

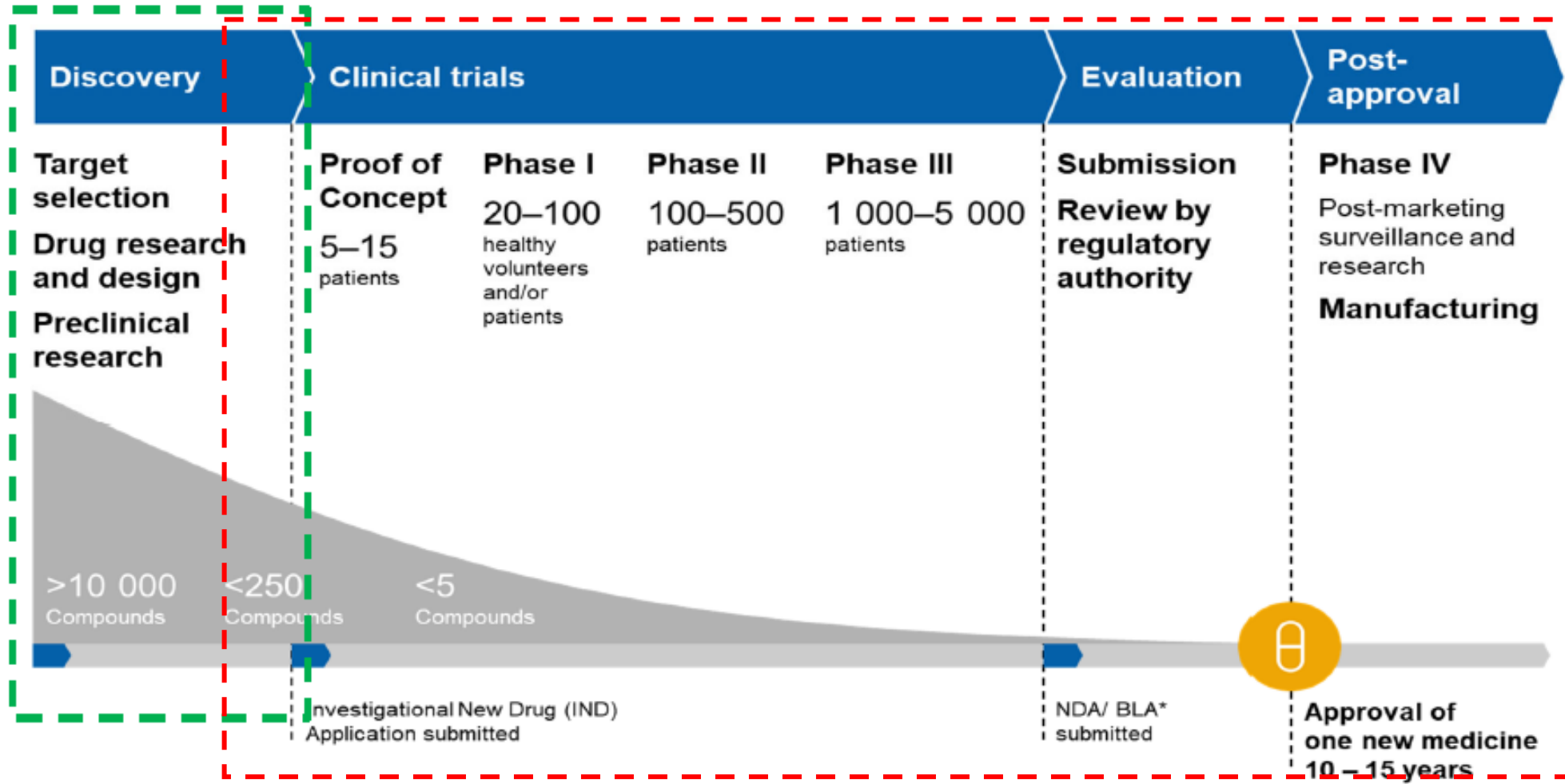
Sustainable Chemistry in Pharmaceutical Industry

Lucie Lovelle
EPFL / ETH
2025

 **NOVARTIS** | Reimagining Medicine



The Path to a New Medicine



*New Drug Application / Biologics License Application

Agenda



Introduction

What is development? What is a process chemist? What are the pharma industry main constraints?



Theory

Sustainability metrics, synthesis, process development



Case Studies

Bedaquiline (commercial drug from Jansen) & Novartis internal compounds (IDH305, LOU064)



Assignment

Presentation of synthesis routes. Comment on pros & cons of each routes, select your favorite.



Questions/Answers

I will try to take the temperature and ask few questions throughout the talk, please do the same!

Pharmaceutical industry 101



Technical Research and Development

Drug Substance = Active Pharmaceutical Ingredient (API)

- Chemical composition (main + impurity profile)
- Physical form (polymorph, particle size distribution)



Drug Product = what the patient see (API + excipients)

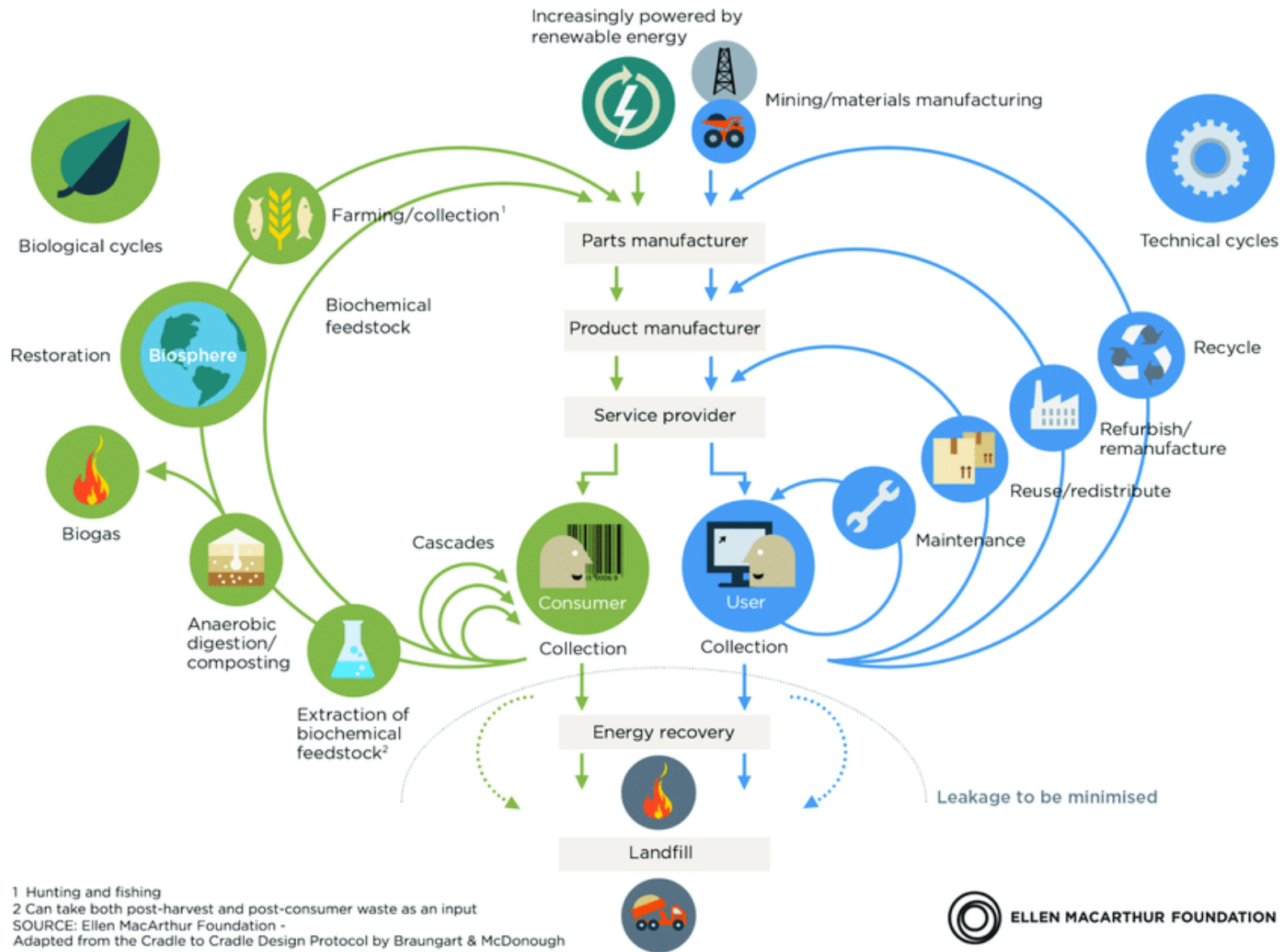
- Tablets, capsules, suspension, powder...
- Choice of excipients (fillers, lubricants, coatings...)
- Packaging (blisters, dessicants...)



Pharma vs other industries

- **Highly regulated industry:**
 - Fragile population
 - Optimized uptake of product
- **Usually higher molecular complexity**
 - Longer synthesis
 - Complex transformation
- **Relatively low volumes to produce**

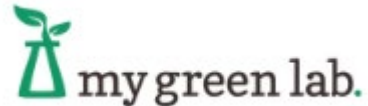




Sustainability in Pharmaceutical Development

- R&D

- Optimization of care pathways
- Waste, energy consumption...



- Manufacturing

- sustainable route of manufacturing, source of raw materials, green logistics, clean energy sources, waste treatment, recycle/recover...

- Packaging

- materials, units per package, collection, recyclability of devices and packaging...

- Clinical trial drug supply

- waste reduction, stock management, shipment optimisation,...

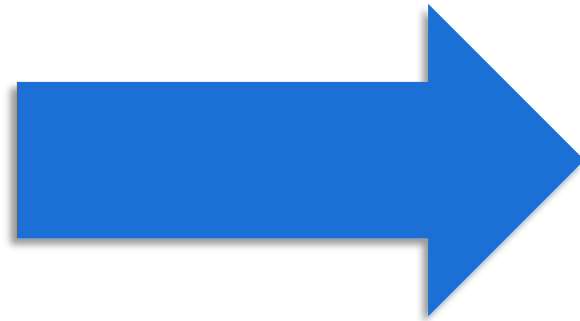


Chemical and Analytical Development

From Research to Production



*from grams
in research...*



*...to tons
in production*



Chemical and Analytical Development

From Research to Production



Design



Supply

Lab
1 – 5 L

Pilot Plant
50 – 2500 L

Production
100 – 12000 L

scale up 500-1000

scale up ~ 2-5

Drug Substance Quality Requirement

As a potential patient, what are your expectations?

As a chemistry student, what do you usually achieve?

Drug Substance Quality Requirement

ICH Q3A guidelines for impurities in new drug substance:

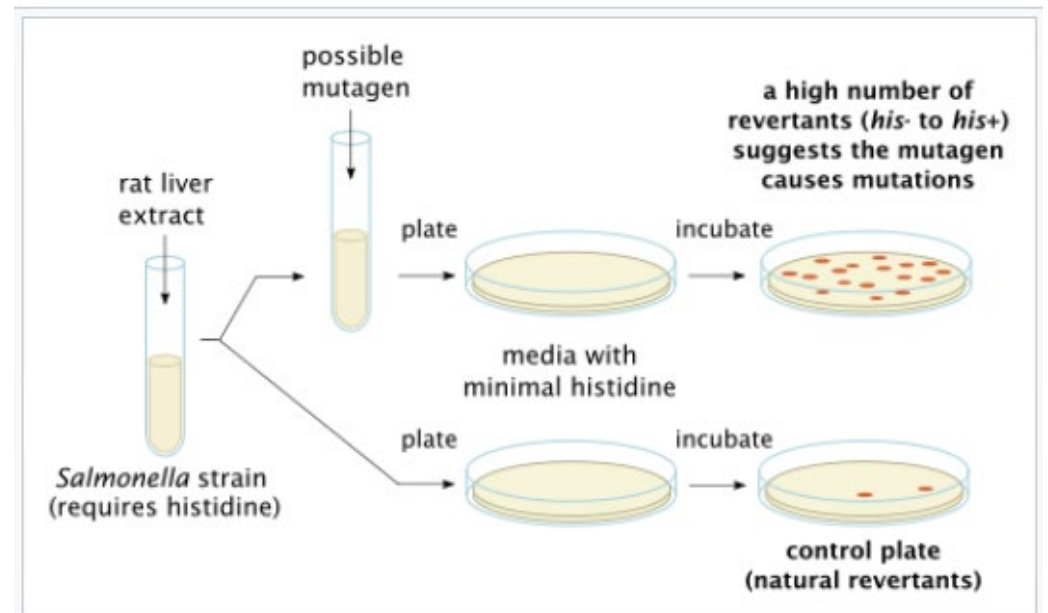
- **Reporting Threshold:** A limit above which an impurity should be reported.
- **Identification Threshold:** A limit above which an impurity should be identified.
- **Qualification Threshold:** A limit above which an impurity should be qualified.

Maximum Daily Dose ¹	Reporting Threshold ^{2,3}	Identification Threshold ³	Qualification Threshold ³
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

³ Lower thresholds can be appropriate if the impurity is unusually toxic.

Mutagenic impurities (MI)

- Mutagenicity is associated with cancer as it often stems from a DNA-mutation.
- When identified, all impurities present in drug substance are first screened in-silico for structural features favoring mutagenicity.
- All molecules giving an in-silico alert are treated as mutagenic unless they are proven non-mutagenic via a bacterial reverse mutation assay (Ames test).
- In absence of specific carcinogenicity data, mutagenic impurities must be controlled according to the conservative threshold of toxicological concern (TTC).



Mutagenic impurities (MI)

- TTC (threshold of toxicological concern): 1.5 $\mu\text{g}/\text{day}$, which correspond to a statistical risk of 10^{-5} of cancer for lifetime exposure.
- From the TTC limit, acceptable intake based on Haber's law, are defined for pharmaceutical development:

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [$\mu\text{g}/\text{day}$]	120	20	10	1.5

- Limit concentration of an MI in paracetamol (MDD = 4 g): 0.375 ppm (0.000038%)



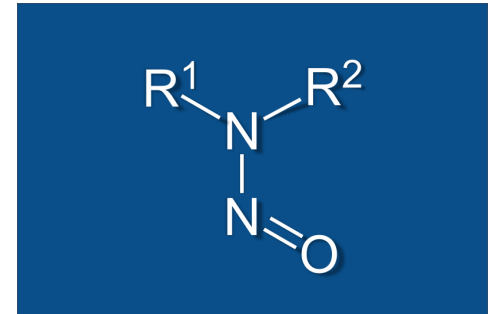
Nitrosamines – a other level of complexity

Nitrosamine are suspected highly carcinogenic compounds.

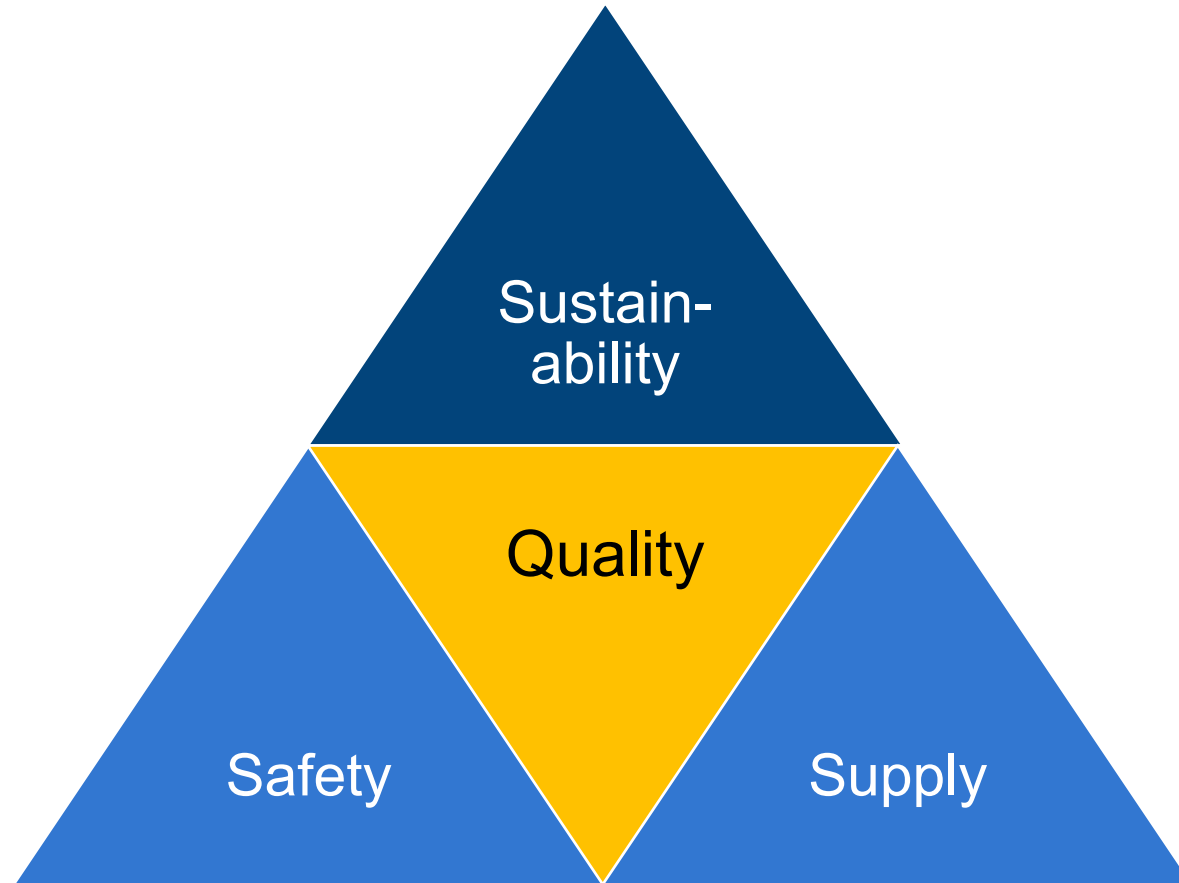
They can easily be formed from secondary amines and a nitrosating species.

Known nitrosating species are present in the air (NO_x), water and a significant number of inorganic bases and salt, excipients...

Nitrosamines needs to be controlled on even lower level.



Sustainability vs other priorities



Where can we act?

Synthesis route design:

- Convergence
- Starting materials from biorenewable feedstock
- Benign by design

Process:

- Choice of reagents
- Choice of solvents
- Reaction conditions
- Optimisation

Waste:

- 3 Rs principle



Synthesis Route



General concept in development

Two stage concept

Fast lock of the practical synthesis:

- Suboptimal for commercial needs
- Allow for a fast clinical trial supply with adequate quality
- Low risk synthesis that will ensure steady supply
- Ensure all quality aspects

Final synthesis for pivotal trials:

- Use clinical development time to identify and develop an optimal synthesis
- Maximizes R&D time while having enough clinical supplies left to improve, optimize and understand the final process



What is a good synthesis route?

Aspects to be considered for the ideal synthesis

Safety

Number of steps

Yield

Ease of scale-up

Robustness

**Ecologically
benign**

**Availability / origin
of raw materials**

**Complexity of
synthesis**

**Environmentally
acceptable**

Which synthetic route is the best one?

Comparison of synthetic routes

How do we assess how «good» a synthesis is?

How do we compare two synthetic routes?

Which synthetic route is the best one?

Comparison of synthetic routes

Examples for route assessment tools:

Kepner-Tregoe decision analysis (Astra-Zeneca)

J. S. Parker, J. D. Moseley, *Org. Proc. Res. Dev.* **2008**, *12*, 1041-1043; J. D. Moseley, D. Brown, C. R. Firkin, S. L. Jenkin, B. Patel, E. W. Snape, *Org. Proc. Res. Dev.* **2008**, *12*, 1044-1059; J. S. Parker, J. F. Bower, P. M. Murray, B. Patel, P. Talavera, *Org. Proc. Res. Dev.* **2008**, *12*, 1060-1077.

→ *Define «Musts» (e.g. safety) and «Wants» (e.g. high yield), weigh the «Wants» (score 1-10), evaluate synthetic routes regarding «Wants» (score 0-10)*

Holistic route selection (Dow)

R. B. Leng, M. V. M. Emonds, C. T. Hamilton, J. W. Ringer, *Org. Proc. Res. Dev.* **2012**, *16*, 415-424.

→ *List route selection criteria (RSC), define metrics for each RSC, weigh RSC, rate each route on a 1-3-9 scale*

Which synthetic route is the best one?

Comparison of synthetic routes

Route ideality

T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, 75, 4657-4673.

→ *Evaluation of «ideality» of synthesis (in %) by comparing the number of construction and strategic redox steps with the total number of steps*

Current complexity (Bristol-Myers Squibb)

J. Li, M.D. Eastgate, *Org. Biomol. Chem.* **2015**, 13, 7164-7176.

→ *Assessment of synthetic complexity, taking into account intrinsic challenges (structure) and current synthetic methodology*

Process complexity (Boehringer Ingelheim)

F. Roschangar, R. A. Sheldon, C. H. Senanayakea, *Green Chem.* **2015**, 17, 752-768.

→ *Number of construction reactions and strategic redox steps*

Which synthetic route is the best one?

Comparison of synthetic routes

SELECT (Astra Zeneca)

M. Butters, D Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J.-P. Sherlock, W. White, *Chem. Rev.* **2006**, *106*, 3002-3027.

→ Six criteria: Safety, Environmental, Legal, Economics, Control, Throughput

Criteria	
Safety	<ul style="list-style-type: none">• Process Safety• Exposure to substances harmful to health
Environmental	<ul style="list-style-type: none">• Volume of wasted natural resources• Substances harmful to the environment
Legal	<ul style="list-style-type: none">• Infringement of intellectual property rights• Regulations that control use of reagents and intermediates
Economics	<ul style="list-style-type: none">• Meeting cost of goods target for future market• Investment costs to support development quantities
Control	<ul style="list-style-type: none">• Control of quality parameters• Control of chemistry and physical parameters
Throughput	<ul style="list-style-type: none">• Time scale of manufacture in available plant• Availability of raw materials

The Novartis Labelling Process

PMI

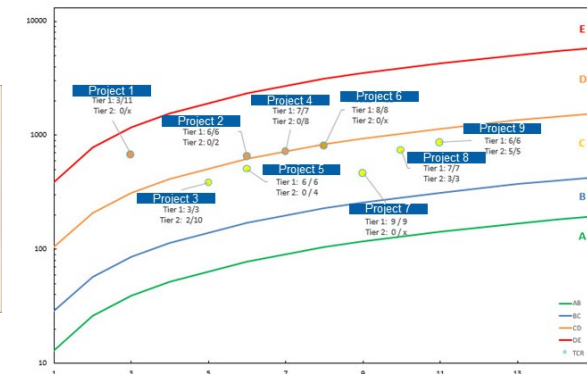
- Process Mass Intensity (all materials used for synthesis, isolation, purification)
- $PMI = \frac{\text{Quantity of raw materials input (kg)}}{\text{Quantity of bulk API out (kg)}}$

TCR

- Total Carbon Dioxide Release (CO₂ release by waste incineration per kg API)
- $TCR = PMI_{\text{organic}} \times 2.3 \text{ kg CO}_2 + PMI_{\text{aqueous}} \times 0.63 \text{ kg CO}_2$

