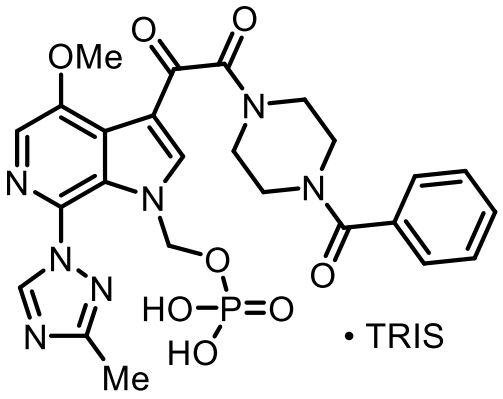
BMS-663068

A Process Chemistry Story



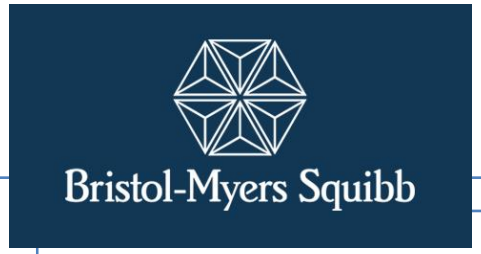
KEVIN A. ROBB

DENMARK GROUP MEETING

JAN. 23, 2018

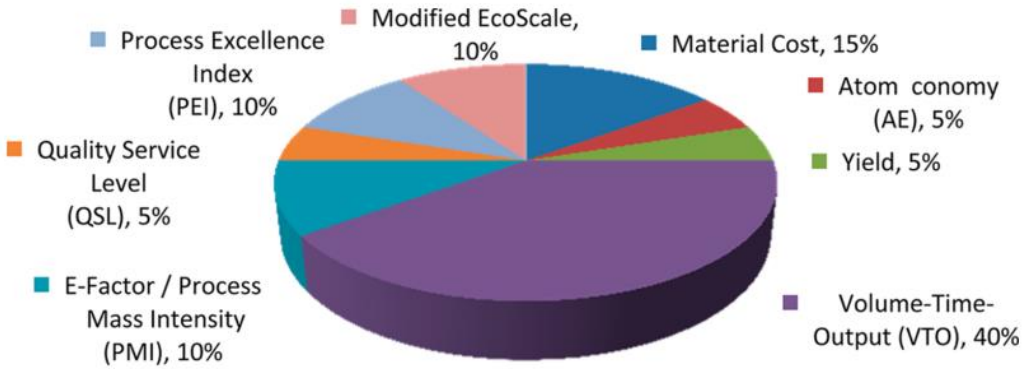
Industrial Organic Chemistry, Part Deux

> 1850 plants & animals, coal
> 1920 acetylene (from coal)
> 1950 oil
> 1973 oil & gas



Bulk chemicals → Fine chemicals → Specialty chemicals

- Medicinal chemistry: *the "ideal" molecule*
- Process chemistry: *the "ideal" synthesis*
  - raw material cost
  - atom economy
  - yield
  - **volume-time-output (throughput)**
  - environmental impact
  - reproducibility



Dach, R. et al. *Org. Proc. Res. Dev.* **2012**, 16(11), 1697-1706.

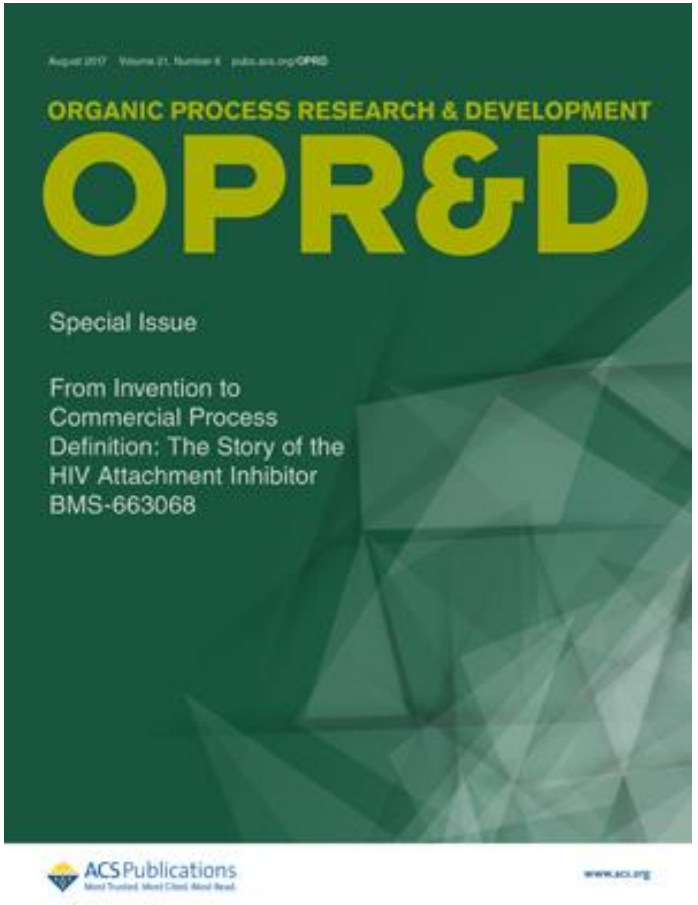
Org. Proc. Res. Dev.

- ACS Journal since 1997, published monthly
  - Today's focus: Aug. 2017 Special Issue
  - "From Invention to Commercial Process Definition: The Story of the HIV Attachment Inhibitor BMS-663068"
  - "Another Quiet Victory for Chemistry"

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Editorial
pubs.acs.org/OPRD

BMS-663068: Another Quiet Victory for Chemistry

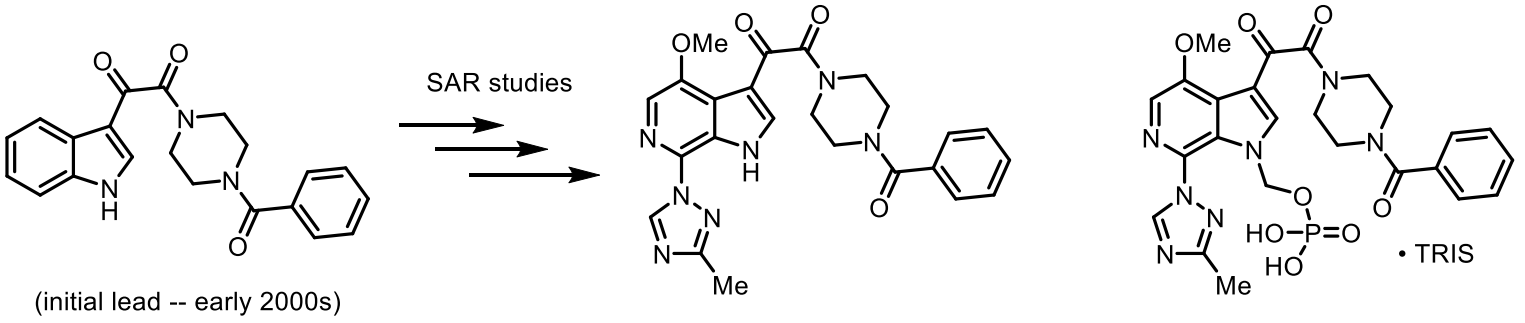
Of the many tabulated lists of humanity's greatest accomplishments circulating on the Internet, few if any acknowledge the advent of modern medicine as a critical inflection point in the evolution of our species. Indeed, the dramatic relief of human suffering, from the alleviation of pain to cures for infectious disease, can be clearly traced to advances in this area. These days, the simple fact that chemical synthesis is at the heart of these wondrous achievements is practically shrouded in secrecy. In fact, most of the society equates chemistry with pollution and being part of a problem rather than celebrating the almost magical solutions it continually provides. One such example of the majesty of chemistry, this time in the development of a potential medicine (BMS-663068) to block the entry of HIV-1 virus into healthy cells, is outlined in this



Baran, P. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1091-1094.

Background

- Development of an HIV attachment inhibitor
  - Inhibits binding between viral gp120 (envelope glycopeptide) and CD4 (host cell receptor)
  - Novel mode of action against HIV
  - Complements existing antiretrovirals
- BMS-626529
  - high inhibitory activity
  - poor solubility, short half-life, low bioavailability
- BMS-663068
  - pro-drug API (active pharmaceutical ingredient)

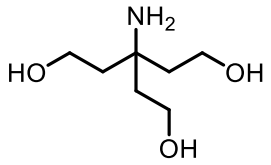


(initial lead -- early 2000s)

BMS-626529 (DRUG)
(2012)

BMS-663068 (PRO-DRUG)

TRIS = tromethamine =



Baran, P. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1091-1094.
Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1095-1109.

Talk Outline

- Enabling Routes (Part 1)
  - Medicinal Chemistry Route
  - First Generation Scale-Up Campaign
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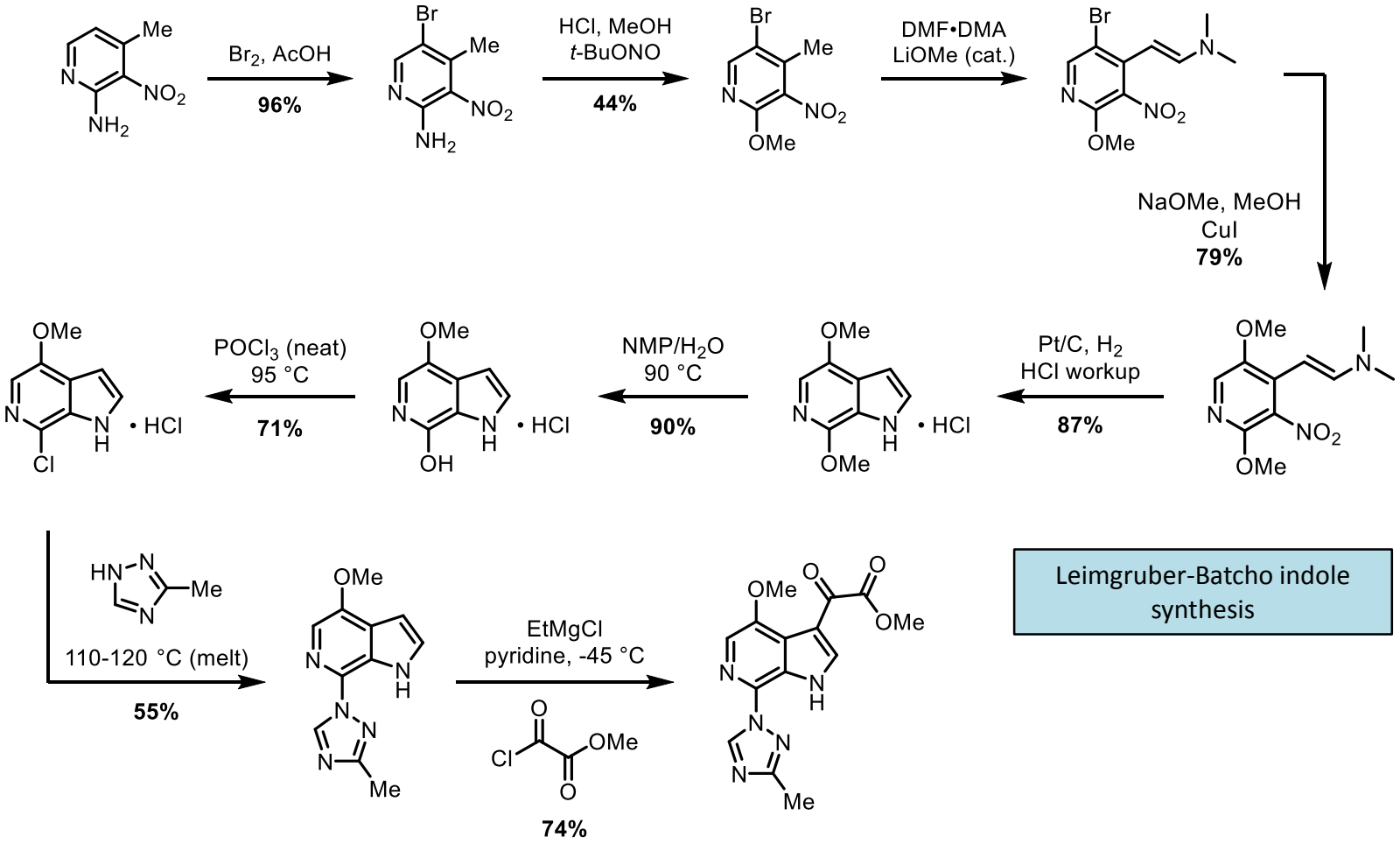
  - API Process Development (9)

Medicinal Chemistry Route

- 12 steps, 3-4% overall yield



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Medicinal Chemistry Route

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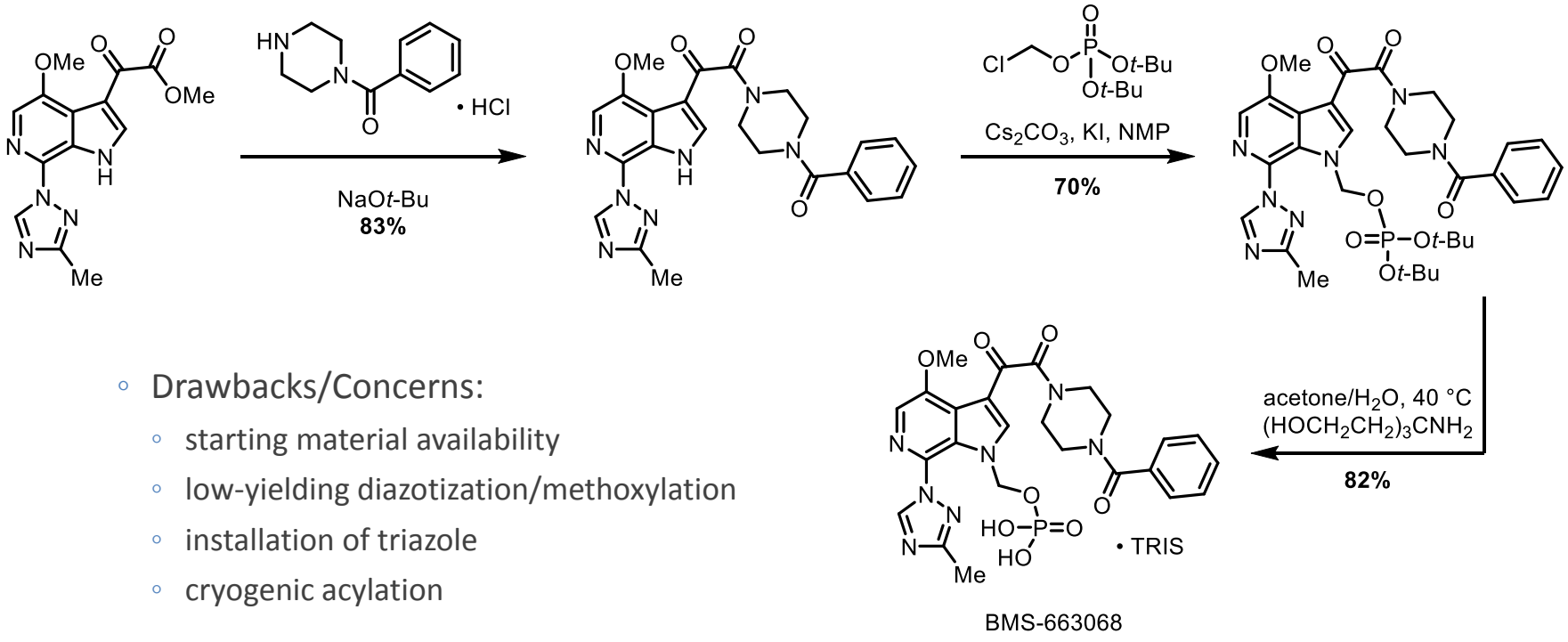
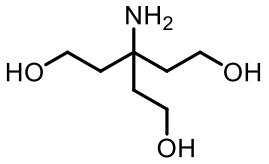


BMS-663068

- Drawbacks/Concerns:
  - starting material availability
  - low-yielding diazotization/methoxylation
  - installation of triazole
  - cryogenic acylation

