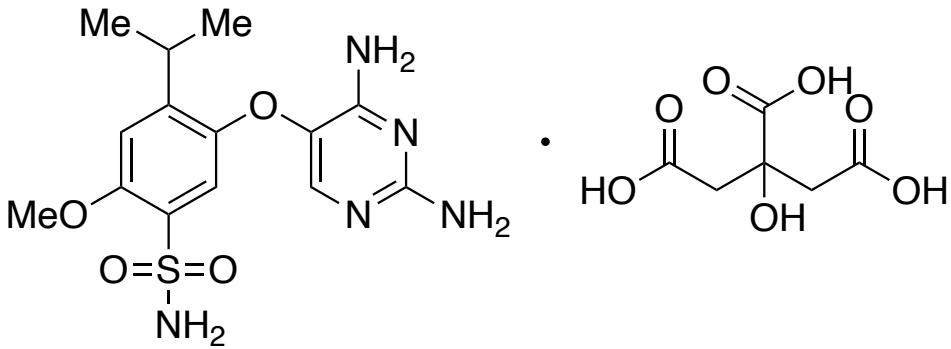
Gefapixant Citrate: A Merck Process Green Synthesis Case Study



Travis Menard

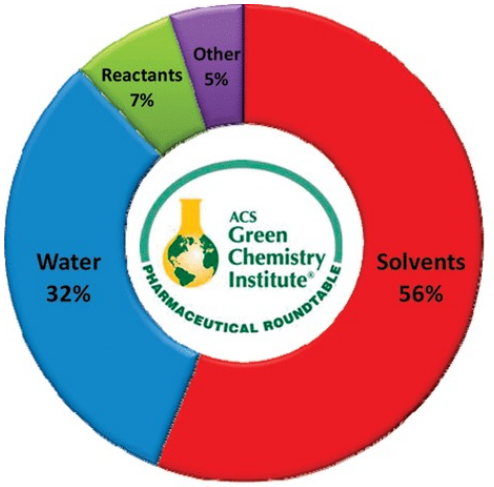
Group Meeting

January 25th, 2022

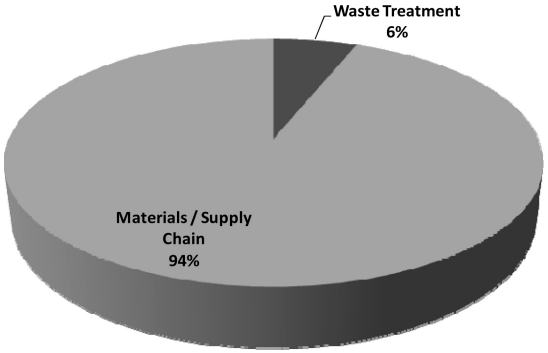
Green Process Principles and Metrics

"**The ideal, green, and sustainable active pharmaceutical ingredient (API) manufacturing route has the aspirational goal of a "zero-waste" process.** This goal is enabled by an innovative, green-by-design, development strategy to progress from initial route design through to a fully optimized and sustainable commercial manufacturing process… **In our experience, the greenest manufacturing processes require explicit design of all aspects,** including starting with the synthetic route. Hence, the strategy commences with route exploration to identify the most direct method to convert commodity chemicals into API, in accordance with the principles of green chemistry. Once the most direct route is prioritized, **the application of new and enabling technologies, and the discovery of new methods, are often required as aspirational routes are rarely a sequence of well-known transformations.** With the proof of concept for this route established, we turn to the core drivers of process development to translate this synthetic route into an efficient and robust process."

Merck processes have received the EPA/ACS Green Chemistry Challenge Green Synthetic Pathways award 5 times (2005, 2010, 2017, 2018, 2019)

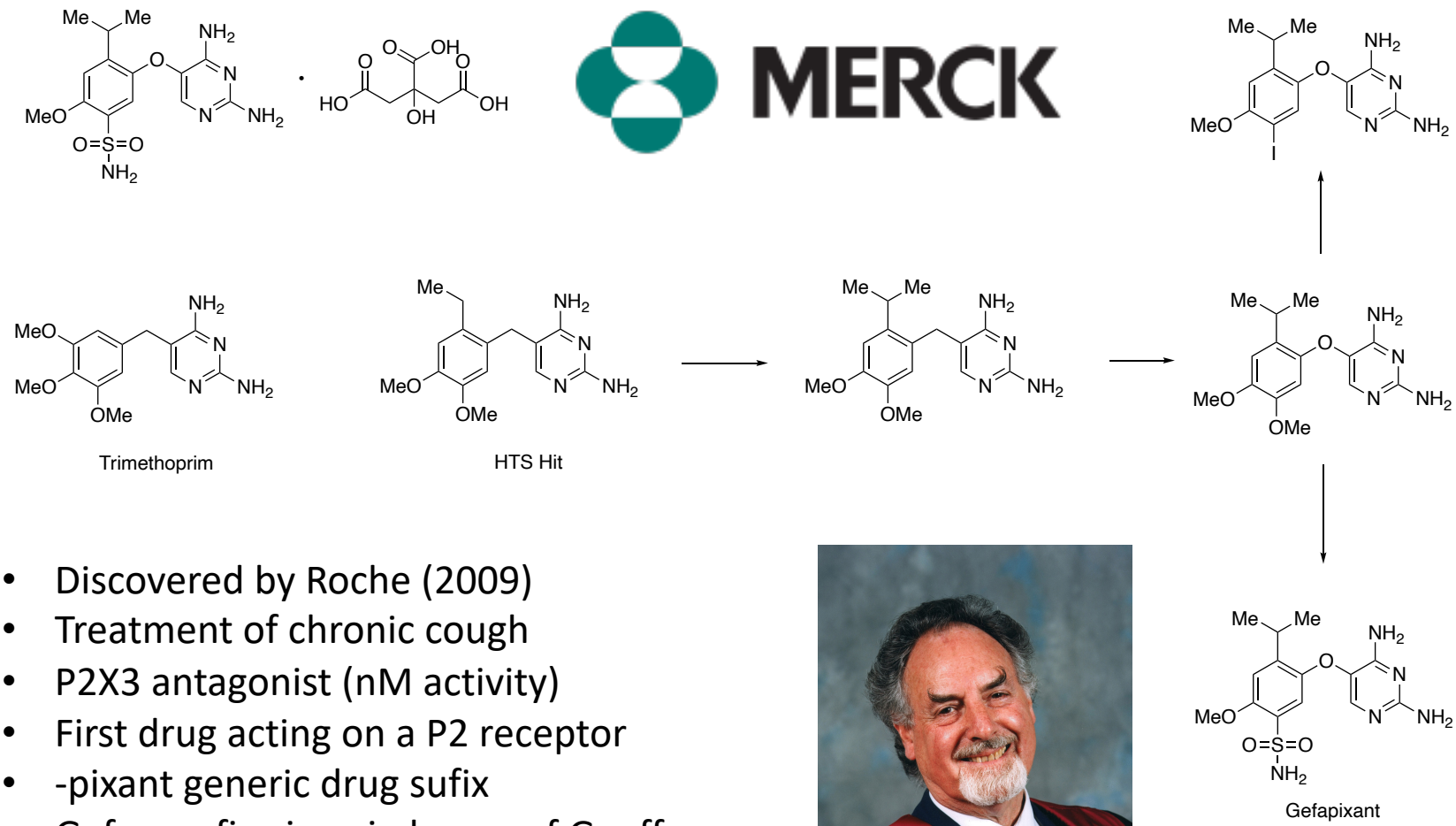


Process Mass Intensity Benchmark

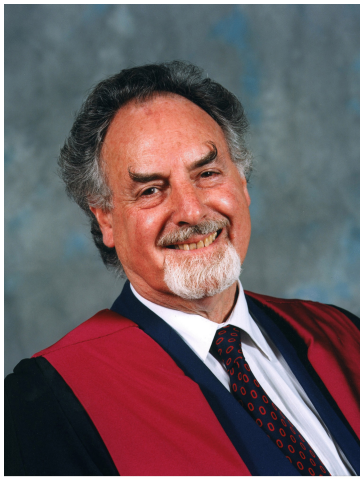


Organic Process Research & Development **2020** *24* (11), 2445-2452
Concepcion Jimenez-Gonzalez, Celia S. Ponder, Quirinus B. Broxterman, and Julie B. Manley *Organic Process Research & Development* **2011** *15* (4), 912-917

Gefapixant Citrate (MK-7264)

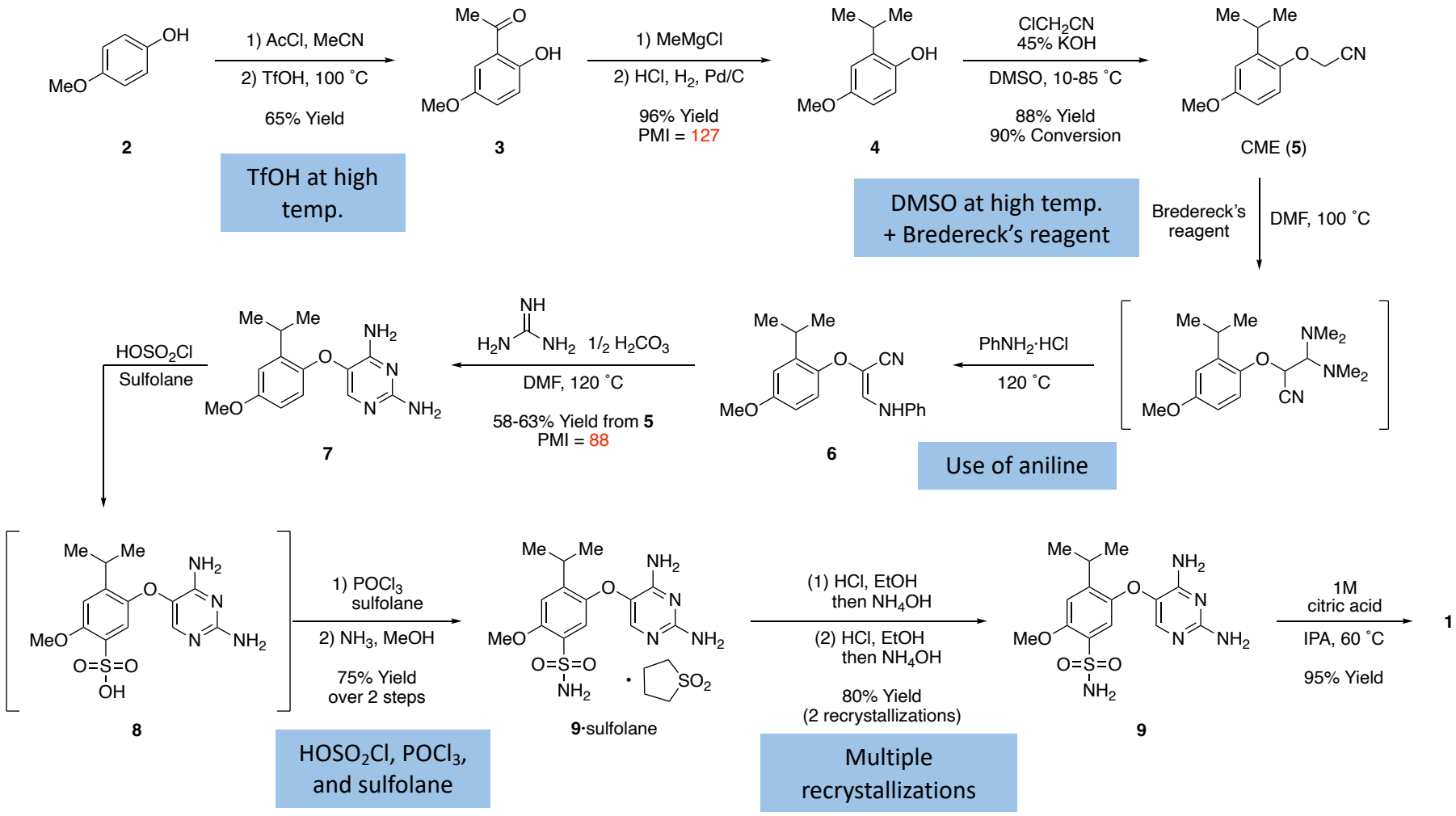


- Discovered by Roche (2009)
- Treatment of chronic cough
- P2X3 antagonist (nM activity)
- First drug acting on a P2 receptor
- -pixant generic drug sufix
- Gefa- prefix given in honor of Geoff Burnstock P2 receptor pioneer (1929-2020)



David S. Carter, Muzaffar Alam, Haiying Cai, Michael P. Dillon, Anthony P.D.W. Ford, Joel R. Gever, Alam Jahangir, Clara Lin, Amy G. Moore, Paul J. Wagner, Yansheng Zhai, Bioorganic & Medicinal Chemistry Letters, 19, 6, 2009, 1628-1631,

Initial Scale-up



11 steps LLS, 16 % overall yield, PMI = 366

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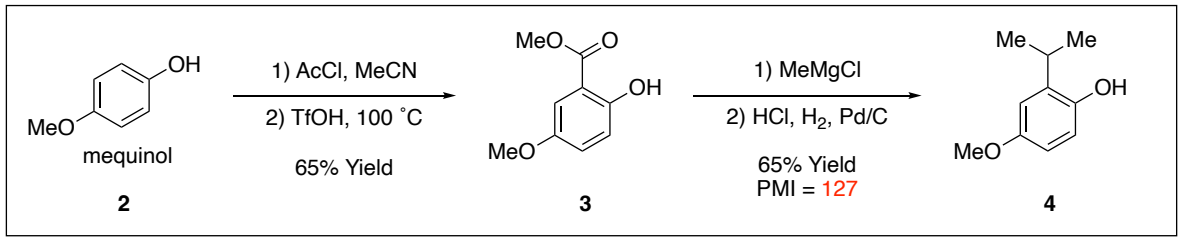
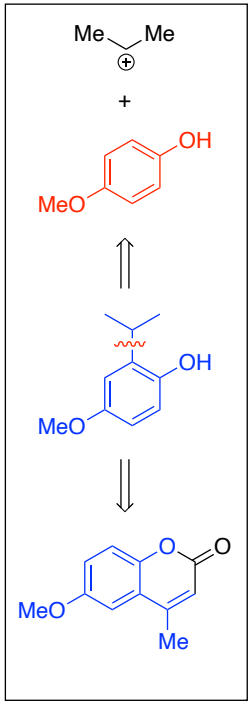
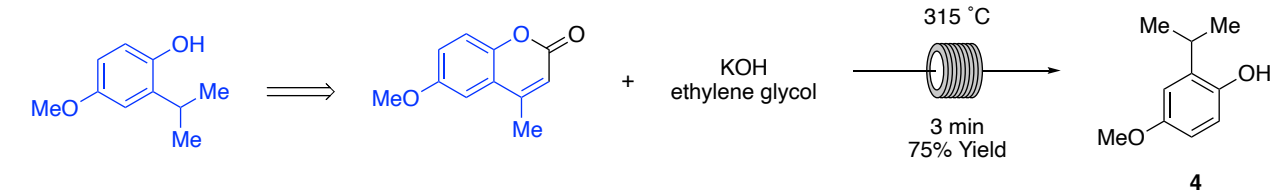
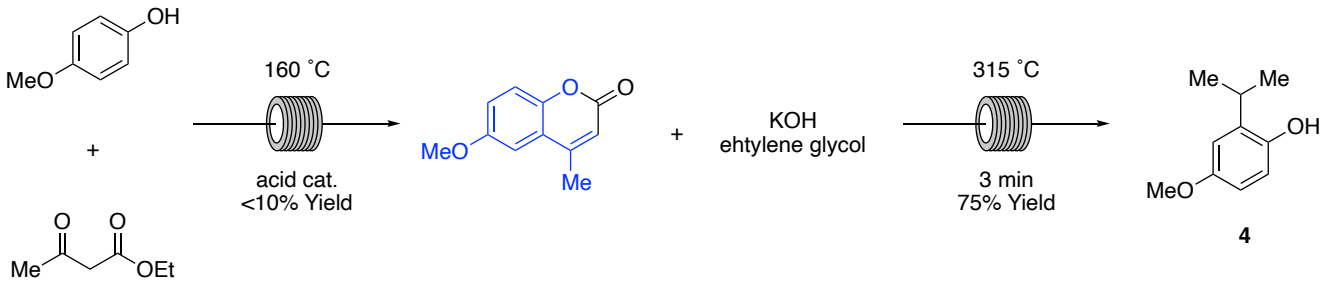
Alternative Routes to 4









