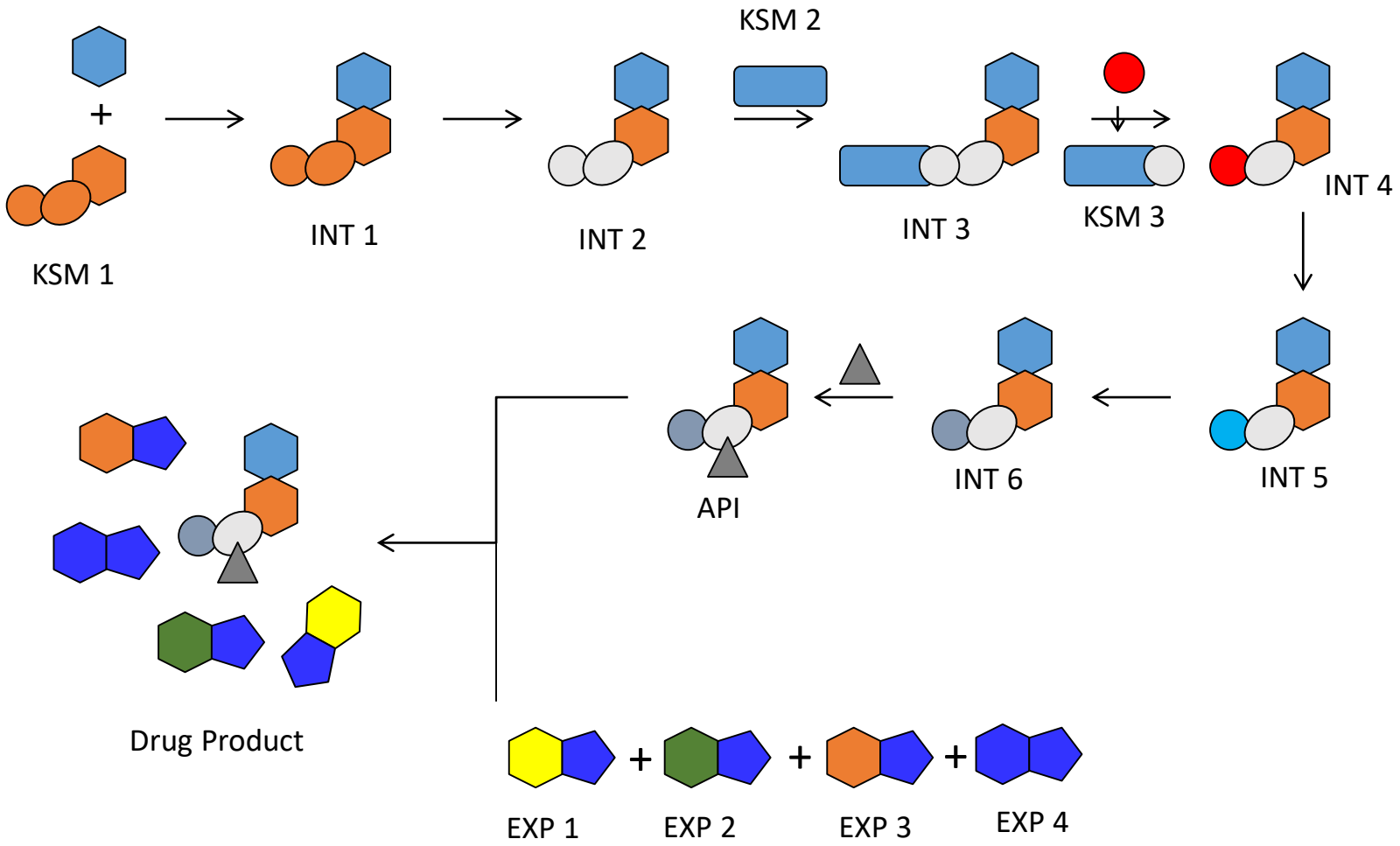
- Pharmacy of the world
- Provide High Quality Medicines at Affordable price
- Serving billions of people across the world everyday
- Saved millions of lives during Pandemic
- Nearly half of all ANDAs filed in US are from India
- Largest number of USFDA approved plant outside US

How green are our pharmaceutical manufacturing processes?

Pharmaceutical Manufacturing process



Pharmaceutical Manufacturing process



- Input materials:
  Solvents, metal catalysts, starting materials, reagents
- Impurities from Input materials:
  Starting materials impurities; impurities within solvents, pesticides...
- By-products and side products:
  Reaction intermediates, related-substances
- Degradation Impurities
  Both API and Intermediates

The Goals of Process Development: The SELECT Criteria

SELECT	Description	Examples of potential issues
Safety	• Process Safety • Exposure to substances harmful to health	• explosions or exotherms; threat to workers or plant • carcinogens or sensitizers
Environment	• Volume of wasted natural resources • Substances harmful to the environment	• Quantity and variety of solvents • aquatic toxins and ozone depleting chemicals
Legal	Infringement of intellectual property rights	Regulations that control use of reagents and intermediates
Economic	Meeting cost of goods and cost of manufacture target for future market	Long synthesis using expensive materials
Control	• Control of quality parameters • Control of chemistry and physical parameters	• Meeting specification and GMP requirements • Non-selective reactions, unstable intermediates
Throughput	• Time scale of manufacture in available plant • Availability of raw materials	• Long route with dilute stages • Use of specially made raw materials

Ref: Chem. Rev. 2006, 106, 3002-3027

The 12 Principles of Green Chemistry

1. **Prevention**
   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**
   Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Synthesis**
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

4. **Designing Safer Chemicals**
   Chemical products should be designed to effect their desired function while minimising their toxicity.

5. **Safer Solvents and Auxiliaries**
   The use of auxiliary substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

6. **Design for Energy Efficiency**
   Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

The 12 Principles of Green Chemistry

7 Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8 Reduce Derivatives

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

9 Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10 Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

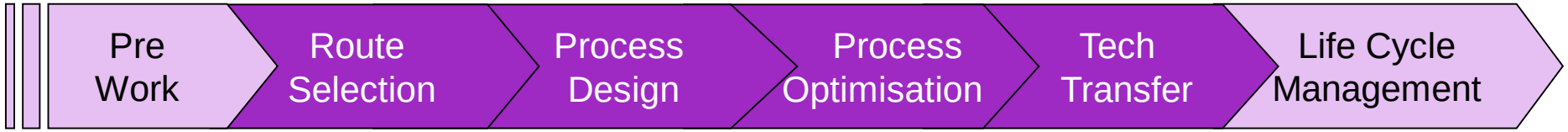
11 Real-time Analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12 Inherently Safer Chemistry for Accident Prevention

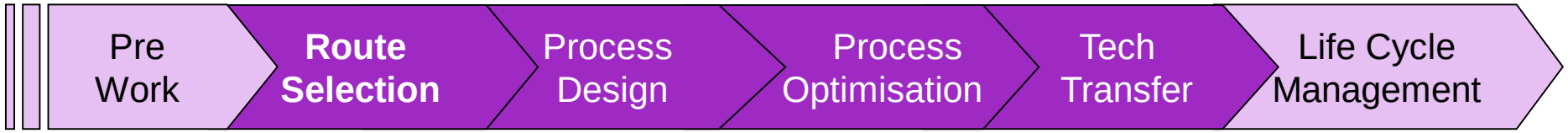
Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

Product Development Overview



- **Product selection**
- **Business targets**
- **Product development strategy**
- **Route Design**
- **Process Design**
- **Process Optimization**
- **Tech Transfer and process validation**
- **Commercialization and LCM**

Route Design and Route Selection



Objectives

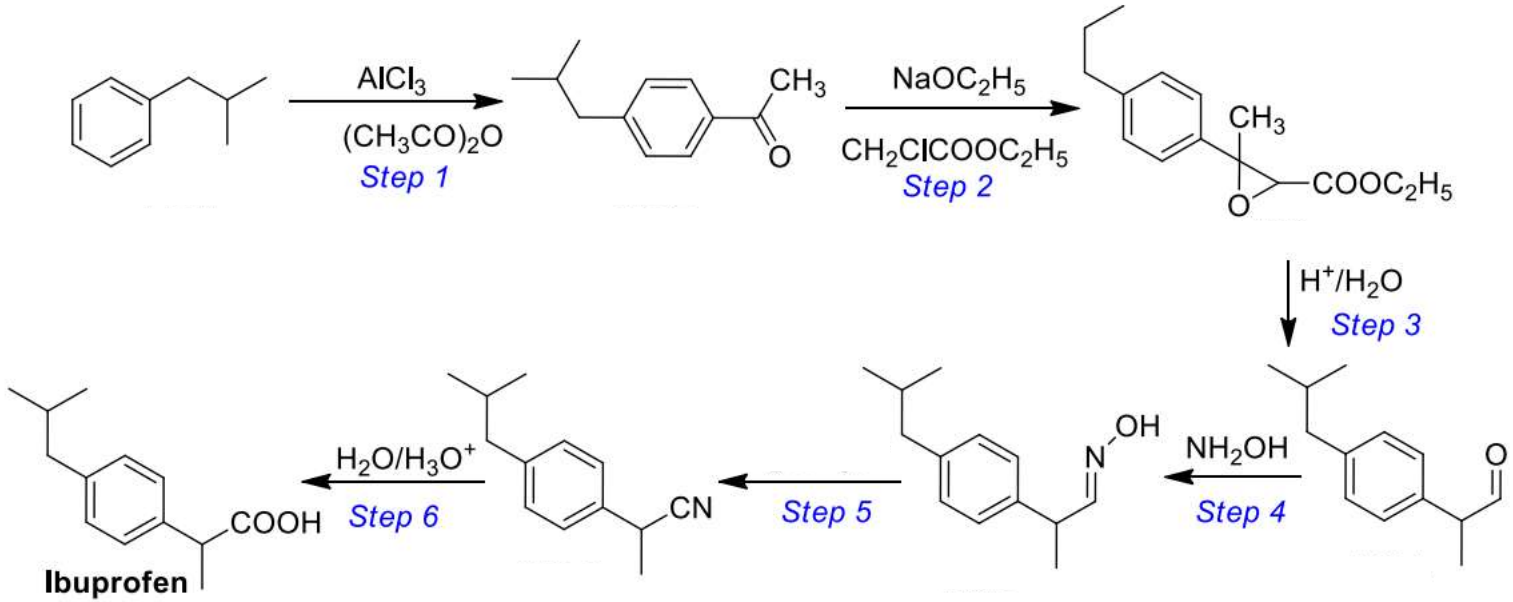
- Cost effective
- Atom Economy & PMI
- Shortest route
- Easy to operate
- Safe to Operate
- High throughput
- Eco friendly

