Sustainable Chemistry in Pharmaceutical Industry

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EPFL / ETH
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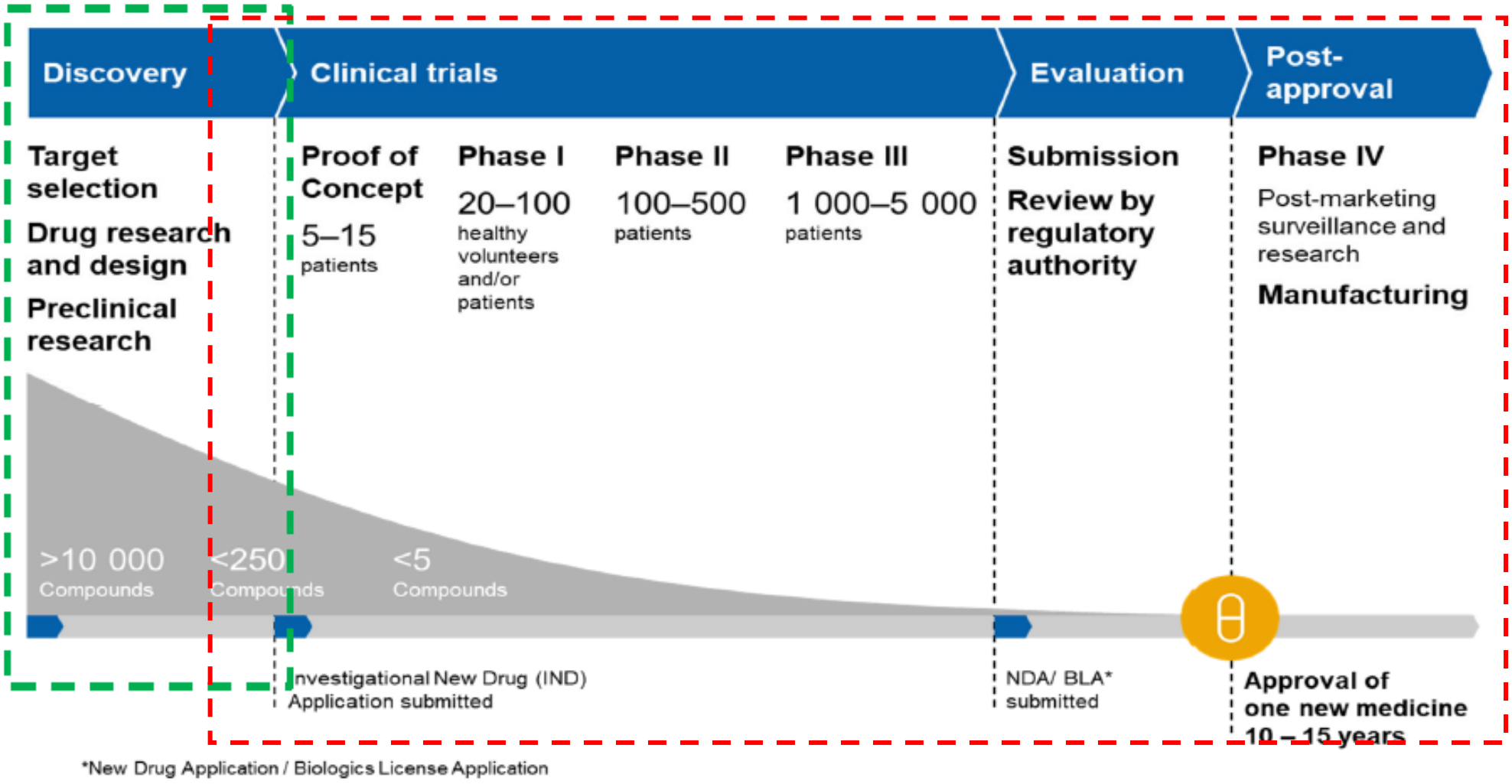
NOVARTIS | Reimagining Medicine

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 constrains?

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

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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)

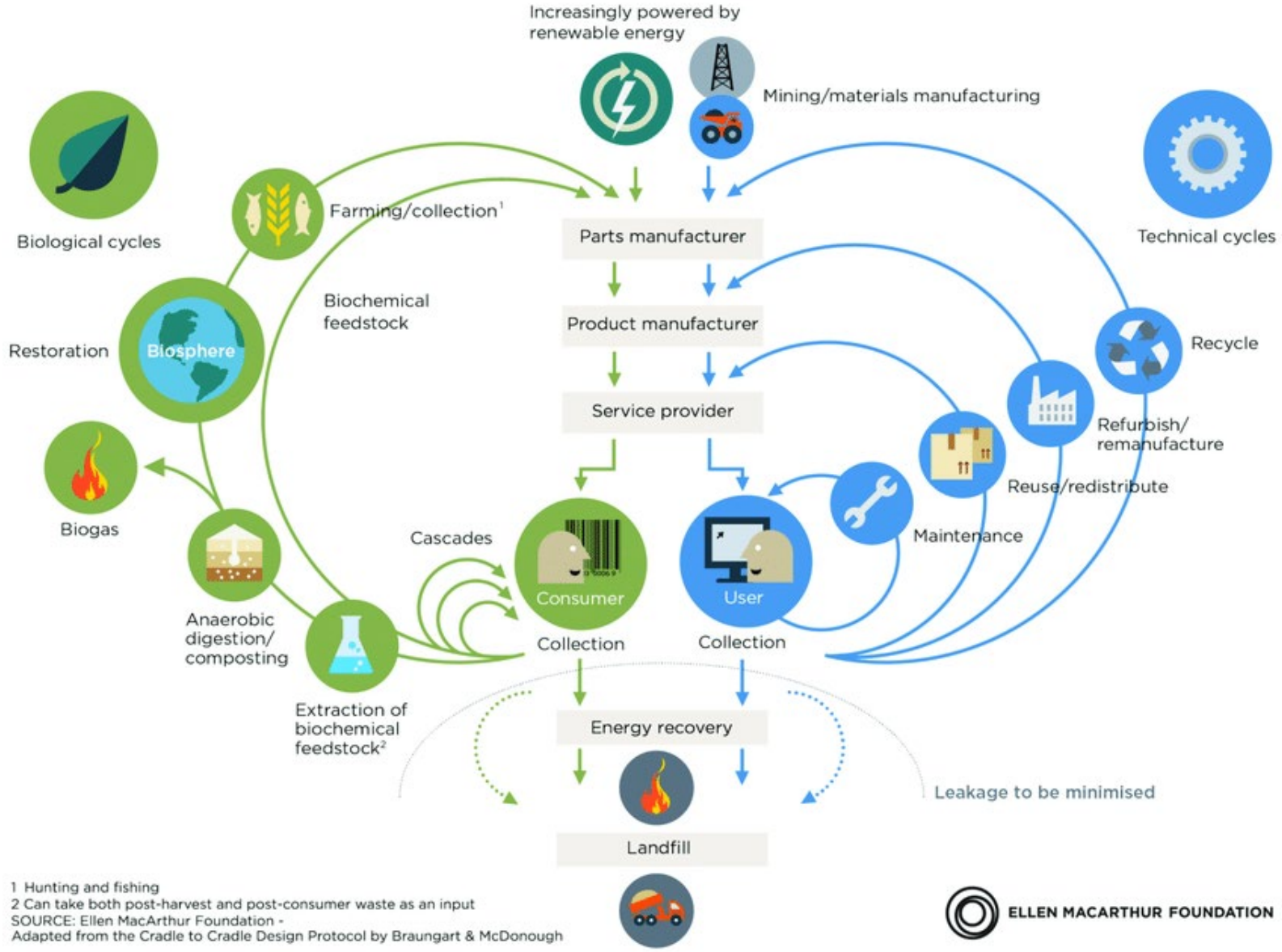
→ Tablets, capsules, suspension, powder...

→ Choice of excipients (fillers, lubricants, coatings...)

→ Packaging (blisters, dessicants...)

Pharma vs other industries

- **Highly regulated industry:**
  - Fragile population
  - Optimized uptake of product
  - “Therapeutic advantage” is fading away
- **Usually higher molecular complexity**
  - Longer synthesis
  - Complex transformation
- **Relatively low volumes to produce**


Increasingly powered by renewable energy
Mining/materials manufacturing
Biological cycles
Farming/collection[1]
Technical cycles
Parts manufacturer
Biochemical feedstock
Product manufacturer
Restoration
Biosphere
Recycle
Service provider
Refurbish/ remanufacture
Biogas
Reuse/redistribute
Maintenance
Cascades
Consumer
User
Anaerobic digestion/ composting
Collection
Collection
Extraction of biochemical feedstock[2]
Energy recovery
Leakage to be minimised
Landfill
1 Hunting and fishing
2 Can take both post-harvest and post-consumer waste as an input
SOURCE: Ellen MacArthur Foundation -
Adapted from the Cradle to Cradle Design Protocol by Braungart & McDonough
ELLEN MACARTHUR FOUNDATION

Sustainability in Pharmaceutical Development

- **R&D**
  - Optimization of care pathways
  - Waste, energy consumption...

my green lab.

- **Manufacturing**
  - sustainable route of manufacturing, source of raw materials, green logistics, clean energy sources, waste treatment, recycle/recover...
- **Packaging**
  - materials, units per package, collection, recycability of devices and packaging...
- **Clinical trial drug supply**
  - waste reduction, stock management, shipment optimisation,...

Chemical and Analytical Development

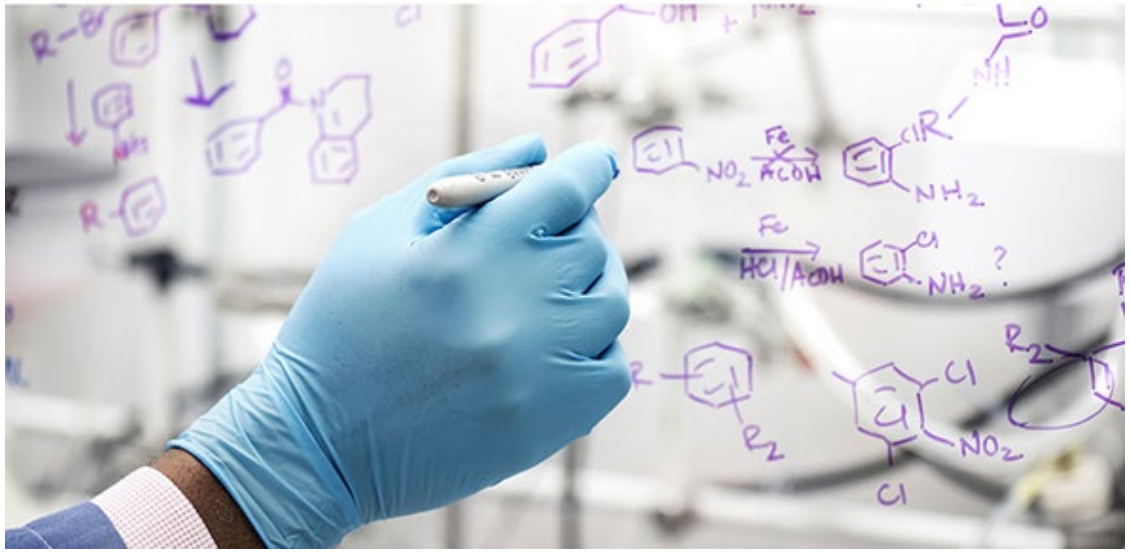
From Research to Production

from grams in research...

...to tons in production

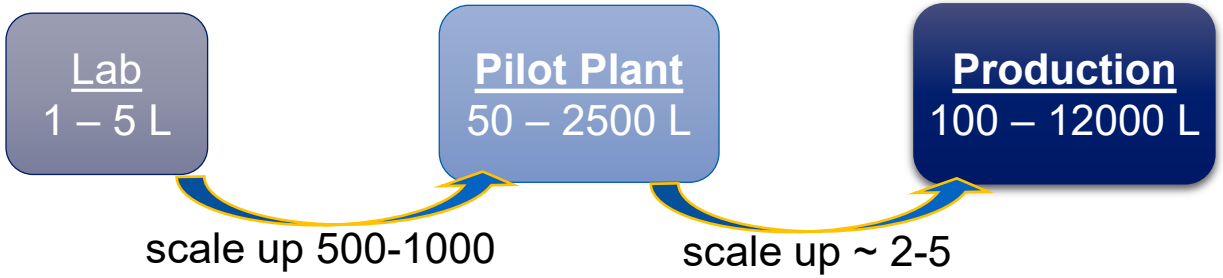
Chemical and Analytical Development

From Research to Production



Design

Supply



Drug Substance Quality Requirement

ICH Q3A guidelines for impurities in new drug substance:

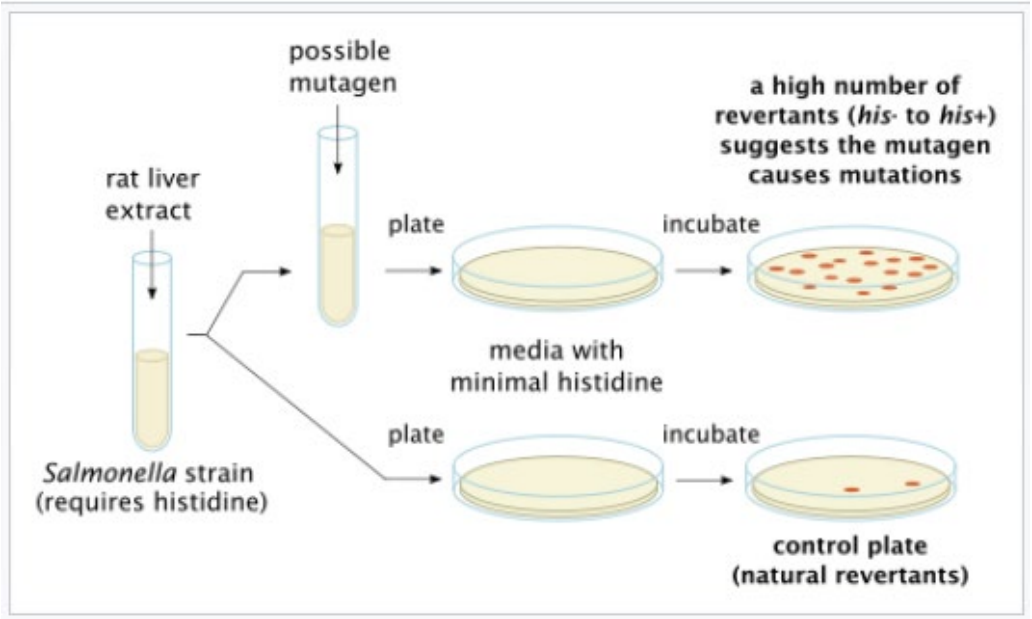
- **Reporting Threshold:** A limit above which an impurity should be reported.
- **Identification Threshold**: A limit above which an impurity should be identified.
- **Qualification Threshold**: A limit above which an impurity should be qualified.

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 µg/day, which correspond to a statistical risk of 10^{-5} of cancer for lifetime exposure.
- From the TTC limit, acceptable intake are defined for development:

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

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

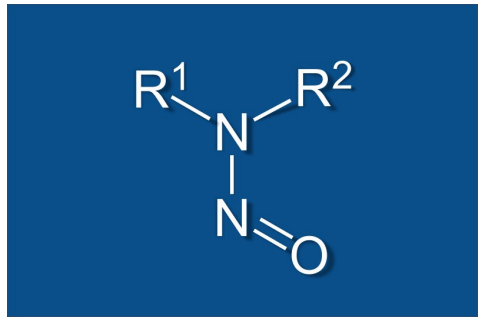
Nitrosamines – a new level of complexity

Nitrosamine are suspected highly carcinogenic compounds.

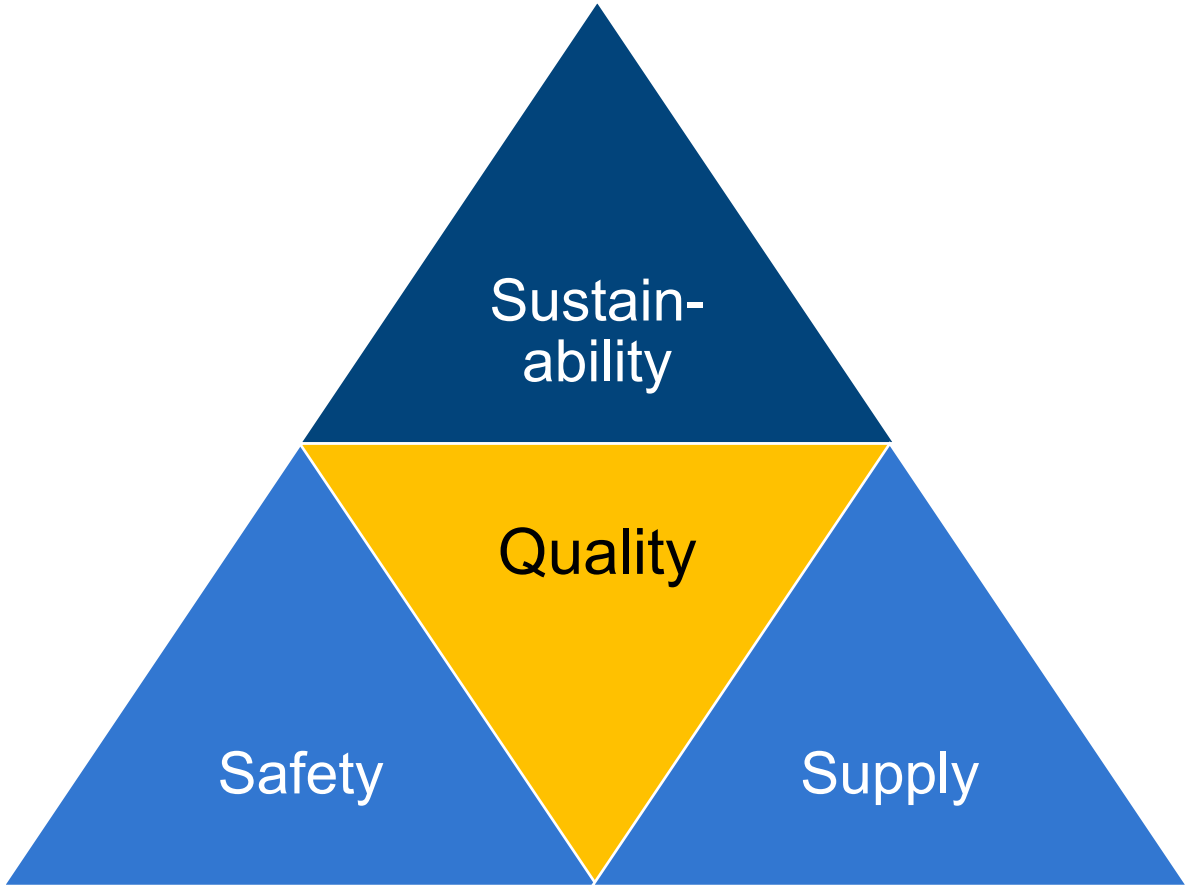
They can easily be formed from secondary amines and a nitrosating species.

Known nitrosating species are present in the air (NOx), 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 pratical 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 bening
- 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	• Process Safety • Exposure to substances harmful to health
Environmental	• Volume of wasted natural resources • Substances harmful to the environment
Legal	• Infringement of intellectual property rights • Regulations that control use of reagents and intermediates
Economics	• Meeting cost of goods target for future market • Investment costs to support development quantities
Control	• Control of quality parameters • Control of chemistry and physical parameters
Throughput	• Time scale of manufacture in available plant • Availability of raw materials

The Novartis Labelling Process

PMI

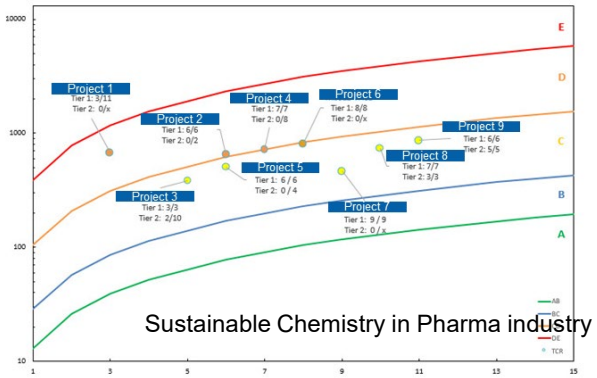
- Process Mass Intensity (all materials used for synthesis, isolation, purification)
- **PMI** $= \frac{\text{Quantity of raw materials input (kg)}}{\text{Quantity of bulk API out (kg)}}$

TCR

- Total Carbon Dioxide Release (CO_2 release by waste incineration per kg API)
- **TCR** $= \text{PMI}_{\text{organic}} \times 2.3\ \text{kg}\ CO_2 + \text{PMI}_{\text{aqueous}} \times 0.63\ \text{kg}\ CO_2$

Steps

- Number of chemical transformations required to reach the respective molecule



Which synthetic route is the best one?

Comparison of synthetic routes

$$\mathrm{iGAL} = \mathrm{mGAL}/1000 \times \mathrm{FMW} = 0.403 \times \mathrm{FMW}$$

iGAL: ideal green aspiration level

mGAL: API complexity adjusted pharmaceutical waste index

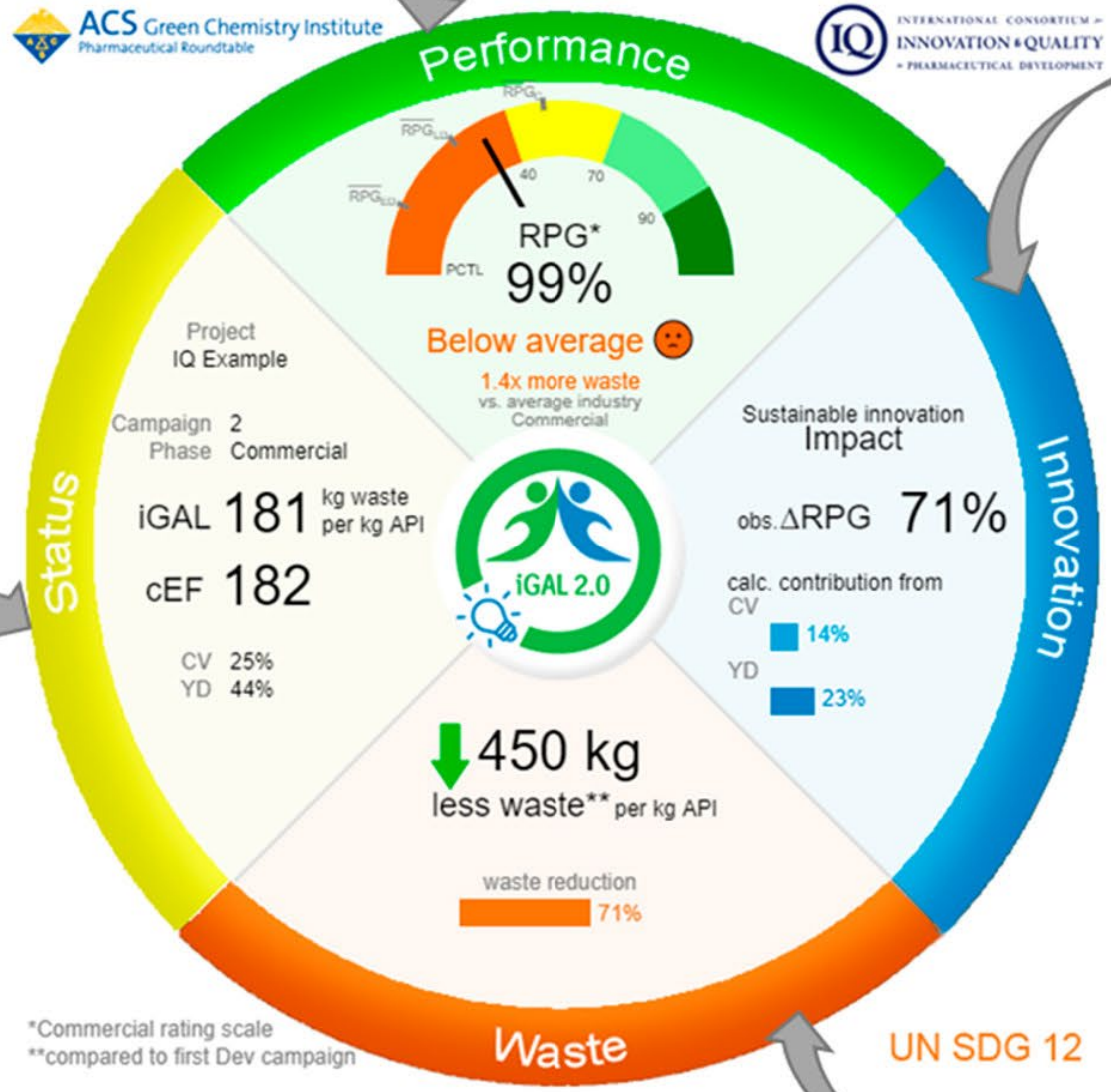
FMW: free molecular weight (i.e. MW without salt, solvate...)

