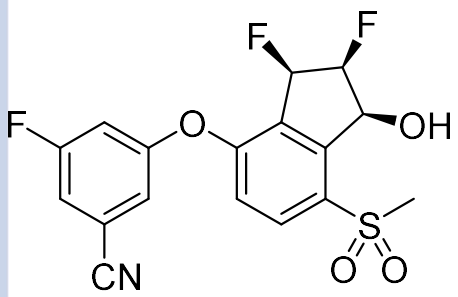
MERCK

Belzutifan: Evolution of a Sustainable Manufacturing Process



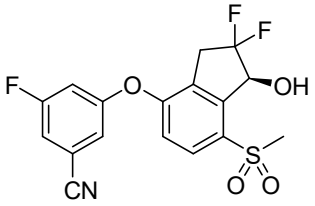
Blake Ocampo

Group Meeting

May 21, 2024

den mark

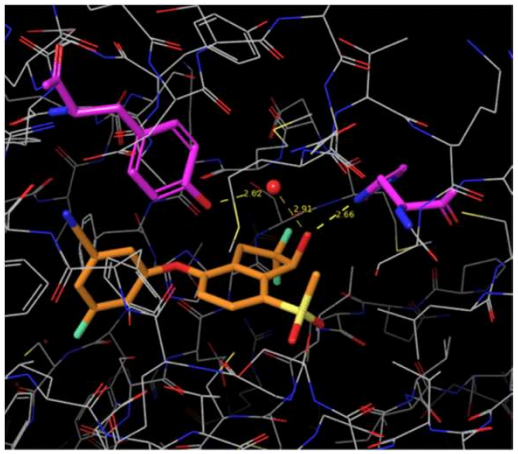
Discovery of an HIF-2α Inhibitor



PT2385
First Generation

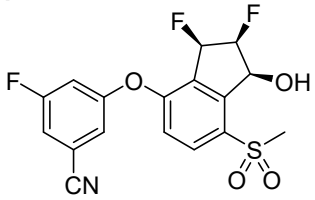
$LogD_{7.4}$: 2.2
VEGFA EC_{50}: 46 nM
Human PPB: 82% bound
Free fraction adjusted EC_{85}: 540 ng/mL

Crystal Structure of PT2385



Xu *et al. J. Med. Chem.* **2019**, 62, 15, 6876–6893.;
Wehn *et al. J. Med. Chem.* **2018**, 61, 21, 9691–9721

- Originally developed by Peloton Therapeutics in 2019 resulting in its acquisition in a $2.2 billion deal with Merck
- Von-Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) is the most common type of kidney cancer
  - VHL is characterized by dysregulation of VHL tumor suppressor gene leading to accumulation of hypoxia-inducible factors (HIF)
- HIF-2α is know to be a key driver in RCC, directly binding to DNA
  - PT2385 was found to allosterically inhibit HIF-2α protein-protein interaction, but was restricted to variable dosing

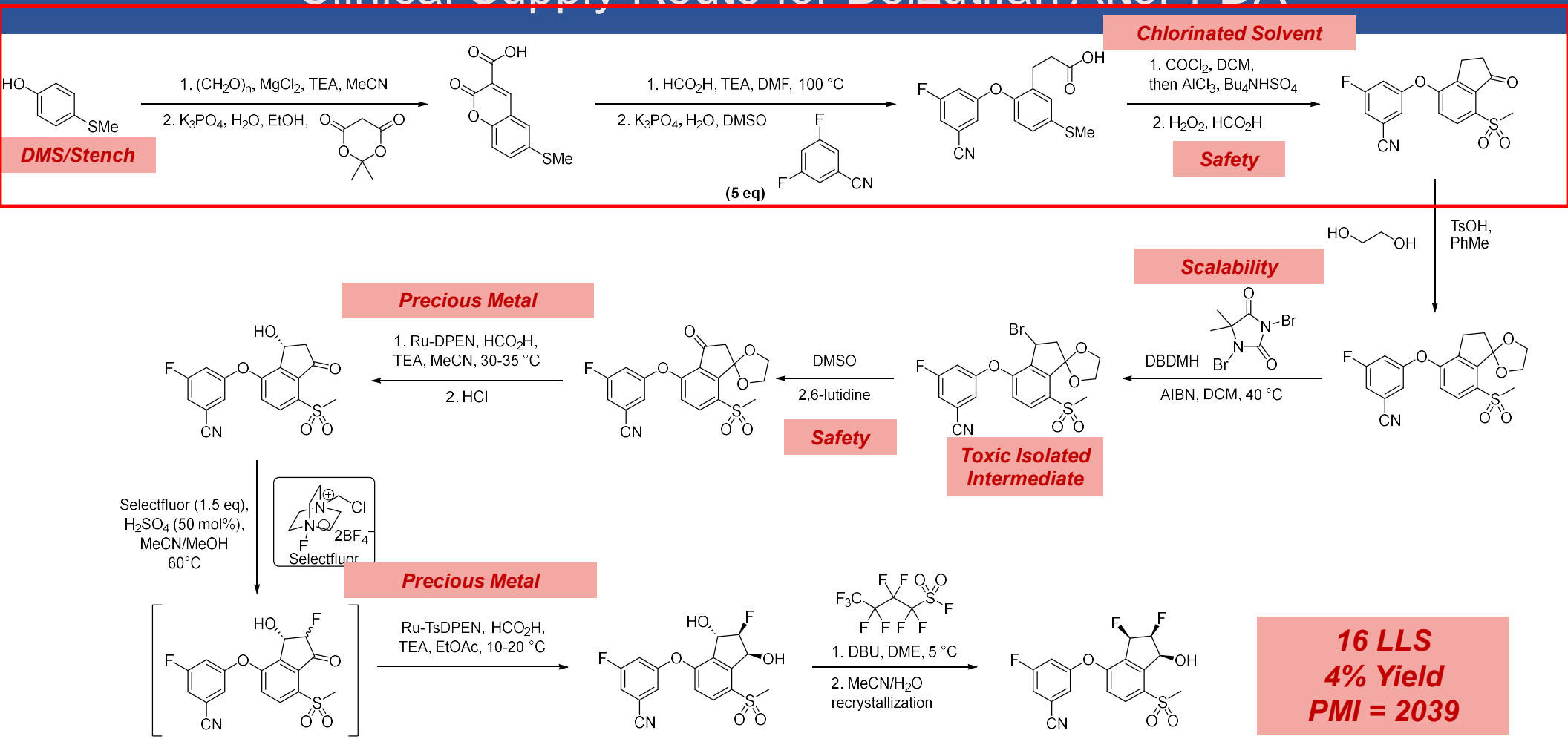


Belzutifan (MK-6482)
Second Generation

$LogD_{7.4}$: 1.2
VEGFA EC_{50}: 17 nM
Human PPB: 52% bound
Free fraction adjusted EC_{85}: 75 ng/mL

- Belzutifan helped attenuate the rate of glucoridination, helping reduce variability in patients

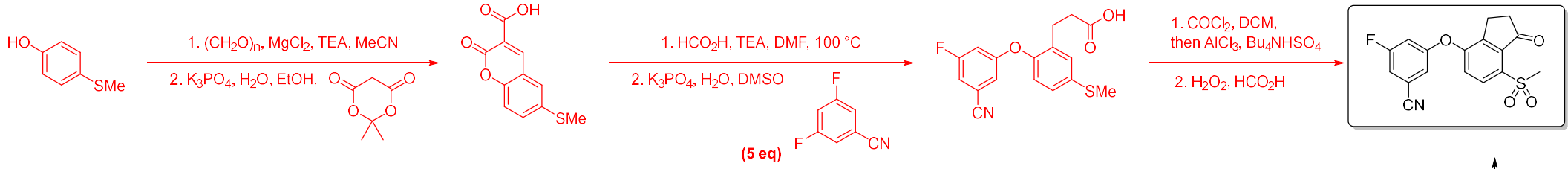
Clinical Supply Route for Belzutifan After FDA



DiRocco *et al. Org. Process Res. Dev.* **2024**, 28, 2, 404–412

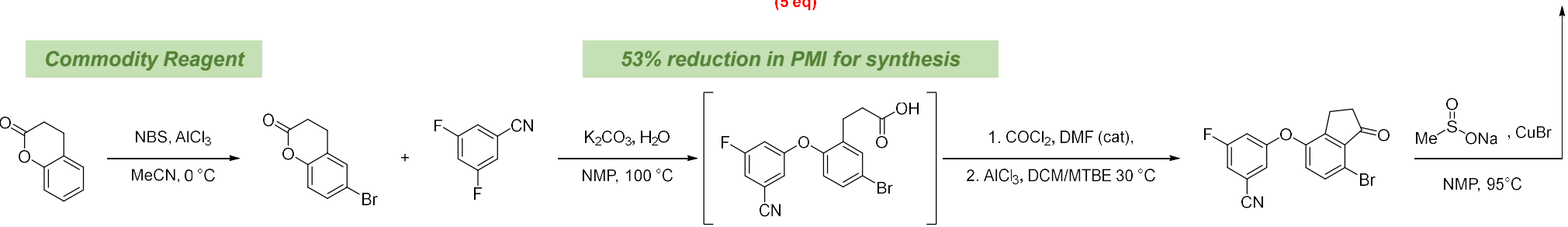
Commercialization Route Improvements for Belzutifan

Improvement of Indanone Synthesis



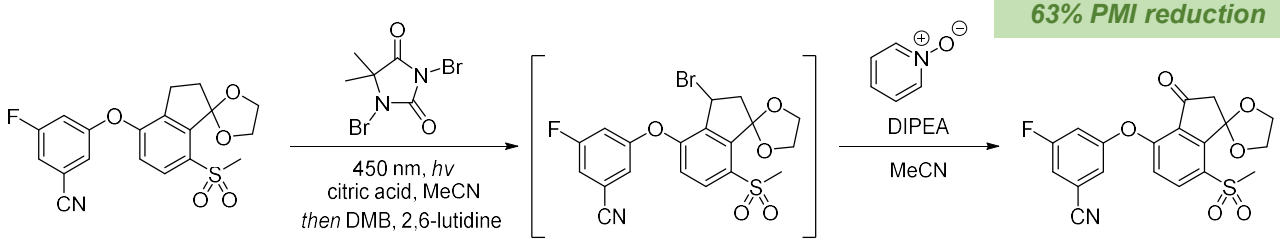
Commodity Reagent

53% reduction in PMI for synthesis



Improvement of Bromination-Oxidation

63% PMI reduction



Photobromination Removes DCM

PNO Prevents Toxic Intermediate Isolation

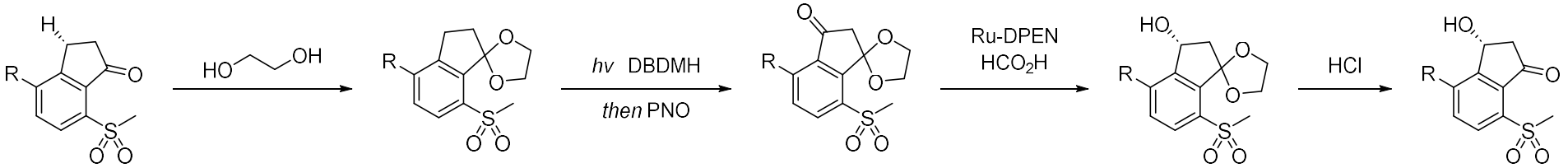
14 LLS
19% Yield
PMI = 761

Where can this process be made more efficient?

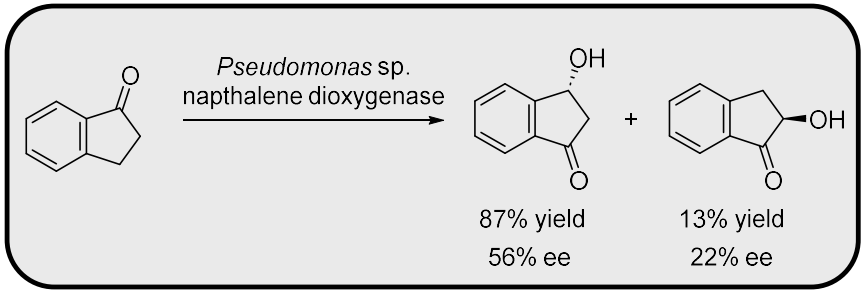
DiRocco *et al. Org. Process Res. Dev.* **2024**, 28, 2, 404–412

Finding a More Sustainable Route via Direct Oxidation

Considering the Redox and Step Economy



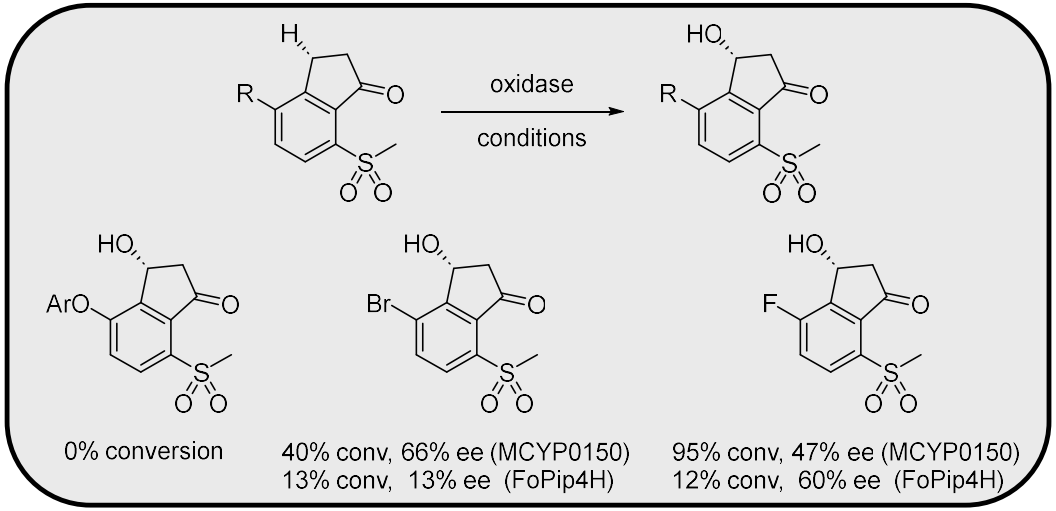
Enantioselective Indanone Oxidation



- Only existing report of this type of oxidation
  - "Unable to reproduce results of this study, which we attribute to the rather complex multicomponent nature of this enzyme class