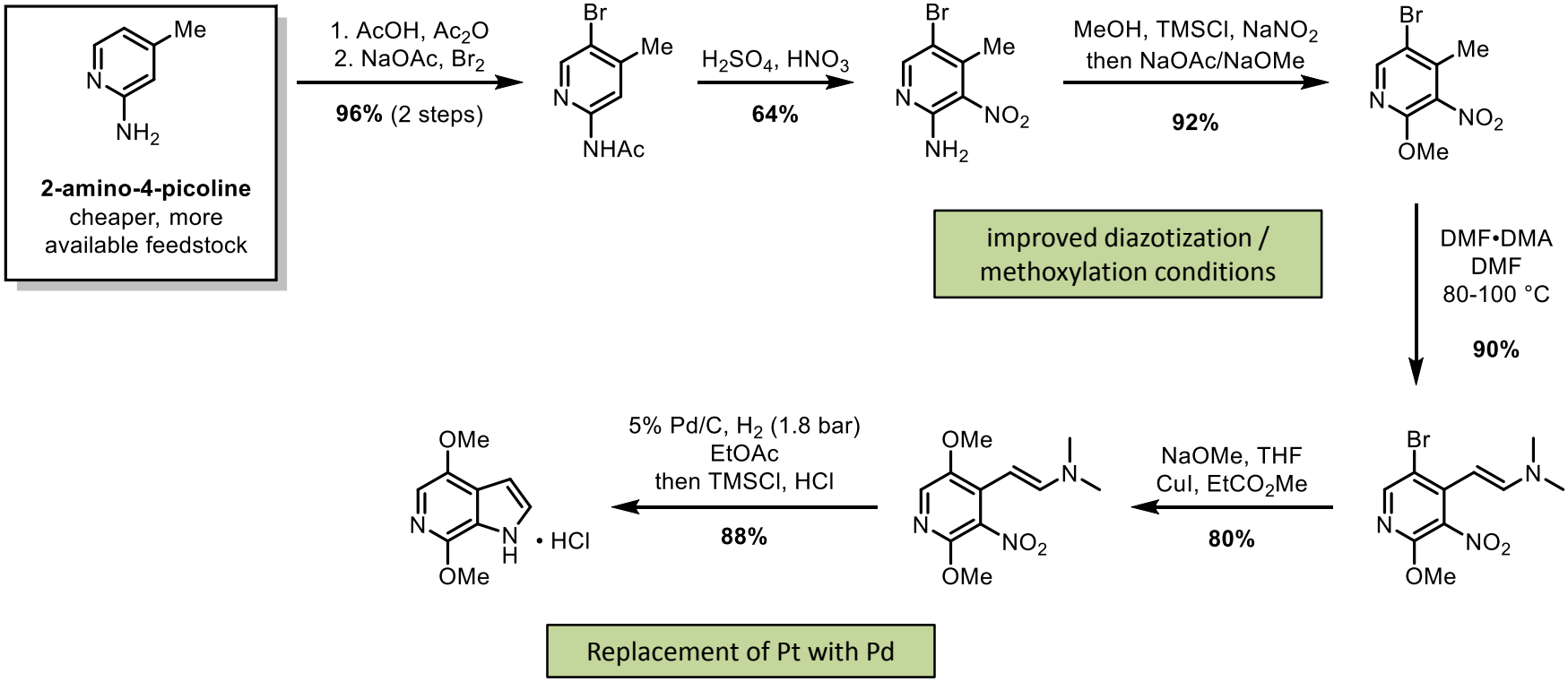
TRIS = tromethamine =



Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1095-1109.

First-Generation

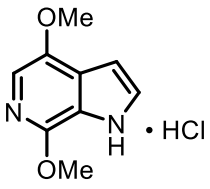
- Goal for first scale-up campaign: 100 kg
- Closely follows medicinal chemistry route
  - Stopgap measures / short-term work-arounds to address problem steps



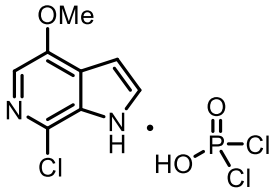
Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1095-1109.

First Generation

removed melt conditions

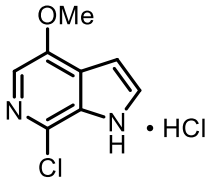


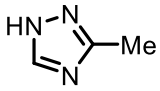
$POCl_3$ (neat)
100 °C, 40 h



MeOH
50 °C

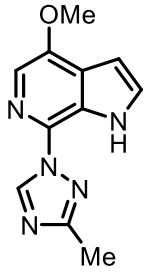
93% (2 steps)





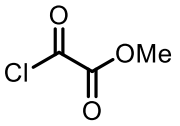
4-Me-2-pentanol
132 °C, 2 days

51%



still requires neat $POCl_3$, phosphate salt difficult to handle

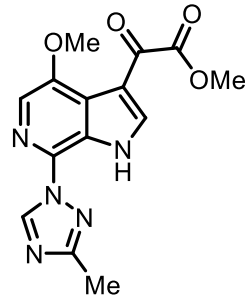
then add slowly to



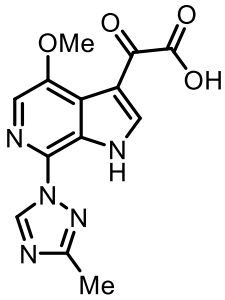
76%

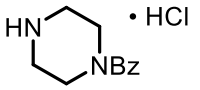
optimized acylation conditions

i-PrMgCl (3.5 equiv)
pyridine (0.5 equiv)
MeTHF, -25 to -10 °C



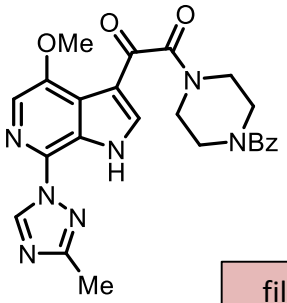
3:1 NMP/water
KO*t*-Bu (3 equiv)



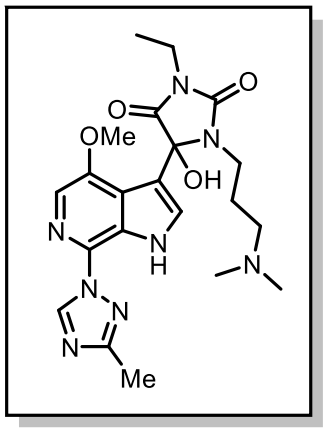


HCl, EDAC

77% (2 steps)

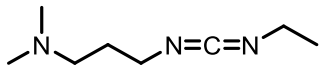


filtration of amide product requires 2 weeks!! (26 kg)



amidation requires rigorous pH control

EDAC =



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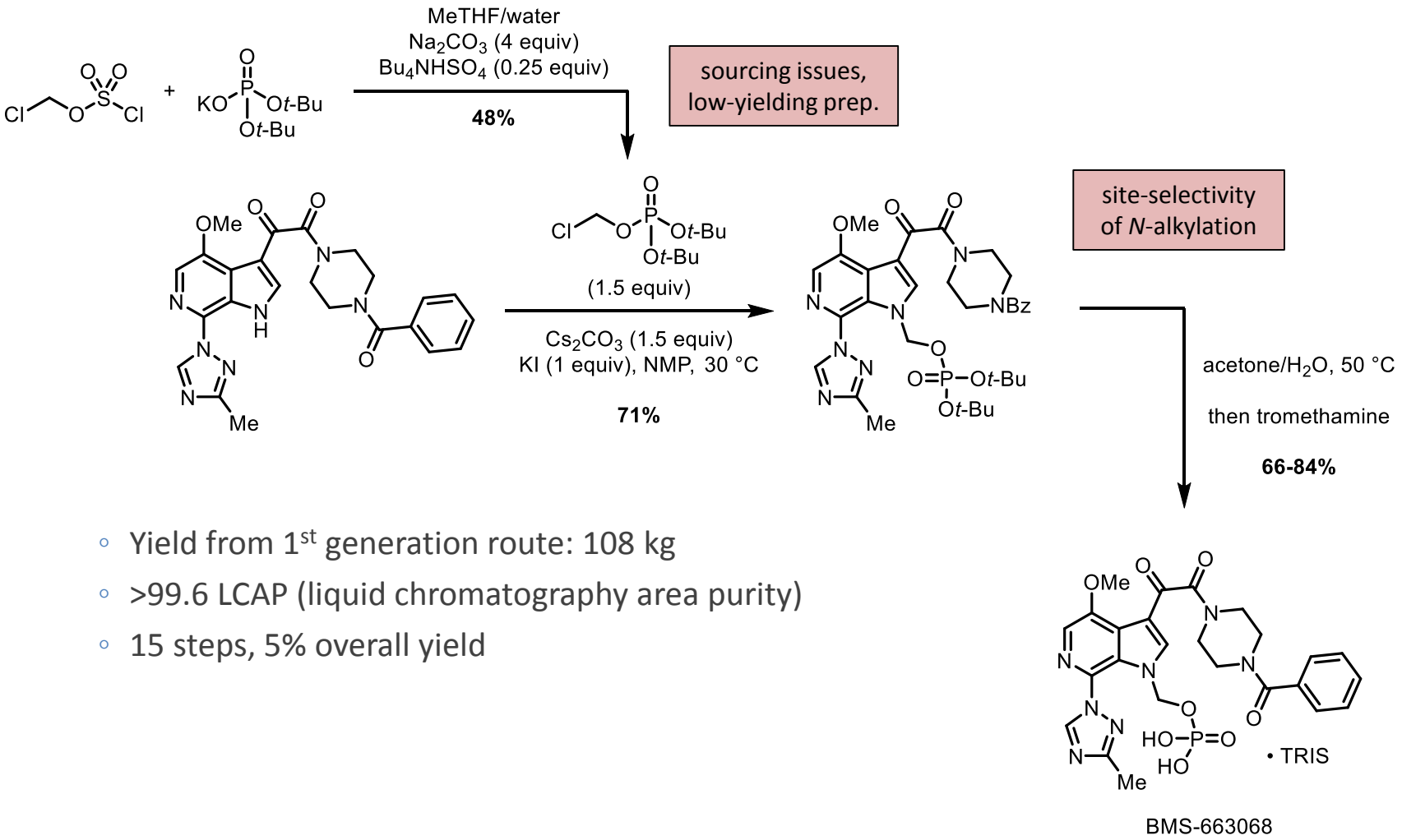
First Generation



- Yield from 1st generation route: 108 kg
- >99.6 LCAP (liquid chromatography area purity)
- 15 steps, 5% overall yield

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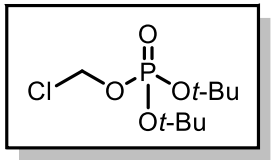
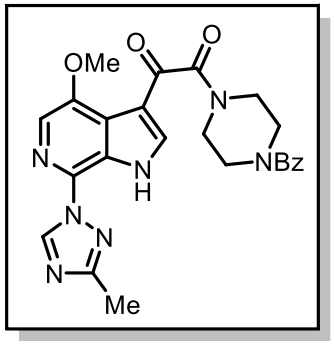
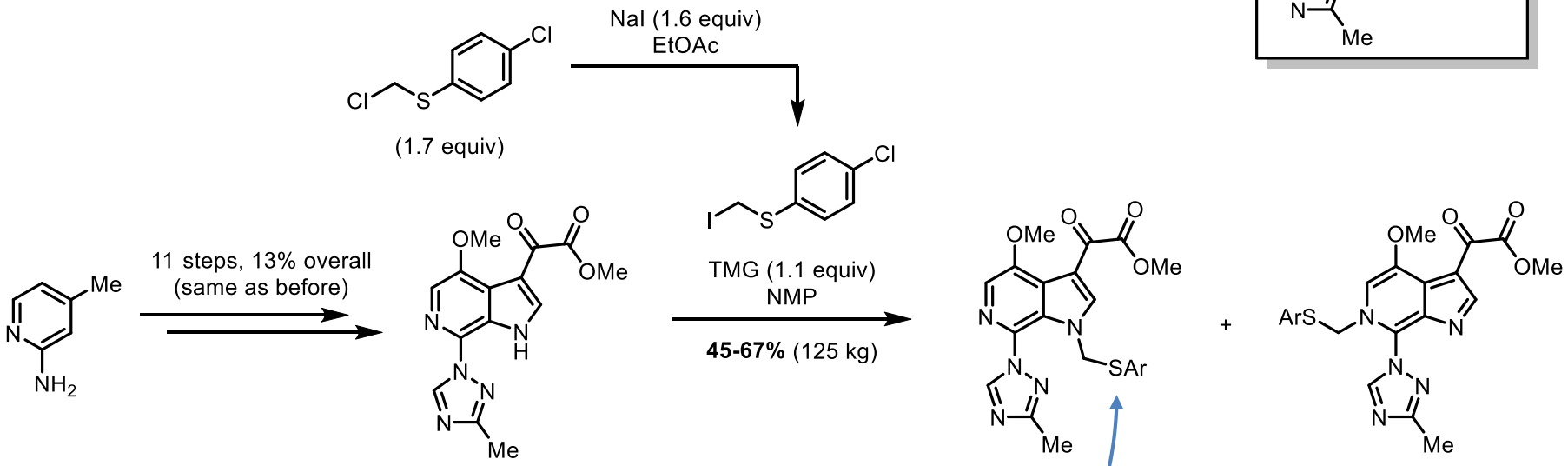
Second Generation

- Focused only on endgame optimization
  - Goal: avoid isolation of problem amide (difficult to filter)
  - Goal: avoid using problem alkylating agent (poor availability, low-yielding synthesis, unstable)





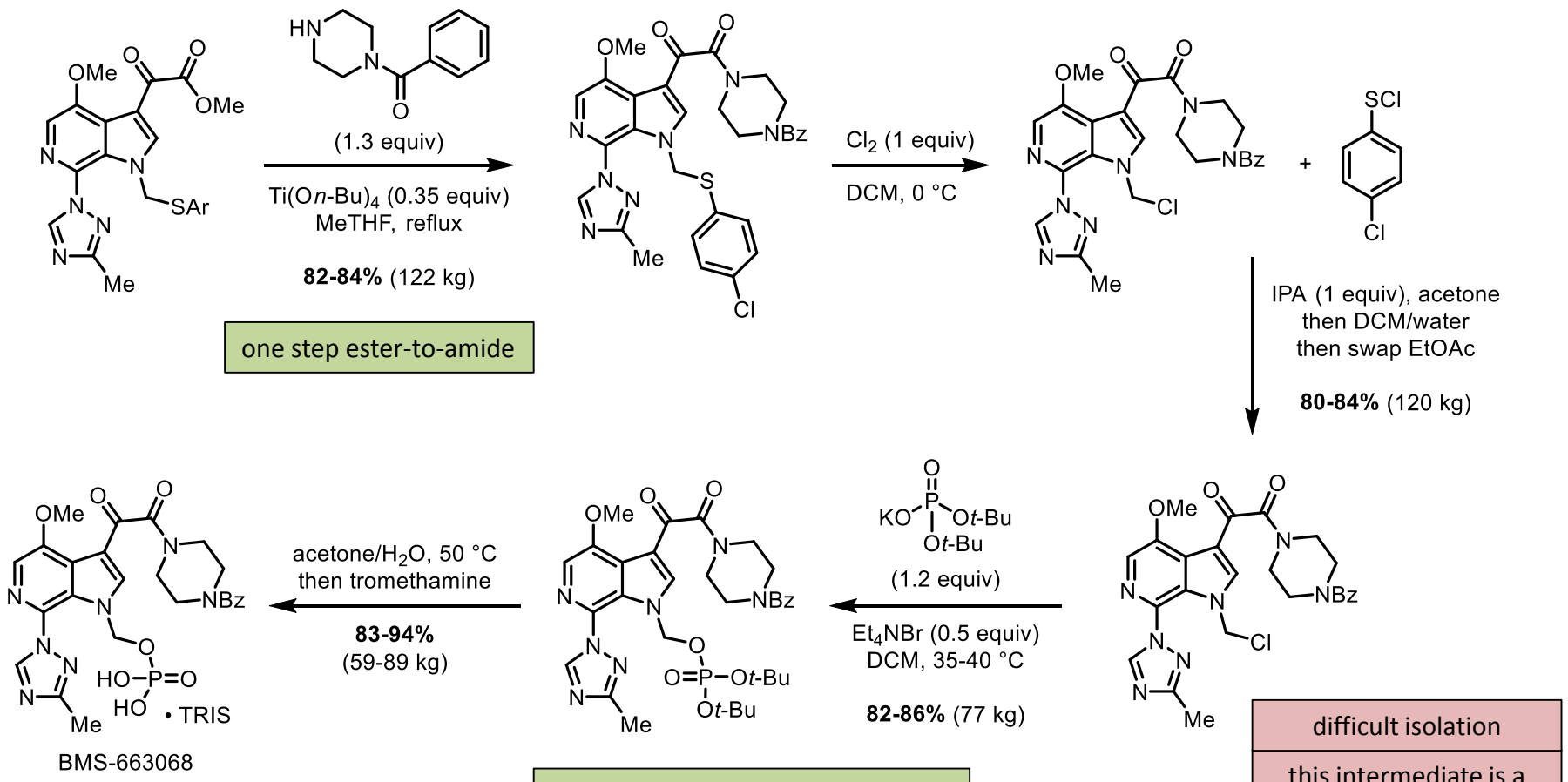


- Strategy: *N*-alkylation with “masked halide” followed by amidation, unmasking, and displacement with di-*t*-butyl potassium phosphate

site-selectivity of *N*-alkylation
but minor isomer is more easily removed than before
extractions are time-consuming

Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1095-1109.