ACS Sustainable Chemistry & Engineering **2022** *10* (16), 5148-5162

- reports % Relative Process Greenness (RPG) comparison to commercial industry average from our database as speedometer dashboard

$$\mathbf{RPG} = \mathbf{iGAL/cEF} \times \mathbf{100\%} \quad \text{(Eqn. 2)}$$

- reports sustainability rating (excellent, good, average and below average) based on RPG rating matrix (Table 5)
- displays how much more/less waste is generated compared to processes in the same phase (Eqn. S9 and S10)



- reports sustainable innovation impact achieved by scientists to an API process as RPG upgrade (ΔRPG, Eqn. 3)

$$\Delta\mathbf{RPG} = \mathbf{RPG(current\ process)} - \mathbf{RPG(1^{st}\ development\ process)}$$

- reports *calculated* contributions from CV_{iGAL} and YD improvements to ΔRPG (SI Chapter 6.2)

- captures API development phase, process waste (cEF), yield (YD) and convergence (CV_{iGAL})
- reports iGAL waste goal

$$\boldsymbol{iGAL} = \mathbf{0.403} \times \mathbf{FMW} \quad \text{(Eqn. 1)}$$

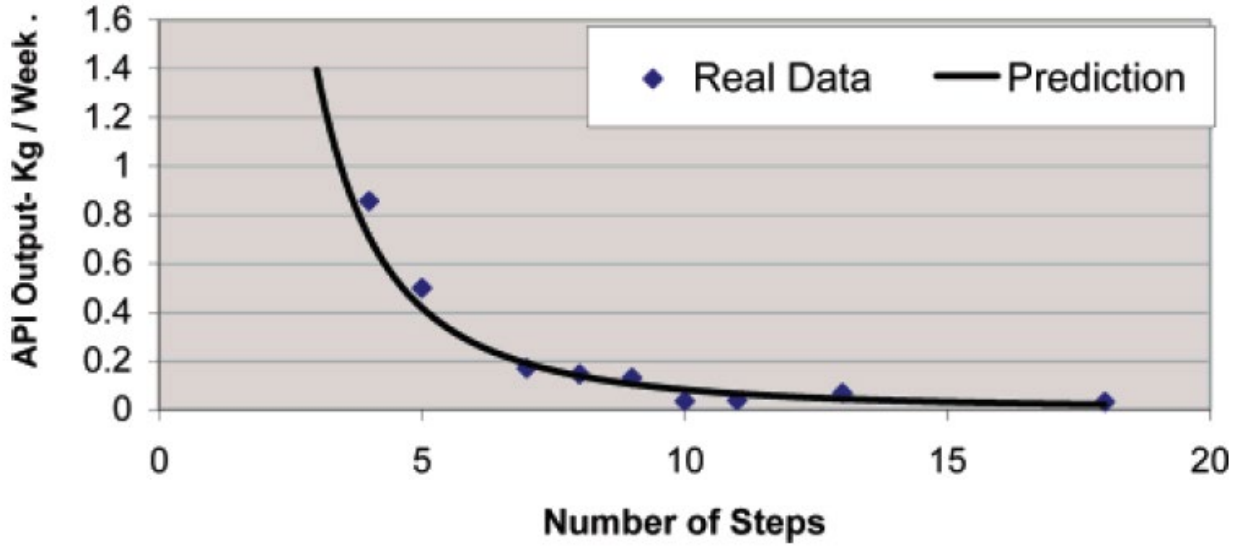
- reports sustainable innovation impact for an API process as kg and % waste reduction per kg API
- emphasizes achieved contribution to UN SDG 12

Break?

Aspects to be considered for the ideal synthesis

- Safety
- Number of steps
- Yield
- Ease of scale-up
- Robustness
- Ecologically bening
- Availability / origin of raw materials
- Complexity of synthesis
- Environmentally acceptable

Effect of sequence length on throughput

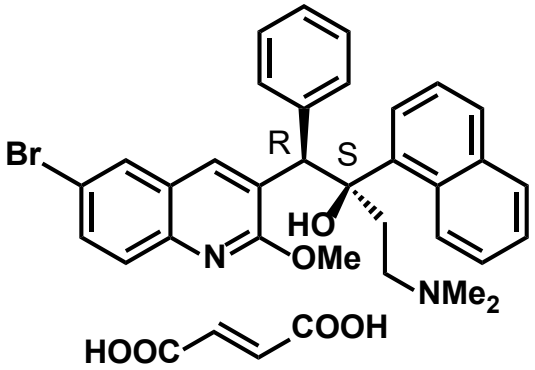


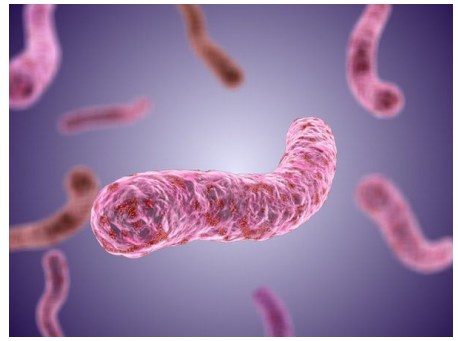
Why?

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

Yield?

Case study: Bedaquiline

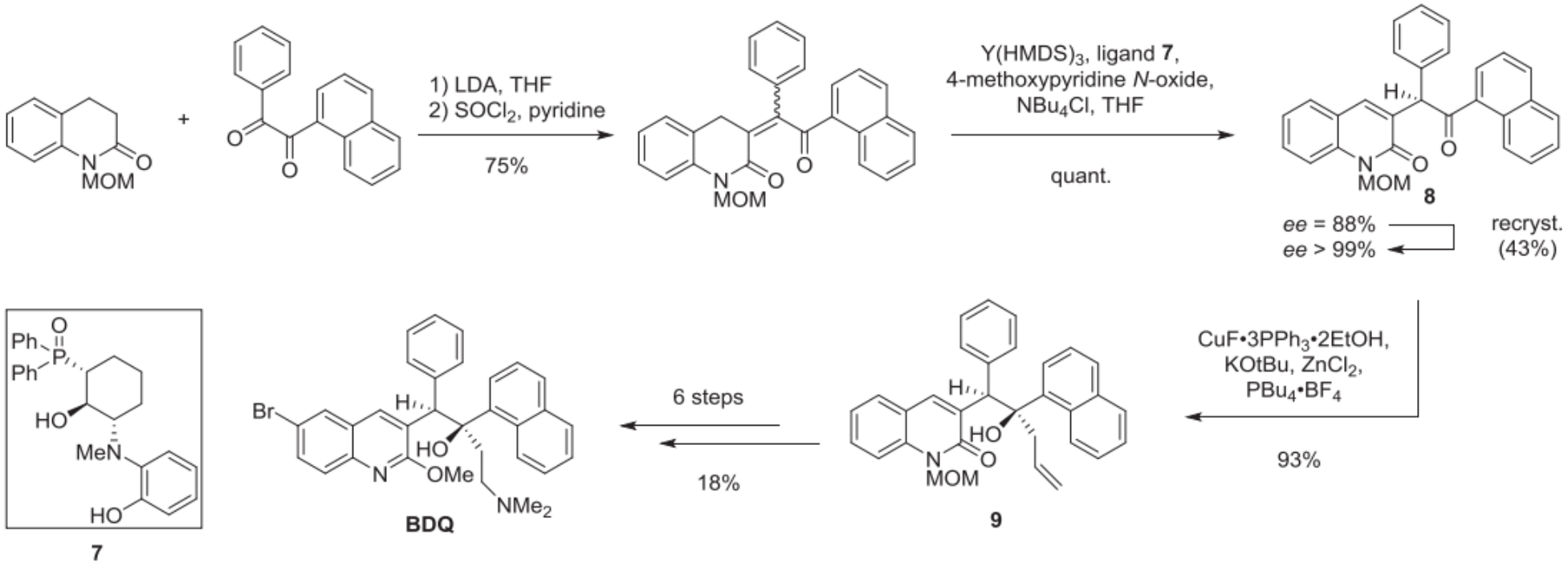




- Janssen drug approved for MDR-TB (2012/2014)
- Lethal infectious disease caused by Mycobacteria
  Mainly affects the lungs but not only (pleura, CNS, lymphatic or genitourinary system, bones and joints)
- Tuberculosis (TB) status in 2013*:
  - 9 million new cases of TB
  - 1.5 million people died from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

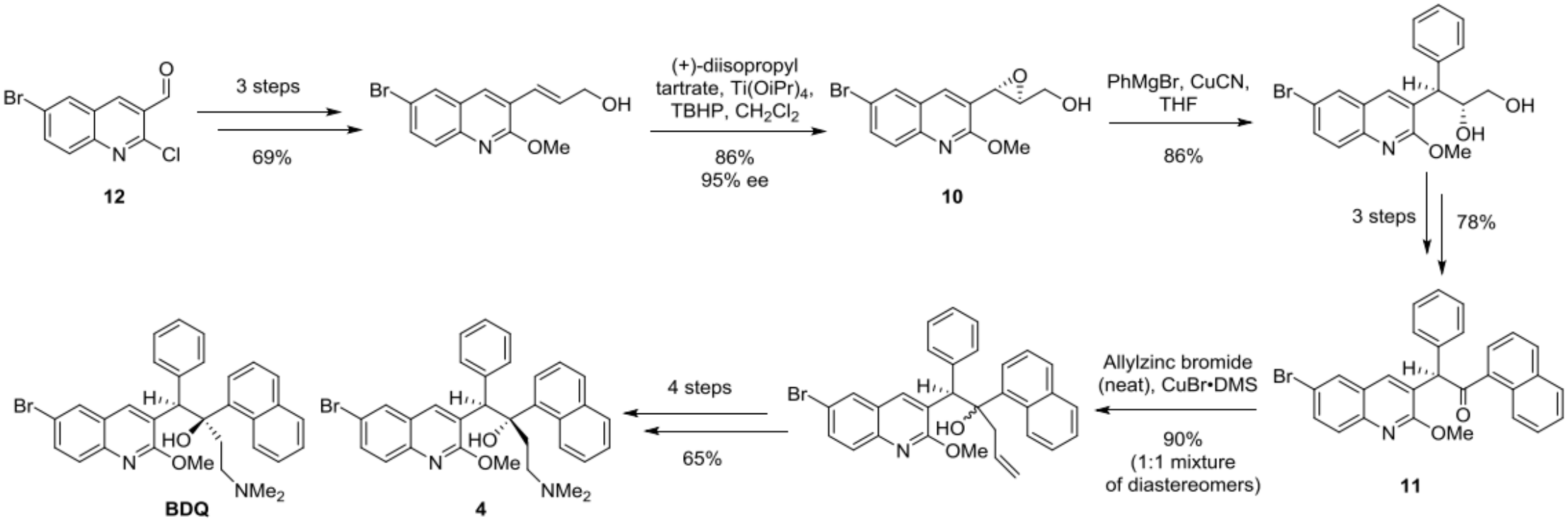
** WHO: Global tuberculosis report 2014*
*** MSF «Out of step» report, Oct 2014*

First enantioselective synthesis



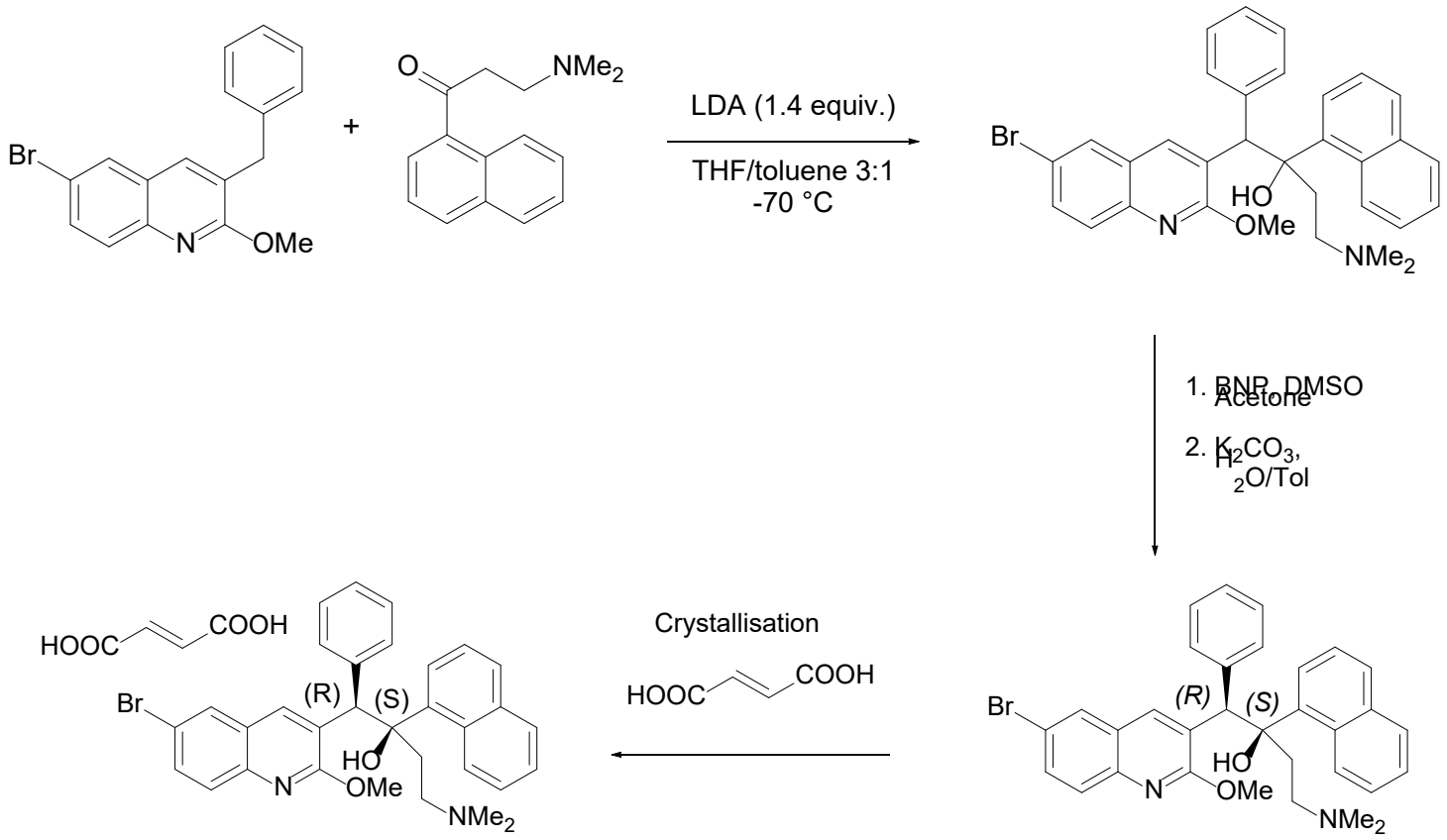
Scheme 3. Shibasaki's enantioselective synthesis of BDQ.

Academic Synthesis

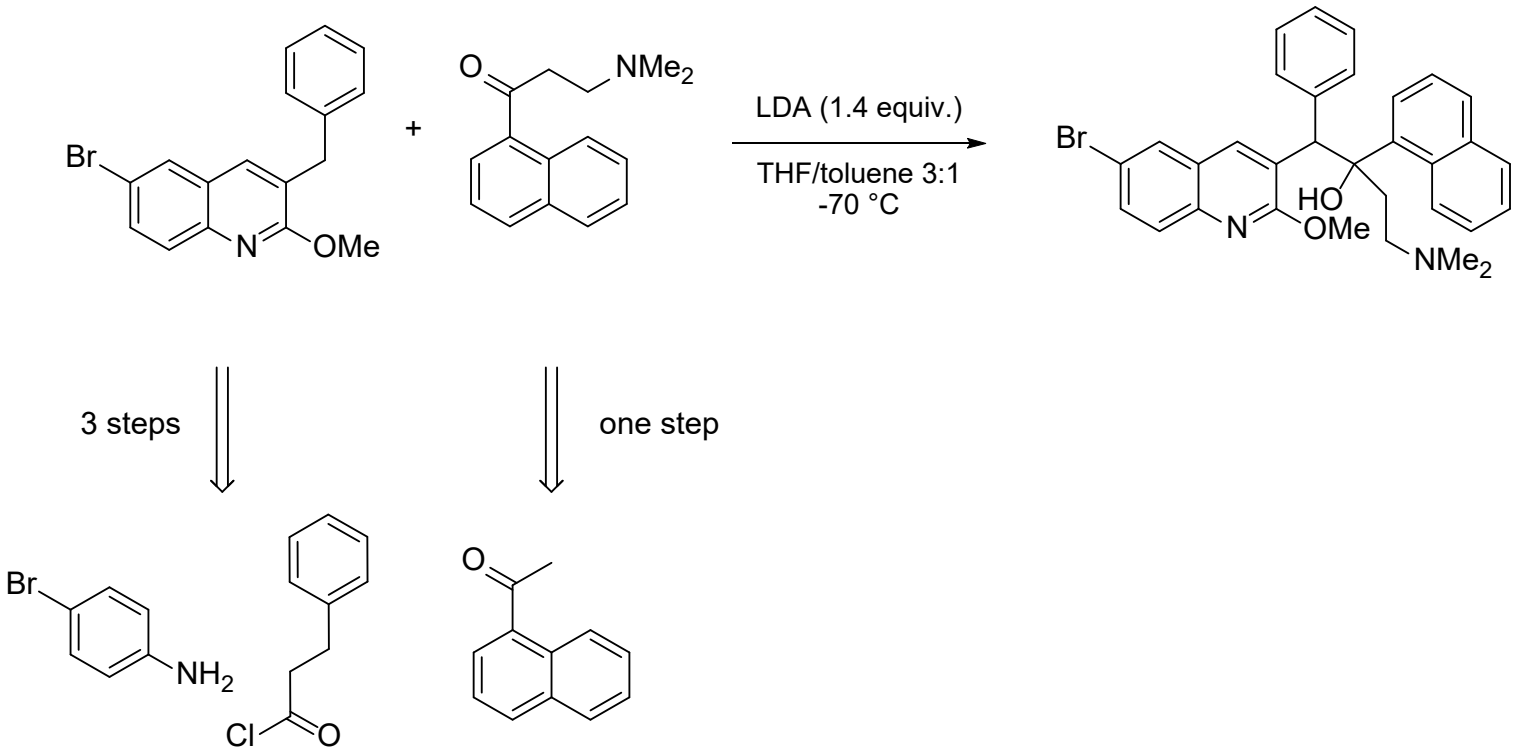


Scheme 4. Chandrasekhar's asymmetric synthesis of BDQ.

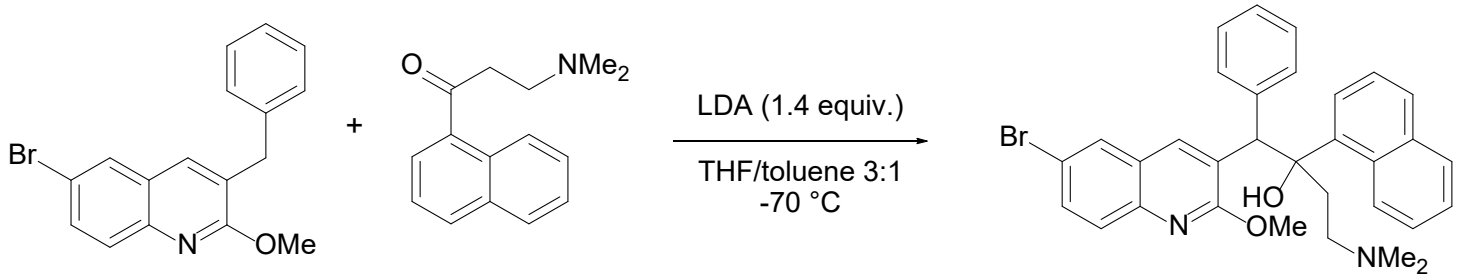
Industrial synthesis

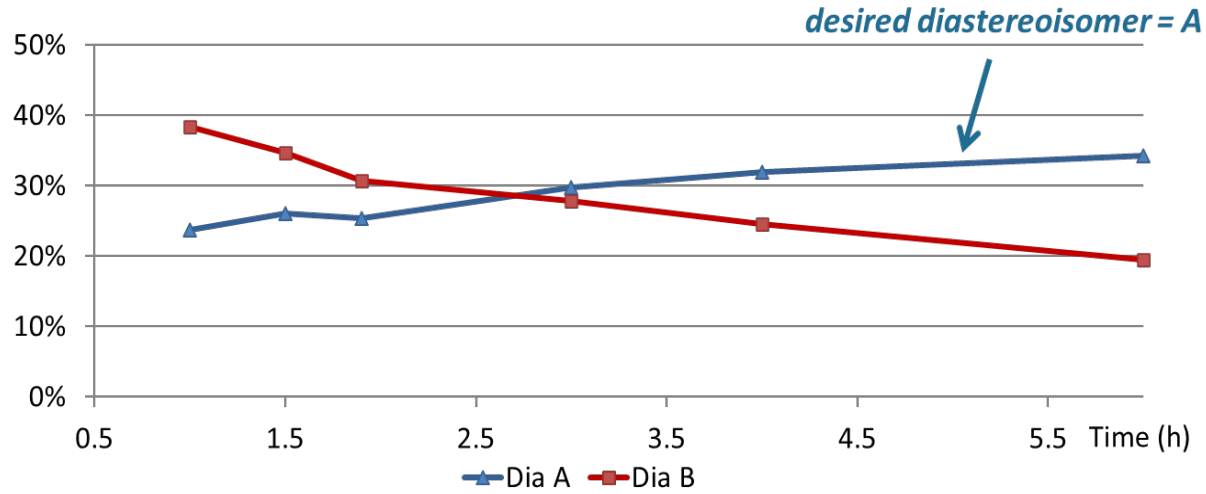


Industrial synthesis



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	*n*-BuLi/**4a**	50:50	33
3	*n*-BuLi/**4a**·LiCl[b]	45:55	31
4	*n*-BuLi/**4a**·LiCl[c]	30:70	32
5	*n*-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 ^{1}H 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.
[b]Addition of LiCl to neutral **4a**.
[c]Addition of *n*-BuLi to **4a**·HCl salt.

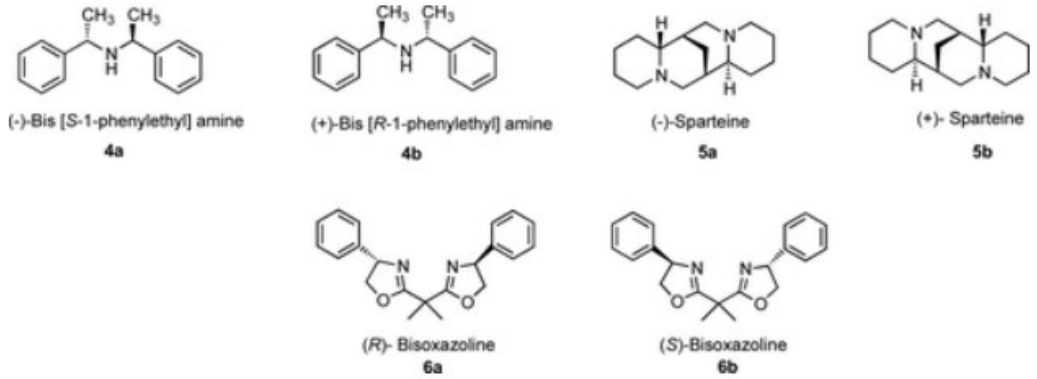


Figure 2. Chiral bases utilized in the lithiation step.

