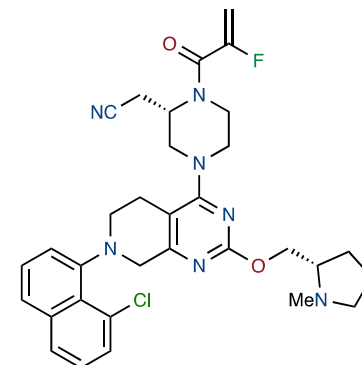
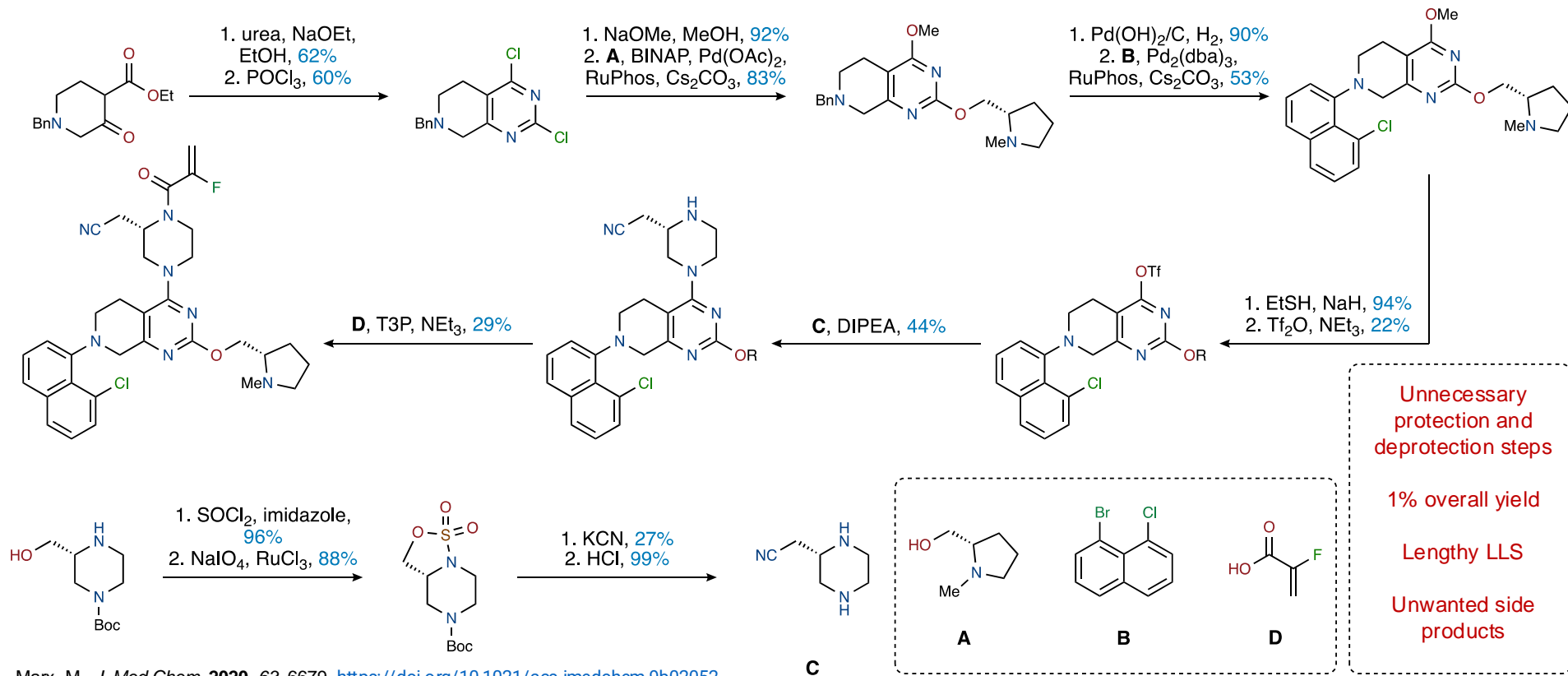