DiRocco *et al. Org. Process Res. Dev.* **2024**, 28, 2, 404–412;
Resnick *et al. Appl. Environ. Microbiol.* **1994**, *60*, 3323– 3328;
Cheung-Lee *et al. Angew. Chem.Int. Ed*. **2024**, *63*, e202316133

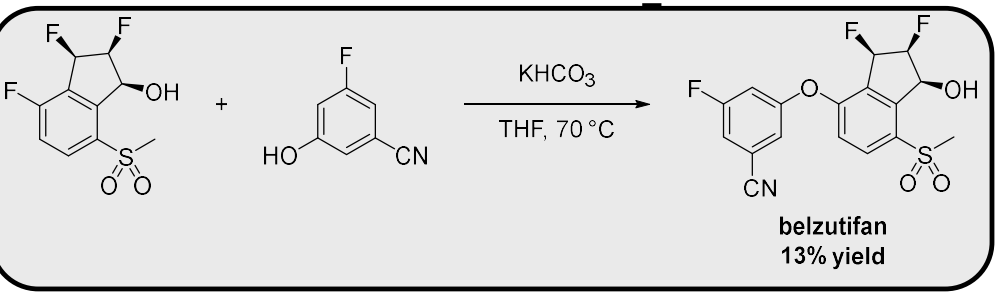
P450 and Fe/αKG-hydroxylase Evaluation



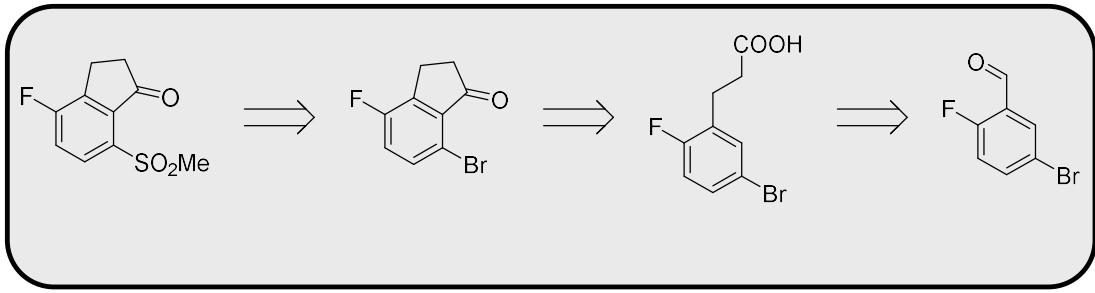
- This is hypothesized to be solubility driven (0.5 g/L)
- Operate below LOC is imperative, so organic solvents can't be added

Taking a Different Approach to Belzutifan via Late-Stage S_NAr

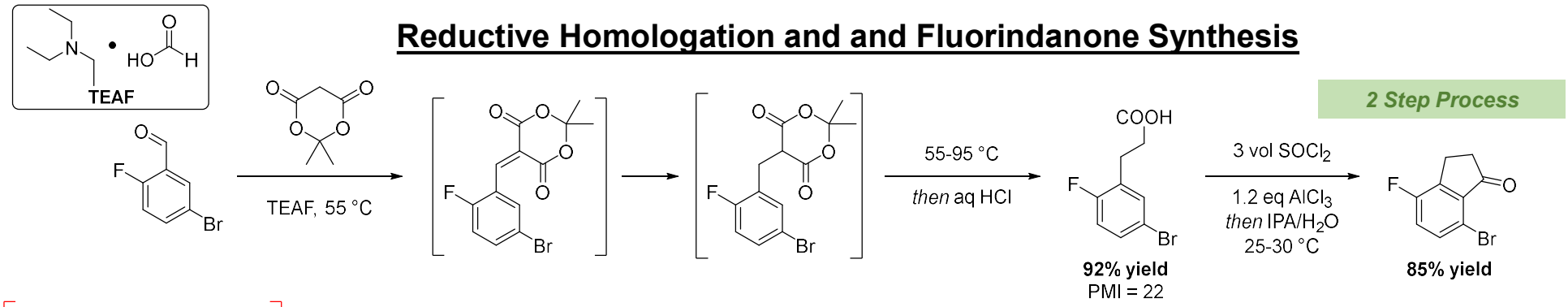
Proof-of-Concept S_NAr



Retrosynthetic Approach



Reductive Homologation and and Fluorindanone Synthesis

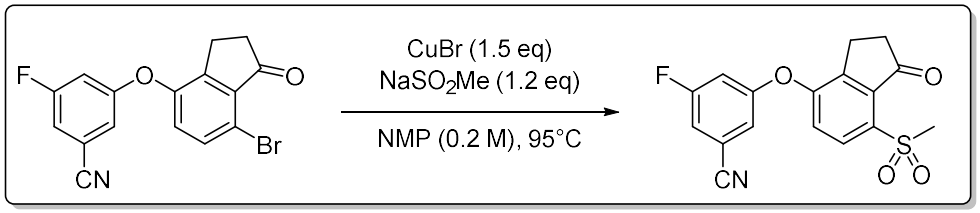


- Chlorinated Solvents were removed
- Stoichiometric $AlCl_3$ is hypothesized to prevent dimerization

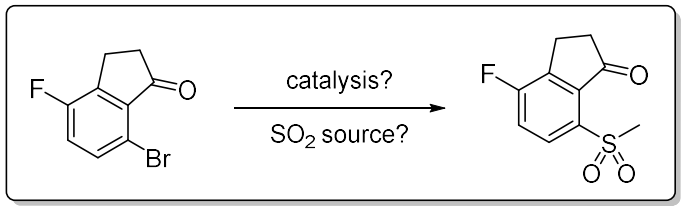
DiRocco *et al. Org. Process Res. Dev.* **2024**, 28, 2, 404–412;

Installation of the Methyl Sulfone

Commercial Route



Goal Reaction

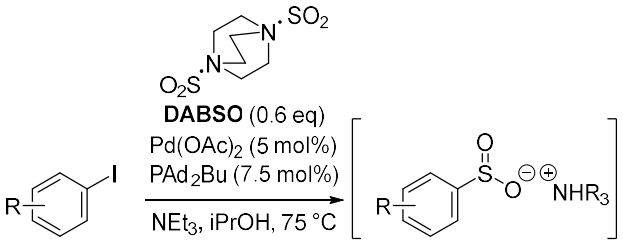


Disadvantages:

- Stoichiometric Cu salts are difficult to work up
- Sodium methanesulfinate is costly ($20 per g)

Key Precedent

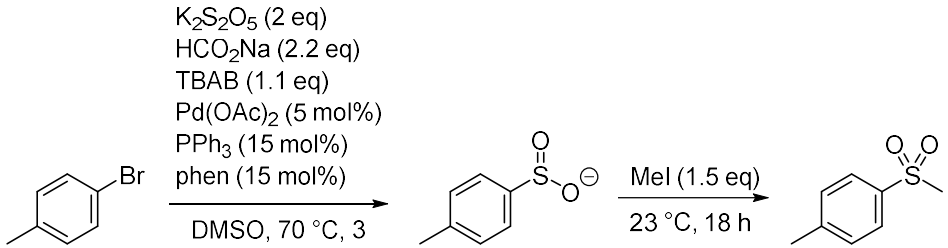
Pd-Catalyzed Sulfonylation with DABSO



18 Examples
64-96% yield

- Effective but limited by cost of DABSO ($71 per g)

Pfizer's Pd-Catalyzed Sulfonylation with Metabisulfite



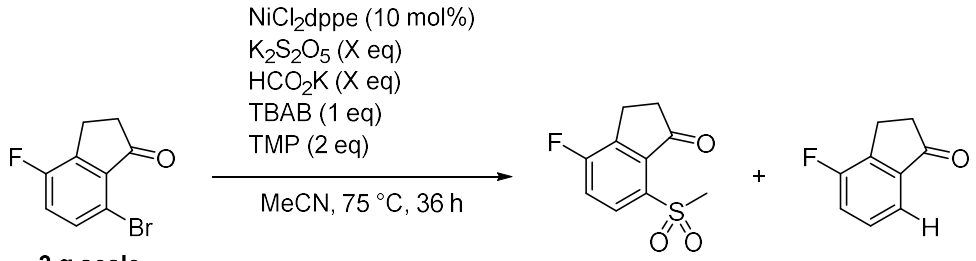
11 Examples
40-72% yield

- Effective but also limited by precious metals

DiRocco *et al. Org. Process Res. Dev.* **2024**, 28, 2, 404–412; Emmet *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 10204; Shavnya *et al. Org. Lett.* **2013**, *15*, 6226

A Nickel-Catalyzed Approach to Sulfonylation

Initial Reaction Discovery

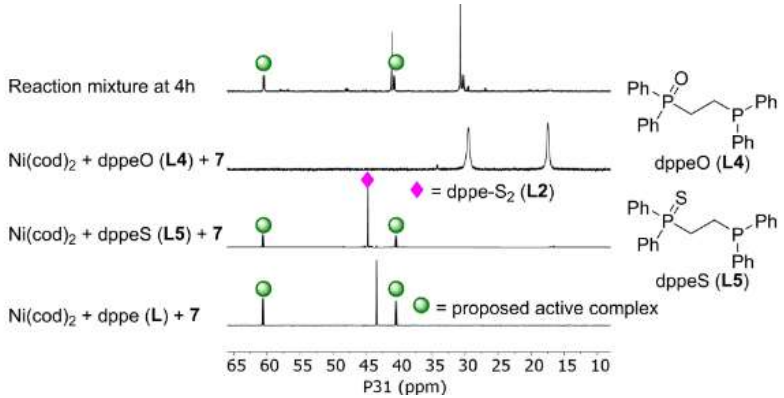


3 g scale

$K_2S_2O_5$ eq	HCO_2M eq, M	Product % Yield	Byproduct % Yield
3	1.5, Na	31.8	1.5
3	1.5, K	81.4	9.1
1	1.0+0.6, K	77.6	10
2	1.0+0.6, K	82.5	3.2
3	1.0+0.6, K	76.2	2.2

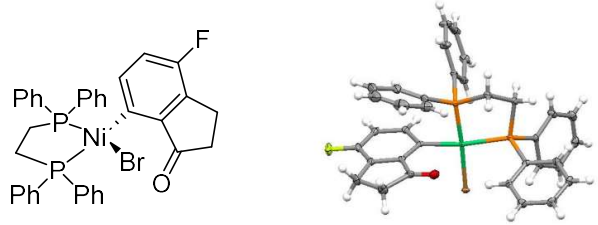
- Protodehalogenation hypothesized from divergence from a common intermediate upon reaction with formate
- Free SO_2 was shown to be in solution via an NaOH trap
- DABSO and free SO_2 were both shown to poison the reaction

Ligand ^{31}P NMR Investigation



- The phosphine oxide was not a viable ligand
- dppeS can disproportionate to dppe-S_2

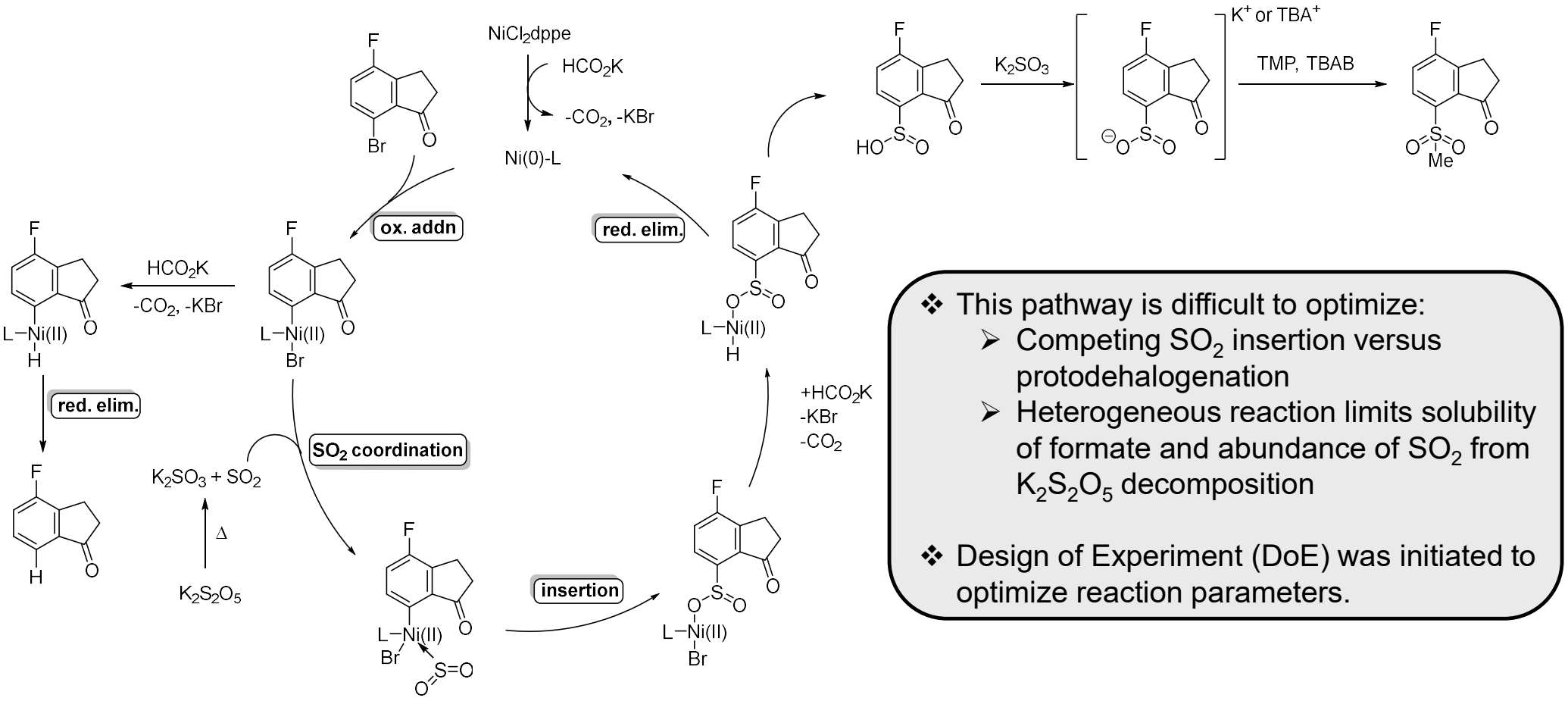
Single-Crystal X-Ray



- Shown to be fully reactive up to 95% yield
- Shown to undergo protodehalogenation in the presence of potassium formate
- Reactive with DABSO, supporting SO_2 insertion pathway