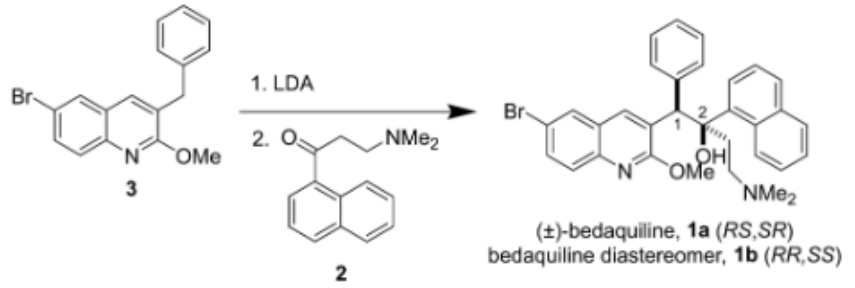
Further optimisation

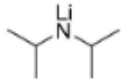
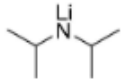
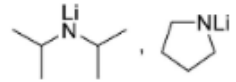
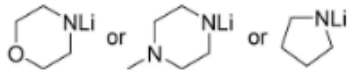
Chemistry–A European Journal | Research Article
doi.org/10.1002/chem.202201311
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

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.

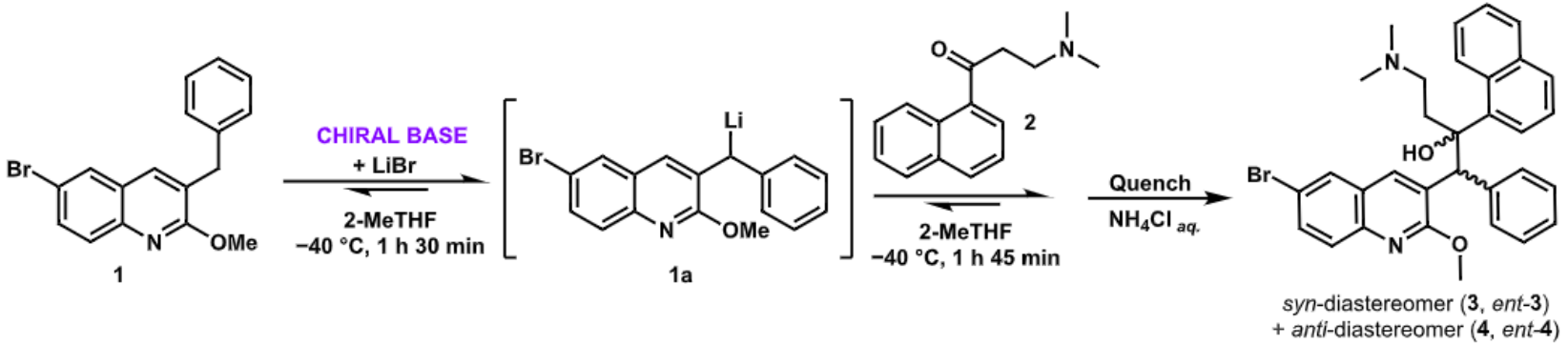
Further optimisation

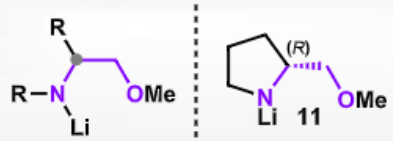
Application of Chiral Transfer Reagents to Improve Stereoselectivity and Yields in the Synthesis of the Antituberculosis Drug Bedaquiline

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)





Additive	d.r. (*syn*:*anti*)	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

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

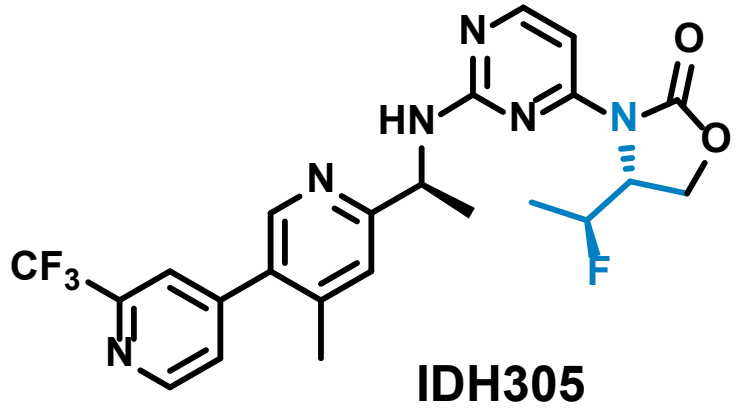
Juliana M. S. Robey,* Sanjay Maity, Sarah L. Aleshire, Angshuman Ghosh, Ajay K. Yadaw, Subho Roy, Sarah Jane Mear, Timothy F. Jamison, Gopal Sirasani, Chris H. Senanayake, Rodger W. Stringham, B. Frank Gupton, Kai O. Donsbach, Ryan C. Nelson,* and Charles S. Shanahan*

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

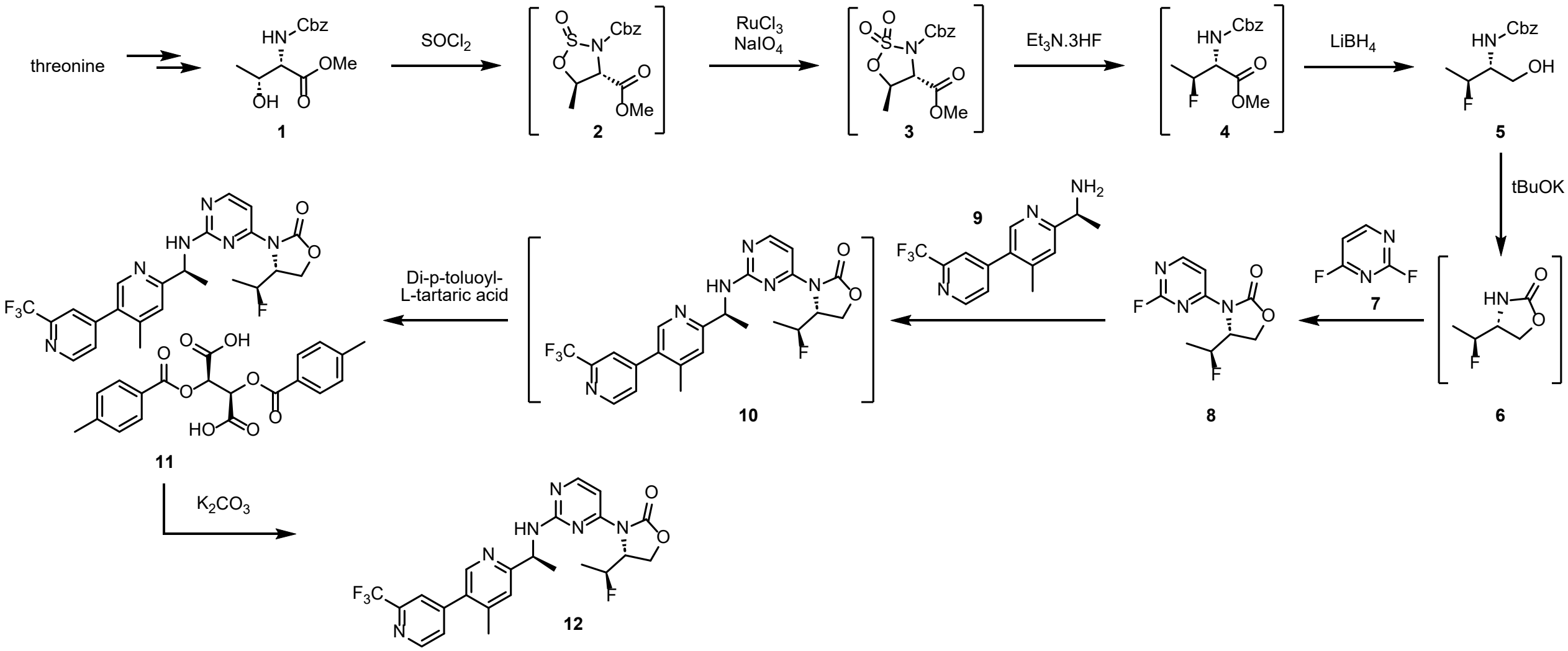
- *Therapeutic Area:* Oncology
- *Mode of action*: Inhibitor of mutant isocitrate dehydrogenase 1 (IDH1)
- *Special biological features:* potential brain penetration
- *Main potential indications*: Acute myeloid leukemia, Glioma & Glioblastoma
- *Special chemical features:* β-fluorooxazolidinone



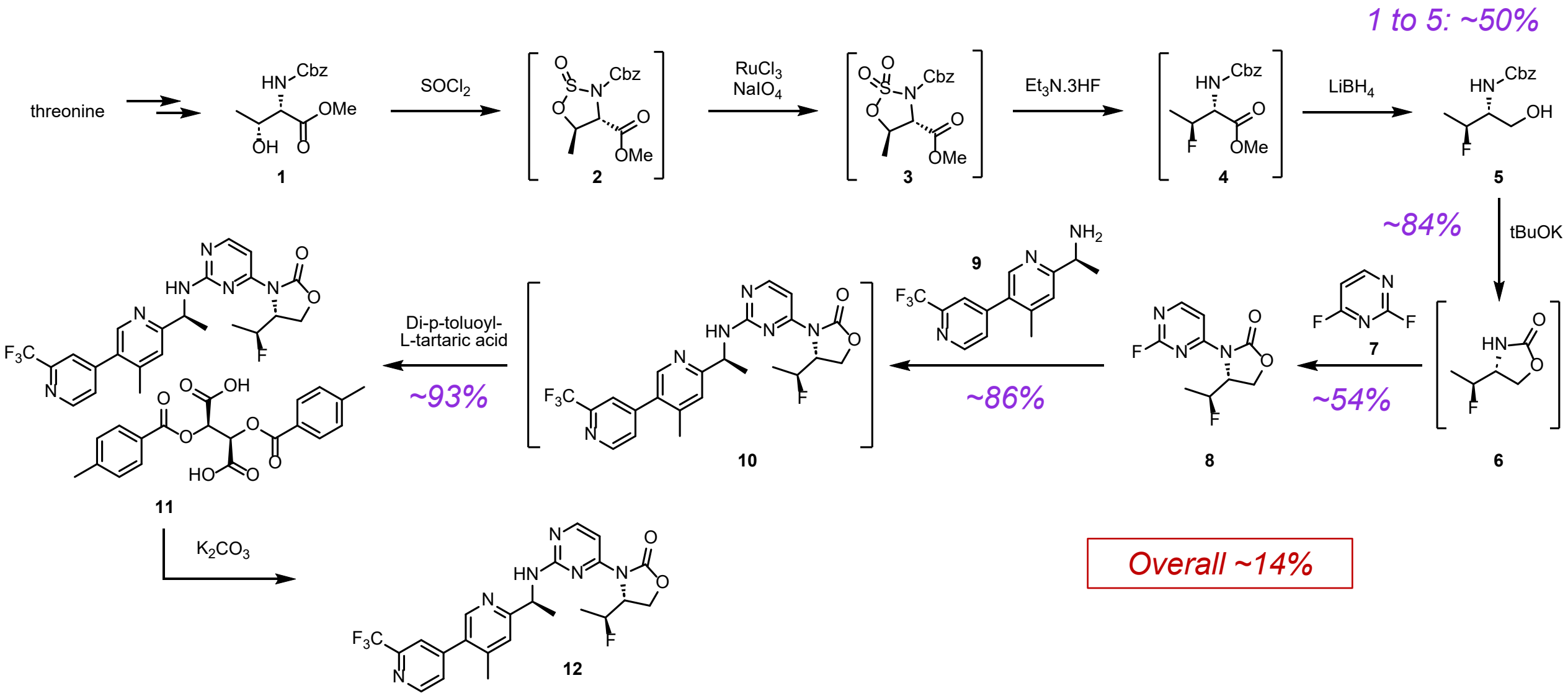
IDH305

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

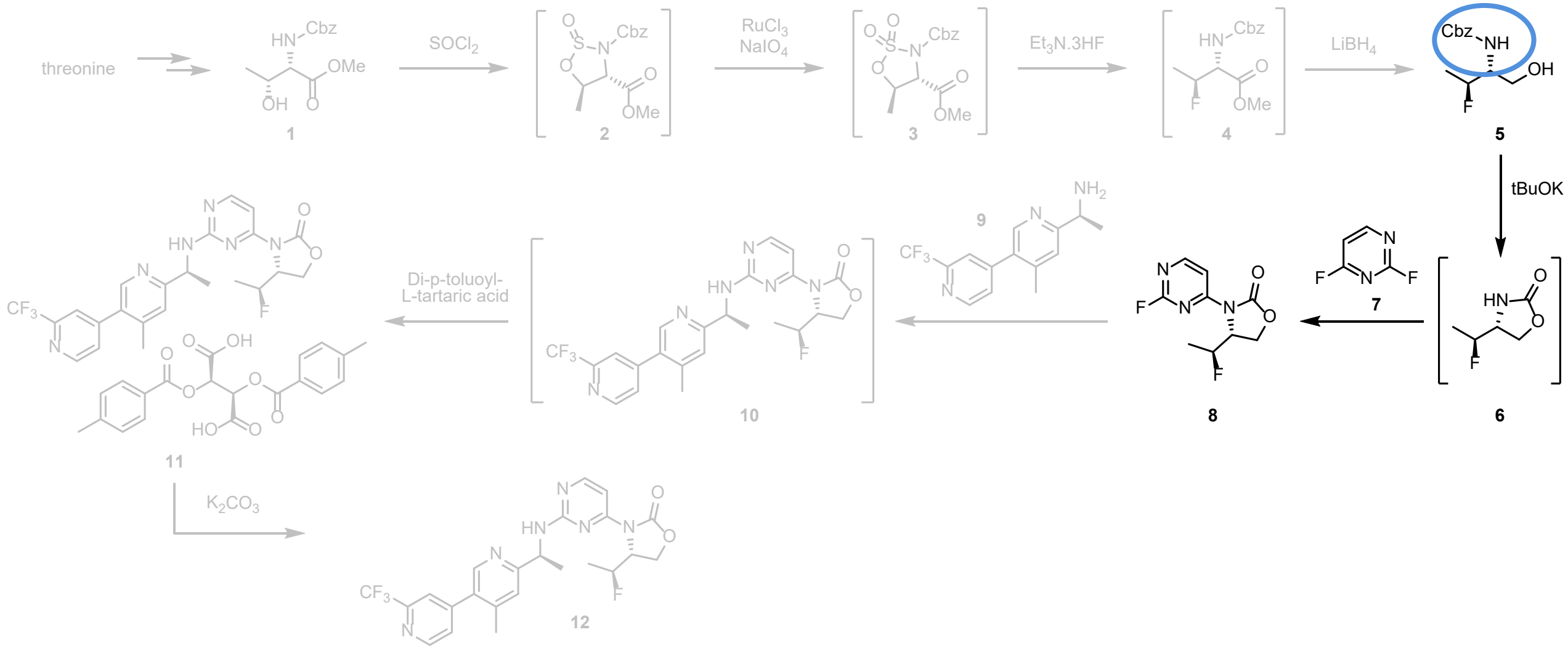
Synthesis for initial scale-up



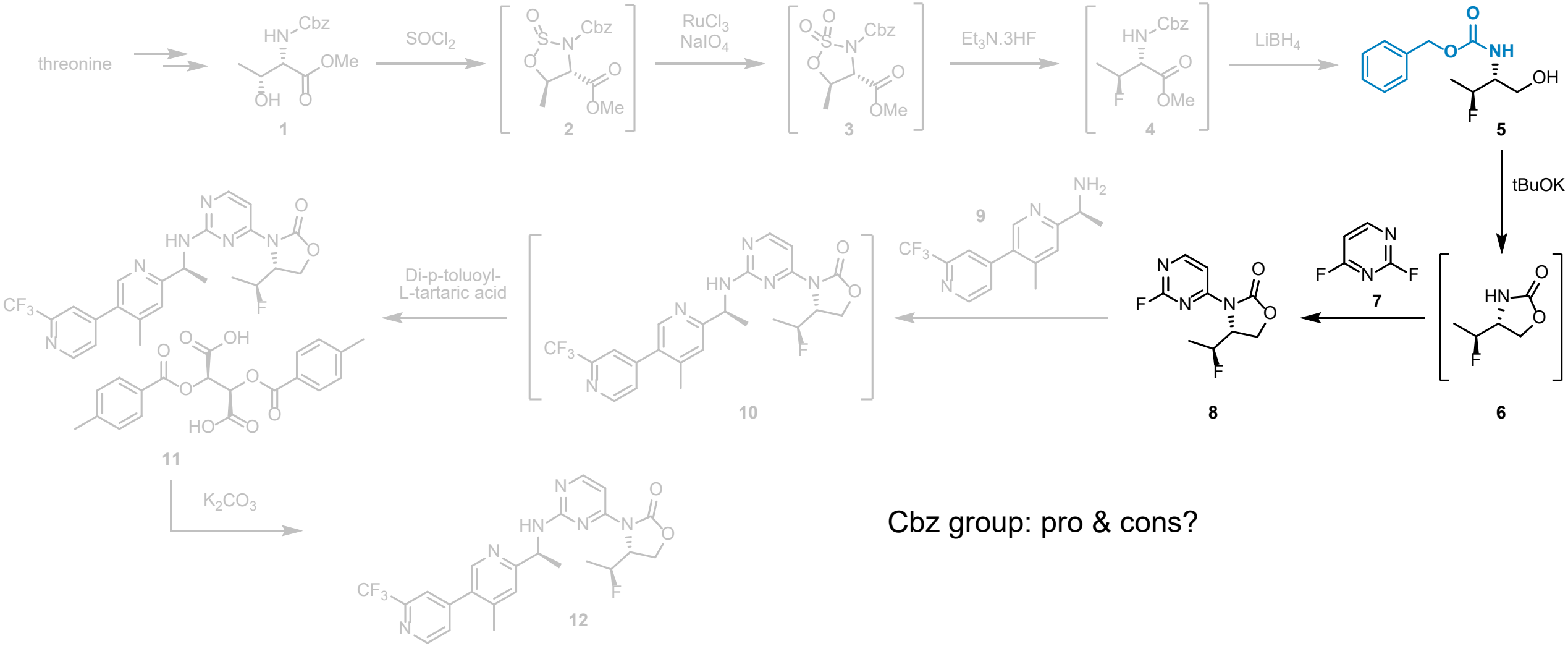
Synthesis for initial scale-up



Main chain: $SN_{Ar}1$

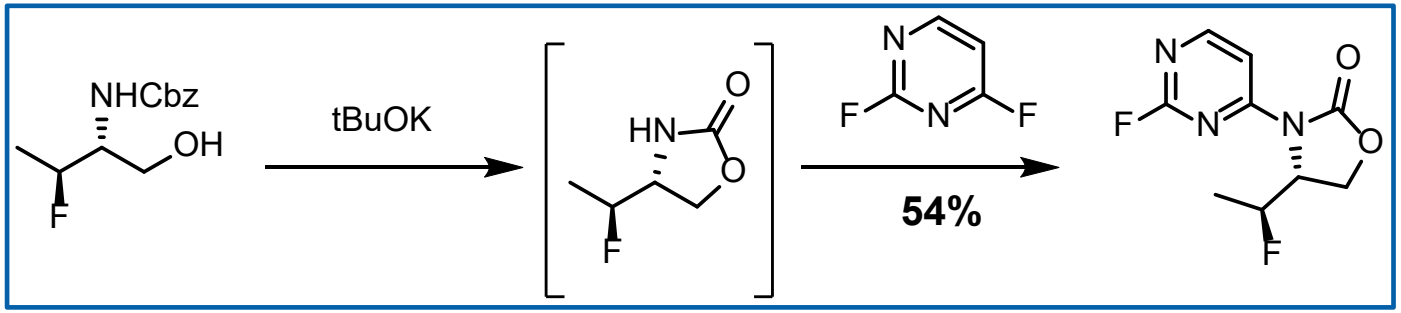


Main chain: $SN_{Ar}1$



Cbz group: pro & cons?

Opportunities



Difluoropyrimidine:

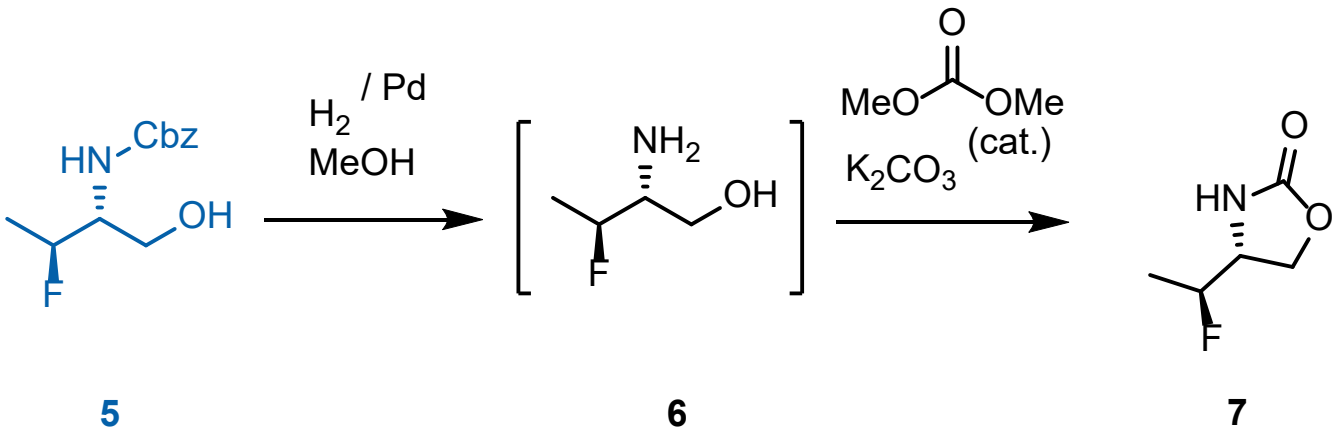
- Very sensitive to hydrolysis and residual BnOH
- Limited availability on scale
- High price

Fluorinated waste

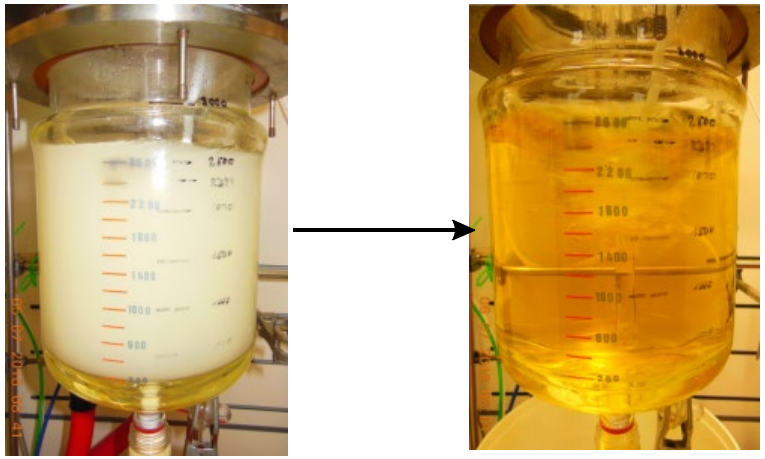
Process unfriendly reaction conditions:

- NaH, Crown ether
- N-Methylpyrrolidinone

Access to a cleaner oxazolidinone

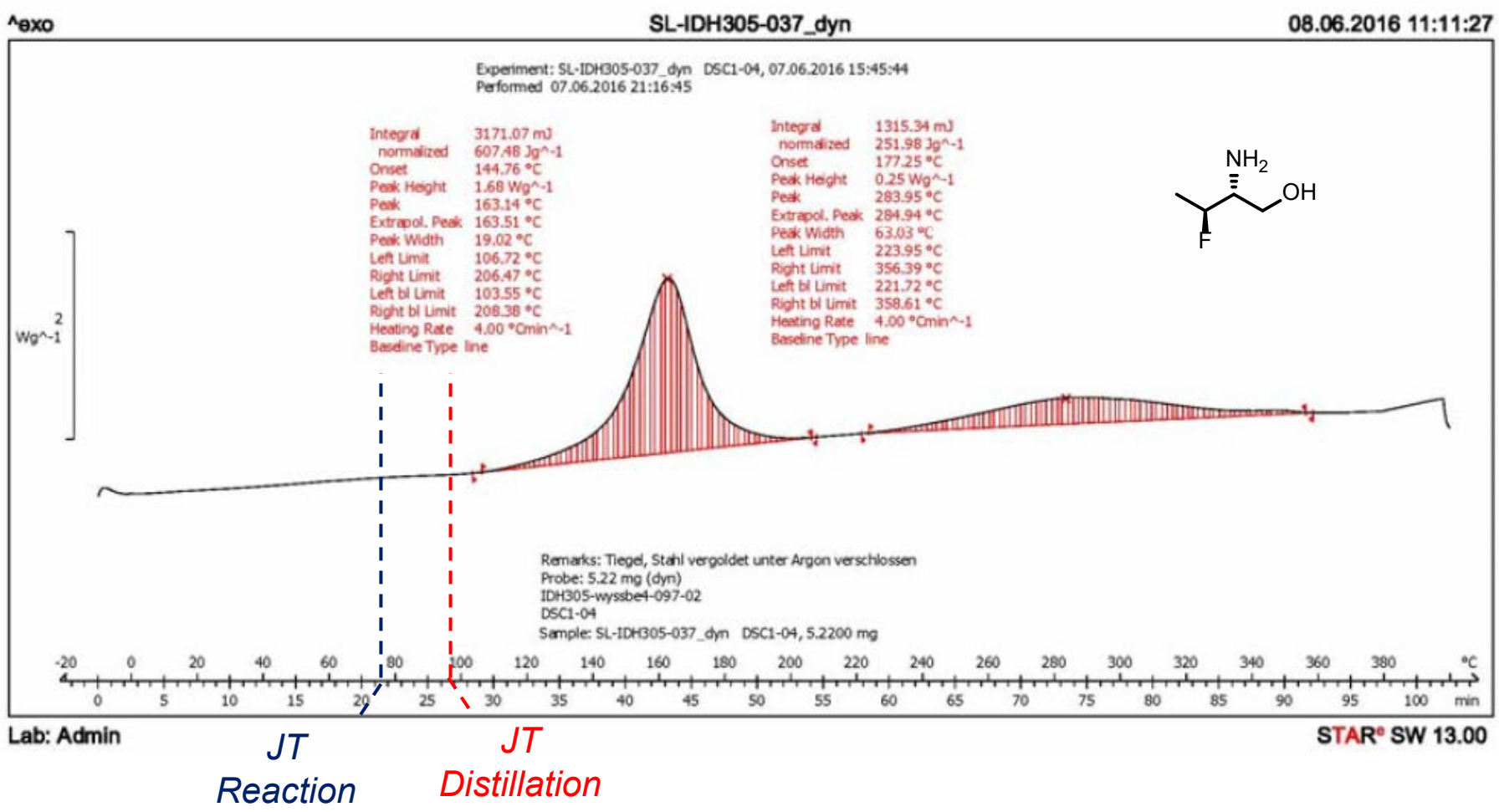


5 6 7

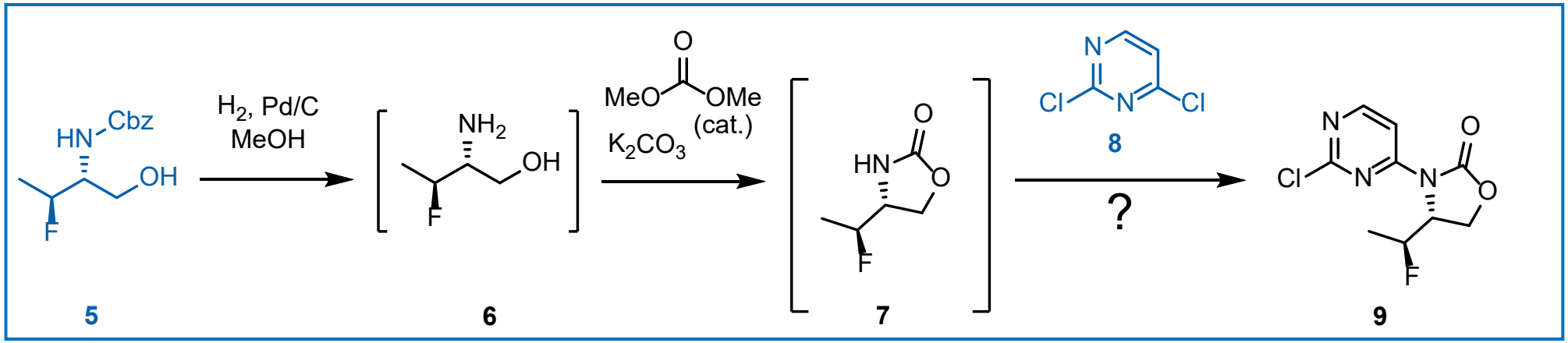


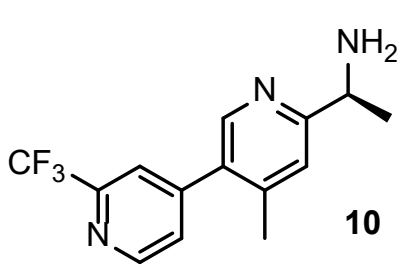
Side products?

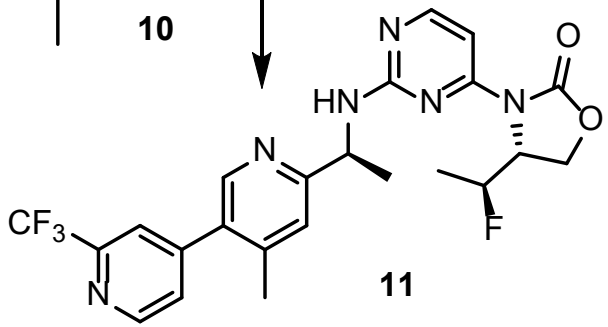
Thermal stability



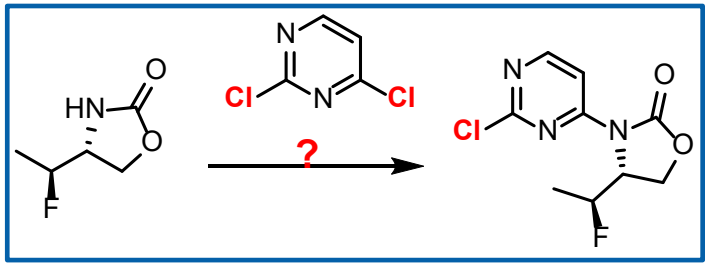
Main chain: $SN_{Ar}1$



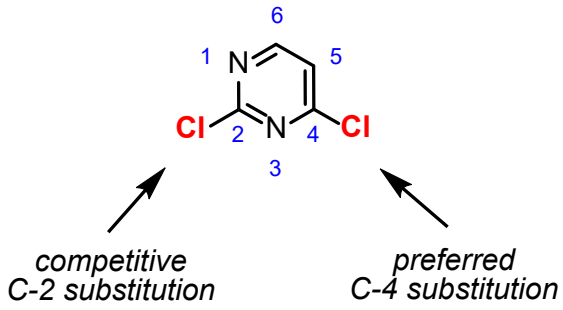




Main chain: $SN_{Ar}1$



2.4-dichloropyrimidine (DCP)



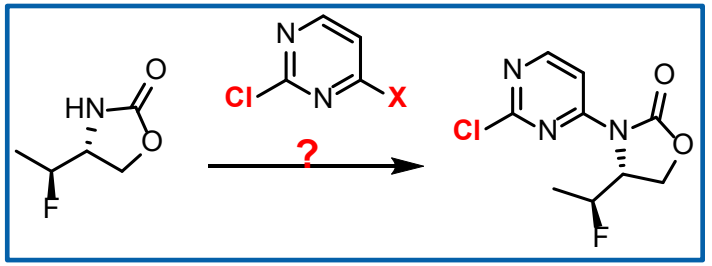
SNAr using weak nucleophiles:
- low reactivity
- uses protic polar solvents and strong bases
- regioselectivity issue between C-4 and C-2 amination

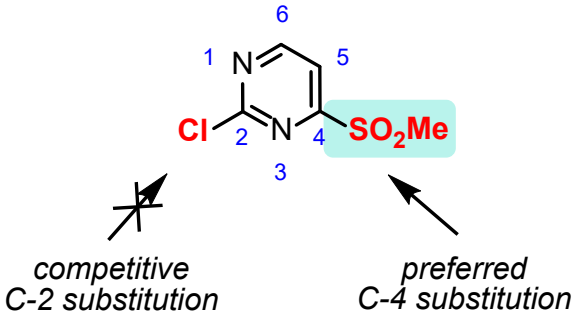
Entry	Solvent	Base (equiv)	Temp (°C)	DCP	C-4	C-2
1	THF	NaH (1.1)	60	26	**15**	14
2	Me-THF	K_2CO_3 (3)	80	49	**24**	15
3	Toluene	K_2CO_3 (3)	110	31	**28**	8
4	MeCN	K_2CO_3 (3)	60	16	**63**	13
5	Sulfolane	K_2CO_3 (3)	110	7	**72**	7
6	N-Butylpyrrolidone	K_2CO_3 (2)	80	1	**75**	5

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

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

Main chain: $SN_{Ar}1$

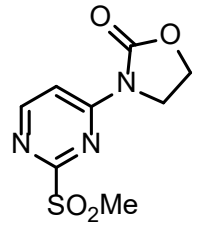




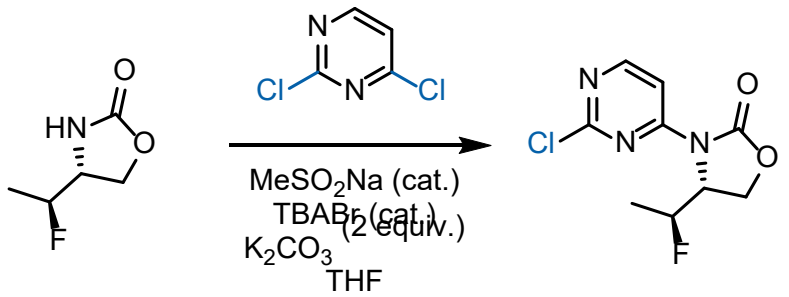
SNAr using weak nucleophiles:
- high reactivity
- excellent selectivity at C-4
- mild conditions
- unstable

Entry	SM	Additive (equiv)	yield	C-4 / C-2
1	Cl,SO_2Me	-	89	>99:1
2[a]	DCP	$MeSO_2Na$ (1)	imp + degradation	
3[a]	DCP	$MeSO_2Na$ (0.03)	22	1.3:1
4[a]	DCP	$MeSO_2Na$ (0.03) + TBABr (0.1)	91	42:1
5[a]	DCP	TBABr (0.1)	72	8:1

[a]Reaction run in THF at 50 °C using unsubstitued oxazolidinone as model substrate



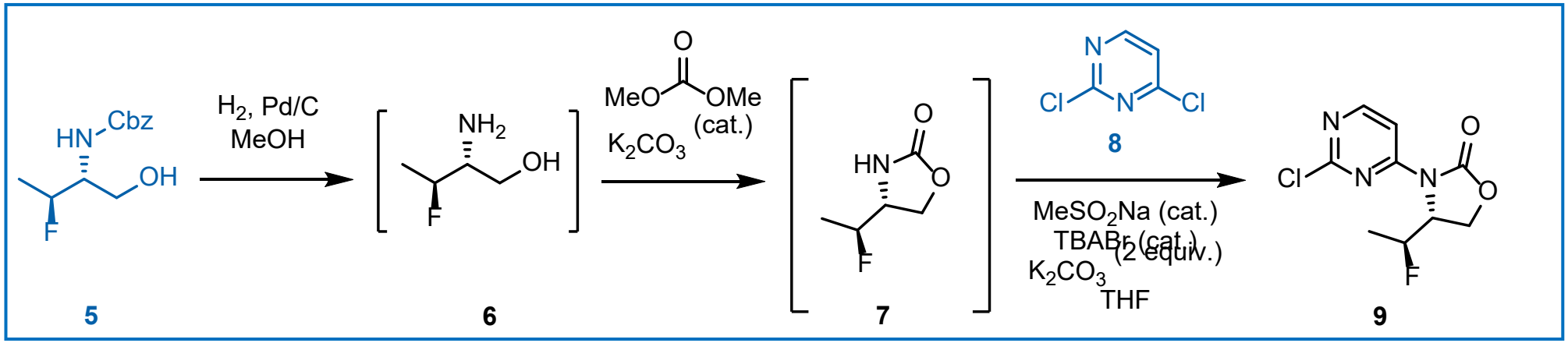
Impurity formed at high $MeSO_2Na$ loading

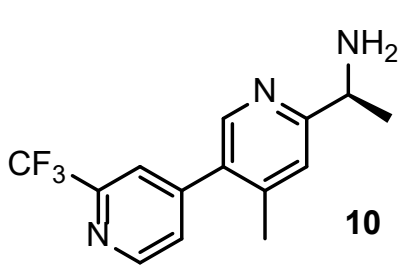


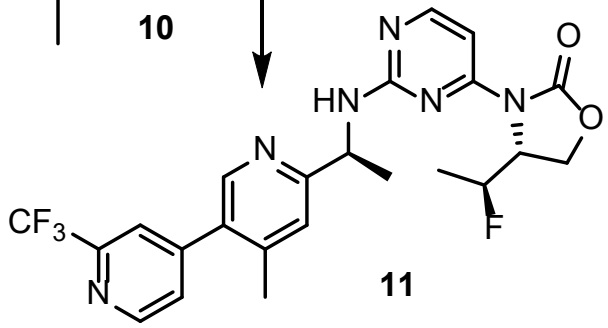
92% isolated yield
C-4/C-2: >99:1

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

Main chain: $SN_{Ar}1$



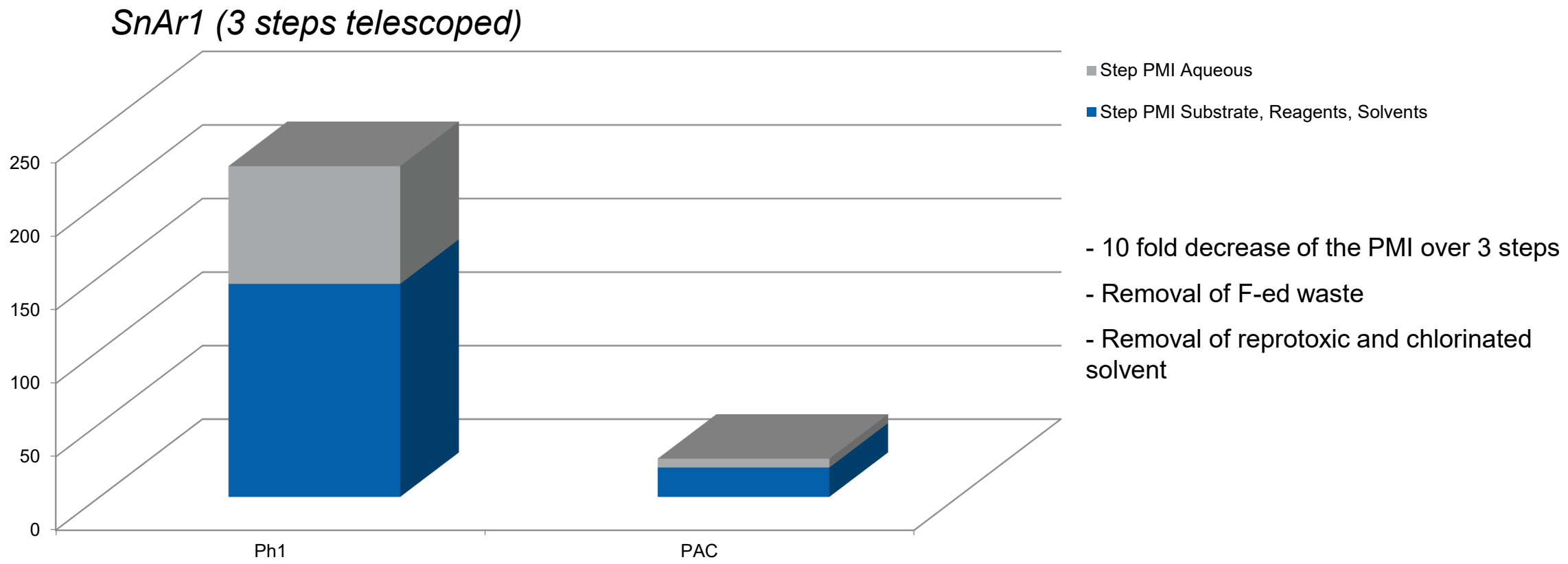




On 1 kg scale:

Isolated yield: 71.3% over 3 steps (ca. 89%/step)
Purity 99.3 A%, regioisomer 0.06 A%

Effect on sustainability



- 10 fold decrease of the PMI over 3 steps
- Removal of F-ed waste
- Removal of reprotoxic and chlorinated solvent

Break?

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

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- **Throughput**
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- **Waste**
- Intellectual property
- Equipment required

Solvent & reagents

Solvent Selection Guide – Chem21

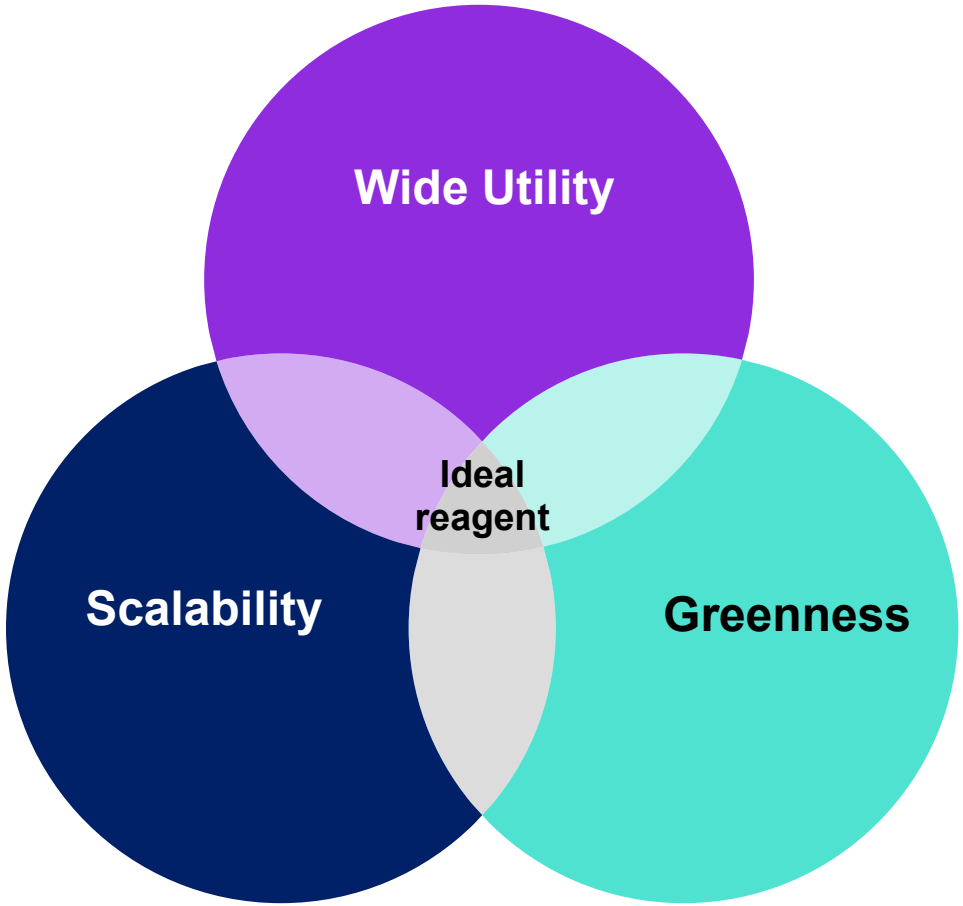
Ranking	Solvents
Recommended	Water, EtOH, iPrOH, nBuOH, AcOEt, AcOiPr, AcOnBu, PhOMe, sulfolane
Recommended or Problematic ?	MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, AcOMe, AcOH, Ac_2O
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylene, chlorobenzene, acetonitrile, DMPU, DMSO
Problematic or Hazardous ?	THF, MTBE, cyclohexane, DCM, formic acid, pyridine
Hazardous	iPr_2O, dioxane, DME, pentane, hexane, DMF, DMA, NMP, TEA, methoxyethanol
Highly hazardous	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane

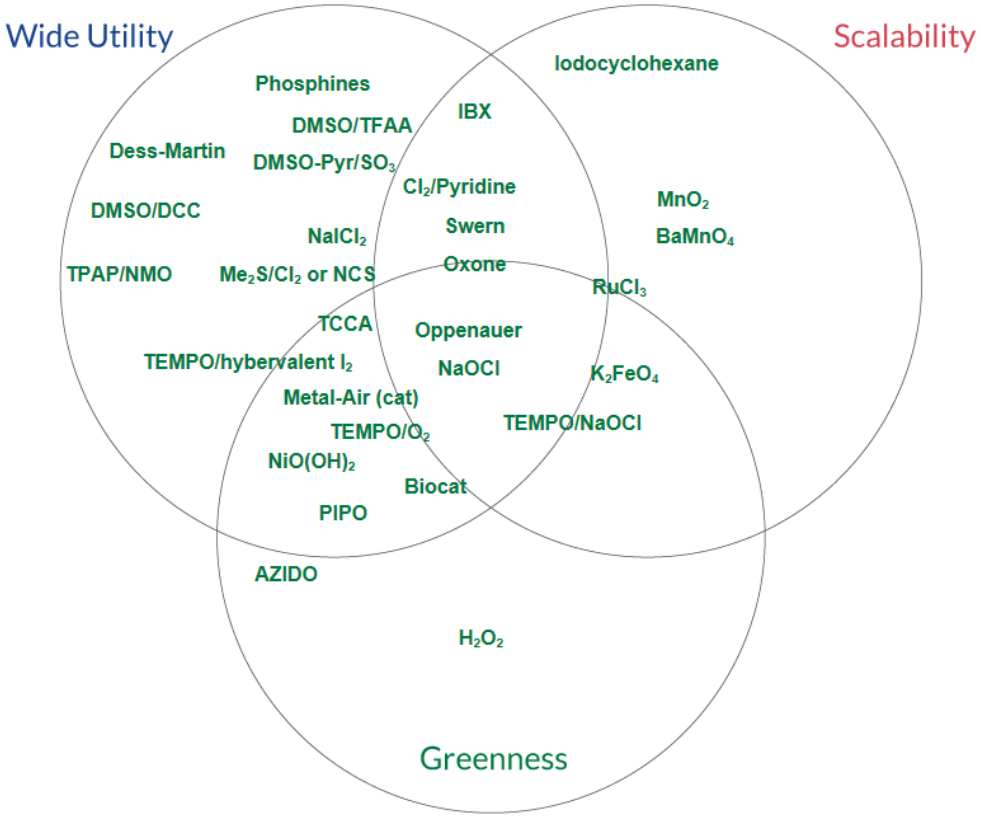
67% convergence (AZ, ACS GCI, GSK, Pfizer, Sanofi)

The divergences reflect the different weighing of criteria

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

ACS reagent guide





2024 Green Assessments

Materials	Particulate matter EF v3.1 no LT Disease incidence	Photochem. ozone formation EF v3.1 no LT kg NMVOC eq	Water use EF v3.1 no LT m3 deprived	Precision Score - Material acc. to Figure 4
2-Bromochlorobenzene	0.00000011	0.01019104	6.44835067	70%
1.3-Dimethoxybenzene	0.00000017	0.01203710	1.64413183	70%
n-Butyl lithium	0.00000125	0.07598894	39.96838526	70%
Chlorodicyclohexylphosph.	0.00000192	0.45346309	20.78250682	50%
Silica gel	0.00000009	0.00379393	0.61007998	80%
Cellulose acetate	0.00000026	0.01574273	8.28030292	80%
Iron(III) chloride	0.00000001	0.00058938	0.12780337	95%
Pd(OAc)2	0.00000274	0.28071208	2.79555207	80%
Methylmagnesium chloride	0.00000366	0.02641772	0.56882861	70%
Tetrahydrofuran	0.00000345	0.24060676	142.59338646	95%
n-Hexane	0.00000002	0.00618925	0.27588895	95%
Ethyl acetate	0.00000334	0.32094189	45.48378411	95%
Acetone	0.00000030	0.03427291	3.54771212	95%
Methanol	0.00000001	0.00190840	0.09609906	95%
Pentane	0.00000066	0.06243819	0.81135036	95%
Water	0.00000000	0.00000006	0.00001227	95%
SUM	0.00001799	1.54529349	274.03417489	-