Constraints

- FTO
- Availability of RMs
- Special Equipments
- Regulatory

Route Design Examples

Traditional Boot's Synthesis of Ibuprofen

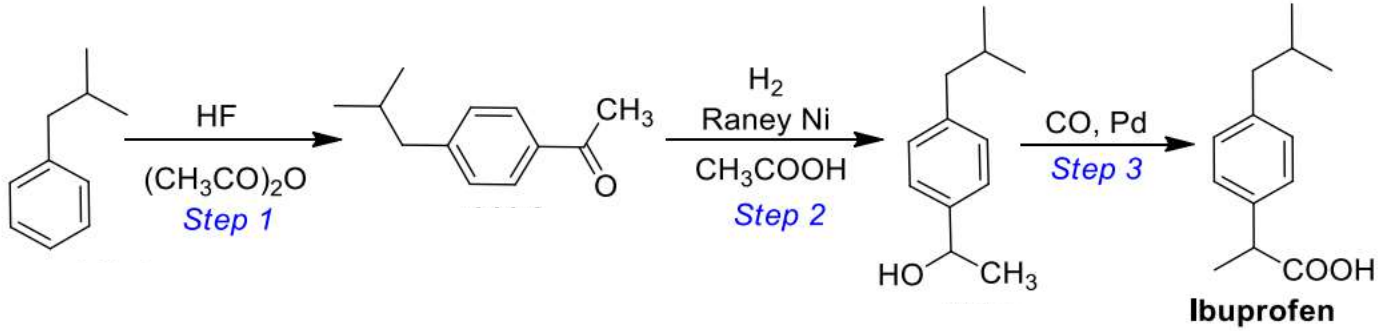


Six steps synthesis with 40% atom economy

Leszczynski et al. Chem Rev 2022, 122, 3637

Route Design Examples

Green Synthesis of Ibuprofen



Three steps synthesis with 77% atom economy
The atom economy is 99% if acetic acid recovery is considered

Leszczynski et al. Chem Rev 2022, 122, 3637

Route Design Examples

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Boots Synthesis						
	reagent		used in ibuprofen		unused in ibuprofen	
atom economy	formula	MW	formula	MW	formula	MW
	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
	$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
	C_2H_5ONa	68	N/A	0	C_2H_5ONa	68
	H_3O	19	N/A	0	H_3O	19
	NH_3O	33	N/A	0	NH_3O	33
	H_4O_2	36	N/A	33	H_3	3
	total		ibuprofen		waste product	
	$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

BHC Green Synthesis						
	reagent		used in ibuprofen		unused in ibuprofen	
atom economy	formula	MW	formula	MW	formula	MW
	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
	H_2	2	H_2	2	N/A	N/A
	CO	28	CO	28	N/A	N/A
	total		ibuprofen		waste product	
	$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

Development of a Robust and scaleable process for AZD3264

•NF-kB is a key regulator of inflammatory genes and plays a critical role in the pathogenesis of a number of human disorders, particularly those with COPD

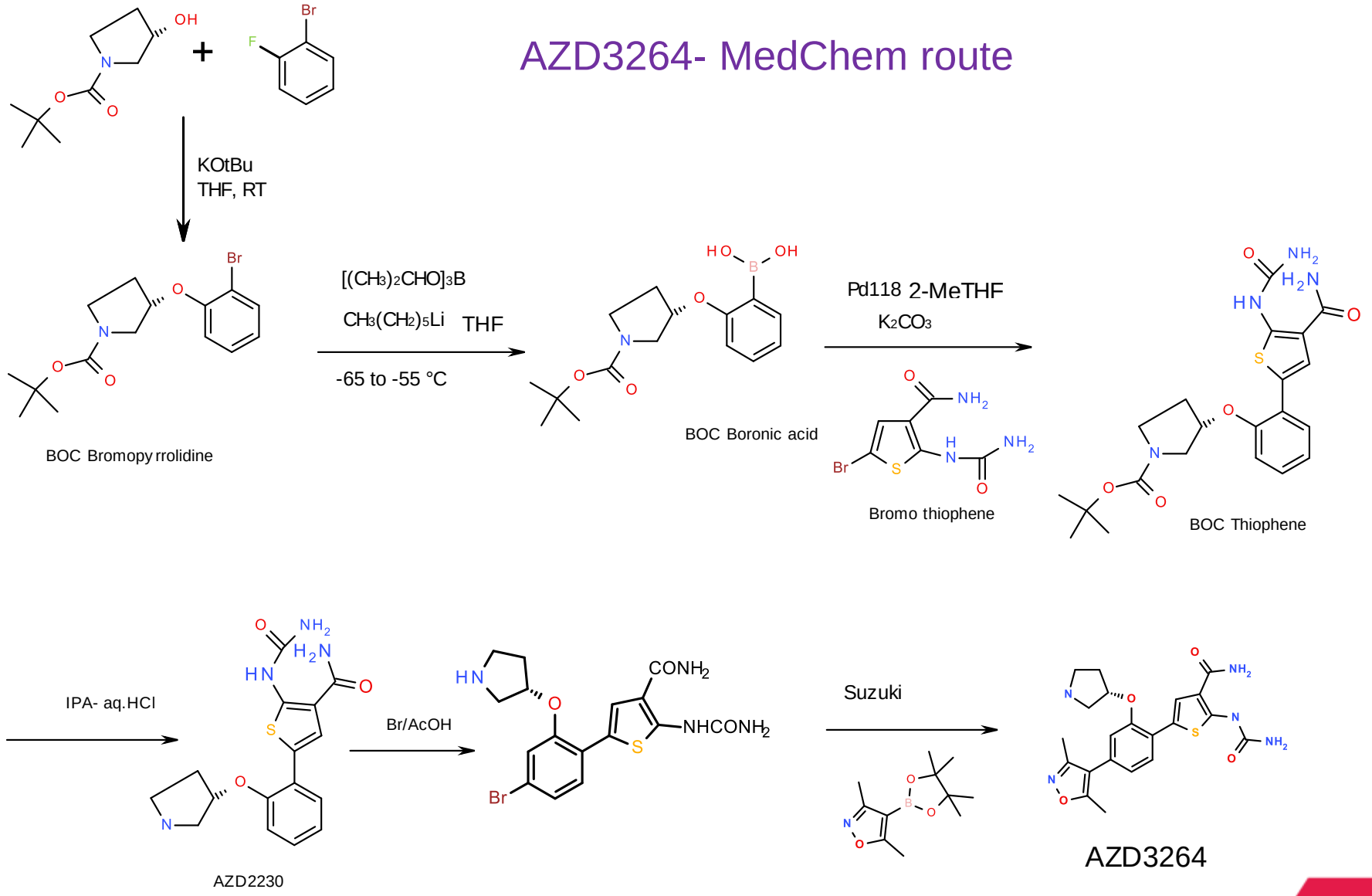
• IKB kinase 2 (IKK2) is a key regulator of the activity and function of NF-kB

• It has now been observed that Inhibiting IKK2 gives an unexpectedly beneficial therapeutic effect in the treatment of COPD and other inflammatory conditions

• AZD3264 was being developed as potential IKK2 inhibitor to treat COPD conditions

Development of a Robust and scaleable process for AZD3264

AZD3264- MedChem route

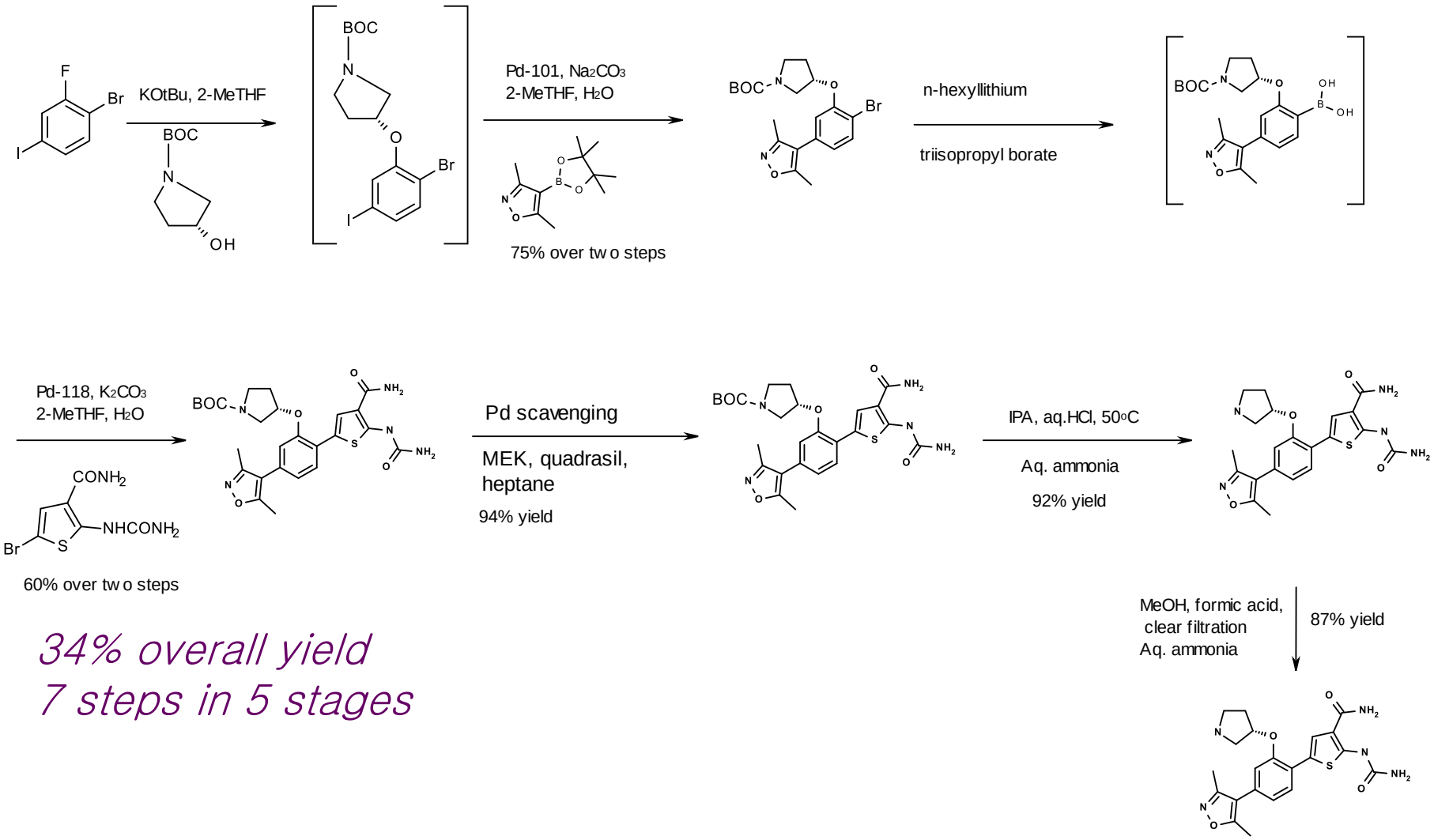


Development of a Robust and scaleable process for AZD3264

AZD3264- MedChem Route challenges

- Poor yield and selectivity during the bromination step
- Poor solubility of the API in most of the solvents
- Poor overall yield (28 kgs of Bromopyrrolidine was used) to deliver 1.5 kg of API
- High Pd content (>700ppm) in the API (because of the API's affinity towards Pd)
- High DMSO content in the API (>20000 ppm)
- Poor solid properties, difficulties during micronization and formulation