- Adagrasib was recently approved for treatment of non-small cell lung cancer
- Targets the G12C point mutation to the Kirsten rat sarcoma oncogene (KRAS)
- KRAS oncogene homologue is associated with top three most fatal cancers (adenocarcinoma, non-small lung cancer, colorectal cancer)
- Lots of interest in KRAS inhibitors after discovery by Shokat lab!
  - KRAS previously considered “undruggable”; however, an allosteric site was identified
- Process route was needed to procure enough material for clinical trials

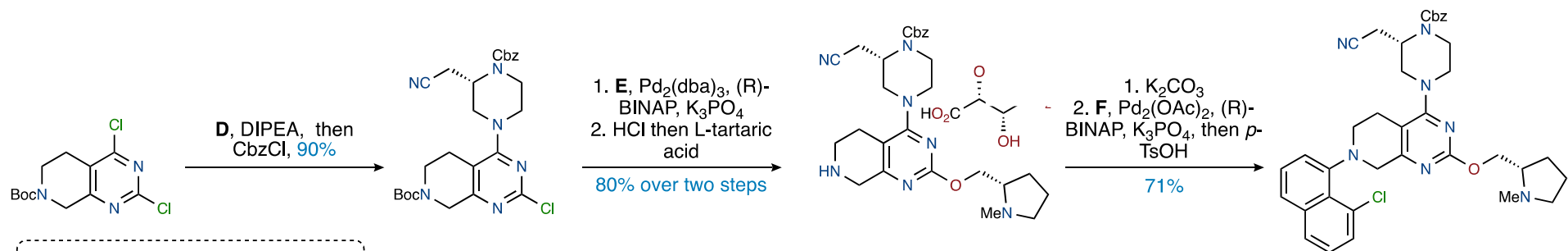


## Medicinal Chemistry Route

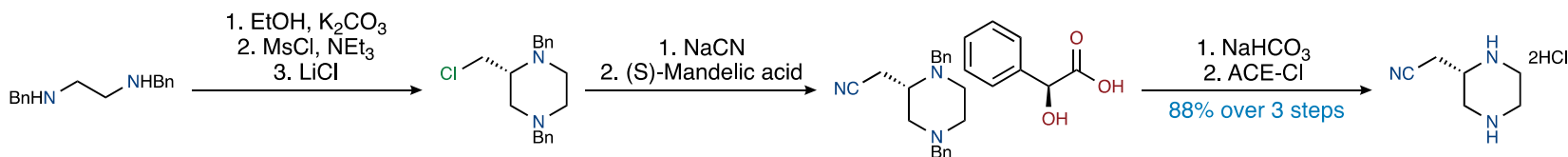
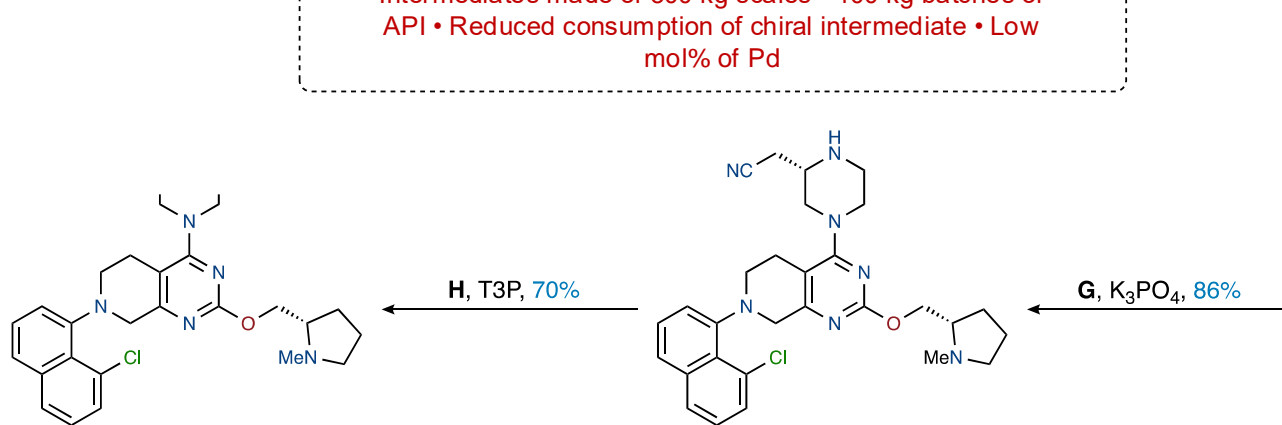
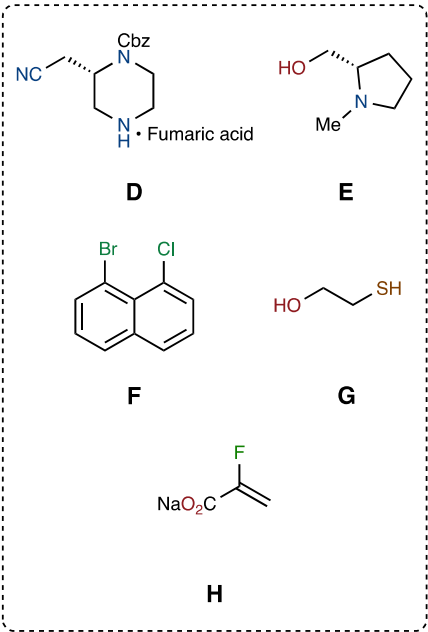