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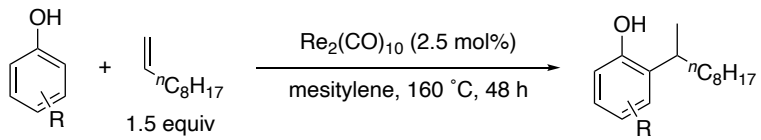
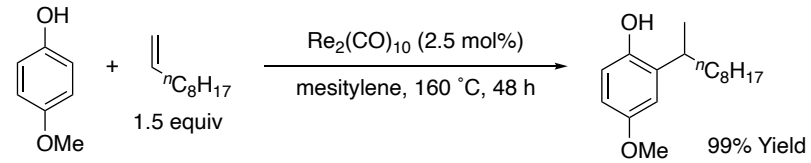
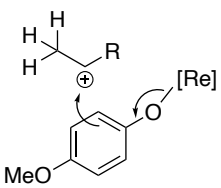
Re-Catalyzed Alkylation

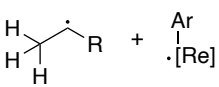
Stoltz (2017)



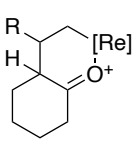




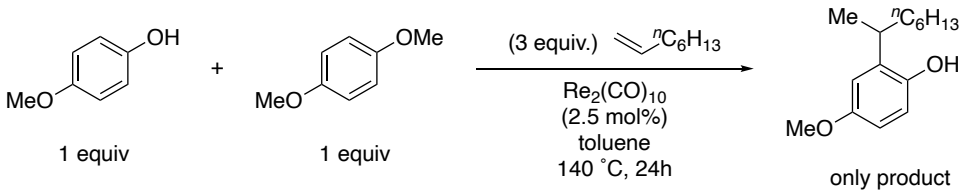
Friedel-Crafts

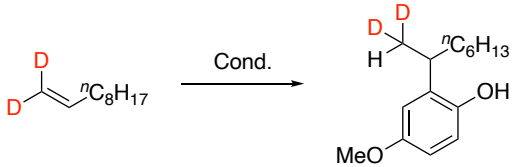


radical pair

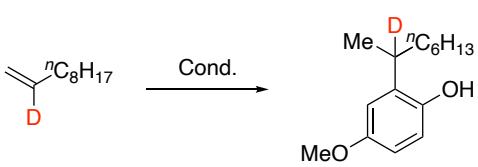


cylcometalation

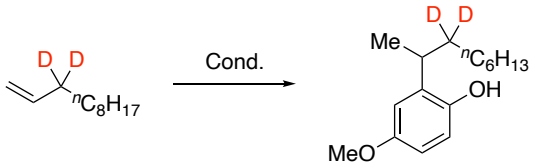




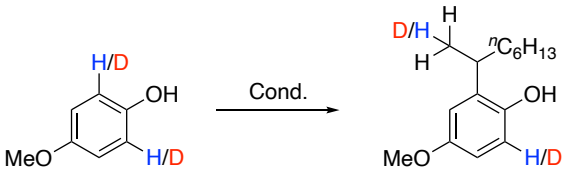
only product



only product



only product

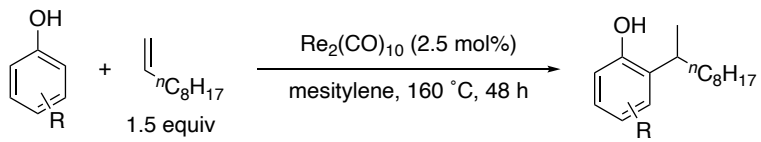


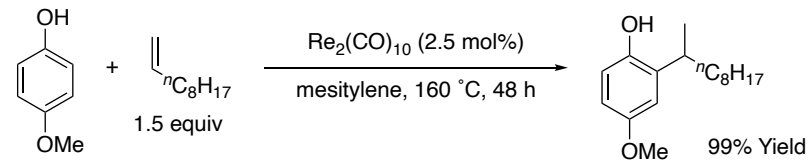
KIE = K_H / K_D = 1.39

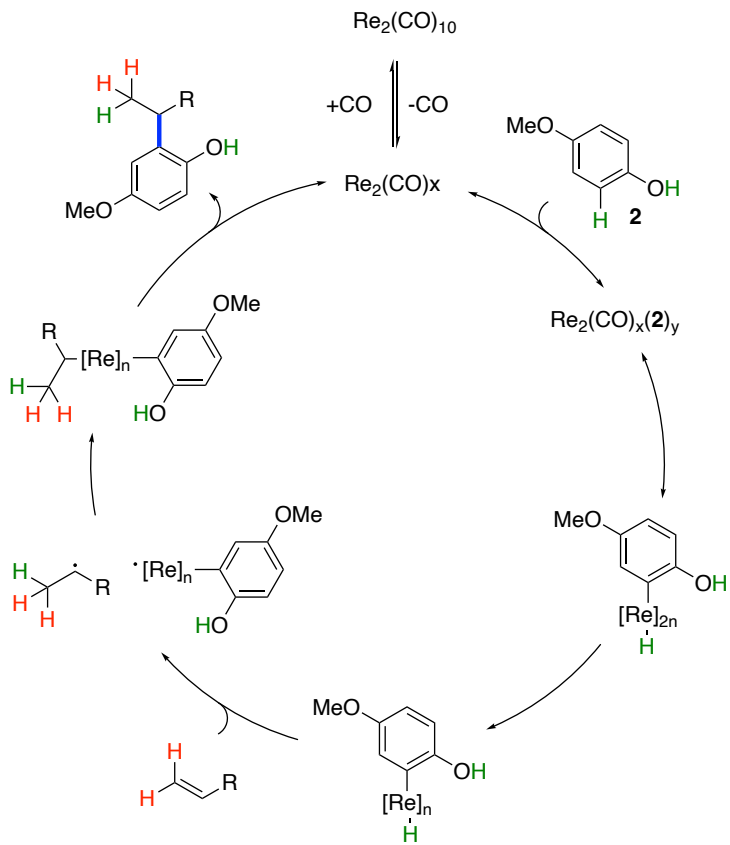
Kuninobu, Y.; Yamamoto, M.; Nishi, M.; Yamamoto, T.; Matsuki, T.; Murai, M.; Takai, K. Org. Synth. **2017**, 94, 280–291
Dan Lehnherr, Xiao Wang, Feng Peng, Mikhail Reibarkh, Mark Weisel, and Kevin M. Maloney; *Organometallics* **2019** *38* (1), 103-118

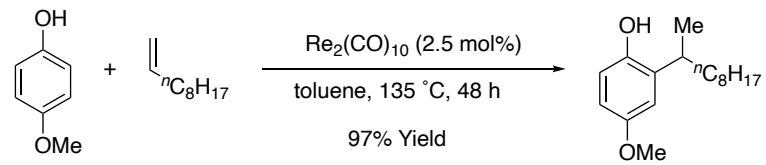
Re-Catalyzed Alkylation

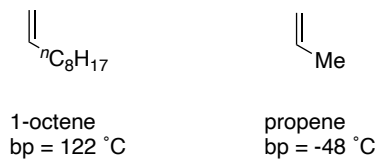
Stoltz (2017)

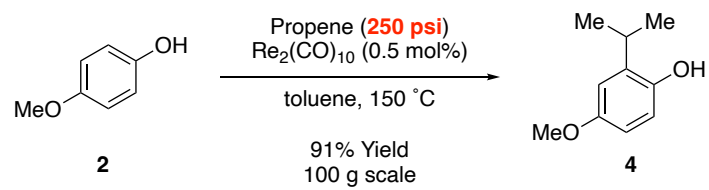












$Re_2(CO)_{10}$ = $36,000/kg

Kuninobu, Y.; Yamamoto, M.; Nishi, M.; Yamamoto, T.; Matsuki, T.; Murai, M.; Takai, K. Org. Synth. **2017**, 94, 280–291
Dan Lehnherr, Xiao Wang, Feng Peng, Mikhail Reibarkh, Mark Weisel, and Kevin M. Maloney; *Organometallics* **2019** *38* (1), 103-118
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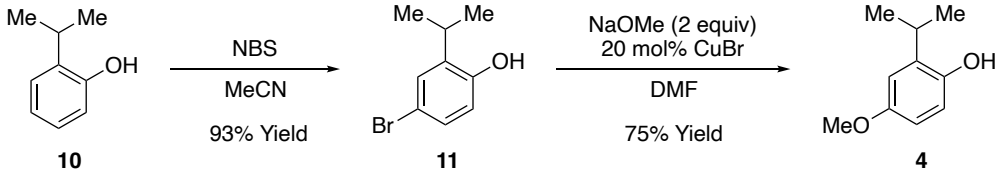
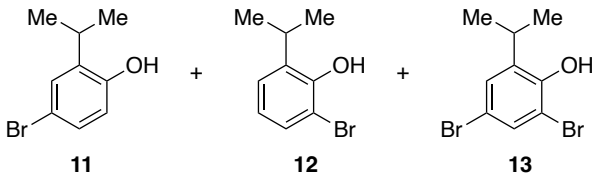
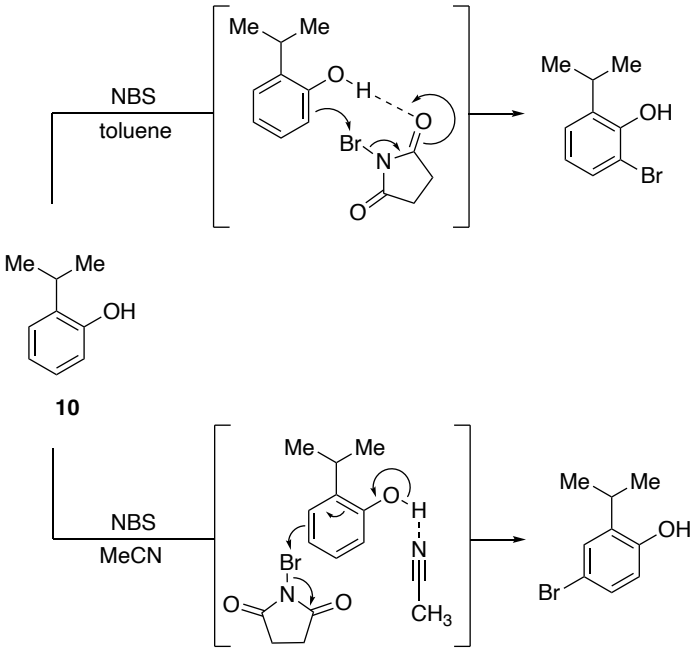
Bromination of 10





reagent	solvent	**11** (LCAP)	**12** (LCAP)	**12** (LCAP)
Br_2	CH_2Cl_2	85.0	7.0	8.0
NBS	MeCN	96.0	1.8	2.2
NBS	toluene	25.0	73.0	2.0
$HBr + H_2O_2$	MeCN	93.0	1.0	6.0
$PyHBr_3$	toluene	94.0	4.0	2.0
$PrHBr_3$	MeCN	88.0	1.5	10.5
NBS	MeCN + 1% MSA	95.0	1.0	2.0



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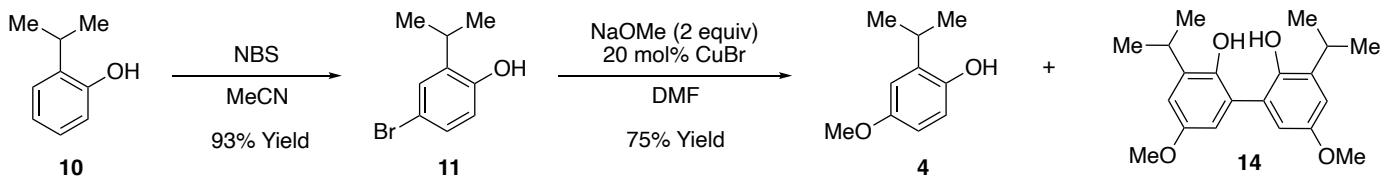
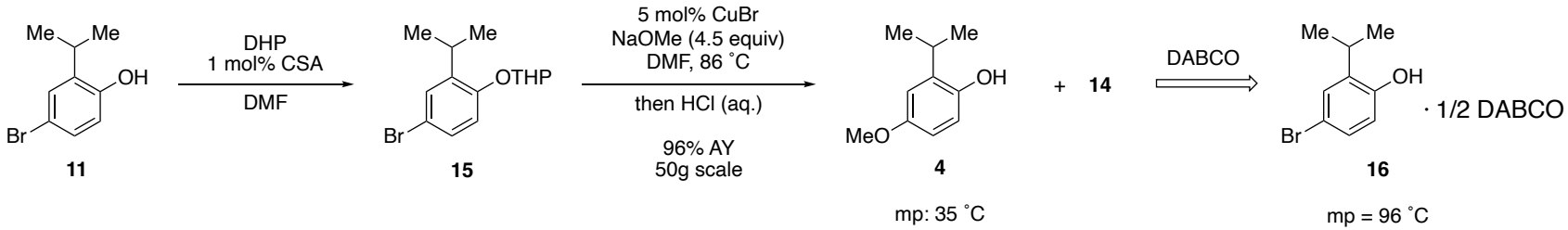
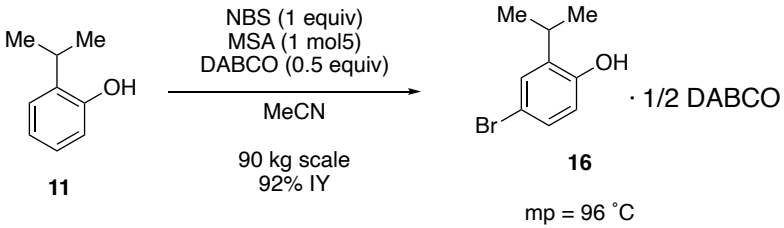
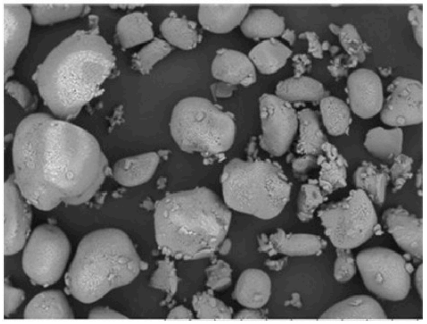
DABCO Adduct