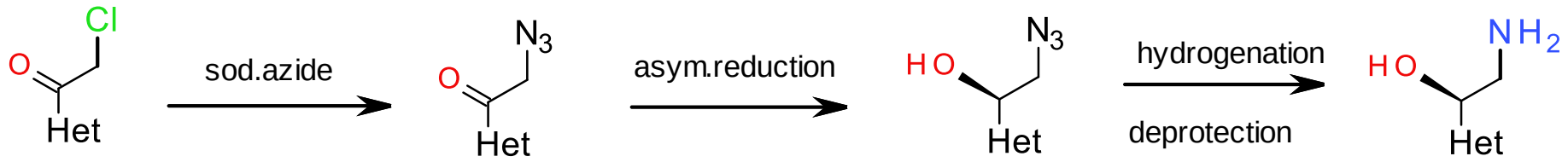
Development of a Robust and scaleable process for AZD3264



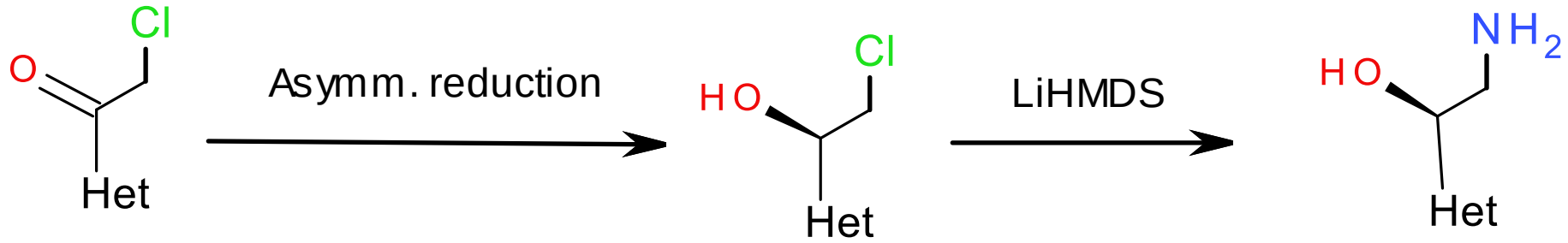
34% overall yield
7 steps in 5 stages

Andiappan et al. OPRD 2014, 18, 646

Route Design Examples- AZD 2115



- Involves energetic Azide intermediates, need for safer long term options



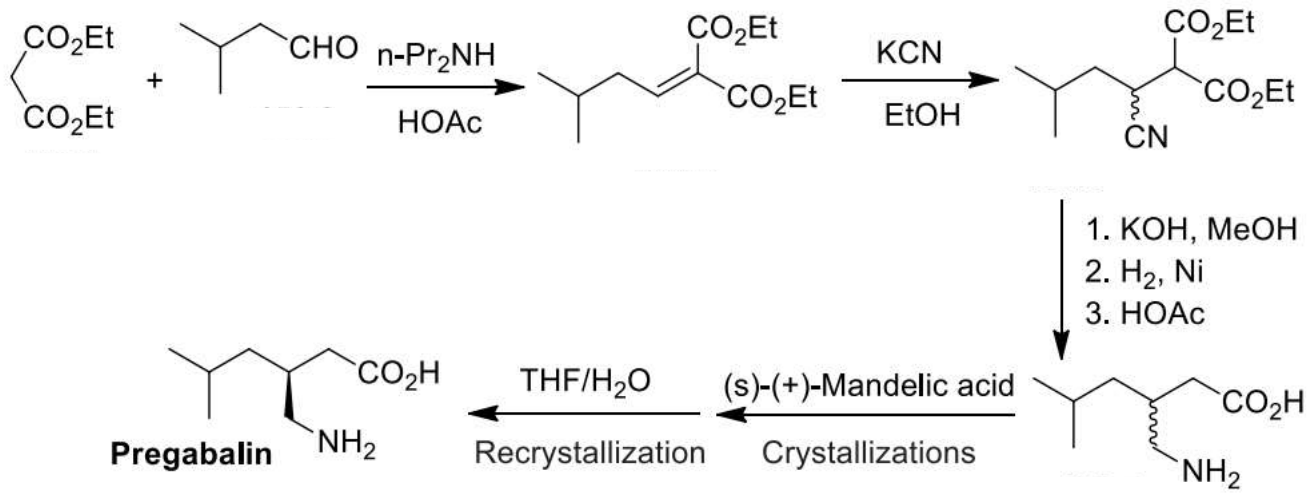
- Straight forward two step process from the chloroketone
- A new reaction, epoxide opening with NaHMDS has been developed
- Opportunity for publication

Ref: WO 2012156693 A1

Andiappan et al. Tetrahedron Letters 2012, 53, 5739

Route Design Examples

First Generation Synthesis of Pregabalin

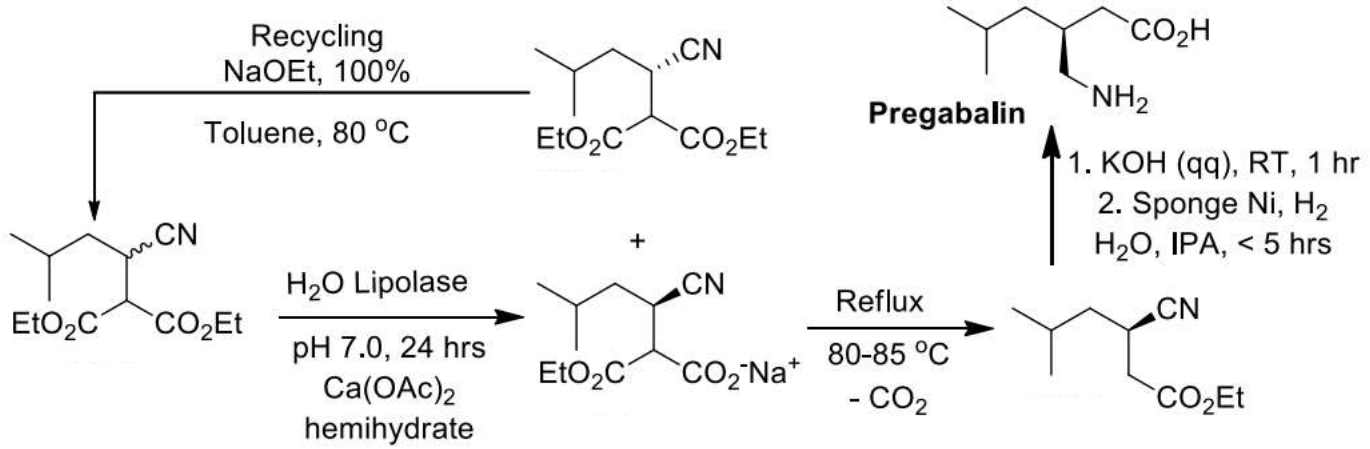


Poor overall yield (<20%), expensive route
Huge of waste generation
Wrong enantiomer can not be recycled

Leszczynski et al. Chem Rev 2022, 122, 3637

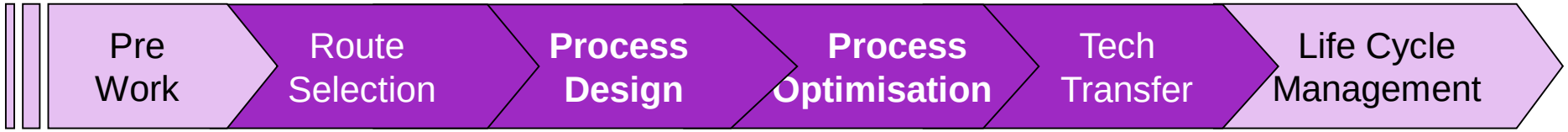
Route Design Examples

Green Synthesis of Pregabalin



Good overall yield (>40%)
Less expensive route
Wrong enantiomer is recycled
2000 tons of raw materials & 10 million gallons of solvents were saved per annum

Process Design



- Focus on Individual Steps
- Multiple possibilities to effect a transformation
- Choice of Reagents
- Choice of Solvents
- Equipment design

- Optimize the quantities of the Raw materials used
- Process Risk Assessment
- Process safety risk assessment
- Safety testing
- Calculate PMIs
- Detoxification and waste treatment

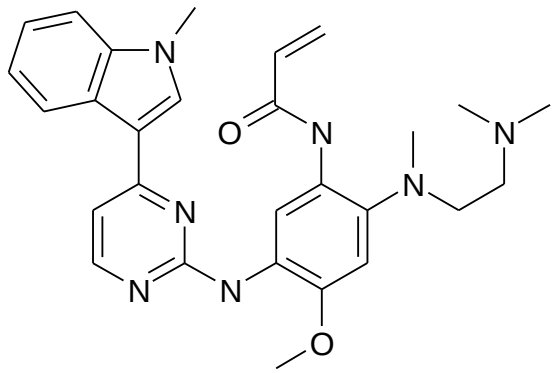
Process Design- Reagent Selection

- **Specific for desired synthetic transformation**
  1. **Should be compatible with other functional groups of the molecule**
  2. **Should be compatible with the other reagents and solvent involved in the transformation**
  3. **Regio & Stereo selective if applicable**
- **Reacts under ambient condition**
- **Reacts at reasonable rate**
- **Non-toxic/least toxic- itself or its metabolic products**
- **Poses no chemical reaction hazard to personnel**
- **Produce no by product/non-toxic by product-lower disposal cost**
- **If catalytic, readily recovered and reused**
- **Recyclable- cost advantage and reduce effluent**
- **Readily available with consistent quality**