Hethcox *et al. Org. Process Res. Dev.* **2024**, 28, 2, 413-421;
Hethcox *et al. Angew. Chem. Int. Ed.* **2023**, 62, e202217623

Proposed Mechanism of $NiCl_2$(dppe) Sulfonylation

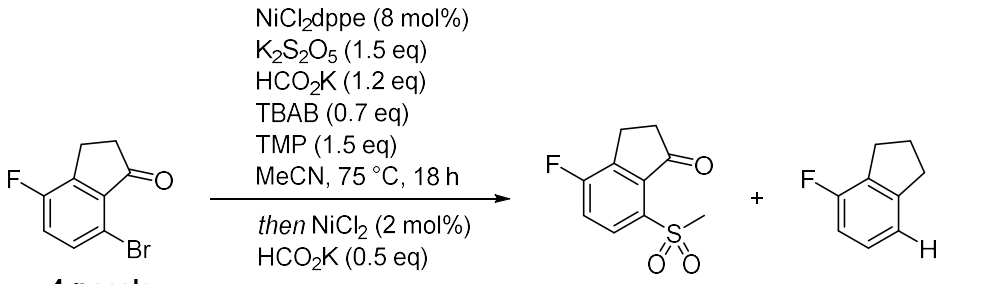


- This pathway is difficult to optimize:
  - Competing SO_2 insertion versus protodehalogenation
  - Heterogeneous reaction limits solubility of formate and abundance of SO_2 from $K_2S_2O_5$ decomposition
- Design of Experiment (DoE) was initiated to optimize reaction parameters.

Hethcox *et al. Org. Process Res. Dev.* **2024**, 28, 2, 413-421;
Hethcox *et al. Angew. Chem. Int. Ed.* **2023**, 62, e202217623

DoE study and Problems on Scale-Up

DoE Study and Scale-Up



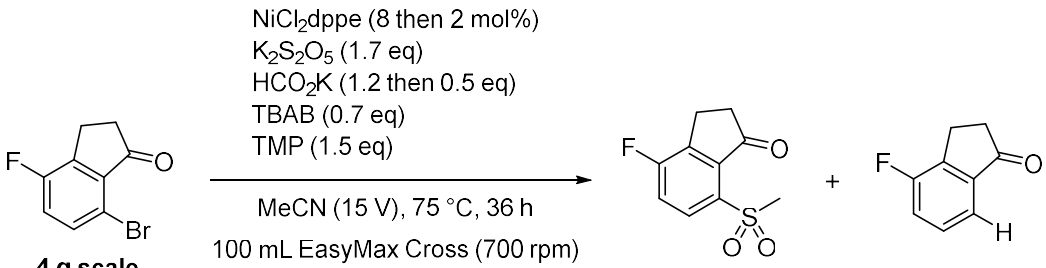
4 g scale
20-30% (Pre-Kicker)
1.0% Final RSM
15 g scale
1.9% Final RSM

60-70% (Pre-Kicker)
81% Final Yield
15 g scale
65% Final Yield

5.0% (Pre-Kicker)
5.6% Final Yield
15 g scale
23.4% Final Yield

- Accomplished with a four-pitched blade turbine (400 rpm) and EasyMax 100 mL flask
- They had never tested blade, rpm, flask, or particle size
- Switching to an RBF and crescent blade resulted in an increase of impurity by 50%
- Small particle size (250 µm to 12 µM) of $K_2S_2O_5$ significantly reduced byproduct formation

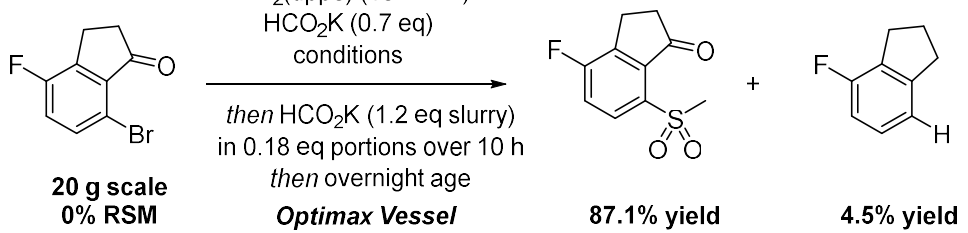
Investigating Particle Size of Reagents



4 g scale

$K_2S_2O_5$ (µm)	HCO_2K (µm)	Product % Yield	Byproduct % Yield
251	279	61.7	2.5
251	12	63.6	8.5
12	279	52.2	0.7
12	12	75.4	6.3

Slow Charge of HCO_2K MeCN Slurry



20 g scale
0% RSM

Optimax Vessel

87.1% yield

4.5% yield

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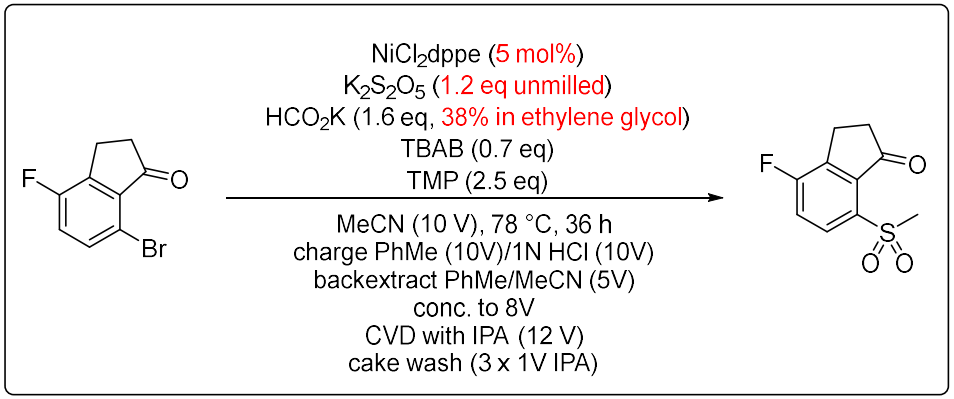
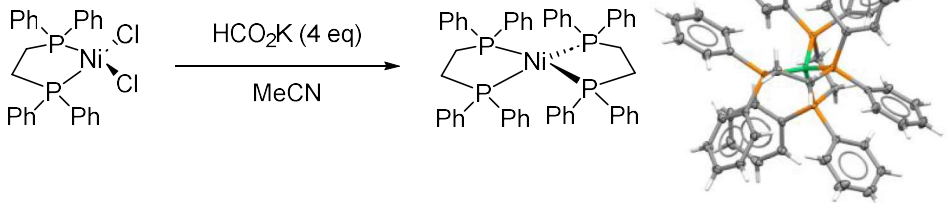
Final Optimized Sulfonylation Scale-Up

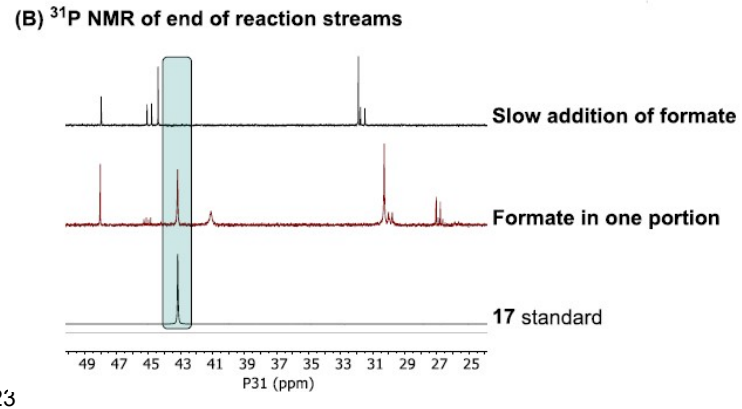
Final Optimized Condition Scale-Up



Scale	AY% Product (AY% Byproduct)	Isolated Yield (%)
6 g	83 (2.9)	73
24 g	80 (4.6)	72
3 kg	82 (2.2)	75.5

Characterization of Ni(0) Catalyst



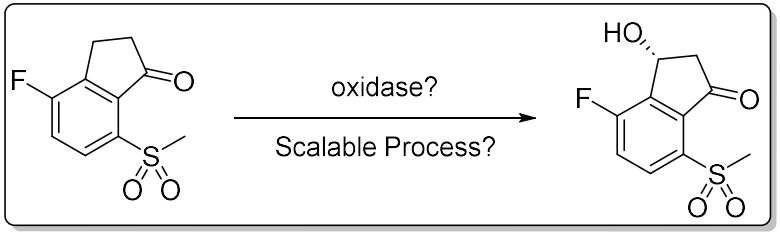


- ❖ Ni(0) catalyst gives 10x more protodehalogenation
- ❖ Slow charge of formate controls both stoichiometry and catalyst speciation

Hethcox *et al. Org. Process Res. Dev.* **2024**, 28, 2, 413-421; Hethcox *et al. Angew. Chem. Int. Ed.* **2023**, 62, e202217623

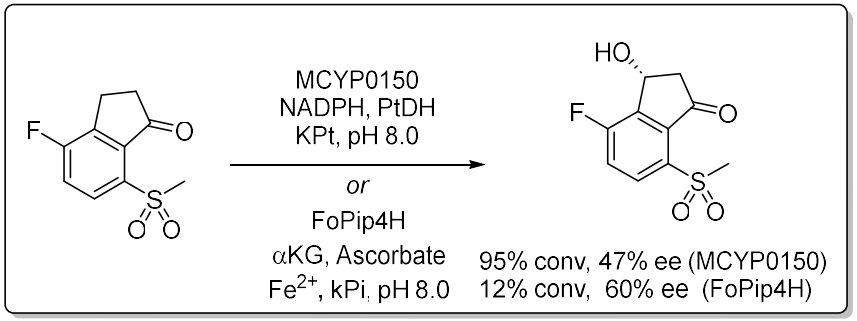
Biocatalytic Hydroxylation of the Indanone

Goal Reaction

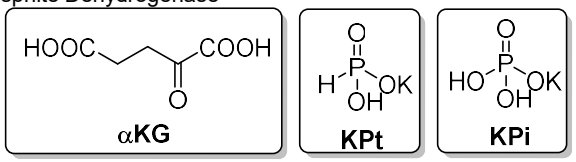


- Despite the low conversion of FoPip4H, it was chosen to be pursued for optimization!
  - NADPH is $1750 per g
  - αKG is ~$0.51 per g

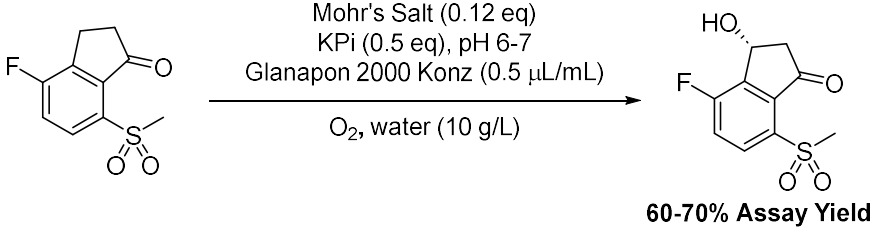
Initial Screen of Enzymes



*PtDH = Phosphite Dehydrogenase



Initial Hydroxylation Conditions

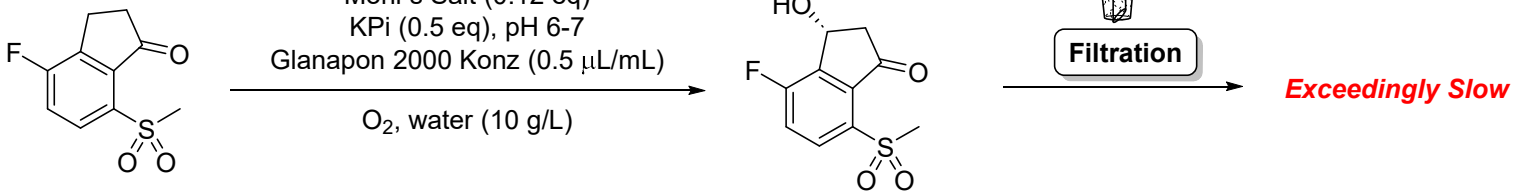


60-70% Assay Yield

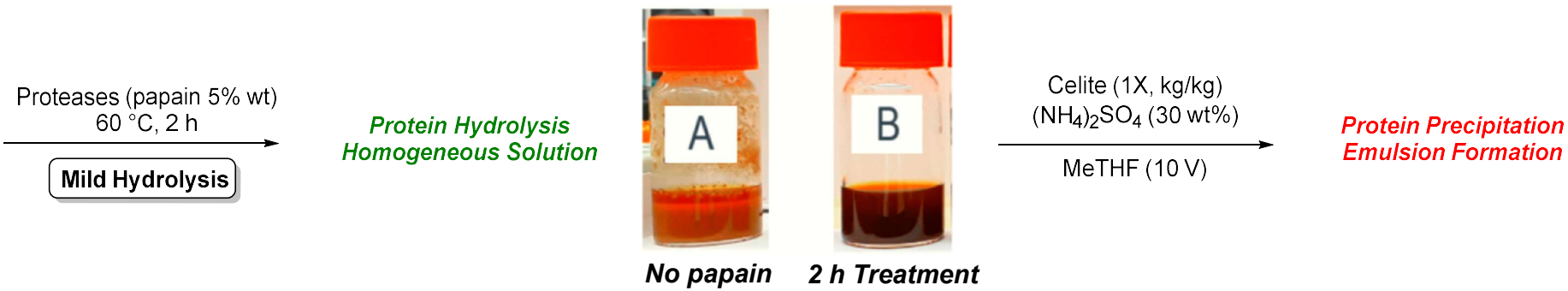
- Mohr's Salt is $(NH4)_2Fe(SO_4)_2$
- Glanapon 2000 Konz is an antifoaming agent that is made up of fatty acid copolymers
- This is not suitable for manufacturing process:
  - High enzyme loading
  - Dilute reaction conditions
- "***To meet program milestones***, …process development pivoted to the reaction workup and product isolation. ***A key challenge encountered was the removal of protein residue***…"