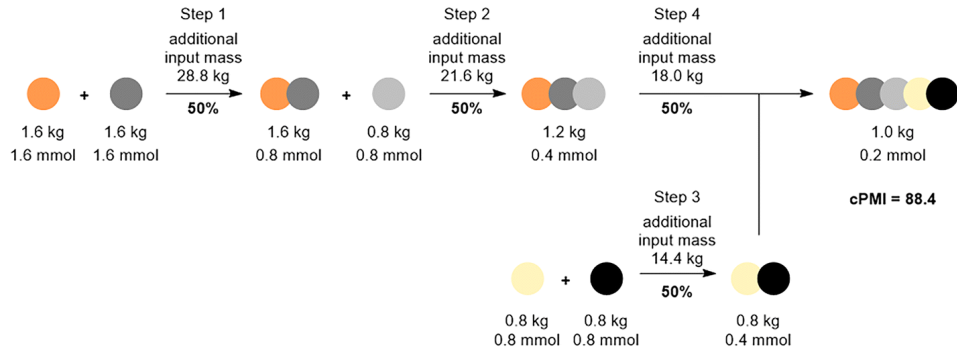
Steps

- Number of chemical transformations required to reach the respective molecule

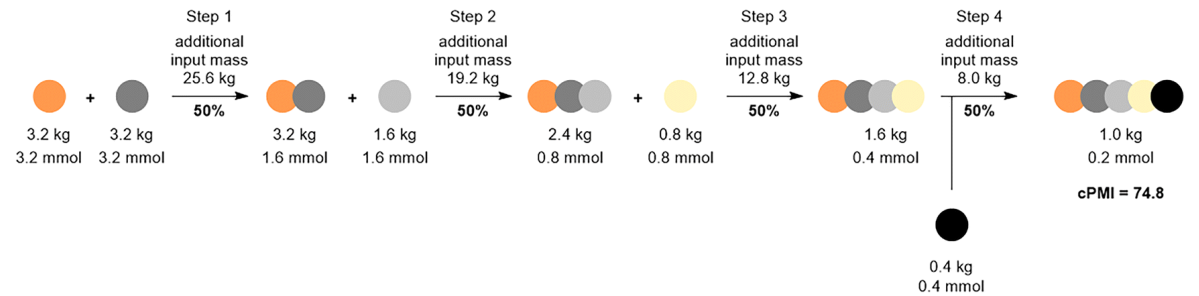


Convergence as a quick assessment tool

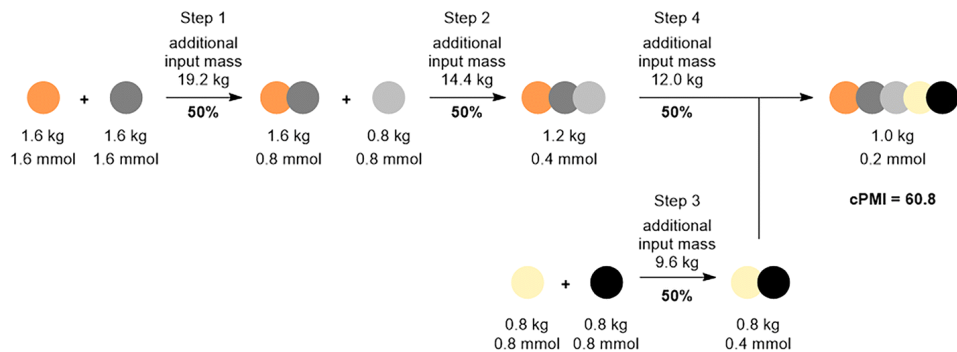
a-1) Conv. = 0.42, step PMI's = 20



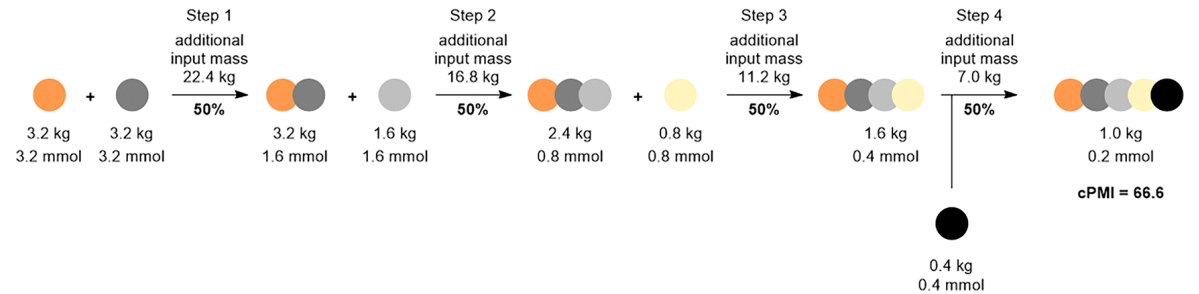
b-1) Conv. = 0.36, step PMI's = 10



a-2) Conv. = 0.42, step PMI's = 14, 30% reduction



b-2) Conv. = 0.36, step PMI's = 9, 10% reduction



Aspects to be considered for the ideal synthesis

Safety

Number of steps

Yield

Ease of scale-up

Robustness

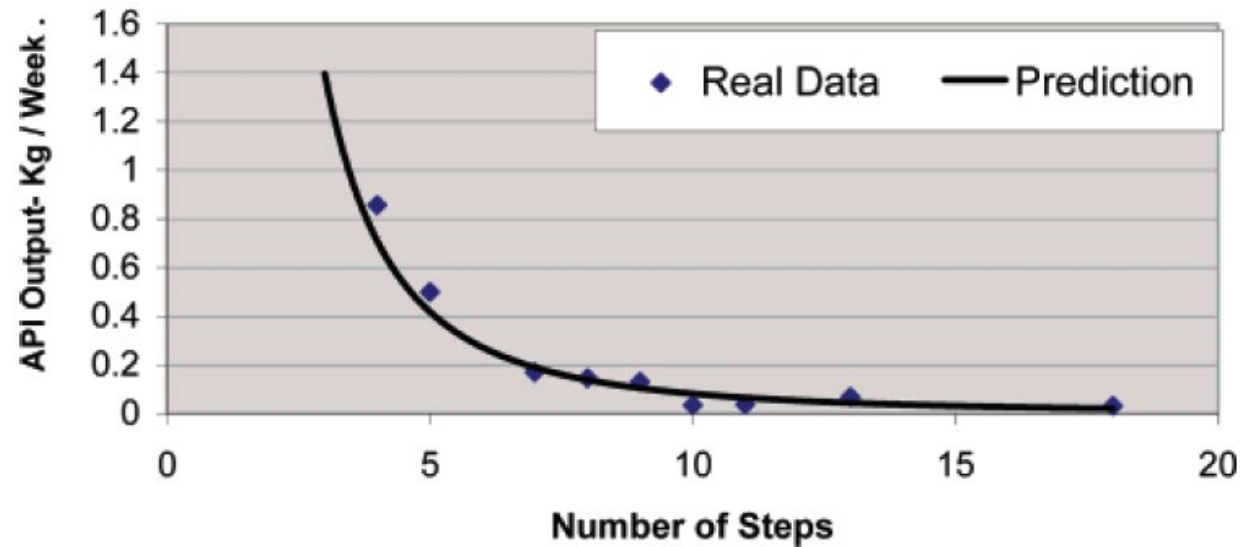
**Ecologically
benign**

**Availability / origin
of raw materials**

**Complexity of
synthesis**

**Environmentally
acceptable**

Effect of sequence length on throughput



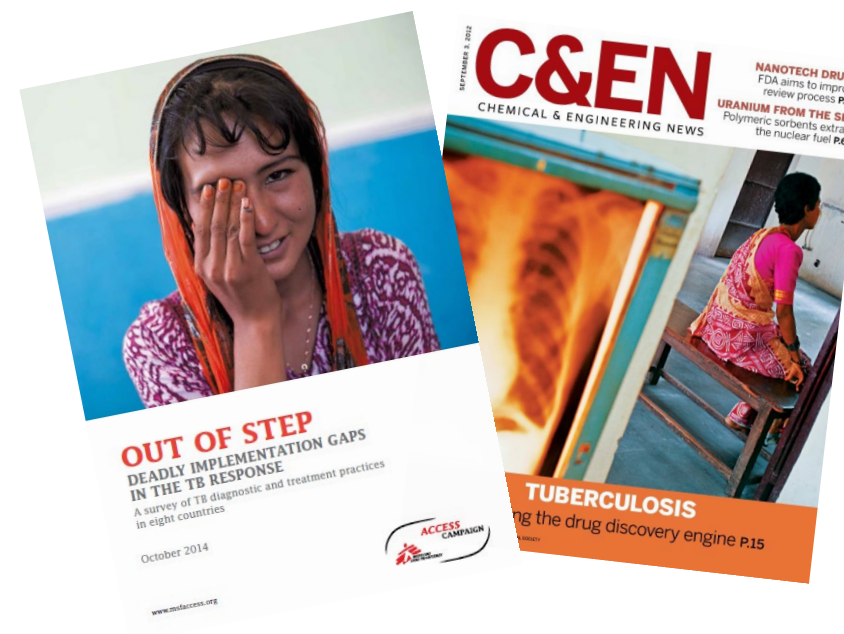
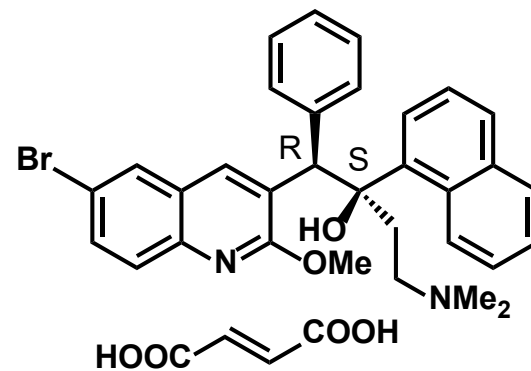
Why?

1. Mathematical effect
2. «Campaign» set-up

Yield?

Case study: Bedaquiline

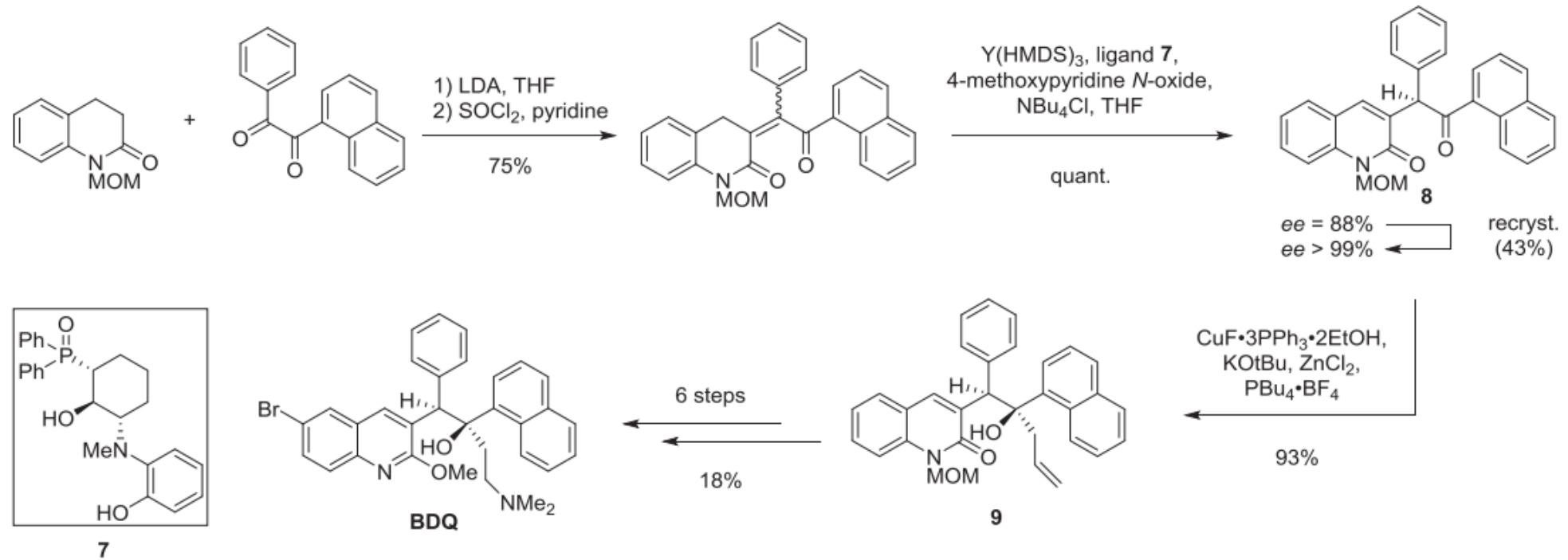
- Janssen drug approved for MDR-TB (2012/2014)
- Lethal infectious disease caused by Mycobacteria
Mainly affects the lungs but not only (pleura, CNS, lymphatic or genitourinary system, bones and joints)
- Tuberculosis (TB) status in 2013*:
 - 9 million new cases of TB
 - 1.5 million people died from TB
 - 480 000 new cases of MDR-TB (more & more as first diagnosis)**
 - 9% estimated XDR-TB



* WHO: *Global tuberculosis report 2014*

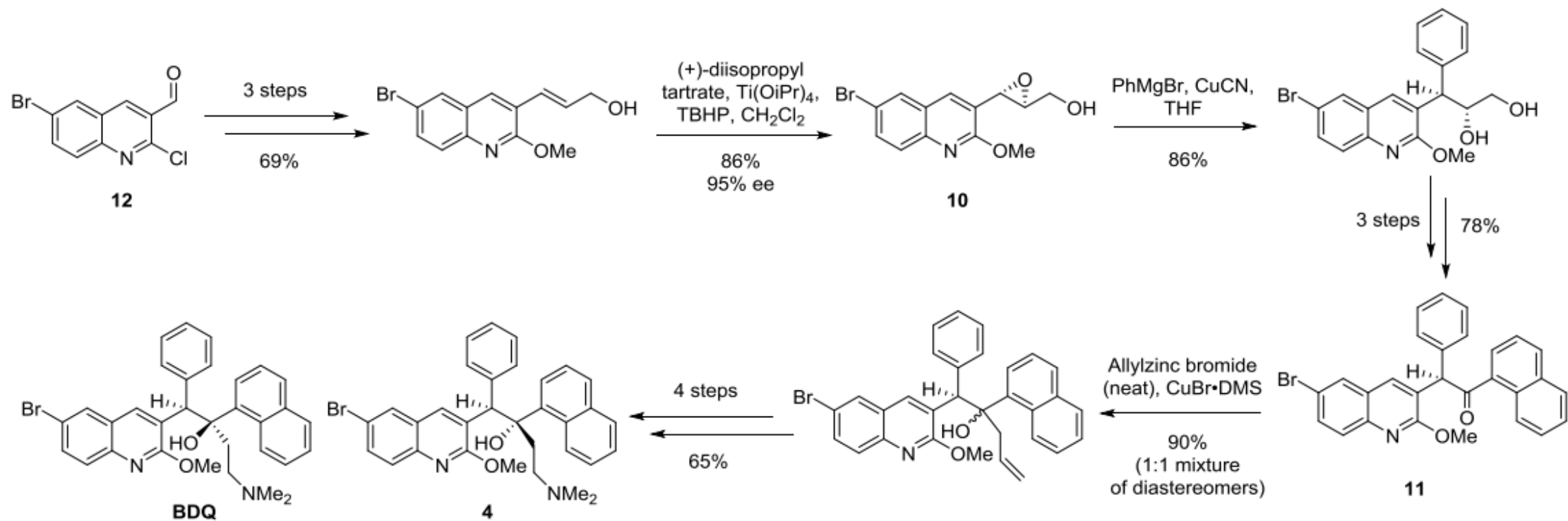
** MSF «*Out of step*» report, Oct 2014

First enantioselective synthesis



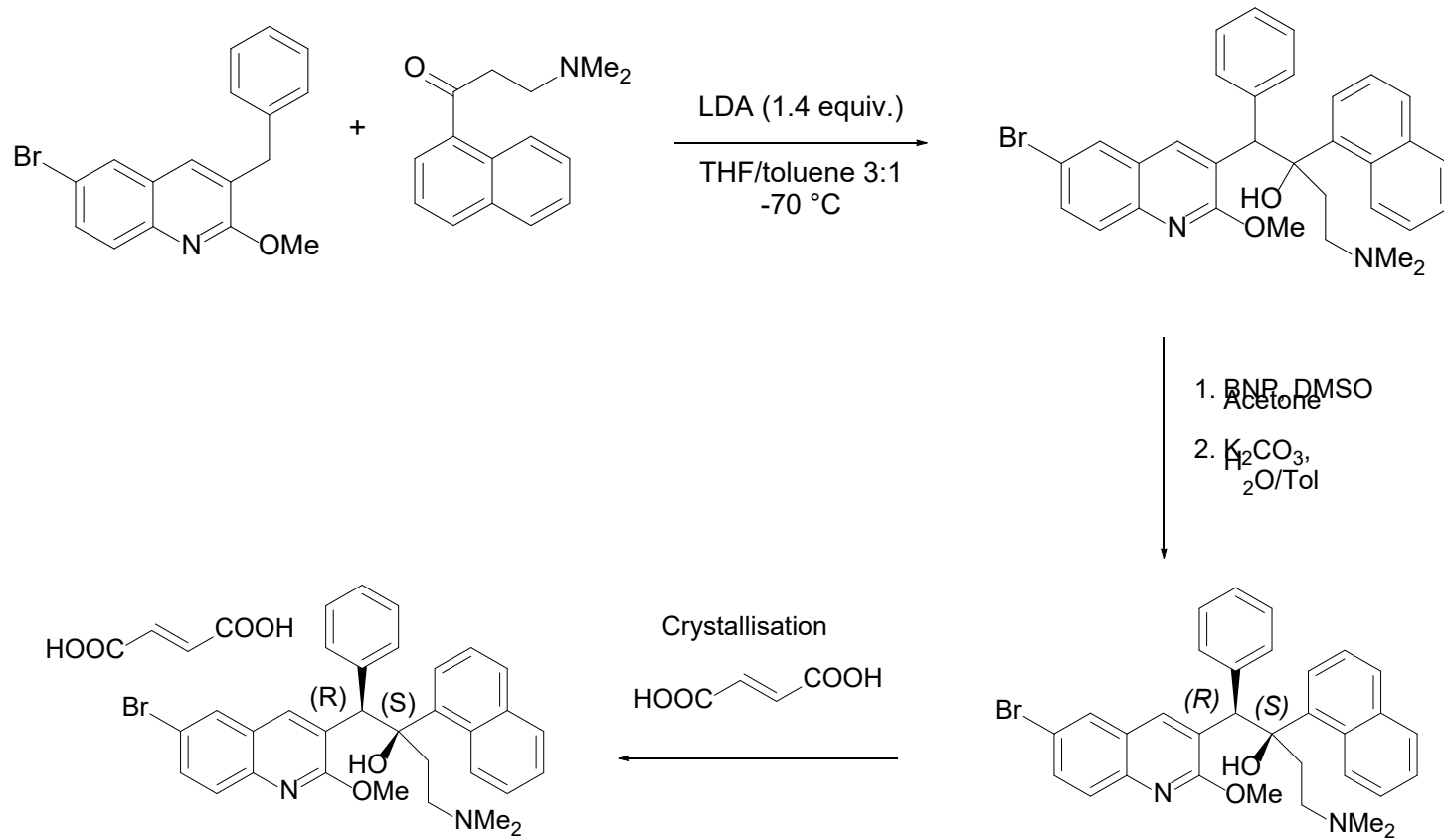
Scheme 3. Shibasaki's enantioselective synthesis of BDQ.

Academic Synthesis

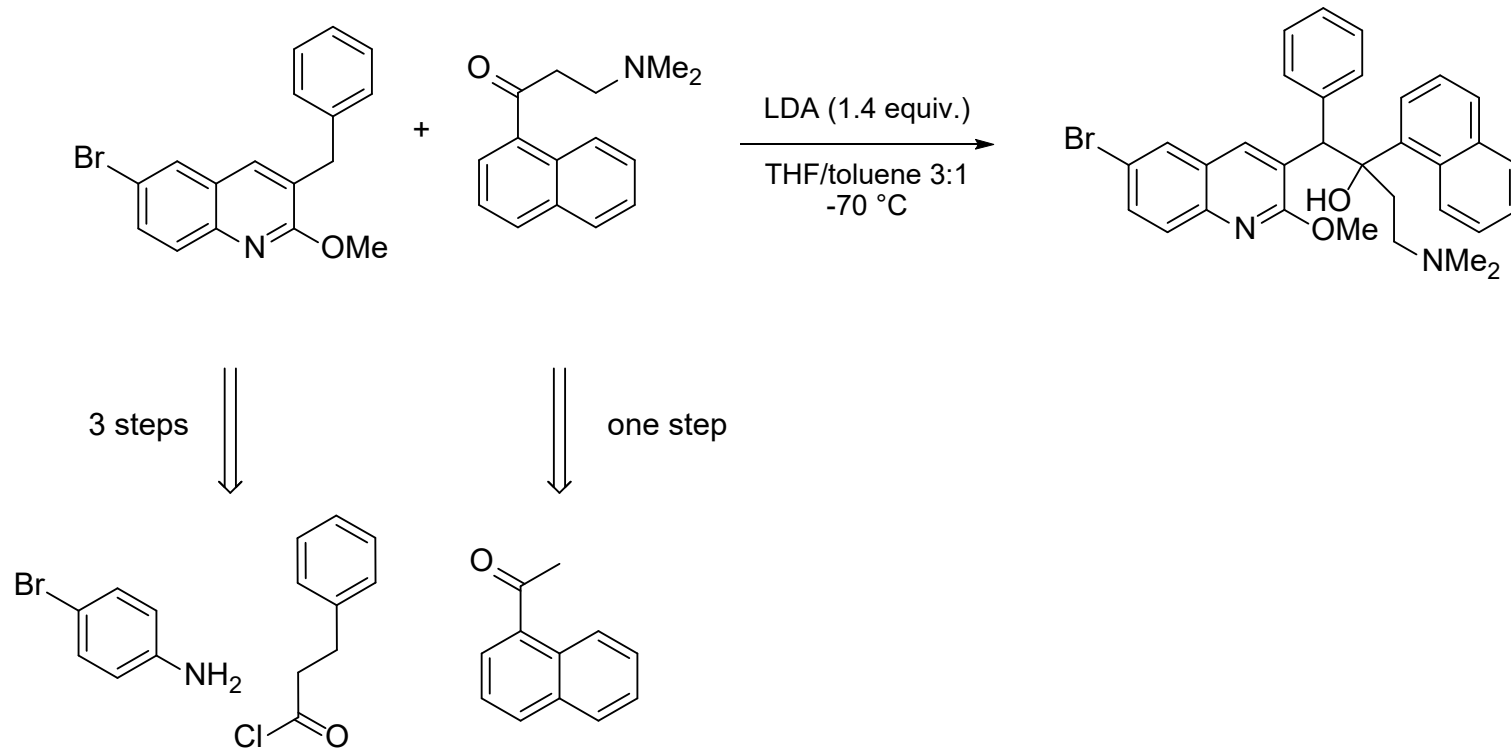


Scheme 4. Chandrasekhar's asymmetric synthesis of BDQ.

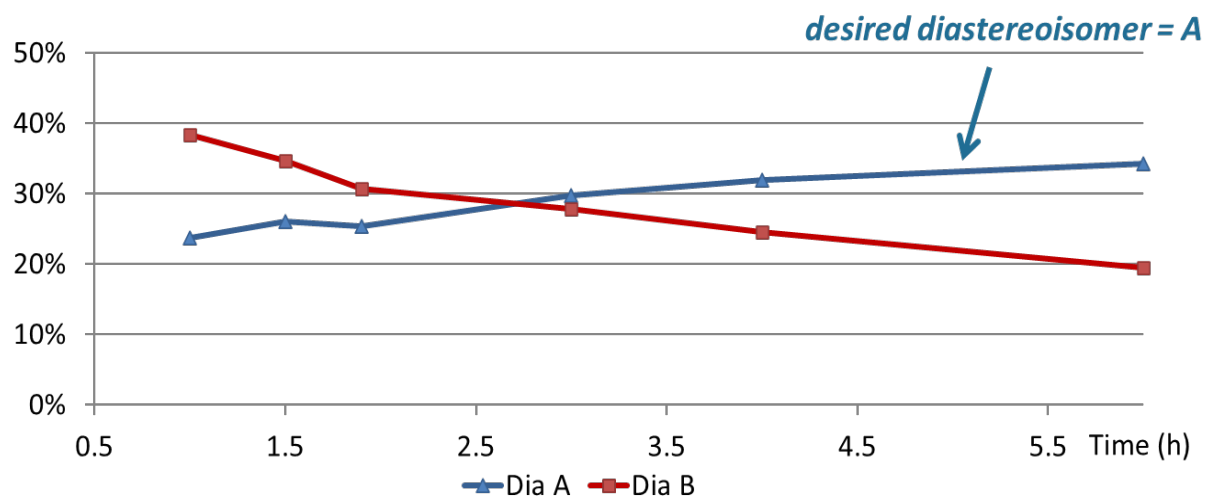
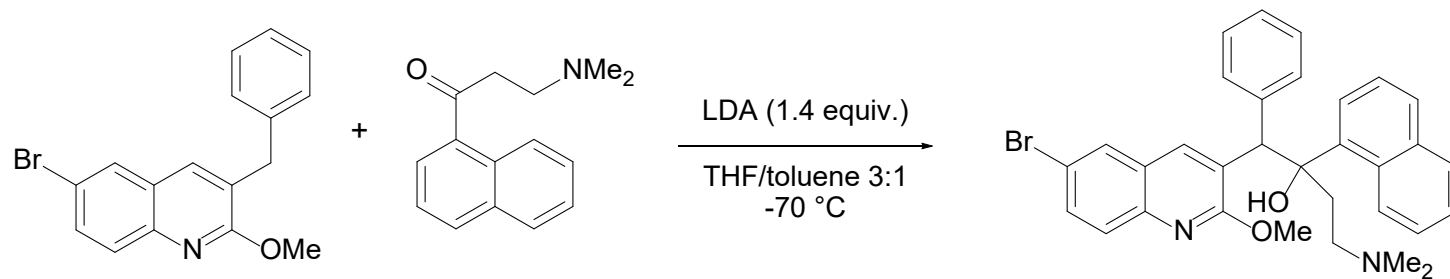
Industrial synthesis



Industrial synthesis



Industrial synthesis



Further optimisation



Table 1. Summary of Modifications Done with the Chiral Ligand 4a-b

entry	base	dr	% conversion ^a
1	LDA	50:50	31
2	<i>n</i> -BuLi/ 4a	50:50	33
3	<i>n</i> -BuLi/ 4a ·LiCl ^b	45:55	31
4	<i>n</i> -BuLi/ 4a ·LiCl ^c	30:70	32
5	<i>n</i> -BuLi/ 4b ·LiCl	90:10	33

^a% Conversion was determined by liquid chromatography–mass spectrometry using a YMC-Triart-C18 column unless stated otherwise, and the dr was determined by crude ¹H NMR. The deprotonation step was conducted at –20 °C for 60 min; thereafter, the reaction proceeded at –78 °C. All optimization reactions were carried out on a 0.15 mmol scale unless stated otherwise.

^bAddition of LiCl to neutral **4a**.

^cAddition of *n*-BuLi to **4a**·HCl salt.