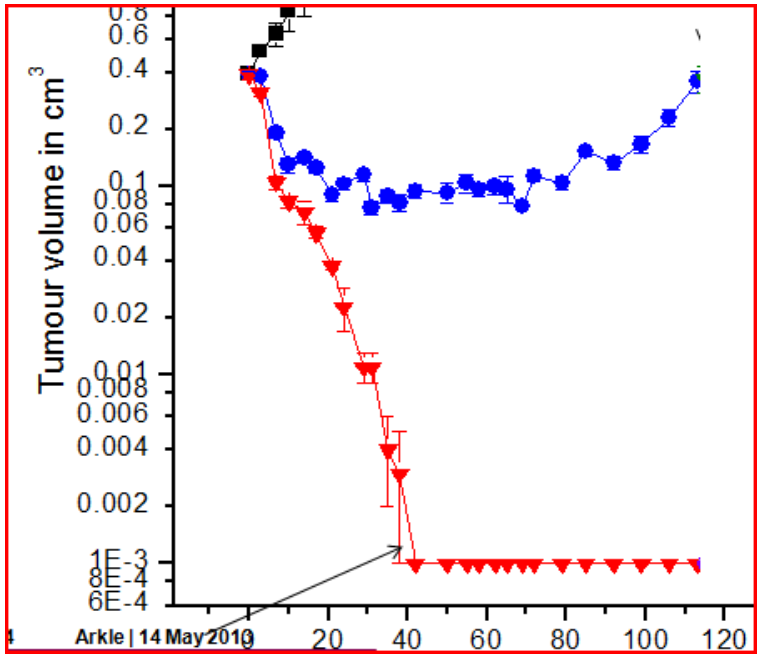
Process Design- Solvent Selection

- Provide safe scale-up condition
- Facilitate the rate of reaction
- Ease of product separation
- Removes impurities and byproducts
- Ease removal from the product
- Safe to operate
- Non-toxic or Least toxic
- From Renewable Sources
- Recovery and reusability
- Commercial availability and cost

Process Design- Osimertinib

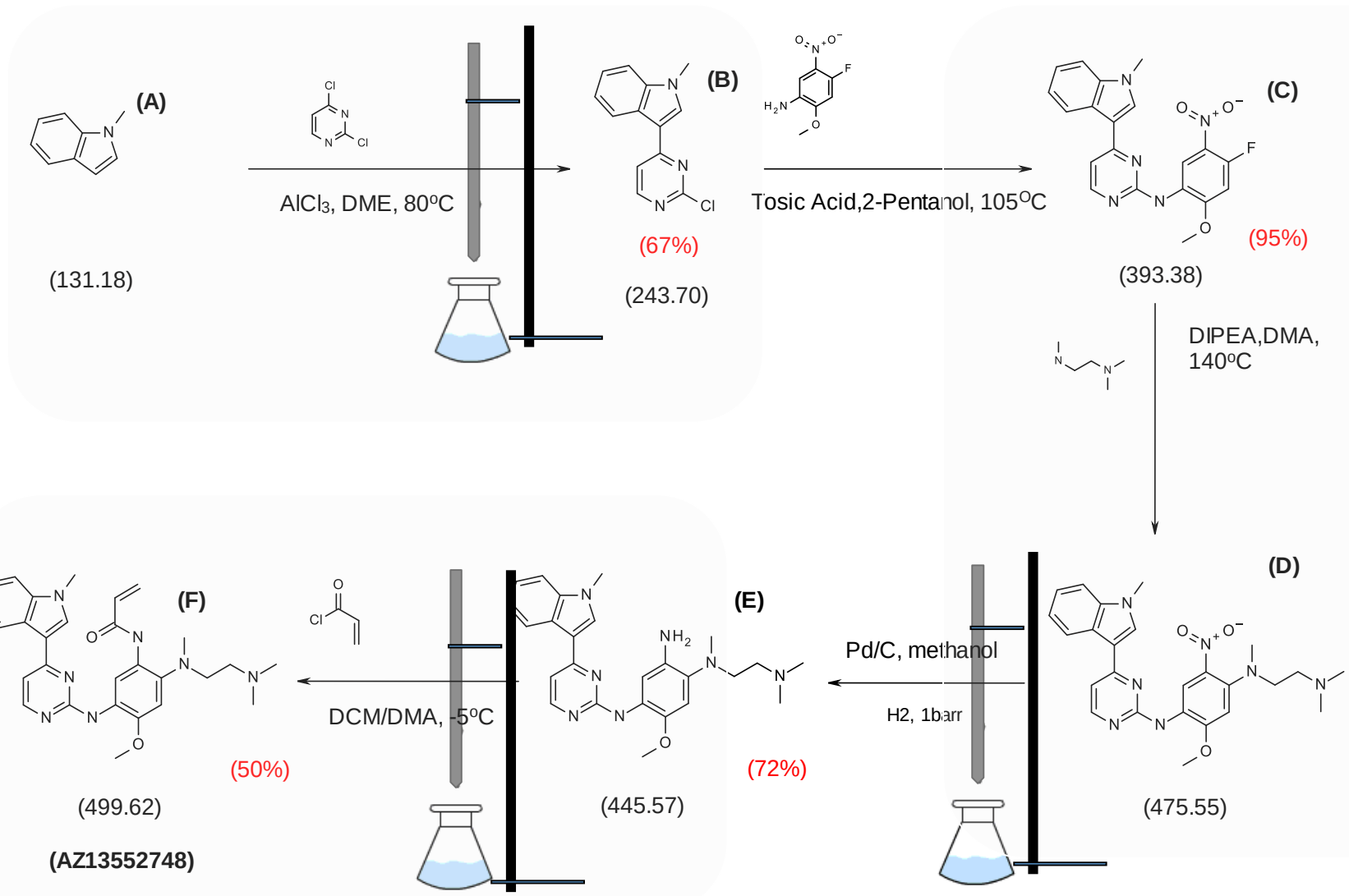


Osimertinib (AZD9291)



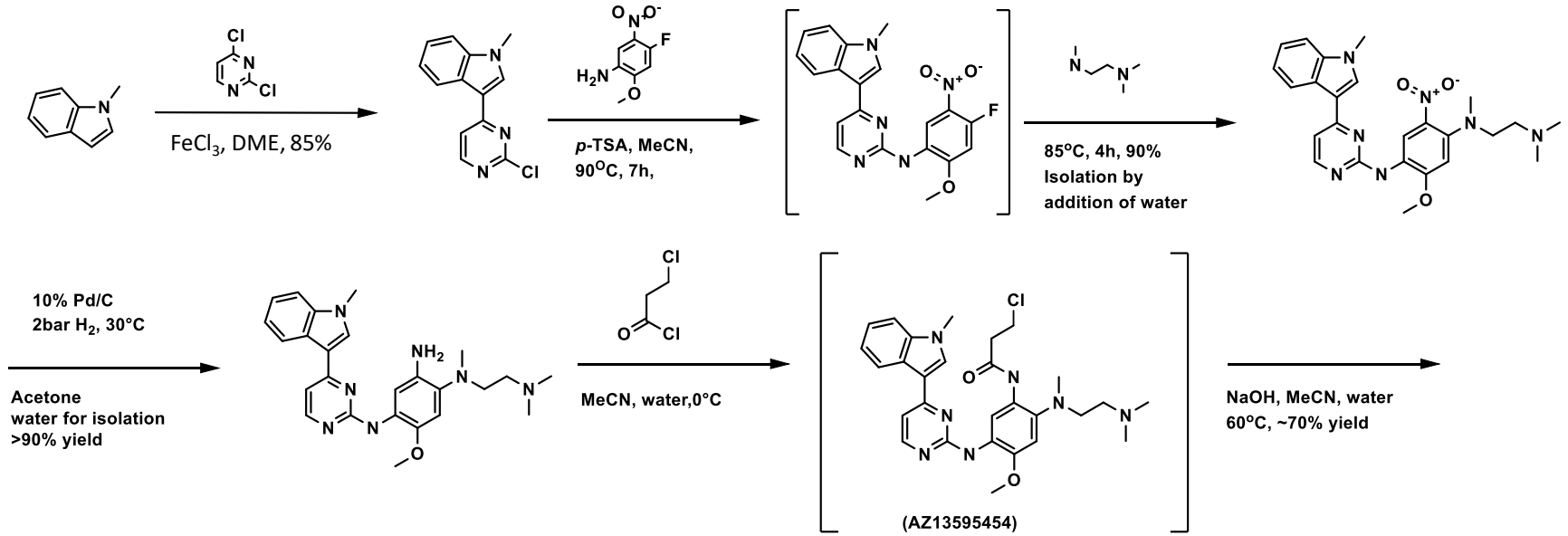
- **EGFRM T790m inhibitor**
- **First in class**
- **Breakthrough Therapy Designation & Fast Track Designation**
- **Took <3 years from FTIM to Launch**
- **Generating revenues > $5 billion**

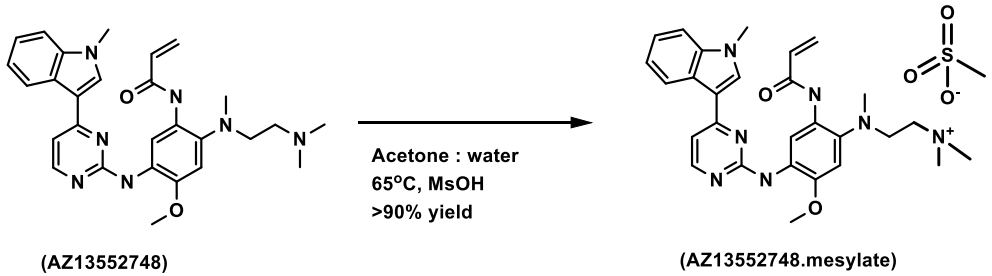
Process Design- Osimertinib



- 3 Chromatographic purifications
- Use of DMA as a solvent
- Polymeric impurities at the last step
- Poor overall yield

Osimertinib- Optimized Process





(AZ13552748)

(AZ13552748.mesylate)

- No Chromatographic purification
- $AlCl_3$ was replaced with $FeCl_3$
- Telescoped process
- Novel chemistry to introduce acrylamide function
- 45% overall yield
- Multiple campaign delivered at very short time to support rapid clinical progress

WO 2013014448 A1

Use of pKa values for process development

- Most of the APIs and their intermediates are either acidic or basic
- Hence pH has great influence in their reactivities, extraction & isolation