Hethcox *et al. Org. Process Res. Dev.* **2024**, 28, 2, 422-431; Cheung-Lee *et al. Angew. Chem.Int. Ed.* **2024**, *63*, e202316133

Attempts at Solving Isolation Problems



60-70% Assay Yield

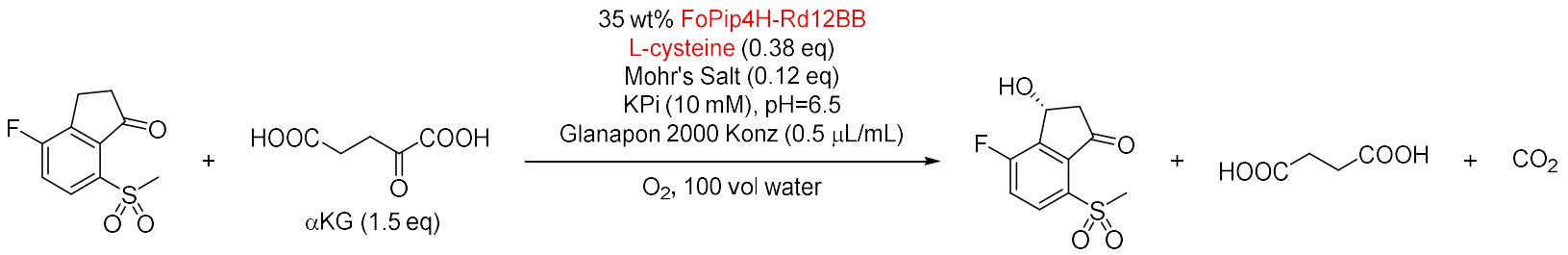


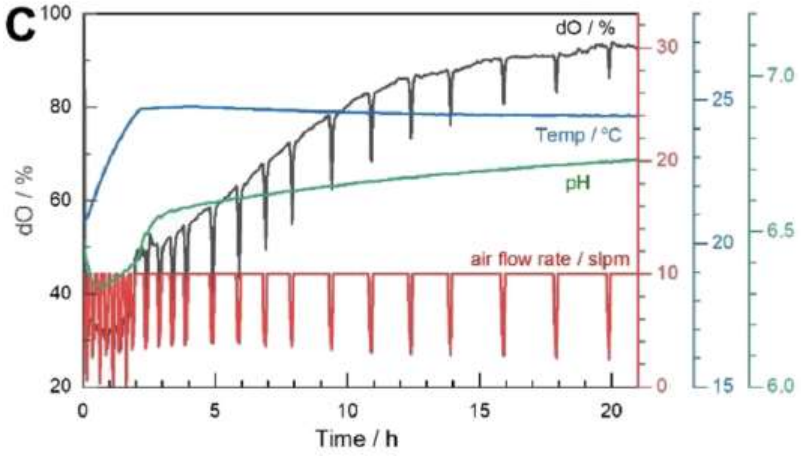
No papain ***2 h Treatment***

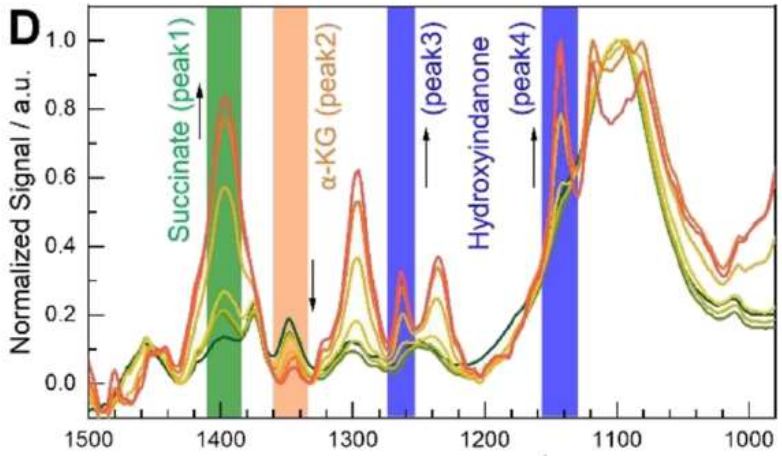
- Additional liquid-liquid extraction to precipitate the protein into the aqueous layer did not fix this problem
- Screening of various filter aids resulted in Celite 545 being identified as the best filter aid, working at 25 and 60 °C
  - The median particle size for standard Celite is 20.9 μm while Celite 545 is 46.5 μm
- ***Demonstrated at a 600 g scale using 35 wt % of enzyme and 100 V of water giving a 75% yield, 99% ee after cryst.***

Hethcox *et al. Org. Process Res. Dev.* **2024**, 28, 2, 422-431; Cheung-Lee *et al. Angew. Chem.Int. Ed.* **2024**, *63*, e202316133

Monitoring Biocatalytic Hydroxylation Under Thin Slurry Conditions







- Process analytical technologies (PAT) allow for full control and monitoring of reaction parameters
  - This can help mitigate risks associated with reaction conditions, such as blocked air sparging tubes

- *In situ* FTIR allowed tracking of various peaks
  - Succinate (1392 cm^{-1})
  - αKG (1347 cm^{-1})
  - Hydroxyindanone (1262 cm^{-1} and 1143 cm^{-1})

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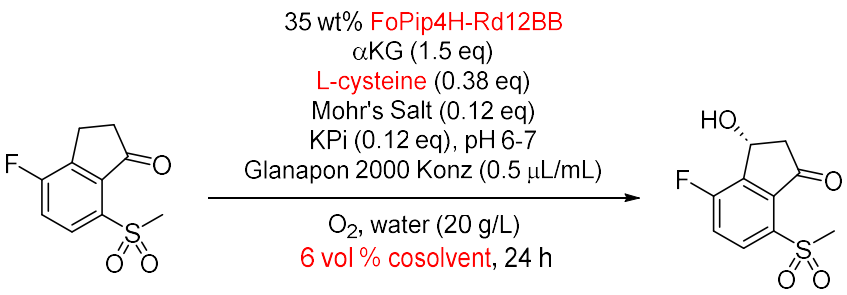
Improving Conversion Through Cosolvent Use

New Conditions

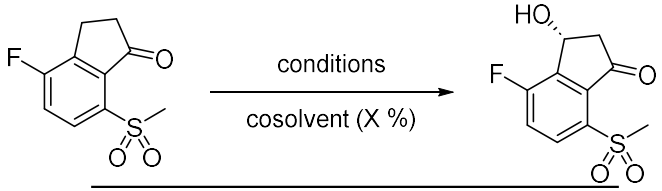


- Enzyme evolution had been taking place concurrently
- L-cysteine was found to improve the oxidation reaction rate
- Additives were screened to no avail in search for higher concentration conditions
- ***Cosolvent was hypothesized to improve reaction conversion by increasing solubility of indanone***

6 vol% of cosolvent	Conversion (%)
None	57.0
DMAc	65.4
IPA	74.0
2-BuOH	90.3
1-hexanol	86.2
1-octanol	94.9
1-nonanol	92.3

- 1-octanol was chosen due to the aerobic environment
  - BP = 195 °C, FP = 81 °C
- 1-octanol has (0.3 mg/mL, 0.03 vol%) solubility in water
  - This results in formation of a second liquid layer

Impact of 1-Octanol on Conversion



Volume (%)	Conversion (%)
0	79.8
0.5	81.0
2	91.9
6	93.4

- 1-octanol has (0.3 mg/mL, 0.03 vol%) solubility in water
  - 1-octanol is thought to have a beneficial impact ***as an additive not a solvent effect on the enzyme***!

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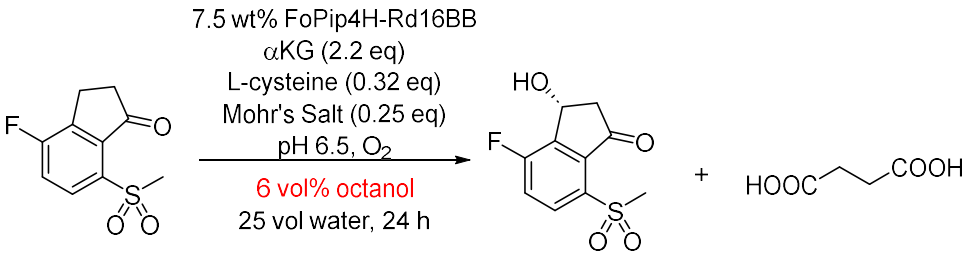
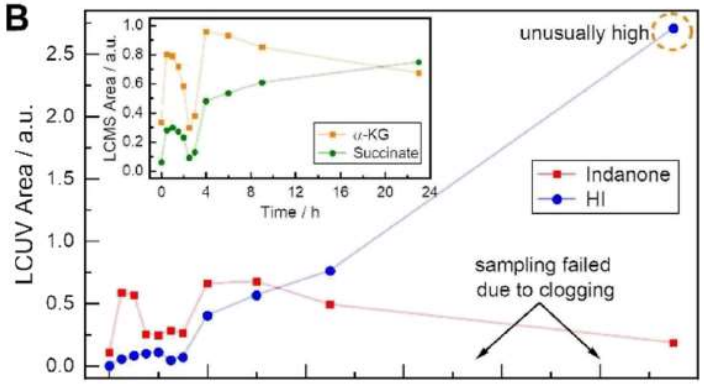
Analytical Techniques for Dense Slurry Applications



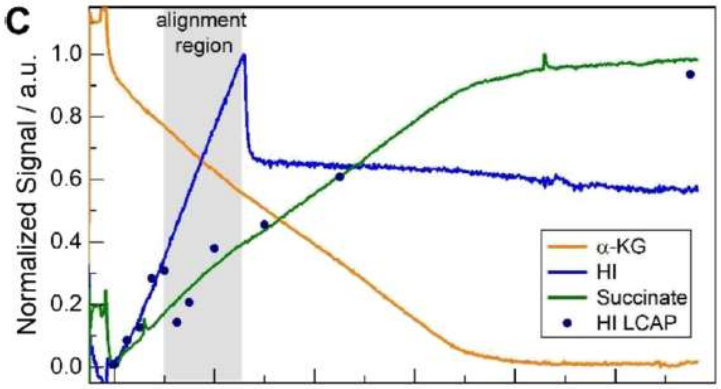
- Indanone and hydroxyindanone are not fully dissolved, leading to a slurry-to-slurry reaction

Monitoring via LCAP

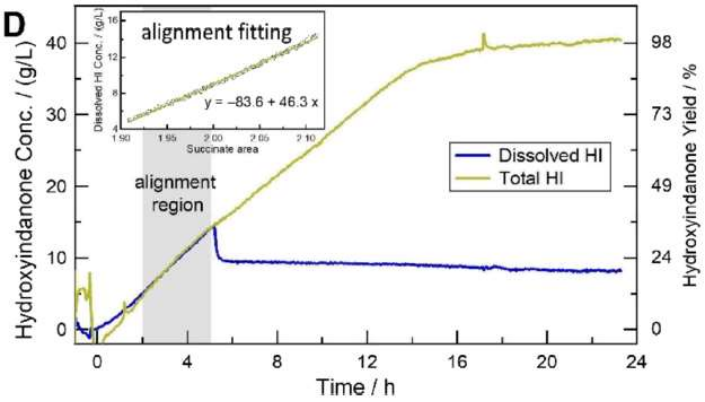


- Autosampling was unreliable in monitoring and characterization

Monitoring via FTIR



- Precipitation of hydroxyindanone (HI) causes unreliability, but HI seems to be highly correlated with succinate