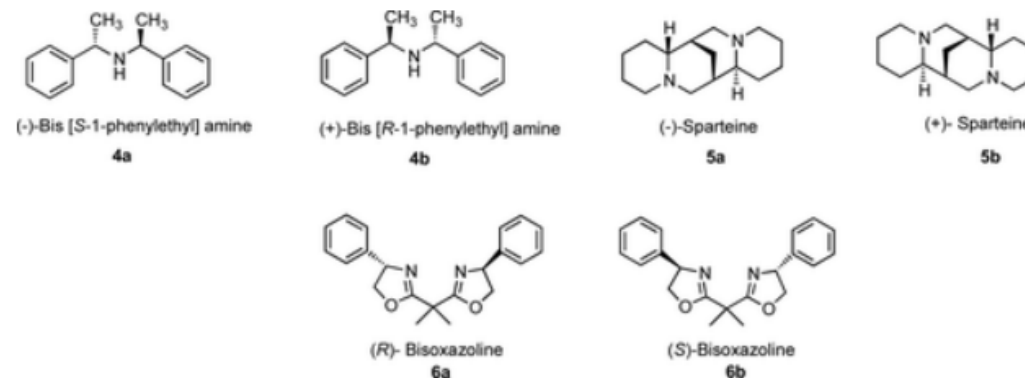


Figure 2. Chiral bases utilized in the lithiation step.

Further optimisation

Chemistry—A European Journal

Research Article
doi.org/10.1002/chem.202201311

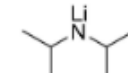
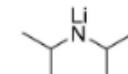
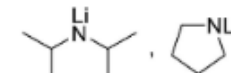
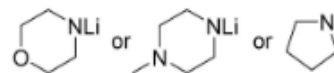
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Diastereoselectivity is in the Details: Minor Changes Yield Major Improvements to the Synthesis of Bedaquiline**

Sarah Jane Mear^{+, [a]} Tobias Lucas^{+, [b]} Grace P. Ahlqvist^{+, [a]} Juliana M. S. Robey,^[c]
Jule-Philipp Dietz,^[b] Pankaj V. Khairnar,^[c] Sanjay Maity,^[c] Corshai L. Williams,^[a]
David R. Snead,^[c] Ryan C. Nelson,^{*, [c]} Till Opatz,^{*, [b]} and Timothy F. Jamison^{*, [a]}

Table 1. Selected examples of synthesis of **1** reported in process patent applications and improvements described herein.

Source	Base	Additive	Yield 1a [%] ^[a]
Janssen 2006 ^[6]		None	32%
SIPI 2017 ^[7]		None	34%
Mylan 2020 ^[8]		None	23%, 14%
This work		LiBr	56–61%

Yield: yield of isolated product [a] Adjusted for purity where reported.

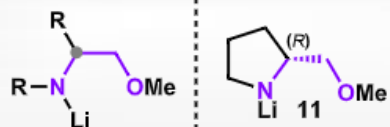
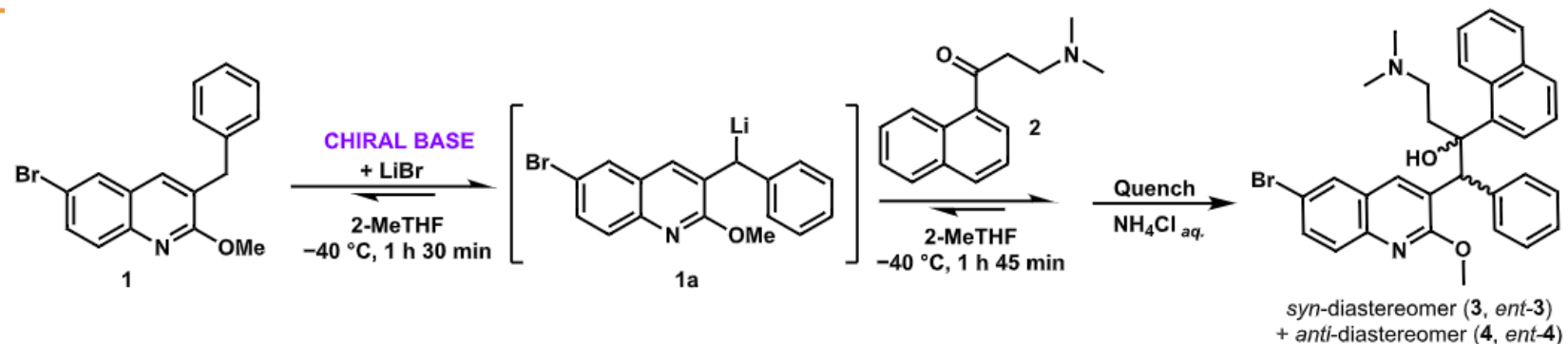
Further optimisation

Application of Chiral Transfer Reagents to Improve Stereoselectivity and Yields in the Synthesis of the Antituberculosis Drug Bedaquiline

Juliana M. S. Robey,* Sanjay Maity, Sarah L. Aleshire, Angshuman Ghosh, Ajay K. Yadaw, Subho Roy, Sarah Jane Mear, Timothy F. Jamison, Gopal Sirasani, Chris H. Senanayake, Rodger W. Stringham, B. Frank Gupton, Kai O. Donsbach, Ryan C. Nelson,* and Charles S. Shanahan*

Cite This: <https://doi.org/10.1021/acs.oprd.3c00287>

Scheme 9. Use of Chiral Lithium Amide of 11 to Promote Enhanced Stereoselectivity toward BDQ (3)



CHIRAL BASE

Additive	d.r. (<i>syn:anti</i>)	ee	BDQ (3) Assay Yield	Scale of quinoline 1
LiBr	13.1:1	51%	64%	25 g
LiBr	13.6:1	56%	64%	75 g

Further optimisation

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Juliana M. S. Robey,* Sanjay Maity, Sarah L. Aleshire, Angshuman Ghosh, Ajay K. Yadaw, Subho Roy, Sarah Jane Mear, Timothy F. Jamison, Gopal Sirasani, Chris H. Senanayake, Rodger W. Stringham, B. Frank Gupton, Kai O. Donsbach, Ryan C. Nelson,* and Charles S. Shanahan*



Cite This: <https://doi.org/10.1021/acs.oprd.3c00287>



Read Online

In general, all results indicate that the diastereoselectivity is the most sensitive parameter during BDQ (3) synthesis. There is a certain level of complexity associated with the formation of lithium aggregates in solution that makes their precise control very challenging, especially at small scales. Considering the sensitivity of this chemistry, it becomes more evident why a simplified procedure that does not make use of many reagents or additives to promote the desired stereoselectivity is ideal for BDQ (3) synthesis. A higher number of reagents and additives introduces additional stoichiometric sensitivities and the potential introduction of perturbing impurities. In this context, the M4ALL's chiral transfer approach for the BA reaction resembles our previous nonchiral approach since the only methodology modification was the replacement of pyrrolidine with the chiral amine 11.

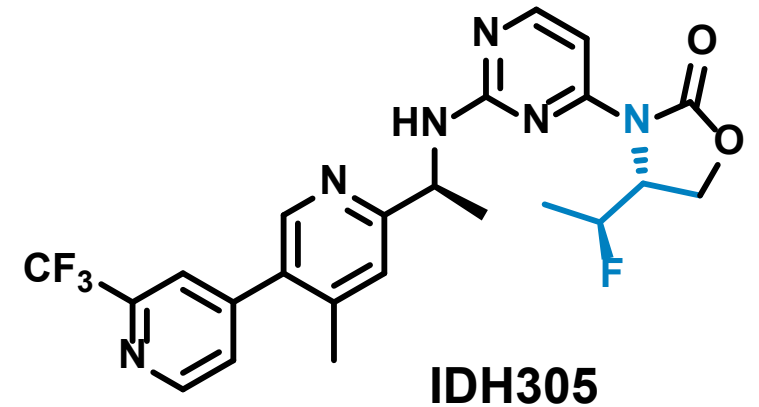


Case study IDH305:

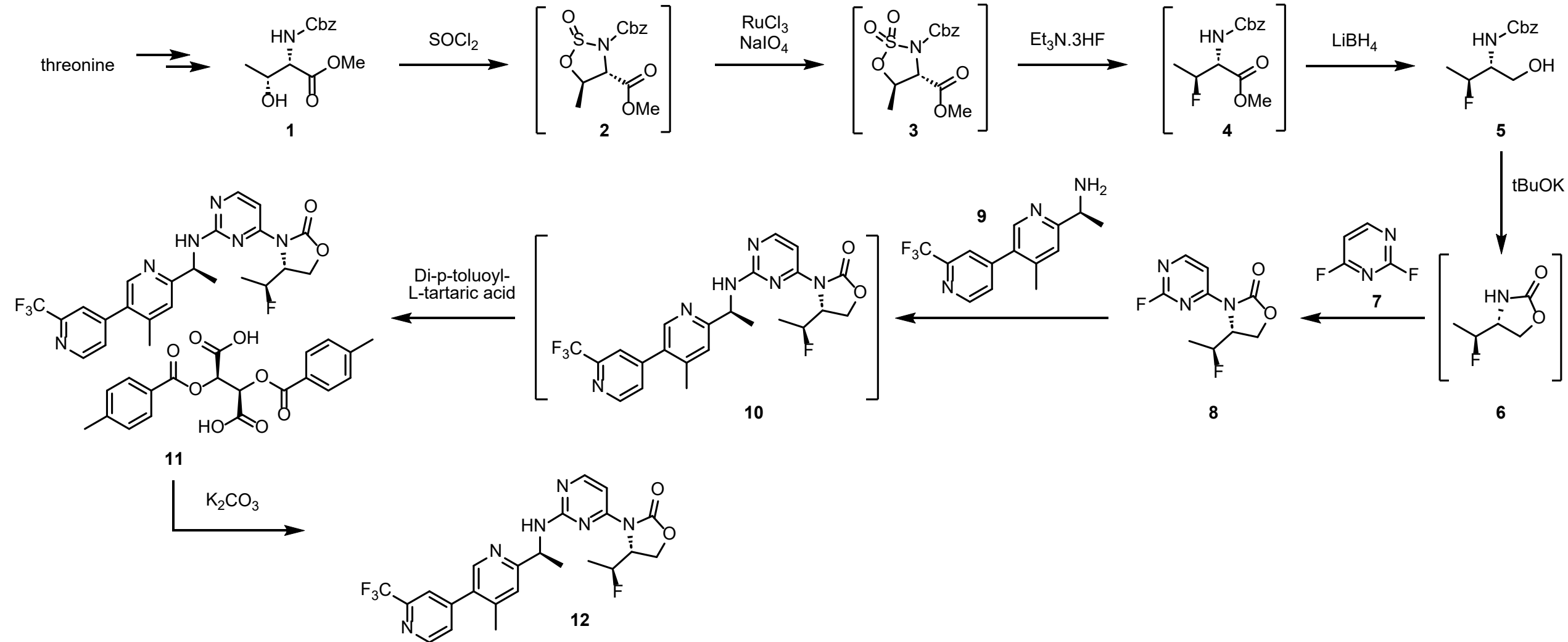
Project background

- *Therapeutic Area:* Oncology
- *Mode of action:* Inhibitor of mutant isocitrate dehydrogenase 1 (IDH1)
- *Special biological features:* potential brain penetration
- *Main potential indications:* Acute myeloid leukemia, Glioma & Glioblastoma
- *Special chemical features:* β -fluorooxazolidinone

Shin Cho *et al.* *ACS Med. Chem. Let.* **2017**, *8*, 1116-1121.

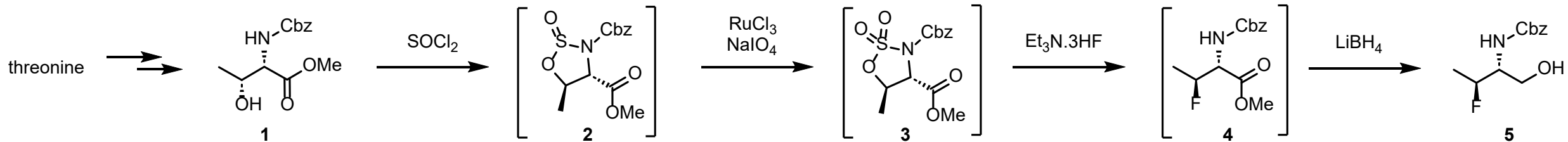


Synthesis for initial scale-up



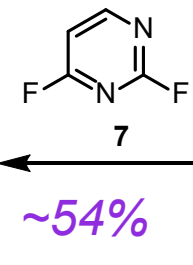
Synthesis for initial scale-up

1 to 5: ~50%



~84%

tBuOK



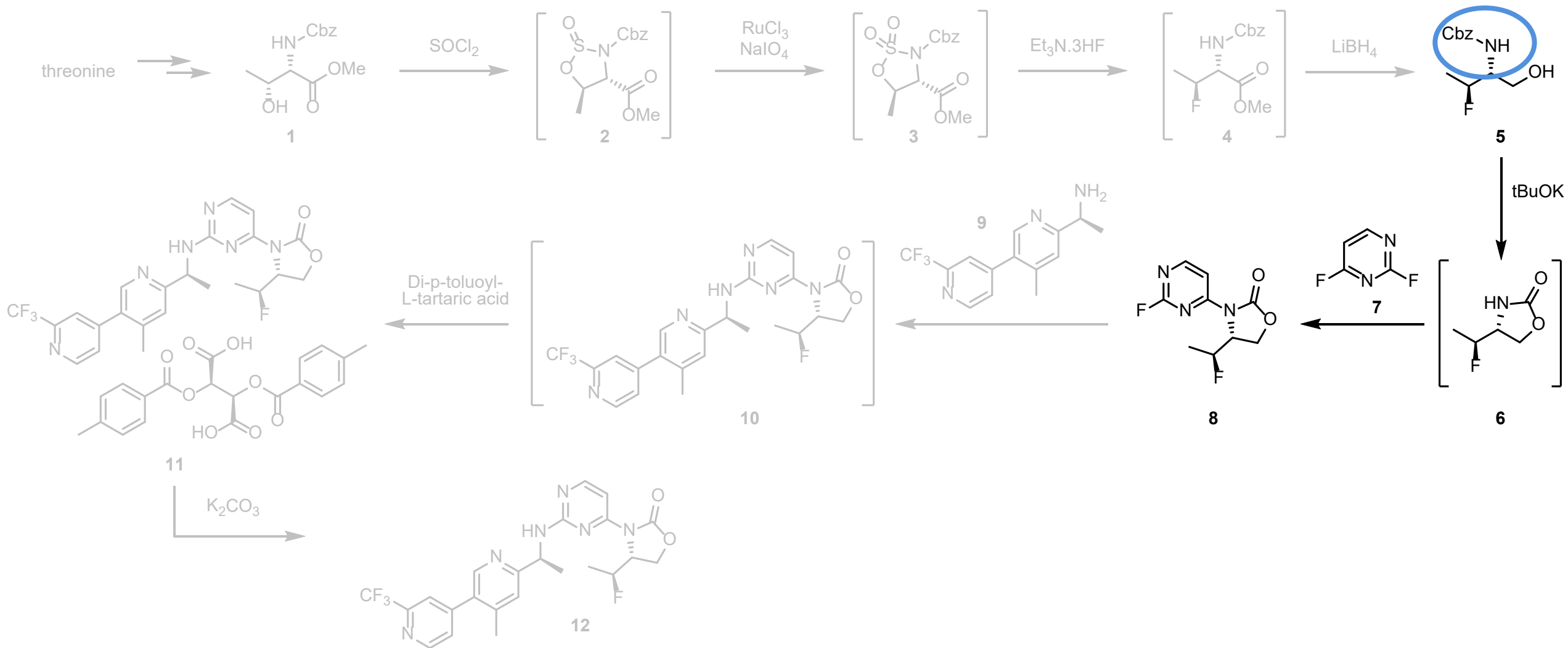
~86%

~54%

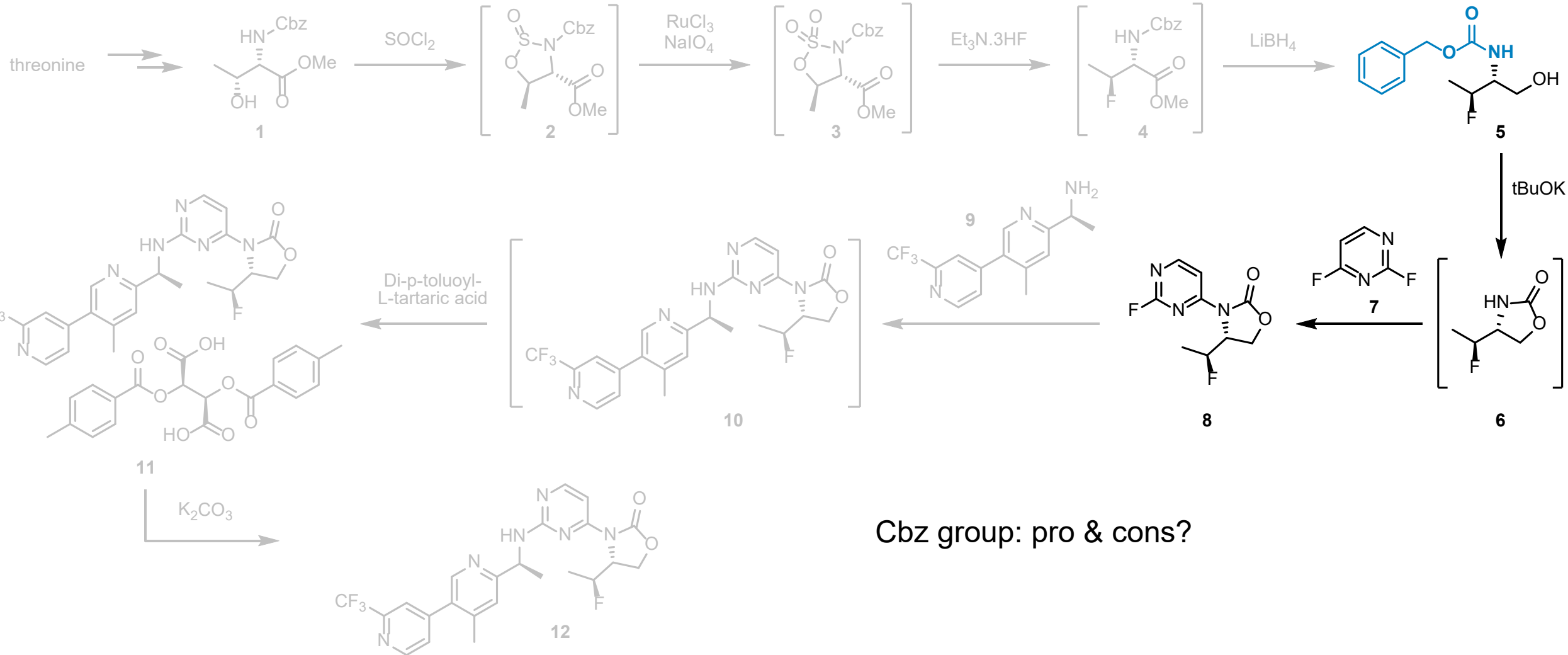
~93%

Overall ~14%

Main chain: $SN_{Ar}1$

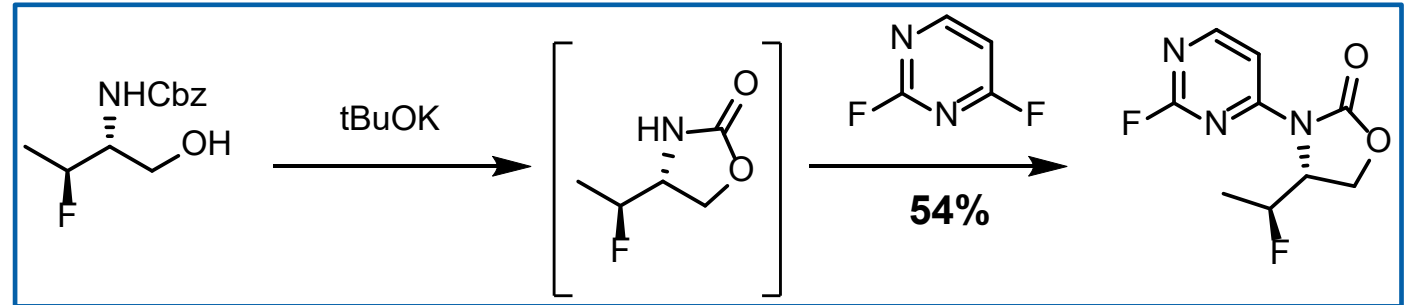


Main chain: $S_N_{Ar}1$



Cbz group: pro & cons?

Opportunities



Difluoropyrimidine:

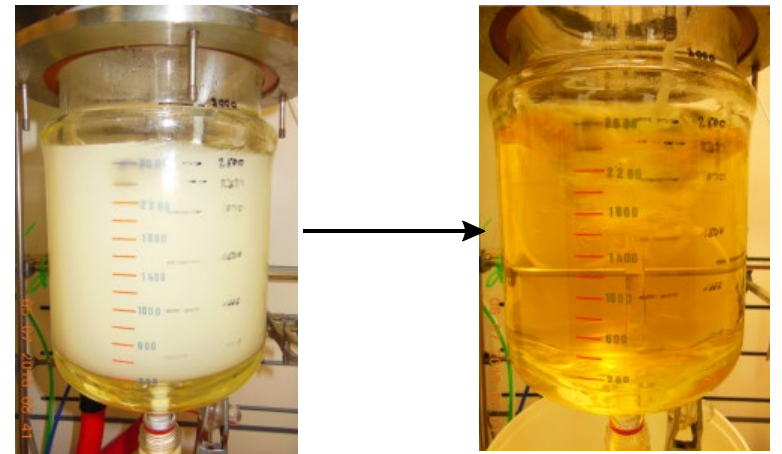
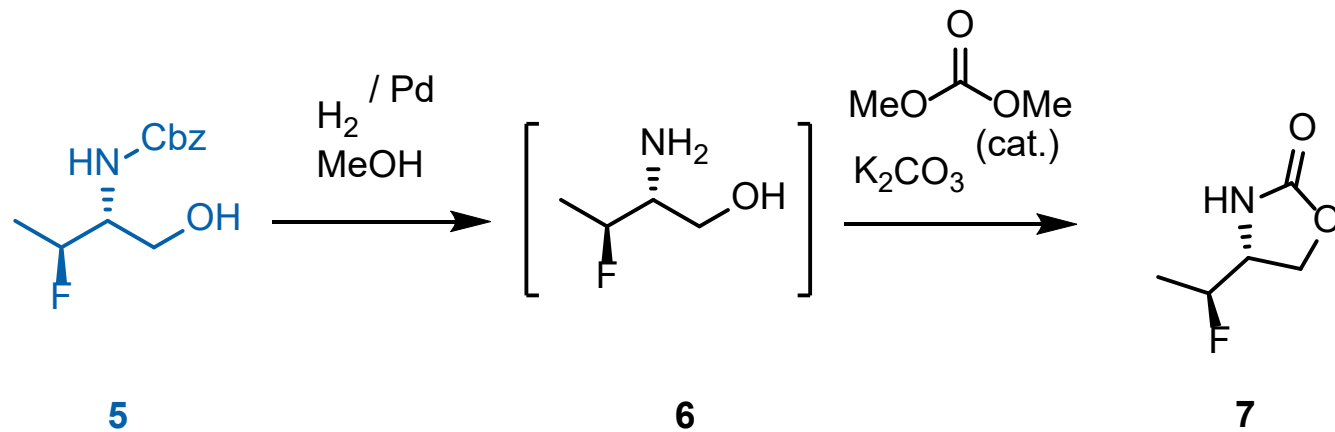
- Very sensitive to hydrolysis and residual BnOH
- Limited availability on scale
- High price

Fluorinated waste

Process unfriendly reaction conditions:

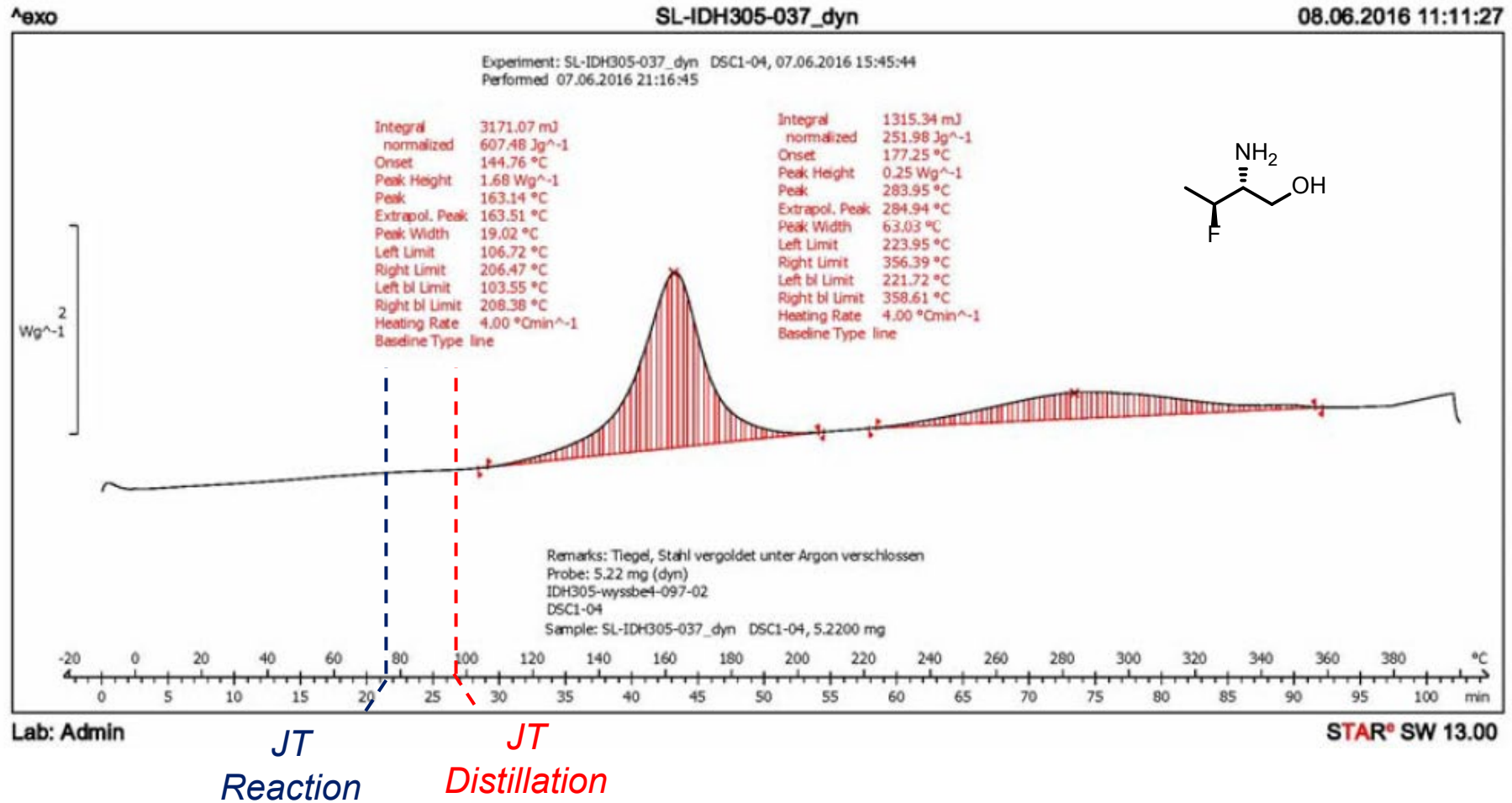
- NaH, Crown ether
- N-Methylpyrrolidinone