Marx. M., *J. Med Chem.* **2020**, 63, 6679. <https://doi.org/10.1021/acs.jmedchem.9b02052>

## Commercial Route

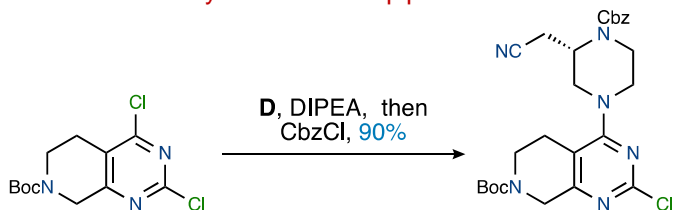


Reduction of step count • Yield of API increased to 32% • Intermediates made of 300 kg scales • 100 kg batches of API • Reduced consumption of chiral intermediate • Low mol% of Pd



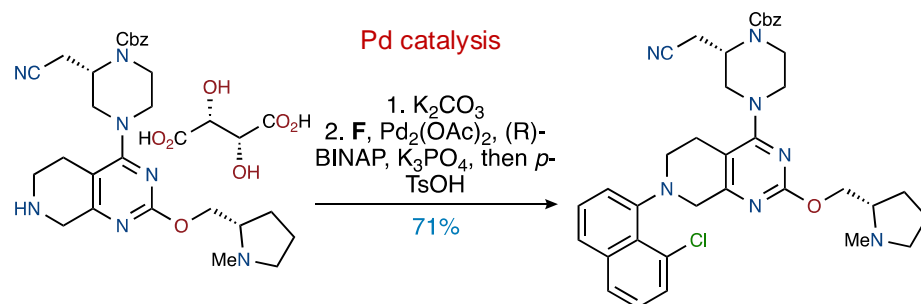
## Commercial Route

Early installation of piperazine



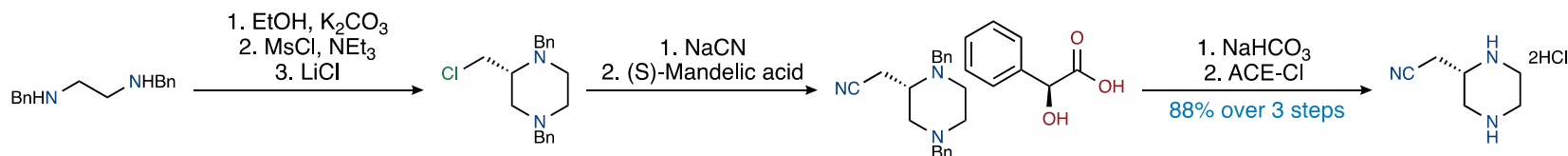
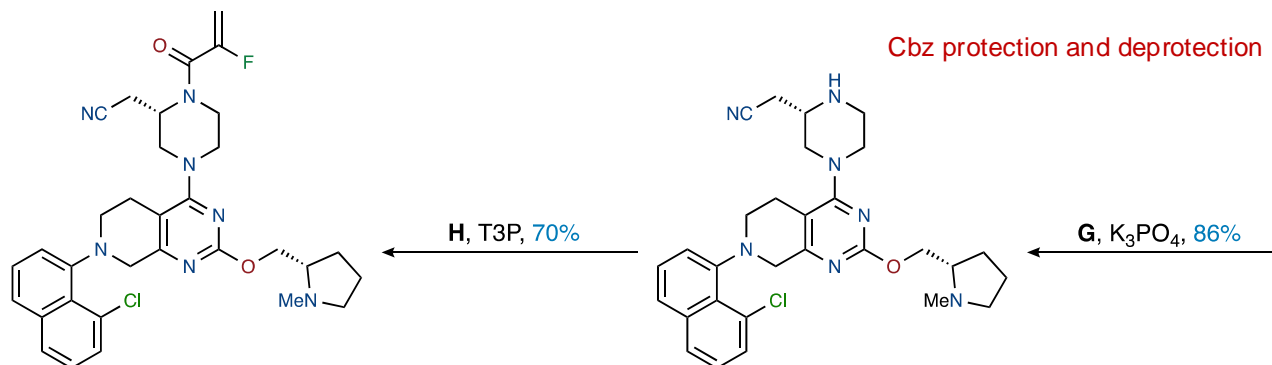
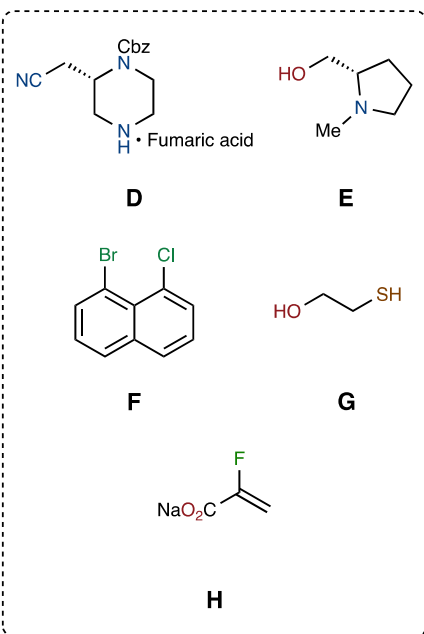
Pd catalysis

1. **E**, Pd<sub>2</sub>(dba)<sub>3</sub>, (R)-BINAP, K<sub>3</sub>PO<sub>4</sub>  
2. HCl then L-tartaric acid  
80% over two steps