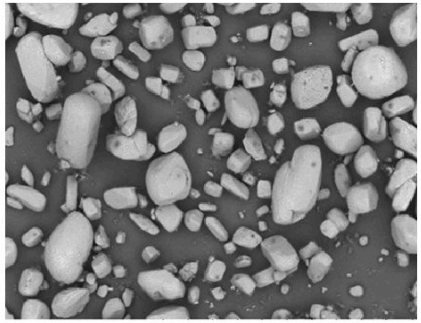








a. Crystallization at 60 °C



b. Crystallization at 30 °C

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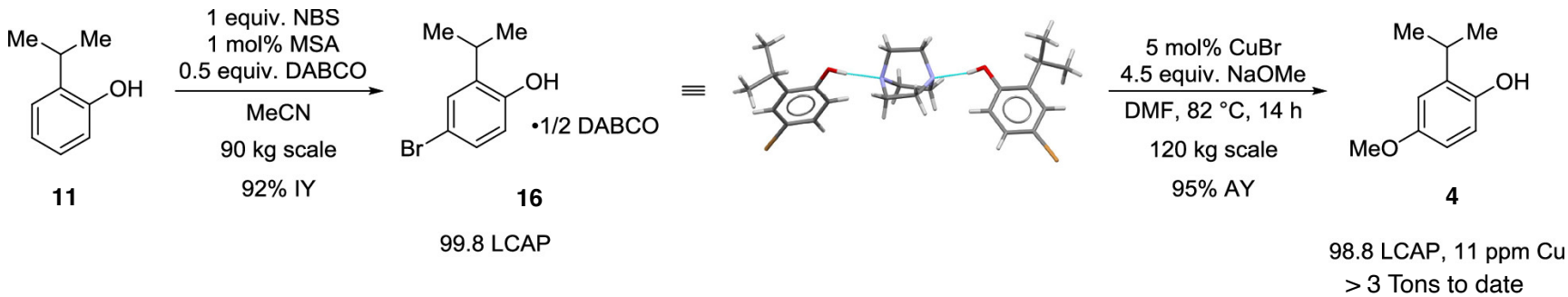
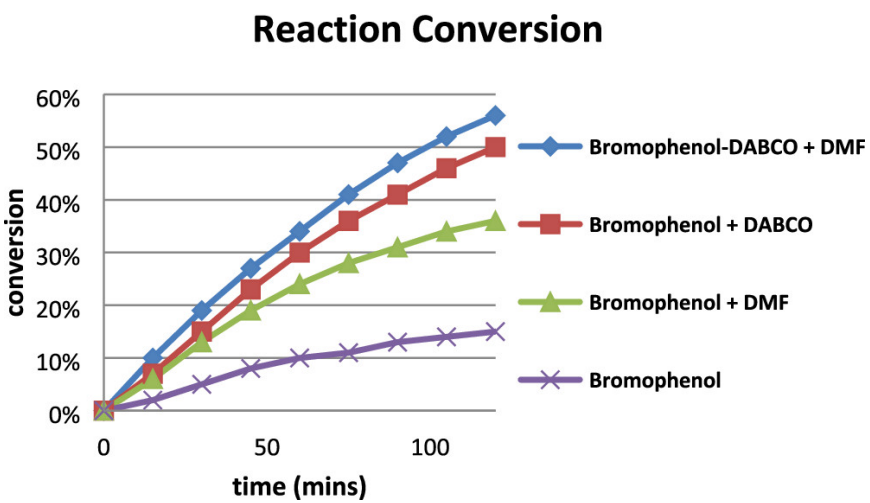
Final Route to 4





- 4 steps down to 2
- PMI from 127 to 23
- 62% to 88% Yield
- No TfOH or Pd/C

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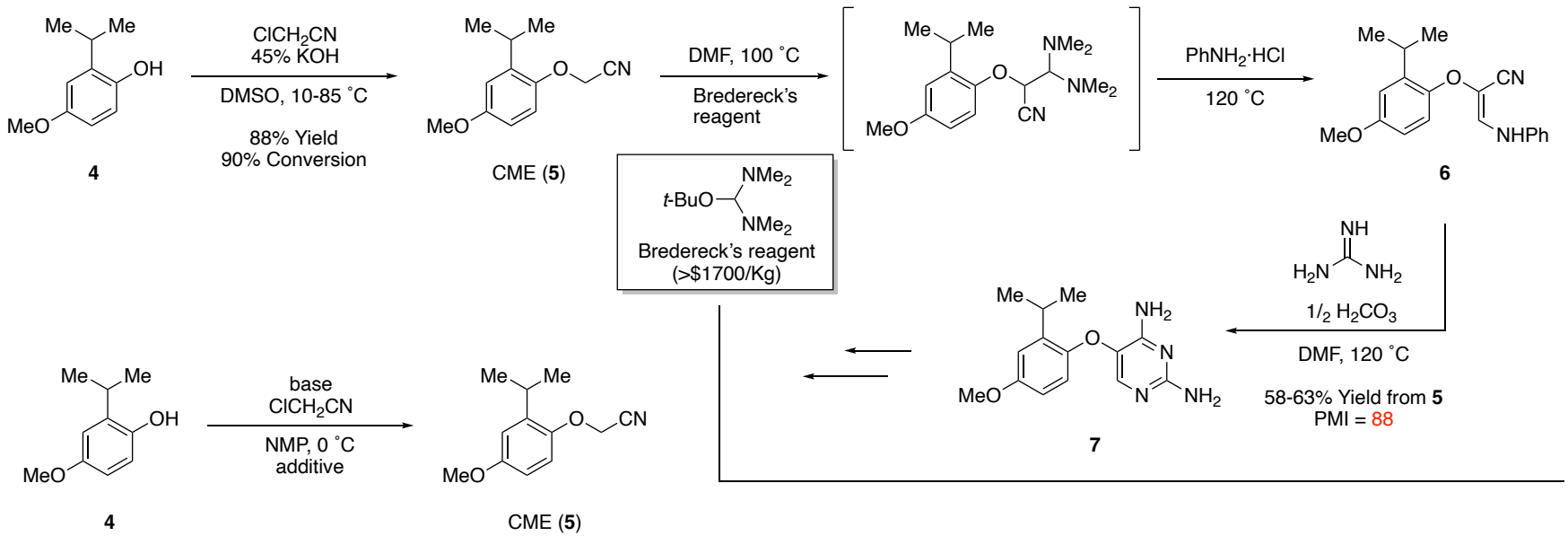
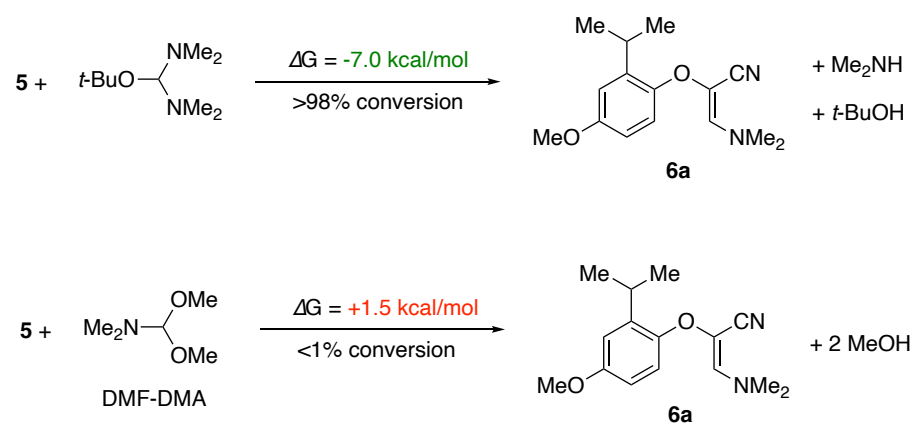
Pyrimidine Synthesis



entry	base	additive	conversion (%)
1	KO*t*-Bu	-	73
2	NaO*t*-Bu	-	81
3	LiO*t*-Bu (lot 1)	-	>99
4	LiO*t*-Bu (lot 2)	-	88
5	LiO*t*-Bu (lot 2)	10 wt% H_2O	>99
6	LiOH		70
7	LiOH	10 wt% H_2O	>99
8	NaO*t*-Bu	10 wt% H_2O	>99
9	KO*t*-Bu	10 wt% H_2O	>99
10	50 wt % NaOH		>99
11	50 wt % NaOH		>99 (97%)



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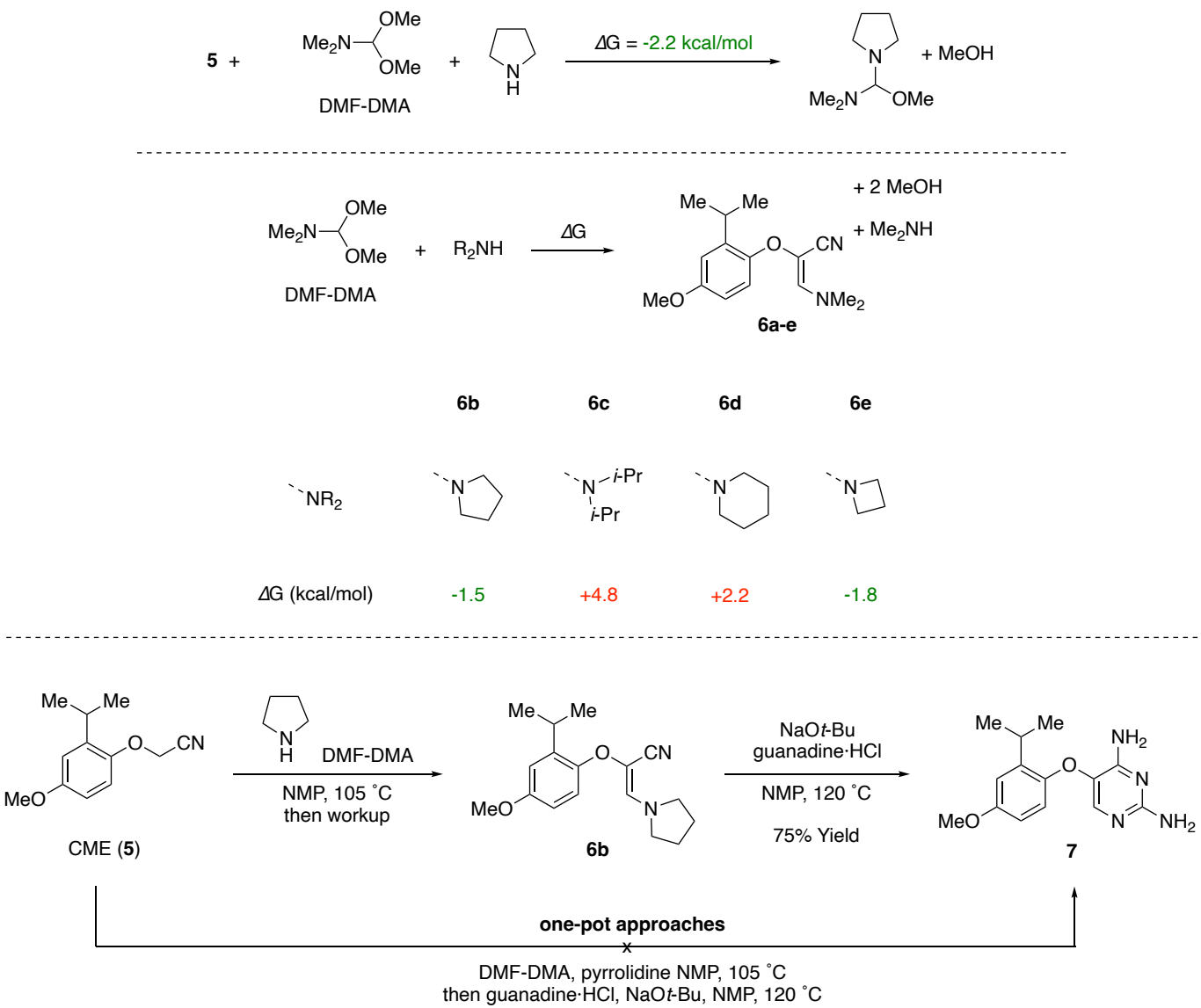
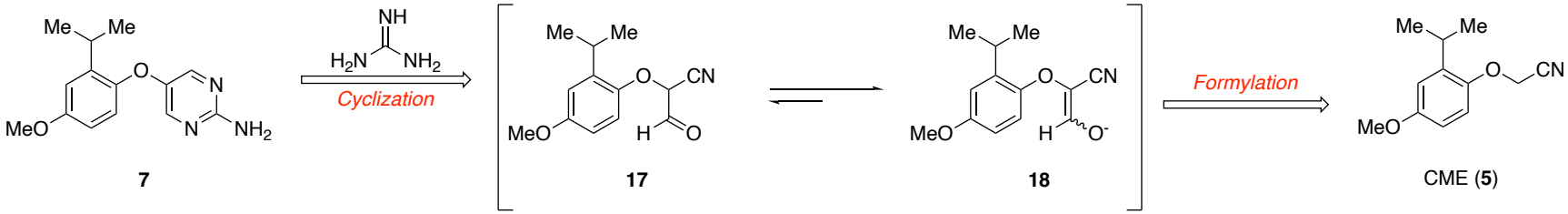
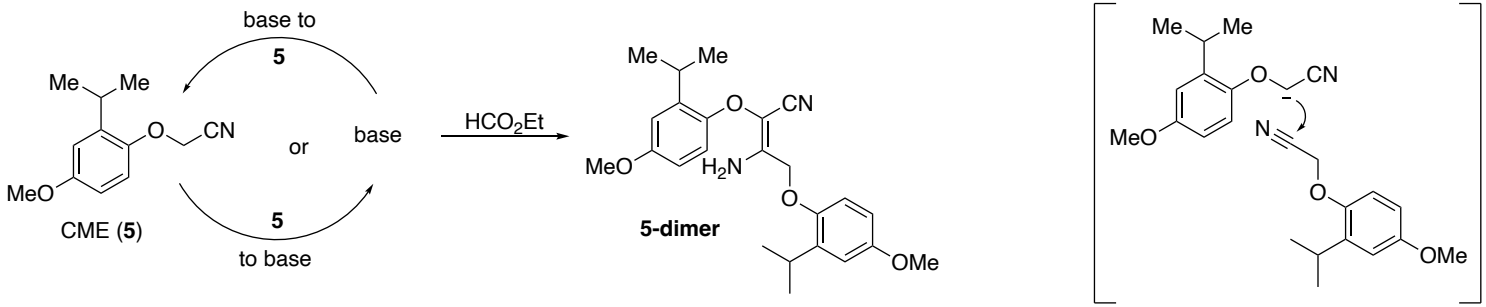
Alternatives to Brederek's Reagent

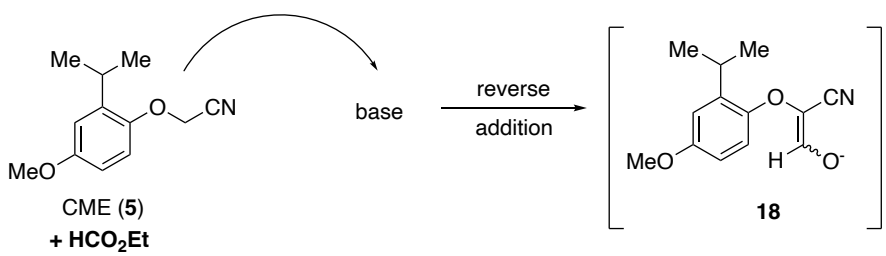


Organic Process Research & Development **2020** *24* (11), 2462-2477

Formylation Strategy







1) Polar-aprotic solvents yield best results
2) Strong bases required for full conversion (K/NaO-*t*Bu, KHMDS)
3) K counterion is essential
4) Low-temp. inhibits dimer formation

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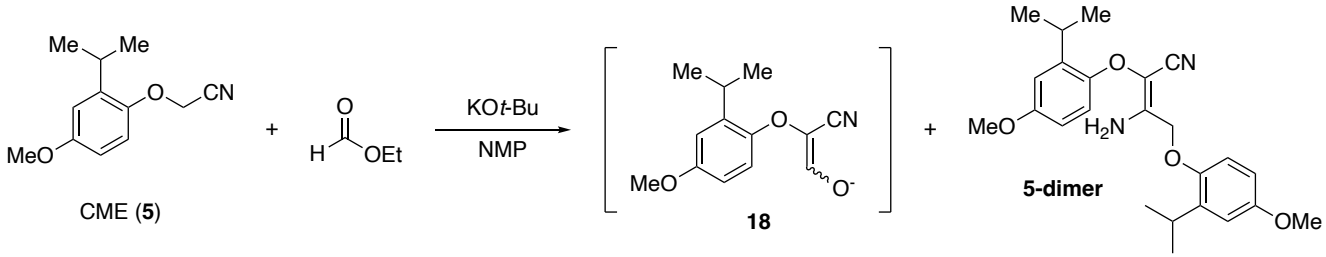
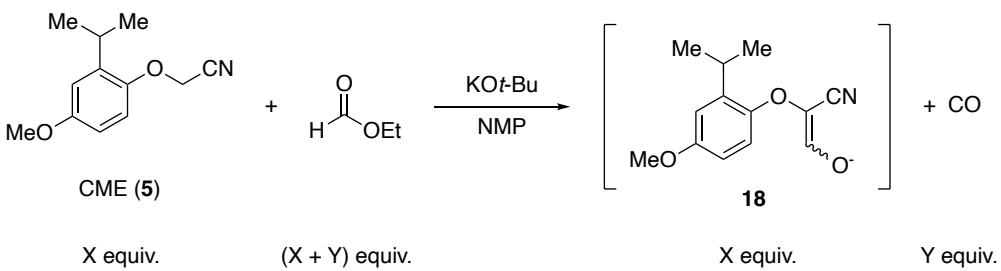
Dimer Minimization