- This was further validated by independent experiments

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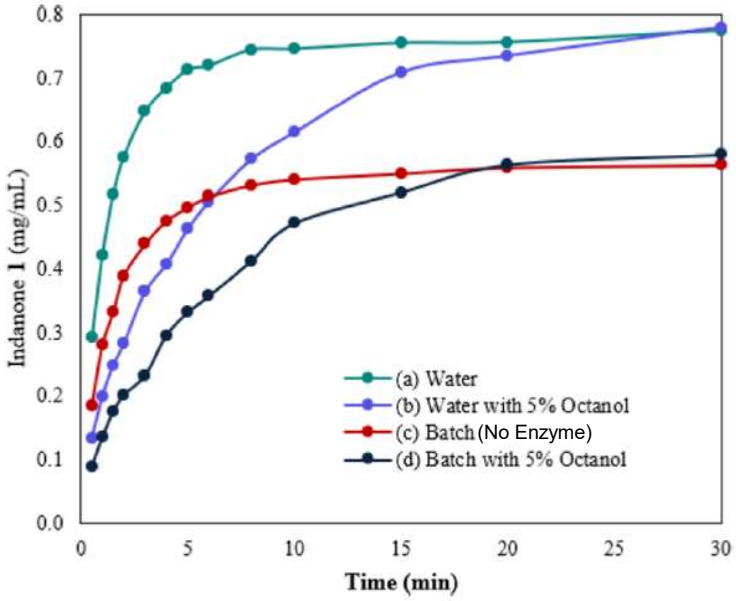
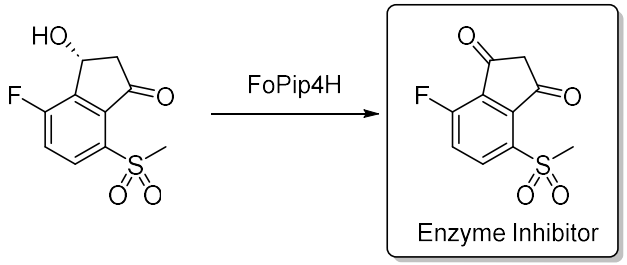
Investigating the Role of Octanol

Indanone Dissolution Rate with Octanol

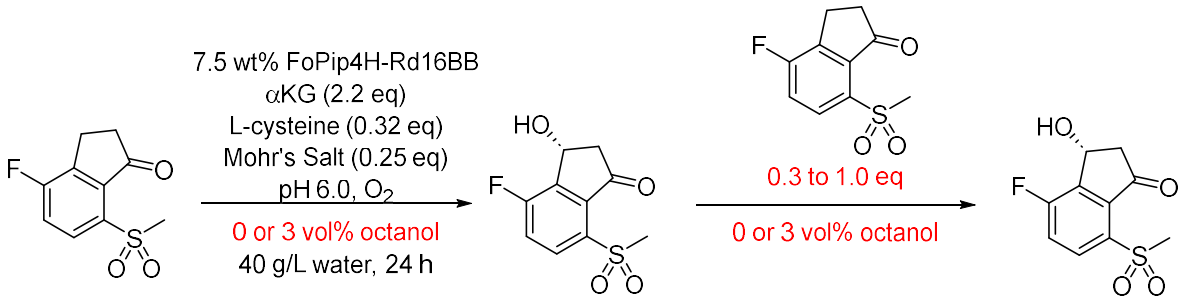


- The reaction generates a slurry mixture, with hydroxyindanone precipitating out
  - 1-octanol results in a well-behaved slurry
- ***1-octanol actually decreases rate of dissolution!***
- In addition, it was shown that 1-octanol offers reduced reaction volumes and enzyme loadings

Known Overoxidation Impurity



Testing Octanol Effect on Enzyme Inhibition



Init. Octanol (%)	Init. Indanone (eq)	Add octanol (%)	Add Indanone (eq)	Conversion (%)
0	0	3	1	80.5
0	0.4	3	0.6	20.8
3	0	0	1	79.5
3	0.4	0	0.6	63.7

1-octanol prevents enzyme inhibition caused by overoxidation!

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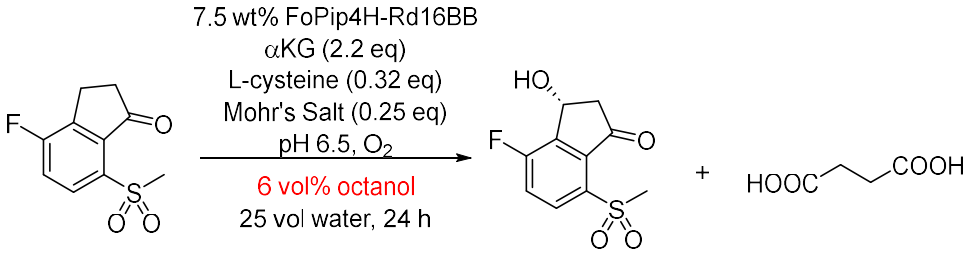
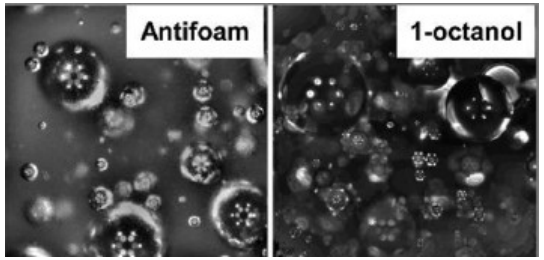
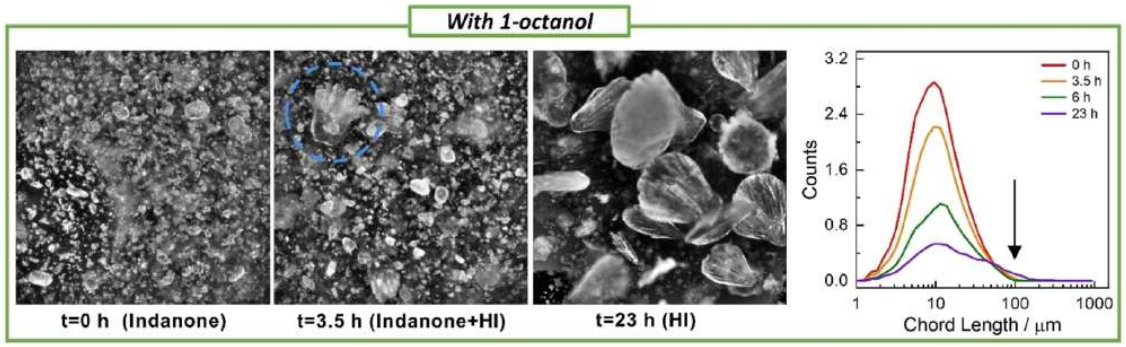
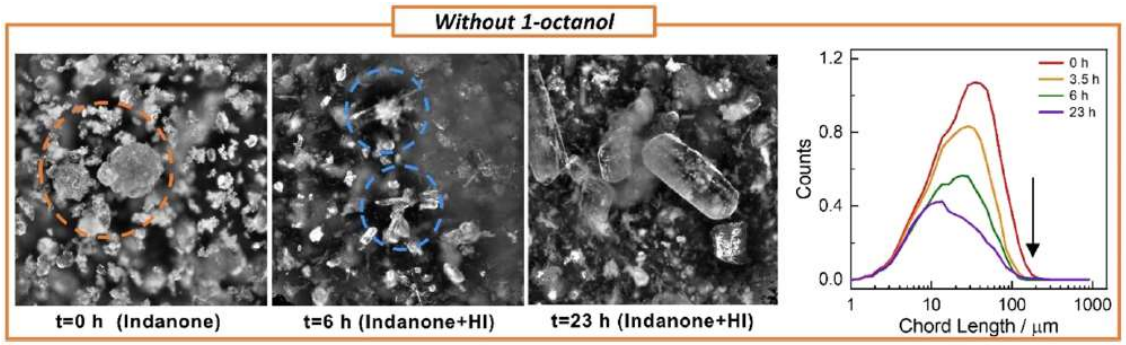
Investigating the Role of Octanol with PAT









- *In situ* imaging tools show formation of droplets much like antifoam.
- When octanol is present, indanone is evenly distributed
- Supersaturation and precipitation occurs at 3.5 hours in
- Crystal morphology adopts a seashell shape

- Without octanol present, indanone aggregates at the beginning
- Supersaturation and precipitation occurs at 5 hours in
- Crystal morphology adopts a needle and rod shape

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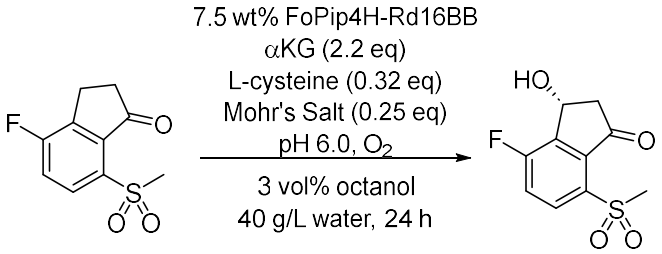
Evaluating the Impact of Indanone Particle Size

Indanone Particle Size Effects on Conversion

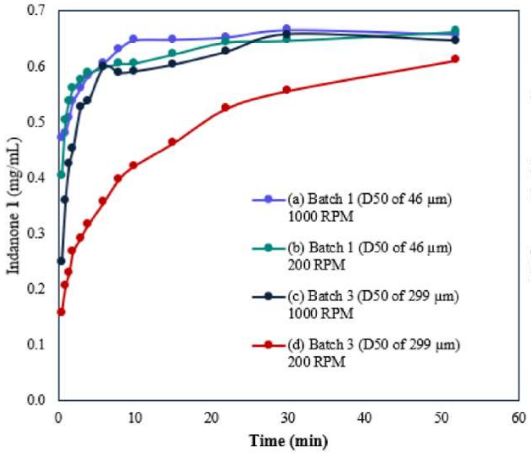


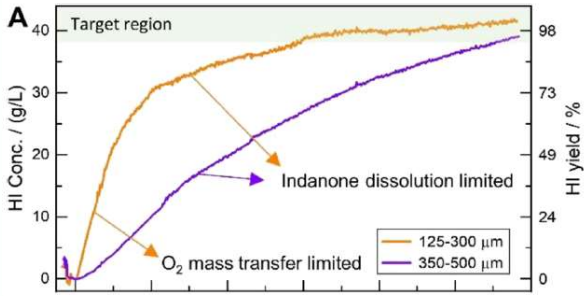
This is a 4-phase system!

Treatment	D50 (µm)	Time (h)	Conversion (%)
None	46	24	94
None	299	24	57/58
Sieved	99	24	95
Wet Milled	11	24	94

- Particle size reduces conversion and conversion plateaus
- Wet milling had little impact in comparison to dry milling

Particle Size and Agitation Impact on Dissolution





- Larger particle sizes in combination with slow rates of agitation result in reduced rates of dissolution.
  - Slow dissolution rates can lead to overoxidation

Mixing modeling studies were performed that illustrated the suspension and dispersion of large indanone particles should improve upon scale-up

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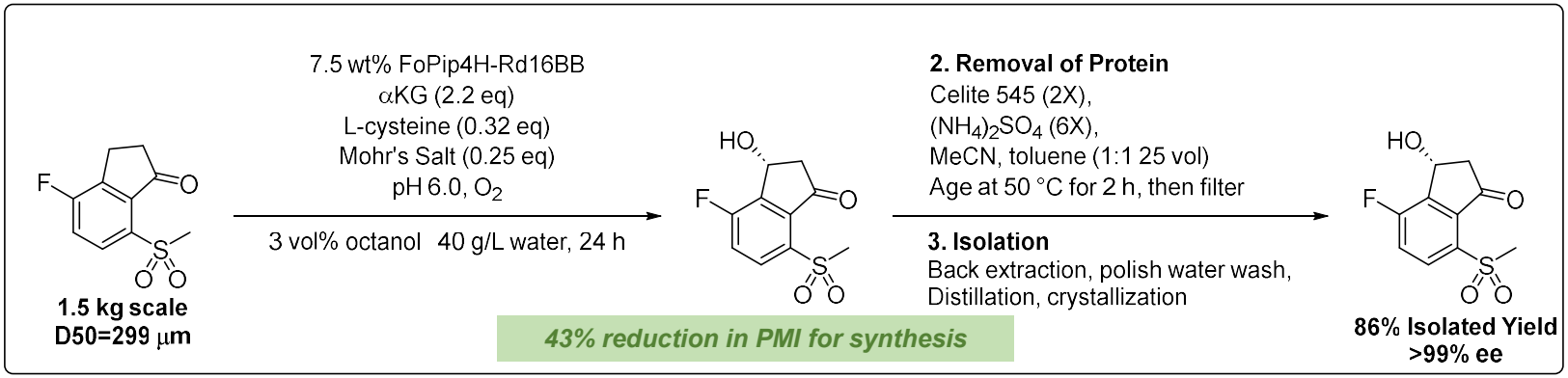
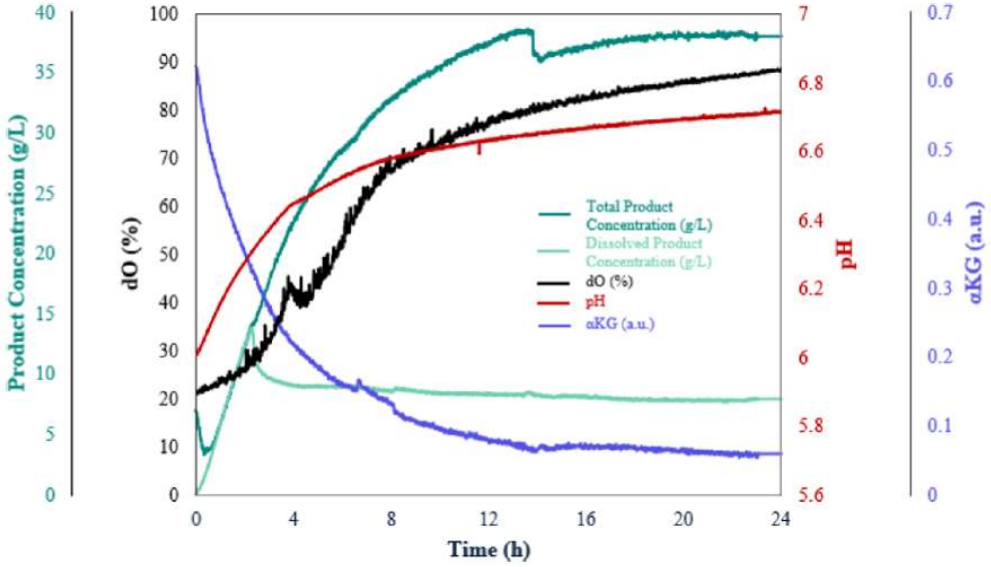
Final Optimized Hydroxylation Scale-Up