Use of pKa values for process development

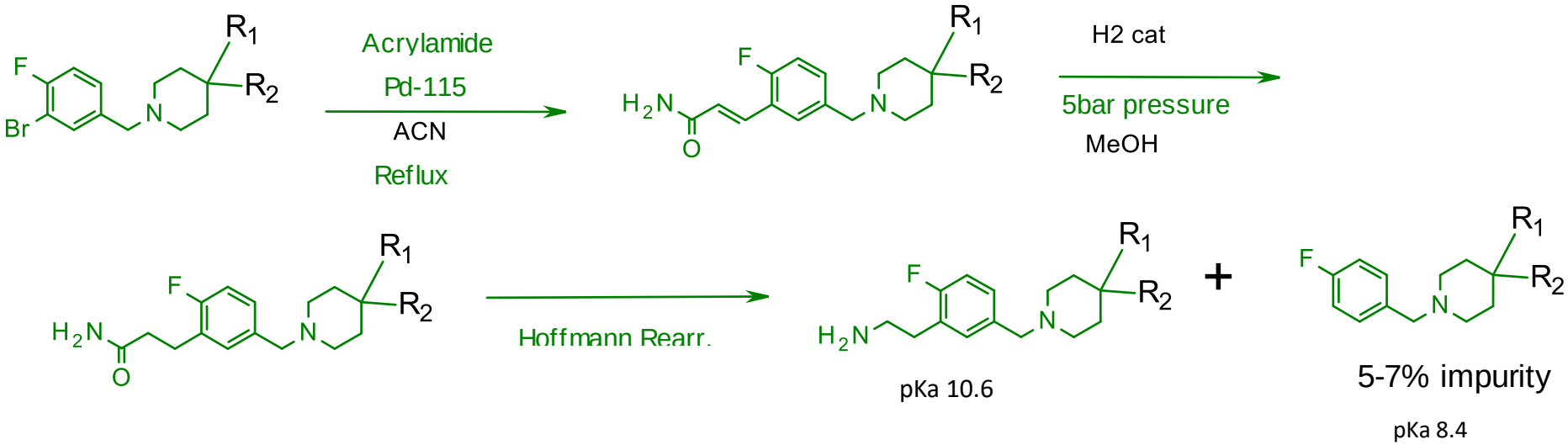
Speciation vs pH

A useful rough guide $$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

pH equals	Ratio HA : A^-	log ($[A^-]/[HA]$)
pK_a - 2	99:1	log (~0.01) = -2
pK_a - 1	9:1	log (~0.1) = -1
pK_a	1:1	log (1) = 0
pK_a + 1	1:9	log (~10) = 1
pK_a + 2	1:99	log (~100) = 2

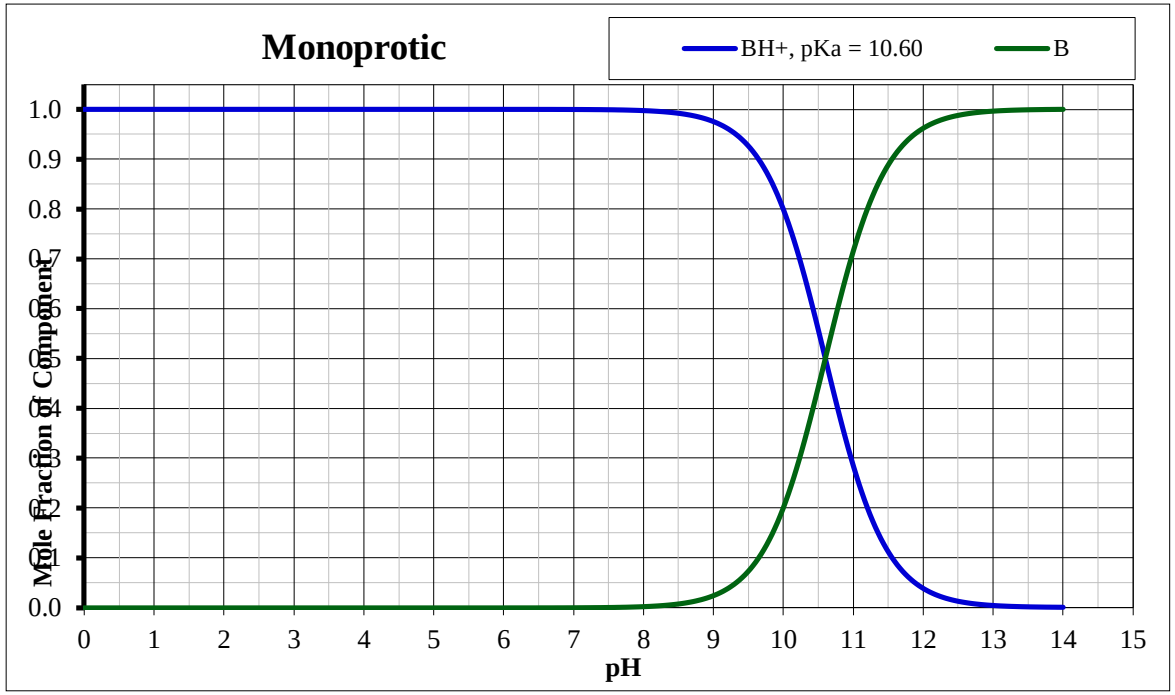
- pKa is a numerical term
- Approximate values can be obtained from databases ... ACD labs, ChemDraw etc
- Accurate values can be obtained by experiments
- Is a handy tool for reagent selection, reactive crystallization (salt formation) and extractions

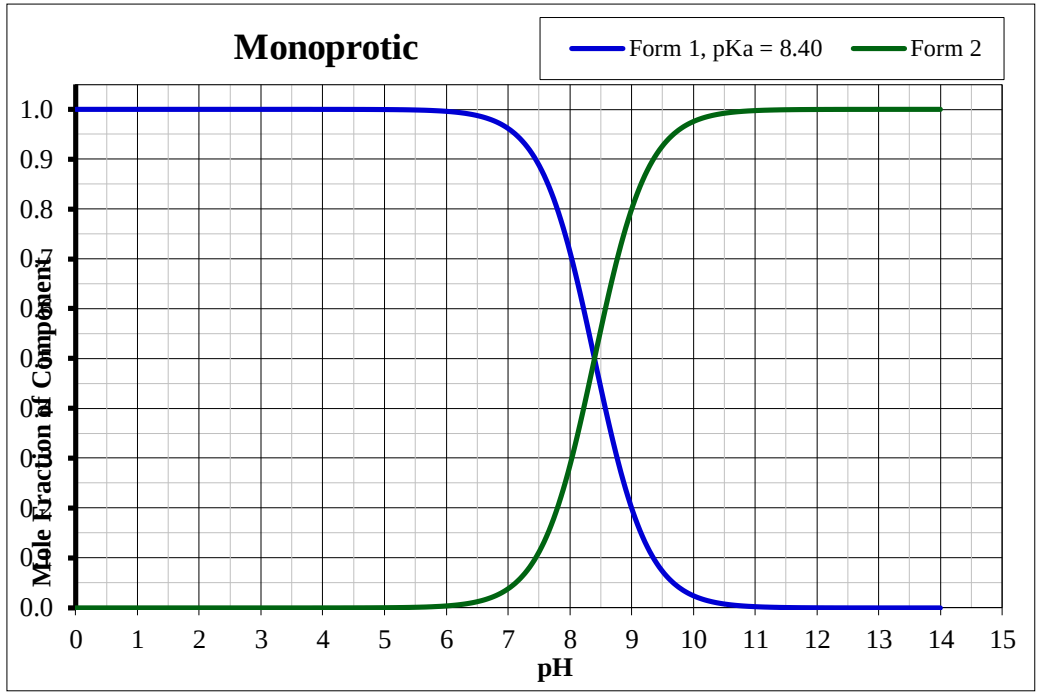
Use of pKa values for efficient work up & purification



- Made use of difference in pKas for purification
- The crude material was dissolved in aq.sulfuric acid
- pH was adjusted between 9 to 9.5 by the addition of aq. NaOH
- Extracted with toluene to remove the impurity
- The MLR with pure material was basified and extracted with 2-MeTHF and the product was precipitated as HCl salt

Speciation of the Product and the impurity Based on their pKa Values

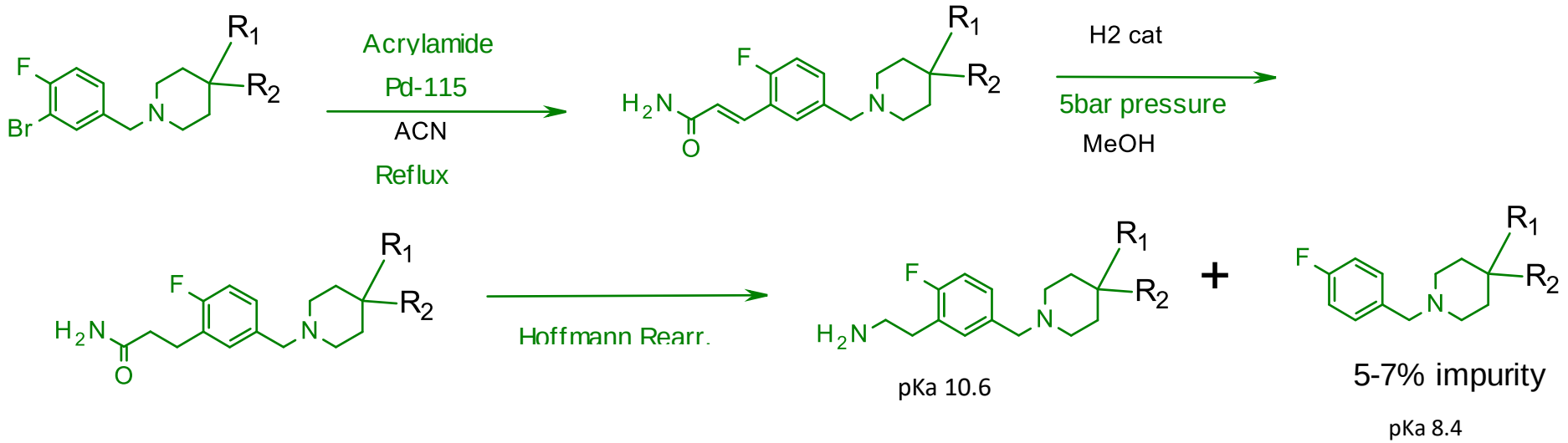




>97% of the product exits in protonated form at pH~9

>80% of the impurity stays in free base form at pH~9

Use of pKa values for efficient work up & purification



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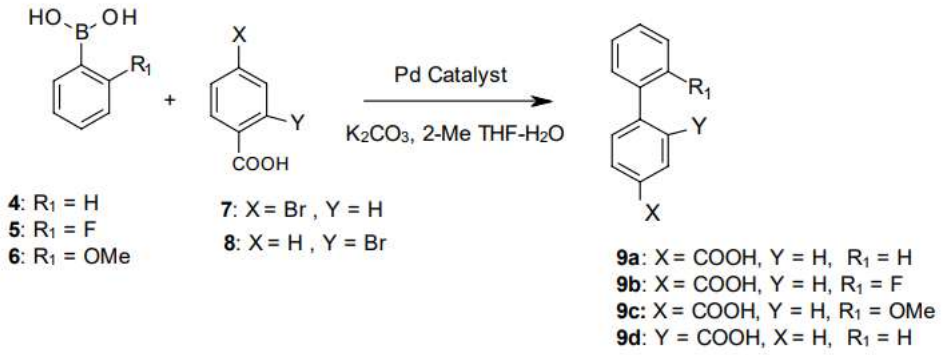
Ref: WO 2012156693 A1