Access to a cleaner oxazolidinone

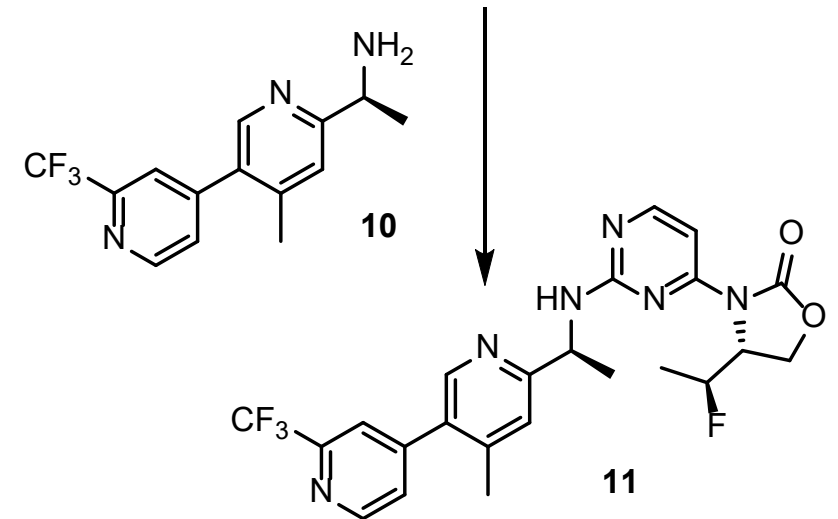
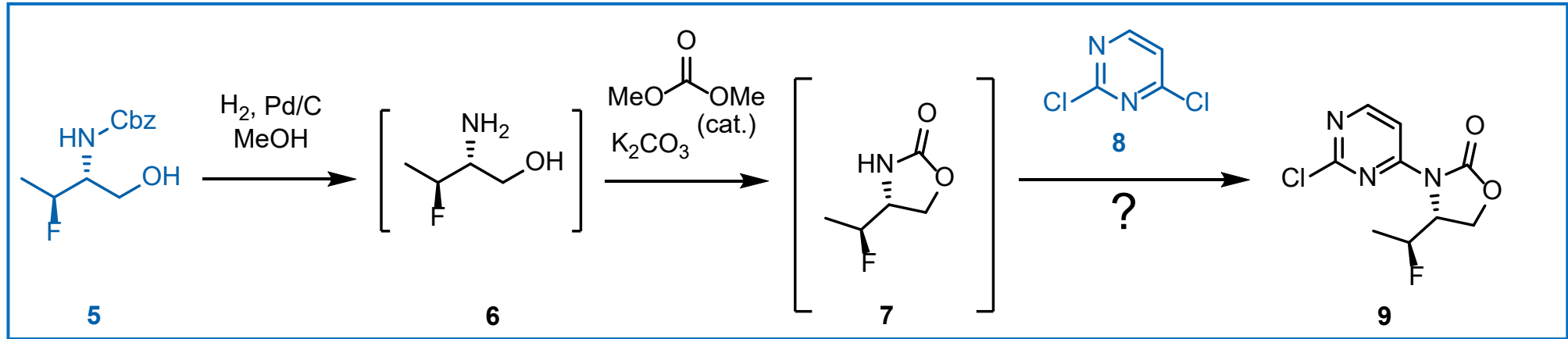


Side products?

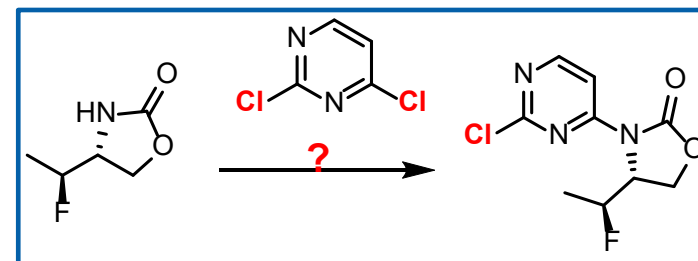
Thermal stability



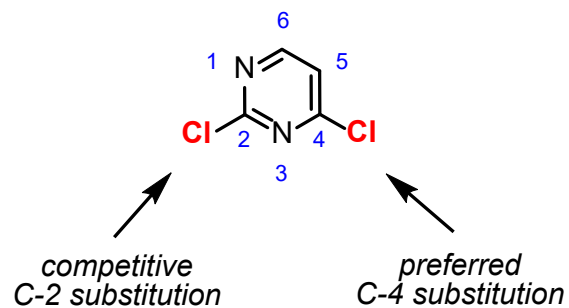
Main chain: $S_N_{Ar}1$



Main chain: S_NAr1



2,4-dichloropyrimidine (DCP)



S_NAr using weak nucleophiles:

- low reactivity
- uses protic polar solvents and strong bases

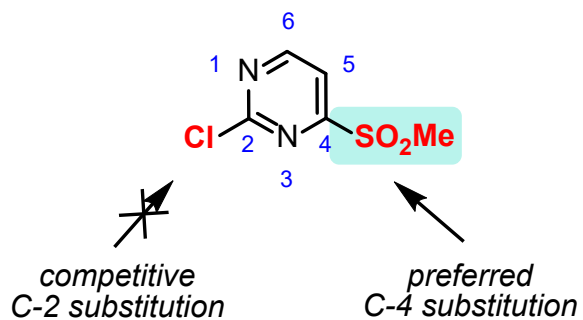
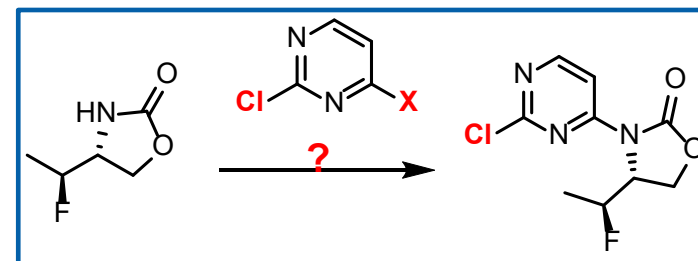
• regioselectivity issue between C-4 and C-2 amination

Entry	Solvent	Base (equiv)	Temp (°C)	DCP	C-4	C-2
1	THF	NaH (1.1)	60	26	15	14
2	Me-THF	K_2CO_3 (3)	80	49	24	15
3	Toluene	K_2CO_3 (3)	110	31	28	8
4	MeCN	K_2CO_3 (3)	60	16	63	13
5	Sulfolane	K_2CO_3 (3)	110	7	72	7
6	N-Butylpyrrolidone	K_2CO_3 (2)	80	1	75	5

→ Isolated yield: 68% with ca. 6% in ML

Bruening, F. *et al. Eur. J. Org. Chem.* **2017**, 3222-3228.

Main chain: S_NAr 1

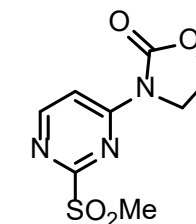


S_NAr using weak nucleophiles:

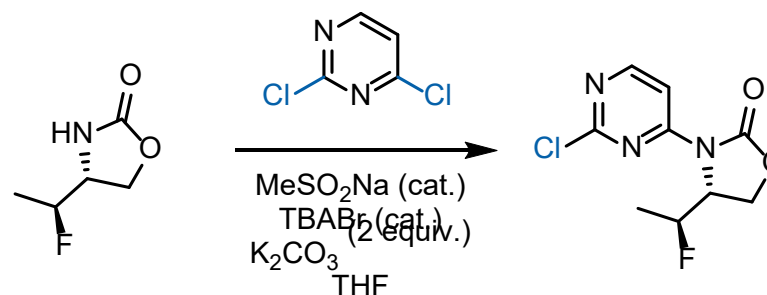
- high reactivity
- excellent selectivity at C-4
- mild conditions
- unstable

Entry	SM	Additive (equiv)	yield	C-4 / C-2
1	Cl,SO ₂ Me	-	89	>99:1
2 ^a	DCP	MeSO ₂ Na (1)	imp + degradation	
3 ^a	DCP	MeSO ₂ Na (0.03)	22	1.3:1
4 ^a	DCP	MeSO ₂ Na (0.03) + TBABr (0.1)	91	42:1
5 ^a	DCP	TBABr (0.1)	72	8:1

^aReaction run in THF at 50 °C using unsubstituted oxazolidinone as model substrate



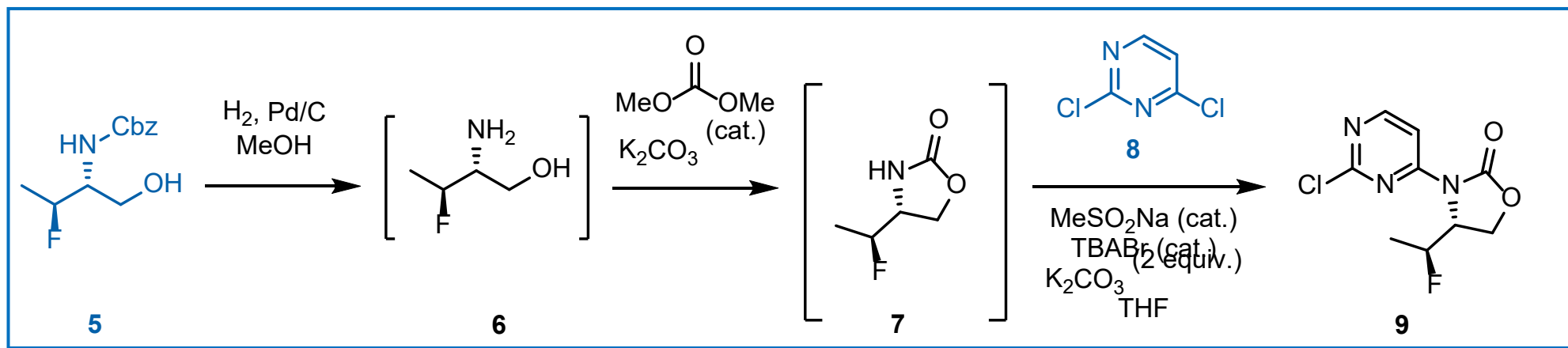
Impurity formed at high MeSO₂Na loading



92% isolated yield
C-4/C-2: >99:1

Bruening, F. *et al. Eur. J. Org. Chem.* **2017**, 3222-3228.

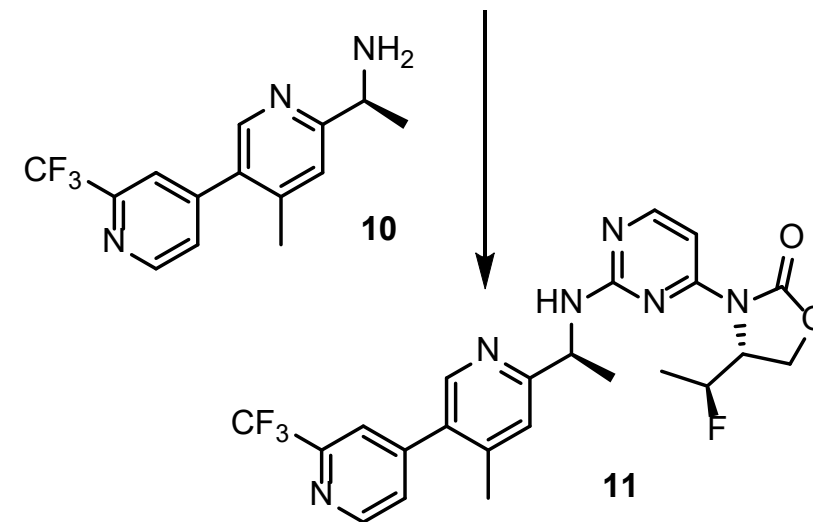
Main chain: S_NAr1



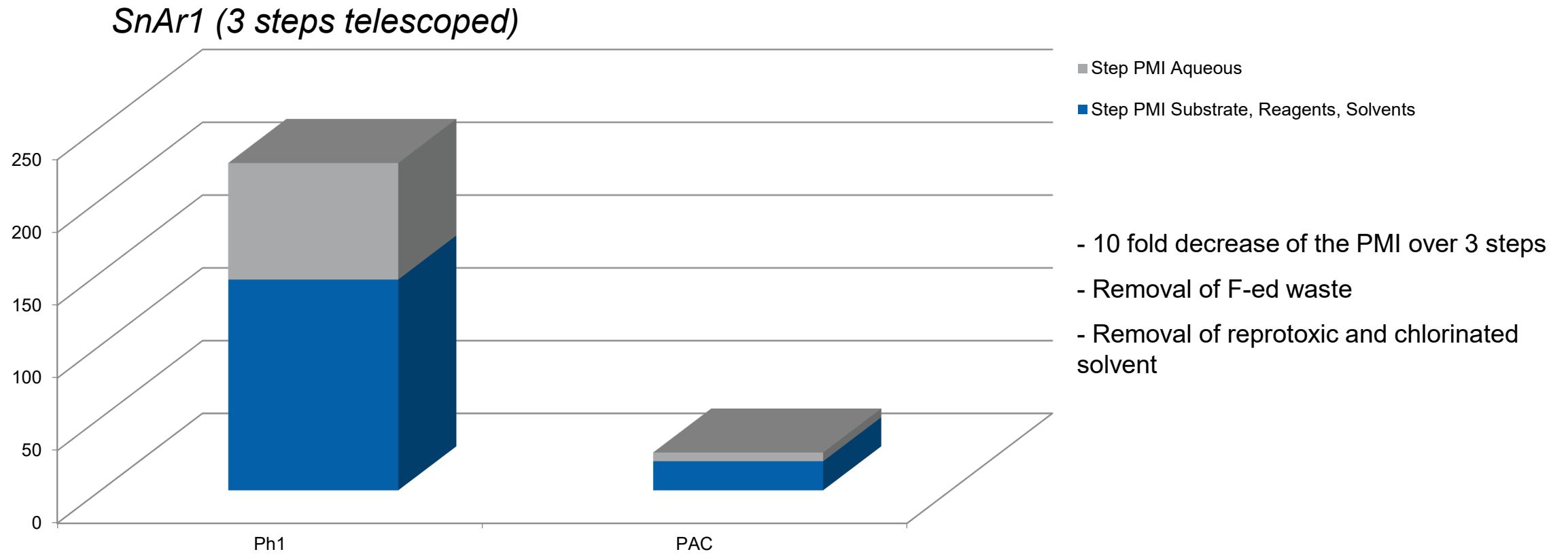
On 1 kg scale:

Isolated yield: 71.3% over 3 steps (ca. 89%/step)

Purity 99.3 A%, regioisomer 0.06 A%



Effect on sustainability



Sustainable Processes



Process development

«The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bathtub and collecting pure product from the drain hole.»

Sir John Cornforth (Nobel Prize, 1976)

Aspects to consider in process development

- ✓ Safety
- ✓ Number of steps
- ✓ Yield
- ✓ Complexity of the synthesis
- ✓ Robustness
- ✓ Ecologically benign
- ✓ Environmentally acceptable
- ✓ Availability of raw materials
- ✓ Economy

- Choice/Stoichiometry of reagents
- Choice of solvent/solvent effects
- Order of addition
- Concentration/volume
- Stirring/Mixing
- Analysis
- Temperature control
- Pressure/gaz evolution?
- Work-up
- Filtration
- Isolation
- Physical form
- (Depletion of) by products
- Purity
- Throughput
- Telescoping
- Waste
- Intellectual property
- Equipment required

Aspects to consider in process development

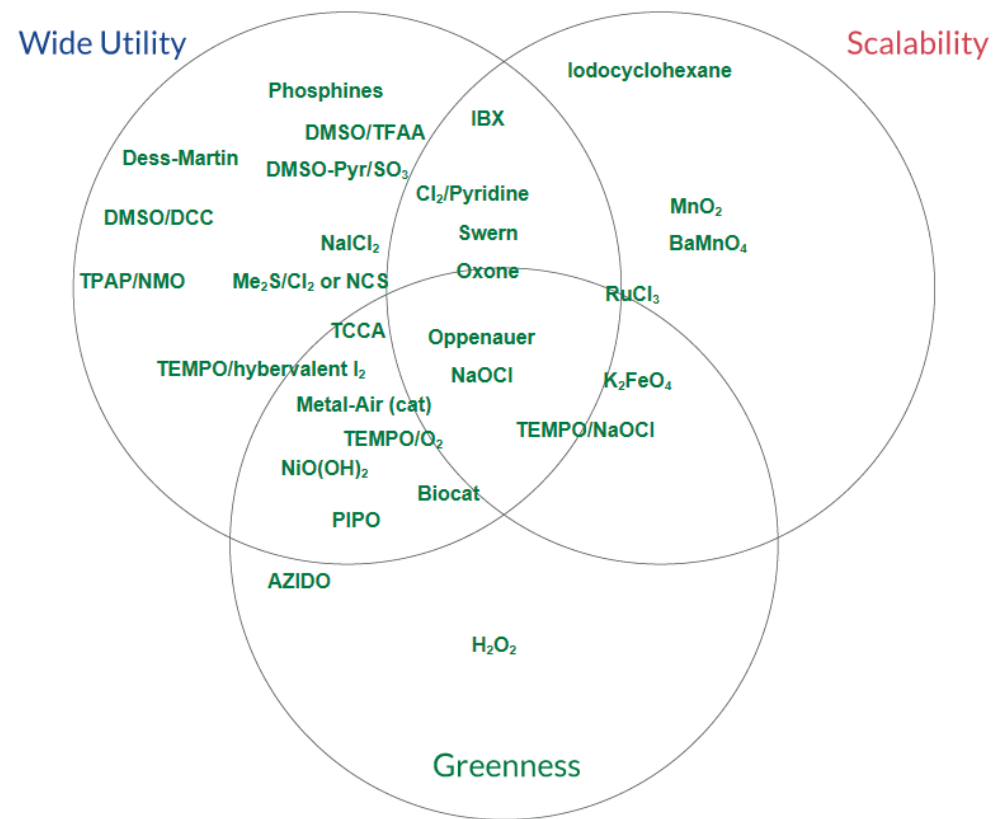
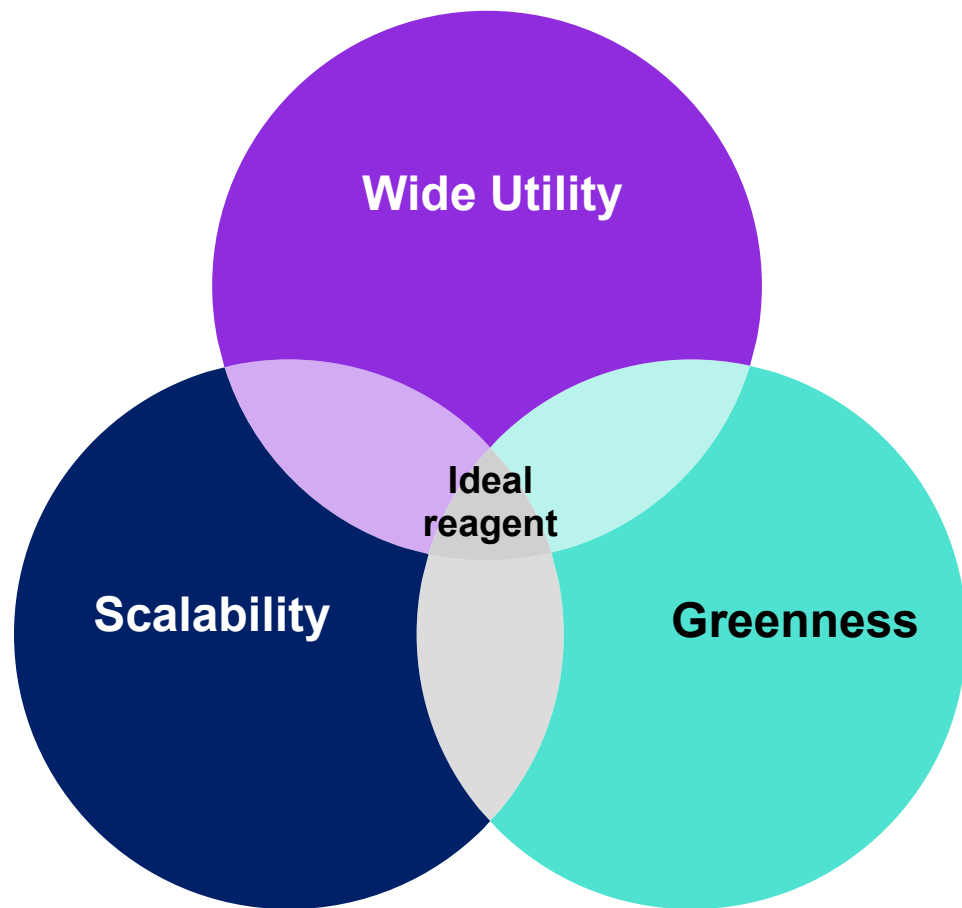
- ✓ Safety
- ✓ Number of steps
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- **Choice/Stoichiometry of reagents**
- **Choice of solvent/solvent effects**
- **Order of addition**
- **Concentration/volume**
- Stirring/Mixing
- Analysis
- **Temperature control**
- Pressure/gaz evolution?
- **Work-up**
- Filtration
- Isolation
- Physical form
- (Depletion of) by products
- Purity
- **Throughput**
- Telescoping
- **Waste**
- Intellectual property
- Equipment required

Often goes in the same direction as sustainability

Solvent & reagents

ACS reagent guide



Solvent Selection Guide – Chem21

Ranking	Solvents
Recommended	Water, EtOH, iPrOH, nBuOH, AcOEt, AcOiPr, AcOnBu, PhOMe, sulfolane
Recommended or Problematic ?	MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, AcOMe, AcOH, Ac ₂ O
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylene, chlorobenzene, acetonitrile, DMPU, DMSO
Problematic or Hazardous ?	THF, MTBE, cyclohexane, DCM, formic acid, pyridine
Hazardous	iPr ₂ O, dioxane, DME, pentane, hexane, DMF, DMA, NMP, TEA, methoxyethanol
Highly hazardous	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane



Only 67% convergence between various companies's assessment (AZ, ACS GCI, GSK, Pfizer, Sanofi)

The divergences reflect the different weighing of criteria and sometimes an incomplete analysis

Denis Prat, John Hayler, Andy Wells
Green Chem. **2014**, *16*, 4546.