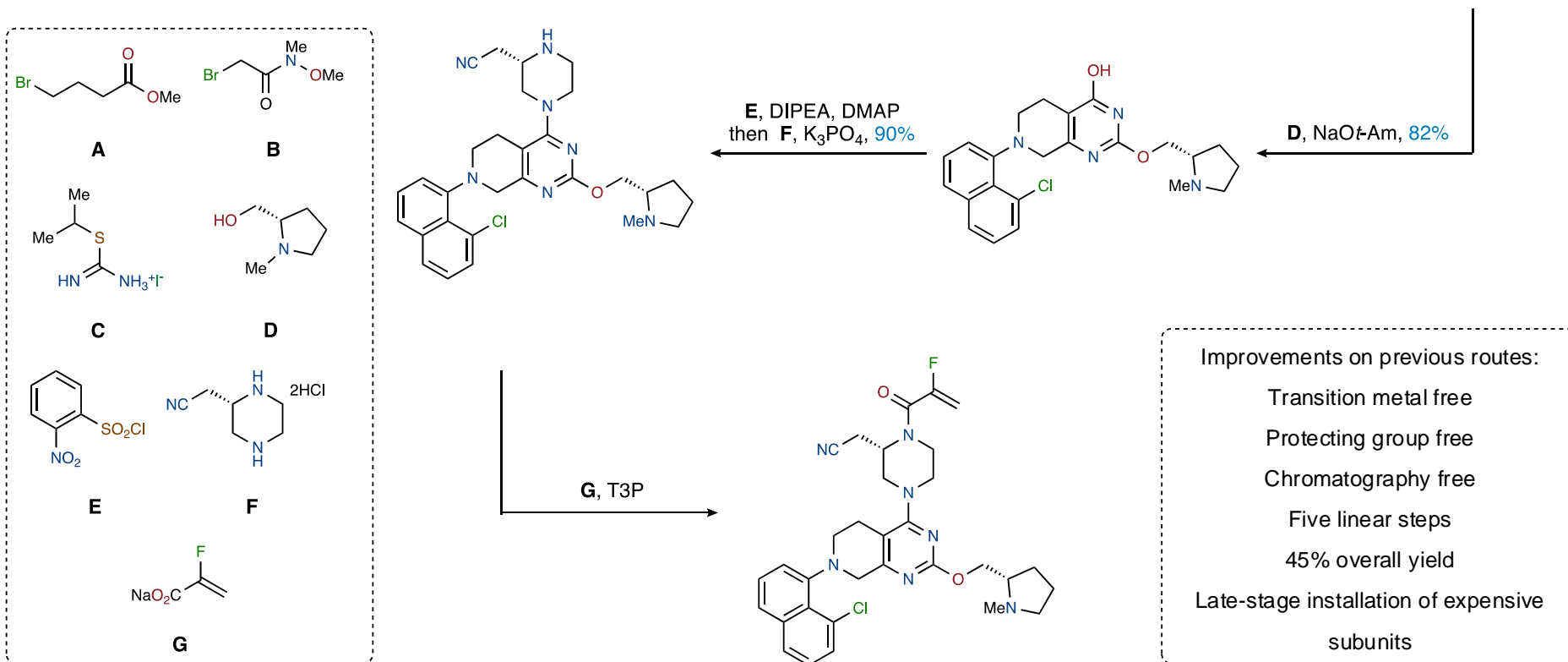
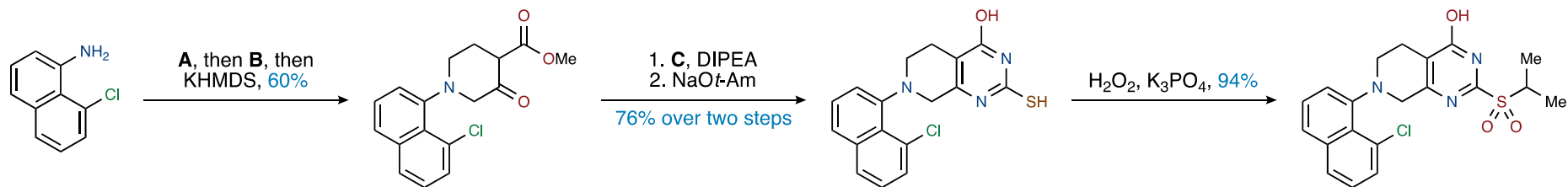


Next step: Proof of concept route that shortens the LLS and avoids palladium and protecting groups