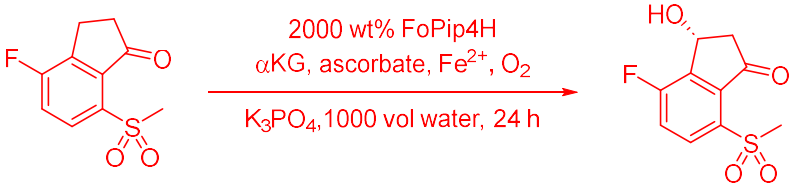


Reaction Profiles at 1.5 kG scale



- pH increases over the course of the reaction
- Dissolved oxygen is consistent with the increase of hydroxyindanone and decrease in αkG

Original Development



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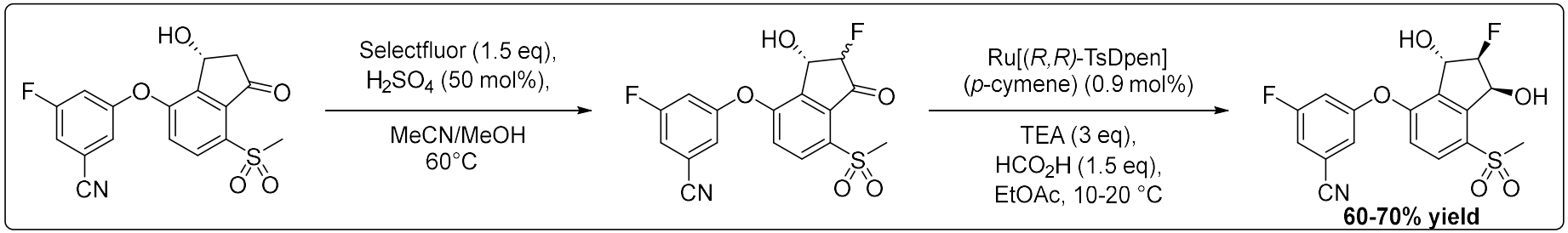
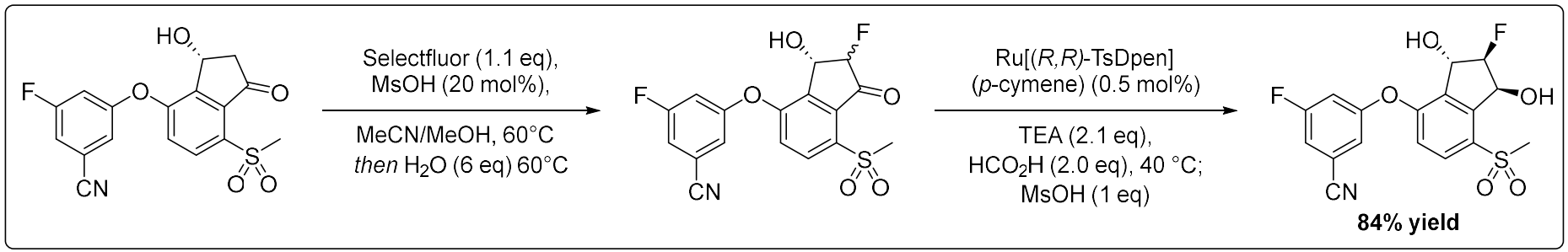
Diastereoselective Fluorination and DKR Developments

Clinical Supply Route



- Desire to streamline to minimize unit operations and minimize other problems
  - The fluorination showed an exotherm of 482 J/g at less than 170 °C even in batch addition
  - Fluorination often failed to meet the end point and concentration to dryness would like to be avoided

Commercial Route



- This new process allowed both a single-pot through process with direct recrystallization
- "Despite the efficiency, ***concerns surrounding price volatility, sourcing, and sustainability*** of the precious metal catalyst motivated the team to replace the ruthenium catalyst with a ketoreductase (KRED), $NADP^+$, and IPA reduction system"

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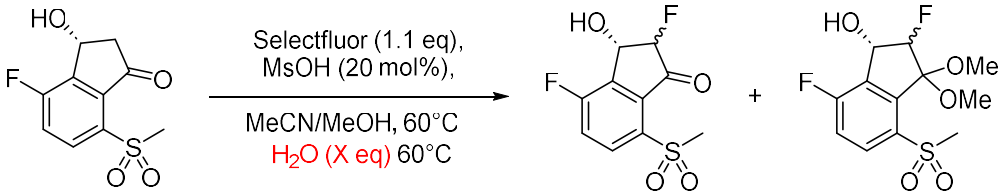
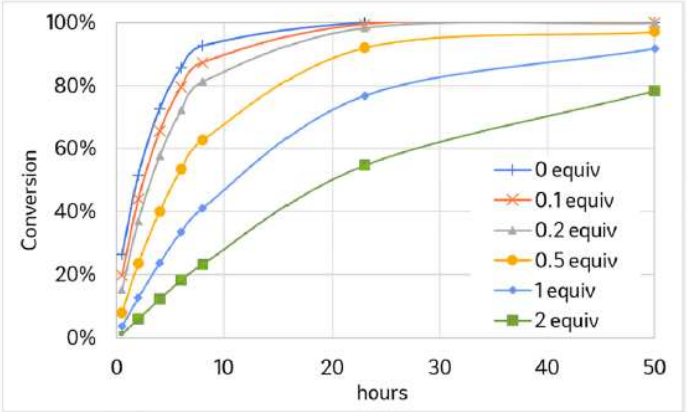
Investigation of the Fluorination

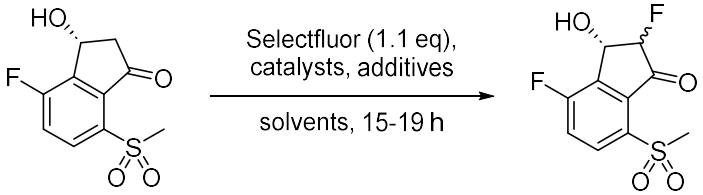
Effect of Water



- Water was known to slow reaction rate
- Quenching with 5 eq of water consumes residual ketals



Further Attempts at Development of Fluorination



- No additives prevented stalling of the reaction with water
- Bulkier bases consistently led to lower conversion, leaving MeCN/MeOH the ideal conditions for the reaction

T	Catalyst/Additive	Solvent	LCAP [Conv.] (%)
80	None	Water	53 [67]
80	SDS* (0.2 M)	Water	54 [67]
80	MsOH (0.2 eq)	MeCN/IPA (1:1)	61 [96]
60	MsOH (0.2 eq)	MeCN/IPA (1:1)	69 [87]
60	MsOH (0.2 eq)	MeCN/MeOH (1:1)	97 [99]

*SDS = sodium dodecyl sulfate

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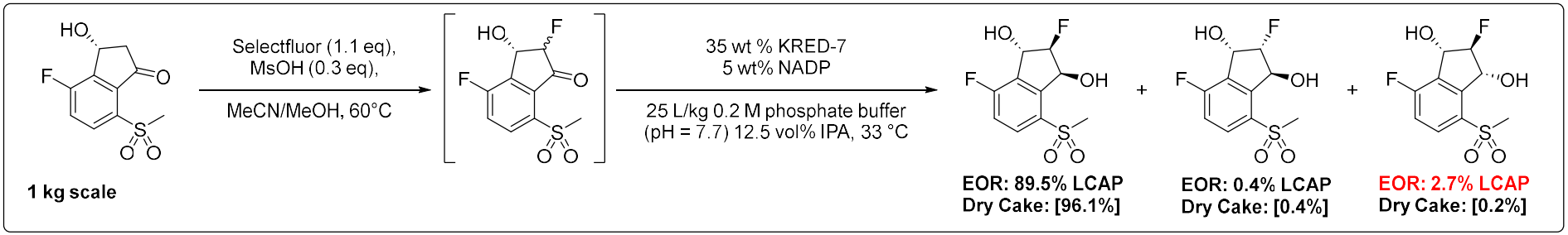
Merging the Fluorination with a KRED

Initial Problems

1. ***KRED hit identified was not natively tolerant to MeCN/MeOH***
   - ✓ Solved via enzyme evolution, with studies regarding it "to be described" in a separate paper
2. ***Residual Selectfluor needed to be quenched prior to introducing KRED/NADP⁺ mixture to avoid DKR interference***
   - ✓ Selectfluor quenched via 1,3 dimethoxybenzene
3. ***Acidic fluorination needs to be neutralized and buffered to stabilize the enzyme and epimerize the α-fluoroketone while also protecting the fluoroketone from decomposition***
   - ✓ Adjust pH from 2 to 6-7, introduce KRED/NADP⁺ mixture, adjust pH to 7.7

First Kilogram Scale Process



- ❖ Selectfluor reaction quenched with DMB, but still required a solvent switch to less than 2% MeCN/MeOH
- ❖ The LCAP at EOR was still to high for the syn-diol diastereomer

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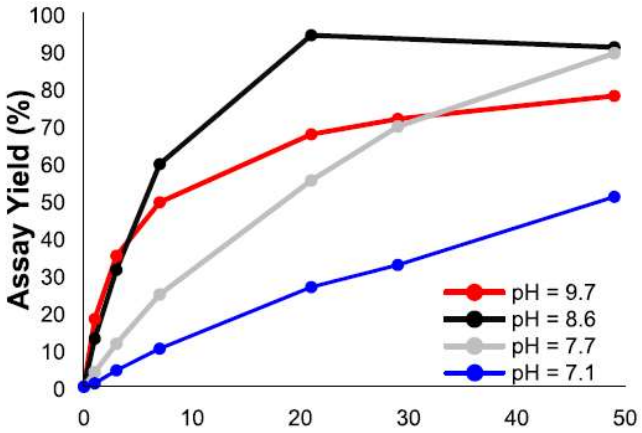
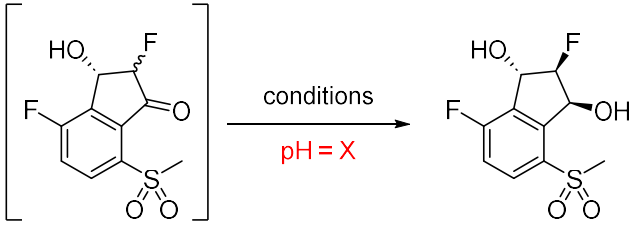
pH Analysis for Second Process Iteration

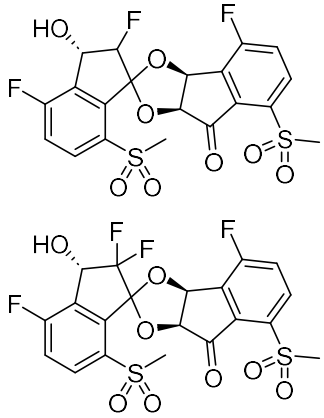
Impact of pH on Reaction Rate and Impurities





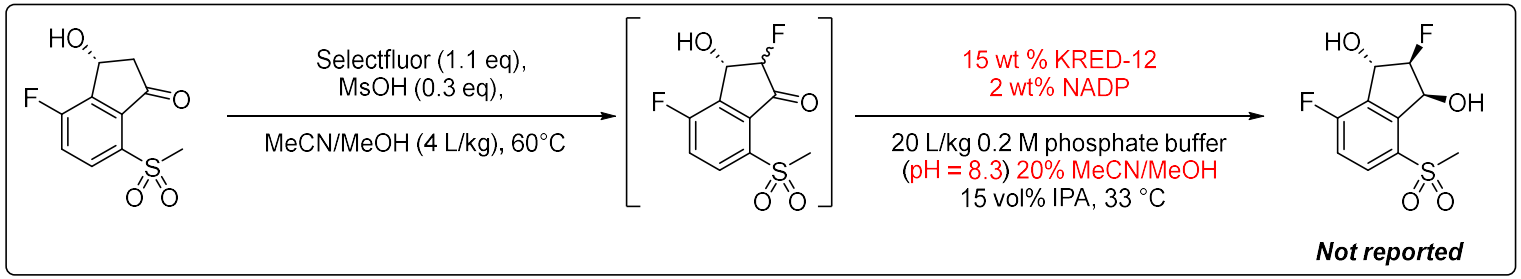
Initial pH	Starting Material LCAP (%)	Combined Dimer LCAP (%)
7.1	39.4	0.96
7.7	0.5	0.98
8.6	0.5	1.47
9.1	1.1	7.9

Known Dimer Impurities



- Maintaining a pH between 7.7-8.6 was found to be ideal trade-off in potential impurities