Second Generation



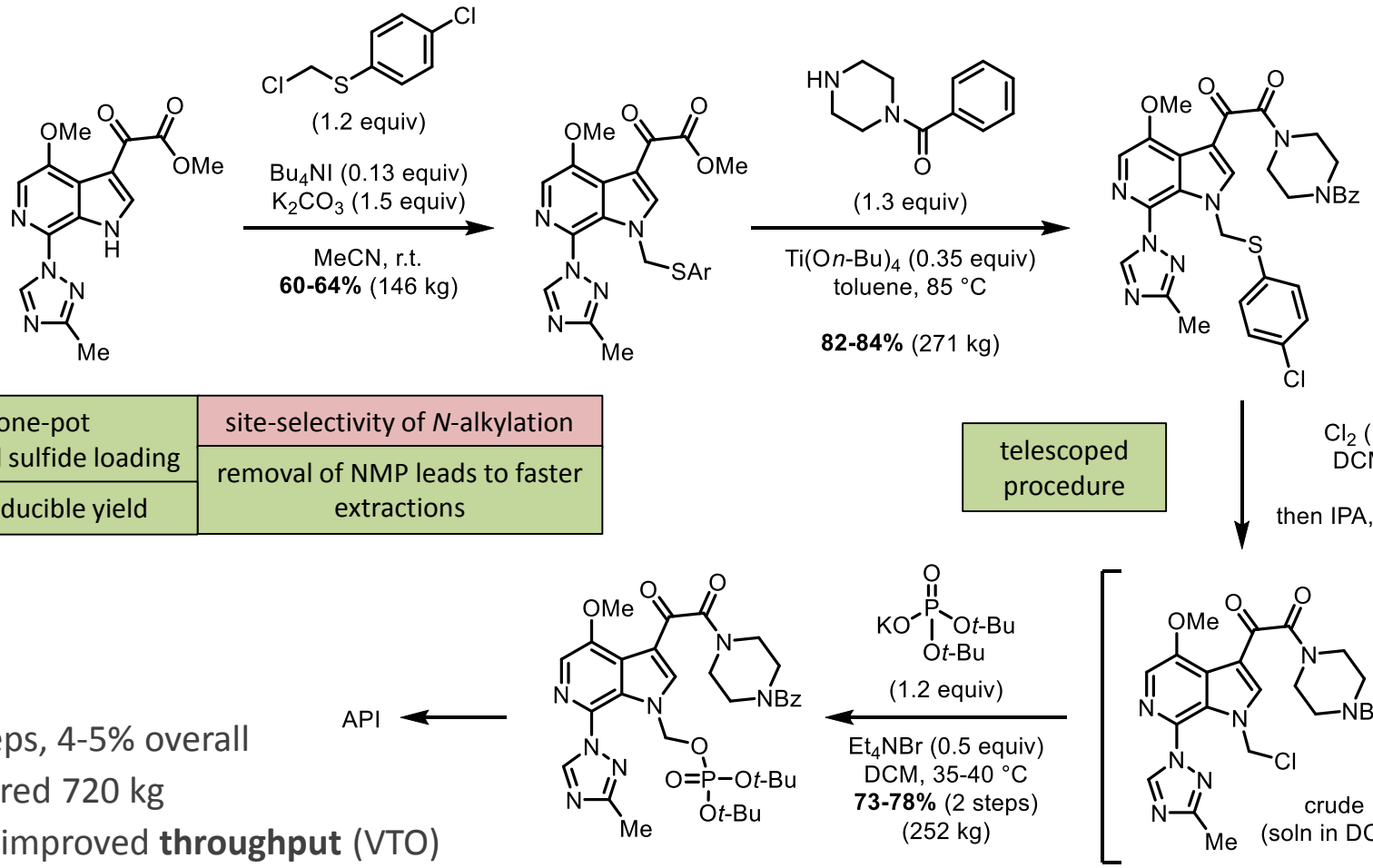
- 16 steps, 3-5% overall yield
- prepared 218 kg
- improved **throughput** (VTO)

Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1095-1109.

Third Generation

- Again, focused only re-optimization of endgame
  - Goal: improve yields/throughputs for 5 endgame steps

MeTHF replaced with toluene



one-pot reduced sulfide loading	site-selectivity of *N*-alkylation
reproducible yield	removal of NMP leads to faster extractions

telescoped procedure

- 16 steps, 4-5% overall
- prepared 720 kg
- again improved **throughput** (VTO)

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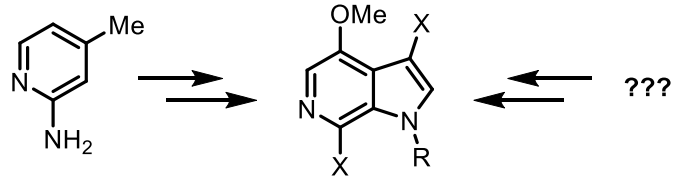
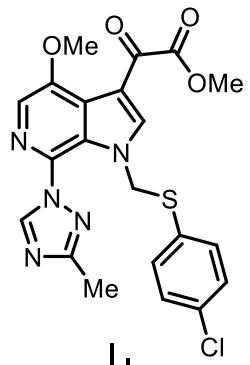
Part 2: Back to the Drawing Board

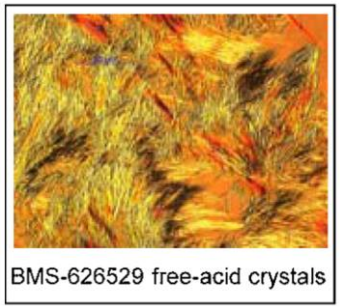
Dr. Martin Eastgate

- Several problems with enabling routes:
  - Lengthy synthesis of 6-azaindole core (several FGI steps, solvent quantities of $POCl_3$)
  - Triazole installation (thermal requirements)
  - Inefficient endgame synthesis to install pro-drug
    - Genotoxic intermediates (GTIs)
    - Chlorine gas

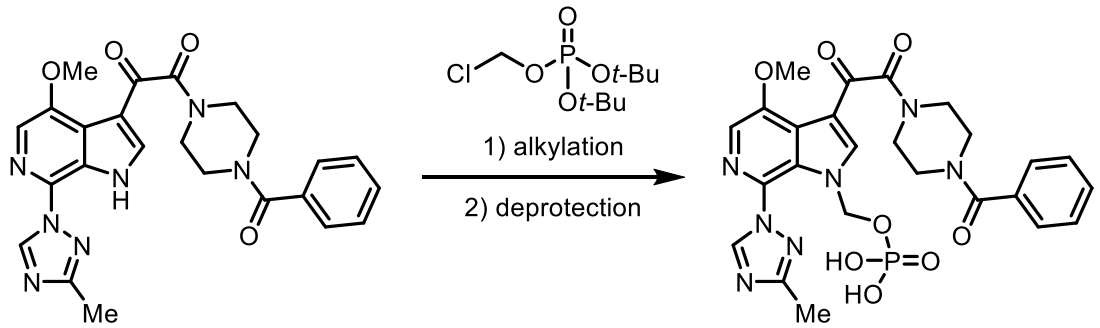


- Two primary goals:
  - More efficient synthesis of 6-azaindole core
    - Desired substitution patterns *without* directing groups
  - Simplify pro-drug installation
    - Possibly involving: addressing the isolation of BMS-626529





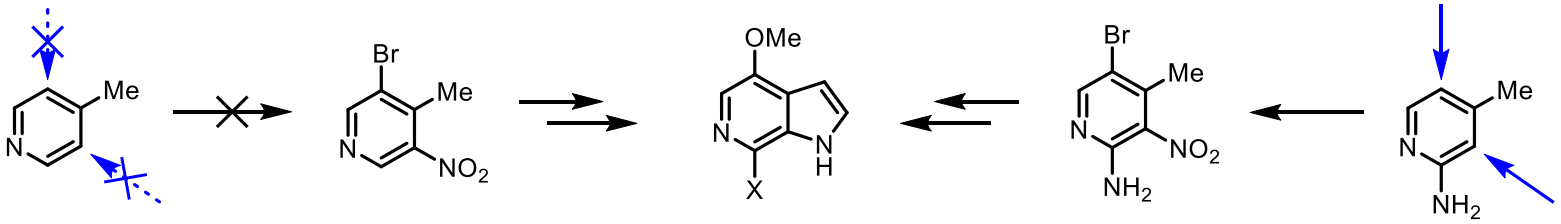
BMS-626529 free-acid crystals



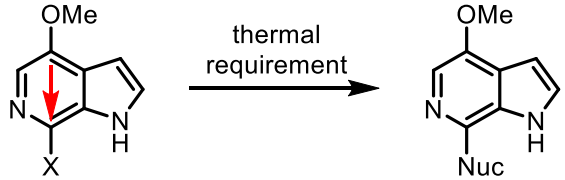
Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1110-1121.

6-Azaindole Core

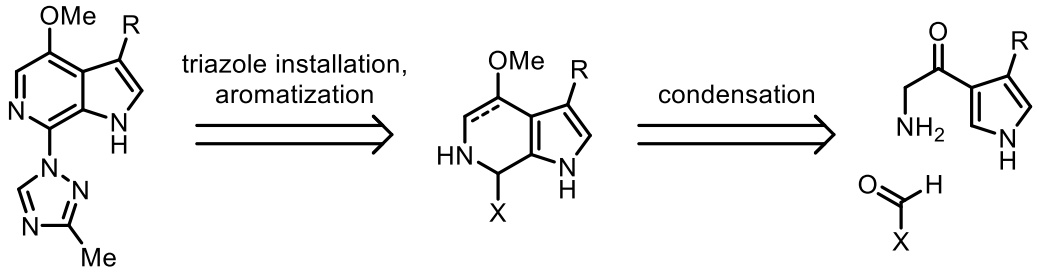
- Most problems arise from using *pyridine* as a starting material
  - Desired: selective *meta* functionalization of methylpyridine … but these are the exact positions which are difficult to functionalize
  - Requires amino group to direct functionalization
  - Both initially installed FGs (-Br and -NO_2) AND directing group (-NH_2) are subject to future FGI!



  - Additionally, C4-methoxy group deactivates system towards S_NAr



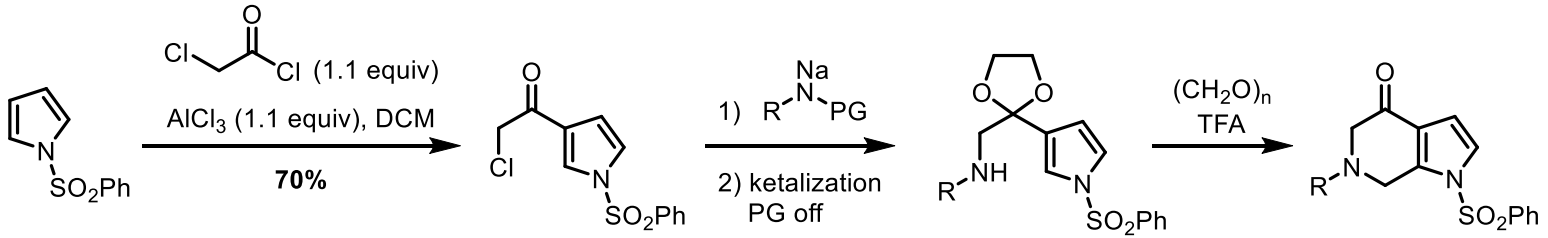
- Proposed solution: use *pyrrole* as a starting material



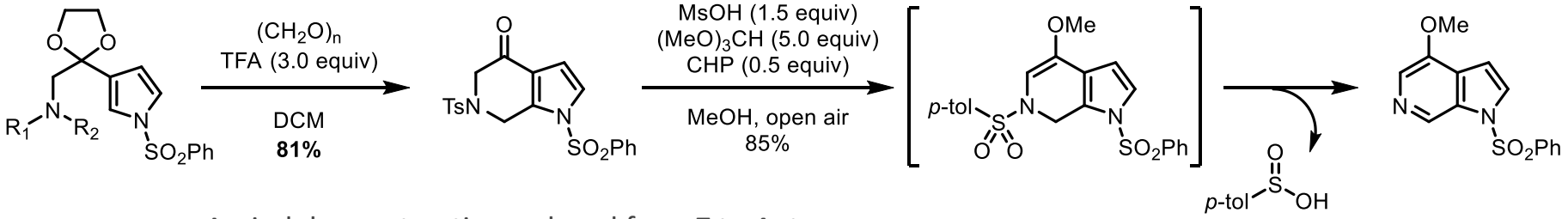
Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1110-1121.

Core Assembly

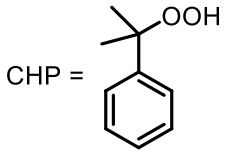
- Construction of 5-6 fused ring system
  - Pyrrole alkylates exclusively at C3 position (desired)
  - Pictet-Spengler reaction is compatible with a number of pendant 1° and 2° amines



  - Prepared several derivatives containing C4-oxo FG, but lacking any C7 functionality
  - Aromatization accomplished by radical-initiated redox-elimination process



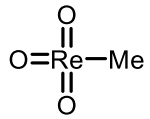
  - Azaindole construction reduced from 7 to 4 steps
  - Relies on inherent electronic selectivities
  - Can employ F-C for the next C3-acylation as well
  - **Still needed:** method for triazole installation



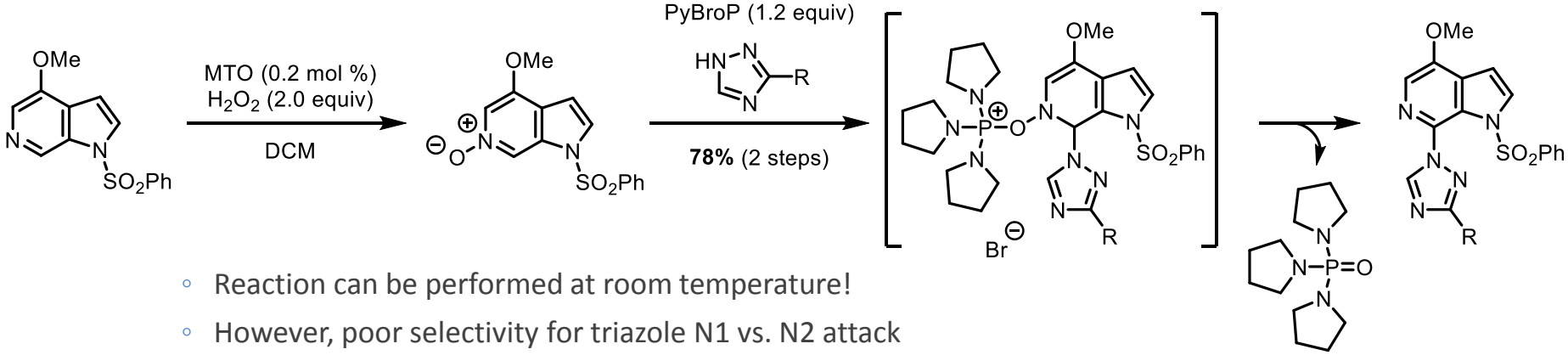
Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1110-1121.