Process Design Examples

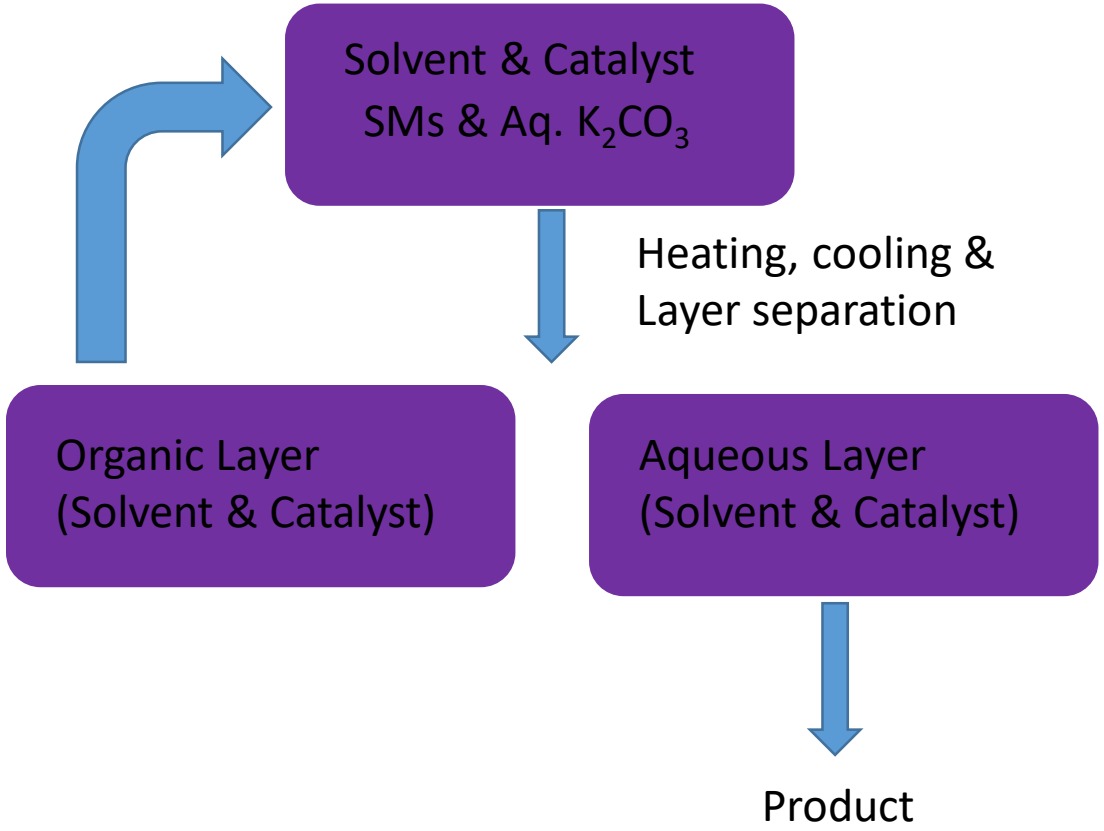
Recycling of Homogeneous Catalyst in Suzuki Reaction



4: R_1 = H
5: R_1 = F
6: R_1 = OMe

7: X = Br , Y = H
8: X = H , Y = Br

9a: X = COOH, Y = H, R_1 = H
9b: X = COOH, Y = H, R_1 = F
9c: X = COOH, Y = H, R_1 = OMe
9d: Y = COOH, X = H, R_1 = H



Manjunatha et al. Green Chemistry Letter & Reviews 2013, 6, 77

Process Design Examples

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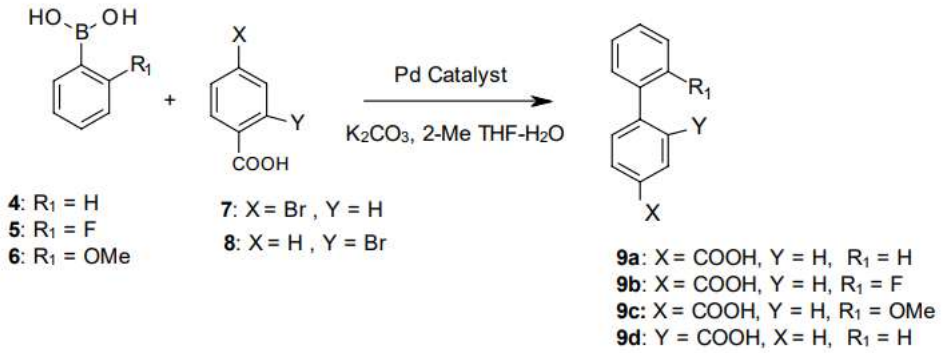

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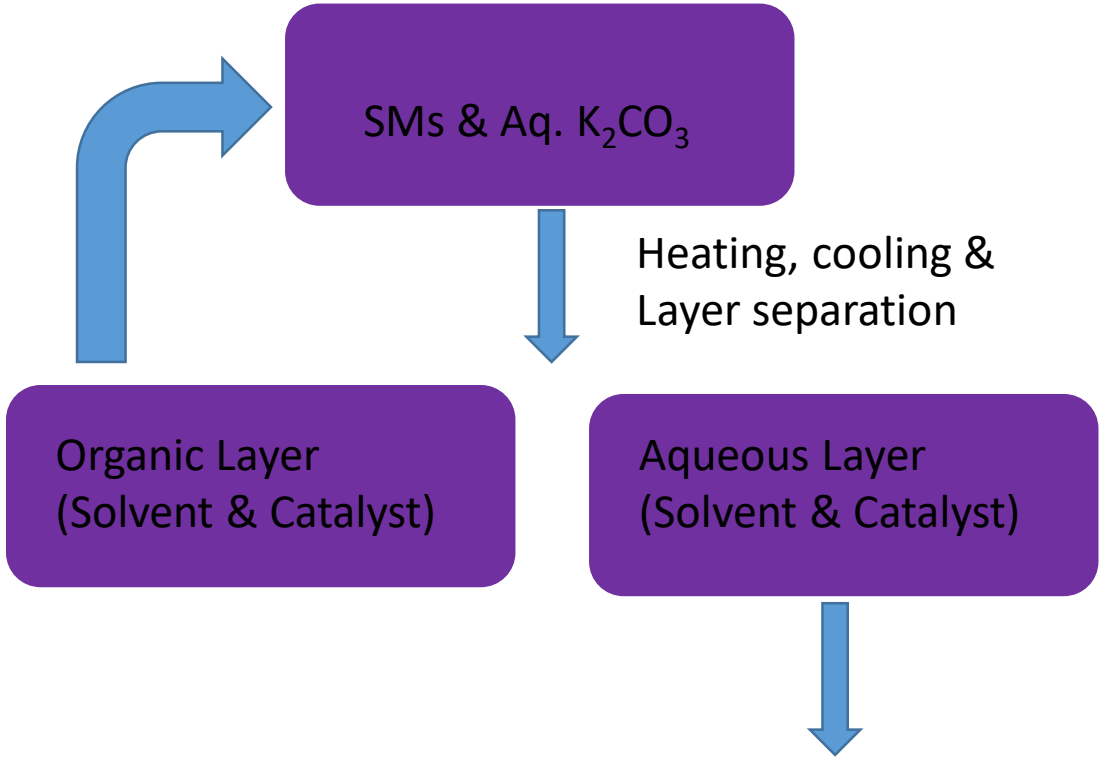


Solvent & Catalyst can be recycled multiple times
If there is drop in activity, topping up of catalyst and solvent may preserve the activity

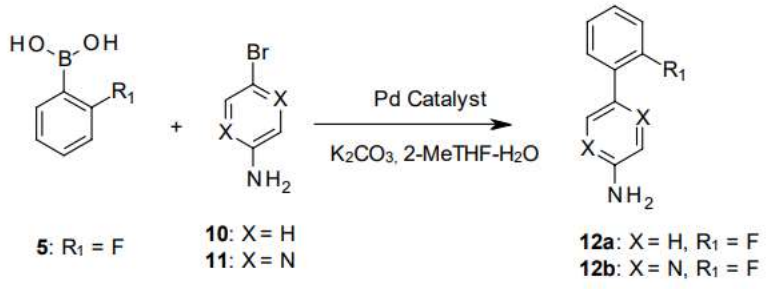
Process Design Examples

Table 1. Recycling of homogeneous catalyst in Suzuki reaction with basic work up (Scheme 1).

Entry	Comp No	R_1	X	Y	Cycle	Catalyst (5 mol%)	% Conv (time in h)[a]	% Yield/purity by HPLC
1	**9a**	H	COOH	H	1	Pd-100	94.3 (4)	85/97.0
2	**9a**	H	COOH	H	2	–	96.0 (4)	82/98.2
3	**9a**	H	COOH	H	3	–	94.5 (3)	70/99.0
4	**9b**	F	COOH	H	1	Pd-100	94.5 (3)	77/95.0
5	**9b**	F	COOH	H	2	–	96.0 (3)	76/96.9
6	**9b**	F	COOH	H	3	–	75.6 (3)	65/96.5
7	**9c**	OMe	COOH	H	1	Pd-100	93 (2)	81/97.9
8	**9c**	OMe	COOH	H	2	–	96.0 (17)	80/98.2
9	**9c**	OMe	COOH	H	3	–	93.3 (10)	80/94.3
10	**9a**	H	COOH	H	1	Pd-106	82.2 (3)	*
11	**9a**	H	COOH	H	2	–	93.2 (3)	*
12	**9a**	H	COOH	H	3	–	88.2 (3)	*
13	**9b**	F	COOH	H	1	Pd-106	97.0 (3)	*
14	**9b**	F	COOH	H	2	–	97.7 (3)	*
15	**9b**	F	COOH	H	3	–	96.6 (3)	*
16	**9c**	OMe	COOH	H	1	Pd-106	93.2 (3)	*
17	**9c**	OMe	COOH	H	2	–	89.2 (3)	*
18	**9c**	OMe	COOH	H	3	–	95.5 (3)	*
19	**9a**	H	COOH	H	1	Pd-118	96.2 (3)	*
20	**9a**	H	COOH	H	2	–	91.8 (3)	*
21	**9a**	H	COOH	H	3	–	94.7 (3)	*
22	**9b**	F	COOH	H	1	Pd-118	96.8 (3)	*
23	**9b**	F	COOH	H	2	–	97.1 (3)	*
24	**9b**	F	COOH	H	3	–	97.1 (3)	*
25	**9c**	OMe	COOH	H	1	Pd-118	95.4 (3)	*
26	**9c**	OMe	COOH	H	2	–	96.3 (3)	*
27	**9c**	OMe	COOH	H	3	–	96.9 (3)	*
28	**9d**	H	H	COOH	1	Pd-118	94.5 (3)	*
29	**9d**	H	H	COOH	2	–	94.6 (3)	*
30	**9d**	H	H	COOH	3	–	93.3 (4)	*