Second Process Iteration



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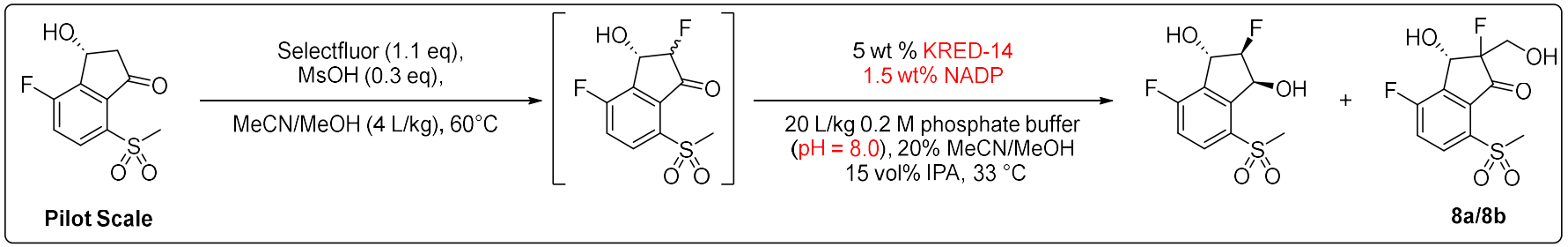
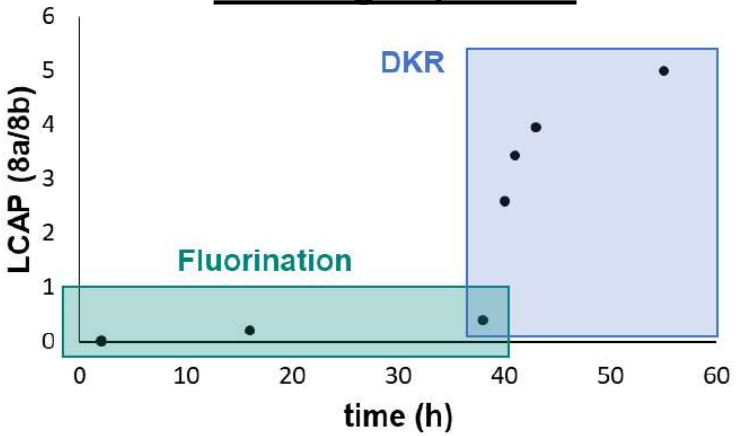
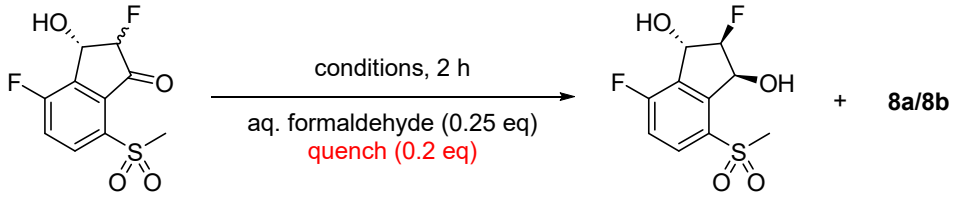
Pilot Scale Results and Analysis



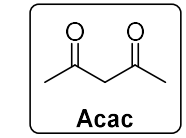
Tracking Impurities

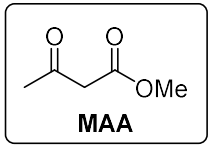


Quenching Study



Quench	LCAP Product (%)	LCAP 8a/8b (%)
DMB	<1	3.6
TMB	<1	2.0
Acac	<1	0.7
MAA	<1	0.8

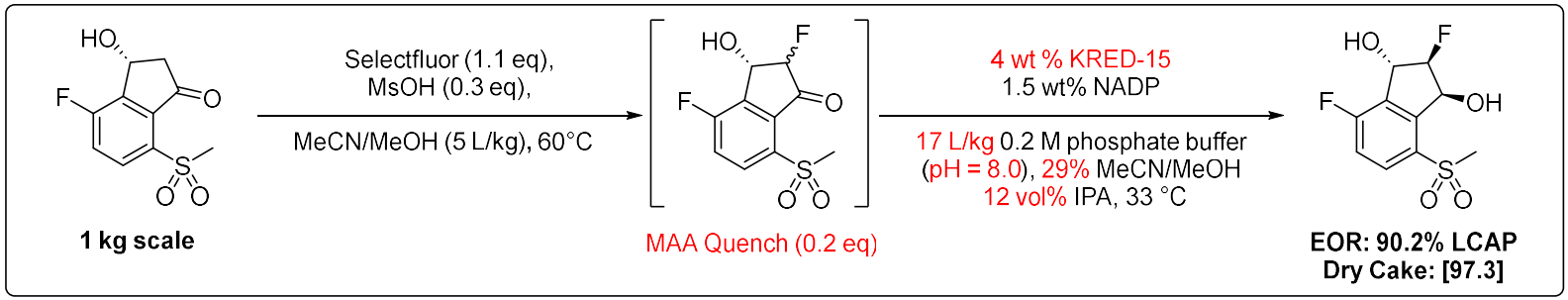




- Multiple kicker charges of Selectfluor necessary at scale, and believed to oxidize MeOH to formaldehyde
  - This caused issue during recrystallization as well

McCann *et al. Org. Process Res. Dev.* **2024**, 28, 2, 441-450; Wang *et al. Org. Process Res. Dev.* **2022**, *26*, 543-550

Final Process for Diastereoselective Fluorination and DKR



- No solvent switch

All impurities

- <1% EOR LCAP
- <0.2% DC LCAP

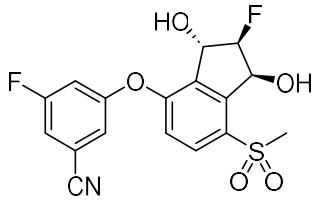
Final Workup and Isolation

Dry Cake

1. Na_2CO_3-treated Celite (1.1:1 w/w enzyme)
2. $(NH_4)_2SO_4$ (35-40 wt% final concentration)
3. Age 45-55 °C 2 h
4. Add EtOAc at 50 °C then cool to 20°C
5. Filter Slurry

Worked-Up Solution
15 L/kg in EtOAc

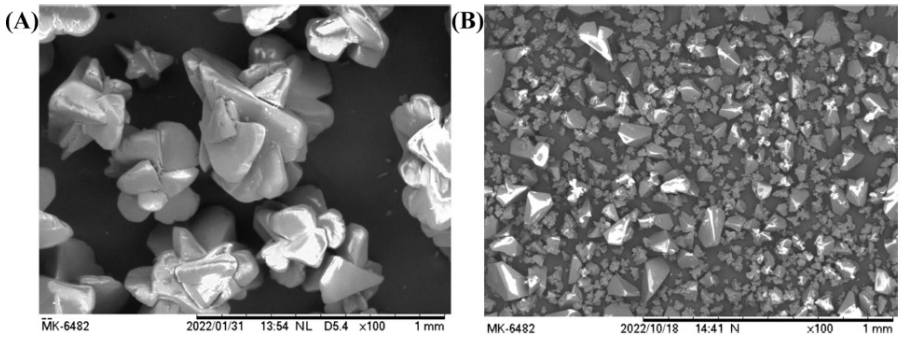
1. Heat to 60 °C, then distill to 10 L/kg
2. Cool to 30 °C, then add seed
3. Dose 8.6 L/kg toluene over 4 h
4. Distill to 6 L/kg, then cool to 20 °C
5. Filter, wash 2 L/kg 1:4 EtOAc/Toluene, wash 2 L/kg Toluene



85% Isolated Yield
>200:1 dr

- Liquid-liquid extraction was not viable due to solubility of the product
- Adding EtOAc after precipitation prevented gumming and clogging of filtrations

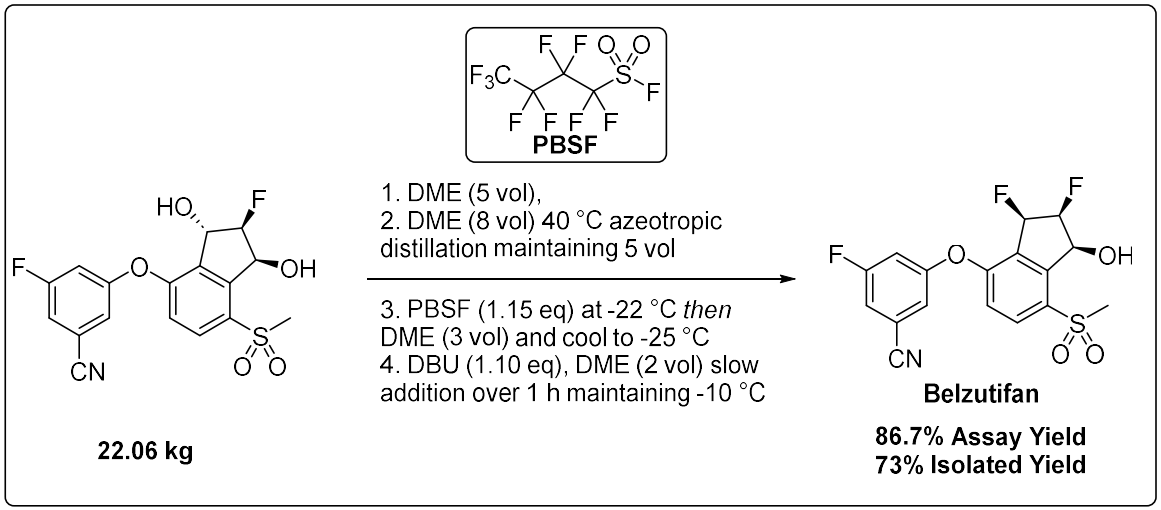
60 °C Seeding ***30 °C Seeding***



McCann *et al. Org. Process Res. Dev.* **2024**, 28, 2, 441-450

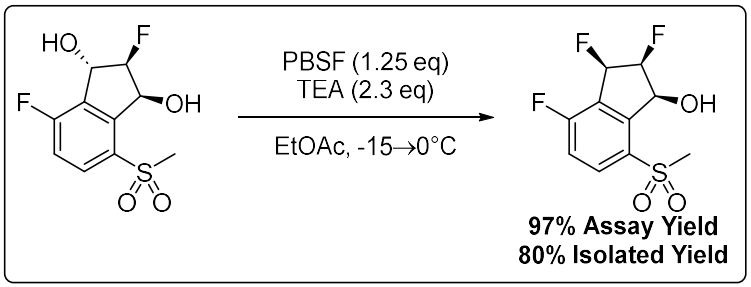
A Quick Note About Deoxyfluorination

Commercial Manufacturing Route



- Residual water resulted in poor conversion, and a PBSF layer would form

New Process with Updated Intermediate



- Solubility no longer a problem allowing wider solvent screen
  - DME is subject to restrictions with reproductive toxicity
- Strong base no longer necessary to reduce other impurities
- Consistent cryogenic temperatures no longer necessary
- PBSA can be isolated as a salt and recycled

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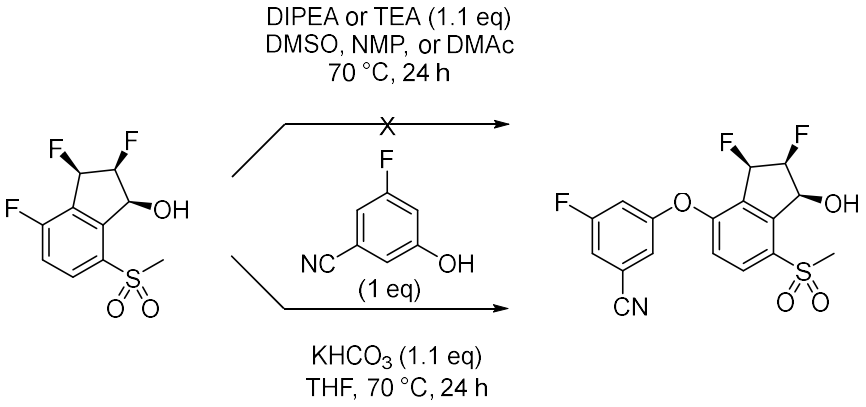
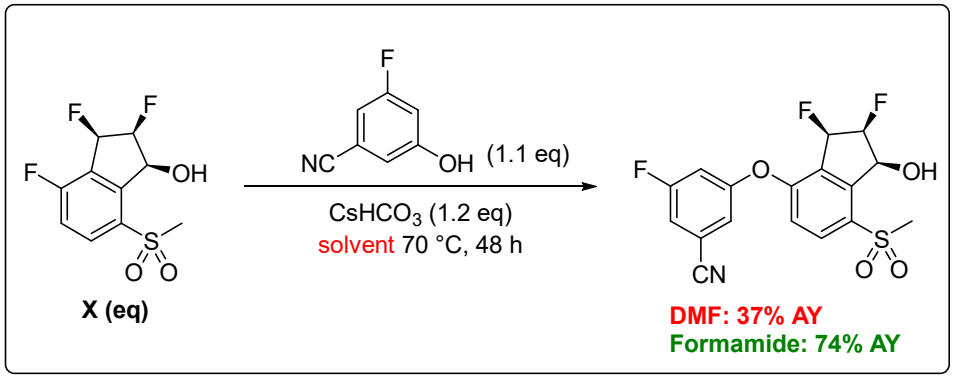
Development of a Nucleophilic Aromatic Substitution

Original Hit on Reactivity

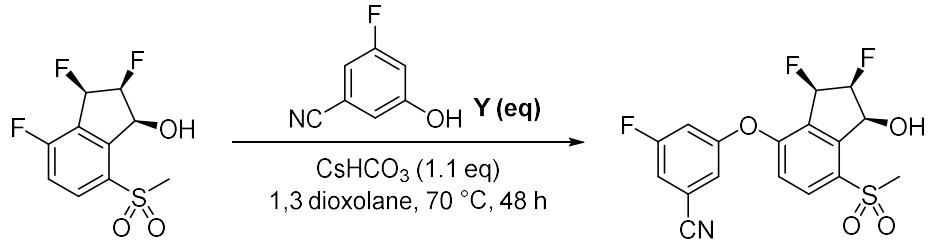


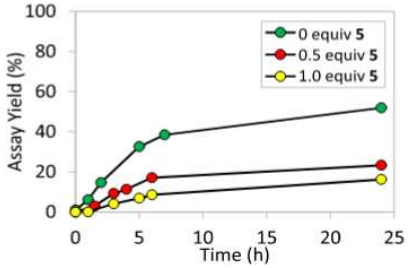
13% Assay Yield

- After an HTE campaign, $CsHCO_3$ and 1,3 dioxolane were identified as the best conditions



