Development and Scale-up of a Convergent Asymmetric Synthesis of a Renin Inhibitor for the Treatment of Hypertension

Jeremy Scott

Director, Global Process Chemistry

Merck Sharp & Dohme Inc.

19th Annual Review Meeting:

Advances In Asymmetric Synthesis

26 Nov 2012, SCI, London

Presentation Outline

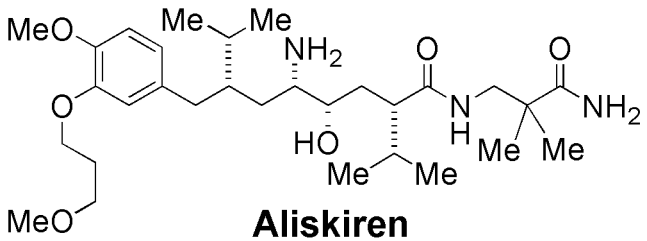
- Rationale for pursuing a renin inhibitor
- Medicinal Chemistry synthesis
- Catalysis at Merck
- First GMP delivery
- Second GMP delivery

Hypertension: An Unmet Medical Need

- Essential (primary) hypertension affects over 1 billion patients worldwide which if left untreated, can lead to end organ failure (brain, kidney, heart).
- The American Heart Association estimated the direct and indirect costs of high blood pressure in 2010 as $76.6 billion.
- Main classes of antihypertensive agents include:
  - Renin-Angiotensin system blockers
    - Angiotensin-converting enzyme (ACE) inhibitors
    - Angiotensin receptor blockers (ARBs)
    - Renin inhibitors
  - Calcium channel blockers
  - Diuretics
  - Beta blockers
- The majority of patients require a combination of antihypertensive agents to achieve the target blood pressure of <140/90 mmHg.

Renin Inhibitor Rationale

- Renin is an enzyme that participates in the body's Renin-Angiotensin-Aldosterone System (RAAS).
- The RAAS plays a key role in the regulation of extracellular fluid volume and blood pressure.
  - Several antagonists of the RAAS pathway have emerged as effective hypertension treatments (ACE inhibitors; ARBs).
- Renin is involved in the first and rate-limiting step of RAAS.
  - Inhibition of renin may offer the best potential for blood pressure control.
  - Only known substrate for renin is angiotensinogen
    - Should avoid mechanism-based adverse effects (e.g. ACE inhibitors)
- Aliskiren was the first renin inhibitor on the market (Novartis/Speedel).
  - Approved by the FDA in 2007 for treatment of hypertension