Materials	Particulate matter EF v3.1 no LT Disease incidence	Photochem. ozone formation EF v3.1 no LT kg NMVOC eq	Water use EF v3.1 no LT m3 deprived	Precision Score - Material acc. to Figure 4	Material resources EF v3.1 no LT Minerals, metals kg Sb eq	Ozone depletion EF v3.1 no LT ODP100 Years kg CFC-11 eq	Particulate mat EF v3.1 no LT Disease inciden
2-Bromochlo					2996	0.00001495	0.00000028	0.00000011
1.3-Dimethox					9535	0.00003007	0.00000019	0.00000017
n-Butyl l					4157	0.00033385	0.00000101	0.00000125
Chlorodicycloh					19536	0.00034103	0.00000979	0.00000192
Silica					7582	0.00004300	0.00000001	0.00000009
Cellulose					9467	0.00006916	0.00000021	0.00000026
Iron(III) cl					1239	0.00000588	0.00000006	0.00000001
Pd(OA					5178	0.00070005	0.00000010	0.00000274
Methylmagnes					4059	0.00001130	0.00000163	0.00000366
Tetrahyd					59248	0.00037177	0.00000136	0.00000345
n-Hex					5620	0.00000460	0.00000004	0.00000002
Ethyl ac					37227	0.00045631	0.00000114	0.00000334
Aceto					7153	0.00003543	0.00000007	0.00000030
Metha					9650	0.00000086	0.00000002	0.00000001
Penta					5874	0.00000954	0.00000008	0.00000066
Wat					7529	0.00000000	0.00000000	0.00000000
SUM	3.09241564	0.00000017	0.00000309	4.78724685	847.51536048	0.00242781	0.00001600	0.00001799
Pentane	0.05229521	11.46541616	24.77166178	36.23707794	6.87779428	796.25235194	0.00002879	0.00979340
Water	0.00000016	0.00001730	0.02323600	0.02325330	0.00192578	0.00020484	0.00000000	0.00000002
SUM	3.31374855	240.56907631	119.24289136	359.81196768	2710.07969230	6371.99212043	0.02707944	0.31503814

Green Chem., **2024**, *26*, 5239

Comparison of material usage

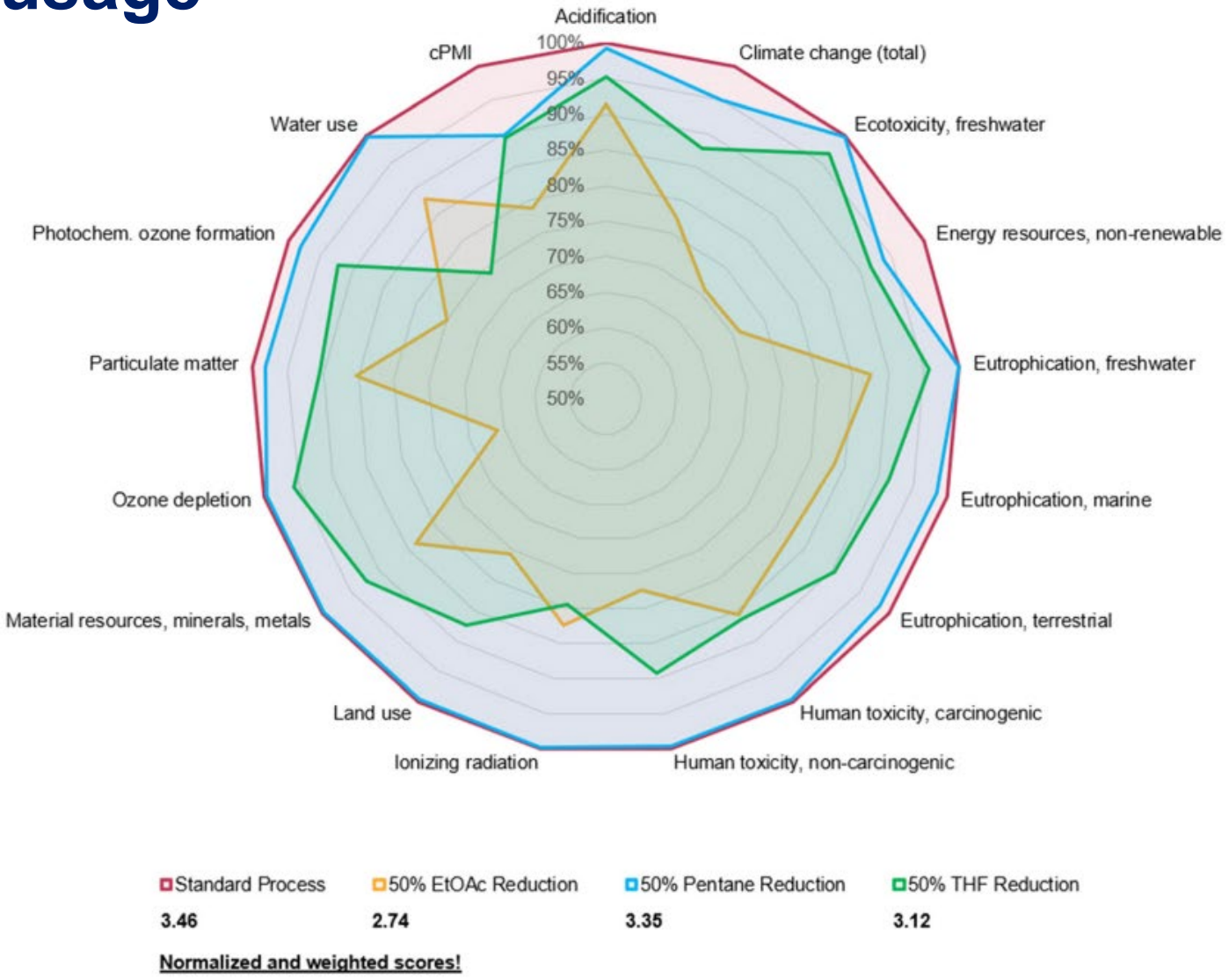


Fig. 6 Relative spider diagram of development scenarios and their normalized and weighted score.

Green Chem., **2024**, *26*, 5239

Aspects to consider in process development

- ✓ Safety
- ✓ Number of steps
- ✓ Yield
- ✓ Complexity of the synthesis
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- Choice/Stoichiometry of reagents
- Choice of solvent/solvent effects
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- Filtration
- Isolation
- **Physical form**
- **(Depletion of) by products**
- **Purity**
- Throughput
- Telescoping
- Waste
- **Intellectual property**
- Equipment required

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- (Depletion of) by products
- Purity
- Throughput
- **Telescoping**
- Waste
- Intellectual property
- Equipment required

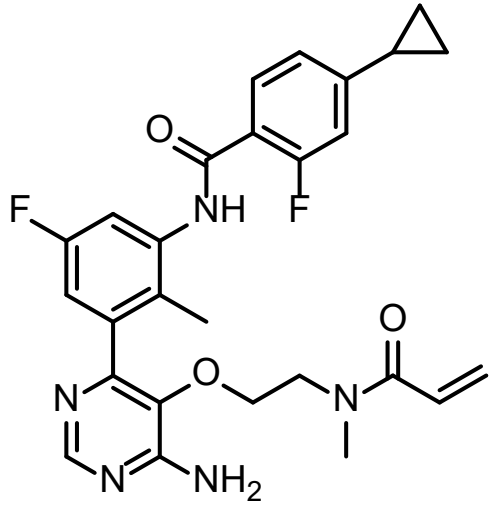
Telescoping

Pros

Cons

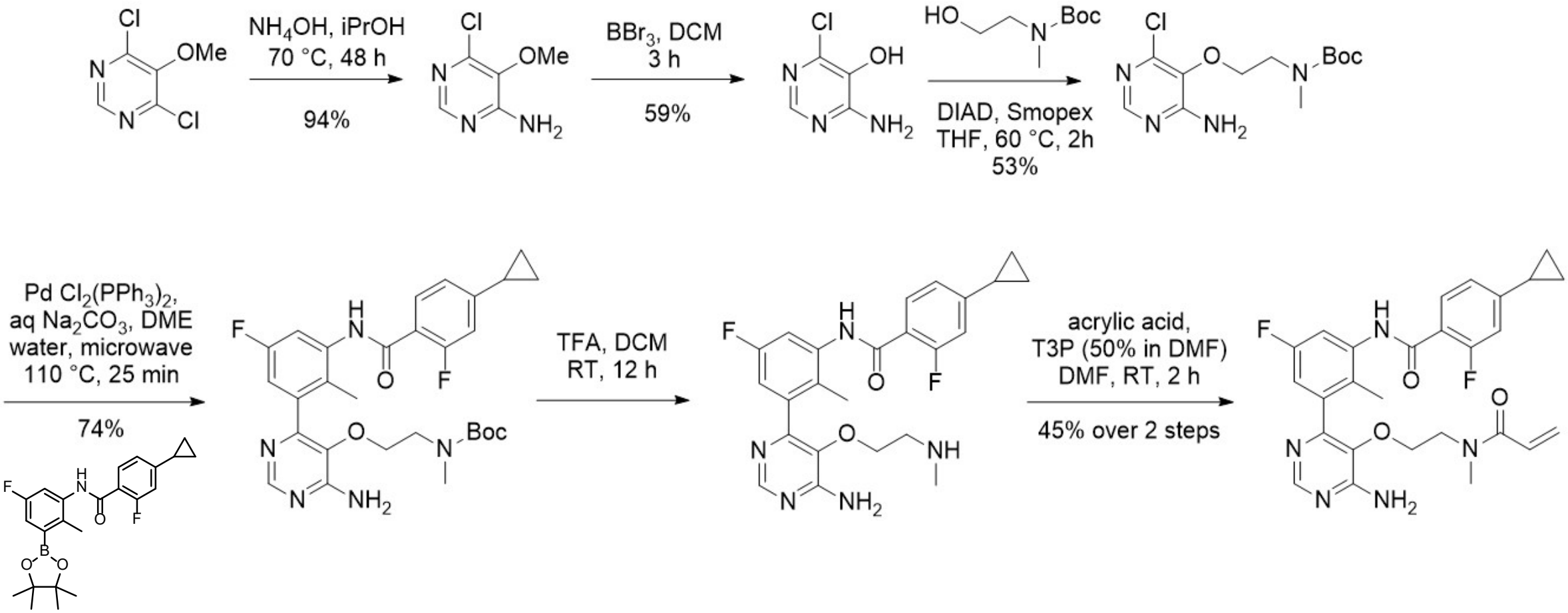
Remibrutinib

- *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

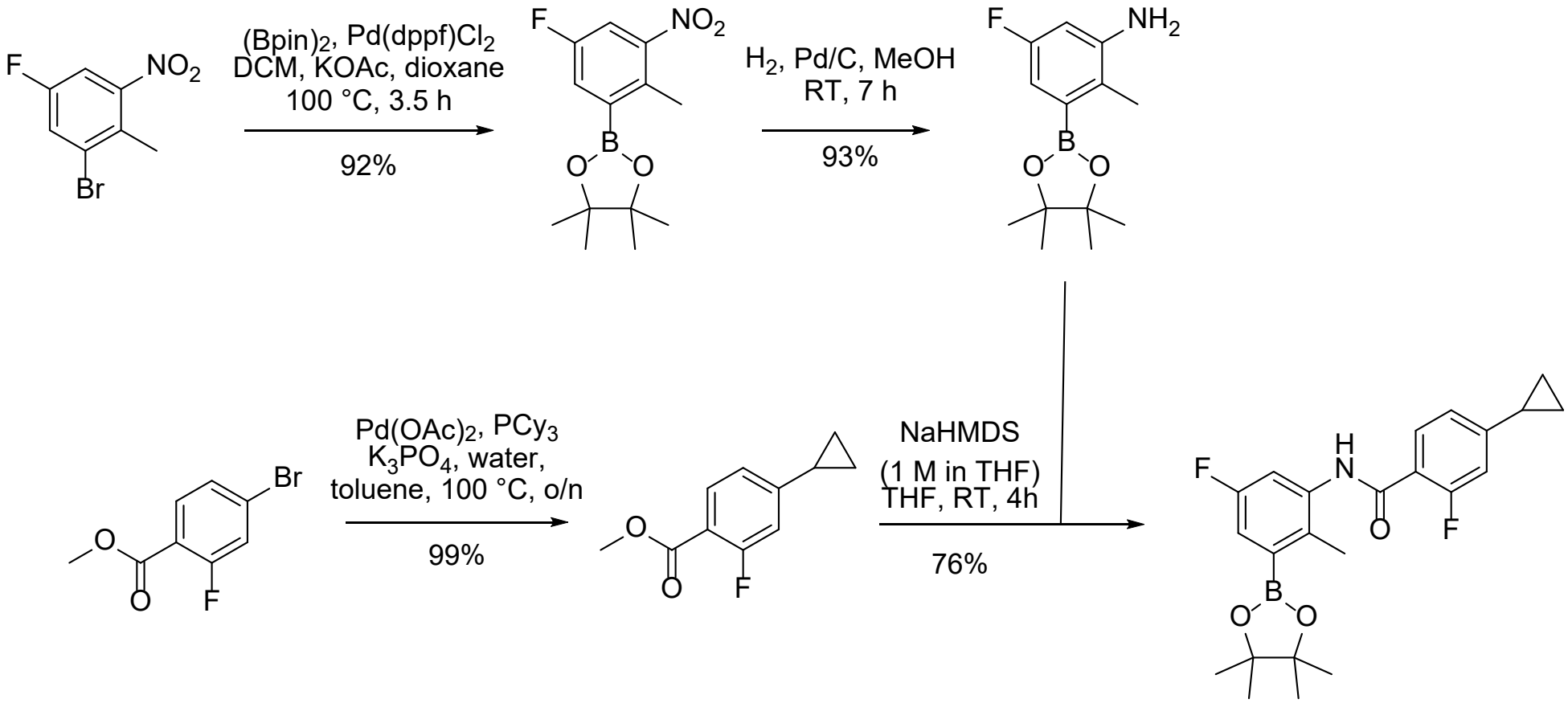


J. Med. Chem. 2020, 63, 10, 5102−5118

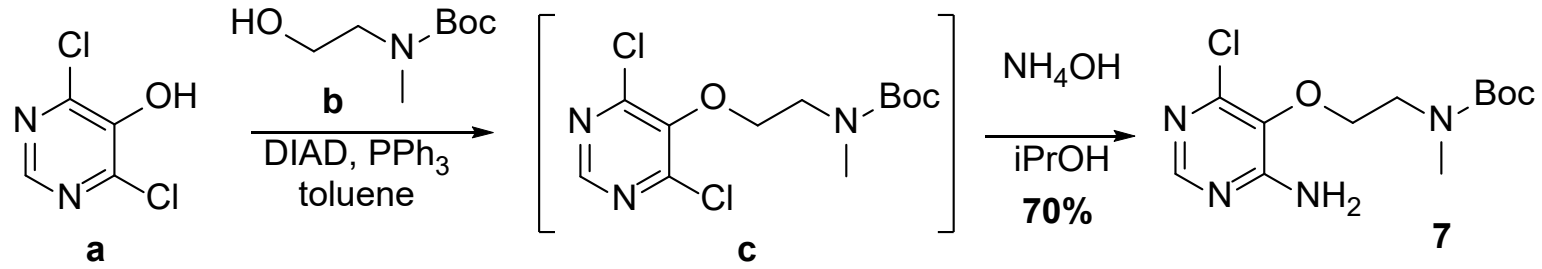
Highly Convergent MedChem Route



Highly Convergent MedChem Route

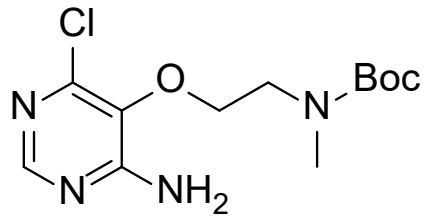


Int. 7 Detailed Process



- Mitsunobu reaction run in anhydrous conditions with 1.3 equiv of **b**, 1.3 equiv of PPh_3 and 1.6 equiv of DIAD.
- At the end of the reaction PPh_3O/H_2-DIAD is crashed out by heptane addition and filtered off.
- Traces of **a** are removed with a basic wash.
- Organic phase is transfered to a hydrogenator, iPrOH and NH_4OH 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

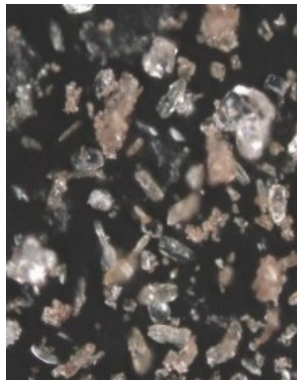


Figure 4. Microscopic pictures of the grinded lumps

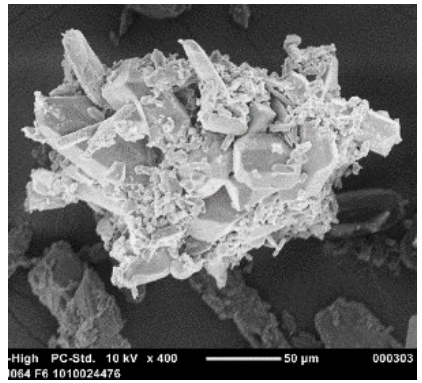
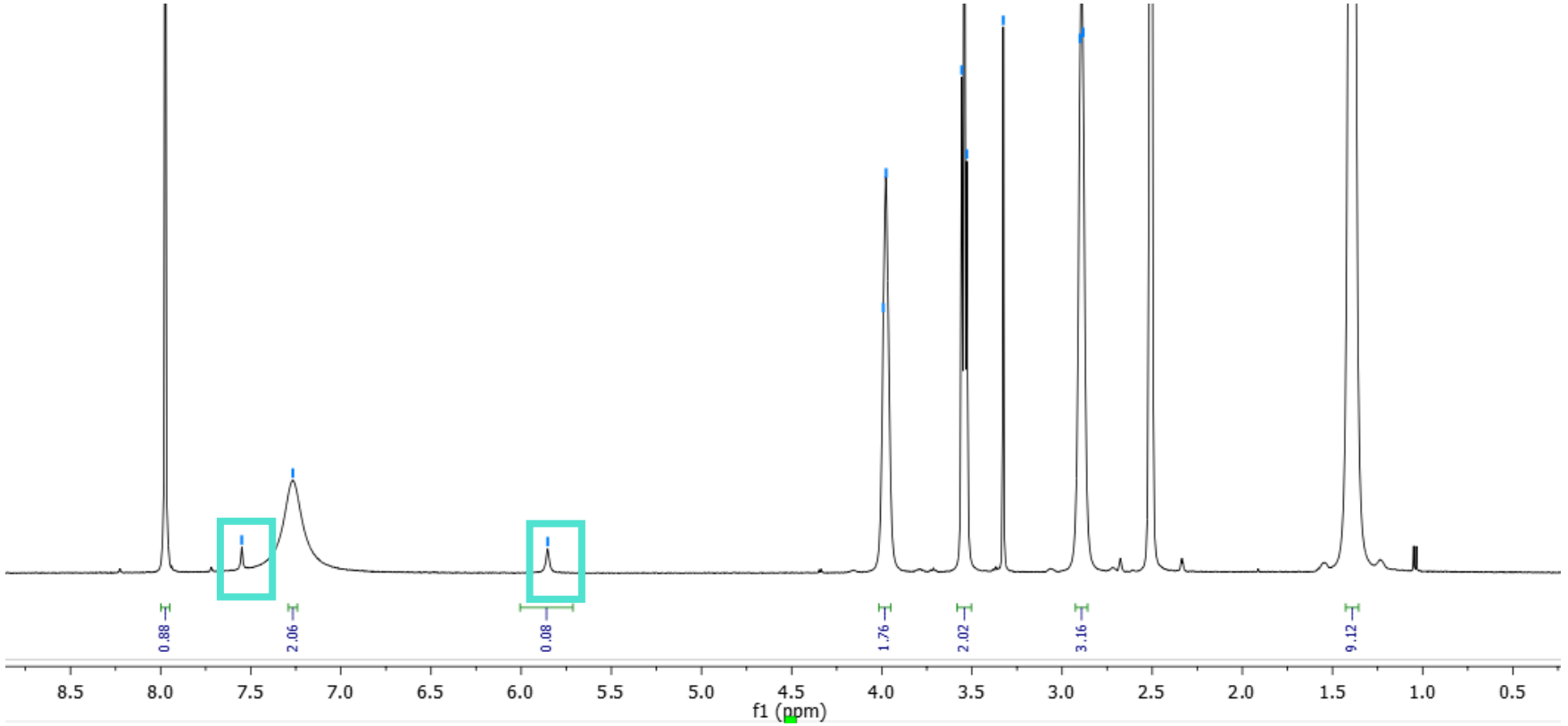


Figure 5. SEM picture of the grinded lumps

Investigation

NMR of sieved 7 (enriched in black matter)



Trituration with Acetone

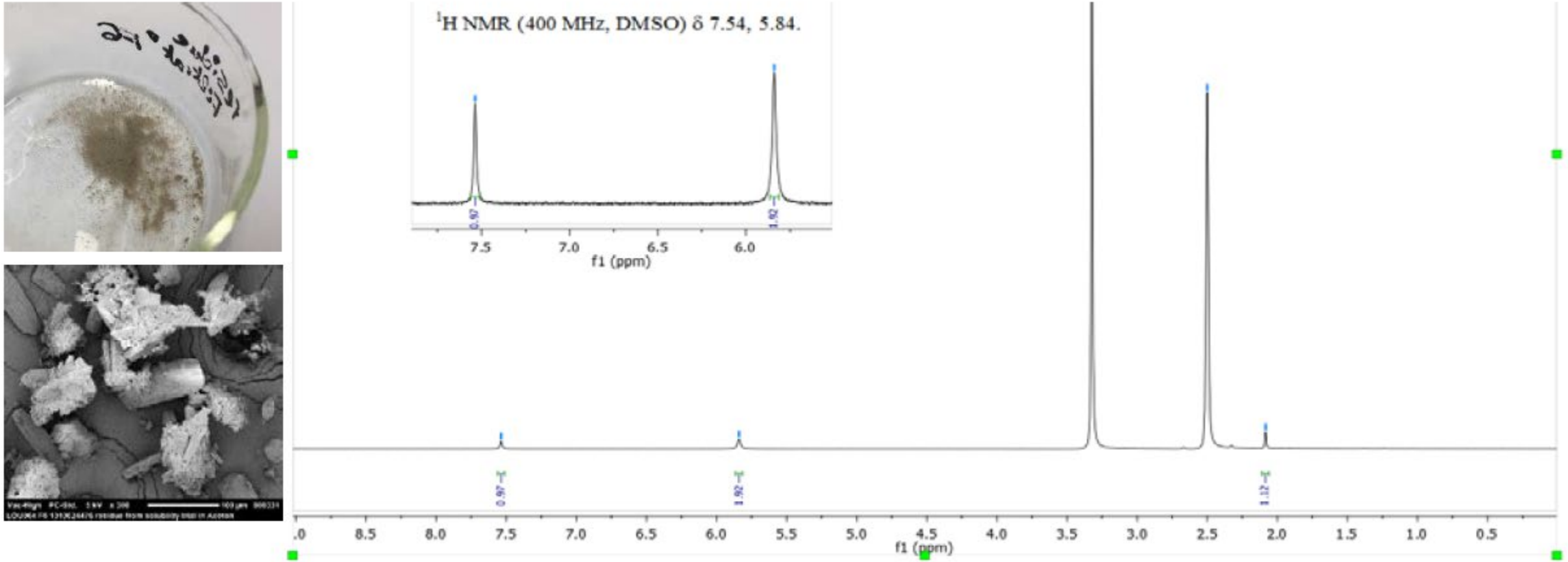
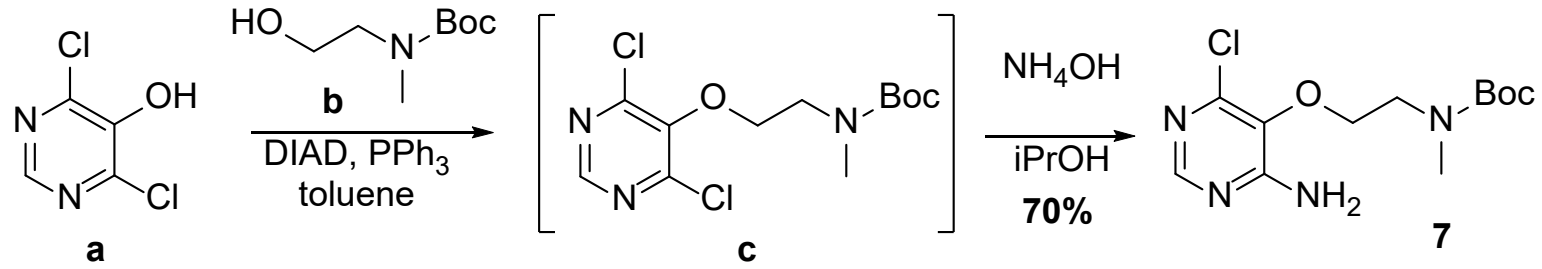