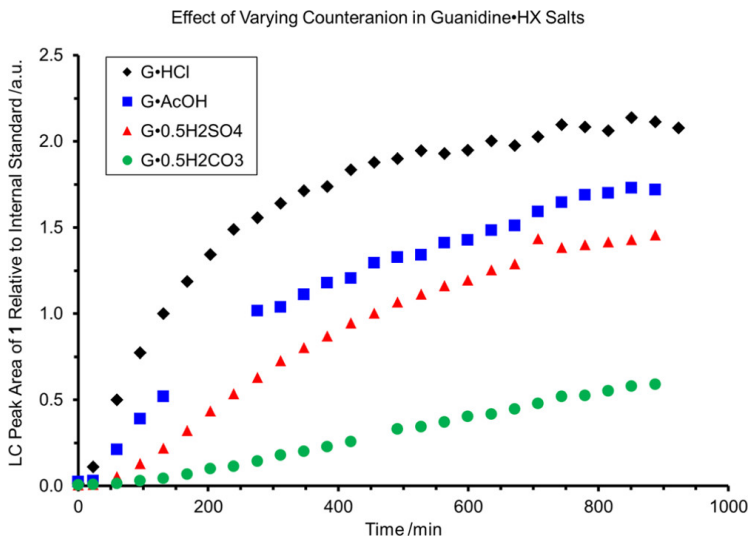


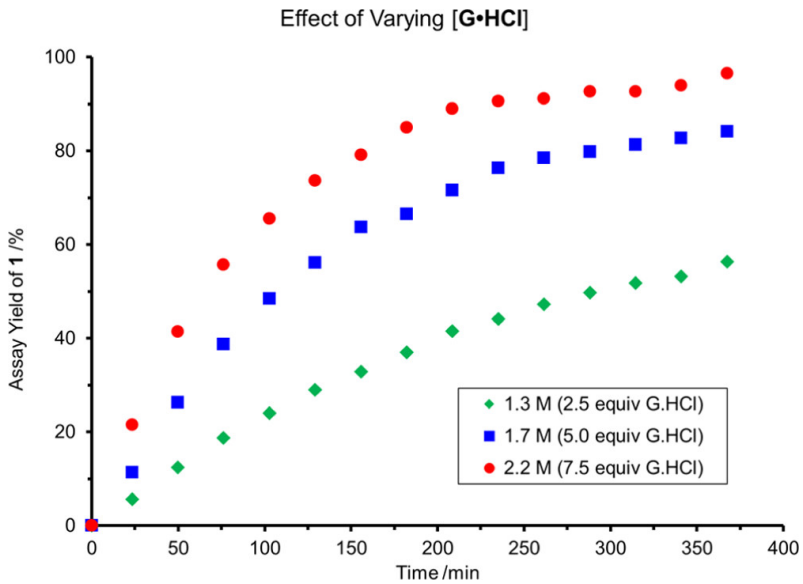
entry	KO*t*-Bu (equiv)	HCO_2Et (equiv)	**18** (LCAP)	**5-dimer** (LCAP)	**5 CME** (LCAP)
1	1.0	2.0	76.0	1.1	19.9
2	1.5	2.0	93.9	1.5	3.7
3	2.3	2.0	98.5	1.0	0.0
4	2.3	1.5	95.4	3.6	0.0

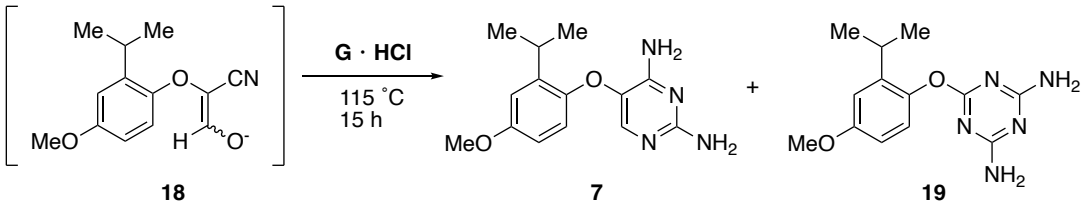


250 kg of CME would generate 75lbs of CO (4lbs/h maximum)

Guanidine Properties







entry	guanidine (equiv)	**7** (LCAP)	**19** (LCAP)
1	2.0	75.0	11.1
2	3.0	87.2	6.6
3	4.5	89.5	4.9
4	6.0	92.0	3.1
5	8.0	93.5	2.1

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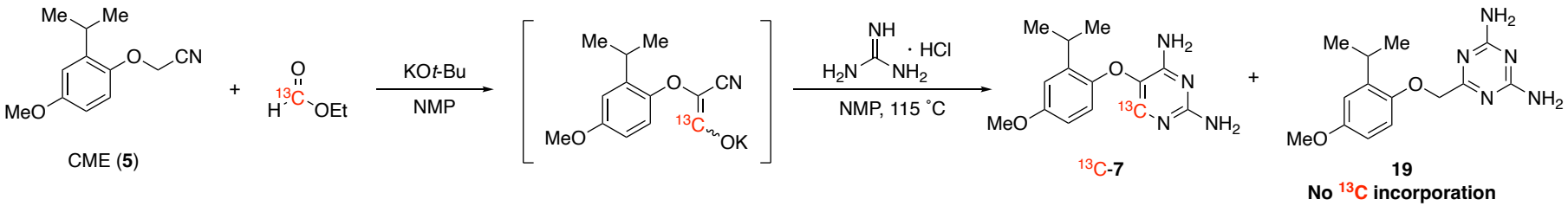
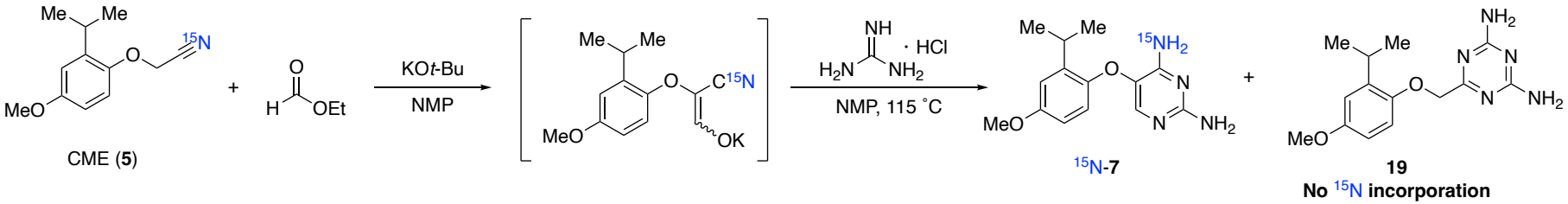
Investigation of Triazine Formation

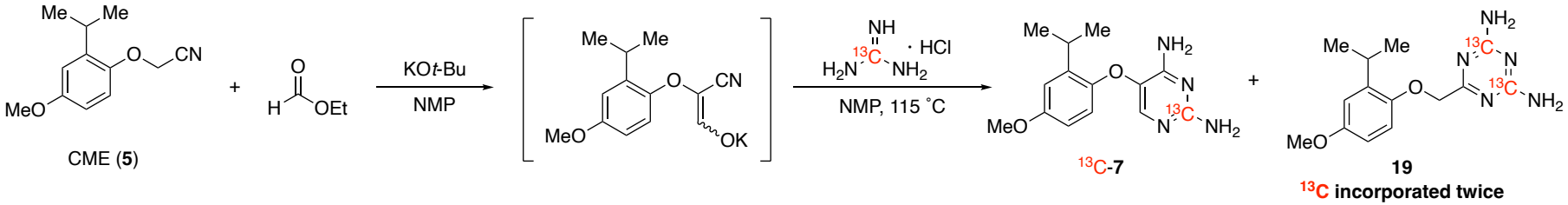
A. ^{13}C-ethyl formate study



B. ^{15}N-CME study



C. ^{13}C-guanidine study



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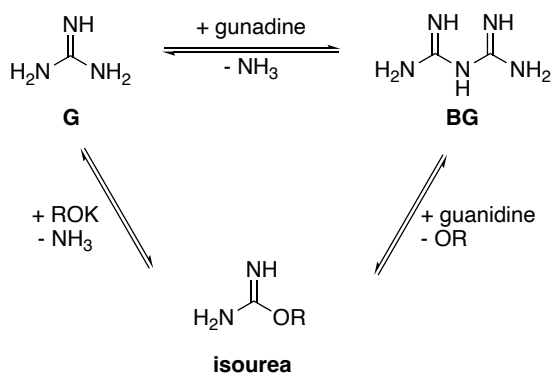
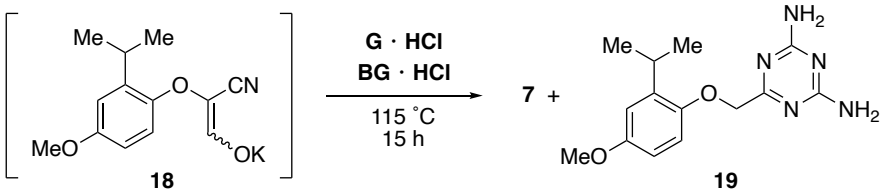
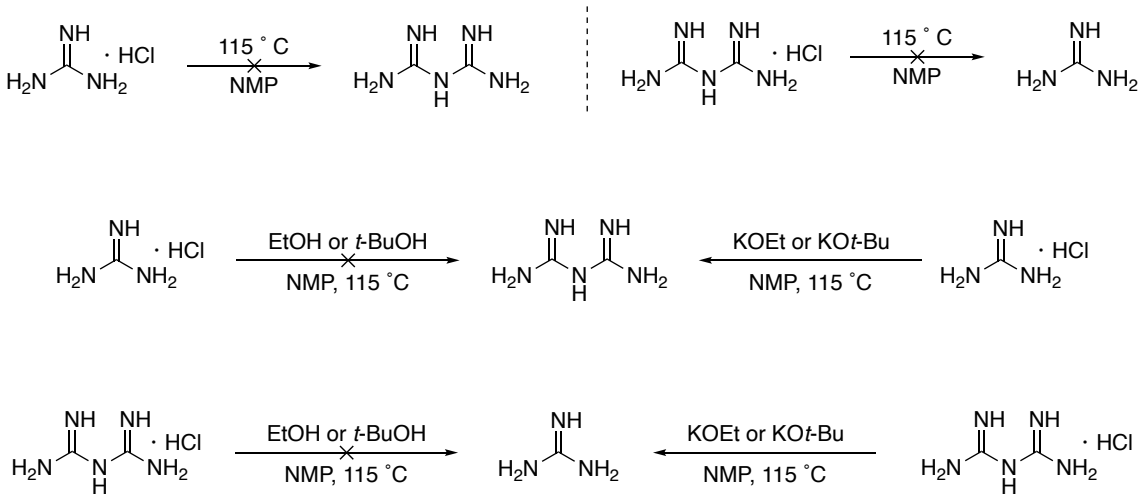
Effects of BiGuanidine





entry	equiv of 7	GHCl	BGHCl	7:9
1	1	0	3	1.9:1
2	1	0	6	1.3:1
3	1	0	9	1.2:1
4	1	3	3	4.5:1
5	1	3	6	3.6:1
6	1	3	9	3.3:1



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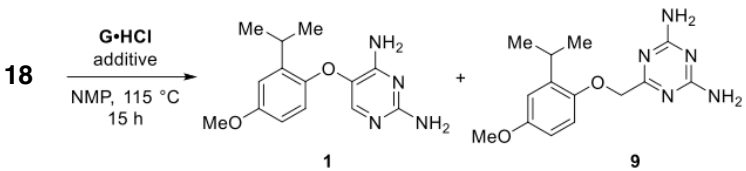
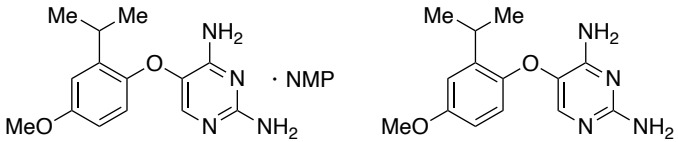
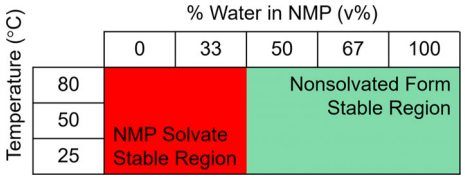
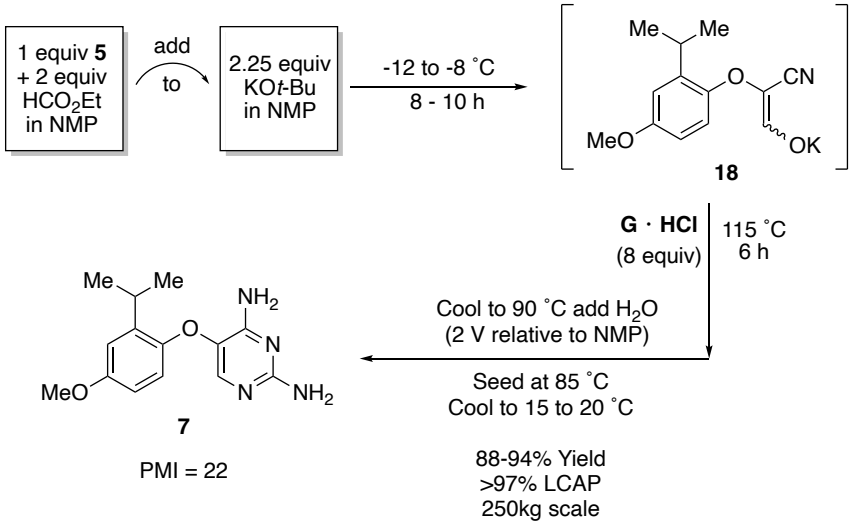
Final Batch Route to 7



entry	G·HCl (equiv)	additive	1 (LCAP)	9 (LCAP)
1	3	none	87.2	6.6
2	3	MeCOOH (0.5 equiv)	91.3	1.5
3	3	CF_3COOH (0.5 equiv)	90.8	1.9
4	3	Me_3CCOOH (0.5 equiv)	92.4	1.3
5	3	conc. HCl (0.5 equiv)	75.0	0.9
6	3	H_2SO_4 (1.0 equiv)	26.0	7.0
7	3	$KHSO_4$ (0.5 equiv)	90.1	1.0
8	3	K_3PO_4 (0.5 equiv)	77.9	8.2
9	3	K_2HPO_4 (0.5 equiv)	86.5	3.2
10	3	KH_2PO_4 (0.5 equiv)	86.6	4.0
11	3	NH_4COOH (0.5 equiv)	87.6	0.5
12	3	NH_4ClO_4 (0.5 equiv)	87.0	1.0
13	3	$NH_4SO_3CF_3$ (0.5 equiv)	87.2	0.8
14	3	NH_4Cl (0.5 equiv)	89.2	0.9
15	3	NH_4Cl (0.75 equiv)	89.7	1.4
16	4	NH_4Cl (0.75 equiv)	92.7	1.0
17	5	NH_4Cl (0.75 equiv)	94.2	0.8
18	5	$(NH_4)_2SO_4$ (0.75 equiv)	80.6	1.7
19	5	$(NH_4)_2CO_3$ (0.75 equiv)	92.9	1.7







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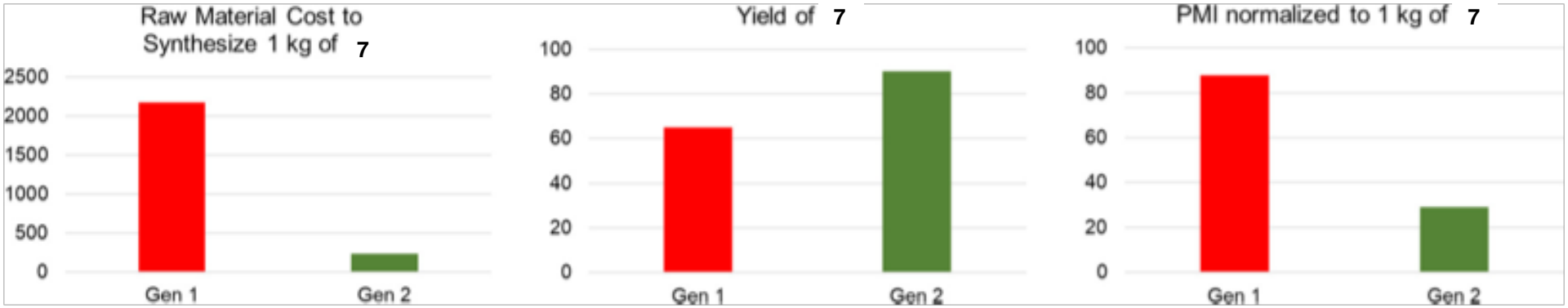
Green Metrics

Table 6. Tabulated Scale-Up Data for the Synthesis of Diaminopyrimidine 7

amount of 2 used (kg)	amount of 1 made (yield[a])	purity of 1 (LCAP)
280	375 kg (89%)	97.8
281	377 kg (88%)	97.7
281	352 kg (92%)	97.8
280	355 kg (92%)	97.2
280	362 kg (94%)	97.6
224	270 kg (89%)	97.4

[a]Isolated yield corrected based on the weight percent of the isolated material.