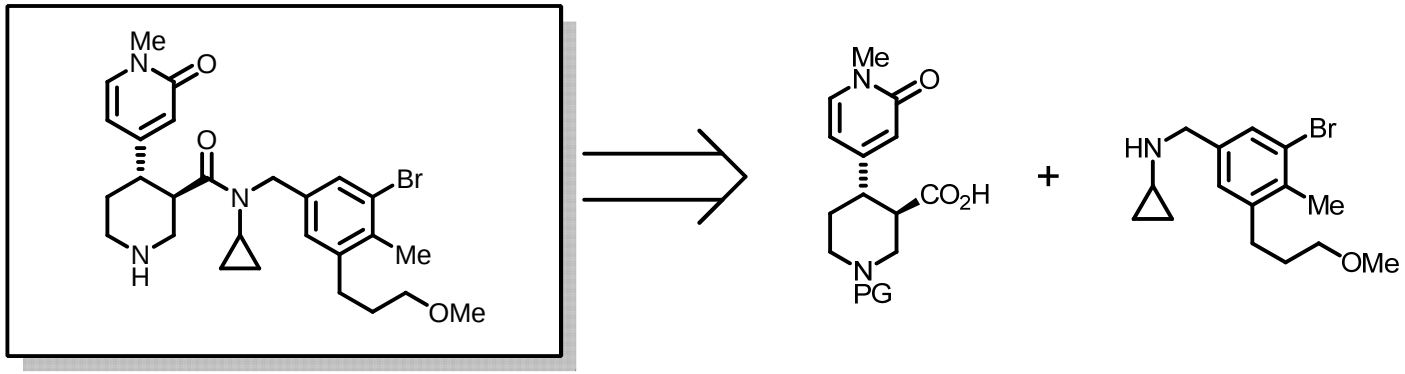


Aliskiren

MERCK SHARP & DOHME
Research Laboratories

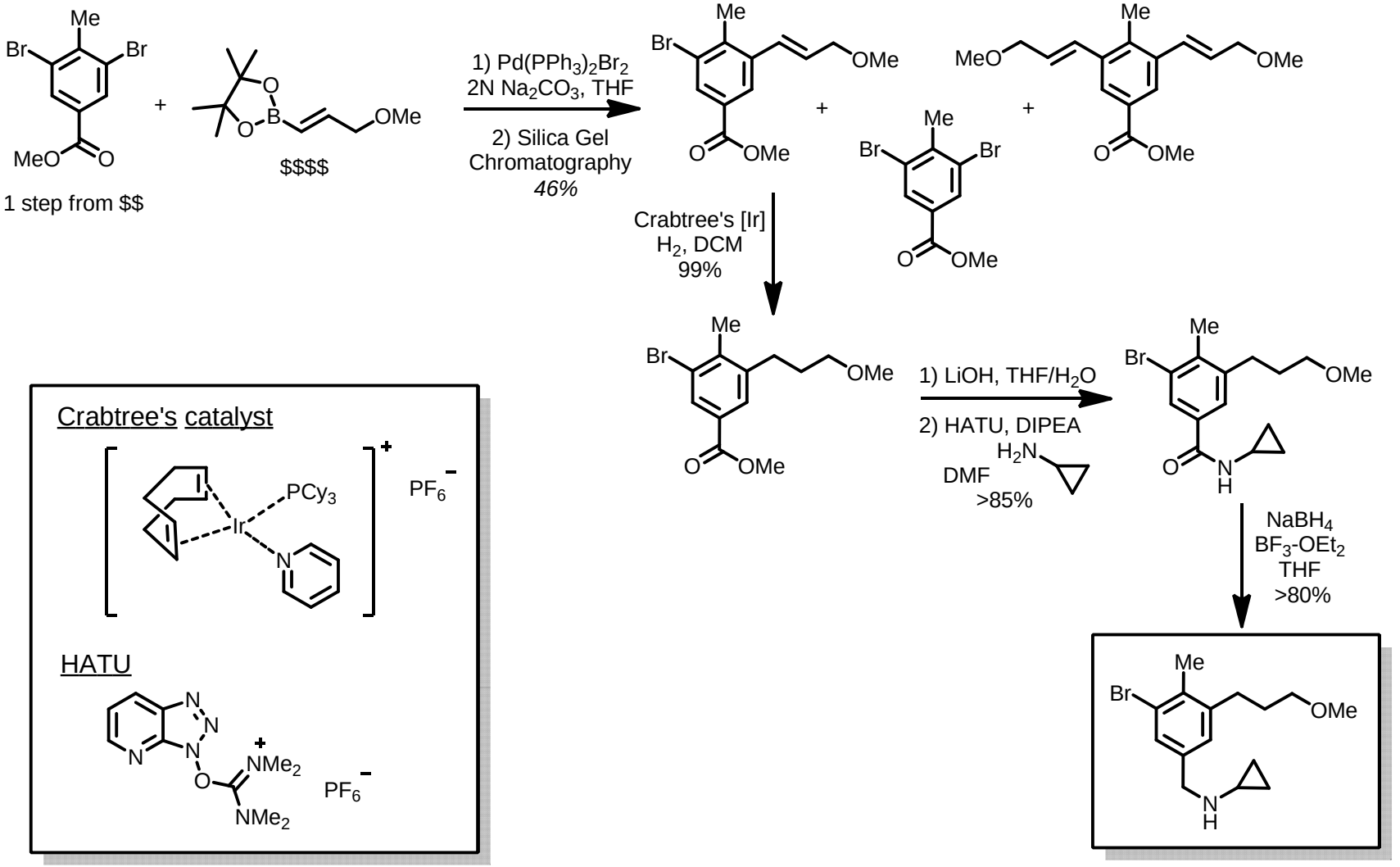
Targeted API

- The target compound was identified as a potent and selective inhibitor of renin.
  - Suitable profile for pre-clinical development.
    - Kilogram quantities required to support this.