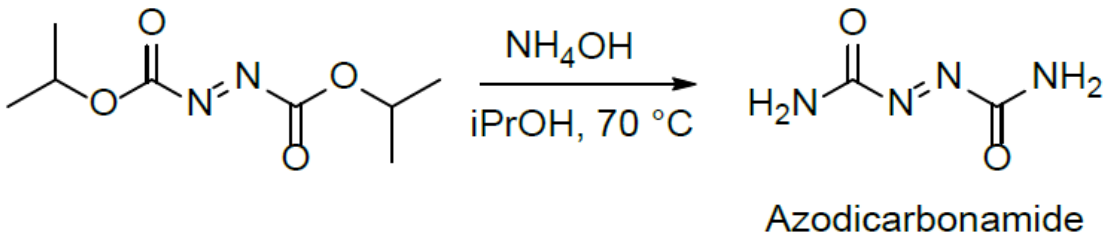
Figure 3: NMR spectra and SEM picture of the isolated grey compound. Only the two previously identified signals belong to the impurity

Int. 7 Detailed Process

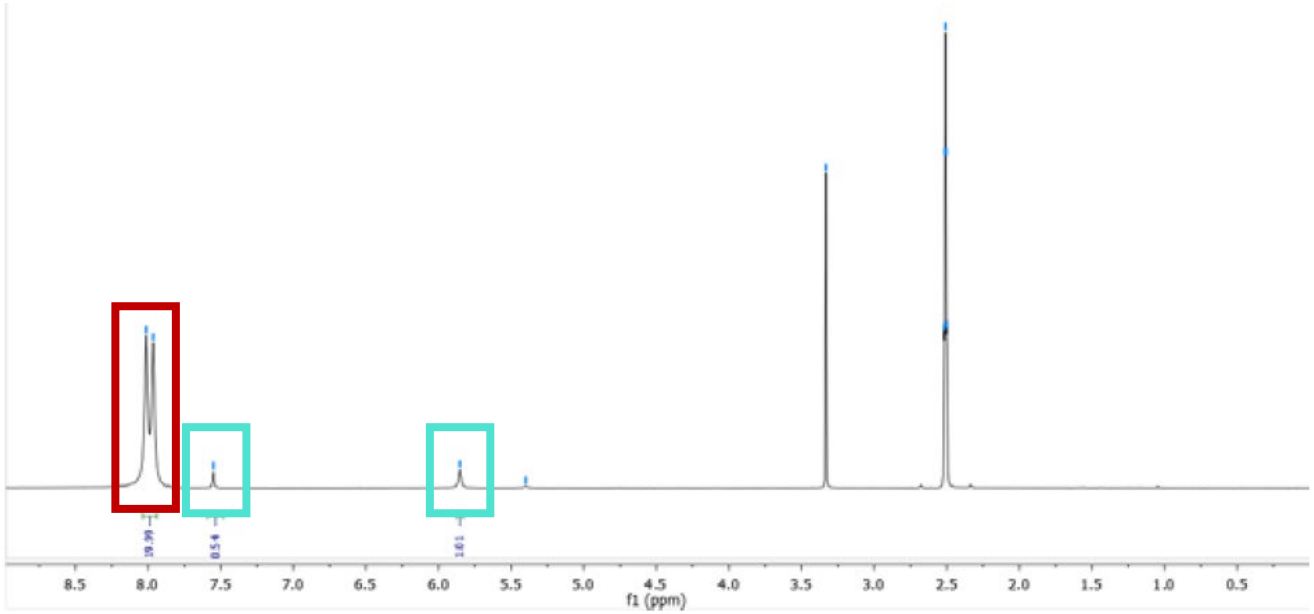


- Mitsunobu reaction run in anhydrous conditions with 1.3 equiv of **b**, 1.3 equiv of PPh_3 and 1.6 equiv of DIAD.
- At the end of the reaction PPh_3O/H_2-DIAD is crashed out by heptane addition and filtered off.
- Traces of **a** are removed with a basic wash.
- Organic phase is transfered to a hydrogenator, iPrOH and NH_4OH are added
- The amination is run overnight at 70 °C
- **7** is crystallized after concentration and addition of water.

Excess Reagent Carry Over



Azodicarbonamide



- 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

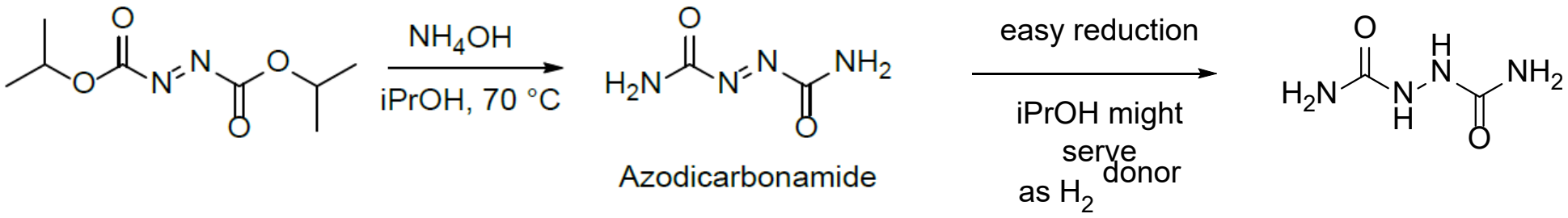
Latest Food Scare: What Is The 'Yoga Mat' Chemical – And Why Is It In Your Food?

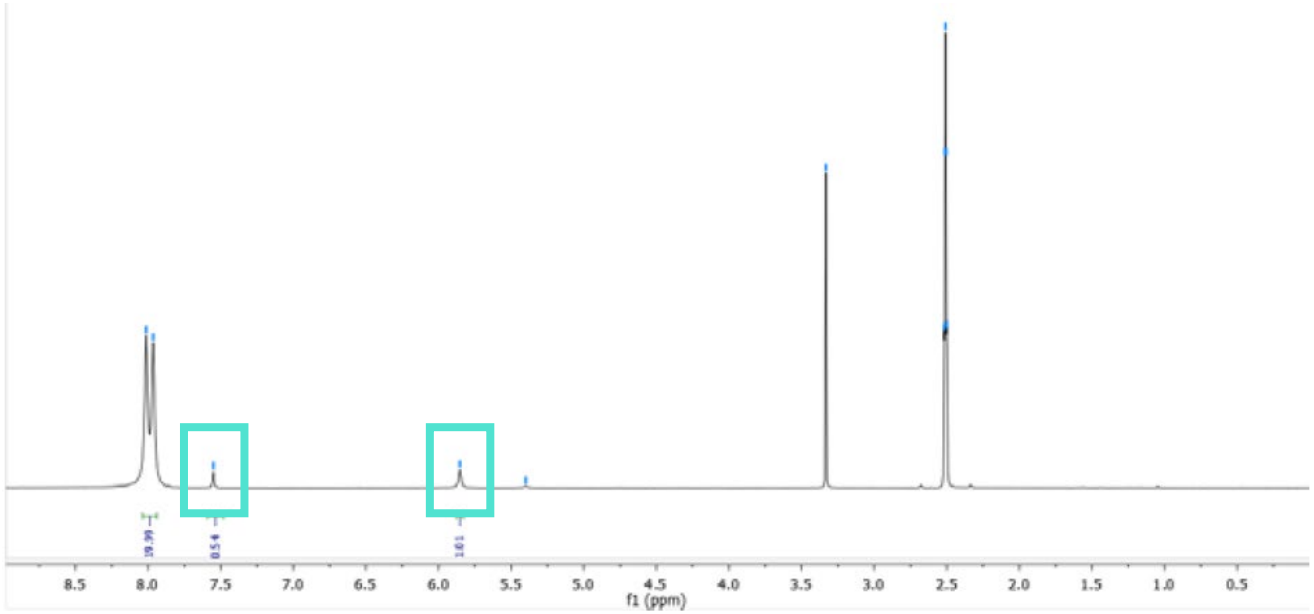
Melanie Haiken Contributor ⓘ
I report the latest in health, nutrition, wellness and healthy travel.

Follow

Feb 27, 2014, 05:45pm EST

Excess Reagent Carry Over



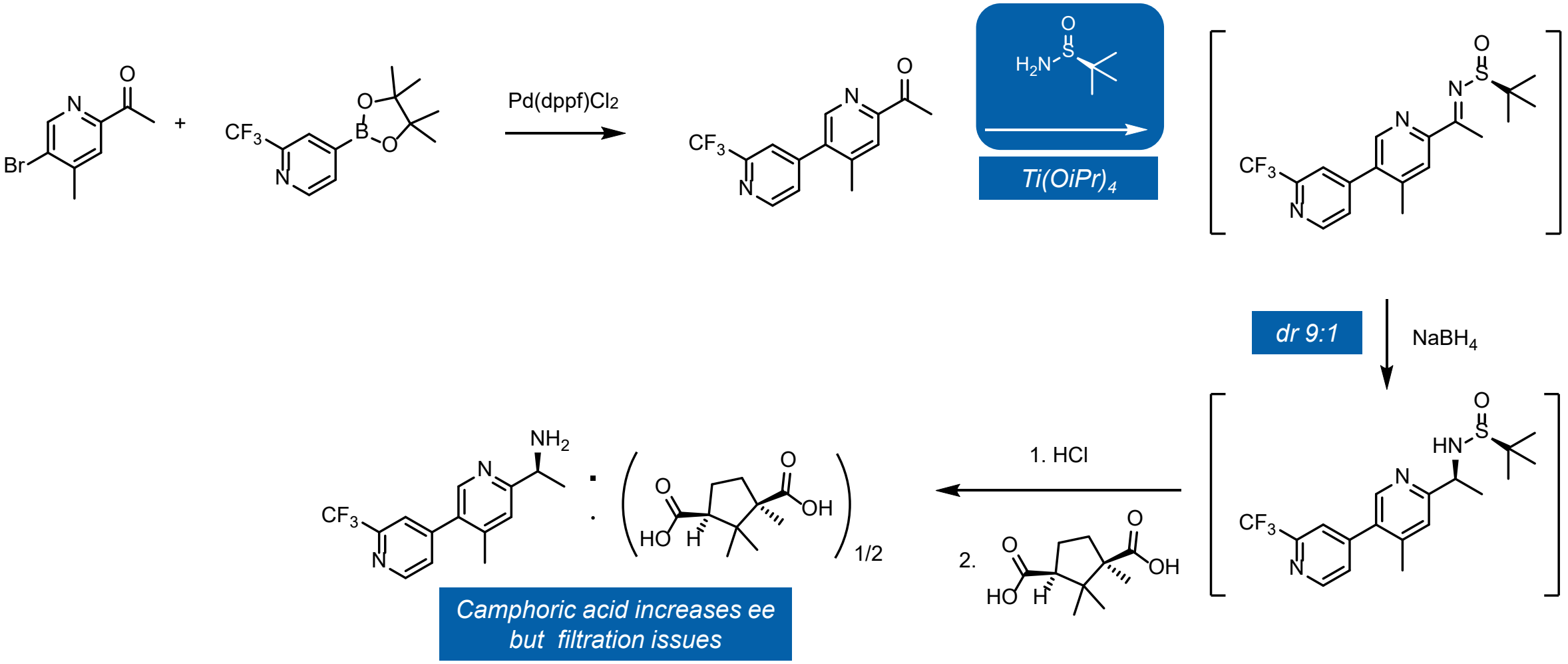


- No toxicological alert
- Real ingredient found in food

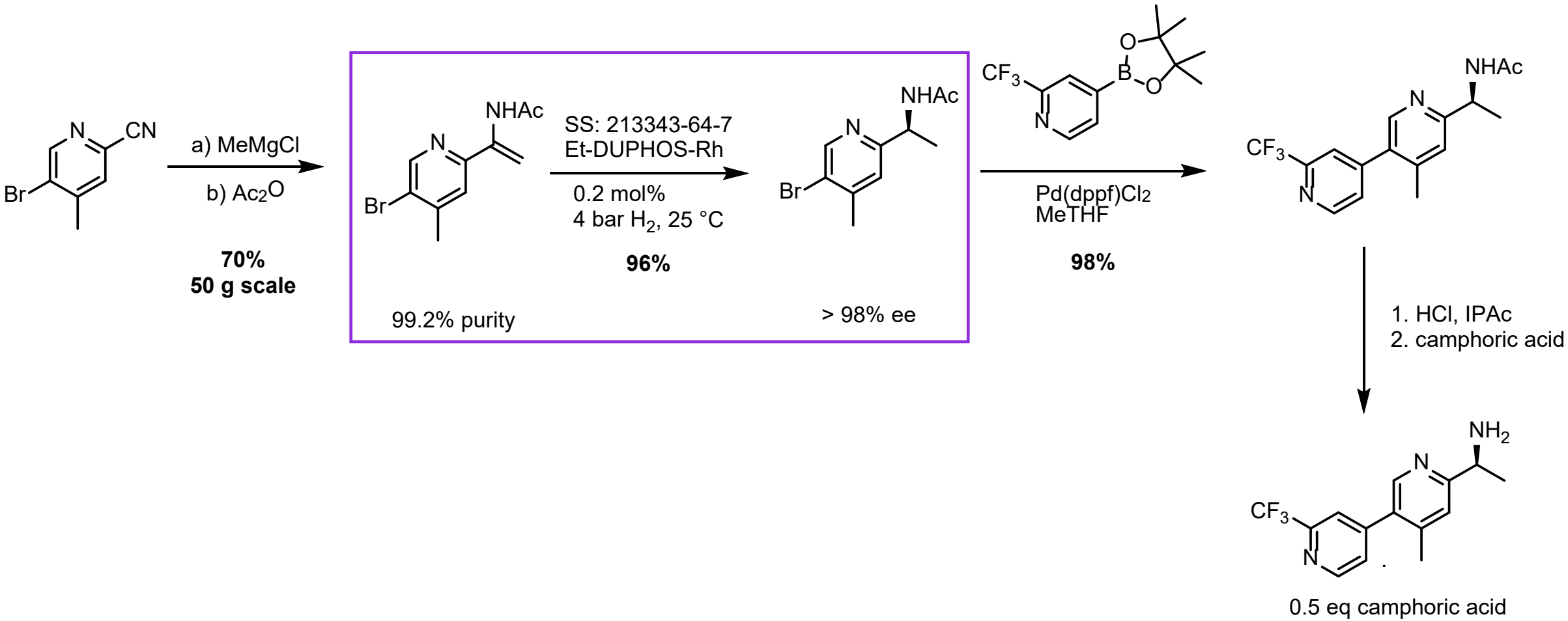
Break?

Use case :
IDH305 side chain

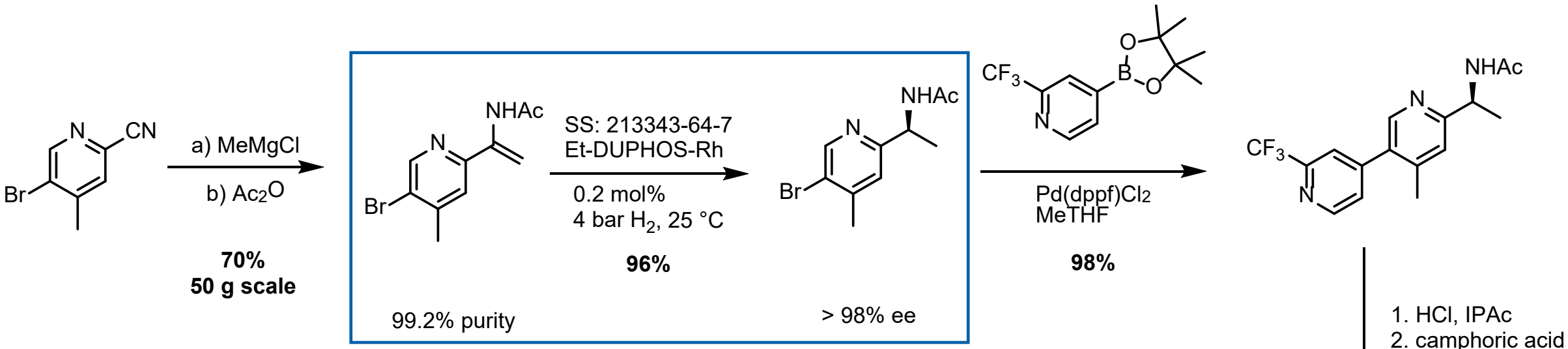
Side Chain - Initial Route:



Side Chain - Alternate Route 1



Side Chain - Alternate Route 1

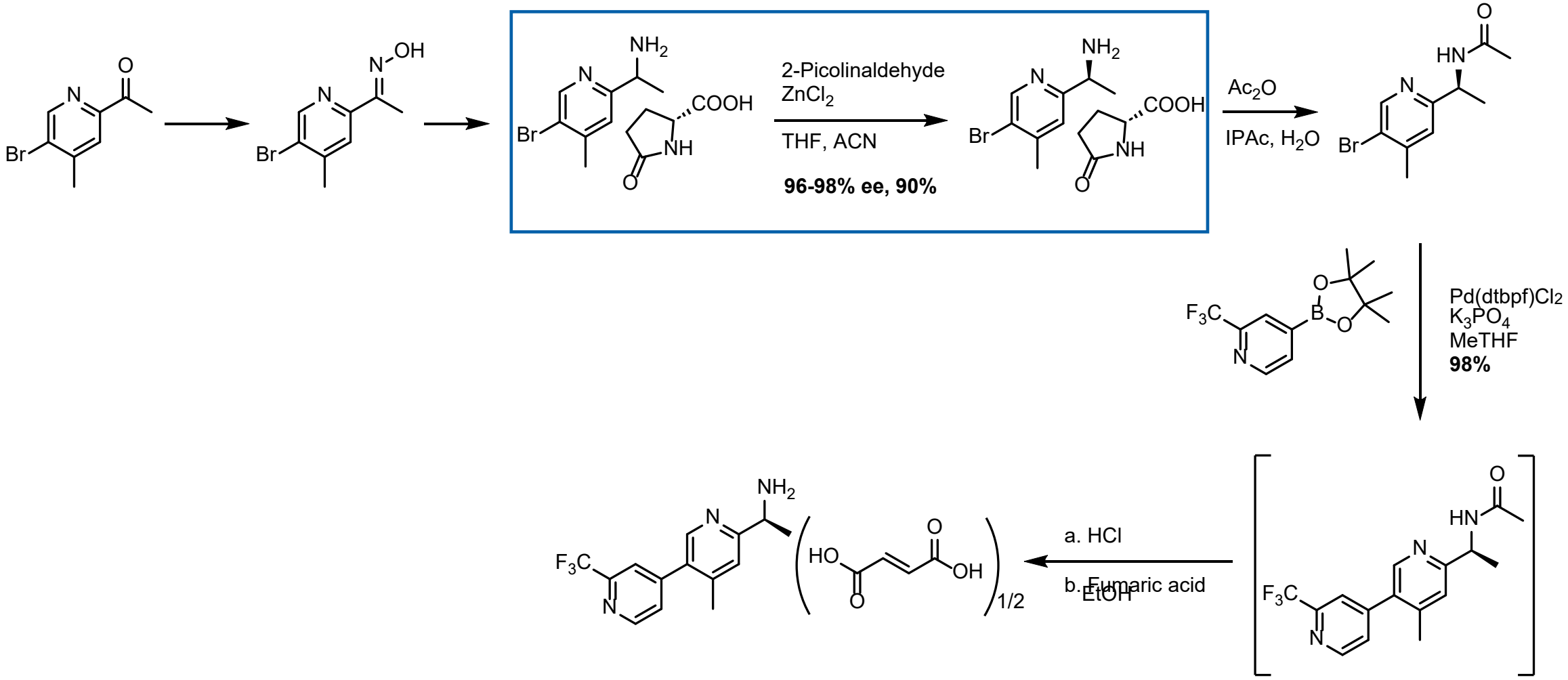


- High enantiopurity obtained (>98% ee)
- Good overall conversion

But:

- Sourcing of starting material of suitable quality uncertain
- 2 transition metals used in the sequence
- Special equipment required (H_2, 4 bar)