Cbz protection and deprotection



## “Proof of Concept Route”



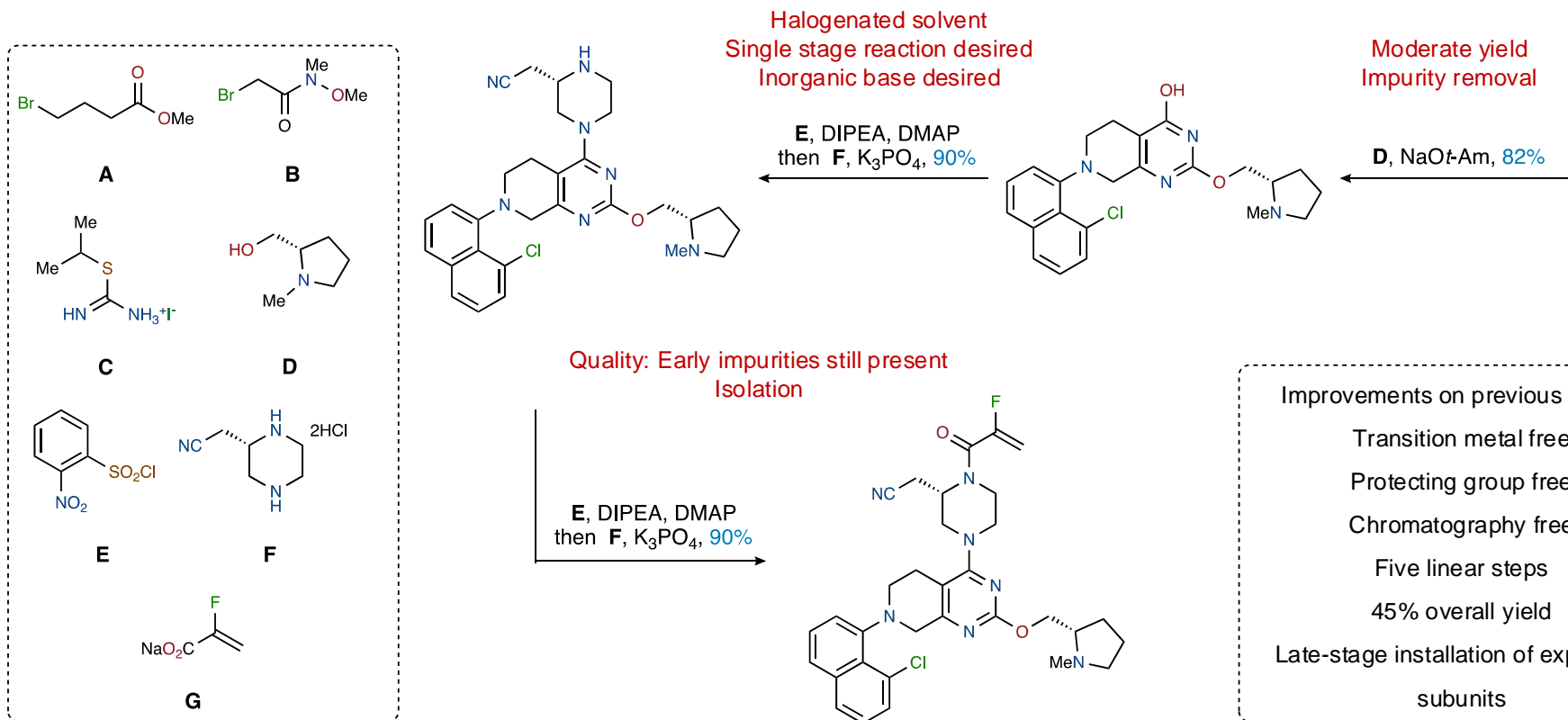
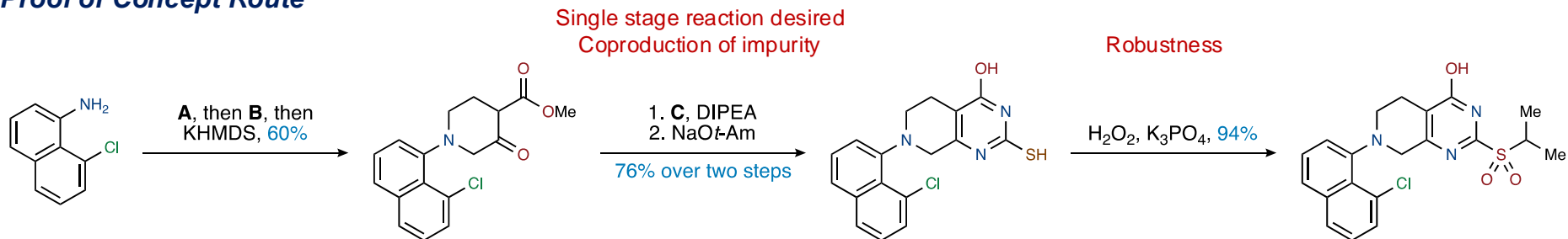
Improvements on previous routes:

- Transition metal free
- Protecting group free
- Chromatography free

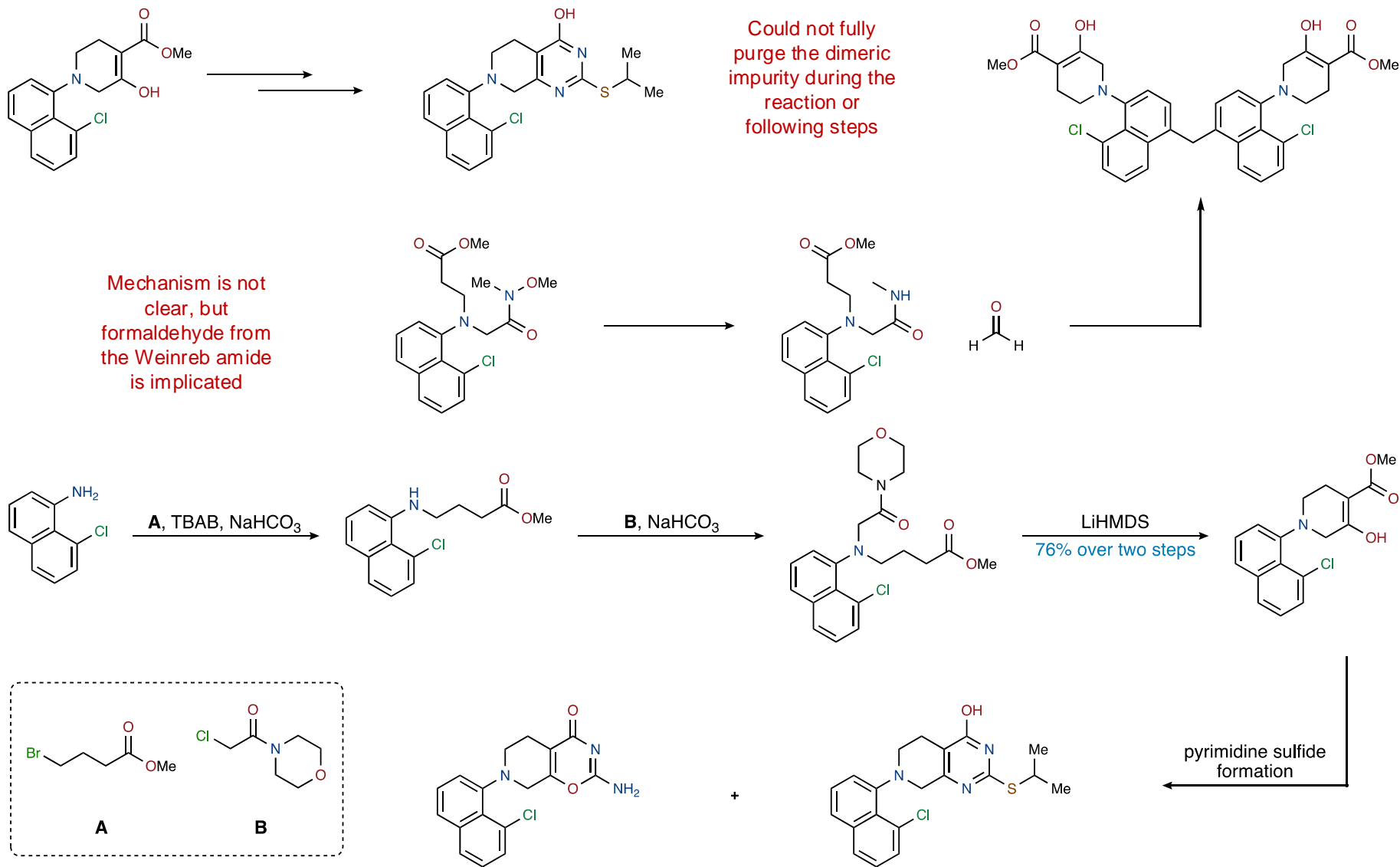
- Five linear steps
- 45% overall yield

- Late-stage installation of expensive subunits

## “Proof of Concept Route”

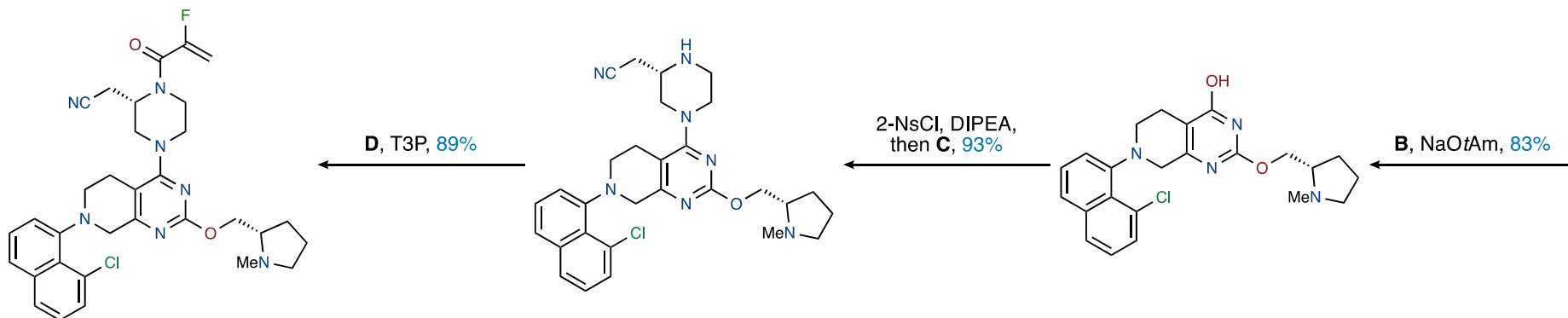
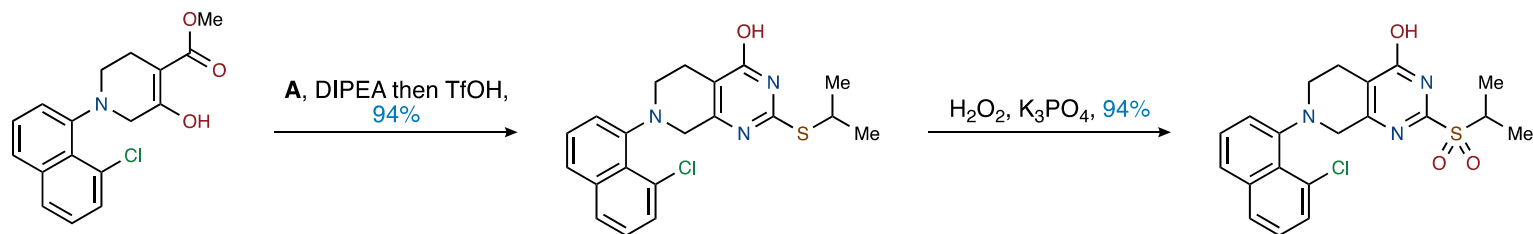


## Final Process Route



## Final Process Route

Impurity arising from base catalysed sulfide elimination, ring cleavage, yielding a nitrile, and ring closure via nucleophilic attack



KSM	API	process design (%)	process development (%)	yield increase (%)
7		77	94	17
6		60	70	10
12		34	74	40
	step 1, 8	74	94	20
	step 2, 9	94	94	0
	step 3, 11	82	83	1
	step 4, 13	85	93	8
	step 5, 1	80	89	9
	overall yield, 1	39	61	21