Triazole Installation

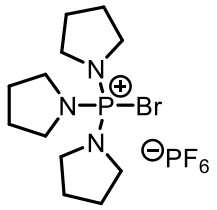
- Modified Reissert reaction
  - Formation of *N*-oxide enhances electrophilicity of C7



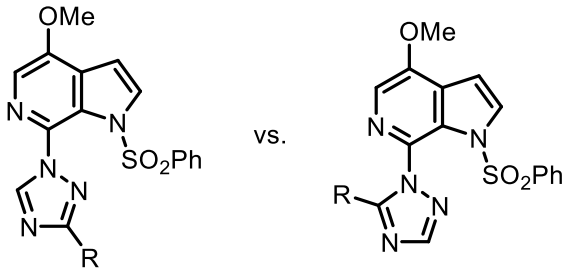
Methyltrioxorhenium(VII)
MTO



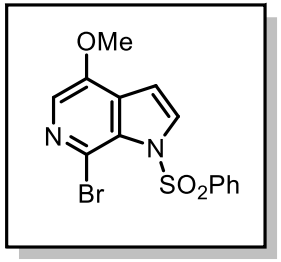
  - Reaction can be performed at room temperature!
  - However, poor selectivity for triazole N1 vs. N2 attack
  - Selectivity could be improved by replacing (R = Me) with (R = CN) or (R = CO_2Me), but this adds additional steps



Bromotripyrrolidinophosphonium hexafluorophosphate
PyBroP



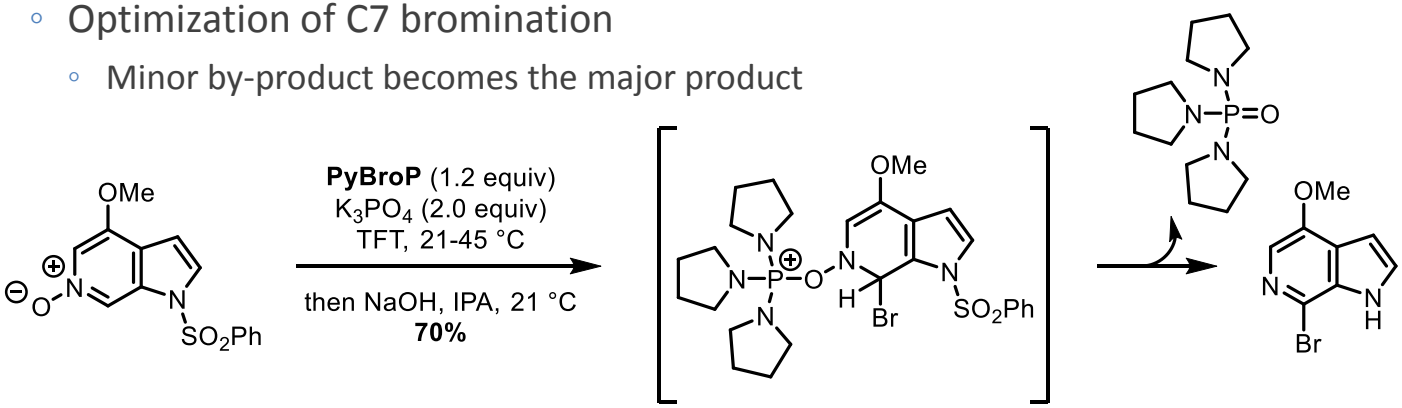
A serendipitous discovery! This compound was identified as a minor impurity



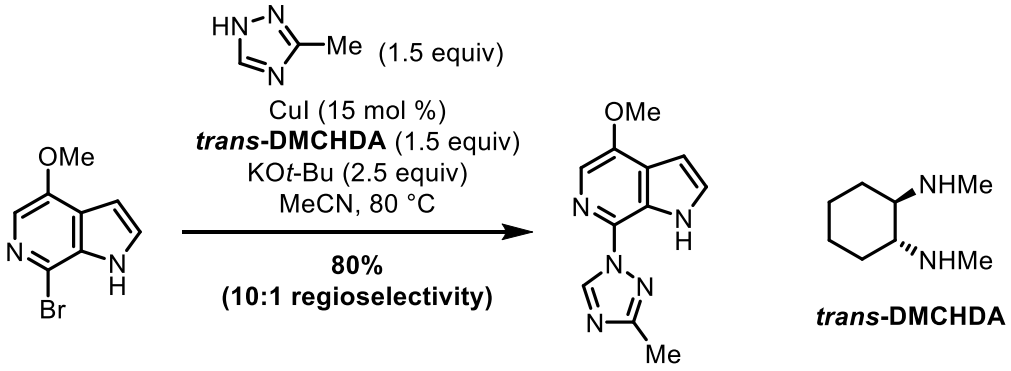
Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1110-1121.

Cross-Coupling Approach

- Optimization of C7 bromination
  - Minor by-product becomes the major product



  - Triazole can now be installed with traditional, TM-catalyzed *cross-coupling*
  - Ullmann-Goldberg-Buchwald conditions offered much improved control over triazole regioselectivity



Now have the option to install triazole very late stage, after C3 acylation and amidation

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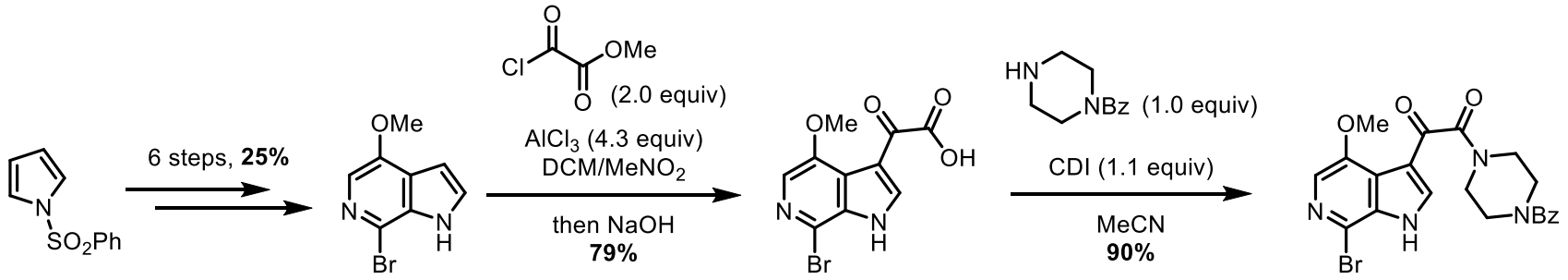
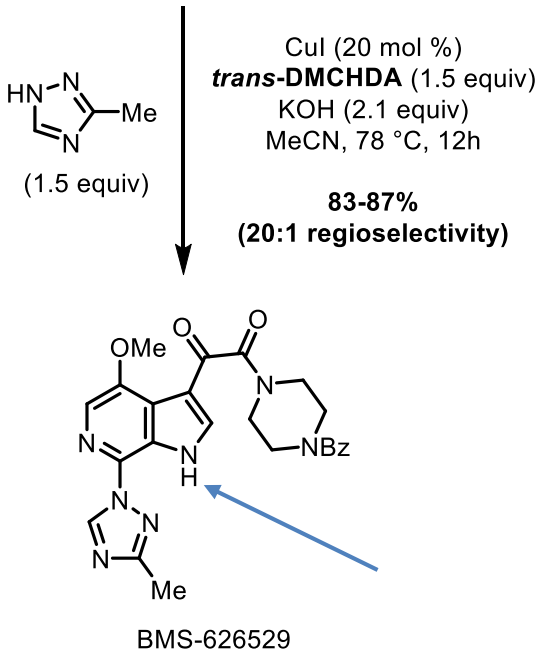
BMS-626529, Revisited

- The parent drug can now be accessed in expedient fashion



- BMS-626529 (drug) has poor crystal morphology, solubility
- Previous routes avoid isolating this molecule as an intermediate
- Can basic NH be exploited to access a more crystalline salt form?



> In taking a fresh look at the data it was apparent that all of the salts and cocrystallizing agents explored with this compound were "pharmaceutically acceptable" options; that is, everything explored was considered safe to be included in the drug substance. As this compound was not the final drug substance (it was an intermediate toward the pro-drug), we asked a simple question—what about "pharmaceutically unacceptable" options?

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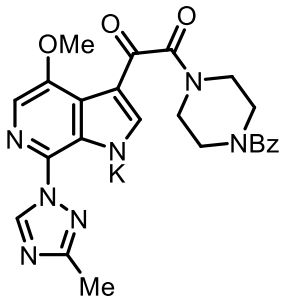
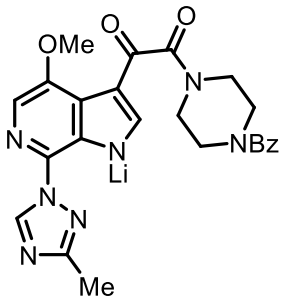
“Unacceptable” Option

- Li salt of BMS-626529 has excellent morphology
  - After Ullmann coupling, a potassium-lithium salt metathesis was performed

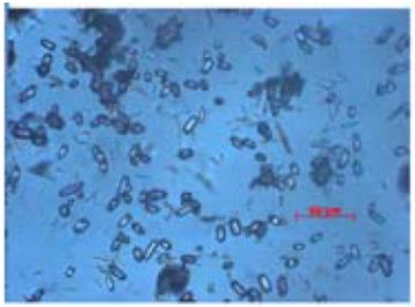


solubility in MeCN
>40 mg/mL

LiBr

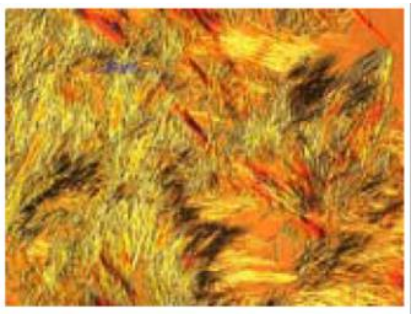


solubility in MeCN
<2 mg/mL



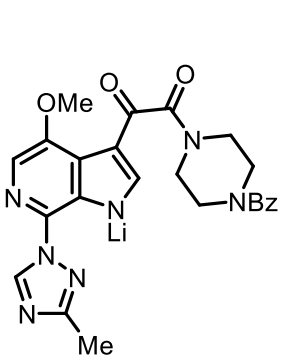
Li-salt
easily filtered

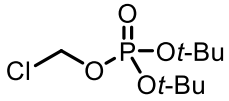
vs.



free base
>2 week filtration

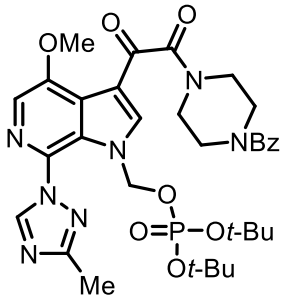
- Alkylation, hydrolysis, and TRIS salt formation completed the synthesis of BMS-663068





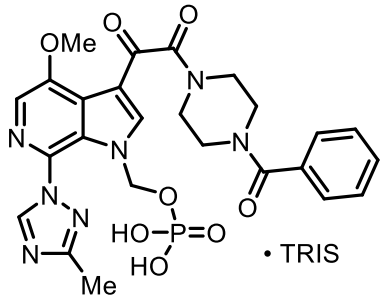
(1.3 equiv)
K_3PO_4 (1.0 equiv)
TEAI (0.5 equiv)

MeCN, 45 °C, **61%**



AcOH, water
TRIS (1.0 equiv)
35 °C, acetone

88%



BMS-663068

11 steps, 6% overall yield

Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1110-1121.

Talk Outline

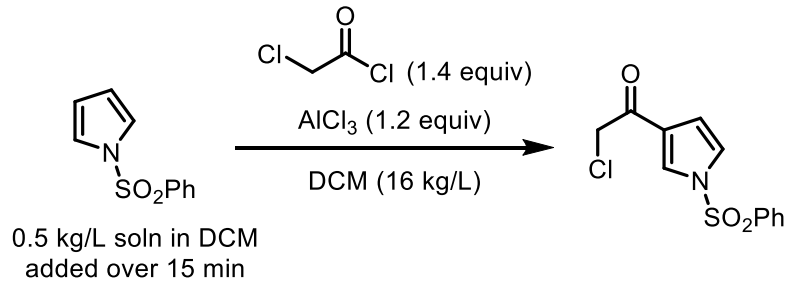
- Enabling Routes (Part 1)
  - Medicinal Chemistry Route
  - First Generation Scale-Up Campaign
  - Second Generation Scale-Up Campaign
  - Third Generation Scale-Up Campaign
- Commercial Route (Part 2)
  - Strategies and tactics for an improved route
  - Key discoveries
  - Completion of the route
- Approaching Ideality (Parts 3-9)
  - Pyrrole Acylation (3)
  - Azaindole Construction (4)
  - Bromination Sequence (5)
  - Acylation/Amidation (6)
  - Cross-Coupling (7)
  - Prodrug Chain Installation (8)
  - API Process Development (9)

Part 3: A Scalable F-C Acylation

Dr. Greg Beutner

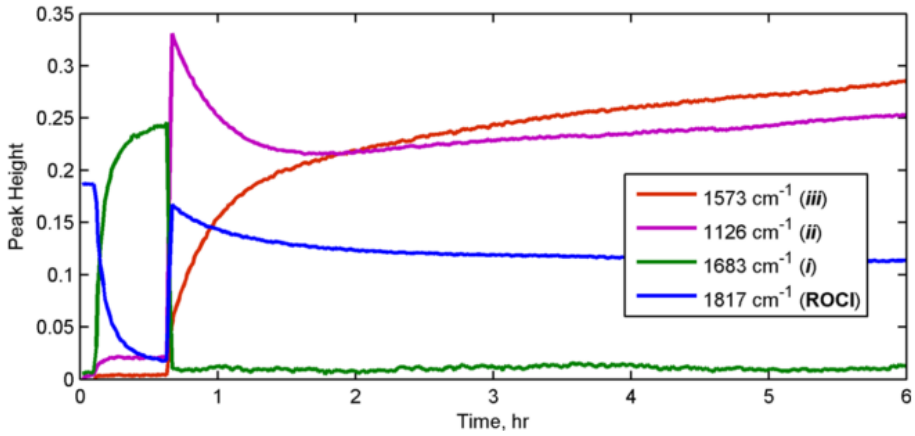
- Pyrrole acylation (first step in commercial route)
  - Optimized with DoE study, but…

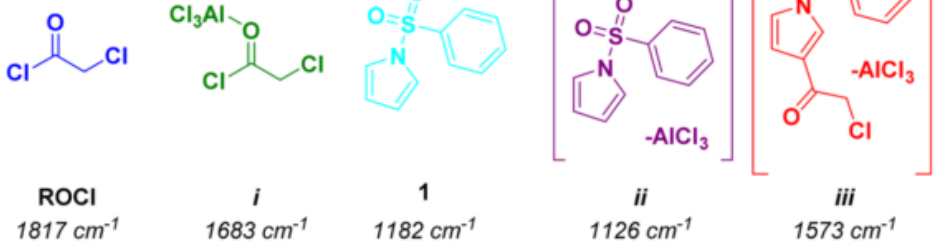
DoE input:
temperature
equiv $ClCH_2COCl$
equiv $AlCl_3$
reactor headspace
conc. of pyrrole soln.
pyrrole rate of addn.
agitation rate



scale	***yield***
120 kg	71%
450 kg	35%

- Rxn is insensitive to temperature and/or reactor headspace
- Rxn is homogeneous with little exotherm (not a heat- or mass-transfer problem)
- Further experiments undertaken to find missing variable



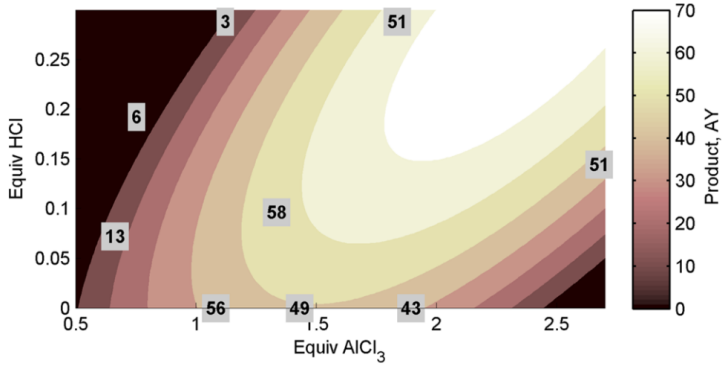


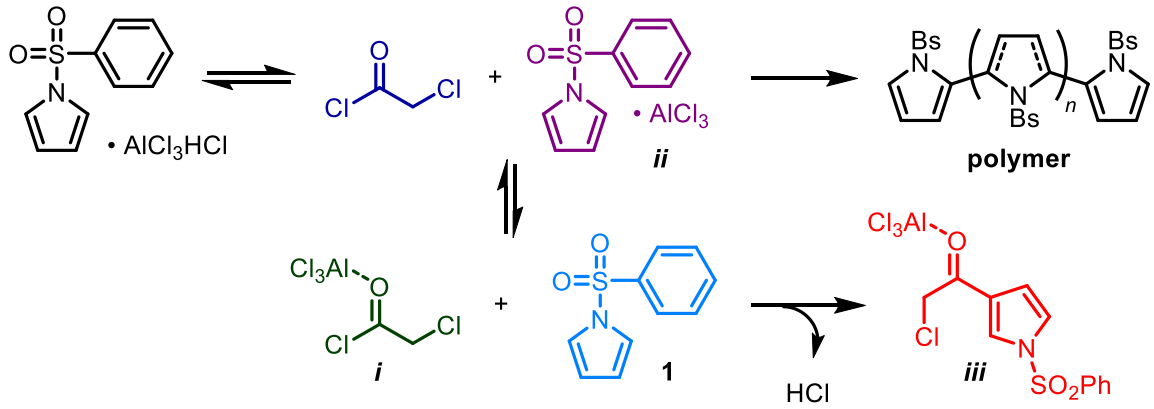
ROCl *1817 cm^{-1}* | ***i*** *1683 cm^{-1}* | **1** *1182 cm^{-1}* | ***ii*** *1126 cm^{-1}* | ***iii*** *1573 cm^{-1}*

Beutner, G. L. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1122-1130.