2025 Green Assessments

Green Chem., 2025, 26, 5239

Materials	Acidification EF v3.1 no LT	Climate change EF v3.1 no LT GWP100 (Production (+ Market))	Climate change EF v3.1 no LT GWP100 (Incineration)	Climate change EF v3.1 no LT GWP100 (Total)	Ecotoxicity, freshwater EF v3.1 no LT	Energy resources, non-renewable EF v3.1 no LT
	mol H+ eq	kg CO2 eq	kg CO2 eq	kg CO2 eq	CTUe	MJ eq
2-Bromochlorobenzene	0.01035450	2.46406895	0.59194730	3.05601625	105.91348811	42.03111044
1,3-Dimethoxybenzene	0.01942815	3.67707236	0.47856189	4.15563425	80.24810825	60.91405049
n-Butyl lithium	0.14256935	19.49315479	0.55959184	20.05274663	361.67137528	232.97795638
Chlorodicyclohexylphosph.	0.22427397	44.98981023	0.72161573	45.71142596	1062.71979747	2193.53632986
Silica gel	0.01099024	0.98598688	0.92872778	1.91471466	13.54821711	11.15479378
Cellulose acetate	0.02953628	4.03842251	0.11593138	4.15435388	74.92793432	48.26634953
Iron(III) chloride	0.00104186	0.15012434	0.36736078	0.51748513	1.22992280	1.83829634
Pd(OAc)2	2.10455974	10.43138540	0.00436861	10.43575401	212.49269367	155.57810822
Methylmagnesium chloride	0.02253249	5.32924541	0.42409085	5.75333626	24.37885065	66.92940739
Tetrahydrofuran	0.31616635	63.17235520	25.36667710	88.53903230	183.42930358	1057.44206687
n-Hexane	0.00301502	0.59572956	1.86258125	2.45831081	14.53574513	29.81019326
Ethyl acetate	0.34142729	66.22762224	50.84978101	117.07740325	522.06122251	1484.00720930
Acetone	0.03466154	7.20421301	11.06054699	18.26476000	44.96465529	176.65315803
Methanol	0.00089641	0.34445197	1.11621108	1.46066305	1.07865806	14.60053375
Pentane	0.05229521	11.46541616	24.77166178	36.23707794	6.87779428	796.25235194
Water	0.00000016	0.00001730	0.02323600	0.02325330	0.00192578	0.00020484
SUM	3.31374855	240.56907631	119.24289136	359.81196768	2710.07969230	6371.99212043

2025 Green Assessments

Green Chem., 2025, 26, 5239

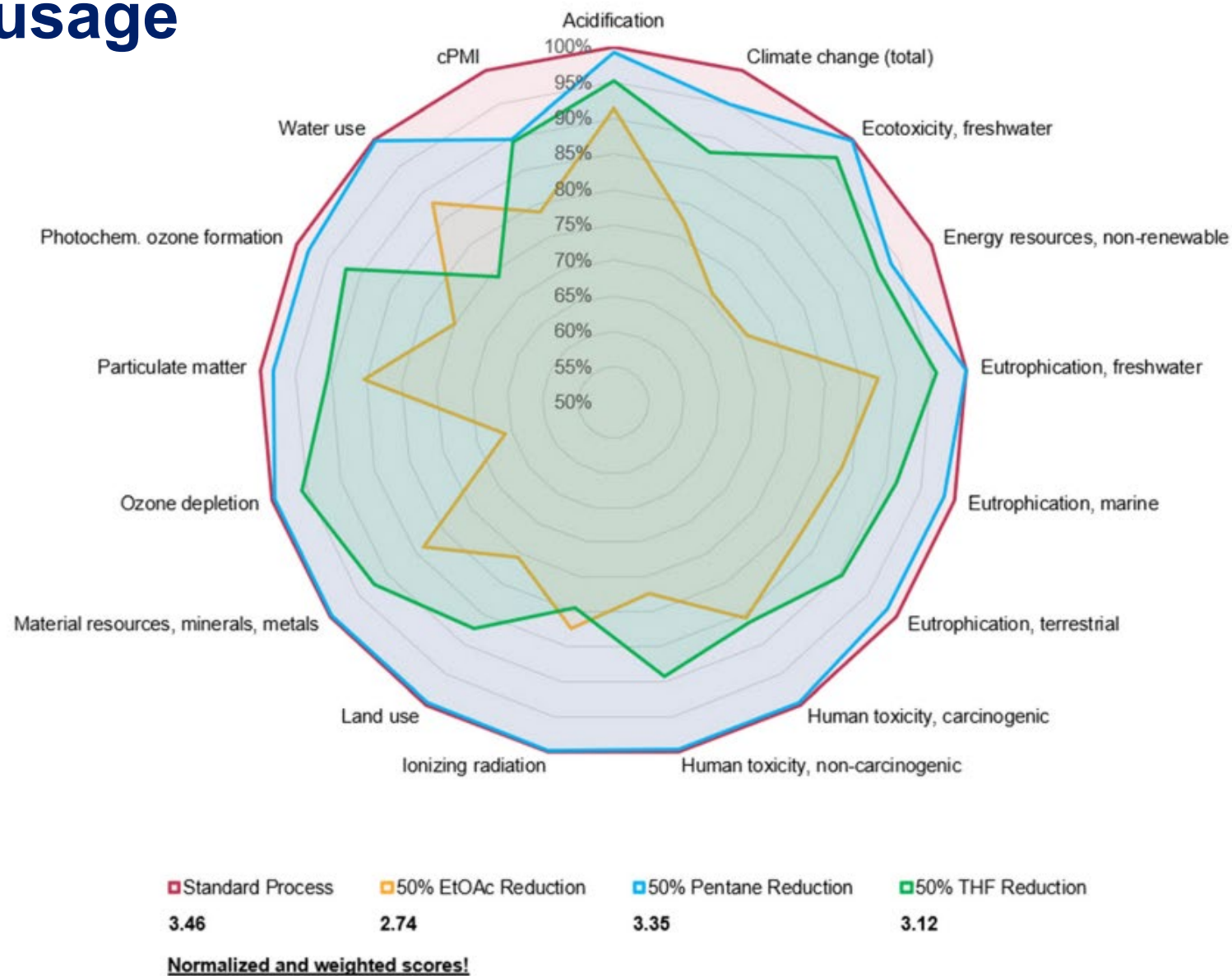
Materials	Eutrophication, freshwater EF v3.1 no LT	Eutrophication, marine EF v3.1 no LT	Eutrophication, terrestrial EF v3.1 no LT	Human toxicity EF v3.1 no LT Carcinogenic CTUh	Human toxicity EF v3.1 no LT Non-Carcinogenic CTUh	Ionizing radiation EF v3.1 no LT
	kg P eq	kg N eq	molc N eq	CTUh	CTUh	kg U235 eq
2-Bromochlorobenzene	0.00006079	0.00161635	0.01784169	0.00000001	0.00000003	0.03176807
1.3-Dimethoxybenzene	0.00008505	0.02411897	0.02486935	0.00000000	0.00000004	0.04620371
n-Butyl lithium	0.01345134	0.04742318	0.27319081	0.00000001	0.00000040	0.54033283
Chlorodicyclohexylphosph.	0.00070515	0.04518489	0.44339803	0.00000002	0.00000055	0.46937790
Silica gel	0.00003691	0.00094636	0.01312969	0.00000000	0.00000004	0.01489236
Cellulose acetate	0.00278673	0.00982472	0.05659730	0.00000000	0.00000008	0.11194146
Iron(III) chloride	0.00000863	0.00017561	0.00199502	0.00000000	0.00000000	0.00569752
Pd(OAc) ₂	0.00104688	0.05161510	0.76903396	0.00000001	0.00000030	0.22056791
Methylmagnesium chloride	0.00022095	0.00502818	0.05610293	0.00000003	0.00000004	0.05372214
Tetrahydrofuran	0.00234846	0.05338818	0.59776359	0.00000005	0.00000067	1.98160708
n-Hexane	0.00000927	0.00060602	0.00591724	0.00000000	0.00000001	0.00628679
Ethyl acetate	0.00604652	0.05906343	0.65525283	0.00000003	0.00000085	1.21891829
Acetone	0.00023564	0.00601389	0.06761257	0.00000001	0.00000006	0.06711120
Methanol	0.00000833	0.00023986	0.00264650	0.00000000	0.00000000	0.00245849
Pentane	0.00002879	0.00979340	0.10706393	0.00000000	0.00000002	0.01636056
Water	0.00000000	0.00000002	0.00000018	0.00000000	0.00000000	0.00000053
SUM	0.02707944	0.31503814	3.09241564	0.00000017	0.00000309	4.78724685

2025 Green Assessments

Green Chem., 2025, 26, 5239

Materials	Land use EF v3.1 no LT	Material resources EF v3.1 no LT Minerals, metals	Ozone depletion EF v3.1 no LT ODP100 Years	Particulate matter EF v3.1 no LT	Photochem. ozone formation EF v3.1 no LT	Water use EF v3.1 no LT
	Pt	kg Sb eq	kg CFC-11 eq	Disease incidence	kg NMVOC eq	m3 deprived
2-Bromochlorobenzene	4.00632996	0.00001495	0.00000028	0.00000011	0.01019104	6.44835067
1.3-Dimethoxybenzene	5.57469535	0.00003007	0.00000019	0.00000017	0.01203710	1.64413183
n-Butyl lithium	73.50484157	0.00033385	0.00000101	0.00000125	0.07598894	39.96838526
Chlorodicyclohexylphosph.	201.55719536	0.00034103	0.00000979	0.00000192	0.45346309	20.78250682
Silica gel	5.38017582	0.00004300	0.00000001	0.00000009	0.00379393	0.61007998
Cellulose acetate	15.22809467	0.00006916	0.00000021	0.00000026	0.01574273	8.28030292
Iron(III) chloride	0.87091239	0.00000588	0.00000006	0.00000001	0.00058938	0.12780337
Pd(OAc) ₂	83.72165178	0.00070005	0.00000010	0.00000274	0.28071208	2.79555207
Methylmagnesium chloride	11.01634059	0.00001130	0.00000163	0.00000366	0.02641772	0.56882861
Tetrahydrofuran	214.06959248	0.00037177	0.00000136	0.00000345	0.24060676	142.59338646
n-Hexane	2.67195620	0.00000460	0.00000004	0.00000002	0.00618925	0.27588895
Ethyl acetate	211.40067227	0.00045631	0.00000114	0.00000334	0.32094189	45.48378411
Acetone	13.70807153	0.00003543	0.00000007	0.00000030	0.03427291	3.54771212
Methanol	0.45459650	0.00000086	0.00000002	0.00000001	0.00190840	0.09609906
Pentane	4.35015874	0.00000954	0.00000008	0.00000066	0.06243819	0.81135036
Water	0.00007529	0.00000000	0.00000000	0.00000000	0.00000006	0.00001227
SUM	847.51536048	0.00242781	0.00001600	0.00001799	1.54529349	274.03417489

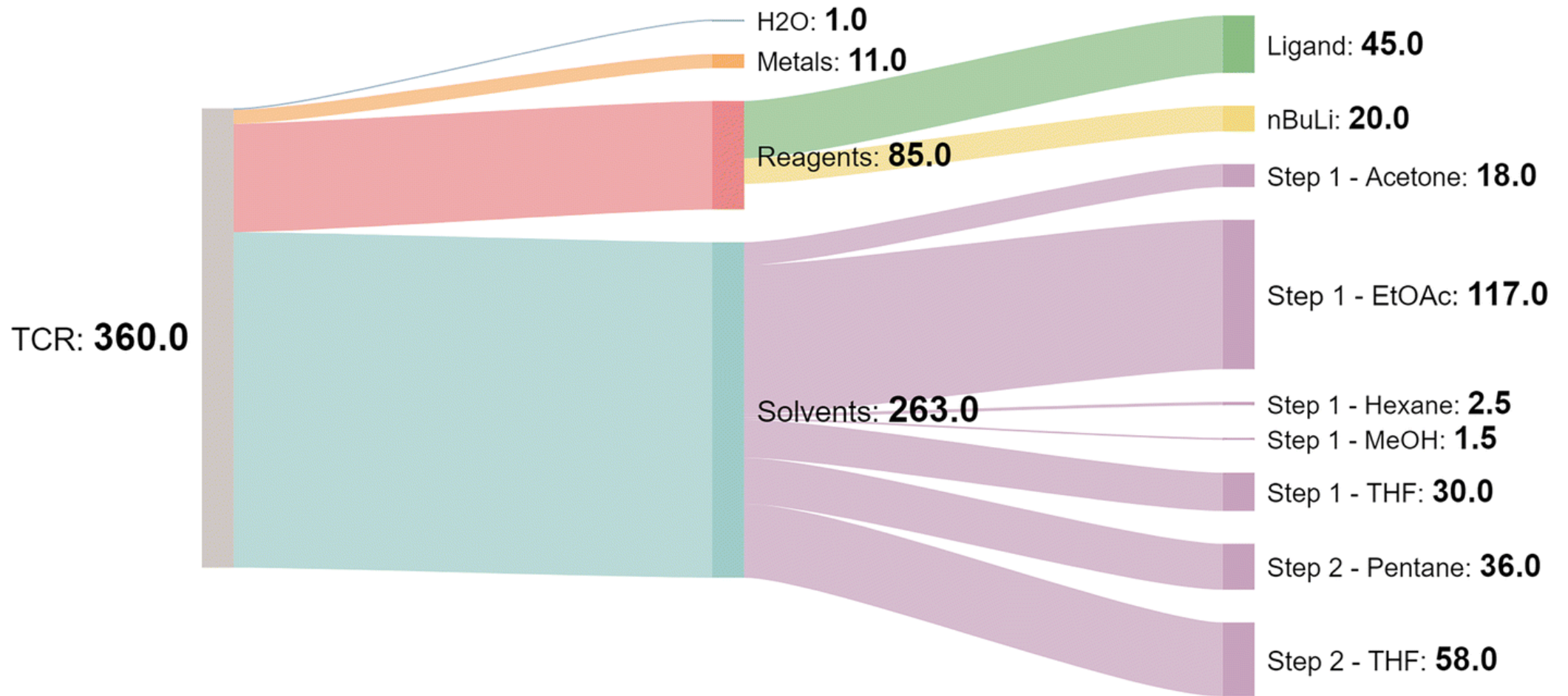
Comparison of material usage



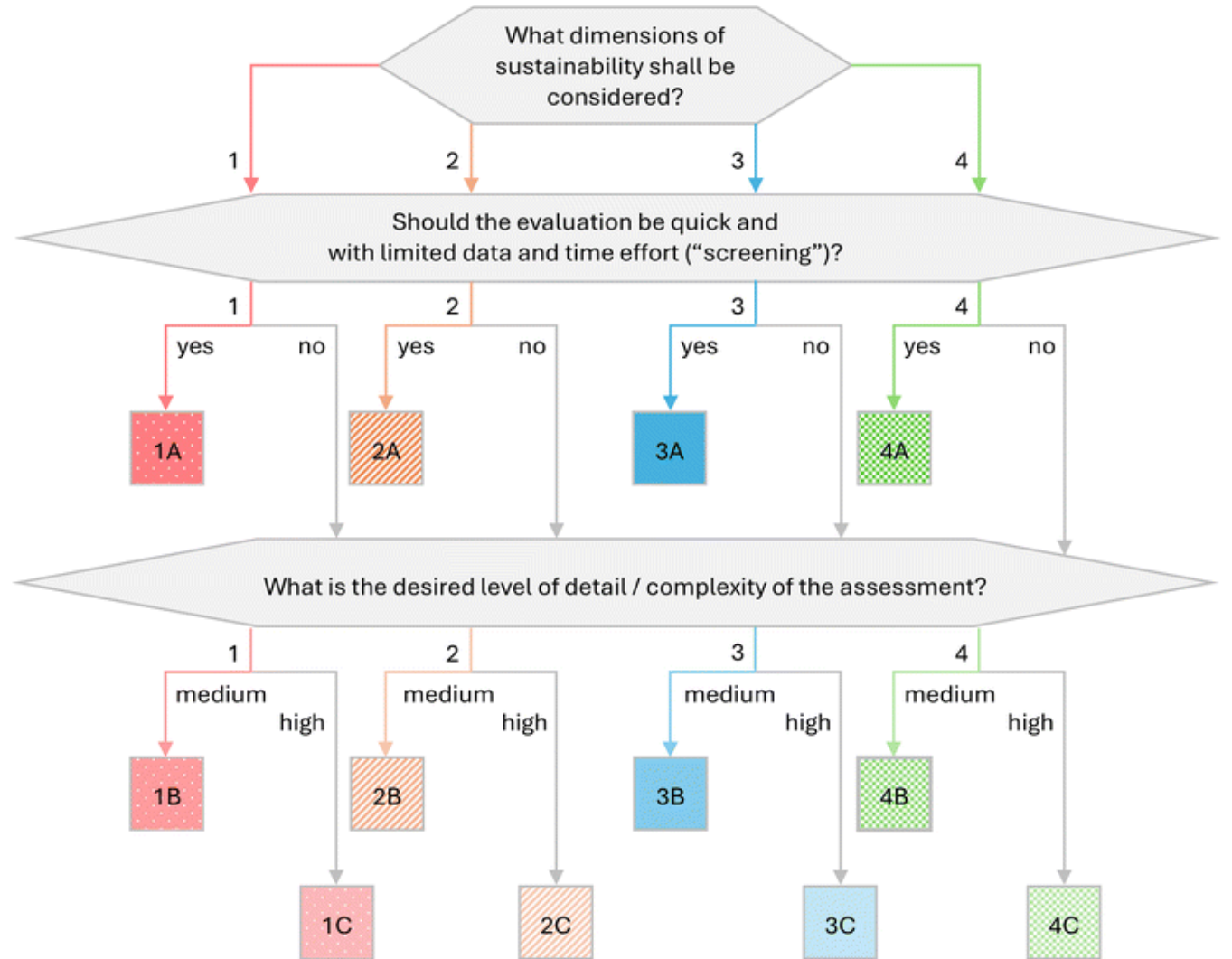
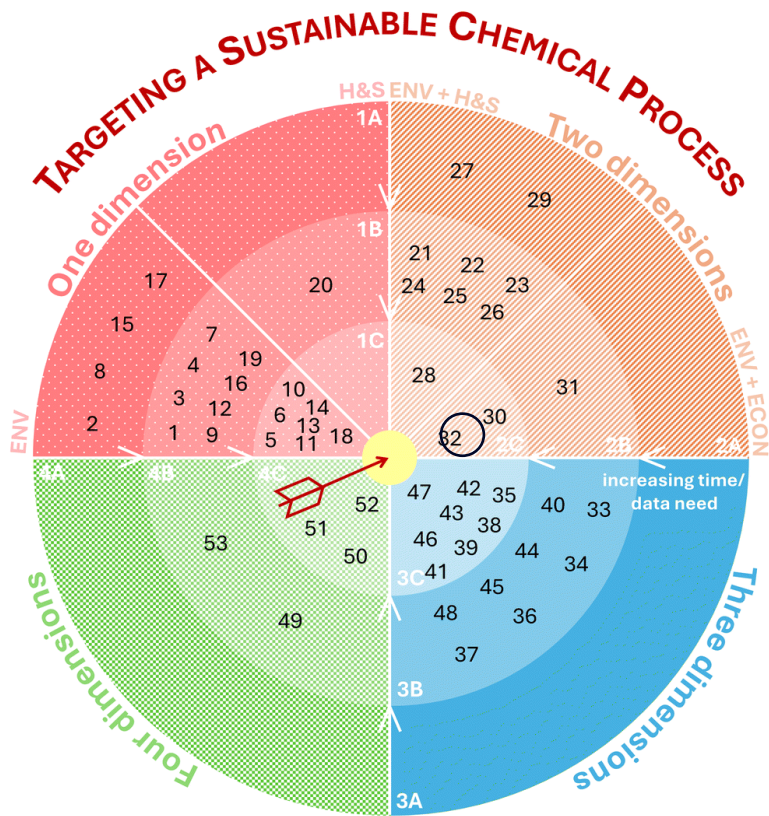
Green Chem., 2025, 26, 5239

Fig. 6 Relative spider diagram of development scenarios and their normalized and weighted score.

Sankey diagram



From qualitative analysis to quantitative insights



Aspects to consider in process development

- ✓ Safety
- ✓ Number of steps
- ✓ Yield
- ✓ Complexity of the synthesis
- ✓ Robustness
- ✓ Ecologically benign
- ✓ Environmentally acceptable
- ✓ Availability of raw materials
- ✓ Economy

- Choice/Stoichiometry of reagents
- Choice of solvent/solvent effects
- Order of addition
- Concentration/volume
- Stirring/Mixing
- Analysis
- Temperature control
- Pressure/gaz evolution?
- Work-up
- Filtration
- Isolation
- **Physical form**
- **(Depletion of) by products**
- **Purity**
- Throughput
- Telescoping
- Waste
- **Intellectual property**
- Equipment required

Often goes in the opposite direction as sustainability

Aspects to consider in process development

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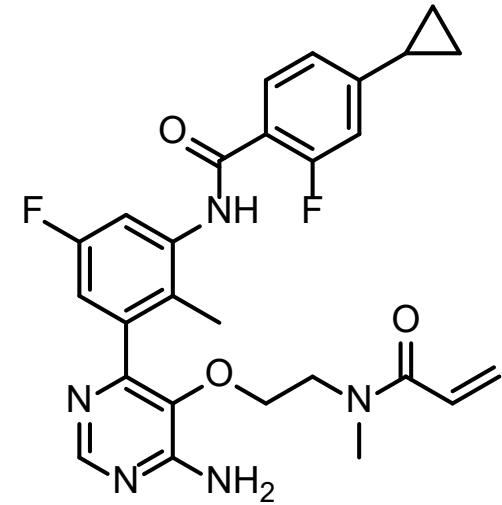
Telescoping

Pros

Cons

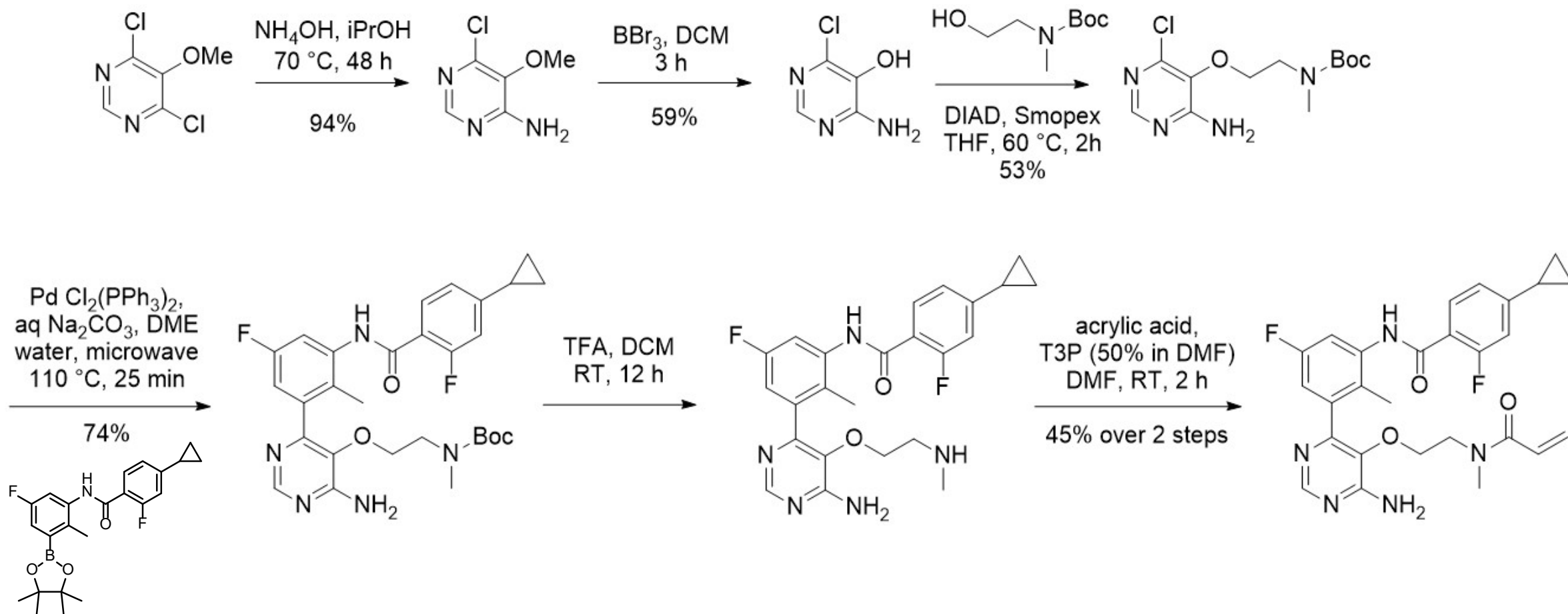
Remibrutinib

- *Therapeutic Area:* Immunology
- *Special biological features:* Highly selective Bruton kinase covalent inhibitor
- *Main indication:* urticaria, affect ca. 40 million people worldwide
- *Special chemical features:* no chiral center, acrylamide moiety

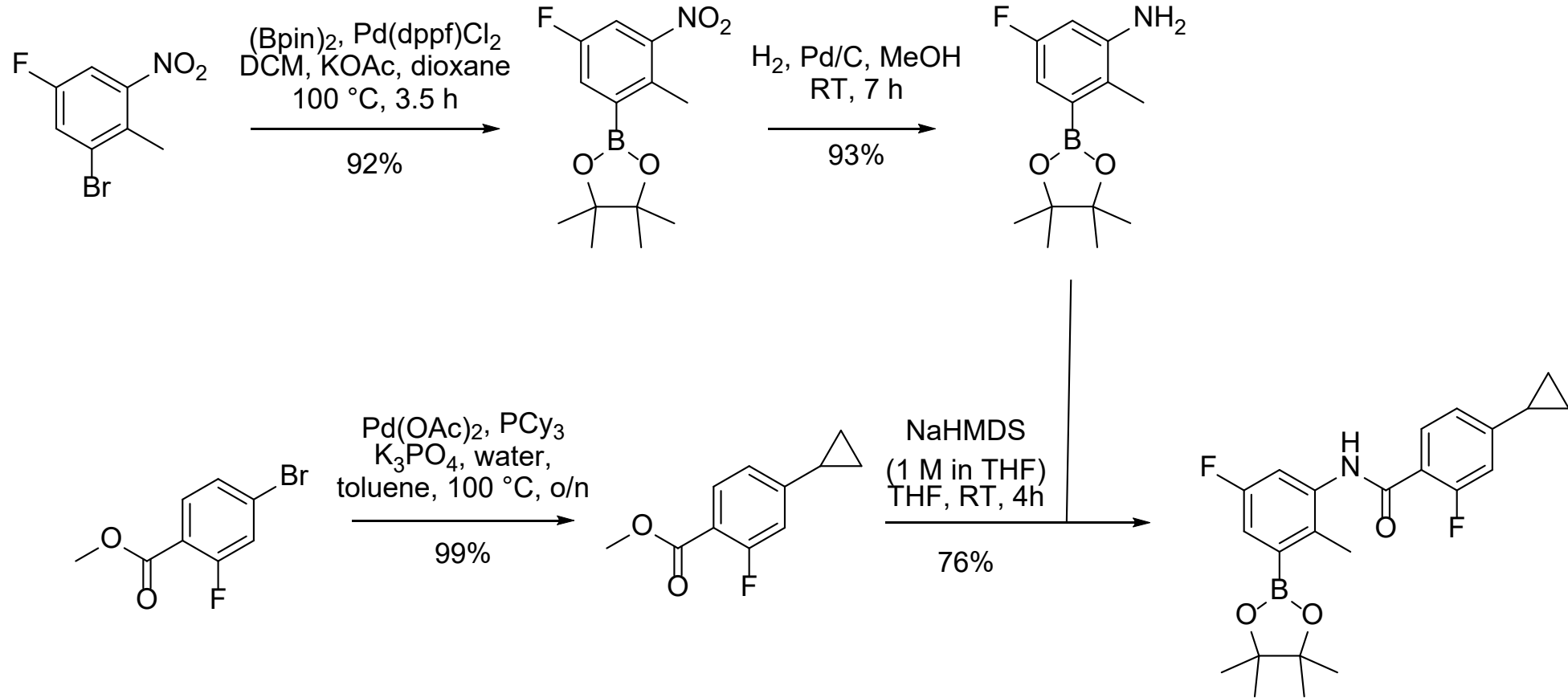


J. Med. Chem. 2020, 63, 10, 5102–5118

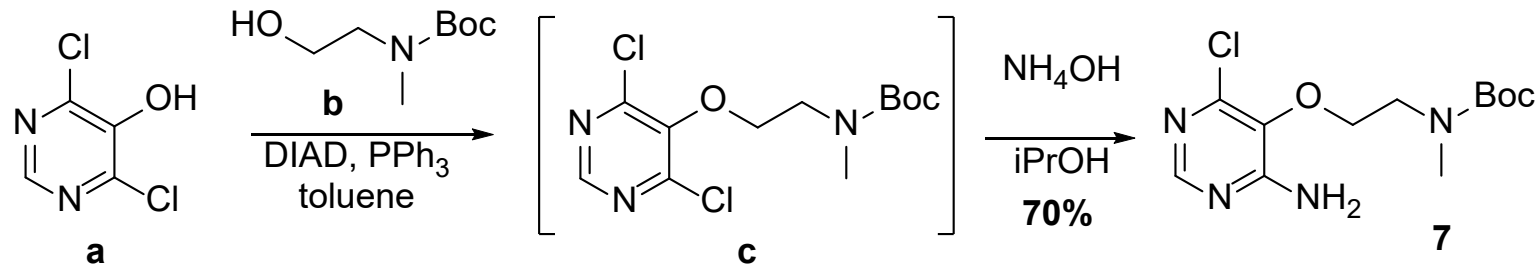
Highly Convergent MedChem Route



Highly Convergent MedChem Route

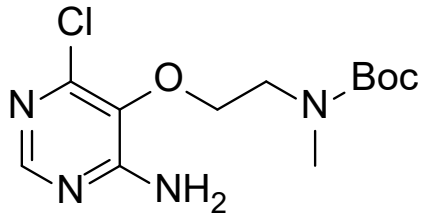


Int. 7 Detailed Process



- Mitsunobu reaction run in anhydrous conditions with 1.3 equiv of **b**, 1.3 equiv of PPh₃ and 1.6 equiv of DIAD.
- At the end of the reaction PPh₃O/H₂-DIAD is crashed out by heptane addition and filtered off.
- Traces of **a** are removed with a basic wash.
- Organic phase is transferred to a hydrogenator, iPrOH and NH₄OH are added
- The amination is run overnight at 70 °C
- **7** is crystallized after concentration and addition of water.