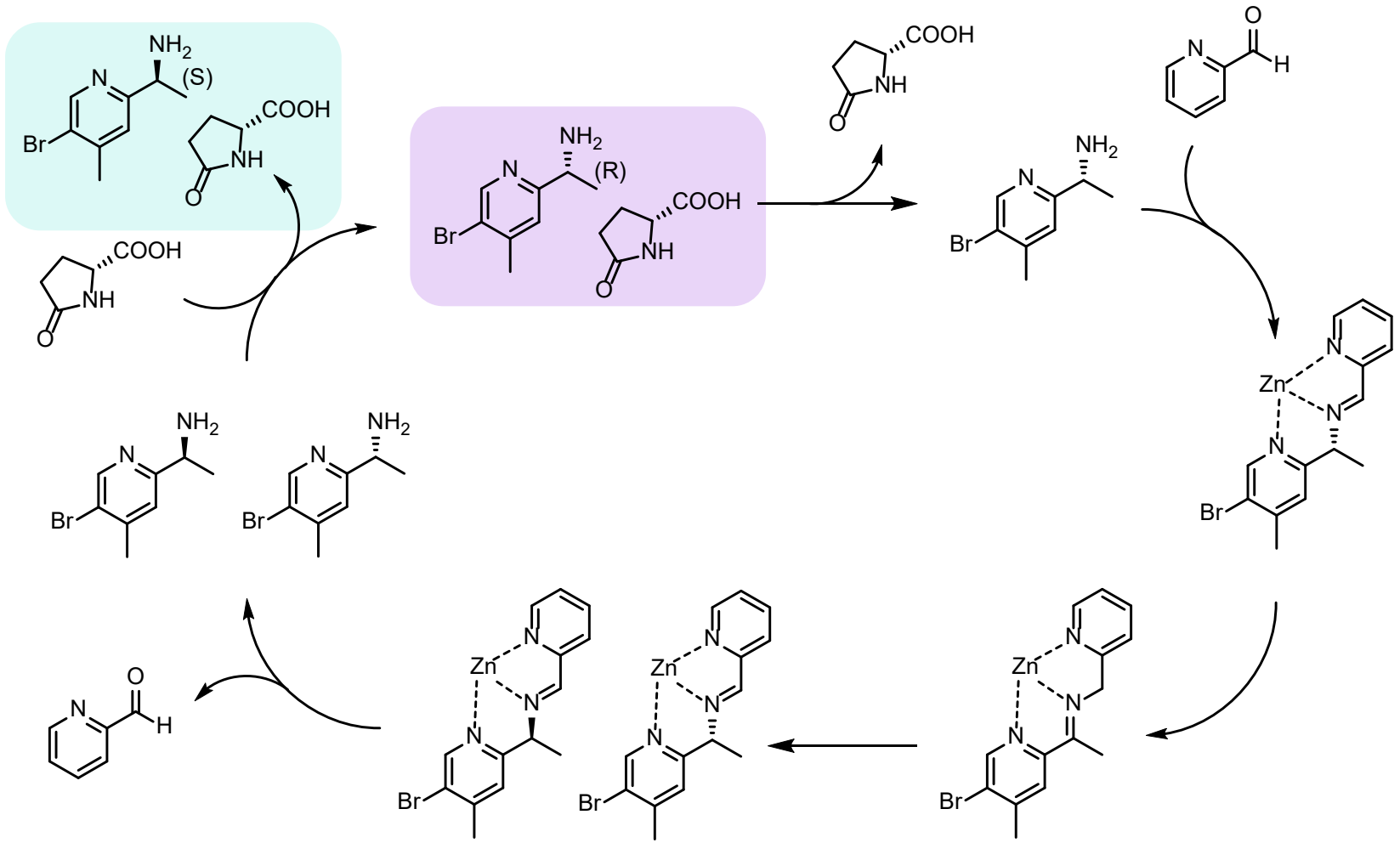
Side Chain - Alternate Route 2: DKR



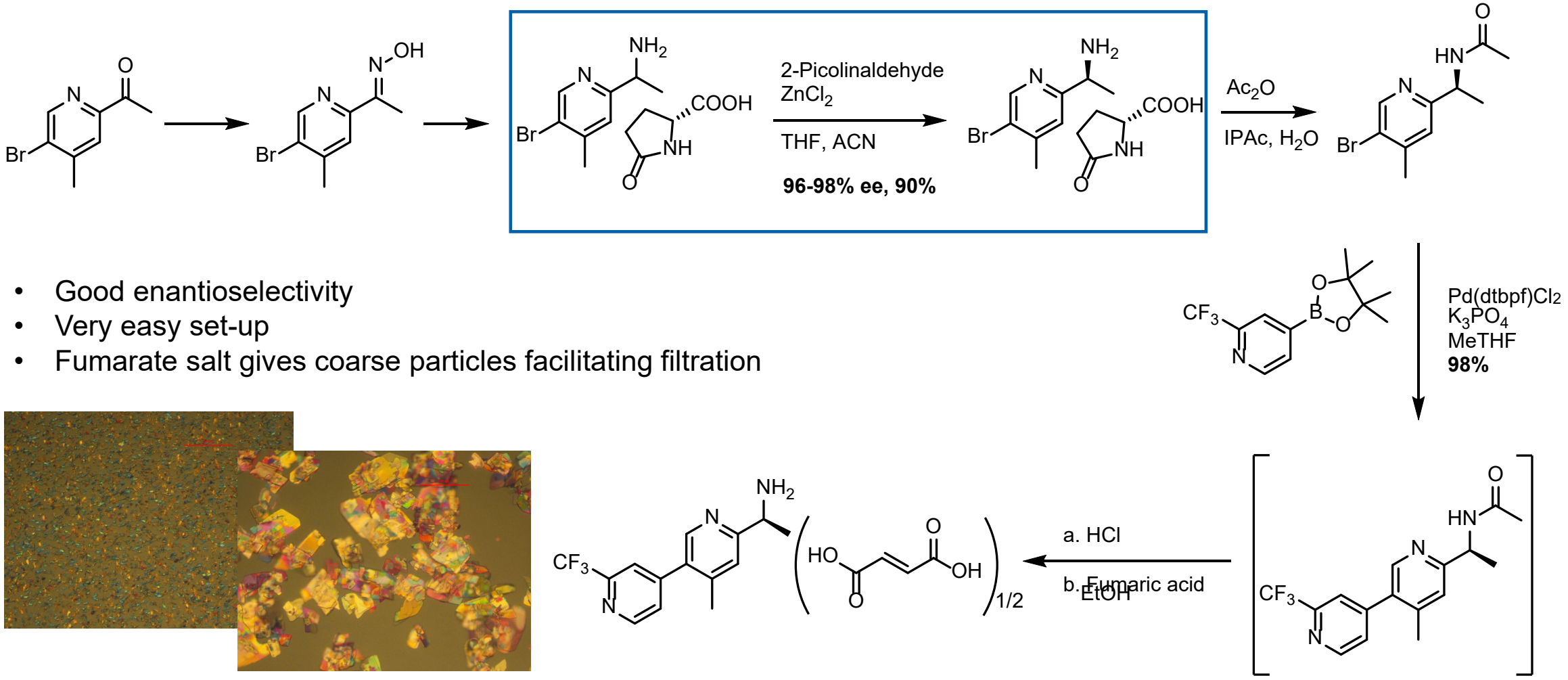
Side Chain DKR - mechanism

Solubility difference between the diastereoisomeric salts:

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

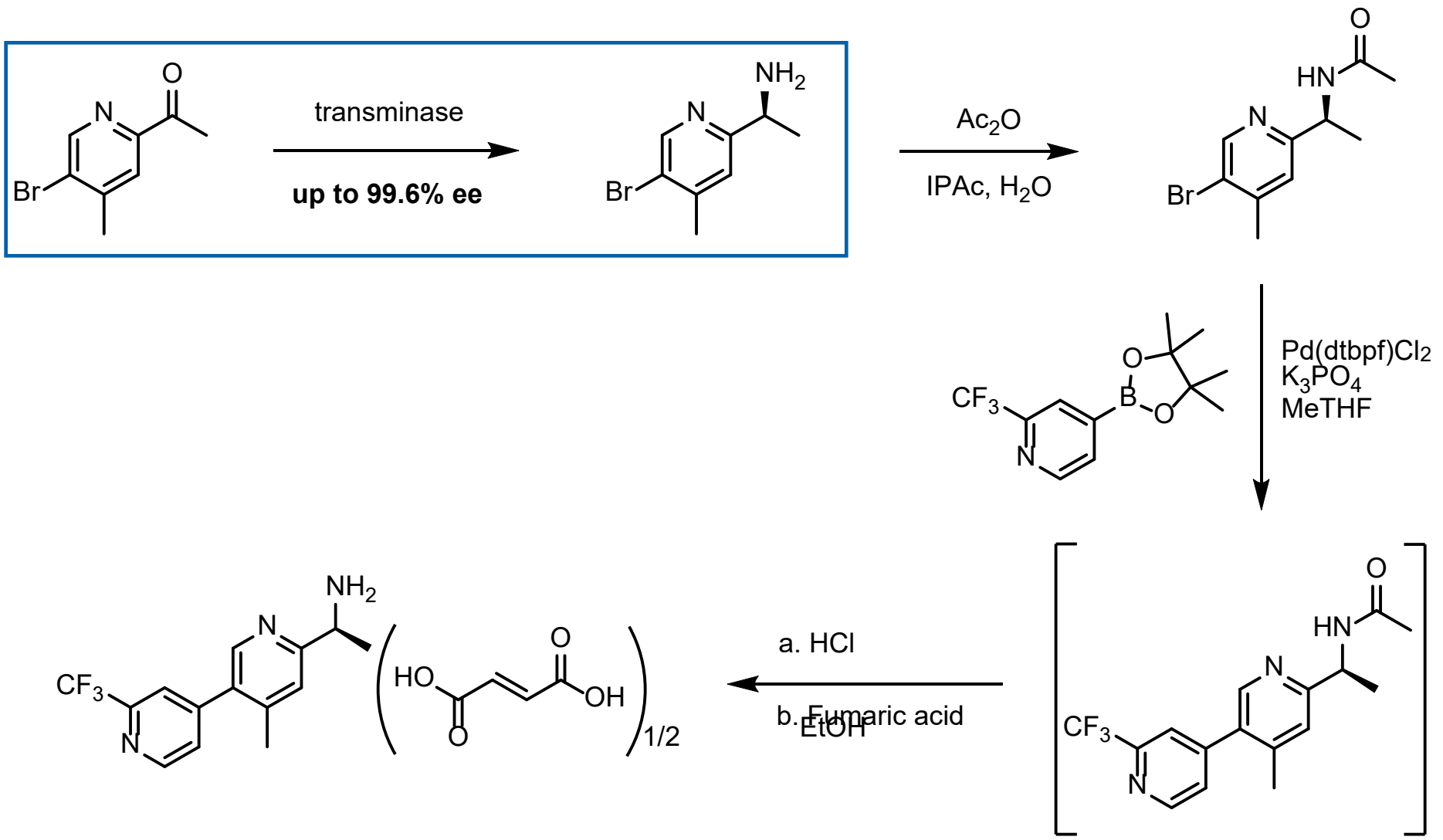


Side Chain - Alternate Route 2: DKR

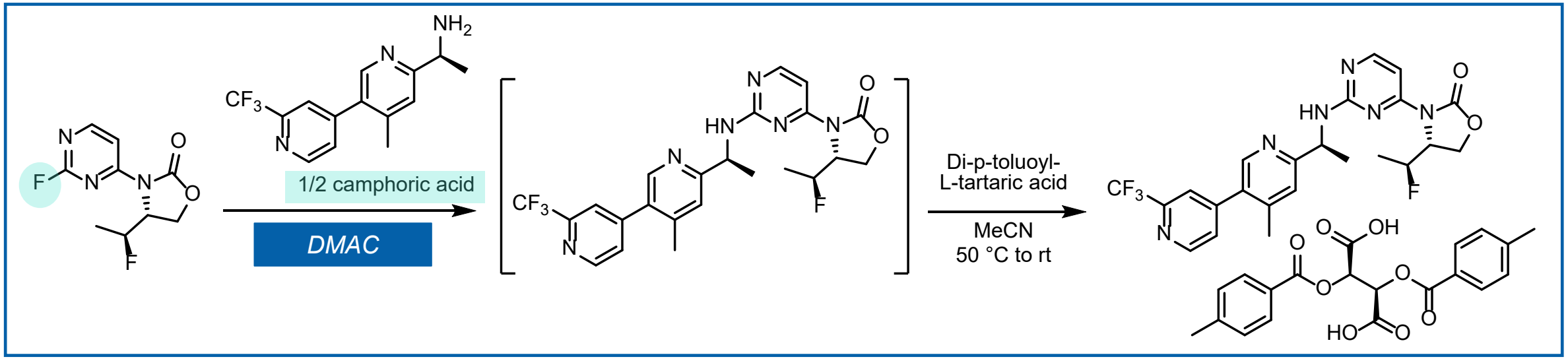


- Good enantioselectivity
- Very easy set-up
- Fumarate salt gives coarse particles facilitating filtration

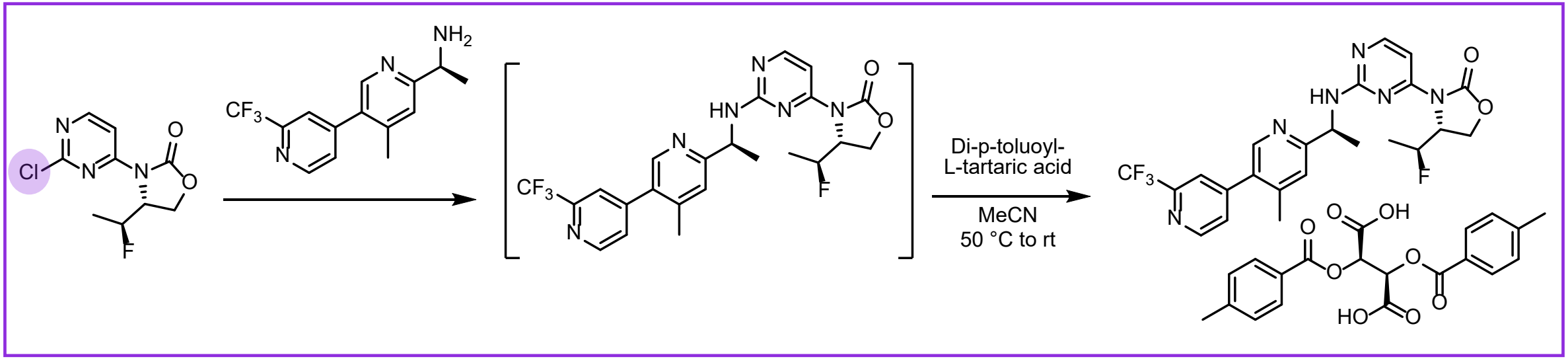
Side Chain Transaminase



Main Chain: $SN_{Ar}2$



Main Chain: $SN_{Ar}2$



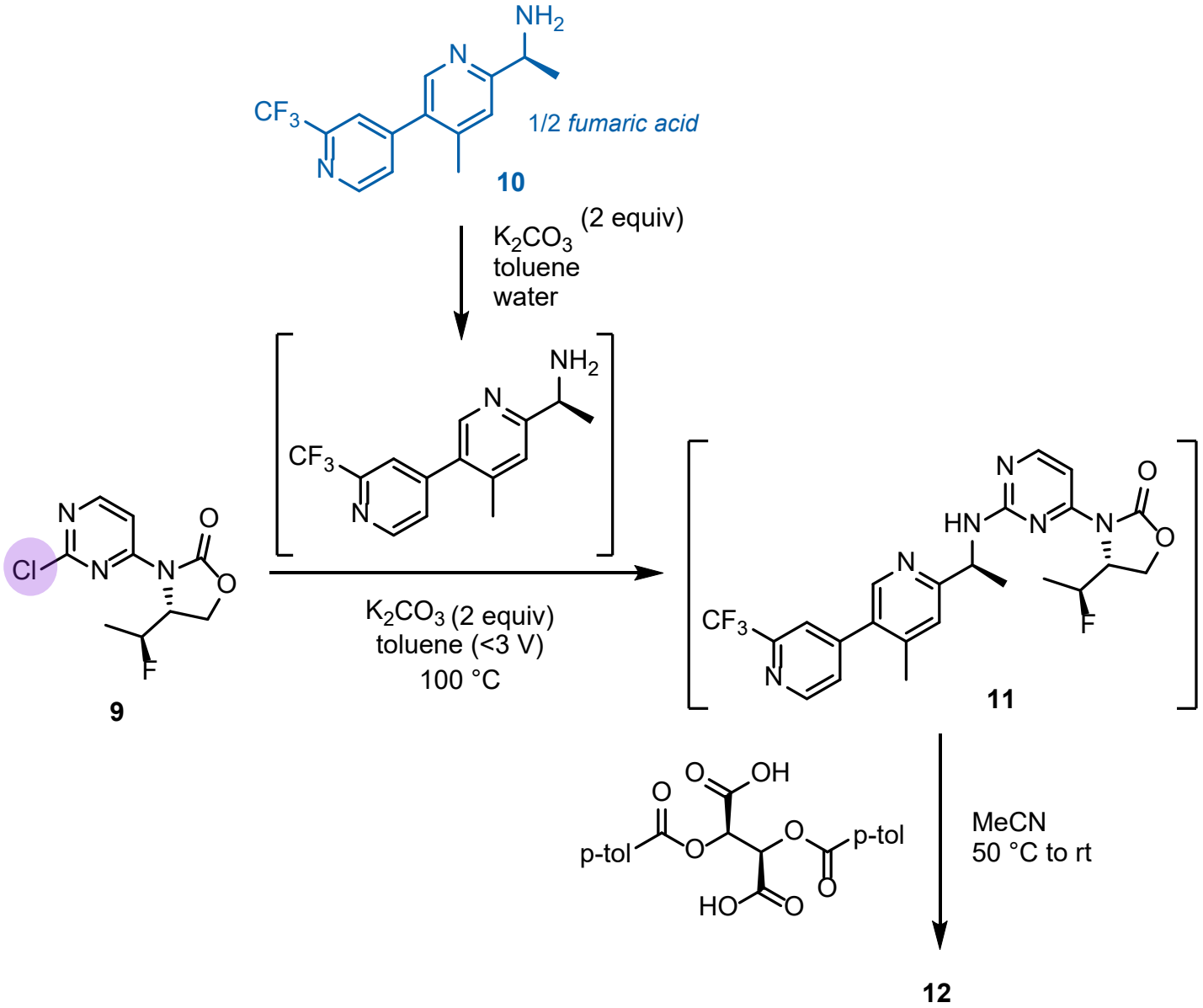
- First trials needed >72 h to reach acceptable conversion in toluene
- Scale up effect was observed between 100 mg and 1 g scale reactions – which gave us a hint on the impact of concentration

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

Main chain: $SN_{Ar}2$

- 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

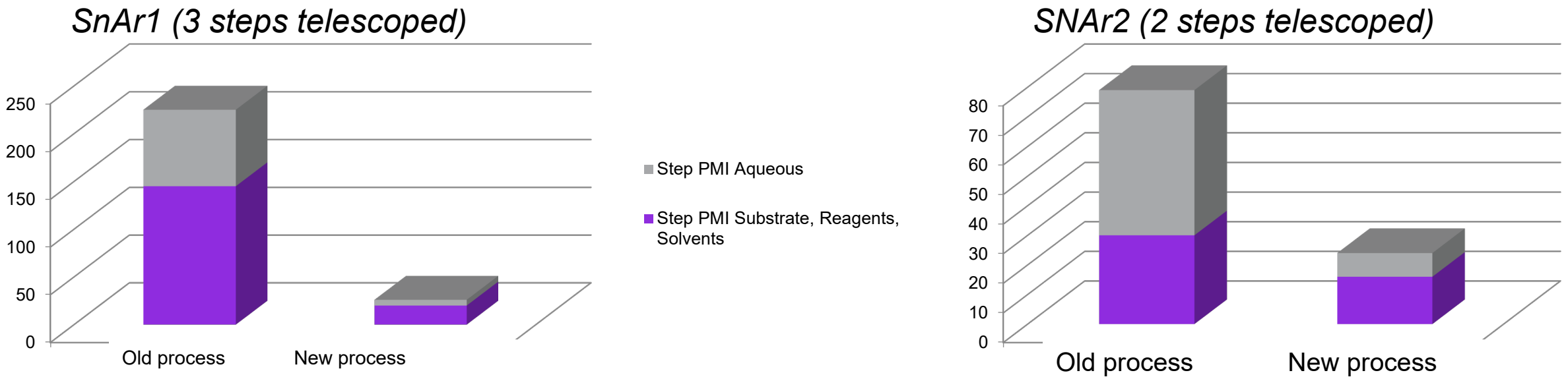
Isolated yield on kg-scale: 87%



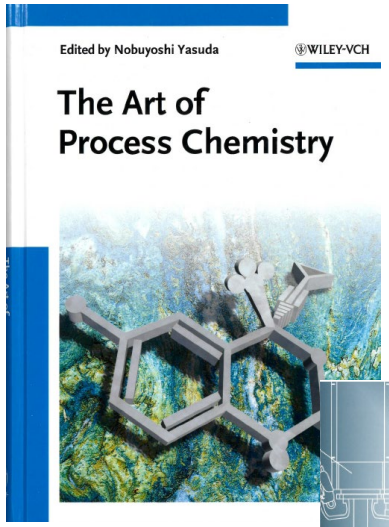
Effect on sustainability

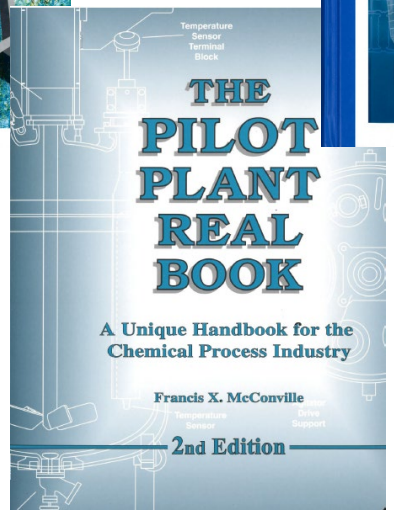
Additional decrease in PMI

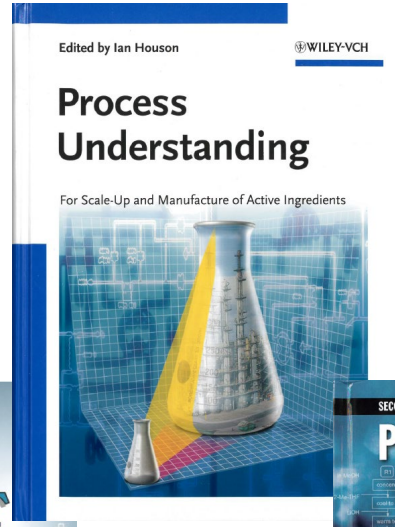
Removal of undesired solvents and fluorinated waste