The Role of HCl

- Hydrogen chloride is produced stoichiometrically
  - Exp. 1: Reactor continuously purged with N_2 (no HCl)
    - Full conversion of pyrrole
    - <5% yield desired product! (polymeric decomp.)
  - Exp. 2: Solvent saturated with HCl
    - no conversion
    - pyrrole recovered (no decomp.)
  - Non-linear dependence of yield on HCl equiv.



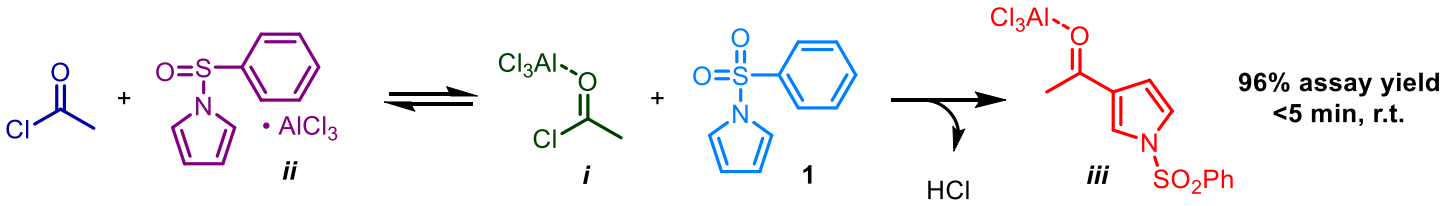


  - Scale-dependence due to inability to control [HCl] over time in large reactors

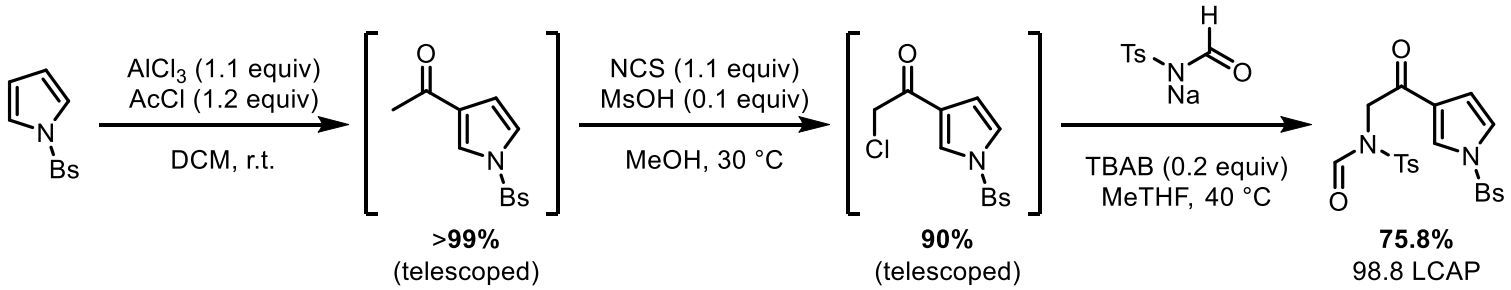
Beutner, G. L. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1122-1130.

A Better Electrophile

- Using AcCl as electrophile led to dramatic increase in rate/yield
- Binds more strongly to $AlCl_3$, shifts equilibrium favorably



- New route adds one linear step, but removes scale-dependence
- Demonstrated on 420 kg scale with consistent yields/purities



- On DoE:

> Although this technique has proven powerful and insightful for such fine-tuning of reaction conditions, it may have limitations if the conditions are at a local, rather than a global, optimum.

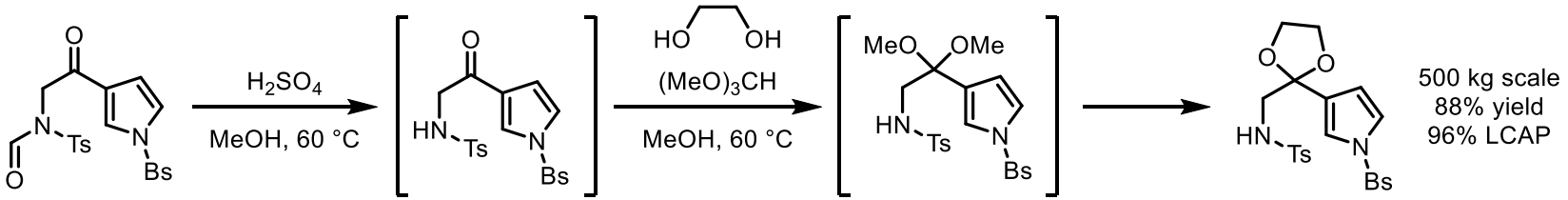
- On step count:

> Exclusive focus on simple metrics like step count may in fact hinder the effort to identify more efficient processes.

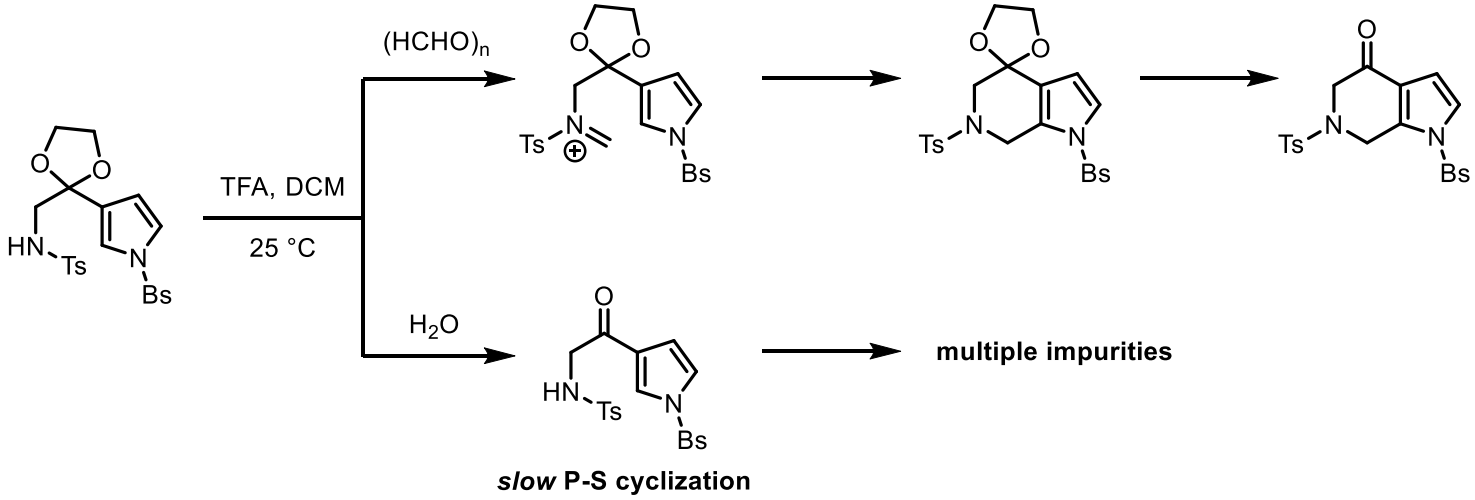
Beutner, G. L. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1122-1130.

Part 4: P-S Troubleshooting

- Ketal formation scaled well
  - One-pot *N*-formyl deprotection, dioxolane formation



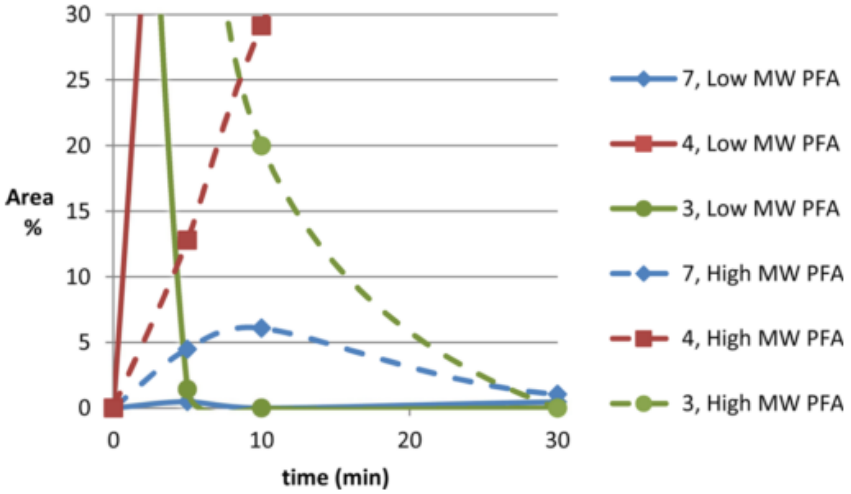
- Pictet-Spengler reaction scaled poorly
  - Above 5 kg, increased impurity levels and variable yields were observed
  - Hypothesized that ketal hydrolysis is competing with iminium ion formation

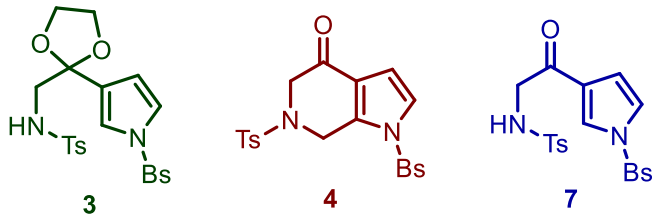


Bultman, M. S. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1131-1136.

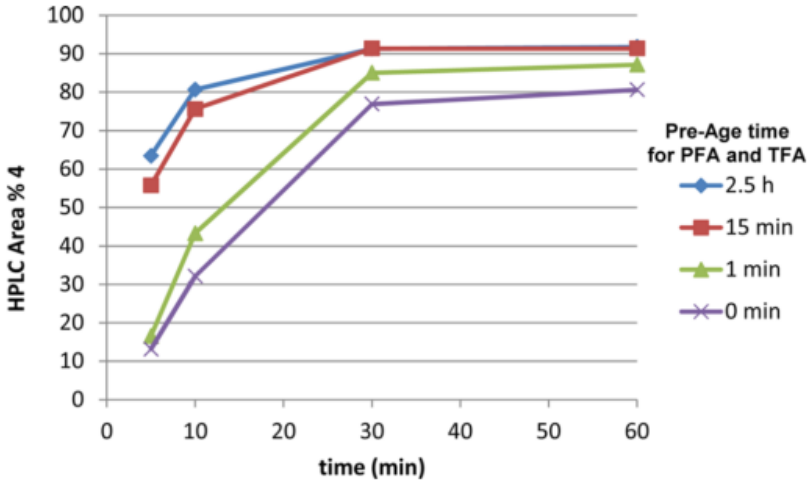
The Source of the Problem

- paraformaldehyde (PFA)
  - different sources (lots) of PFA gave vastly different results
  - *molecular weight* of the polymer was the key variable
    - high MW = low solubility in DCM = low monomer concentration = decreased rate & yield





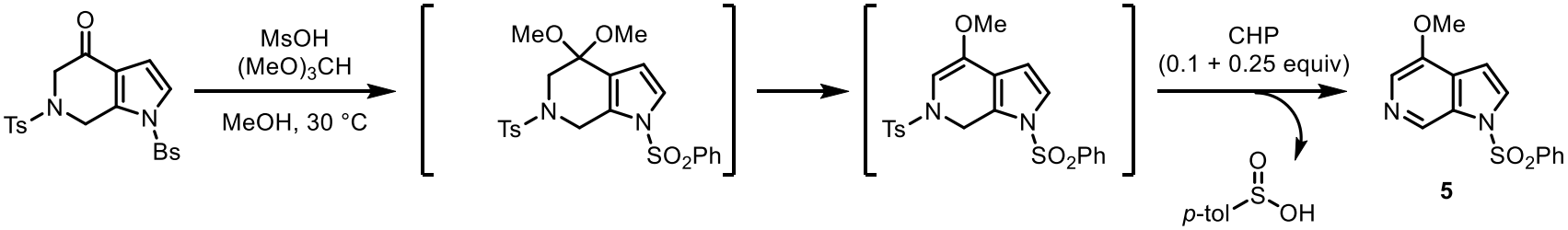
- Sourcing only low MW PFA is expensive
- Premixing high MW PFA with TFA leads to reproducible results
- 480 kg scale, 81% yield, >99 LCAP



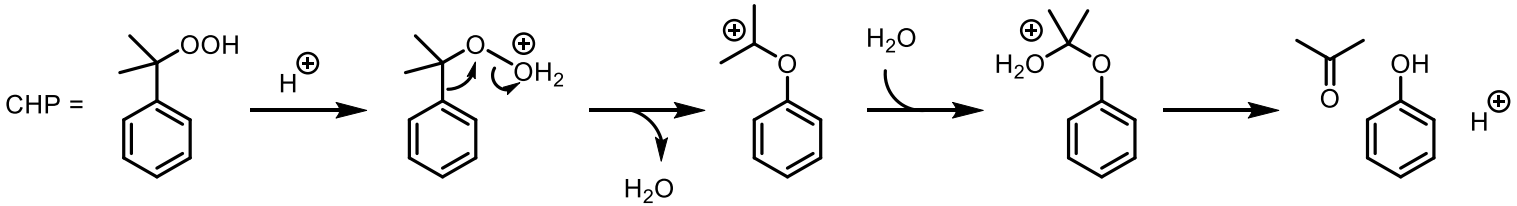
Bultman, M. S. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1131-1136.

Aromatization

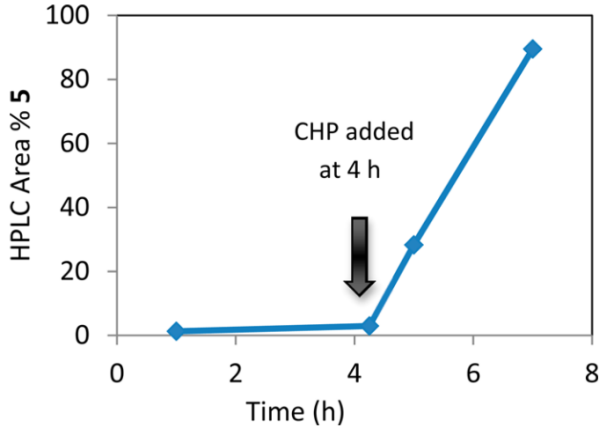
- No major changes from commercial route



- CHP is consumed unproductively via Hock rearrangement



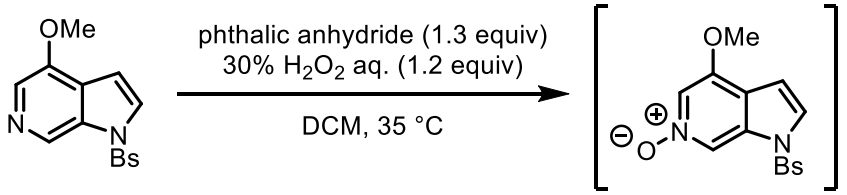
- The optimized condition used a delayed CHP charge (0.1 equiv) after 4h, plus "kicker" charges (0.25 equiv)
- 345 kg scale, 90-92% yield



Bultman, M. S. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1131-1136.