Intermediate Received For Campaign



Sl.	Tests	Results		
1	Appearance	Off white solid along with black particles		
2	Identification (HPLC-RT)	Complies		
3	Purity (By HPLC)	99.4 %		
	Sum of impurities	0.5 %		
	Other by-products each	RRT	% Area	
		0.726	0.05	
		0.733	0.06	
		0.91	0.20	
0.93		0.09		
1.02	0.11			
4	Assay (By potentiometric titration)	96.8 %		
STORAGE: Preserve in an air tight container, store at below 30°C				
CONCLUSION: Complies				

Compound received from our Supplier



Figure 1. Hand picked lumps



Figure 2. Dark lumps sieved off from the batch



Figure 3. Grinded sieved off lumps

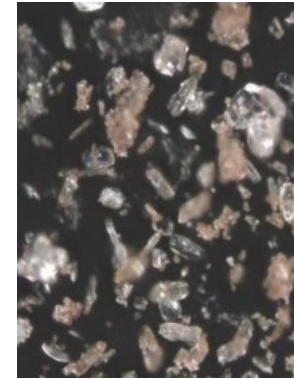


Figure 4. Microscopic pictures of the grinded lumps

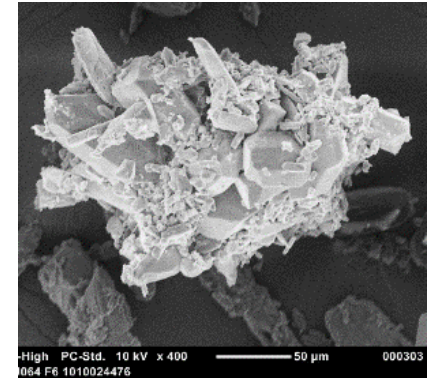
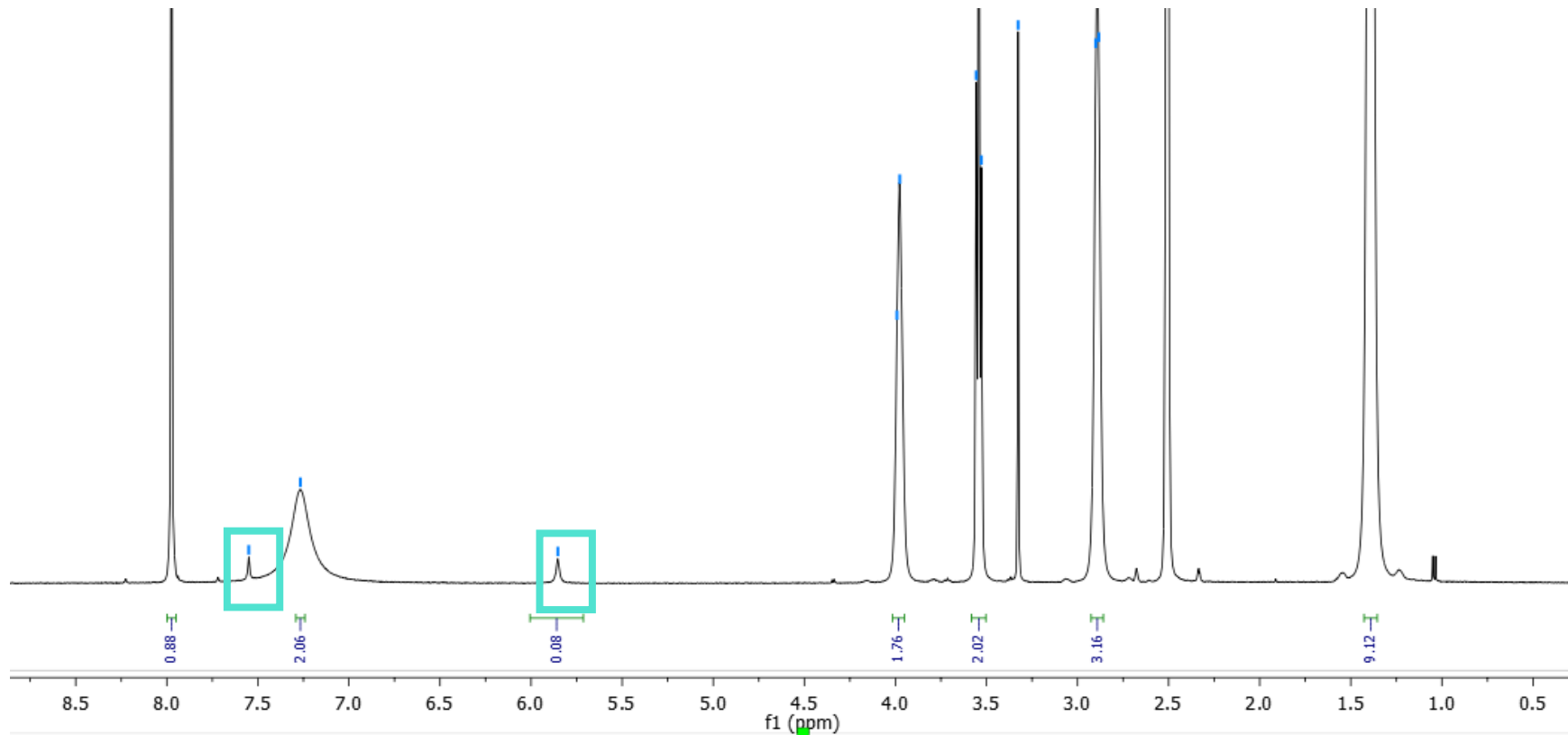


Figure 5. SEM picture of the grinded lumps

Investigation

NMR of sieved 7 (enriched in black matter)



Trituration with Acetone

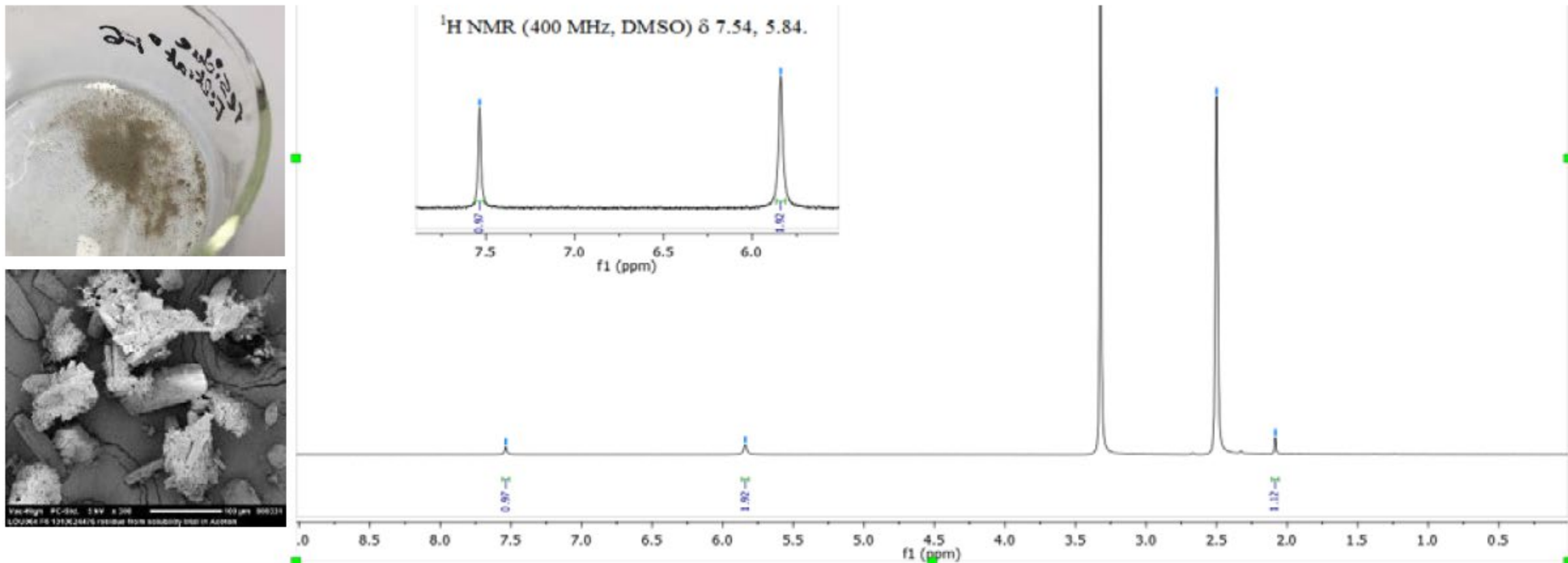
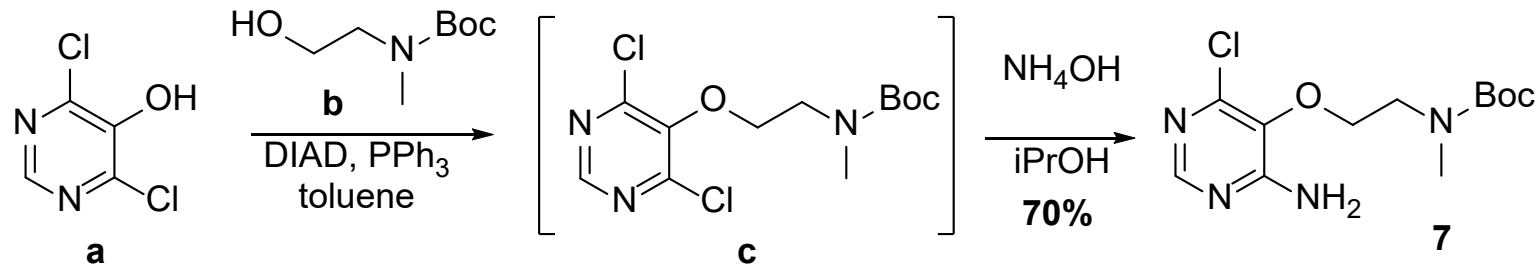


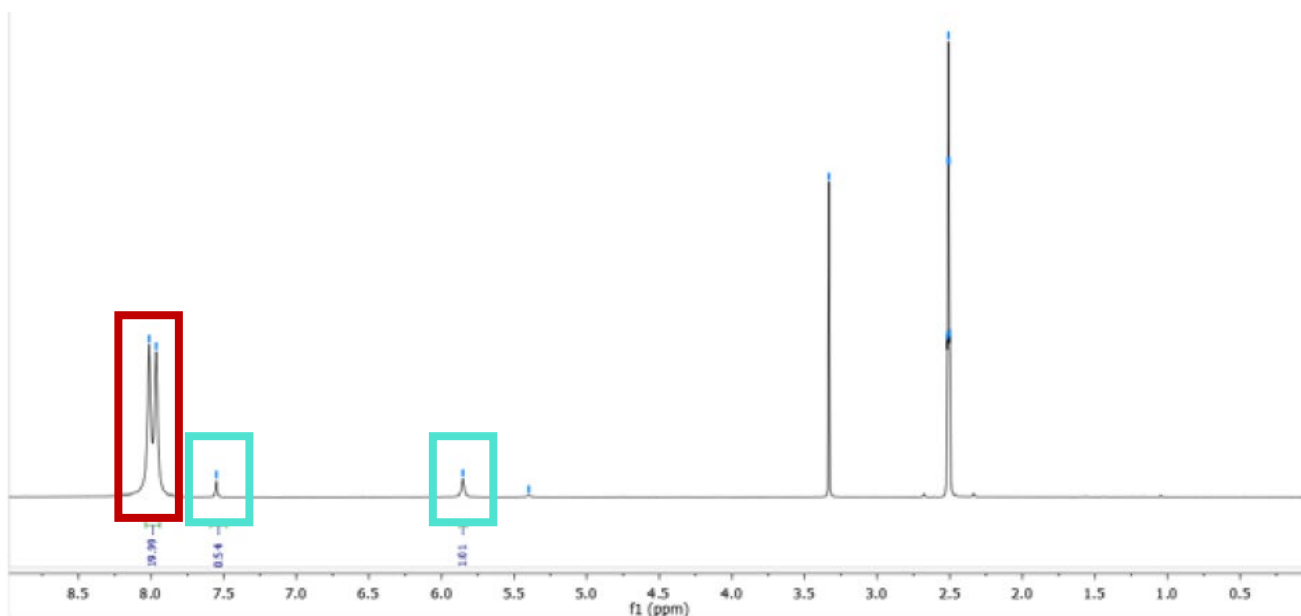
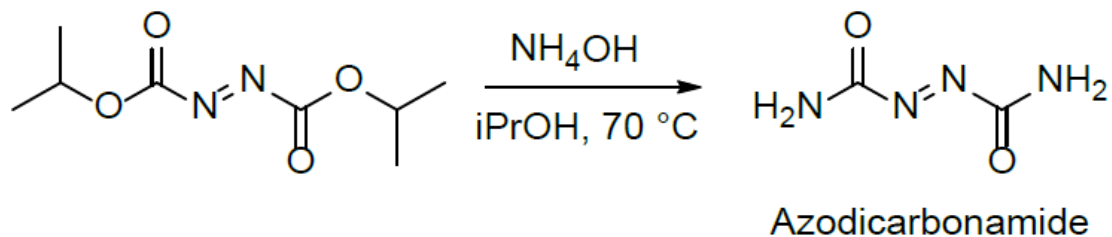
Figure 3: NMR spectra and SEM picture of the isolated grey compound. Only the two previously identified signals belong to the impurity

Int. 7 Detailed Process



- Mitsunobu reaction run in anhydrous conditions with 1.3 equiv of **b**, 1.3 equiv of PPh₃ and 1.6 equiv of DIAD.
- At the end of the reaction PPh₃O/H₂-DIAD is crashed out by heptane addition and filtered off.
- Traces of **a** are removed with a basic wash.
- Organic phase is transferred to a hydrogenator, iPrOH and NH₄OH are added
- The amination is run overnight at 70 °C
- **7** is crystallized after concentration and addition of water.

Excess Reagent Carry Over



- Widely used as foaming agent
- Used in food chemistry outside of EU (E927) to bleach flour and as a dough conditioner
- «Yoga mat» chemical

Forbes

FORBES > BUSINESS > PHARMA & HEALTHCARE

Latest Food Scare: What Is The 'Yoga Mat' Chemical - And Why Is It In Your Food?

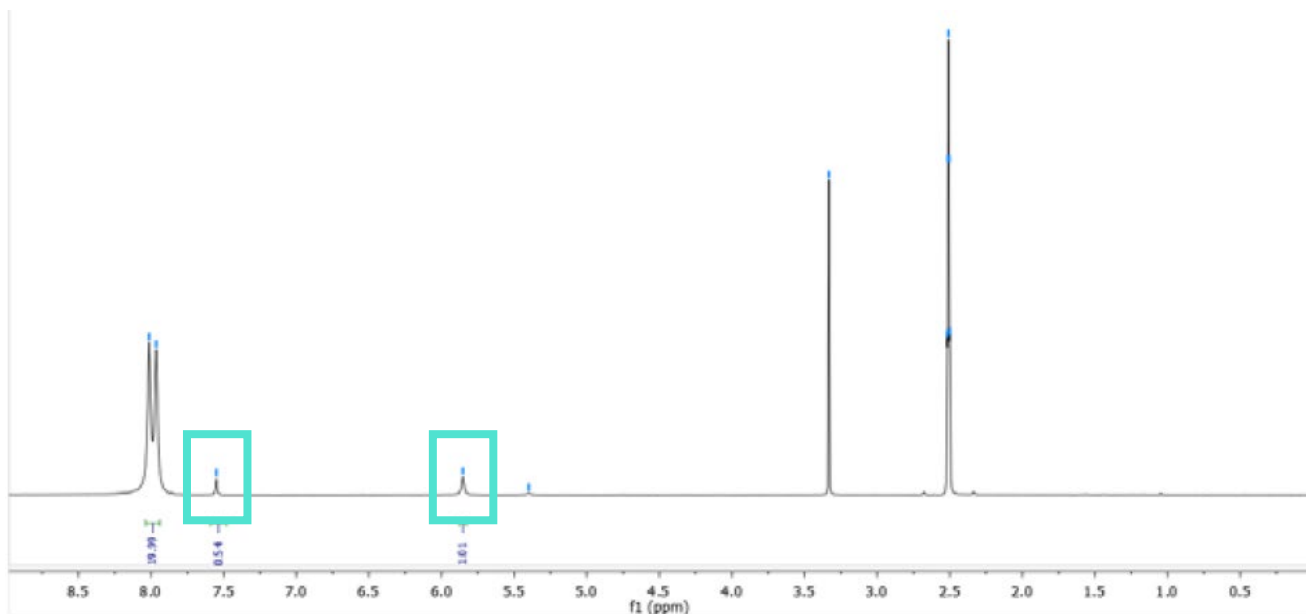
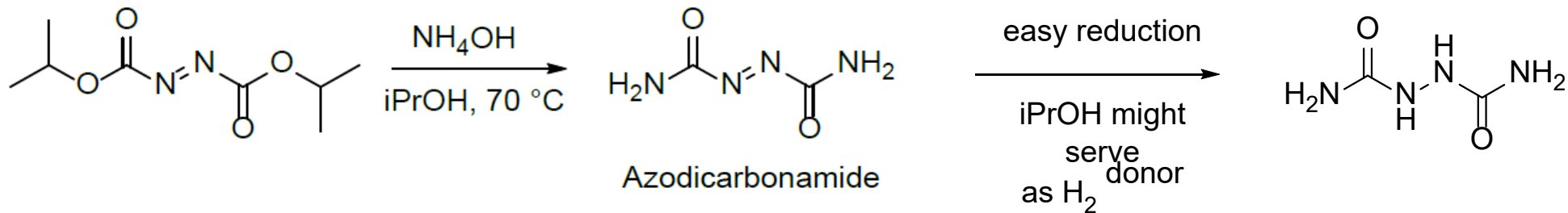
Melanie Haiken Contributor @

I report the latest in health, nutrition, wellness and healthy travel.