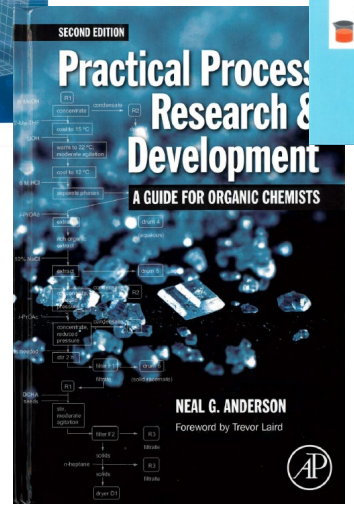


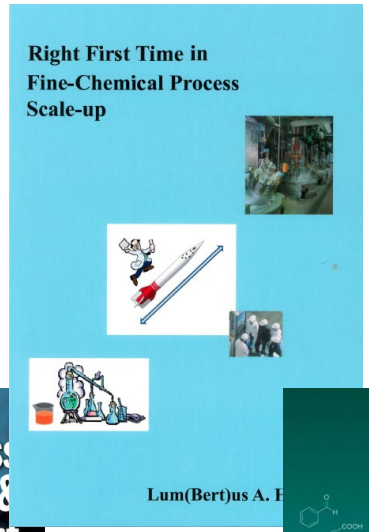
Book recommendations

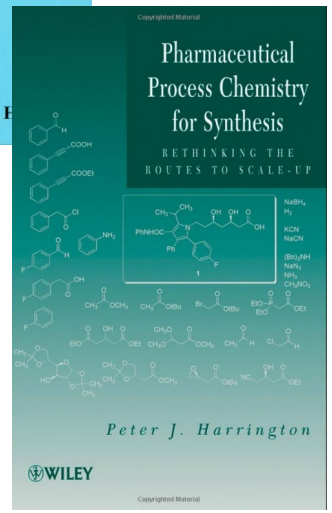


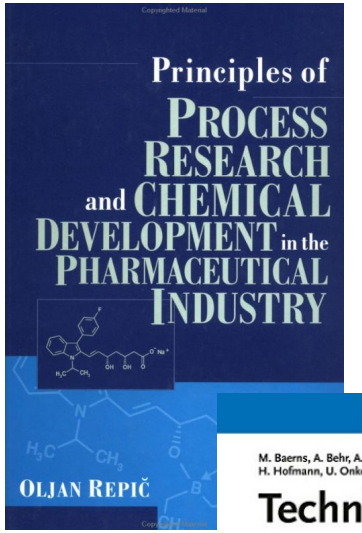






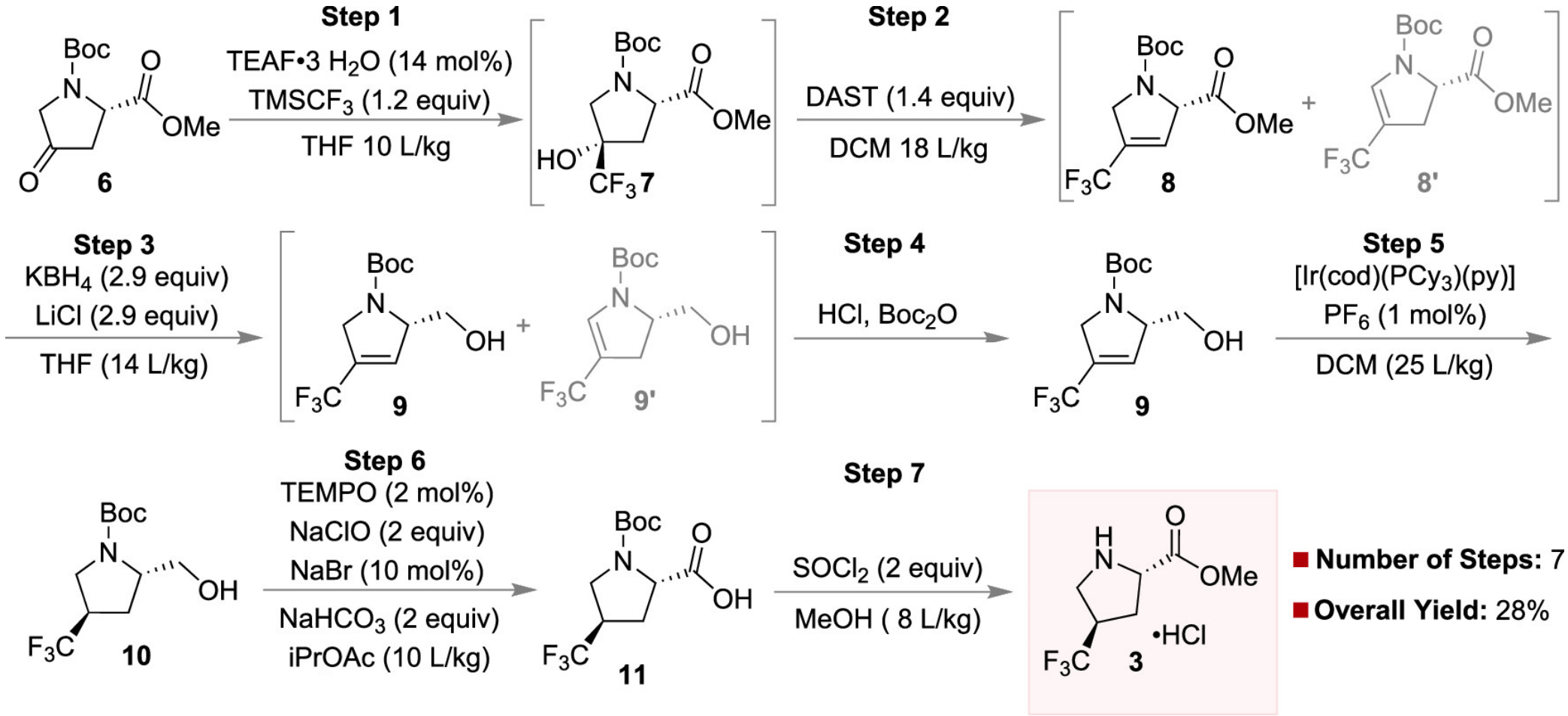






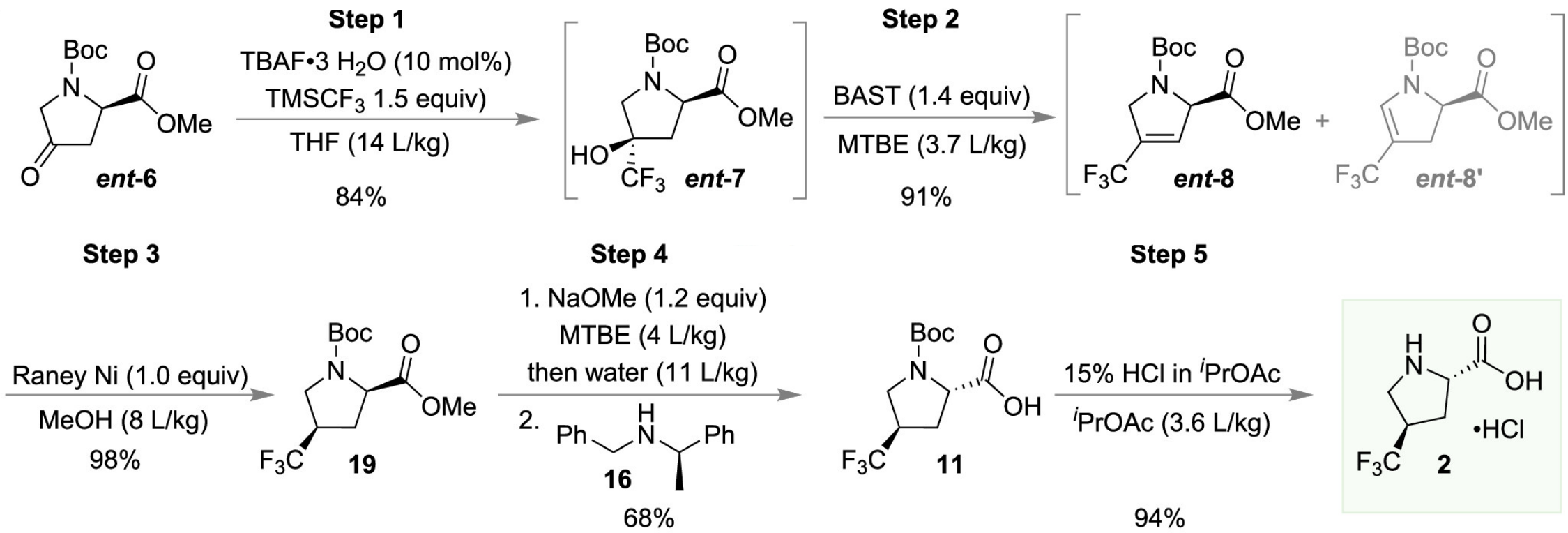
Assignement 2024

Synthesis 1



- **Number of Steps:** 7
- **Overall Yield:** 28%

Synthesis 2


Step 1
TBAF•3 H2O (10 mol%)
TMSCF3 1.5 equiv)
THF (14 L/kg)
84%
ent-6
ent-7
Step 2
BAST (1.4 equiv)
MTBE (3.7 L/kg)
91%
ent-8
ent-8'
Step 3
Raney Ni (1.0 equiv)
MeOH (8 L/kg)
98%
19
Step 4
1. NaOMe (1.2 equiv)
MTBE (4 L/kg)
then water (11 L/kg)
2.
16
68%
11
Step 5
15% HCl in iPrOAc
iPrOAc (3.6 L/kg)
94%
2
•HCl

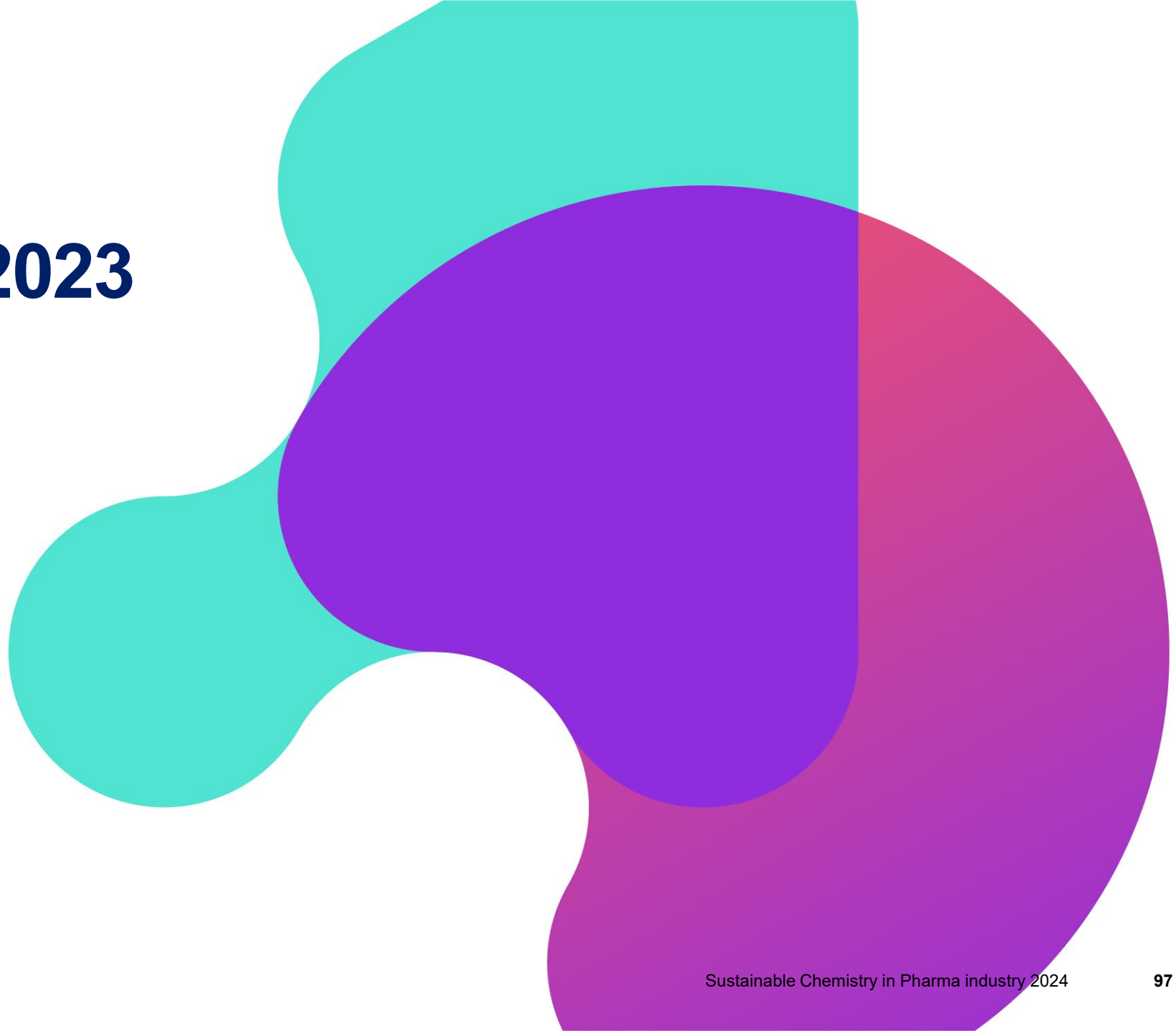
Assignement

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?

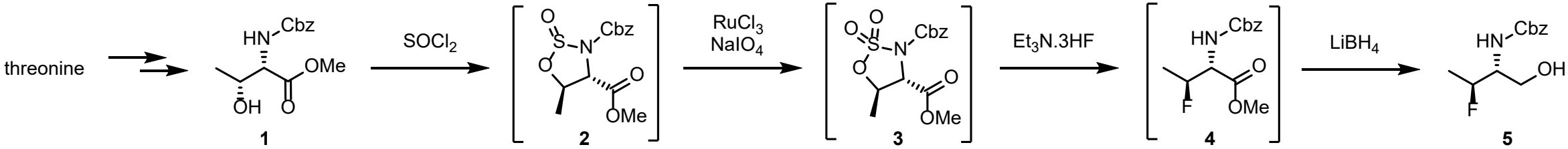
2. **Discuss the pro and cons of each routes according to efficiency, thermal safety, equipment, environmental concerns...**

3. **Justify your choice of the route based on pharmaceutical industry priorities.**

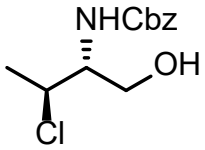
Assignement 2023



Back to the early main chain of IDH305

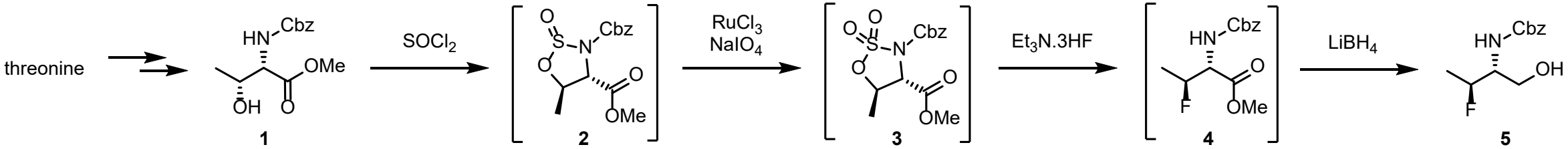


Impurity profile of 5: formation of the chloroanalogue (up to 0.2 A%):

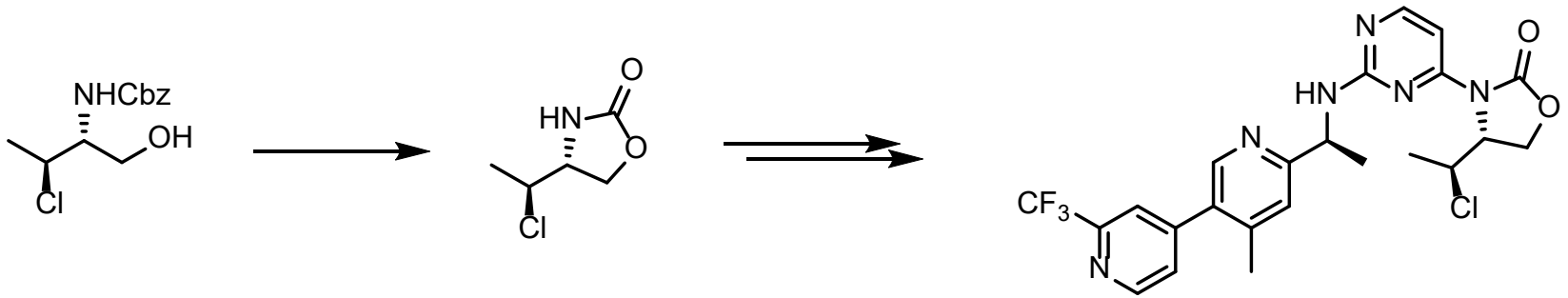


How is it formed? Is that an issue?

Back to the early main chain of IDH305

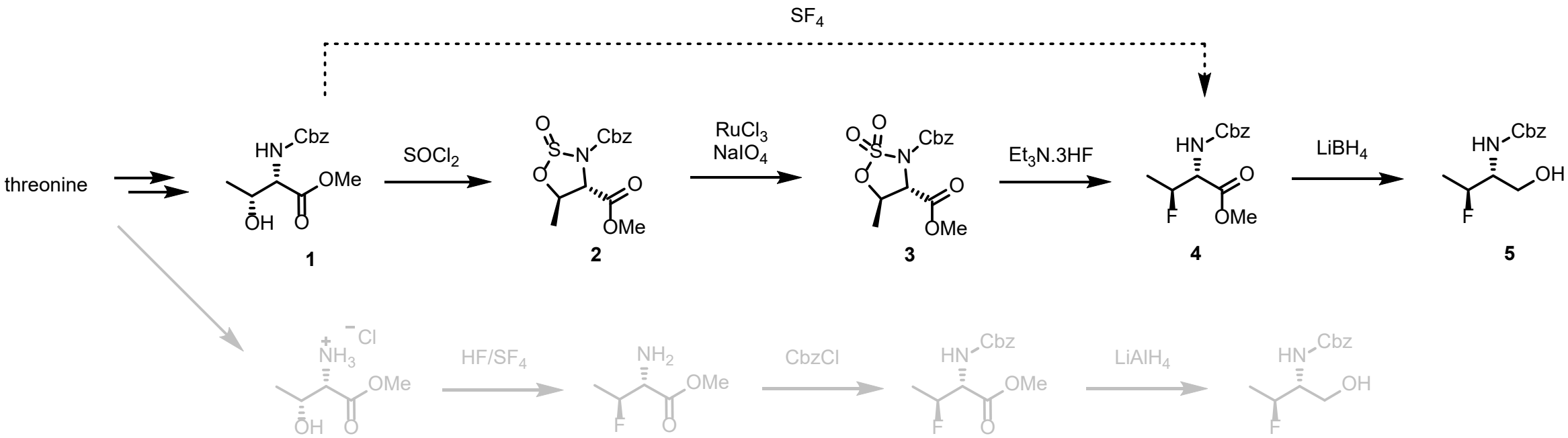


Impurity profile of 5: formation of the chloroanalogue (up to 0.2 A%)

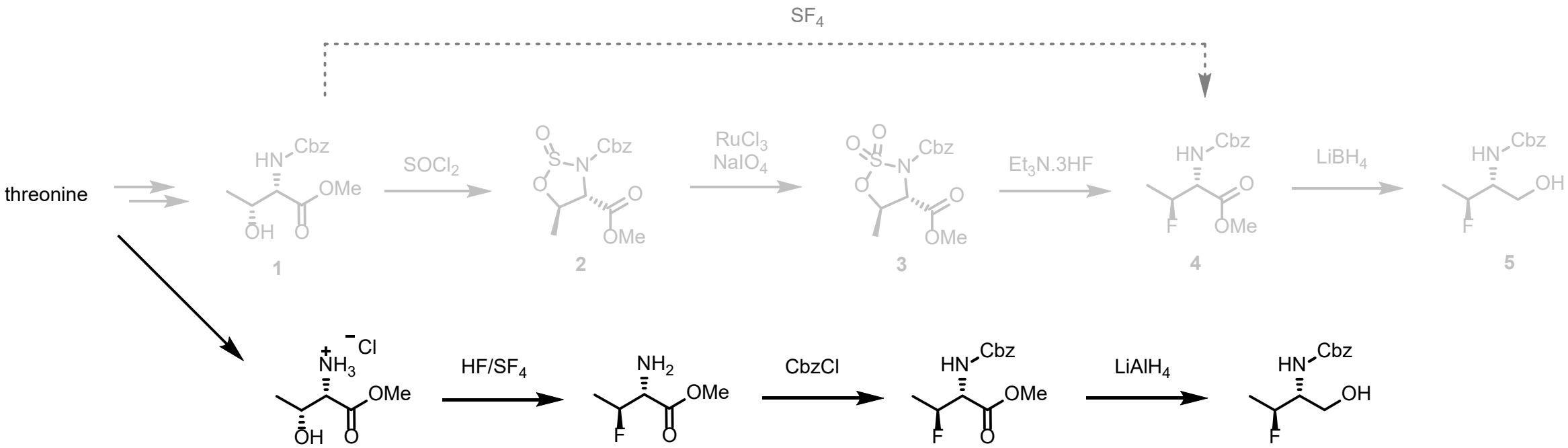


Mutagenic in Ames test

Deoxofluorination with HF/SF_4



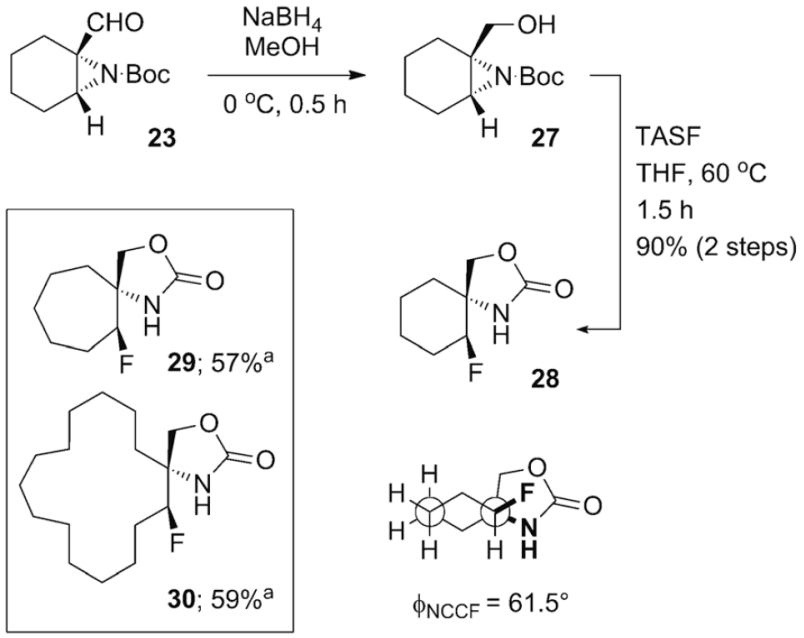
Deoxofluorination with HF/SF_4



- Excess HF necessary to avoid formation of iminosulfur derivatives:
  5 equiv HF, 3.0 equiv SF_4, 5 V DCM, -78 °C, o/n
- Overall yield 67%, dr 92:8

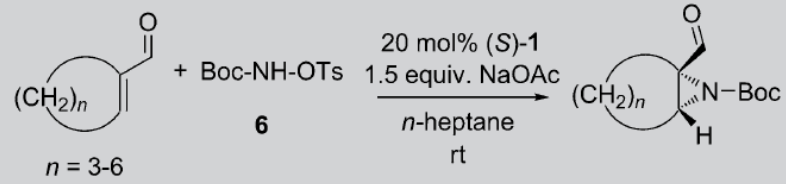
Aziridine opening

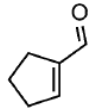
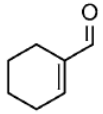
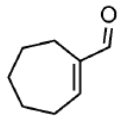
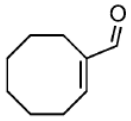
Collaboration with Prof. Gilmour



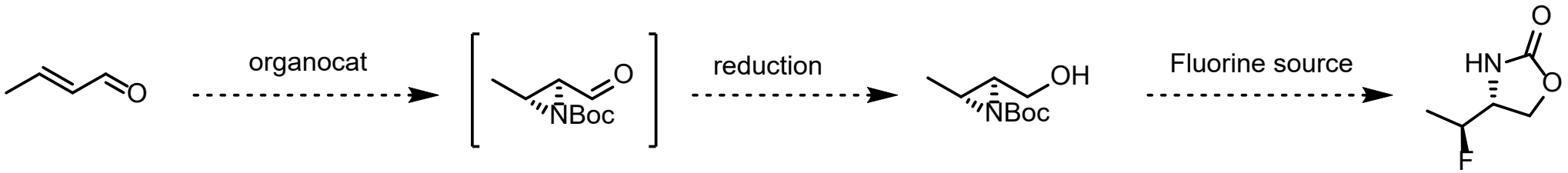
Molnár, I. *et al Chem. Eur. J.* **2014**, *20*, 794-800.

Table 4. Enantioselective, organocatalytic aziridination of small and medium cyclic enals (**15**→**18**) using catalyst (*S*)-**1**.[a]



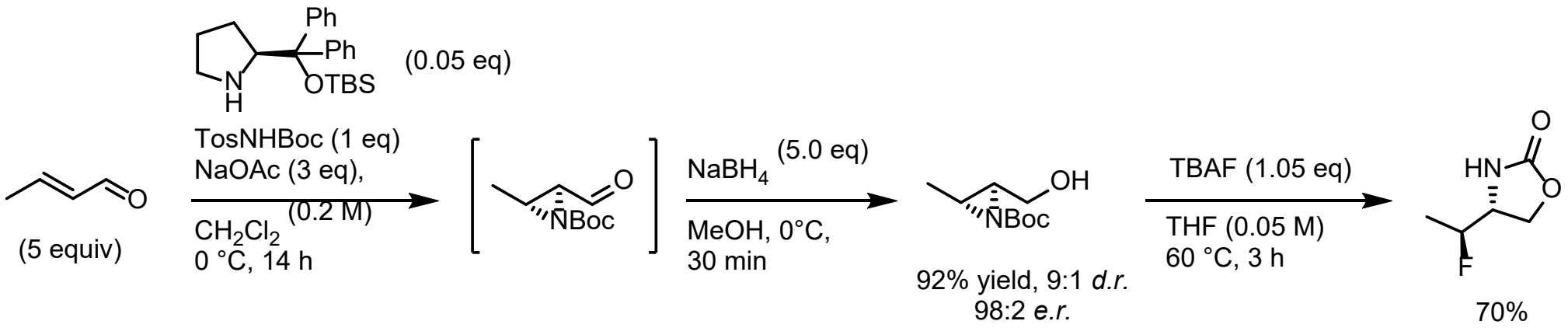
	Substrate	Conditions	Yield [%][b] (conversion)	*d.r.*[c]	*e.r.*
1	 **15**	0.1 mmol scale 4 h	78 (>99)	>20:1	98.5:1.5[d]
2	 **16**	0.1 mmol scale 29 h	84 (>99)	>20:1	97.5:2.5[d]
3		1.00 mmol scale 39 h	81 (>99)	>20:1	96.0:4.0[d]
4		5.00 mmol scale 3 d	83 (97)	>20:1	95.5:4.5[d]
5	 **17**	0.1 mmol scale 8 d	93 (>98)	>20:1	98.5:1.5[e]
6		1.00 mmol scale 13 d	91 (95)	>20:1	98.5:1.5[e]
7	 **18**	0.1 mmol scale 6 d	85 (97)	>20:1	99.0:1.0[e]
8		1.00 mmol scale 8 d	85 (96)	>20:1	99.5:0.5[e]

Aziridine opening



- Organocatalyst should be easy to access and affordable
- High loading of catalyst
- TASF is too expensive for large scale manufacturing
- Reaction conditions should be mild and compatible to a multi-purpose lab/plant

Aziridine opening



Dr. J. Metternich

Assignement

1. Propose a mechanism for the formation of the chloro impurity.

2. Calculate the authorized concentration of the chloro impurity assuming lifetime treatment and a daily dose of 500 mg.

3. Three options were presented for the early main chain of IDH305:
   - analyse each routes (pros & cons) by keeping in mind pharmaceutical industry priorities
   - pick your favorite and explain your decision.

Thank you!

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078 615 2016

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