Part 5: Bromination Sequence

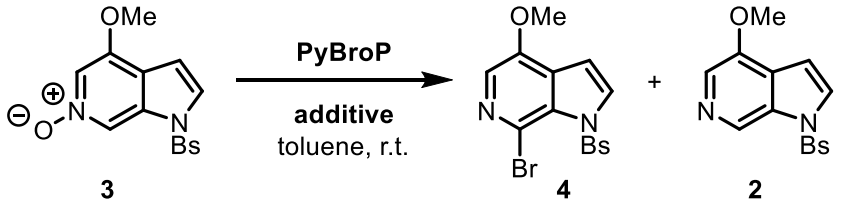
- 1) *N*-oxide formation
  - optimized with cheapest oxidant
  - presence of $^{-}$OOH causes decomposition

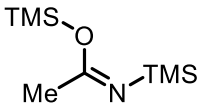


90±3% soln yield
process stream in toluene

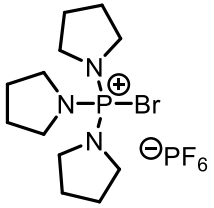
H_2O_2 addition	H_2O_2 (equiv)	anhydride (equiv)	aqueous quench	solution yield
uncontrolled (20 °C)	1.4	1.2	Na_2SO_3 *and* K_3PO_4	85 ± 10%
120 min (35 °C)	1.2	1.3	Na_2SO_3 *then* K_3PO_4	90 ± 3%

- 2) Bromination
  - significant deoxygenation problem
  - rxn stalling also observed
  - prompted NMR studies to elucidate detrimental side reactions





BSA
N,*O*-bis(trimethylsilyl)acetamide
dehydrating agent



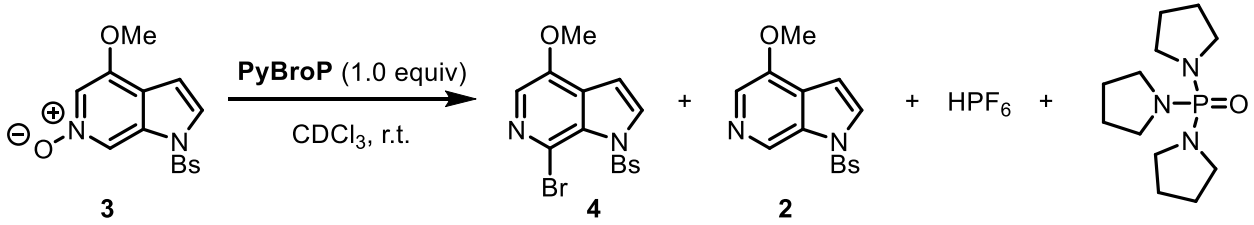
PyBroP
Bromotripyrrolidinophosphonium
hexafluorophosphate

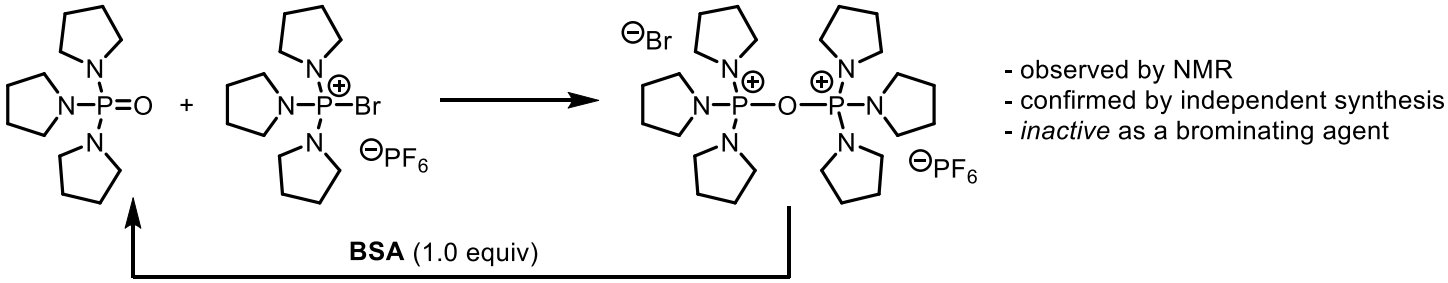
entry	***additive***	***conversion***	***4:2 ratio***
1	**DIPEA**	**100%**	**4:1**
2	**none**	**50%**	**7:1**
3	**mol sieves**	**80%**	**40:1**
4	**BSA**	**95%**	**12:1**

González-Bobes, F. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1137-1144.

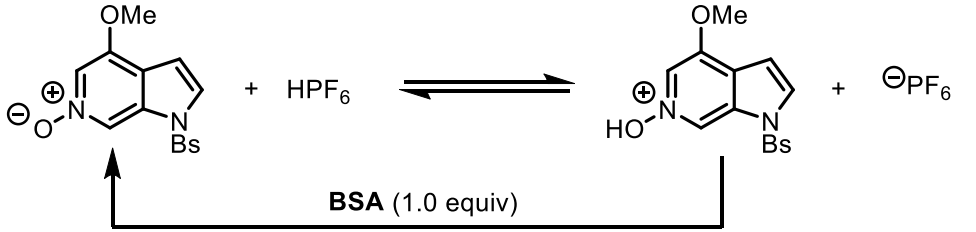
Role of BSA

- Reaction suffers from two types of product inhibition
- BSA eliminates both





- observed by NMR
- confirmed by independent synthesis
- *inactive* as a brominating agent



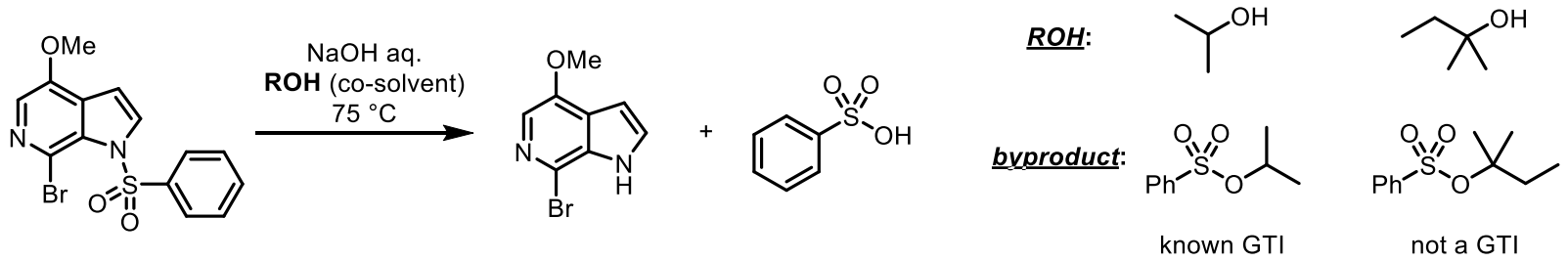
- observed by NMR (downfield shifts)
- protonated *N*-oxide slow to react
- **BSA** acts as proton sponge

Mechanistic studies ongoing

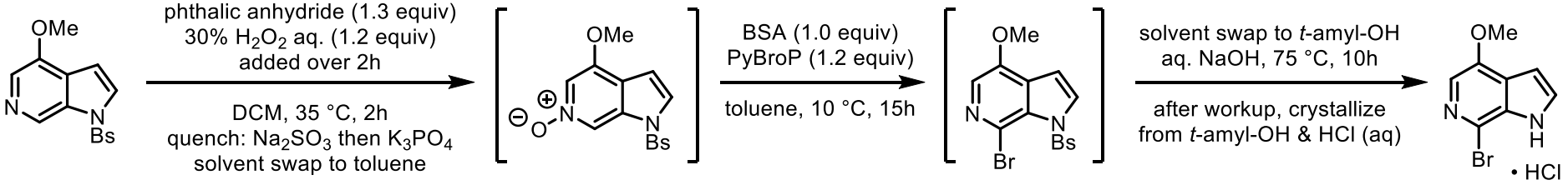
González-Bobes, F. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1137-1144.

N-Bs Hydrolysis

- Solvent switch prevents formation of GTIs (genotoxic impurities)



- Combined sequence:



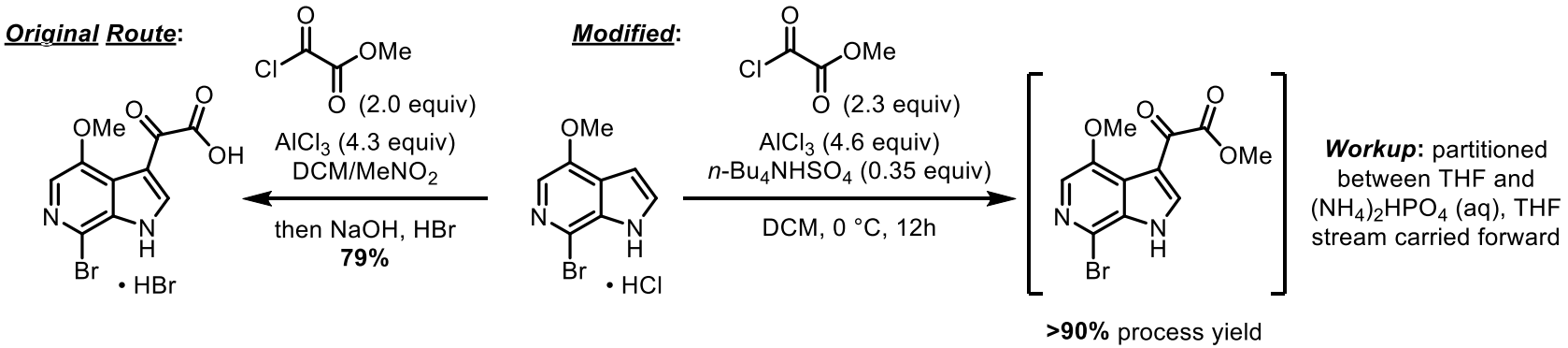
	enabling process	optimized process
scale demonstrated (kg input per batch)	110 kg	230 kg
average isolated yield	49.6%	64.3%
average purity	97.7 area %	99.4 area %
average potency (wt % as HCl monohydrate)	93.6%	97.1%

Single isolation! Other steps are carried forward as process streams in toluene.

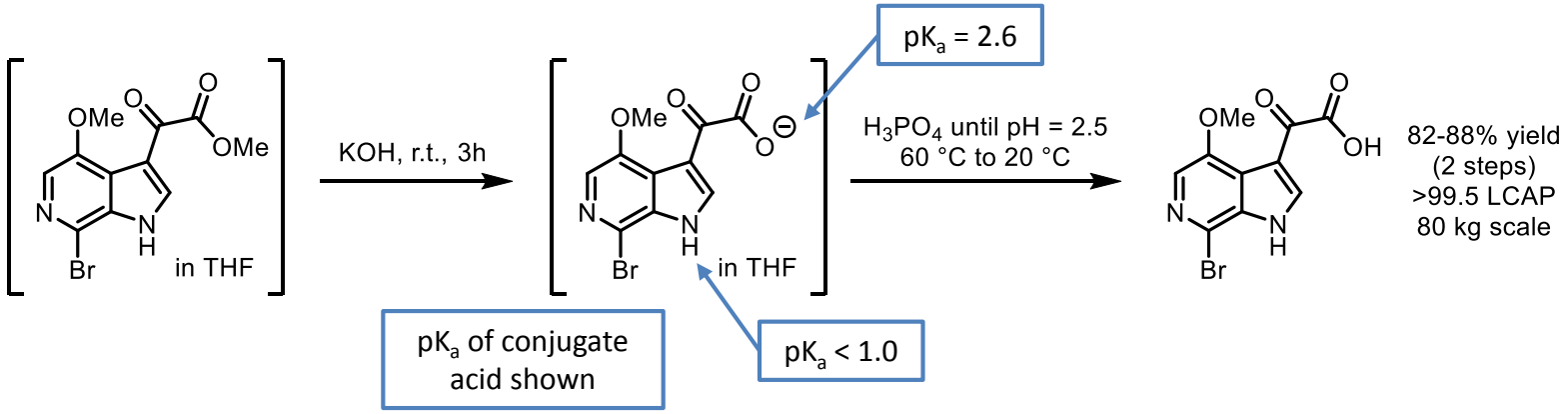
González-Bobes, F. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1137-1144.

Part 6: Acylation/Amidation Sequence

- Original F-C acylation used $MeNO_2$ as co-solvent (undesirable on scale)
- Removing $MeNO_2$ resulted in a thick gel/gum
- Slurry consistency could be retained using an alkylammonium salt additive



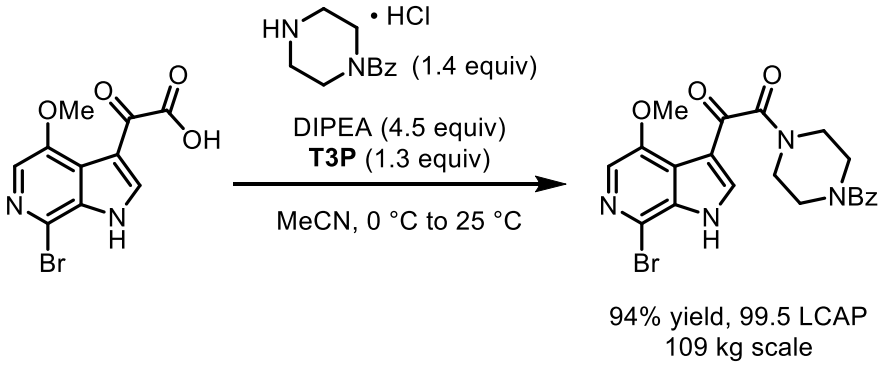
- Ester hydrolyzed with KOH (aq), neutralized to isolate *free acid* (crystalline)
- Choice of H_3PO_4 (pK_a = 2.1) prevented over-protonation in case of excess acid charge



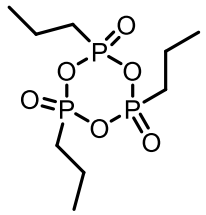
Zheng, B. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1145-1155.

Peptide Coupling

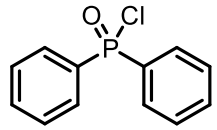
- Several peptide coupling agents were screened
- T3P was ideal! (acid pre-activation not necessary, high yielding, high LCAP, scalable)
- … unfortunately, T3P is prohibitively expensive



n-propylphosphonic anhydride
T3P

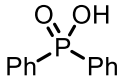


diphenylphosphinic chloride
DPPCl



cheaper substitute?

- DPPCl is a good substitute, but by-product DPPOH is difficult to remove



DPPOH

entry	DIPEA (equiv)	pH, mother liquor	isolated yield (%)	DPPOH (AP)	mother liquor losses of **3** (%)
1	2.0	1.14	56	45.1	1.7
2	3.0	2.81	91	35.1	1.8
3	4.0	3.29	84	0.19	2.6
4	5.0	8.95	74	0.16	15.7
5	6.0	9.57	42	0.46	50.2

Narrow success window for DIPEA loading … not a robust procedure!

Zheng, B. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1145-1155.

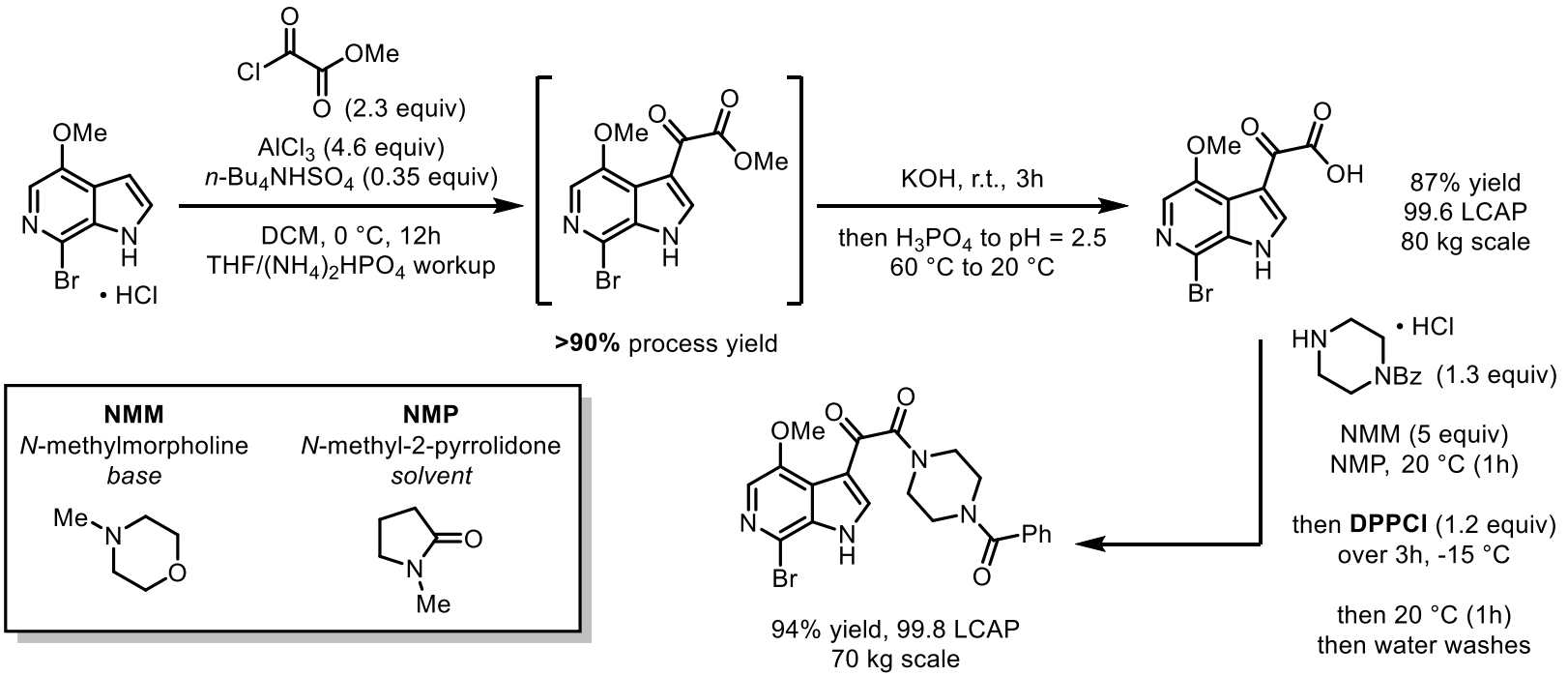
Peptide Coupling

- Base screen
  - NMM identified as a superior base for DPPCl-mediated coupling

Anywhere between 4 and 6 equiv NMM give consistent results … robust!

entry	base, 5 equiv	pK_a	mother liquor losses of **3** (%)	isolated yield	DPPOH (AP)
1	DIPEA	11.4	15.7	74	0.16
2	*cis*-2,6-dimethylpiperidine	10	6.3	76	0.20
3	*N*-methylpiperidine	10.1	7.6	N.D.[a]	N.D.
4	DBU	12	>20	N.D.	N.D.
5	NMM	7.4	3	91	0.35

- Optimized process:

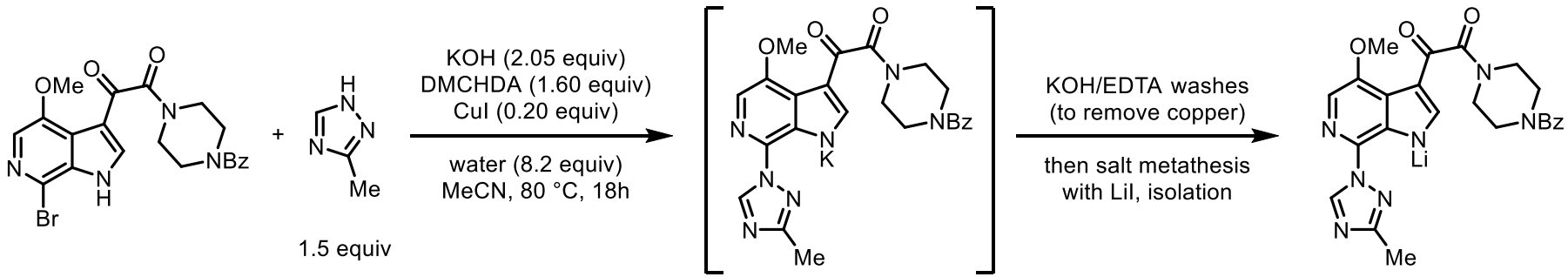


Zheng, B. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1145-1155.