Follow

Feb 27, 2014, 05:45pm EST

Excess Reagent Carry Over

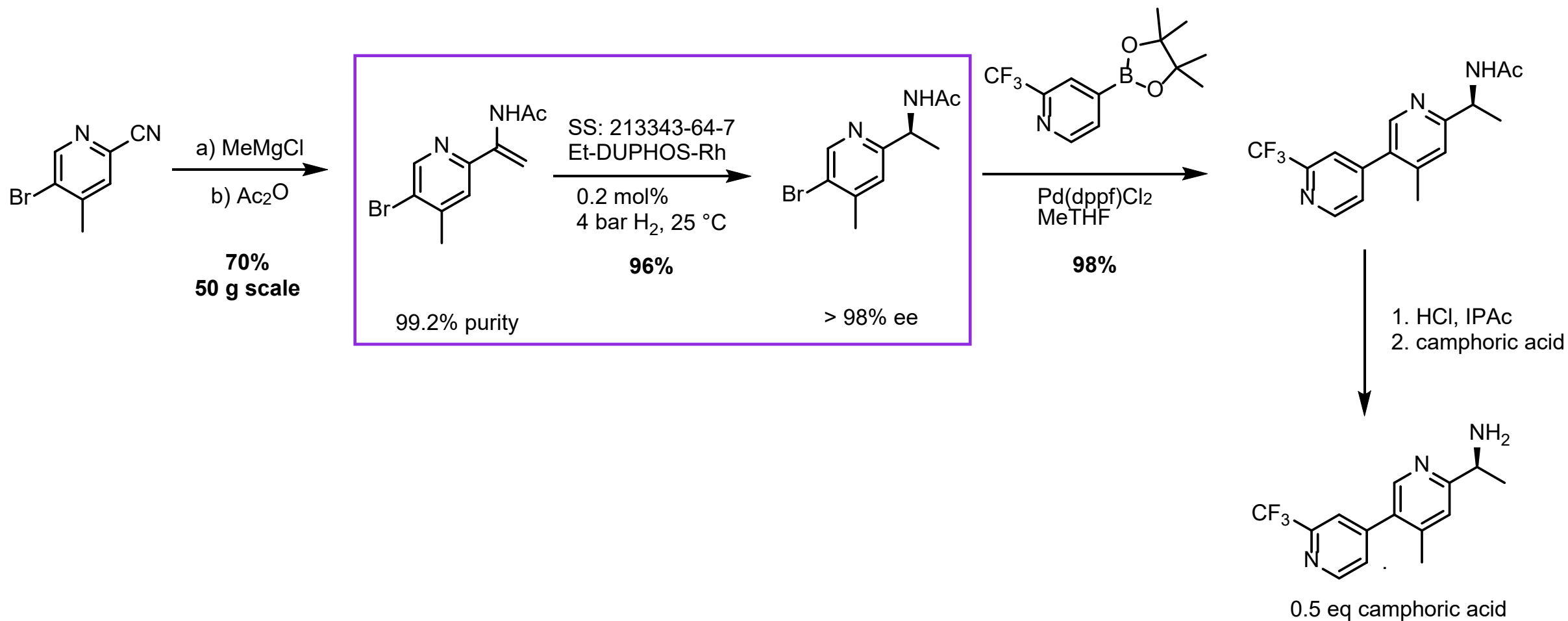


- No toxicological alert
- Real ingredient found in food

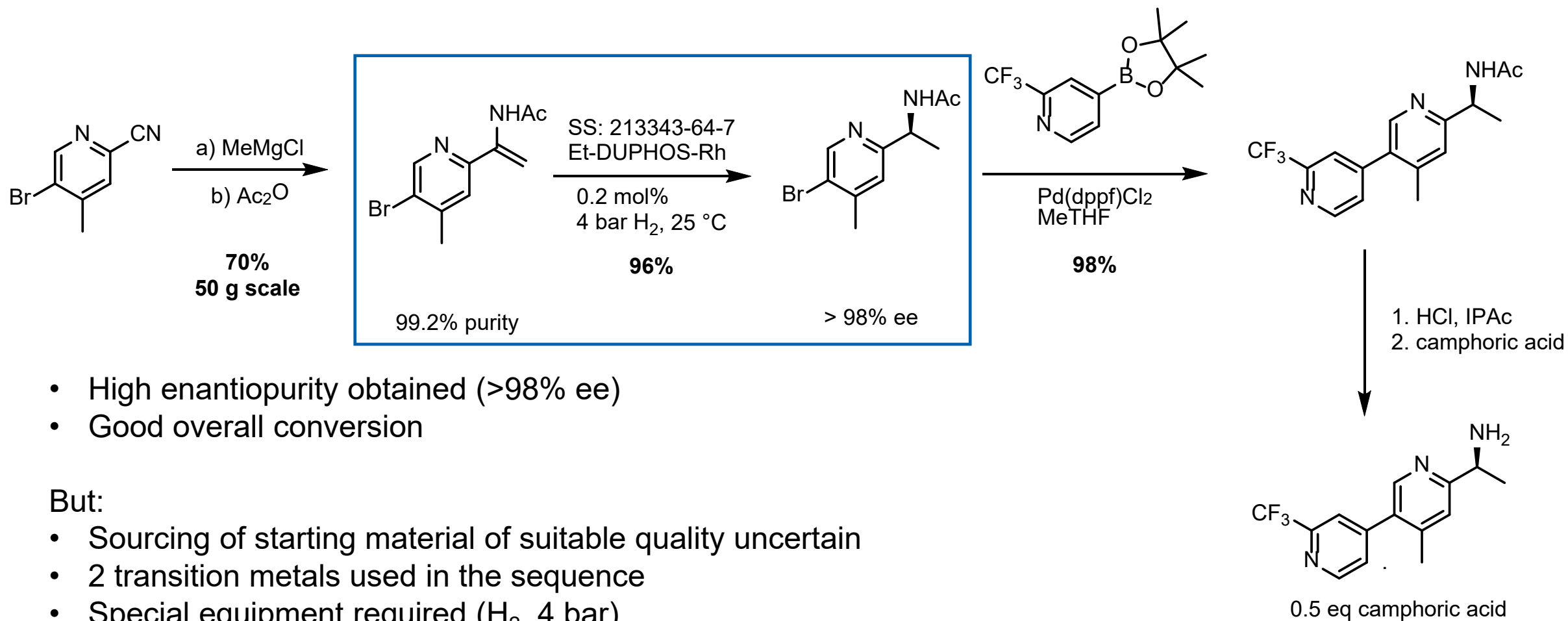
Use case : IDH305 side chain



Side Chain - Alternate Route 1



Side Chain - Alternate Route 1

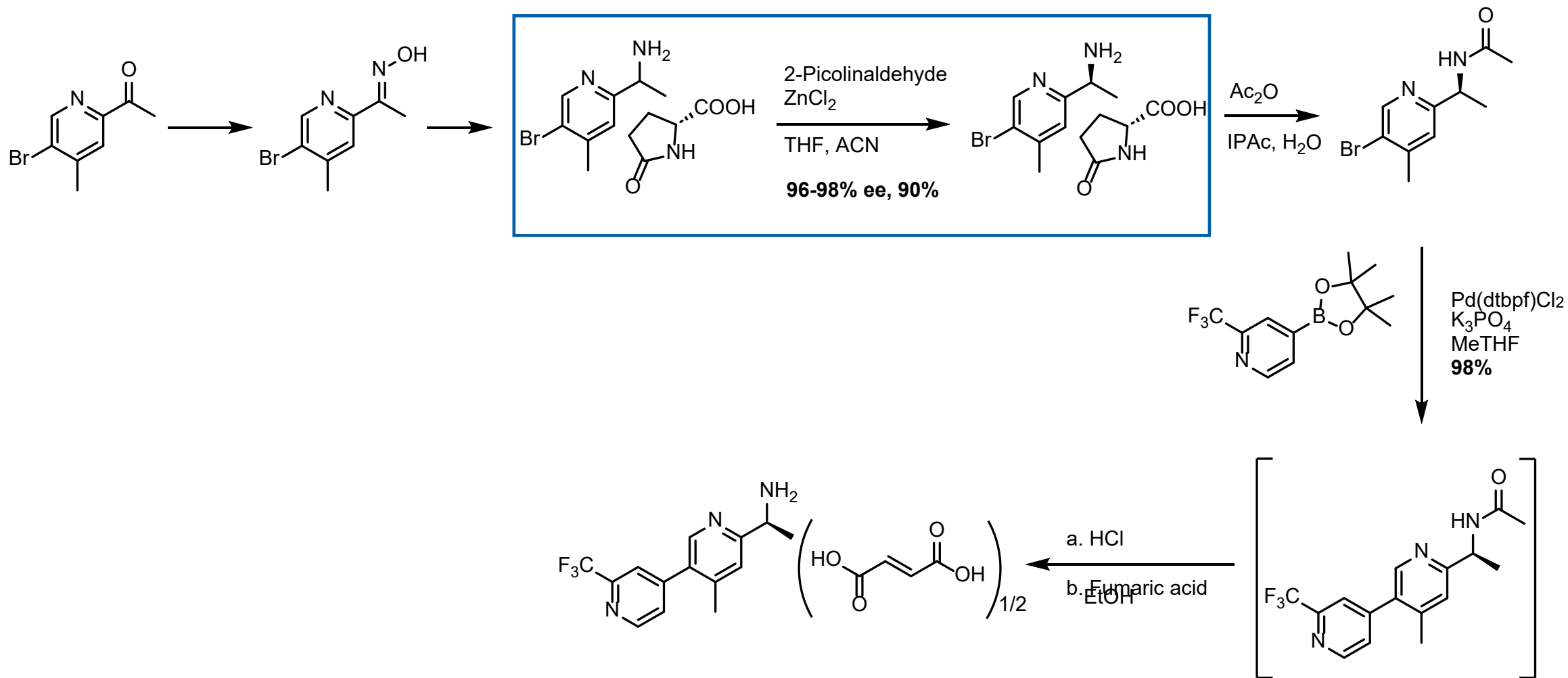


- High enantiopurity obtained (>98% ee)
- Good overall conversion

But:

- Sourcing of starting material of suitable quality uncertain
- 2 transition metals used in the sequence
- Special equipment required (H₂, 4 bar)

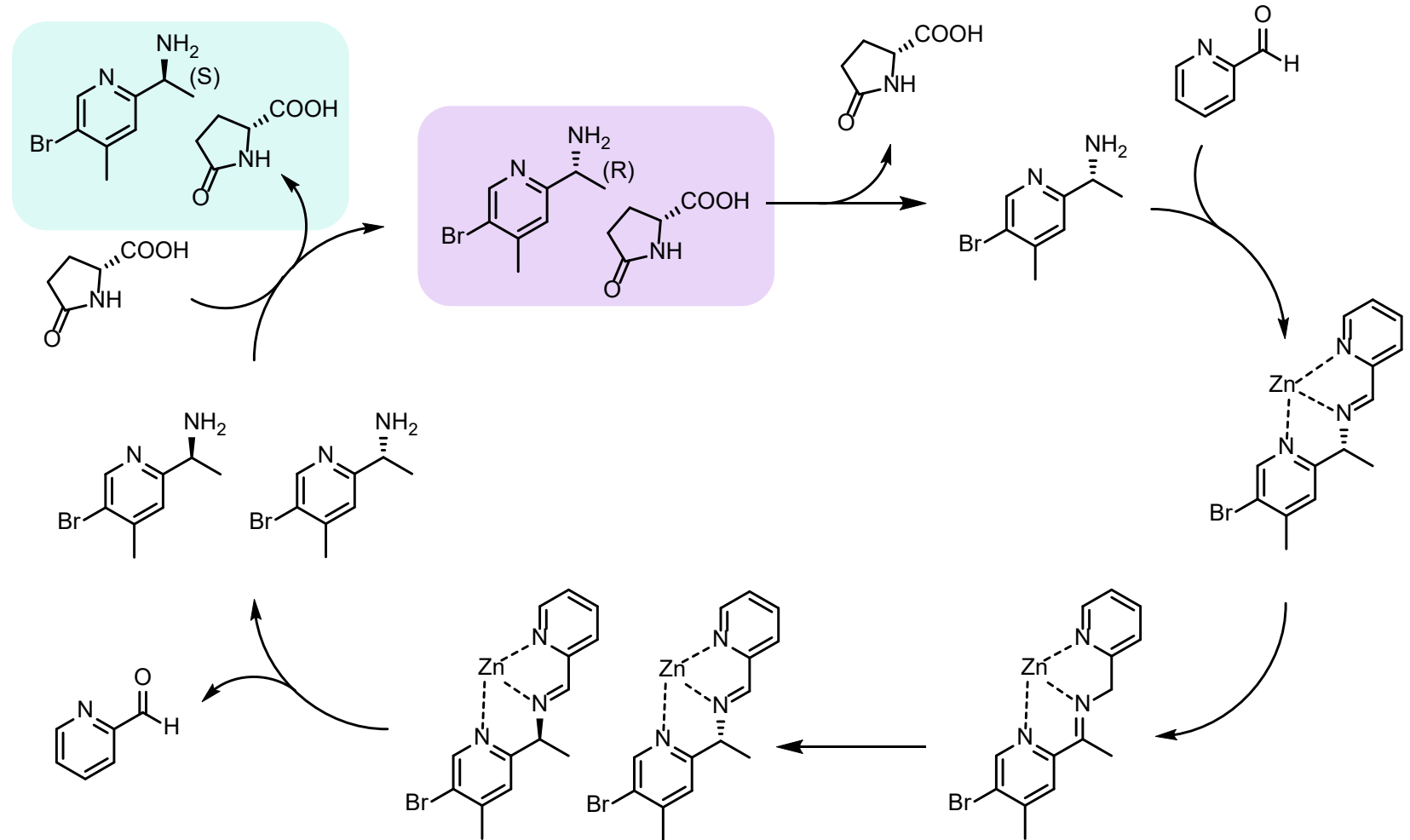
Side Chain - Alternate Route 2: DKR



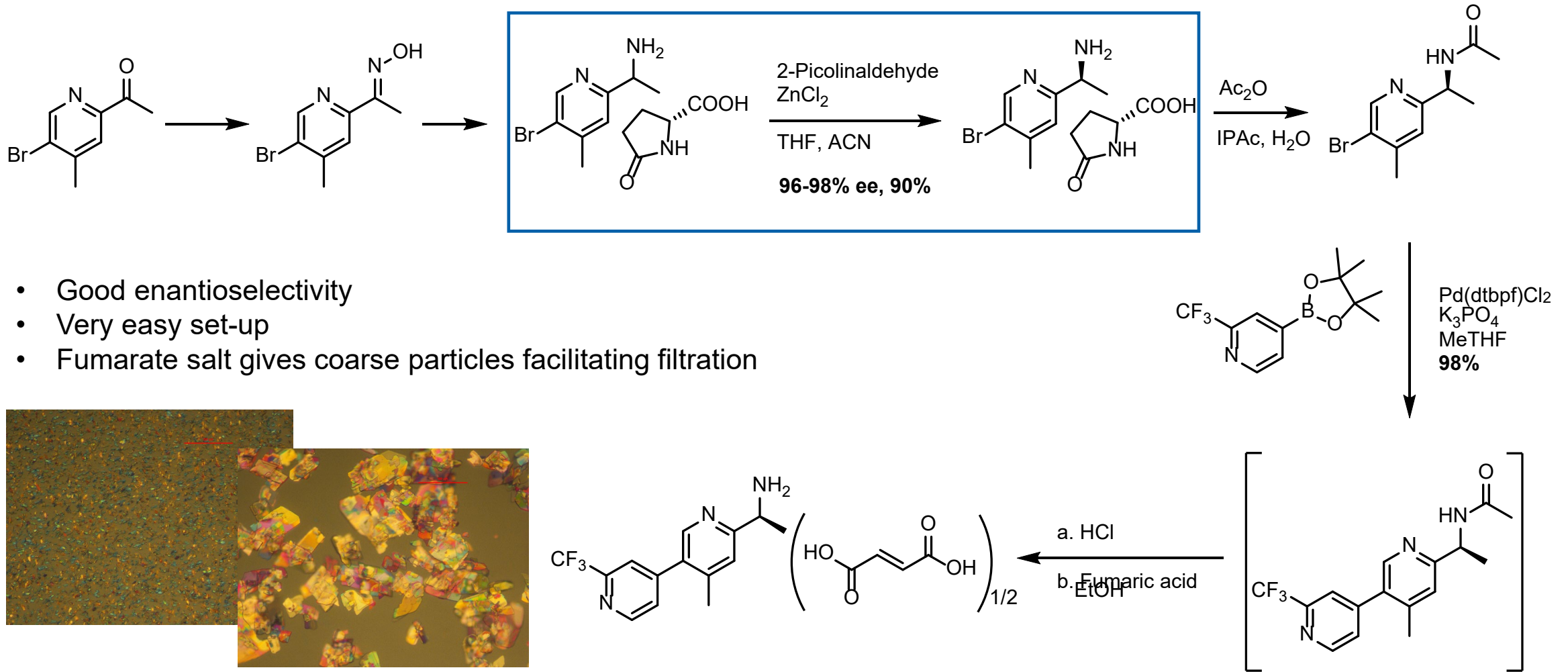
Side Chain DKR - mechanism

Solubility difference between the diastereoisomeric salts:

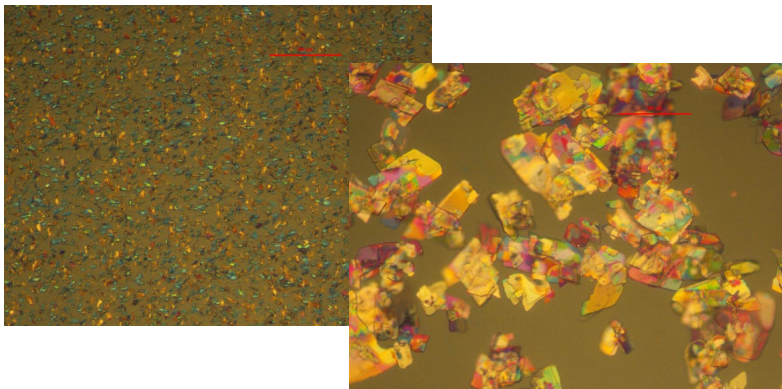
1.2% (R, R) vs 0.6% (S, R)



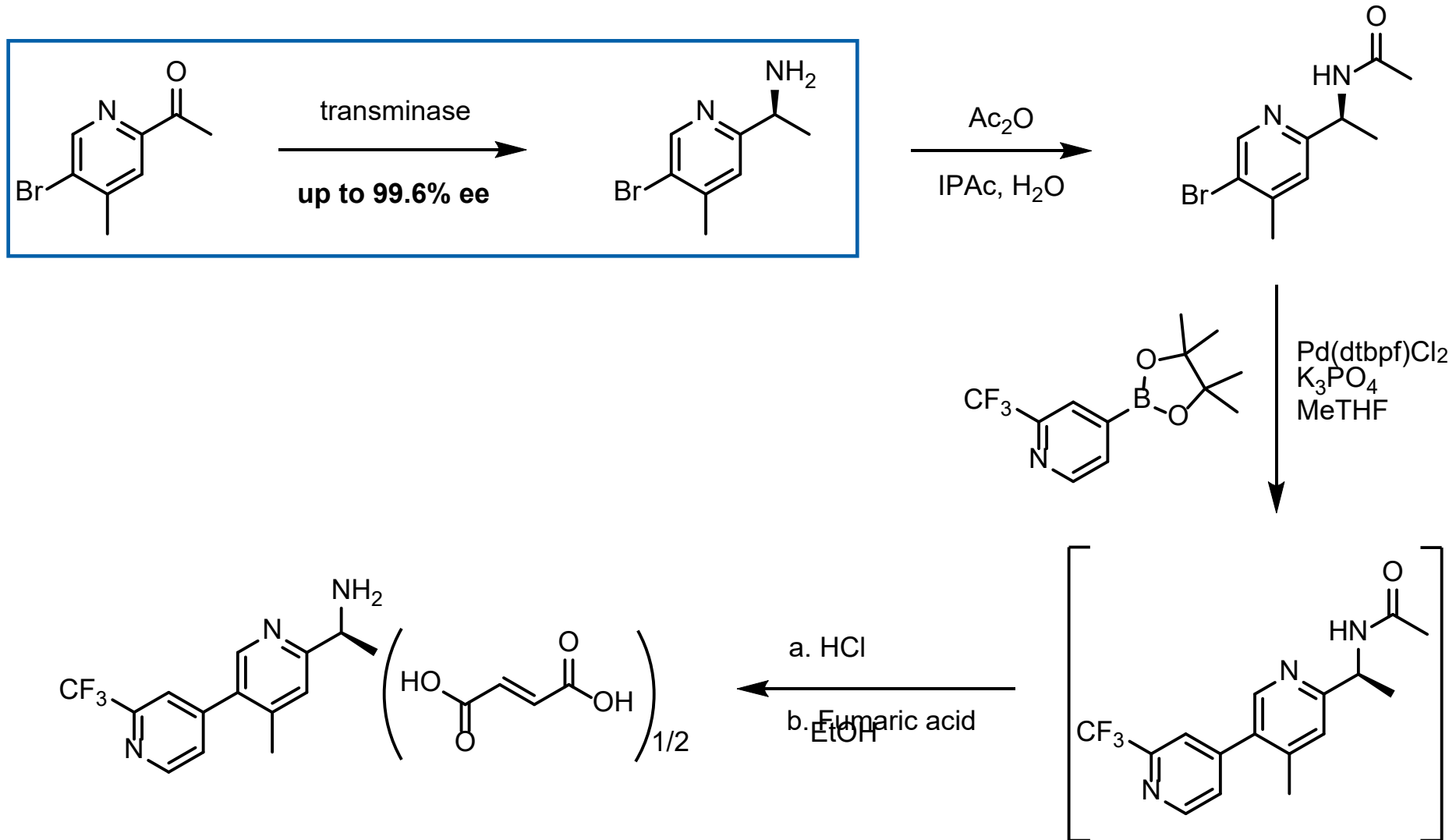
Side Chain - Alternate Route 2: DKR



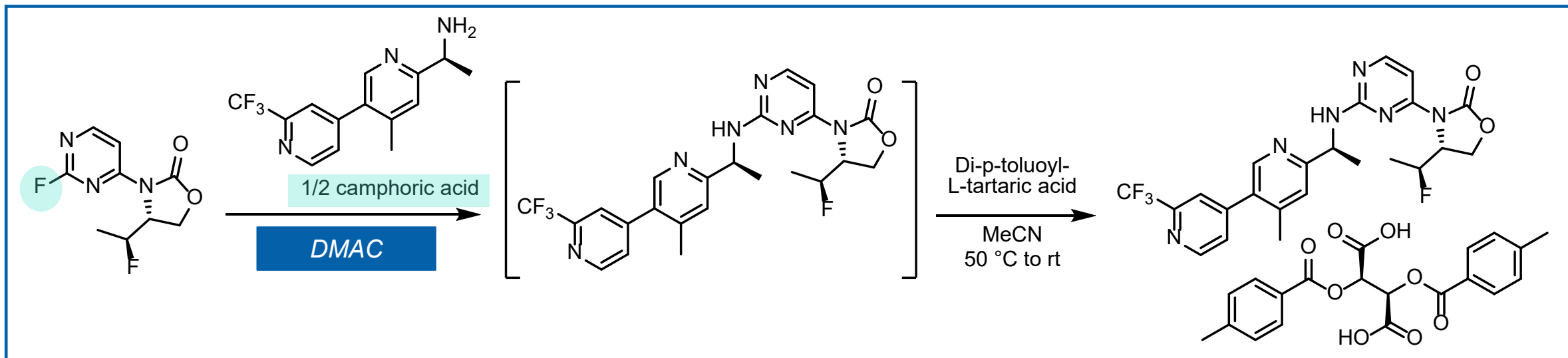
- Good enantioselectivity
- Very easy set-up
- Fumarate salt gives coarse particles facilitating filtration



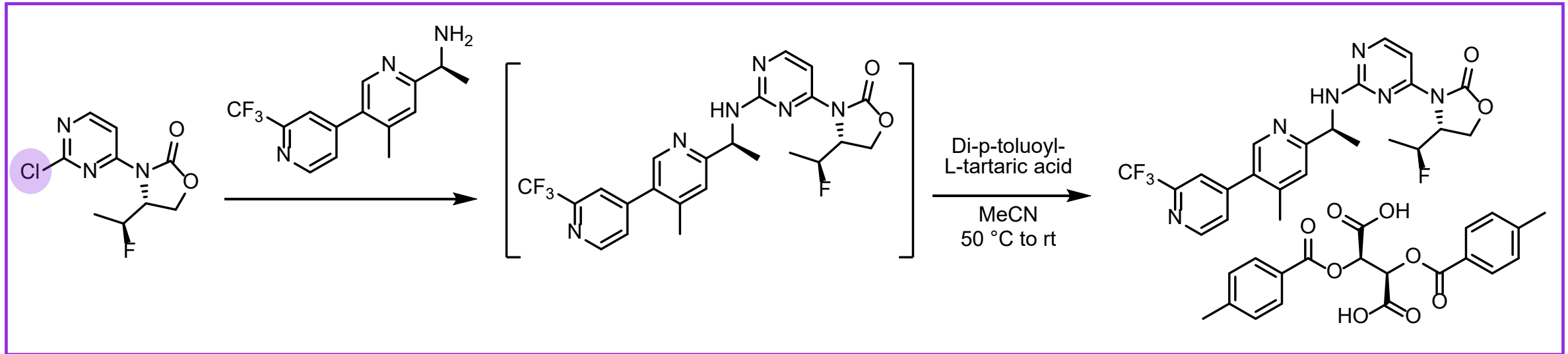
Side Chain Transaminase



Main Chain: $S_N_{Ar} 2$



Main Chain: S_NAr 2



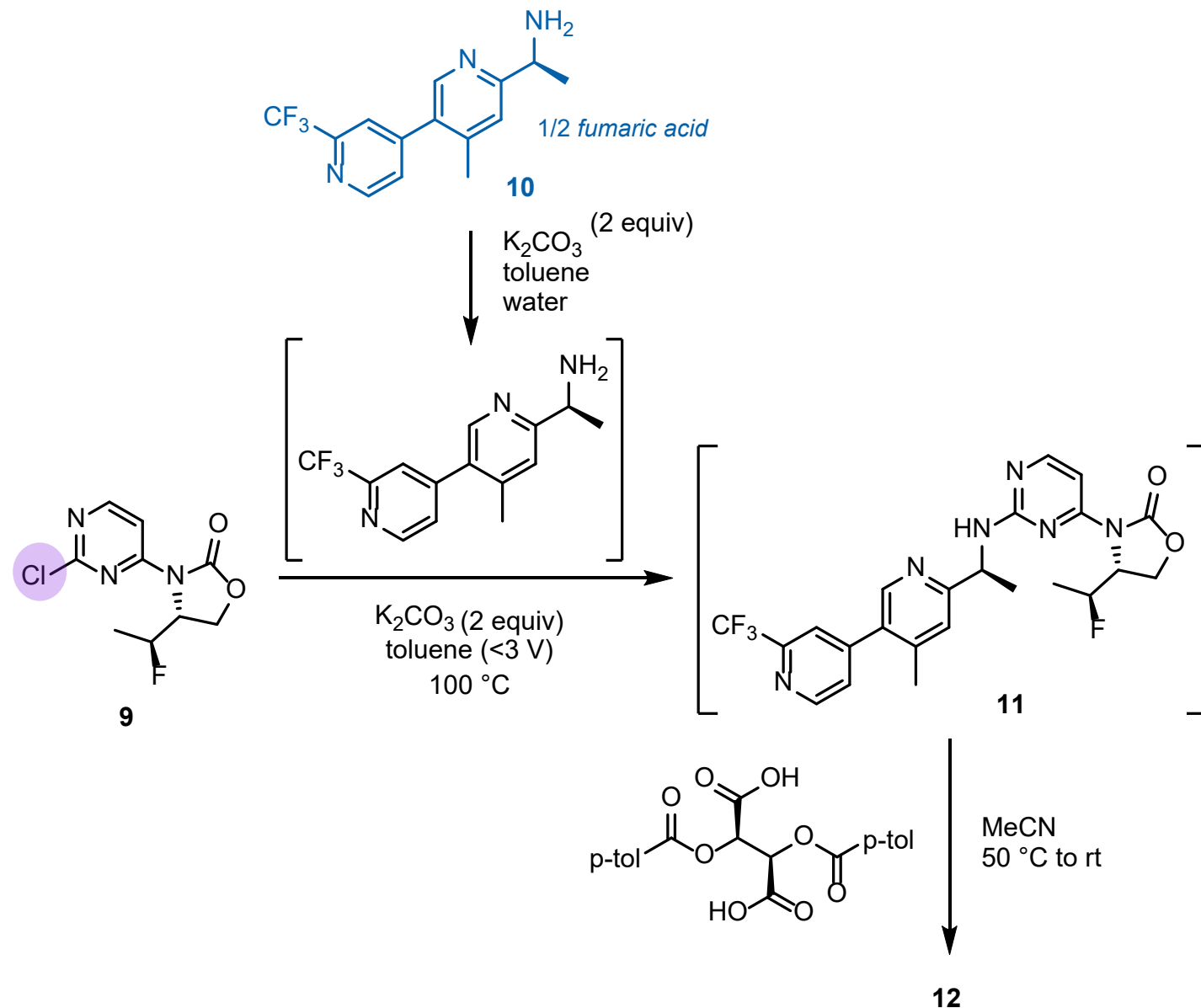
- First trials needed >72 h to reach acceptable conversion in toluene
- Scale up effect was observed between 100 mg and 1 g scale reactions – which gave us a hint on the impact of concentration

→ use of 3 V of toluene gave >98% conv. in less than 24 h

Main chain: S_NAr2

- Free basing of the side chain has to be done prior to the reaction
- Toluene suitable for free basing
- After conversion, an AcOH 1N wash removes traces of the side chain
- A solvent switch to MeCN and addition of tartaric salt allows for an easily isolation
- Crystallisation purges all remaining impurities except desfluoro