Investigation into Reaction Stalling





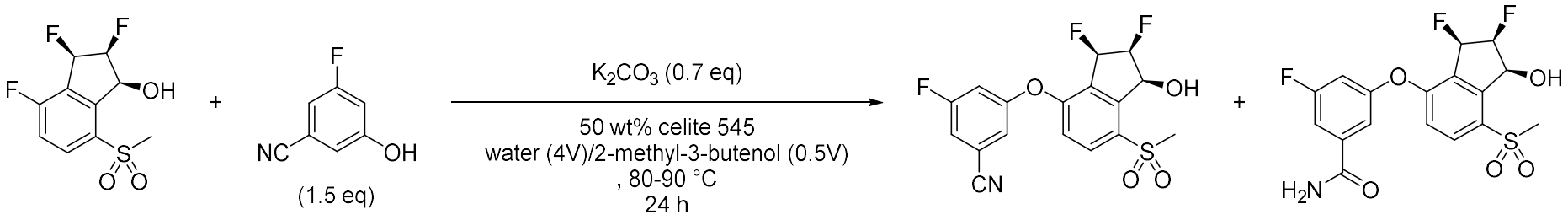
- Competitive inhibition of the product was causing the reaction to stall
- This was also observed via ^{19}F NMR

Concerns about the long-term utility of formamide due to toxicity, impurity profile, and drying operation issues pushed towards development of a reactive crystallization

Le *et al. Org. Process Res. Dev.* **2024**, 28, 2, 451-459; Le *et al. Org. Lett.* **2024**, *26*, 804-808

Development of a Nucleophilic Aromatic Substitution

Initial Base and Additive Evaluation



Additive/Change	Time (h)	Belzutifan AY (%)	Benzamide AY (%)
None	40	80	2.33
25 mol% Ca propionate	40	84	2.58
25 mol% Ca pyruvate	22	69	0.84
25 mol% K pyruvate	22	72	0.81
25 mol% Na pyruvate	22	70	0.82
20 mol% NaCl	22	69	2.25
100 mol% H_2O_2	66	51	15.07
100 mol% H_2O_2, 25 mol% Na pyruvate	66	64	8.99

- Celite was necessary as visible corrosion was seen otherwise
- 2-methyl-3-buten-2-ol with K_2CO_3 provided the best yields and a well-behaved slurry at the EOR
- Salting effects were ruled out indicating pyruvate was uniquely preventing hydrolysis
- The reaction is also oxygen sensitive

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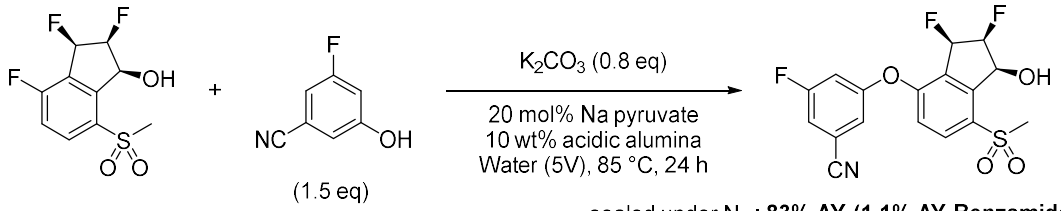
Understanding the Headspace Effects

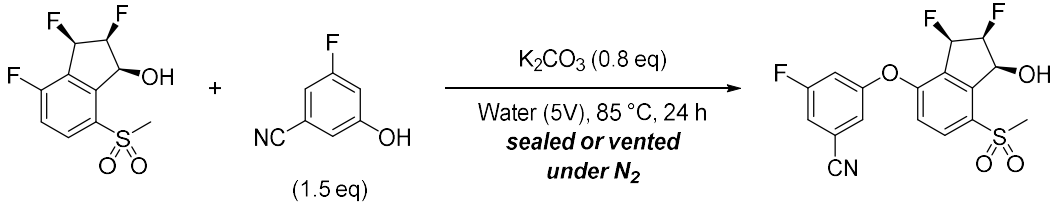
Further Development



sealed under N_2 : **83% AY (1.1% AY Benzamide)**

vented with N_2, no Na pyruvate or alumina: **83% AY (1.2% AY Benzamide)**

Nitrogen Vent and Reaction Headspace Effects



Vent Conditions	Conversion (%)	Belzutifan AY (%)	Benzamide AY (%)
16 gauge needle	98.1	88	1.7
22 gauge needle	95.6	88	1.4
100 mg phenol, sealed	82	76	2.1
250 mg phenol, sealed	77	73	1.4
500 mg phenol, sealed	70	66	0.7

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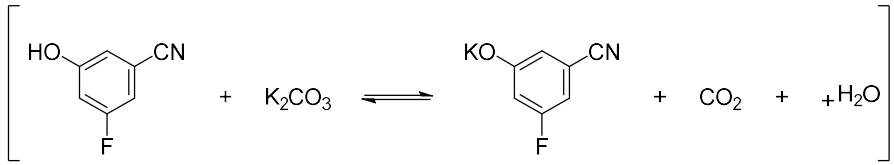
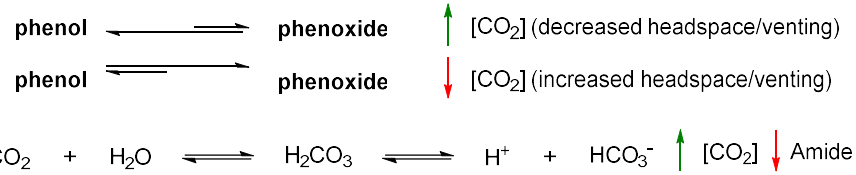
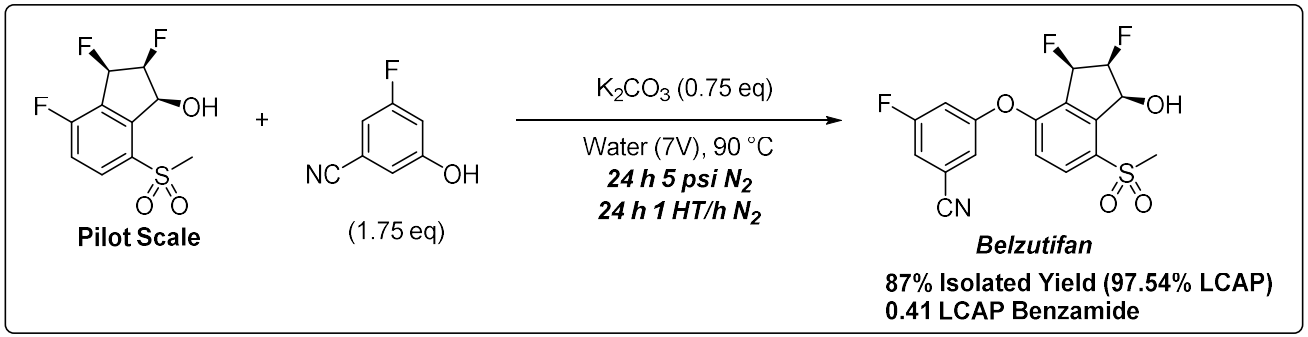
Acid-Base Equilibrium Hypothesis





- Additives such as alumina and Celite were abandoned due to heterogeneity and isolation problems
- Both increasing vent and fill volume resulted in decreased conversion of product indicating headspace place an important role in reactivity

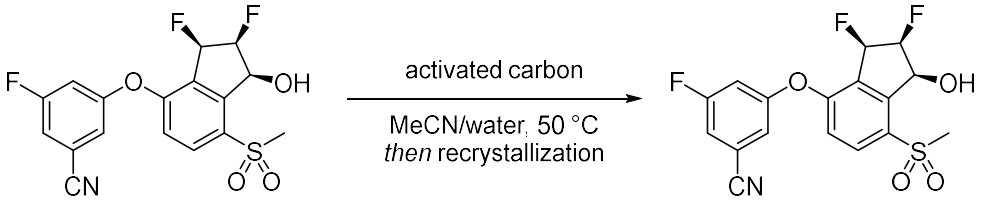
Final Process for Belzutifan formation via S_NAr in Water



Solubility Screen for Slurry Formation

Solvent	Trifluoride (mg/mL)	Phenol (mg/mL)	Belzutifan
MeCN	98.2	5.7	24.2
H_2O	17.6	8.7	0.0
Acetone	80.3	101.6	26.7
IPA	12.6	25.2	0.2
90:10 IPA/H_2O	63.1	80.8	0.5
50:50 IPA/H_2O	>100	>100	0.6

Carbon Treatment/Recrystallization



Crude Belzutifan

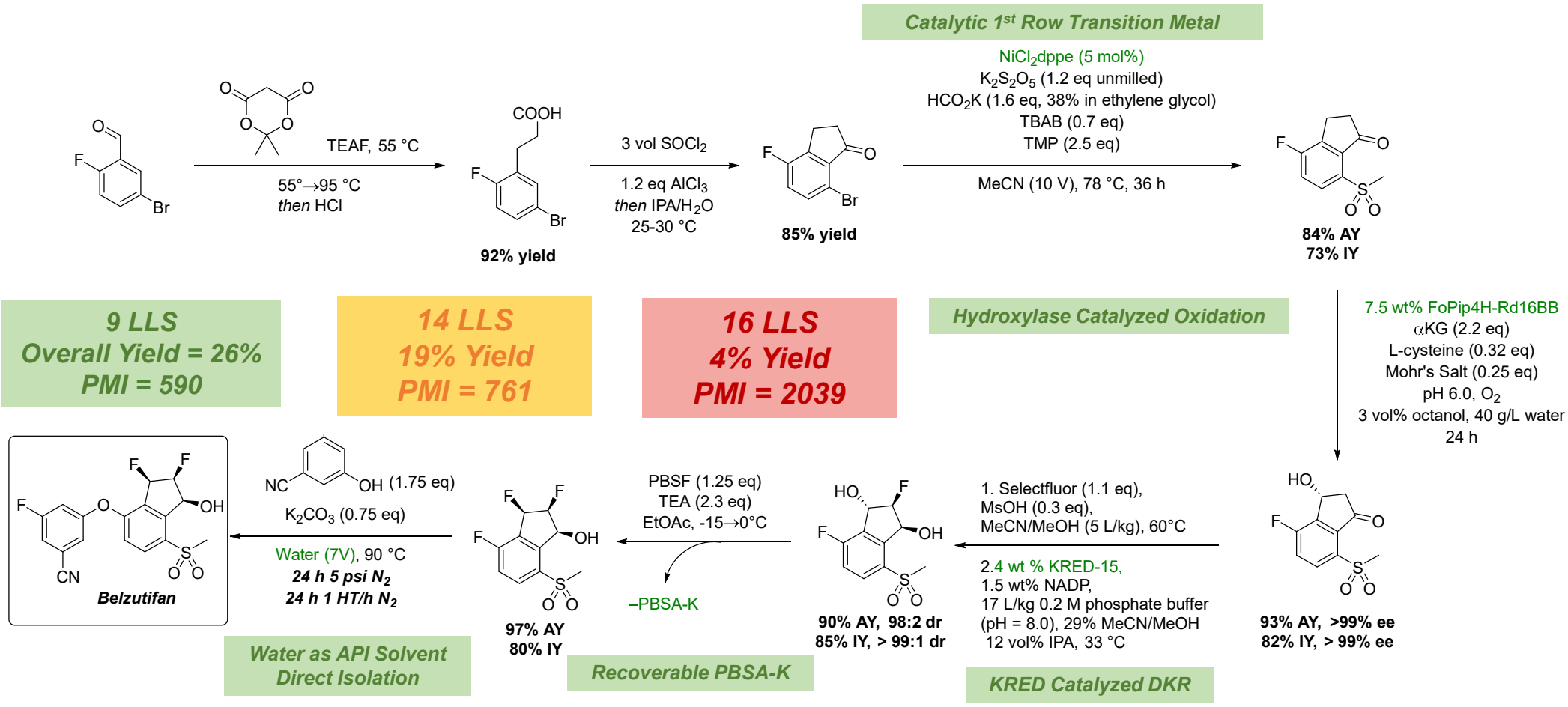
97.54% LCAP
(0.41% LCAP Benzamide)

Pure Belzutifan

99.83% LCAP
(0.15% LCAP Benzamide)

Le *et al. Org. Process Res. Dev.* **2024**, 28, 2, 451-459

Completed Process for Belzutifan



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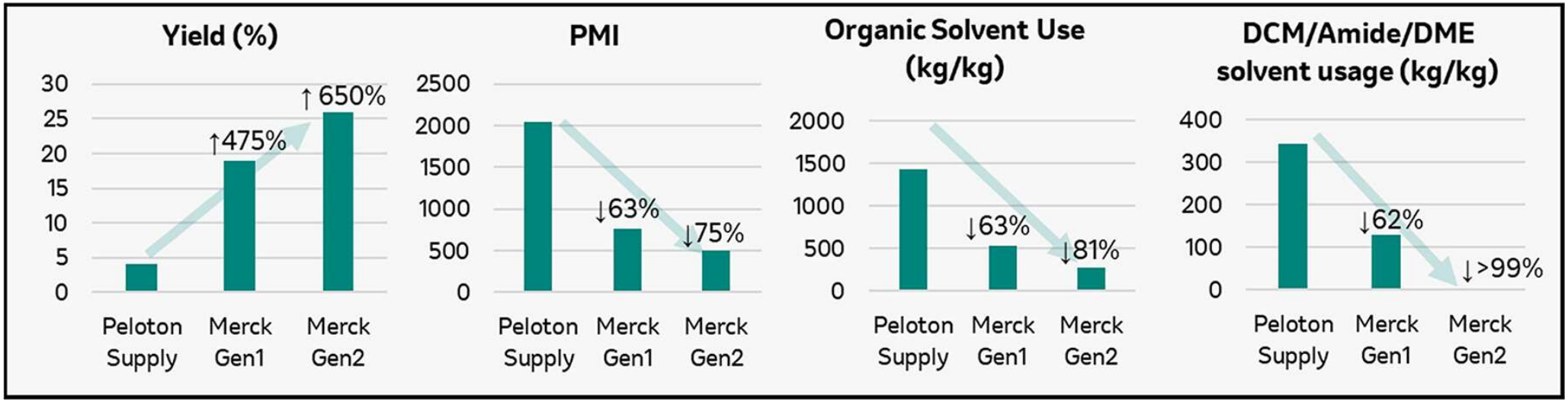
Green and Sustainable Manufacturing Process Results



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Questions?