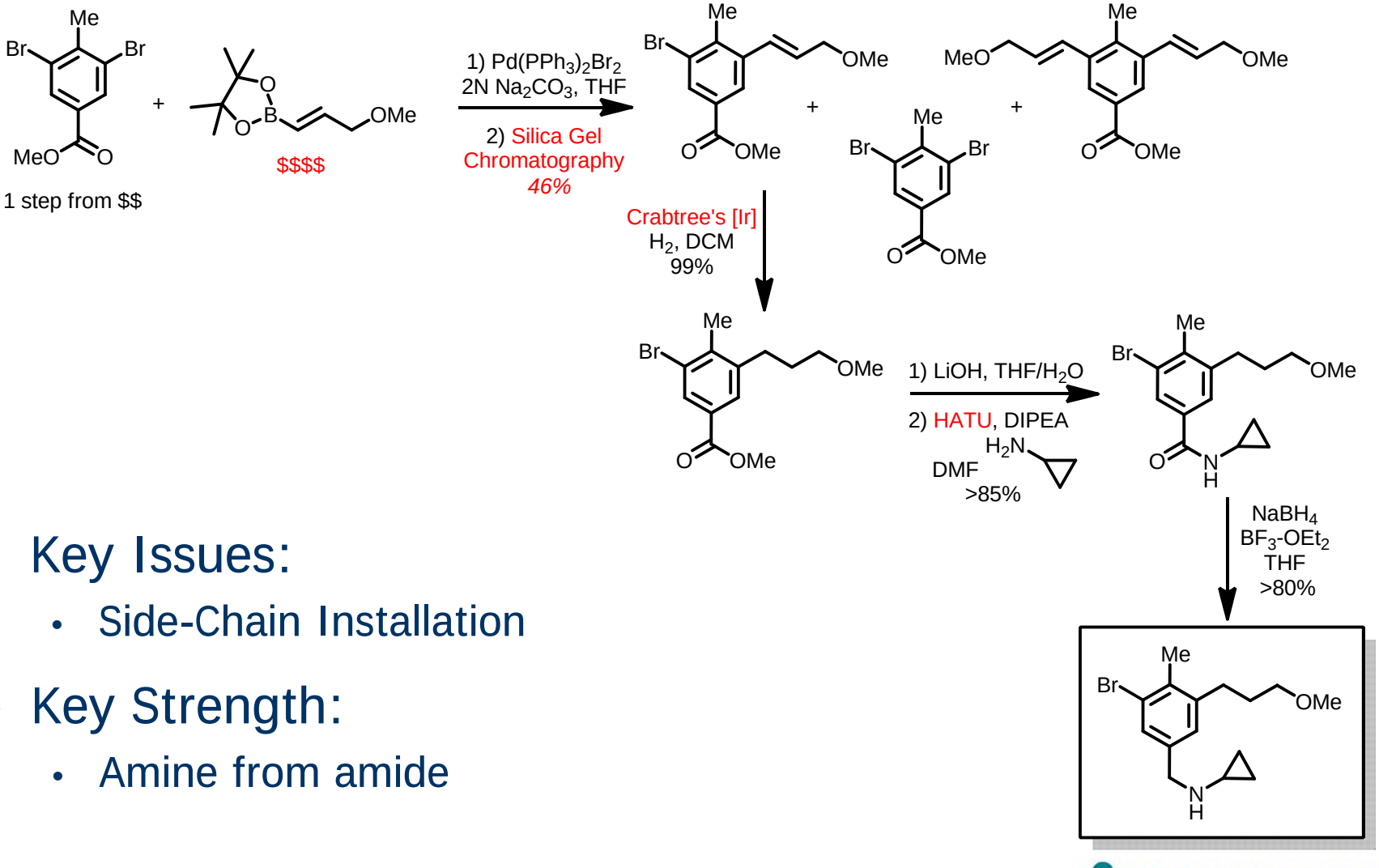
- Compound contains two adjacent stereogenic centres.
- Approaches based on a late-stage amide coupling.