Process Design Examples

Recycling of Homogeneous Catalyst in Suzuki Reaction

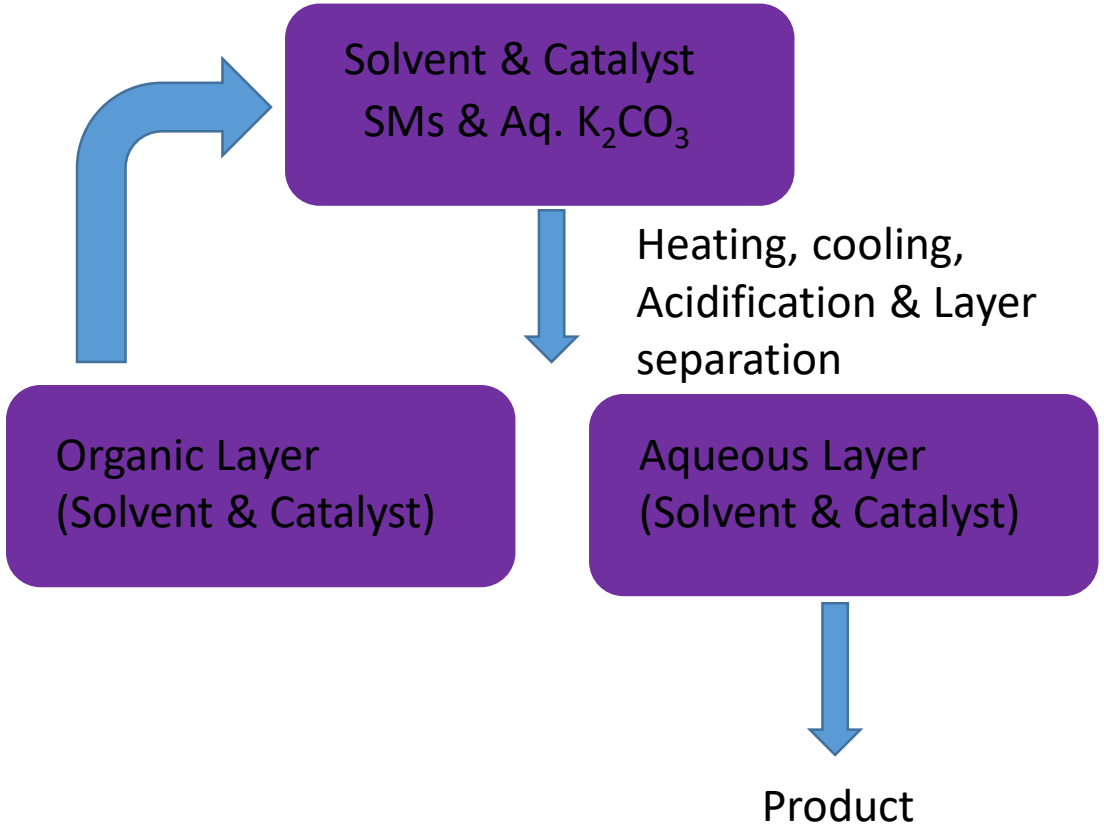


5: R_1 = F

10: X = H
11: X = N

12a: X = H, R_1 = F
12b: X = N, R_1 = F

Suzuki coupling of phenylboronic acid and aromatic amine.



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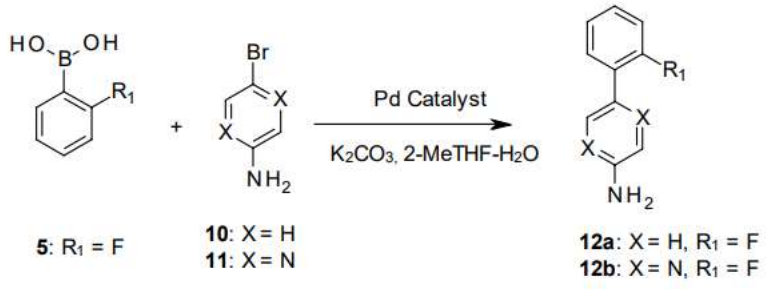

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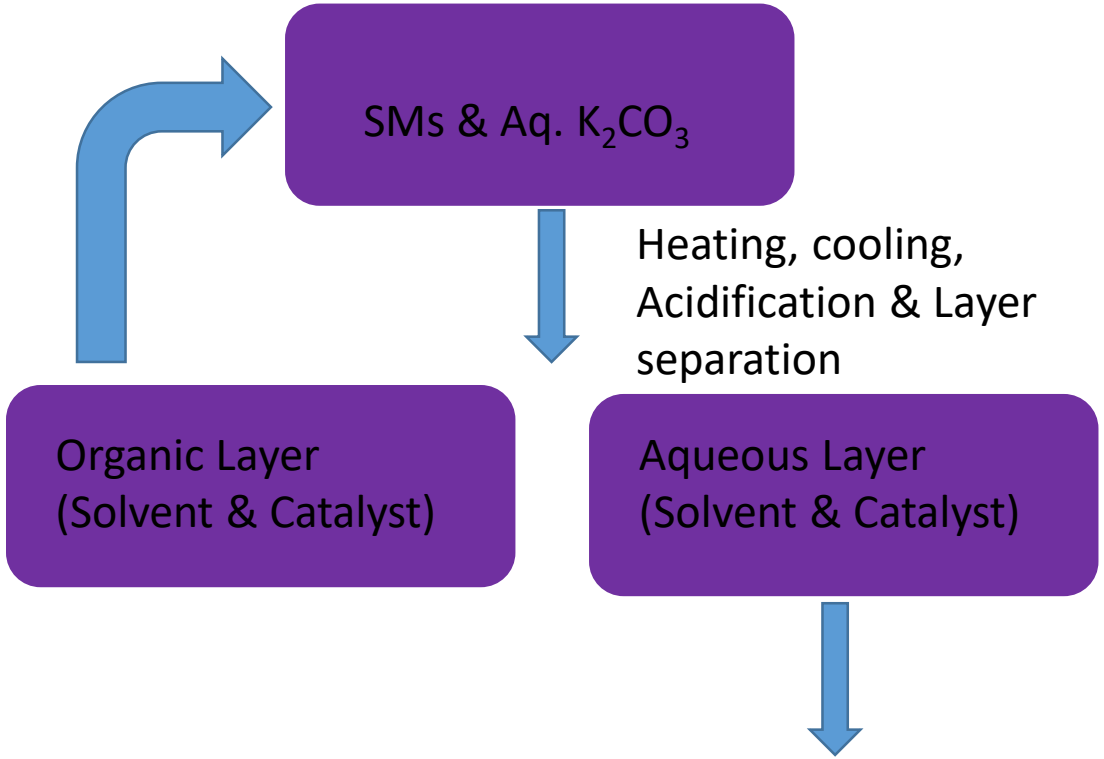


Solvent & Catalyst can be recycled multiple times
If there is drop in activity, topping up of catalyst and solvent may preserve the activity

Process Optimization

Table 2. Recycling of homogeneous catalyst in Suzuki reaction with acidic work up (Scheme 2)

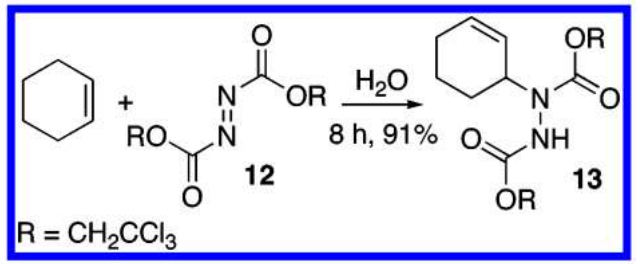
Entry	Product	X	R_1	Cycle	Catalyst (5 mol%)	% Conv (time in h)[a]
1	**12a**	H	F	1	Pd-118	98 (1)
2	**12a**	H	F	2	–	98 (1)
3	**12a**	H	F	3	–	92 (1)
4	**12a**	H	F	1	Pd-100	85 (2)
5	**12a**	H	F	2	–	72 (4)
6	**12a**	H	F	3	–	57 (4)
7	**12b**	N	F	1	Pd-118	90 (4)
8	**12b**	N	F	2	–	88 (5)
9	**12b**	N	F	3	–	72 (5)
10	**12b**	N	F	1	Pd-100	71 (24)
11	**12b**	N	F	2	–	53 (24)
12	**12b**	N	F	3	–	27 (24)

[a]% Conversion to product, with respect to starting material.

Various Catalysts, Reagents & Solvents can be explored

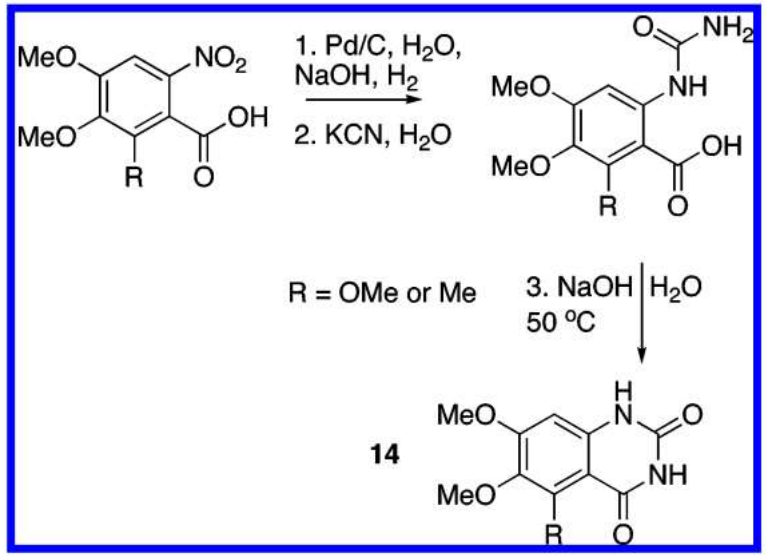
Reactions in Aqueous Medium

- The solubility of the organic substrates in water often considered as a limitation
- High temperature water (>200°C) and super critical water (>374°C) behave more like organic solvents



- The reaction between Azido dicarboxylate and cyclohexene in organic solvent or neat require 24h for completion with 60-70% yield
- The same reaction "**on water**" completed in 8h with 91% yield