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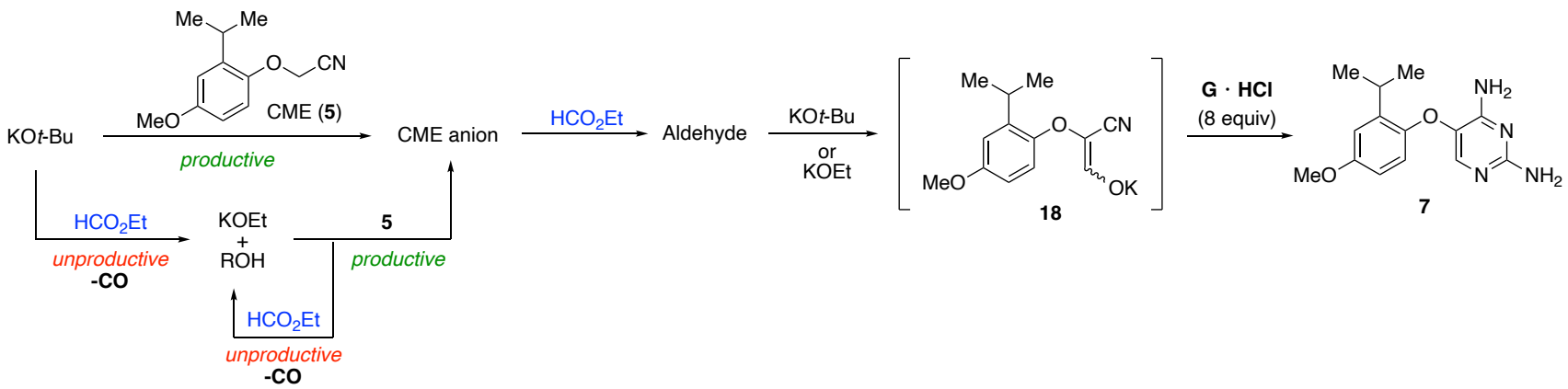
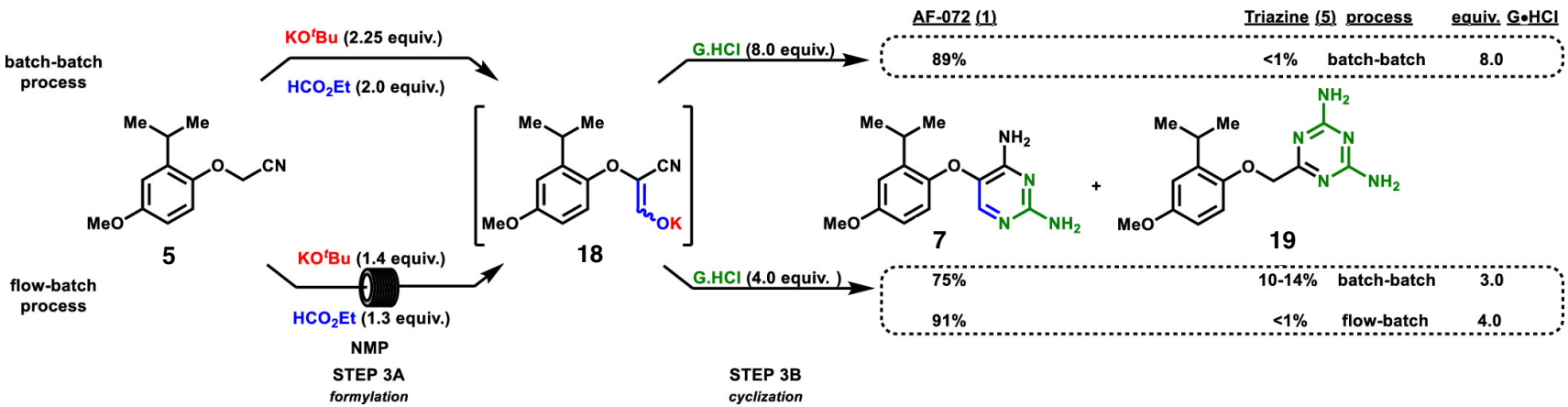
Investigating Flow





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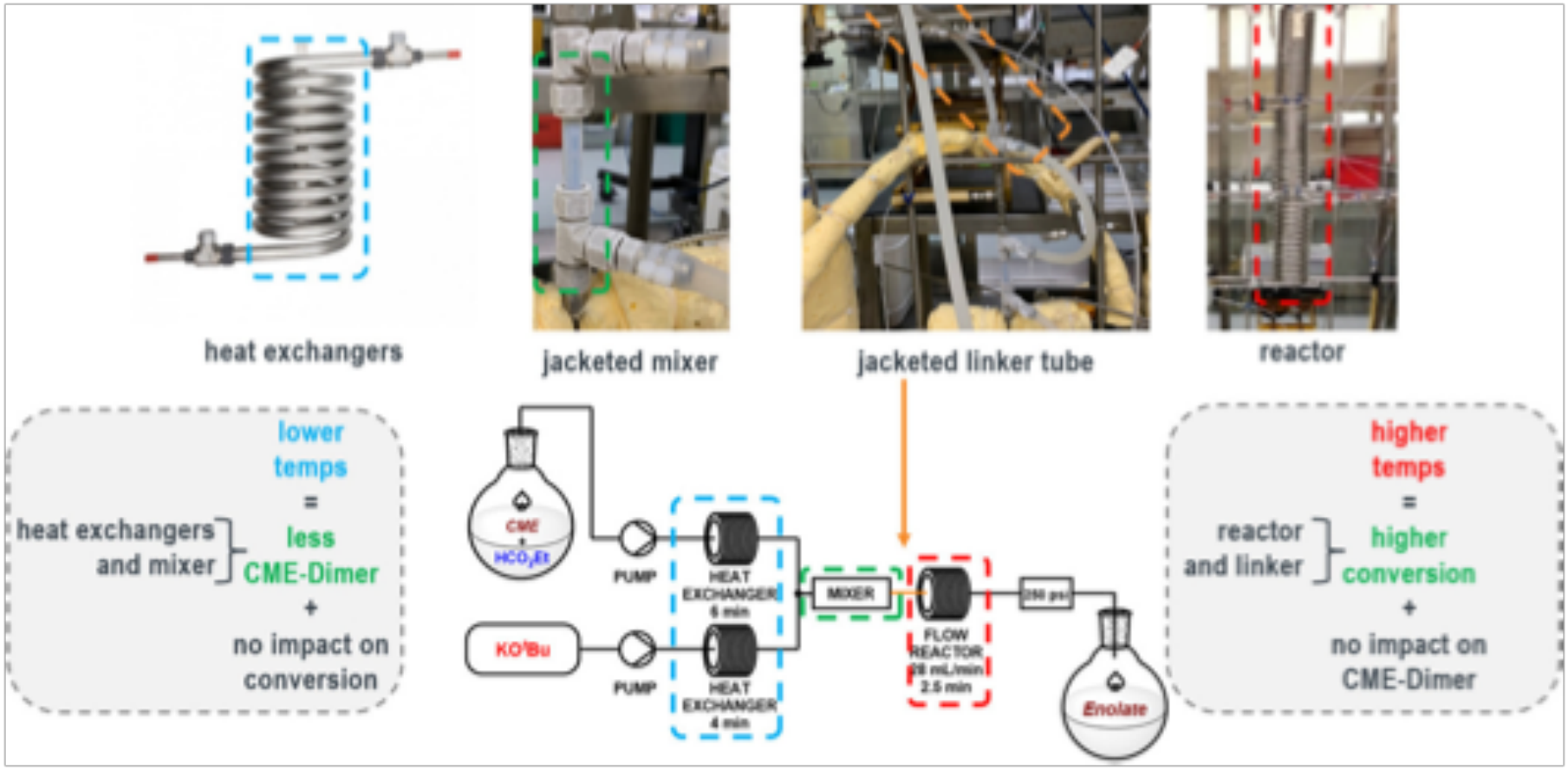
Flow Components



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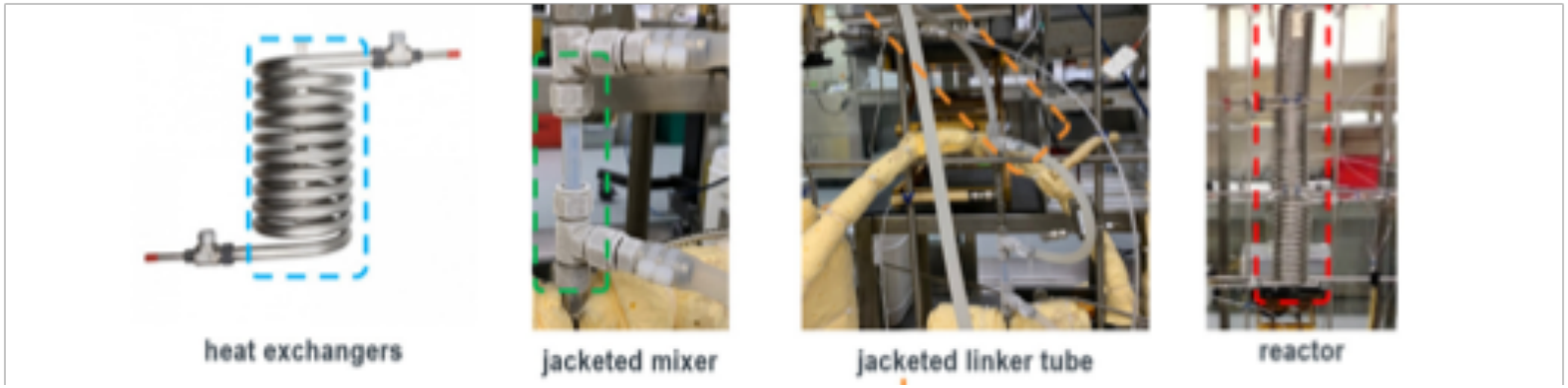
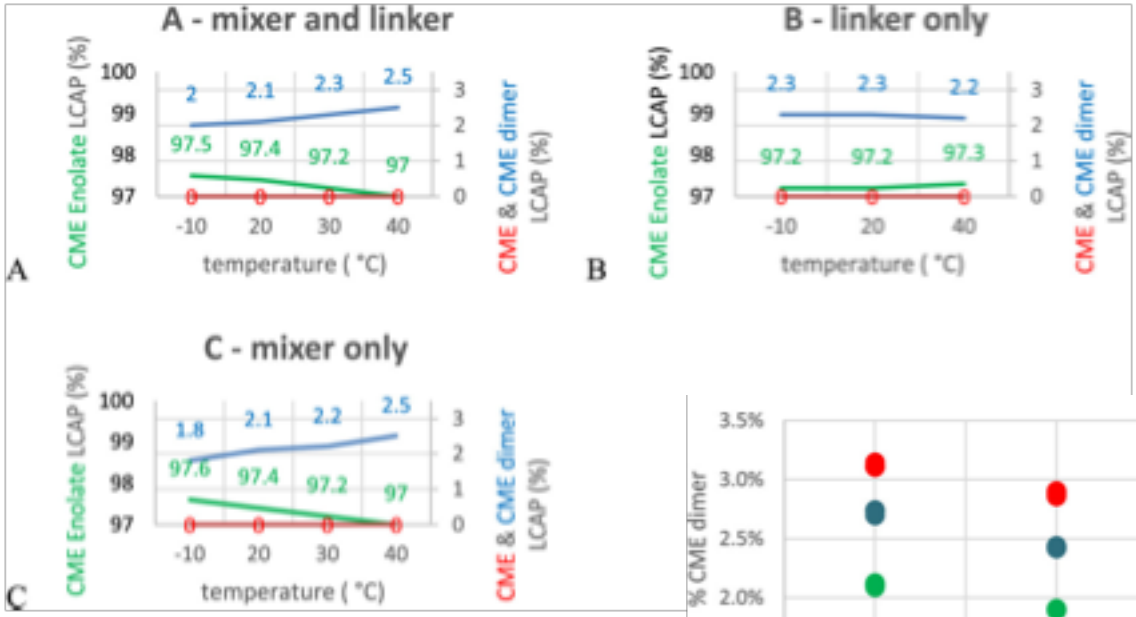
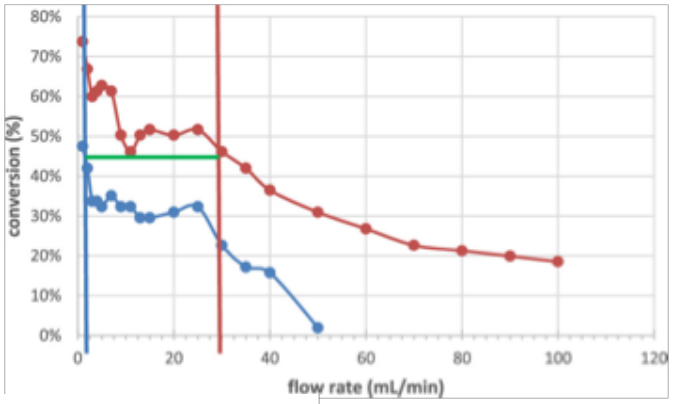
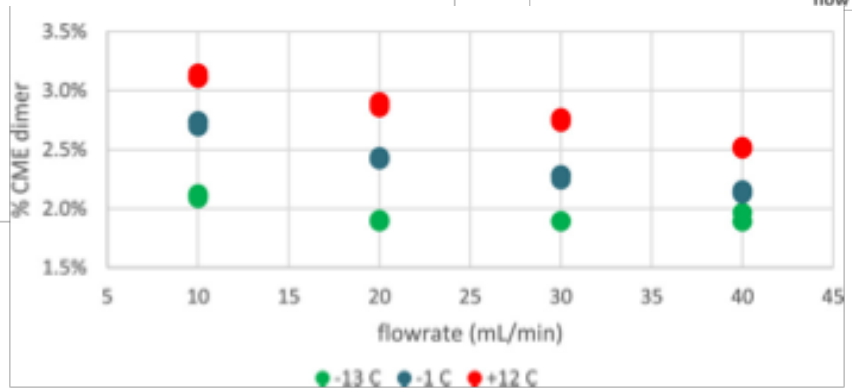
Mixing and Temperature Effects