Isolated yield on kg-scale: 87%

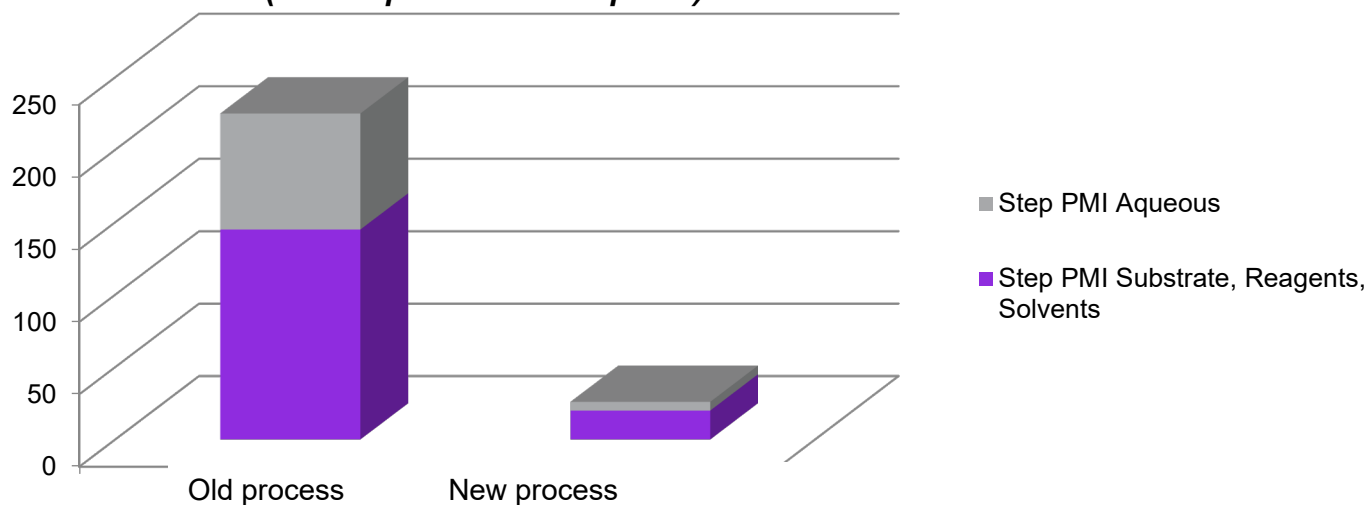


Effect on sustainability

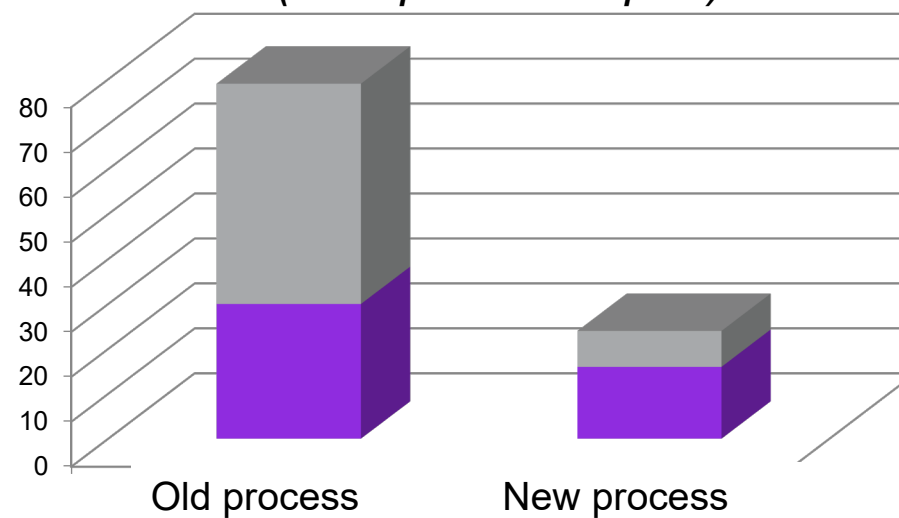
Additional decrease in PMI

Removal of undesired solvents and fluorinated waste

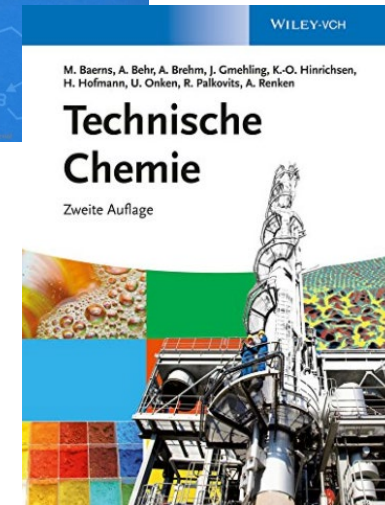
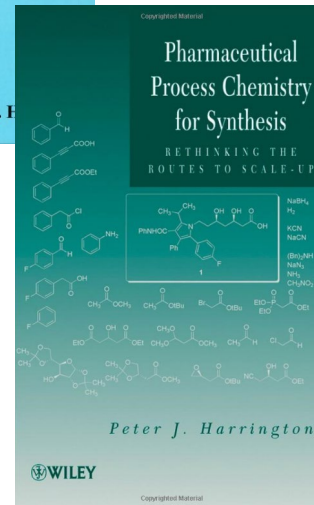
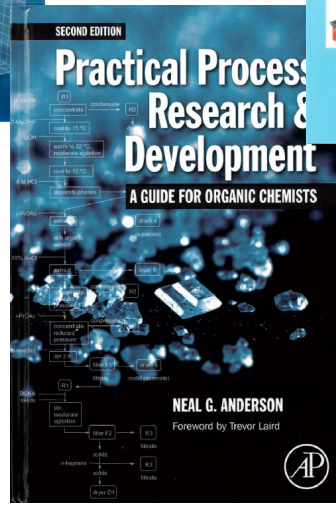
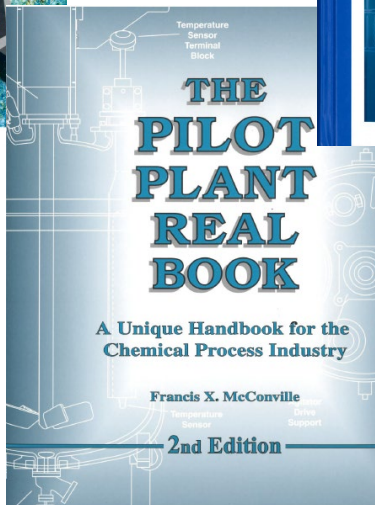
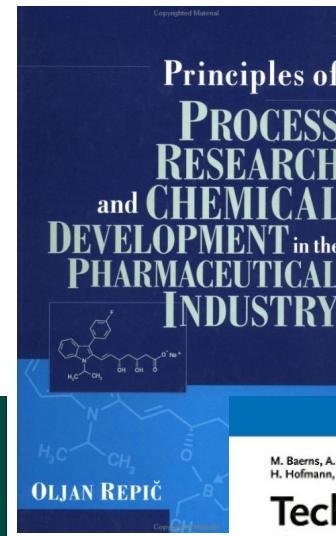
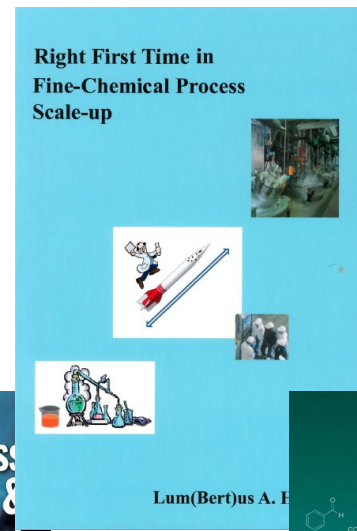
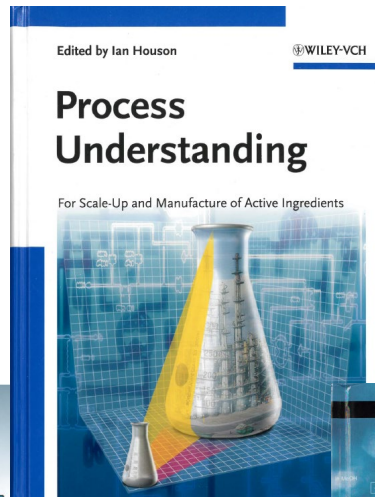
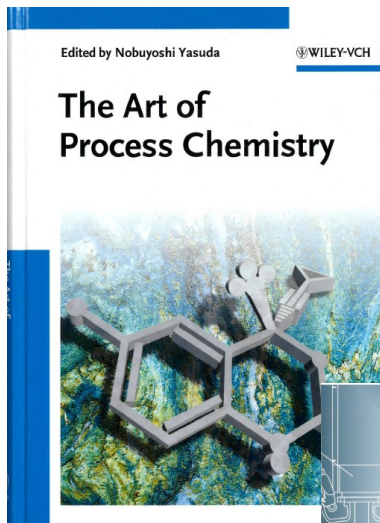
SnAr1 (3 steps telescoped)



SNAr2 (2 steps telescoped)

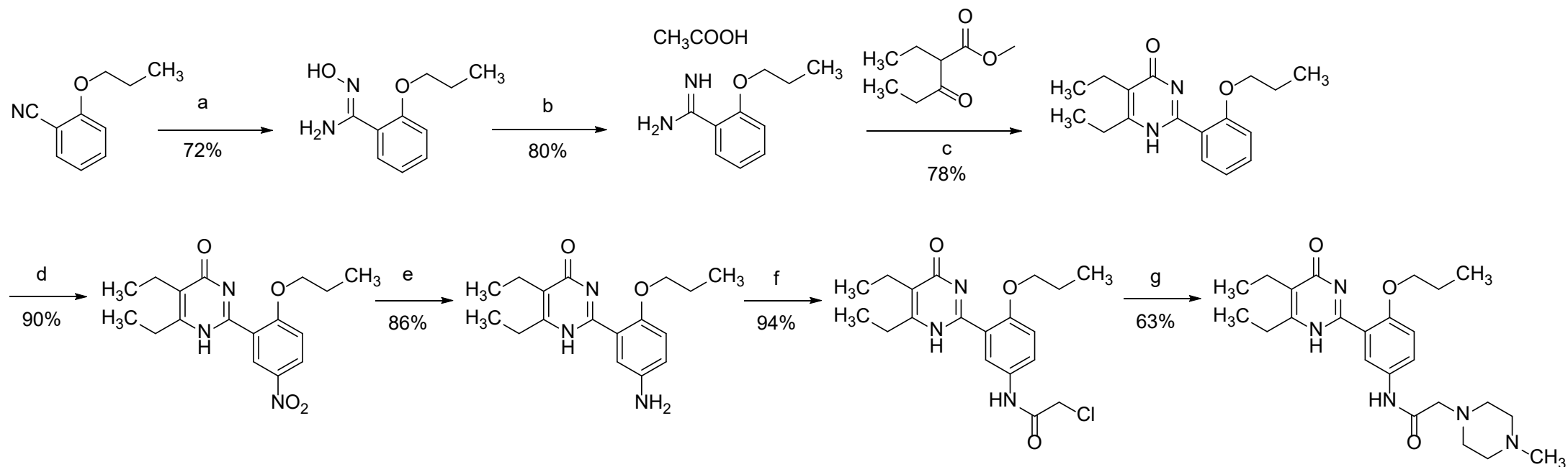


Book recommendations



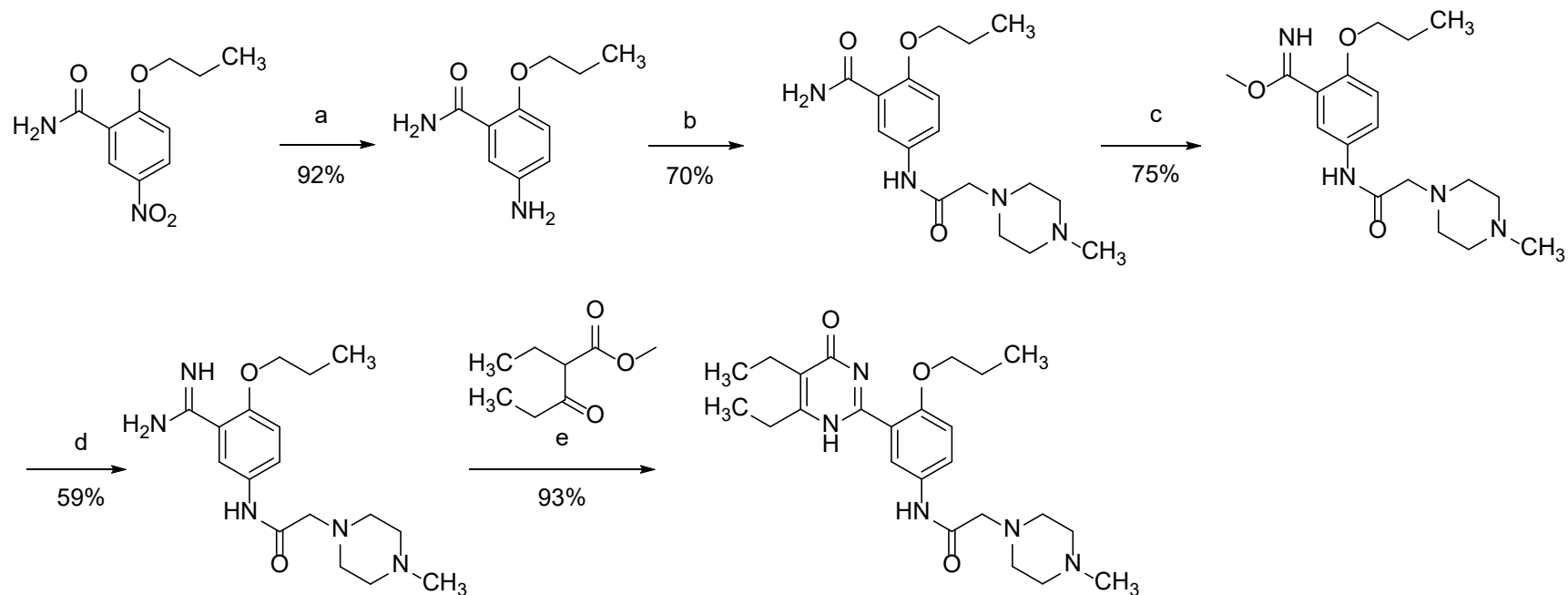
Assignment 2025

Synthesis 1



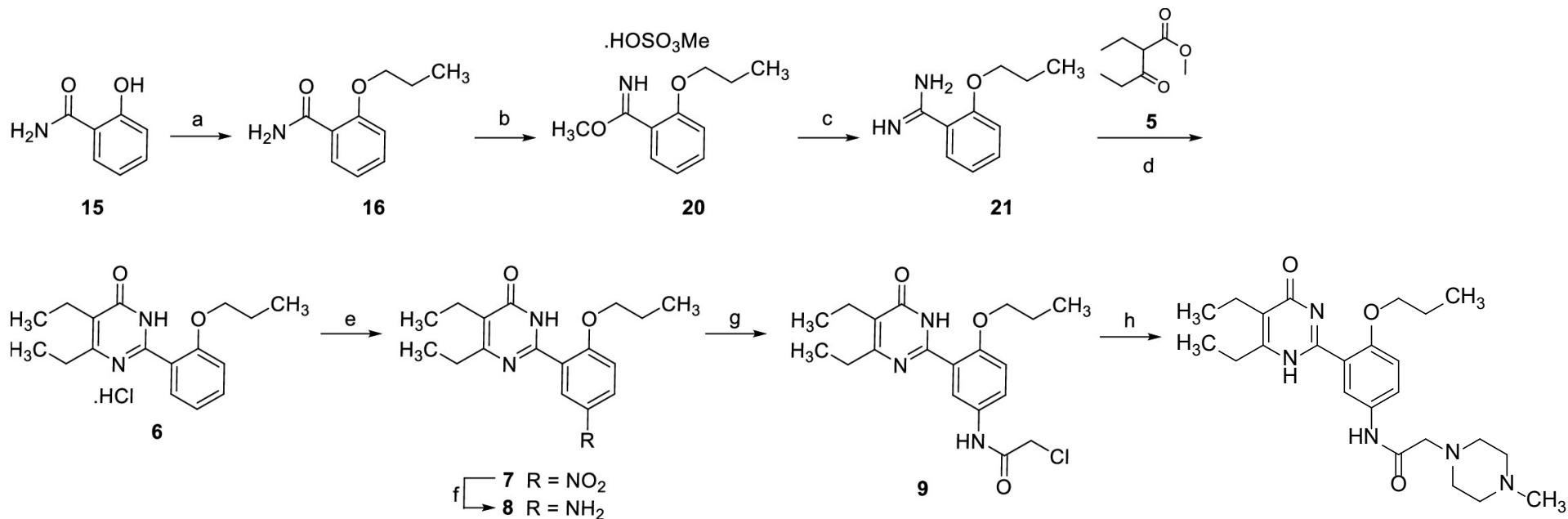
^a Reagents and conditions: (a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, K_2CO_3 , $\text{CH}_3\text{OH}/\text{H}_2\text{O}$, reflux; (b) H_2 , Pd/C, AcOH, 65 °C, 3 MPa; (c) K_2CO_3 , DMF, 100 °C; (d) HNO_3 , H_2SO_4 , 0 °C–RT; (e) H_2 , Pd/C, CH_3OH , RT; (f) chloroacetyl chloride, Et_3N , DCM, 0 °C; and (g) 1-methylpiperazine, Et_3N , DMF, 60 °C.

Synthesis 2



^a Reagents and conditions: (a) H_2 , Ni, CH_3OH , RT; (b) (4-methylpiperazin-1-yl)acetic acid, CDI, DCM, RT; (c) Me_2SO_4 , K_2CO_3 , DMF, 40–50 °C; (d) NH_3 (gas), CH_3OH , 50 °C; and (e) CH_3ONa , CH_3OH , reflux.

Synthesis 3



^aReagents and conditions: (a) 1-bromopropane, NaOH, EtOH, reflux, 95%; (b) Me_2SO_4 , 70 °C, 83%; (c) $\text{NH}_3 \cdot \text{H}_2\text{O}$, MeOH, 50 °C, 93%; (d) i. toluene, reflux; ii. HCl (aq), MeOH, 83%; (e) HNO_3 , H_2SO_4 , 0–5 °C, 93%; (f) ammonium formate, Pd/C, CH_3OH , reflux, 92%; (g) chloroacetyl chloride, DCM, 0–5 °C, 89%; and (h) 1-methylpiperazine, K_2CO_3 , acetone, reflux, 82%.

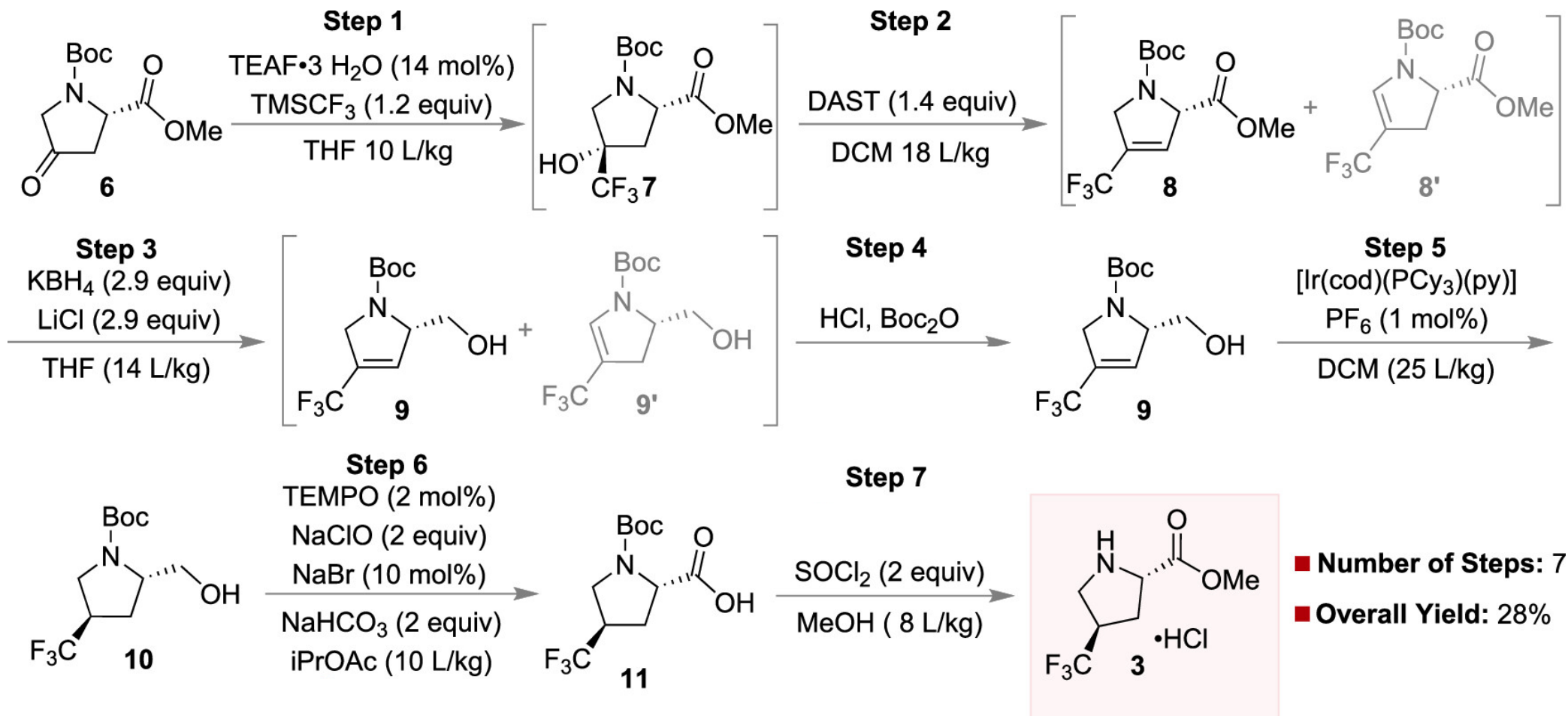
Assignment

- 1. Assume that maximum daily dose for this drug is 200 mg. What would be the maximum concentration for an impurity that:**
 - has no structural alerts?
 - has a structural alert for mutagenicity?
 - has a acceptable intake of 100 ng/day?
- 2. Discuss the pro and cons of each routes according to efficiency, thermal safety, equipment needs, environmental concerns...**
- 3. Justify your choice of the route based on pharmaceutical industry priorities.**

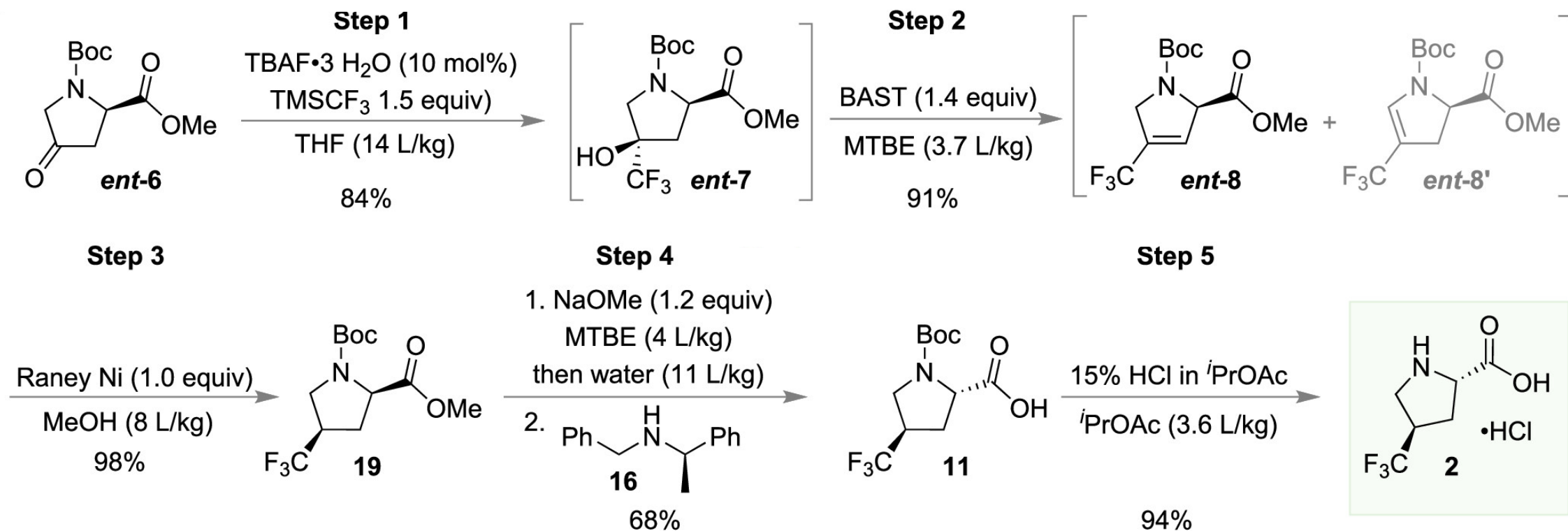
Assignment 2024



Synthesis 1



Synthesis 2



Assignment

- 1. Assume that maximum daily dose for this drug is 200 mg. What would be the maximum concentration for an impurity that:**
 - has no structural alerts?
 - has a structural alert for mutagenicity?
 - has a acceptable intake of 100 ng/day?
- 2. Discuss the pro and cons of each routes according to efficiency, thermal safety, equipment, environmental concerns...**
- 3. Justify your choice of the route based on pharmaceutical industry priorities.**

Thank you!



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078 615 2016