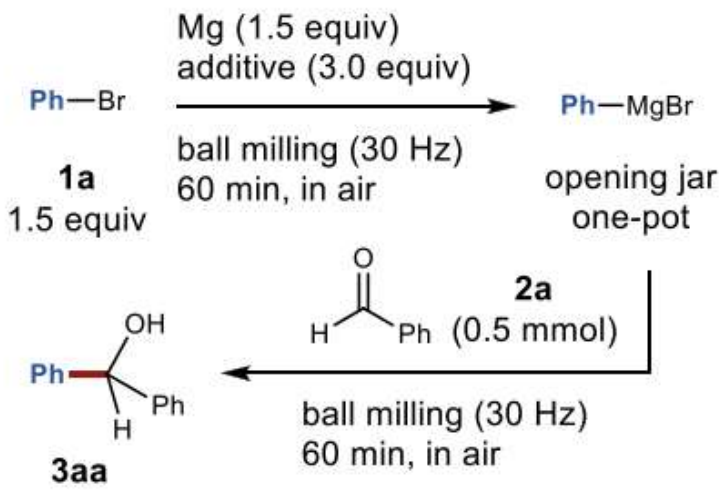
Sharpless et al. Angew Chem Int Ed 2005, 44, 3275



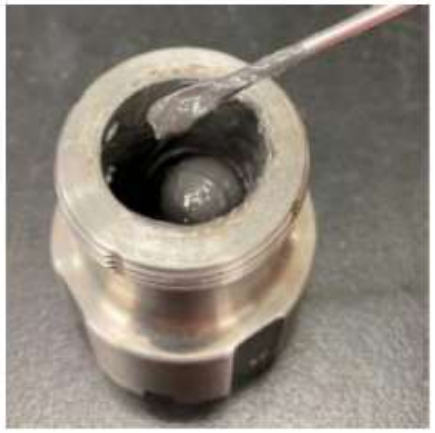
- Hydrogenation of the nitrobenzoic acid under basic condition, filtration of the catalyst and treatment with KCN afforded the urea.
- At pH>13 and on heating the urea cyclized to afford the quinazoline dione in excellent yield

Sukhtankar et al. Geen Chem Int Ed 2005, 7, 586

Mechano-chemical Reactions



additive (3.0 equiv)	yield of **3aa** (%)
none	6
THF	**94**
Et_2O	79
CPME	87
hexane	1

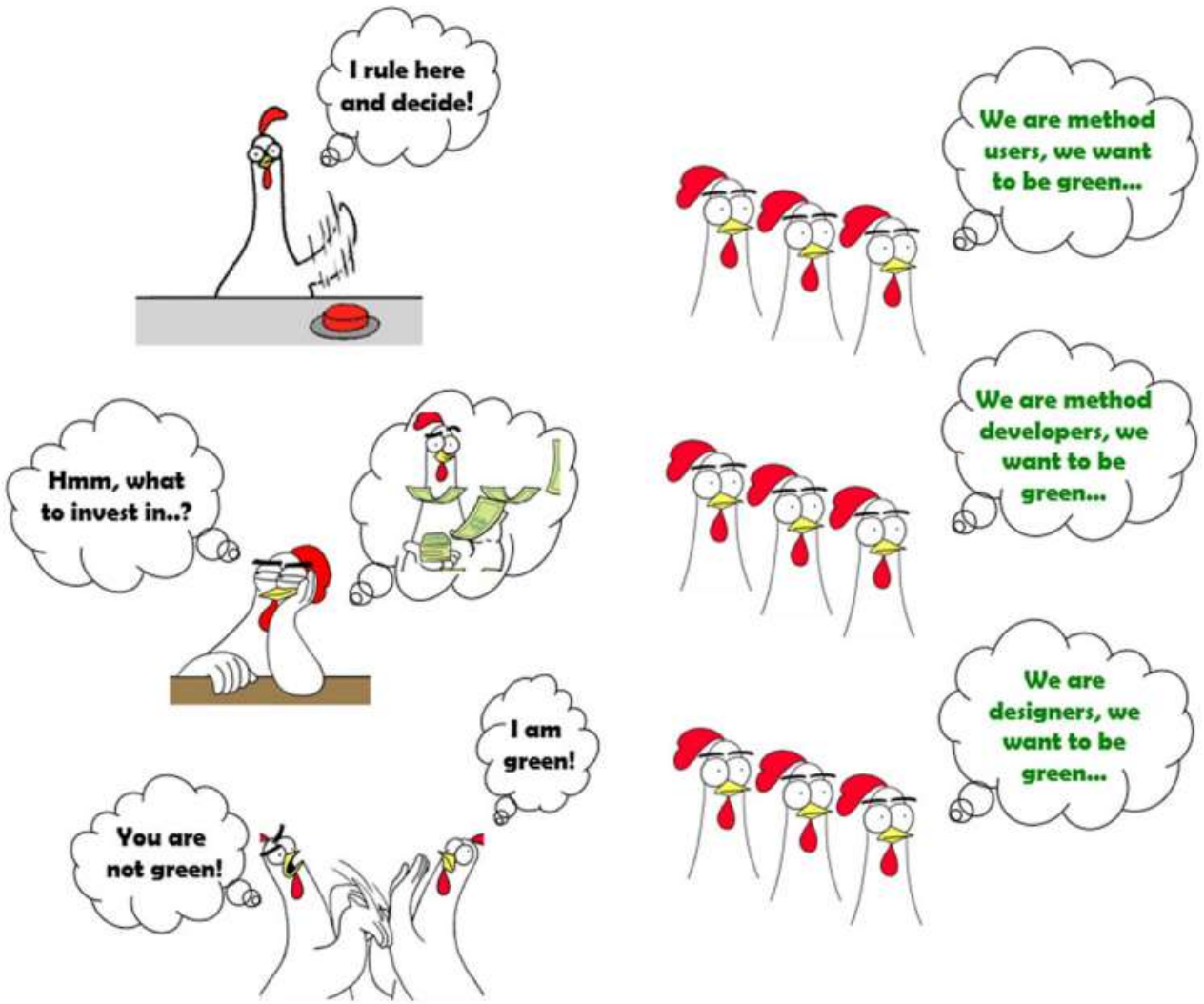


reaction without additive

reaction with THF

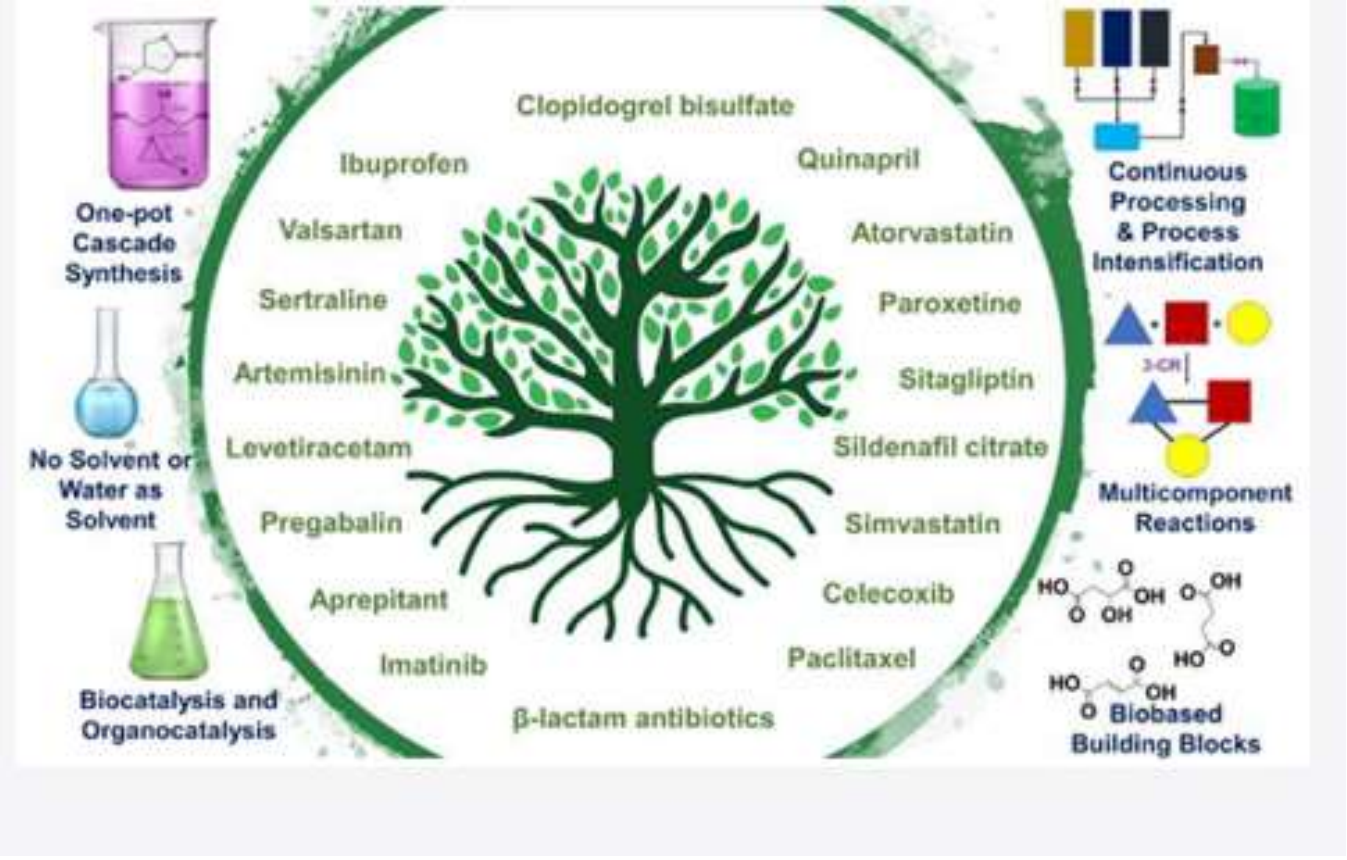
Koji Kabota et al. Nature Communications 2021, 12, 6691

Implementation



An illustration of the need to integrate various groups of people, educate, cooperate at different levels and look for agreement

Green Chem., 2023, 25, 4625


Clopidogrel bisulfate
Ibuprofen
Quinapril
Valsartan
Atorvastatin
Sertraline
Paroxetine
Artemisinin
Sitagliptin
Levetiracetam
Sildenafil citrate
Pregabalin
Simvastatin
Aprepitant
Celecoxib
Imatinib
Paclitaxel
β-lactam antibiotics
One-pot Cascade Synthesis
No Solvent or Water as Solvent
Biocatalysis and Organocatalysis
Continuous Processing & Process Intensification
Multicomponent Reactions
Biobased Building Blocks

THANK YOU