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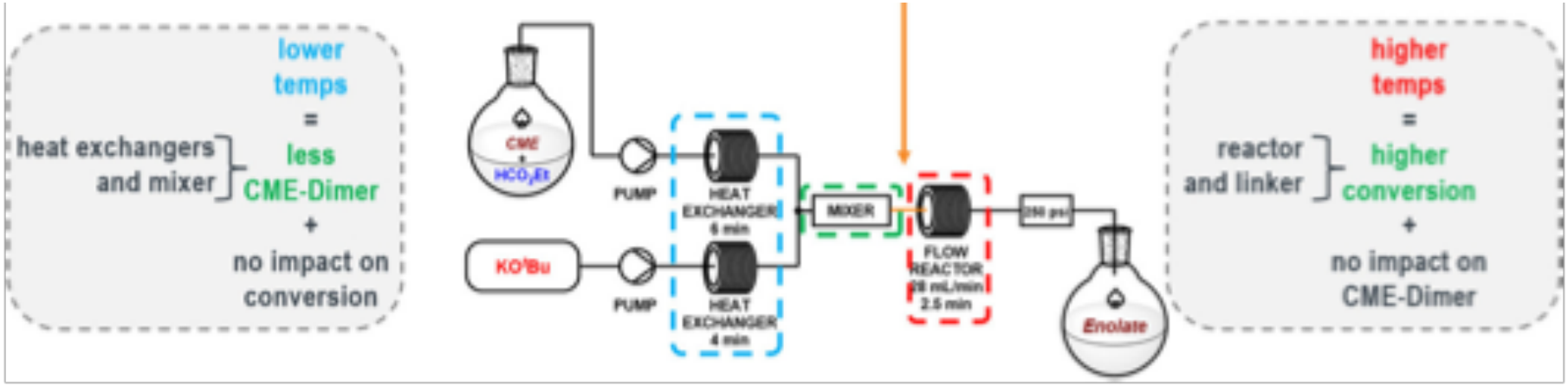
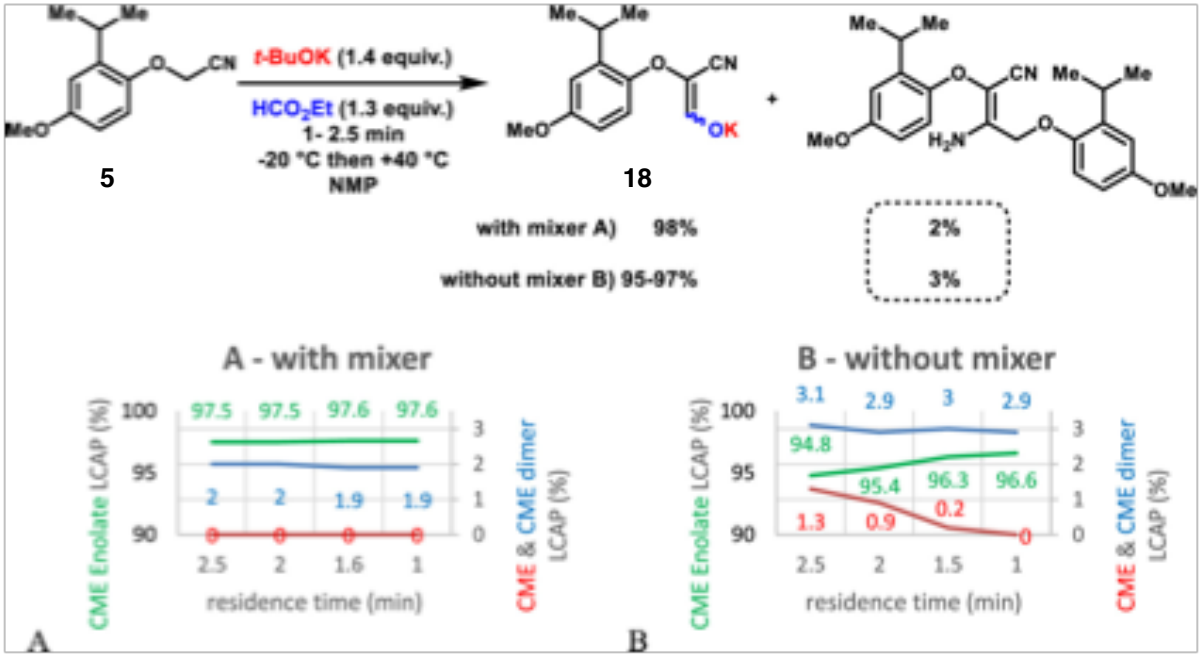
Mixing and Temperature Effects





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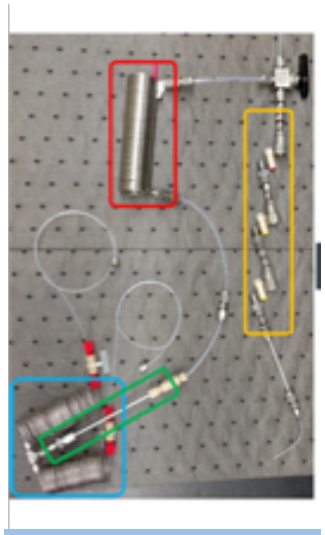
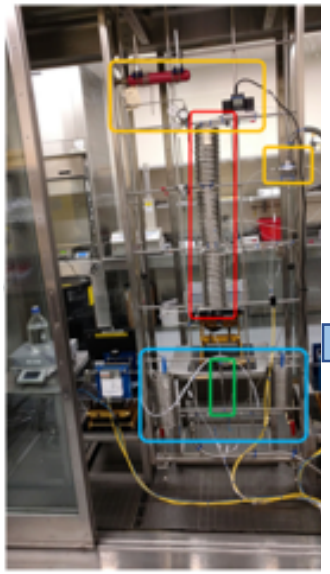
Flow Reactor Pictures



Exploratory scale

Scaled-up



Kg scale

Scaled-up

Pilot-plant scale

Scaled-out

Full-production scale

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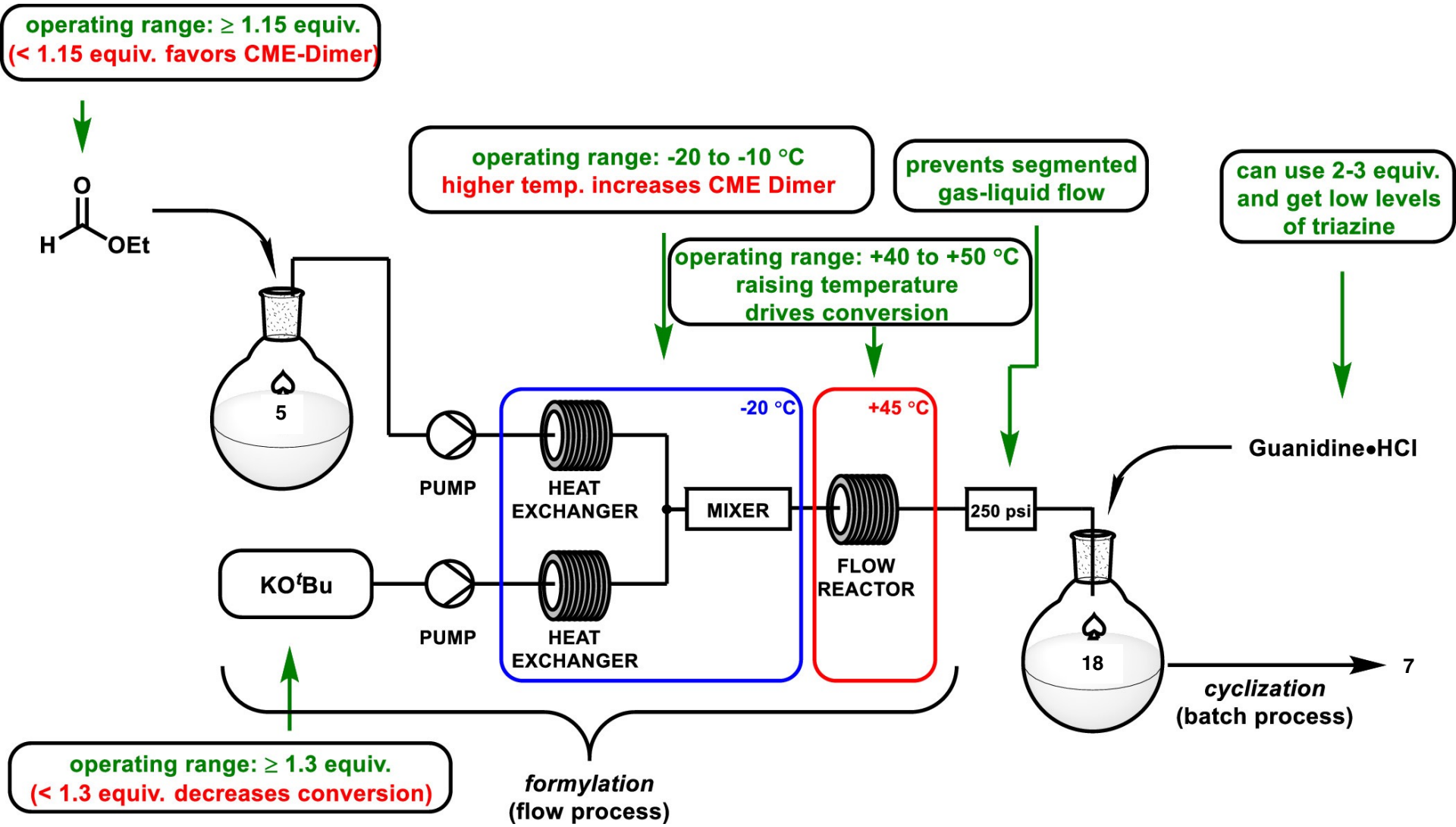
Flow Summary



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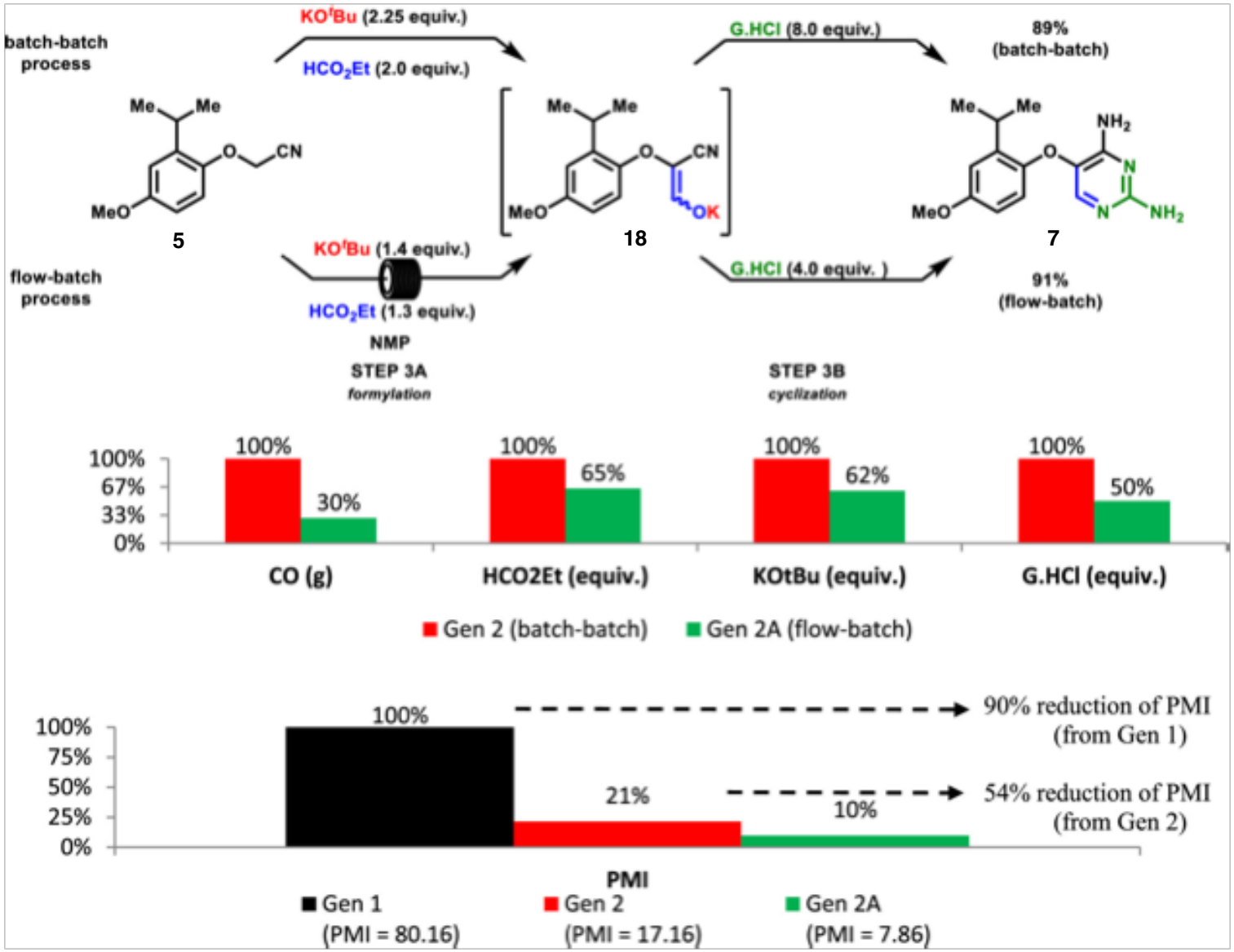
Flow Process Green Metrics



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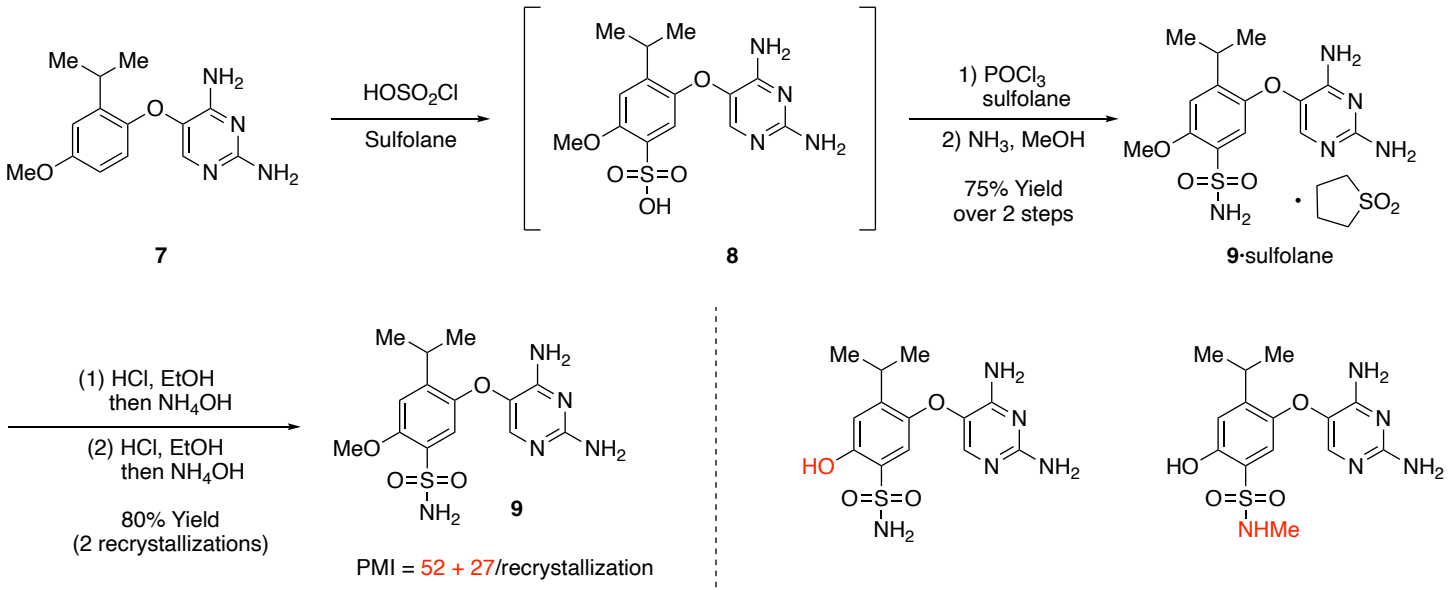
Optimization of Sulfonamide Synthesis