Part 7: Cross-Coupling

- Ullmann-Goldberg-Buchwald coupling optimized with DoE
  - End result is a highly regioselective, high yielding process

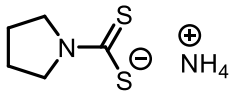
Impact on Regioselectivity	*Impact on Conversion*	*Impact on Impurity*
Factors that have positive effect: *(in the order of significance)* 10 < Water equiv < 20 1.9 < Base equiv < 2.2 1.4 < Triazole **2** equiv < 1.6	**Factors that have positive effect:** *(in the order of significance)* 10 < Water equiv < 30 15 < CuI mol% < 30 7 < Ligand/Cu ratio < 10 2 < Base equiv. < 2.2 1.4 < Triazole **2** equiv < 1.6	**Factors that have negative effect:** Water equiv > 20 equiv Base equivalence > 2.2 equiv.
Factors that have negative effect: Ligand/Cu ratio (marginal) < 6:1	**Factors that have negative effect:** MeCN volume > 10 mL/g	**Factors that no or a minor effect:** KBr content MeCN volume Ligand/Cu ratio



Gallagher, W. P., Soumeillant, M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1156-1165.

The best-laid plans…

- Purification issues on pilot plant scale
- Superb O_2 control in the pilot plant equipment resulted in high conc. of Cu(I), which is poorly complexed by EDTA
- On lab scale, most of the Cu(I) was oxidized to Cu(II)
- Dithiocarbamates (DTCs) were found to be superior Cu(I) scavenging agents



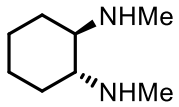
Ammonium pyrrolidinedithiocarbamate
APDTC

> On pilot scale, the initial triazole coupling performed as expected, with 20:1 regioselectivity of **3**:**4** and excellent control of oxidative dimer **8** (<0.15% in-process), due to control of O_2 to <500 ppm. However, after performing the copper scavenging process with 45% KOH/EDTA, the crystallization of **3b** did not perform as expected and was extremely sluggish. Additionally, a pronounced blue-gray coloration of the supernatant developed during the crystallization. Upon filtration and drying, compound **3b** was isolated in a mediocre 46% crude yield as a pale yellow solid containing bluish lumps with 8300 ppm of residual copper.[17]

batch	input (**1**)	output (**3b**)	yield (%)	purity[a] (LCAP)	potency[b] (wt %)	Cu (ppm)
1	26.8 kg	18.8 kg	69.0	98.6	96.7	1
2	26.8 kg	20.2 kg	73.5	98.5	96.0	3
3	26.7 kg	20.7 kg	75.7	98.6	96.0	1
4	26.3 kg	20.1 kg	74.8	98.8	96.5	7

[a]LCAP = HPLC area %. [b]wt % compared to a known standard by HPLC analysis.

Process is still very costly due to high ligand loading (1.60 equiv)

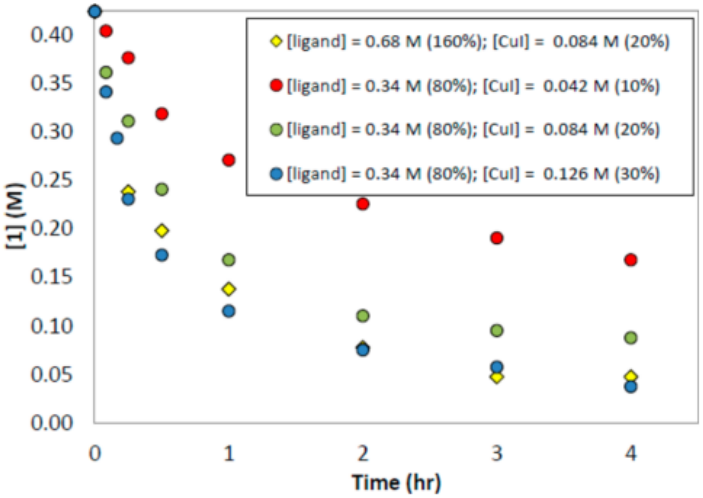


trans-*N*,*N*-1,2-dimethylcyclohexane-diamine
DMCHDA

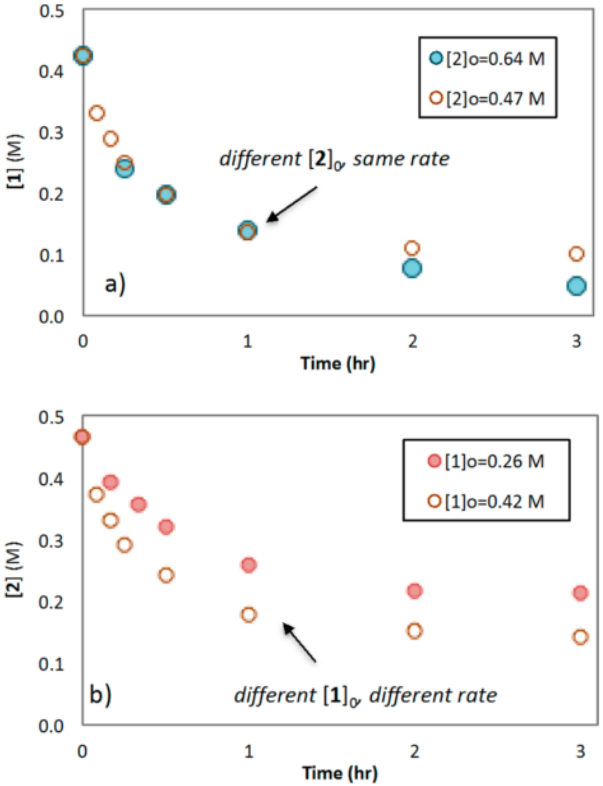
Gallagher, W. P., Soumeillant, M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1156-1165.

Kinetic Studies

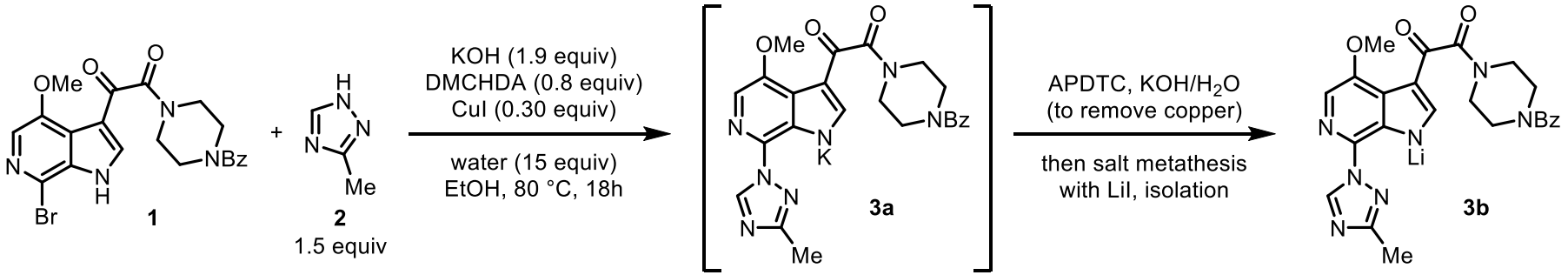
- Ligand loading can be reduced by 50% if Cu loading is increased to 0.30 equiv



Prof. Donna Blackmond (Scripps)



- Optimized Conditions:

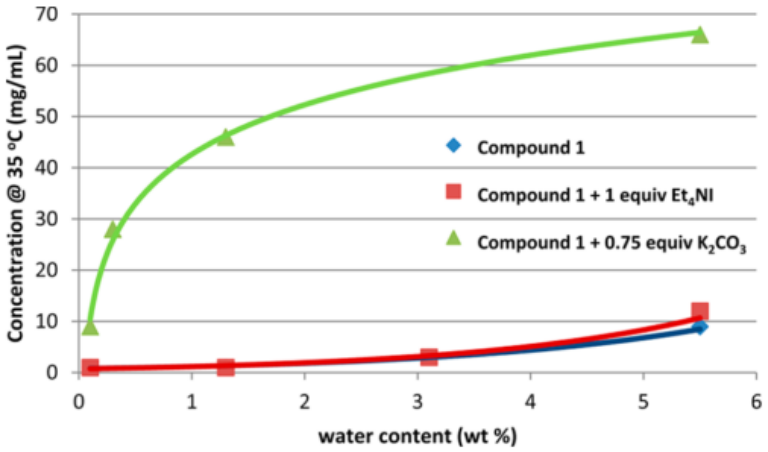


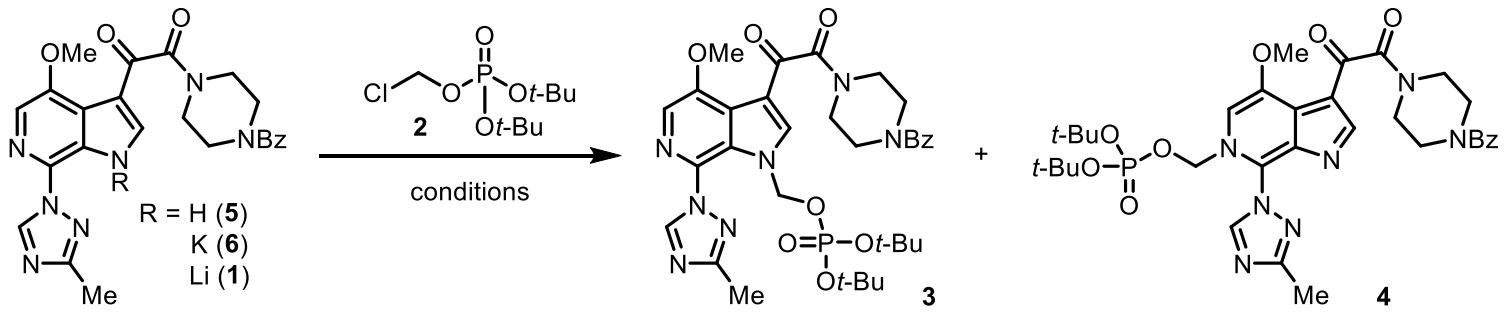
66% yield, >98 LCAP, 158 kg scale

Gallagher, W. P., Soumeillant, M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1156-1165.

Part 8: Prodrug Moiety

- Starting material is Li-salt form of BMS-626529
  - Alkylates poorly due to low solubility
  - Both free-base (NH) and K-salt perform better
  - Solution: another salt metathesis!!
    - Importance of water





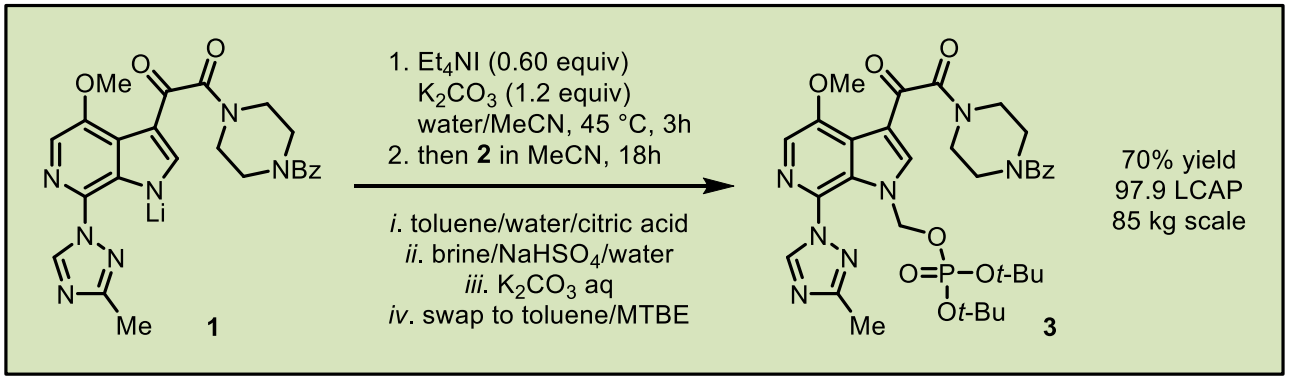
entry	R	solvent (L/kg)	temp. (°C)	equiv 2	base (equiv)	additive (equiv)	water (wt %)	ratio 3:4[d]	soln yield 3 (%)[d]
1	H	NMP (10)	30	1.7[a]	Cs_2CO_3 (1.7)	KI (1.2)	<100 ppm	8:1	80
2	K	CH_3CN (10)	35	1.3[b]	K_2CO_3 (0.75)[c]	Et_4NI (1.0)	<100 ppm	8:1	80
3	Li	CH_3CN (10)	35	1.3	K_2CO_3 (0.75)	Et_4NI (1.0)	<100 ppm	20 LCAP[e] 3 after 20 h	
4	Li	CH_3CN (10)	50	1.3	K_2CO_3 (0.75)	Et_4NI (1.0)	<100 ppm	42 LCAP 3 after 20 h	
5	Li	CH_3CN (10)	65	1.3	K_2CO_3 (0.75)	Et_4NI (1.0)	<100 ppm	30 LCAP 3 after 20 h	
6	Li	CH_3CN:NMP (10)[f]	35	1.3	K_2CO_3 (0.75)	Et_4NI (1.0)	<100 ppm	35 LCAP 3 after 20 h	
7	Li	CH_3CN (10)	35	1.3	K_2CO_3 (0.75)	Et_4NI (1.0)	0.5%	8:1	80

[a]Utilized solution of **2** in NMP. [b]Utilized solution of **2** in DCM (entries 2–7). [c]Utilized 325 mesh K_2CO_3 (entries 2–7). [d]Calculated by HPLC. [e]LCAP = liquid chromatography area percent. [f]Ratio CH_3CN:NMP = 7:3.