- HSO_3Cl and $POCl_3$
- Sulfolane (bp = 285 ˚C, Class II solvent
- Multiple recrystallizations

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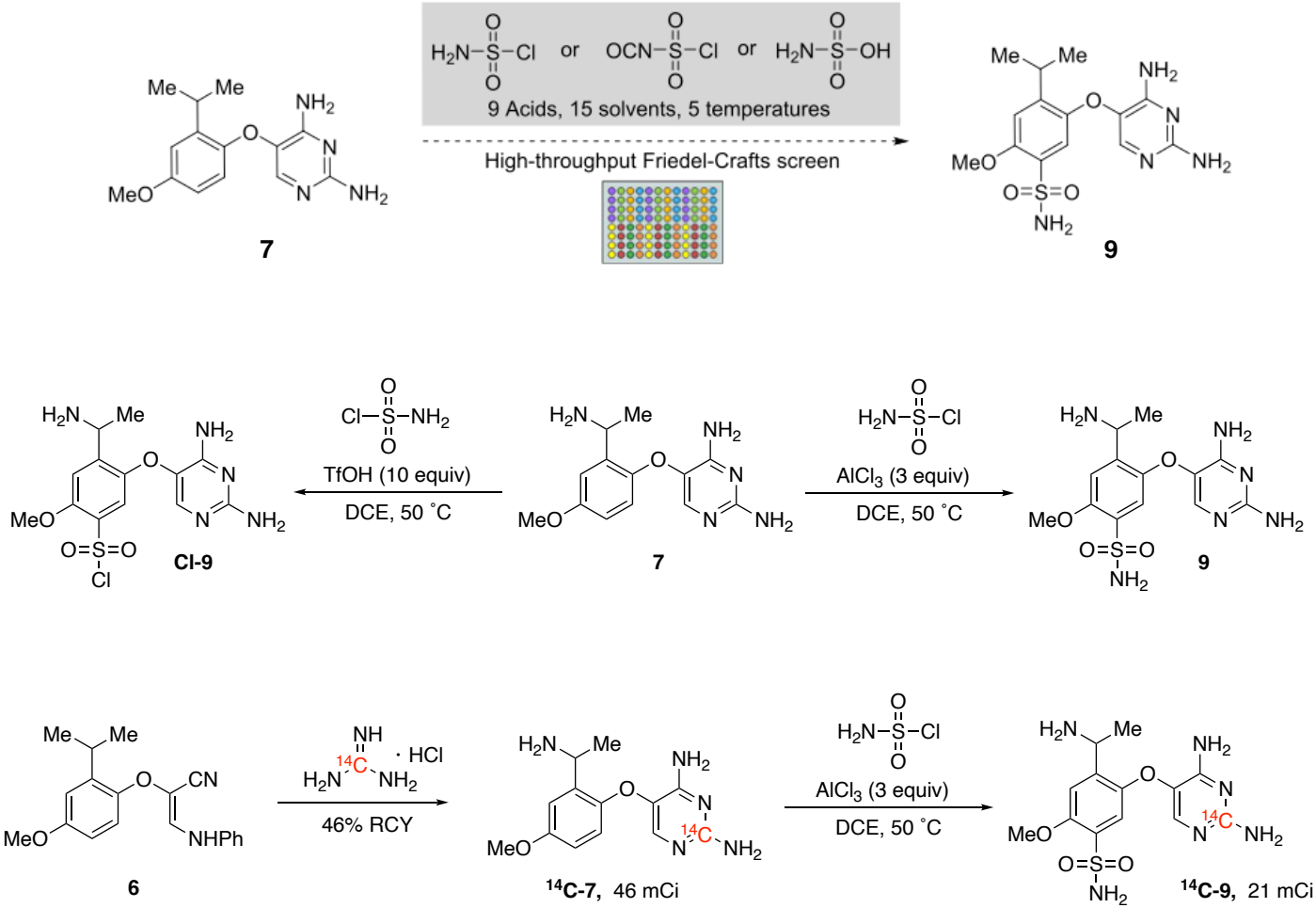
High-Throughput Studies



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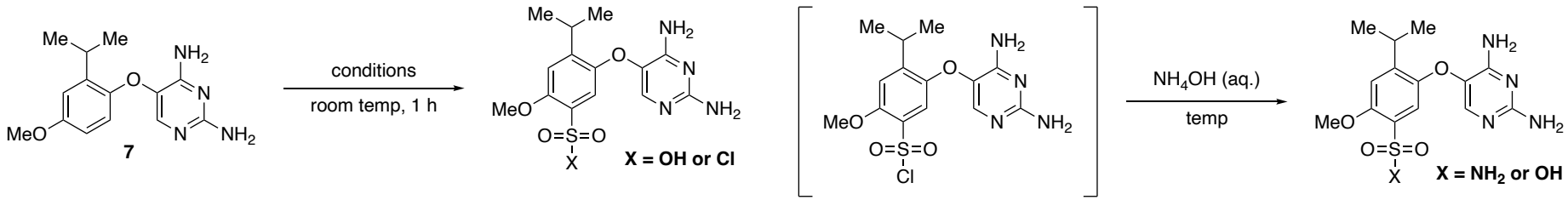
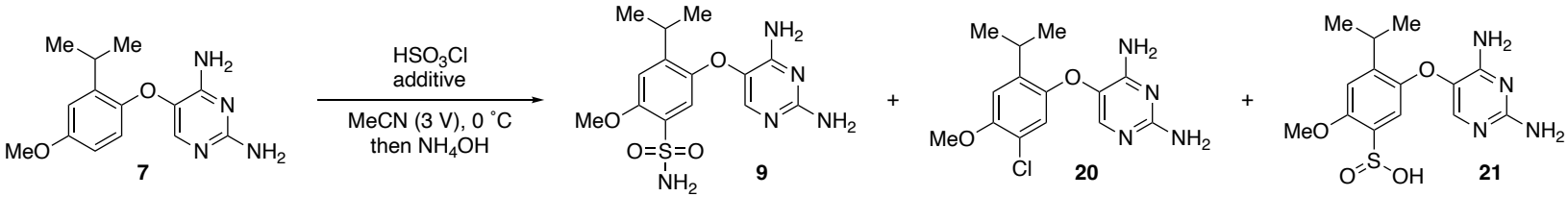
Solvent, Temperature, and Additives



entry	solvent	equiv HSO_3Cl	conversion	ration **OH:Cl**
1	sulfolane	3	100	98:2
2	DMAc	3	<5	nd
3	DMSO	3	<5	nd
4	NMP	3	<5	nd
5	MeCN	3	100	30:70
6	MeCN	4	100	6:94
7	MeCN	5	100	1.6:98.4

entry	temp (˚C)	**NH_2** (LCAP)	**OH** (LCAP)
1	0	89.9	1.0
2	15	87.0	5.4
3	30	82.5	11.3



entry	conditions	**9** (LCAP)	**20** (LCAP)	**21** (LCAP)
1	99% HSO_3Cl (supplier A)	93.0	0.2	0.2
2	99% HSO_3Cl (supplier B)	80.6	4.1	3.7
3	99% HSO_3Cl + 1 equiv SO_2Cl_2	32.0	22.0	21.0
4	99% HSO_3Cl + 20% DMB	93.0	0.9	2.3

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Initial Crystallization Studies

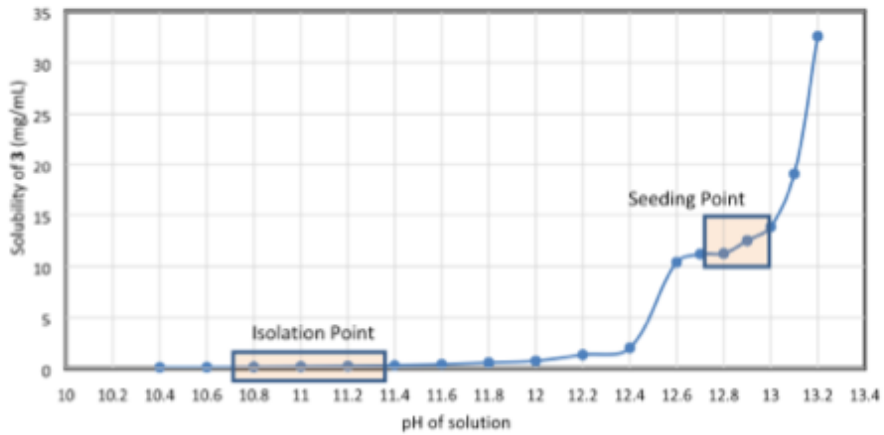
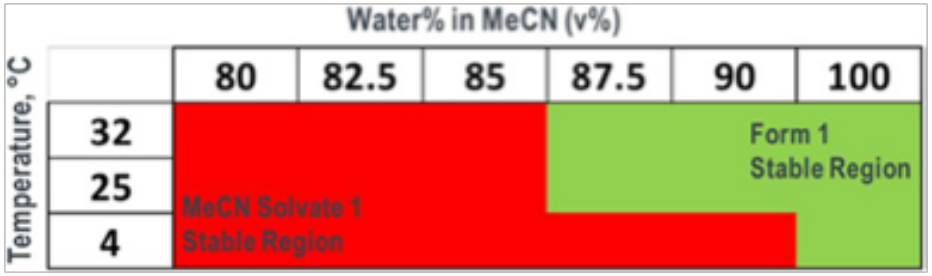


Figure 1. Solubility of sulfonamide **3** in the reaction solvent based on solution pH. pH was adjusted using a 2 M aqueous citric acid solution.

Table 5. Crystal Form Studies for the Isolation of API Free Base 9

MeCN/Water solution → Seed with Form 1 or MeCN solvate → Slurry → Wash/Dry (*End of Crystallization*) → Dry Cake

solvent composition	<15% MeCN	>15% MeCN	<15% MeCN	>15% MeCN
seed form	form 1	form 1	MeCN solvate	MeCN solvate
slurry form	form 1	MeCN solvate	form 1	MeCN solvate
dry cake form	form 1	form 1	form 1	form 1
impurities (LCAP)	0.20, 0.21	0.04, 0.02	0.20, 0.21	0.04, 0.02



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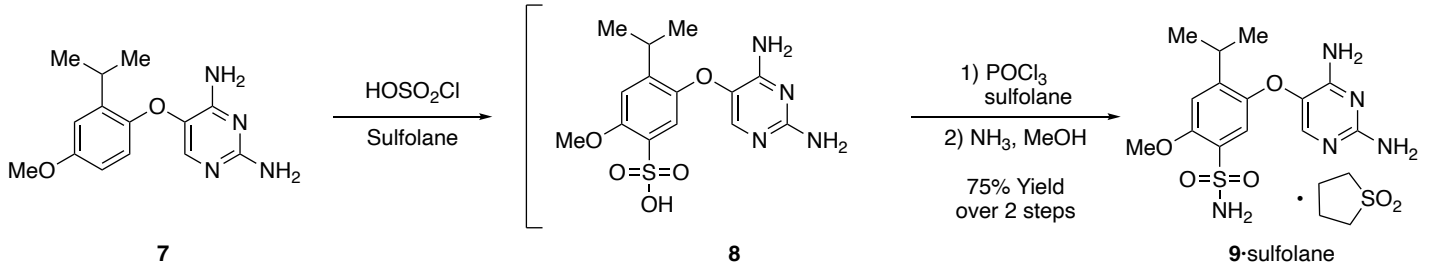
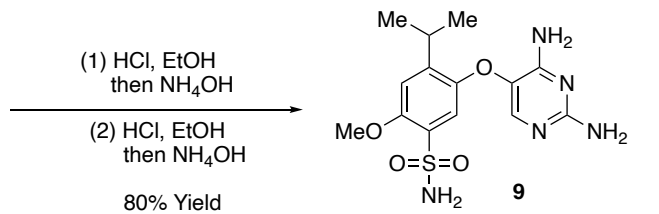
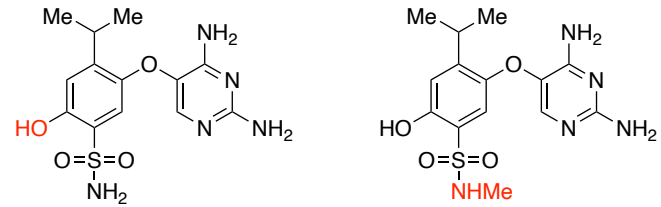
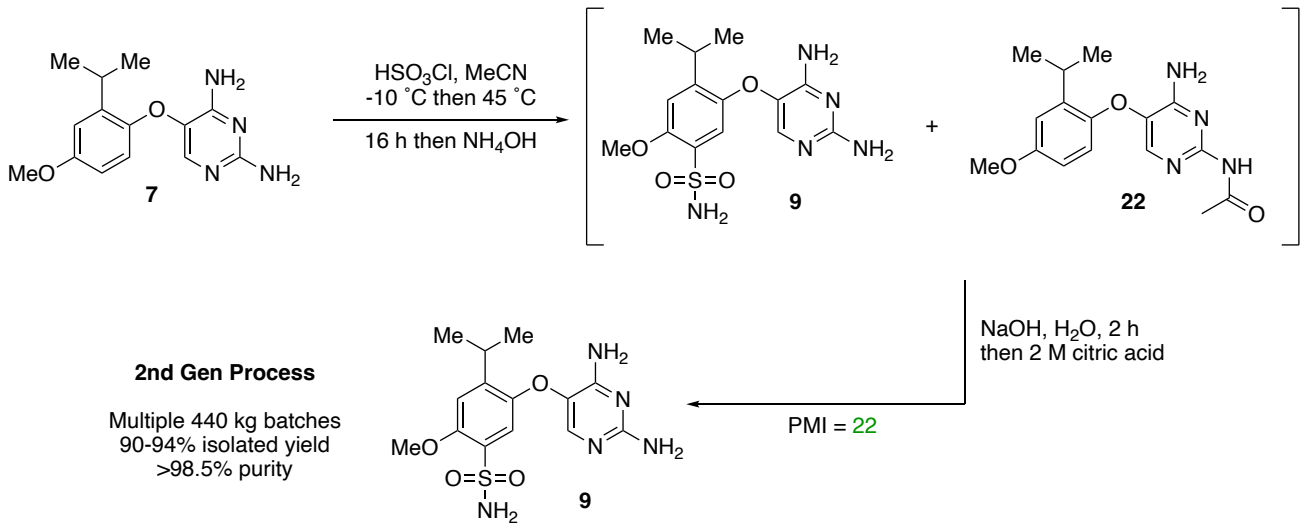
Sulfonamide Synthesis Summary