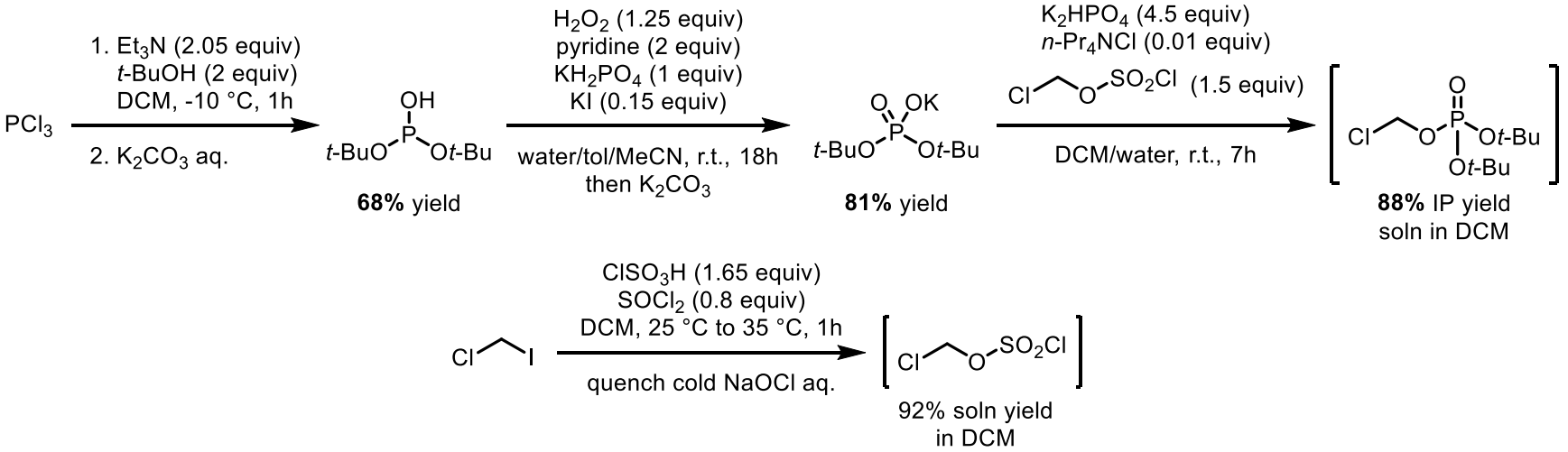
Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1166-1173.

Finishing Touches

- Procedure (and workup) optimized by DoE
  - toluene/$NaHSO_4$ workup effectively removed isomer **4**
- Final conditions:



- Aside: synthesis of **2**



Zheng, B.; Eastgate, M. D. et al. *Org. Proc. Res. Dev.* **2012**, 16(11), 1827-1831.

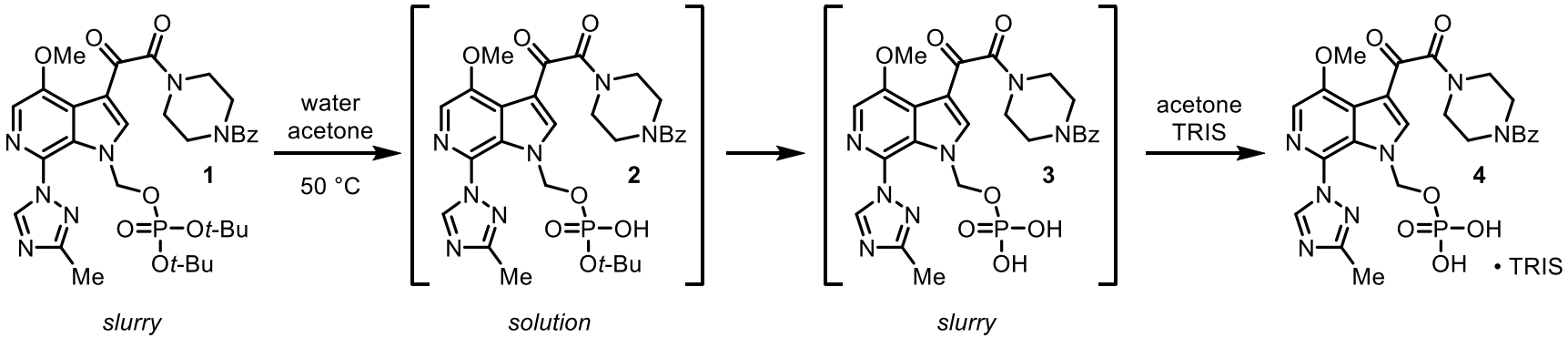
Fox, R. J. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1166-1173.

Zheng, B.; Fox, R. J. et al. *Org. Proc. Res. Dev.* **2014**, 18(5), 636-642.

Part 9: Synthesis of API

- Key challenges in any API process:
  - *Robustness* (consistent quality, regardless of small variations in input quality)
  - API properties must be absolutely consistent, high purity … this is going into humans!

Original:



  - slurry-to-slurry nature resulted in entrainment of **2** in **3**
  - acetone/water was a poor recrystallization system for purging process/input impurities
  - desired a homogeneous reaction solvent

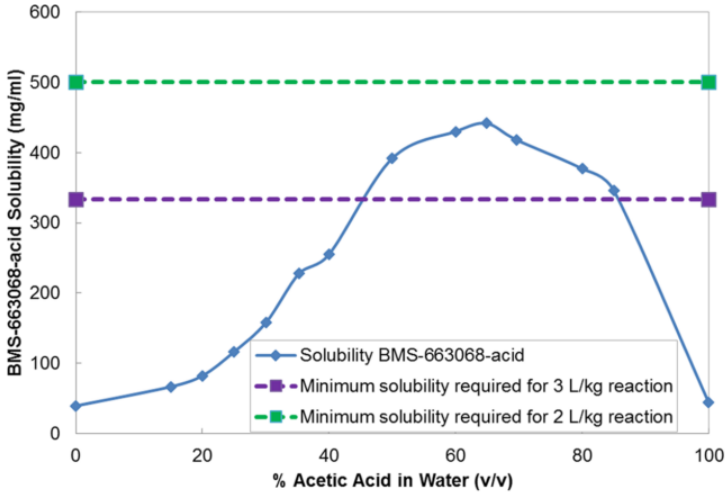
Solvent Properties to Consider for BMS-663068 Process

- MeOH, EtOH: Crystal form incompatability
- DMSO: Difficult to remove during drying
- DMF: Difficult to remove during drying
- DMA: Difficult to remove during drying
- NMP: Difficult to remove during drying
- Ethers, esters and DCM: Immiscible in water
- Trifluoroacetic acid: Product stability issues
- Glyoxylic acid: pKa 3.2, Bp 111 °C
- Glycolic acid: pKa 3.8, Bp decompose
- Pyruvic acid: pKa 2.5, Bp 165 °C
- Acetic acid: pKa 4.76, Bp 118 °C
- Propionic acid: pKa 4.88, Bp 141 °C

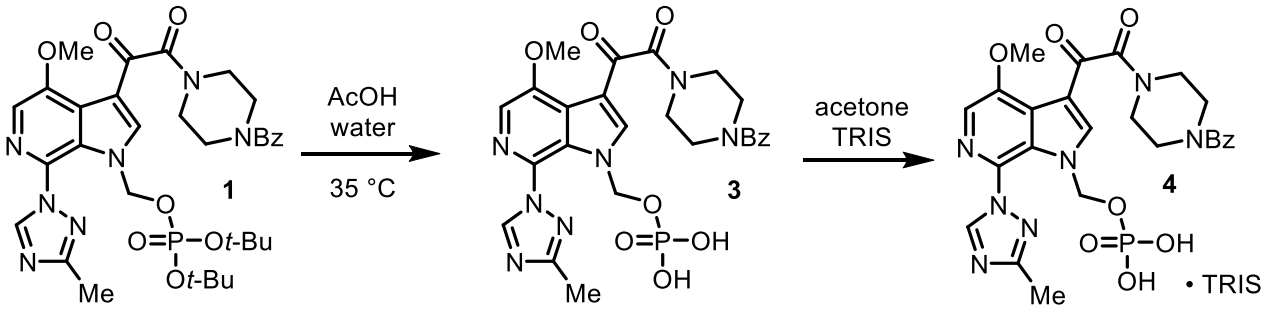
La Cruz, T. E.; Saurer, E. M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1174-1185.

New Solvent

- Acetic acid identified as optimal co-solvent
  - homogeneous reaction throughout
  - faster reaction (35 °C, fewer process impurities)
  - better purging during recrystallization

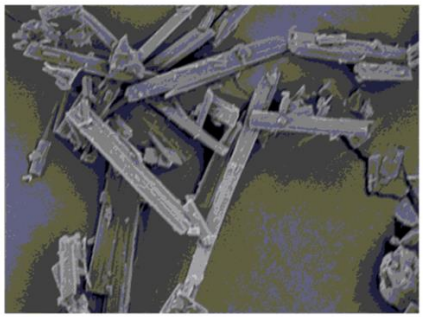


Modified:



solution *solution*

pK_{a1} = 2.6; pK_{a2} = 6.1
AcOH pK_a = 4.76



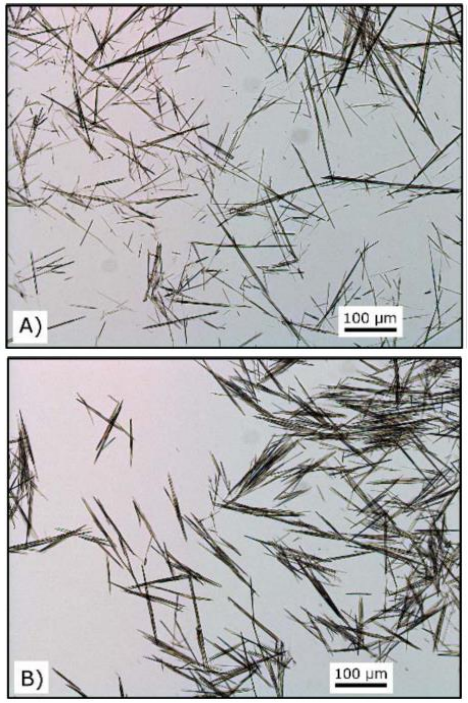
BMS-663068-TRIS Salt Particle Morphology

Crystallization/Isolation:

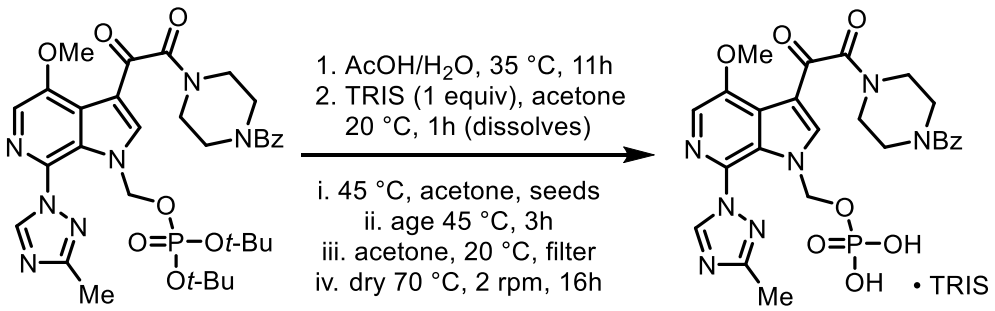
La Cruz, T. E.; Saurer, E. M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1174-1185.

The Finest Quality

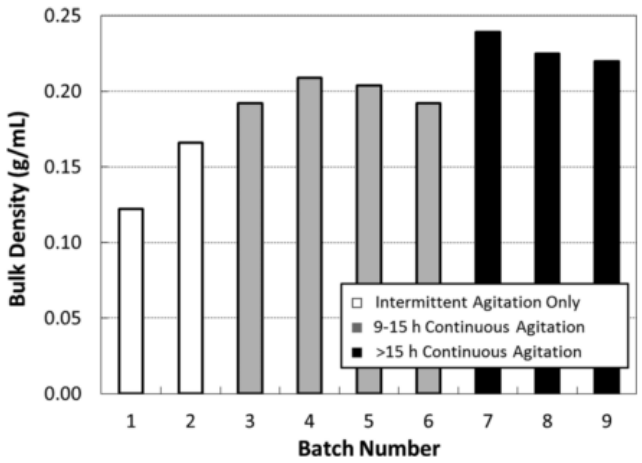
- Crystal morphology is good, but not great
  - Long needles (low bulk density, high surface area) results in slow filtration, inconsistent flow during formulation
  - Cubic is ideal, but could not be obtained here



- Solutions:
  - Extended seed age time (thicker crystals, lower SA)
  - Drying with agitation (leads to needle breakage)
    - sharply increased bulk density, only slight increase in SA

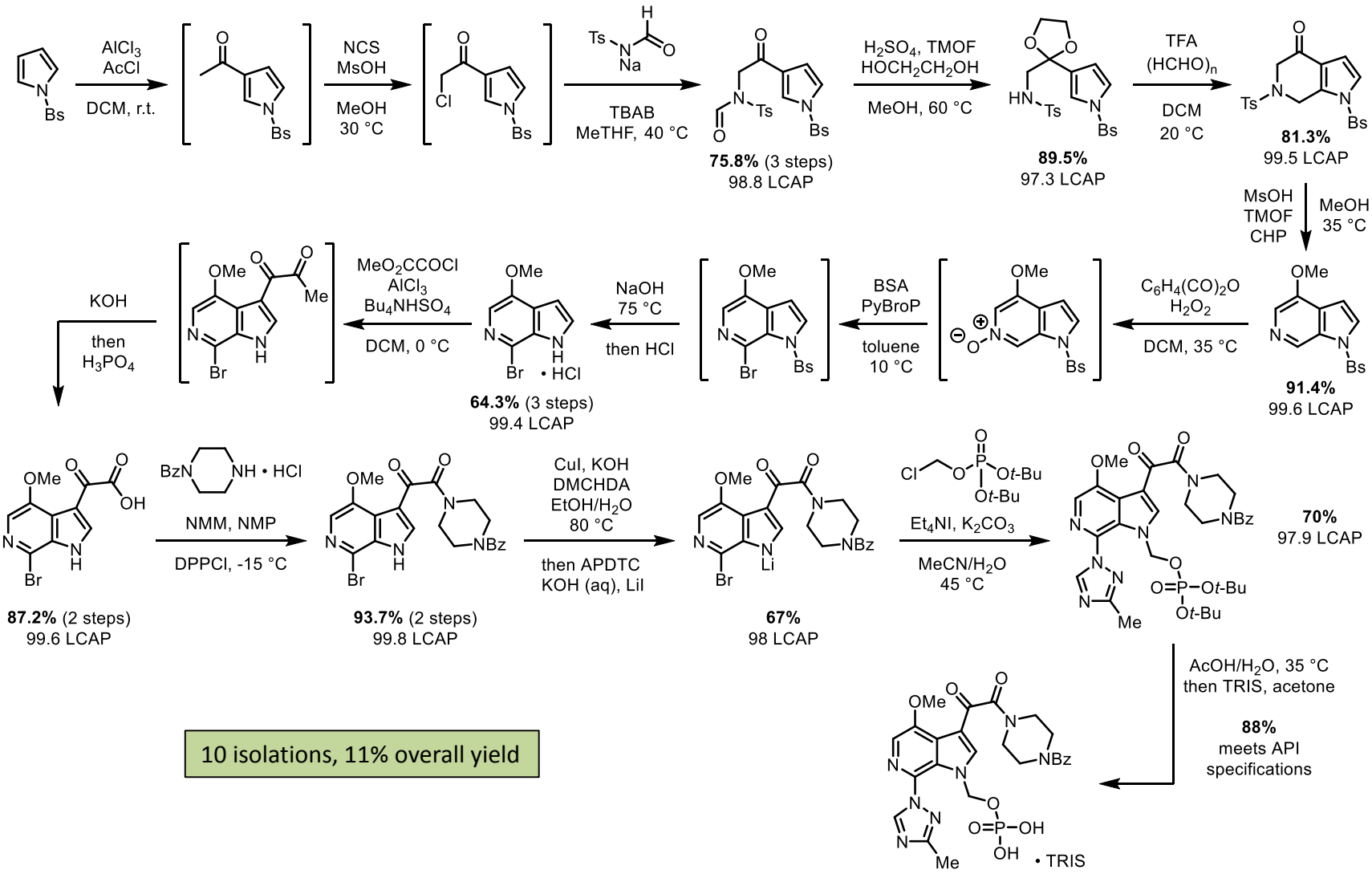


88% yield, 100 kg scale
meets all specifications



La Cruz, T. E.; Saurer, E. M. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1174-1185.

Summary: Optimized Commercial Route



10 isolations, 11% overall yield

Concluding Remarks

- BMS-663068 is currently in late-stage clinical trials
- Commercial route deviated sharply from enabling route
  - Not enough to perform DoE for each step in the enabling route …
  - Complete re-design involves significant creativity, return to first principles, etc.
- Literally every step is studied in exhaustive detail
  - Including (particularly including) purifications
  - Impurities must be closely monitored and purged, particularly GTIs
  - Operations which are annoying on gram-scale can be disastrous on kilogram-scale
  - Process chemists face daunting task of finding the most efficient route with the *cheapest starting materials*

> While this incredible story is eye-opening and brimming with innovation, it is not a singularity within the realm of pharmaceutical development.[19] Legions of talented and passionate chemists toil away over the span of decades with the mission of providing cures to patients in an efficient and environmentally friendly way. Their victories go mostly unnoticed by the society they humbly seek to serve, with the details of exciting conquests mostly deposited into the quiet storm of the patent literature. In this regard, the Bristol-Myers Squibb chemists should be applauded for scholarly summarizing this huge body of work into such an educational and coherent set of must-read publications.

Baran, P. et al. *Org. Proc. Res. Dev.* **2017**, 21(8), 1091-1094.