PMI = 52 + 27/recrystallization





2nd Gen Process

Multiple 440 kg batches
90-94% isolated yield
>98.5% purity

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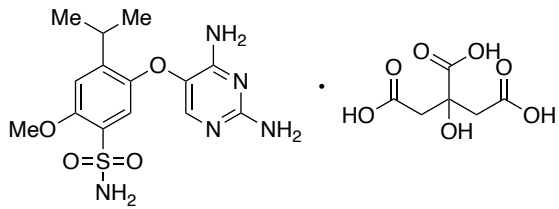
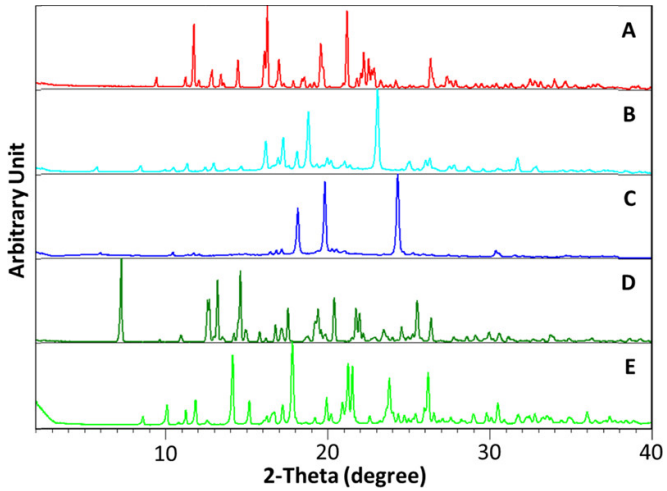
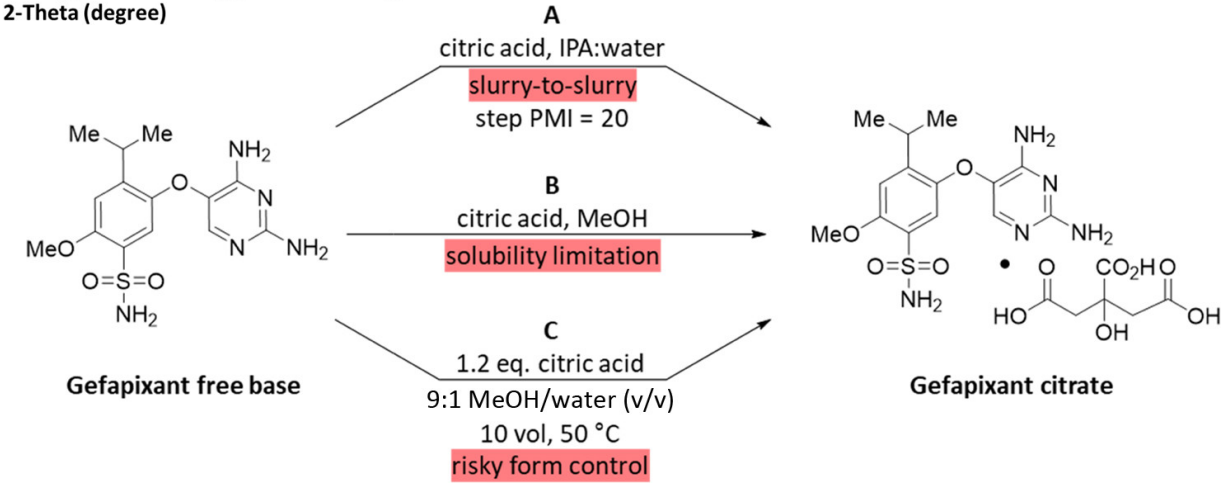
Final Crystallization





Solvent	Free base (mg/mL)	Citrate salt (mg/mL)
0.1 N HCl (pH 1.8)	5.45	11.12
phosphate buffer (pH 3)	2.21	11.31
phosphate buffer (pH 5)	0.30	12.05
water	0.16	8.30
MeOH	2.15	11.09
9:1 MeOH/water (v/v)	2.24	14.12
EtOH	1.07	0.71
IPA	0.22	0.02
acetone	1.19	0.59
MeCN	1.25	0.03
NMP	73.24[a]	>100[a]
DMF	>100[a]	>100[a]
DMSO	>100[a]	>100[a]



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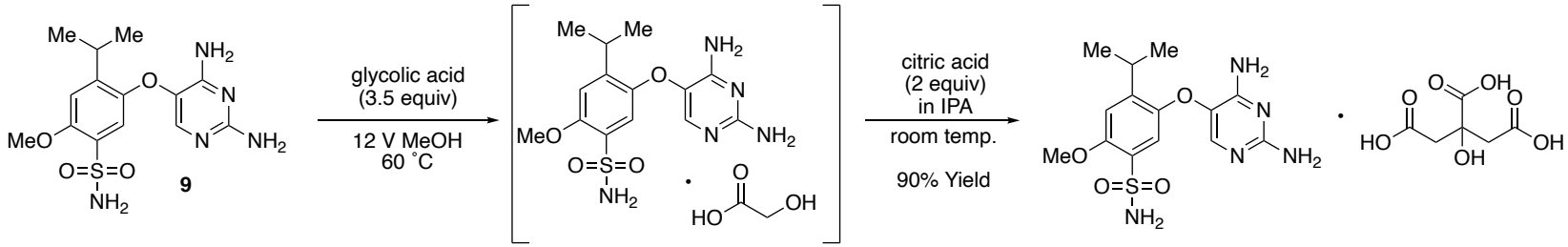
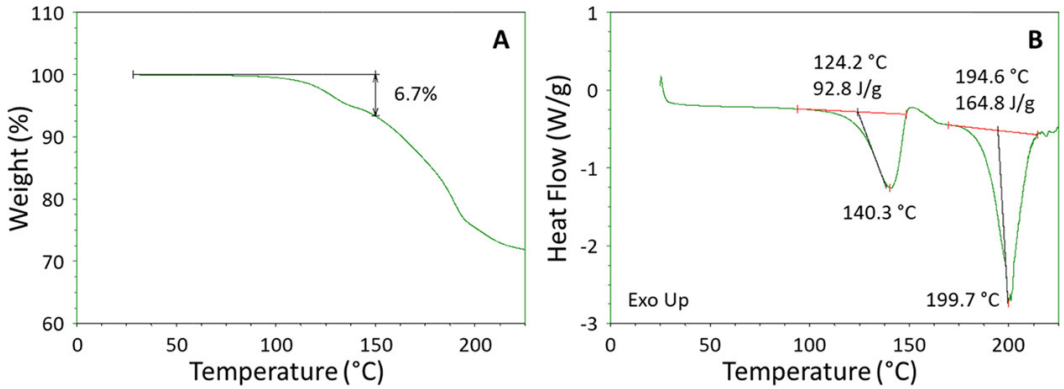
Crystallization Considerations

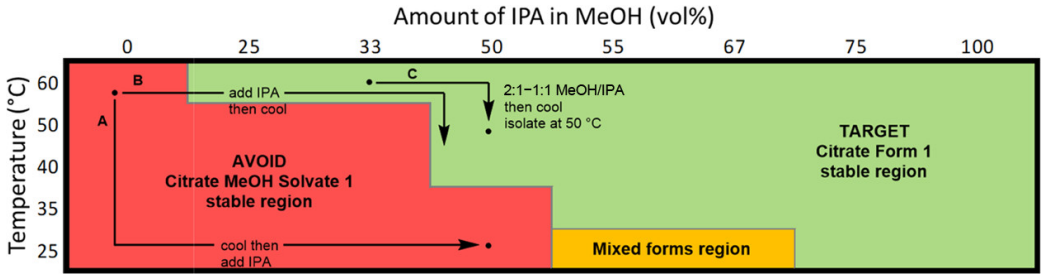


Gefapixant free base
Solubility in MeOH = 2mg/mL

Gefapixant glycolate
> 100mg/mL

Gefapixant citrate
11 mg/mL





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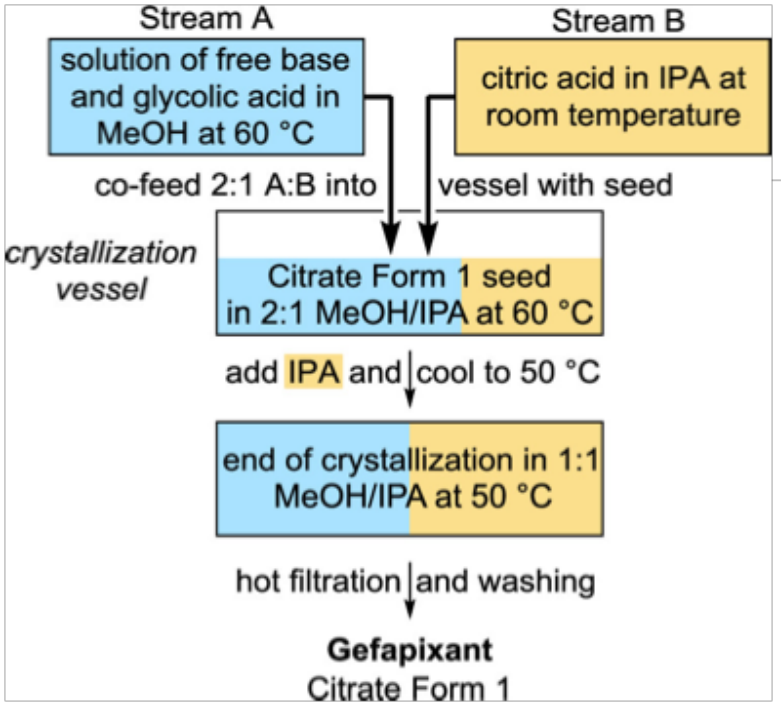
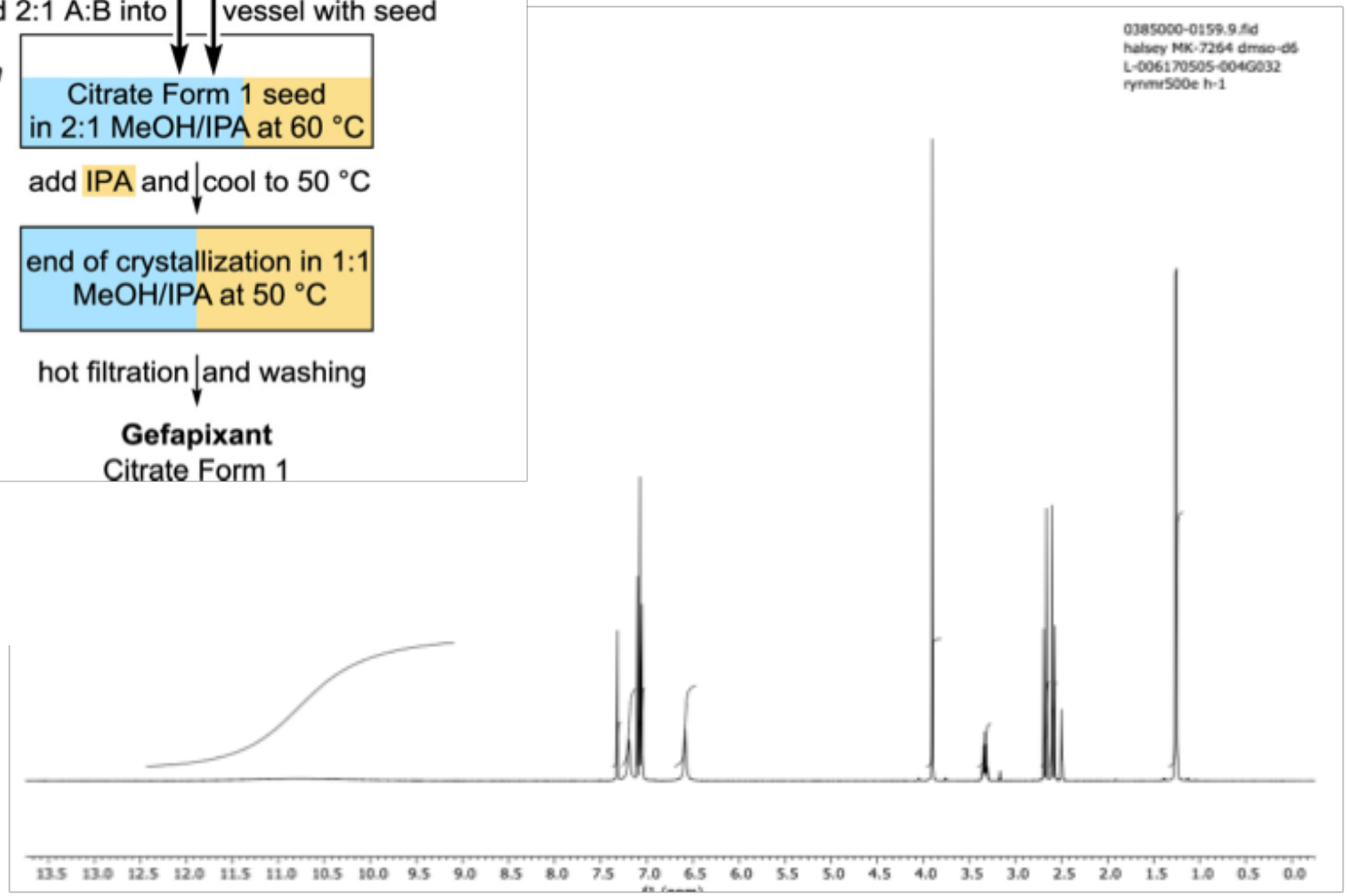
Final Crystal Procedure





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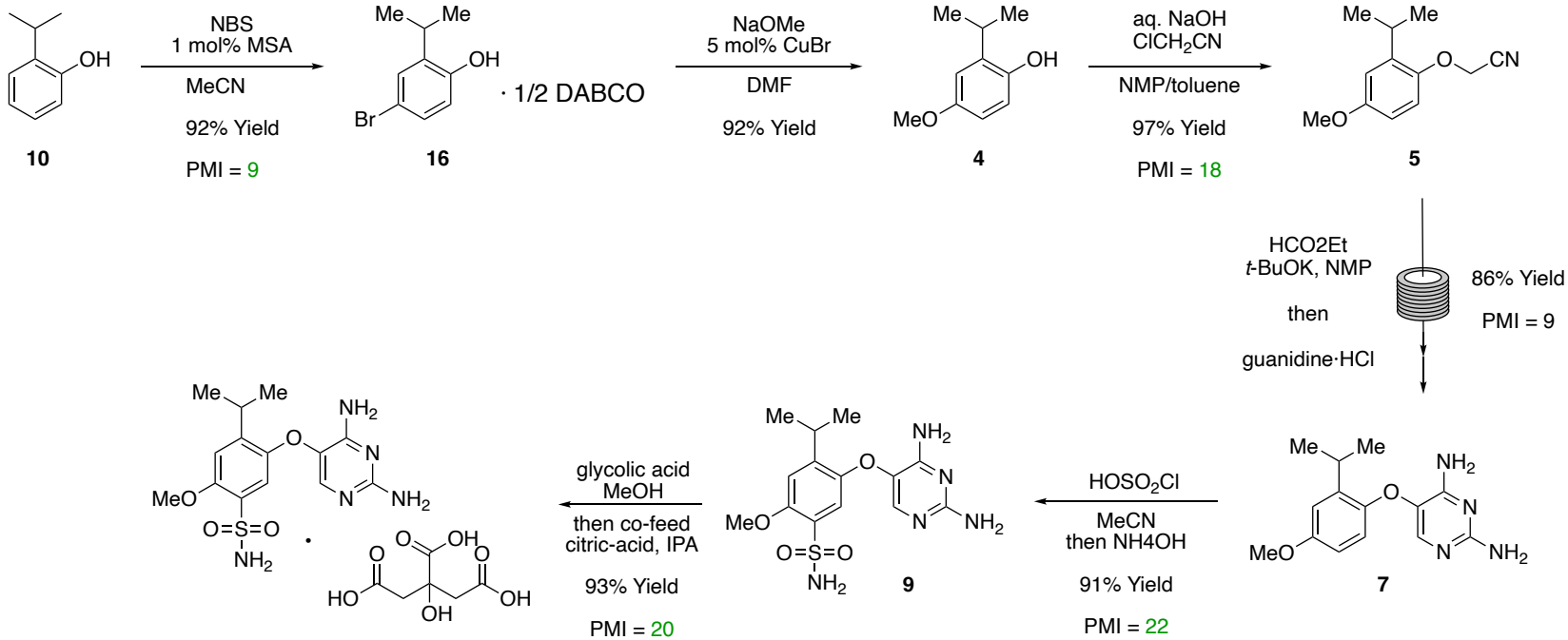
Overall Route Summary



- PMI = 78 (500% reduction)
- 60% overall yield (up from 16%)
- 600% reduction in raw materials cost
- > 300 kg of API made as of 2020

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