Medicinal Chemistry Route



MERCK SHARP & DOHME
Research Laboratories

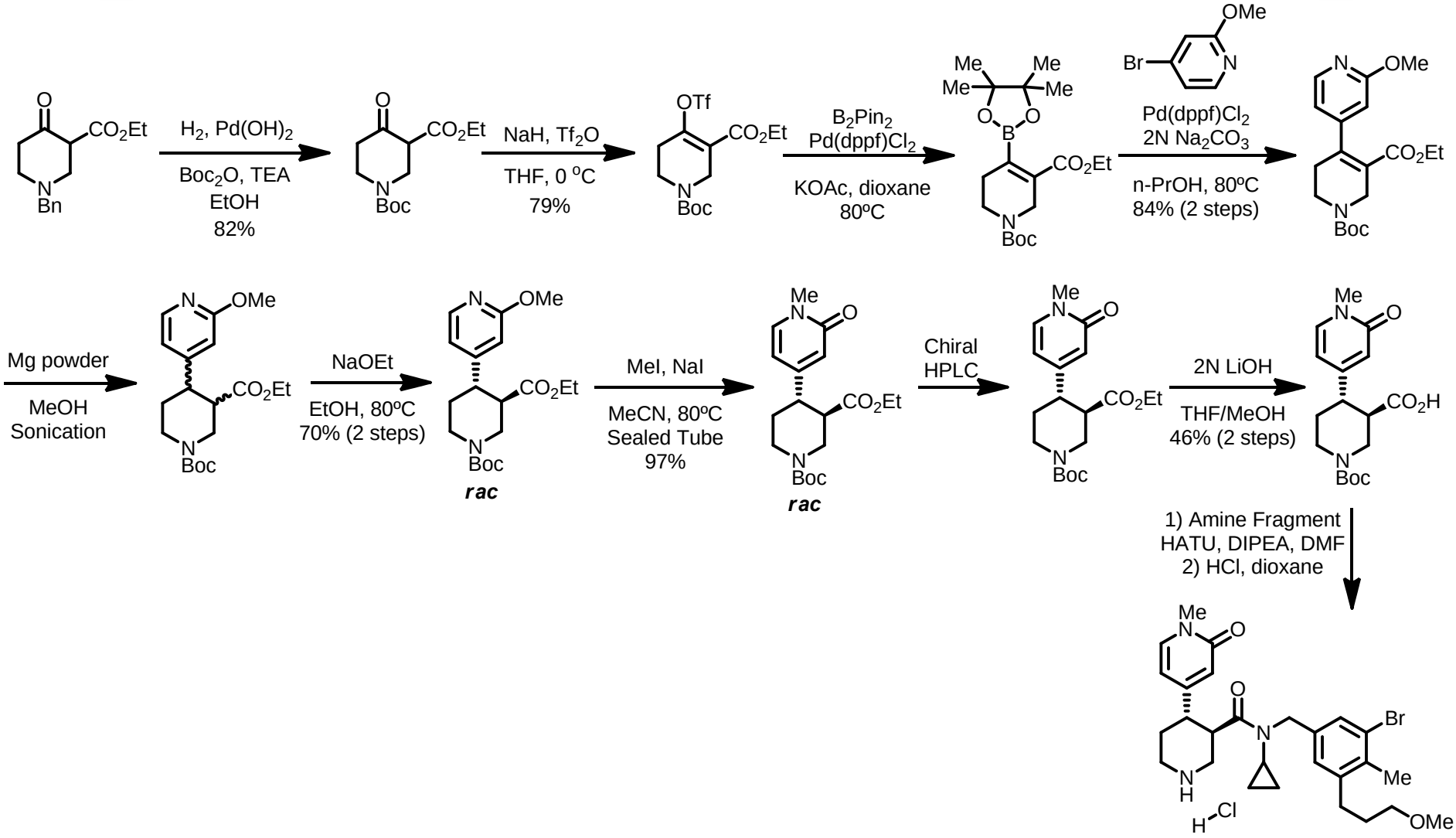
Medicinal Chemistry Route



- Key Issues:
  - Side-Chain Installation
- Key Strength:
  - Amine from amide

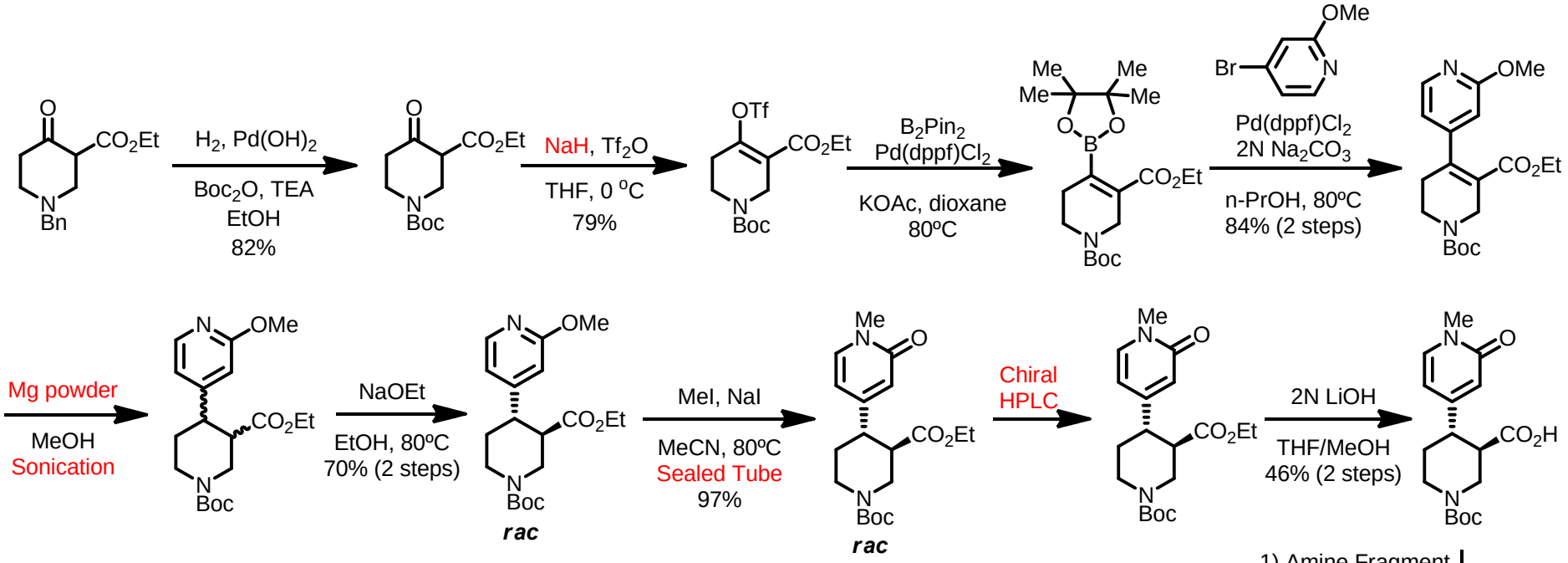
MERCK SHARP & DOHME
Research Laboratories

Medicinal Chemistry Route



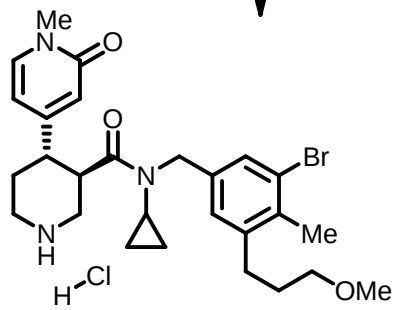
MERCK SHARP & DOHME
Research Laboratories

Medicinal Chemistry Route



- Key Issues:
  - Racemic Synthesis (Chiral Separation)
  - Scalability
- Key Strength:
  - Key bond disconnection
  - Epimerization Step

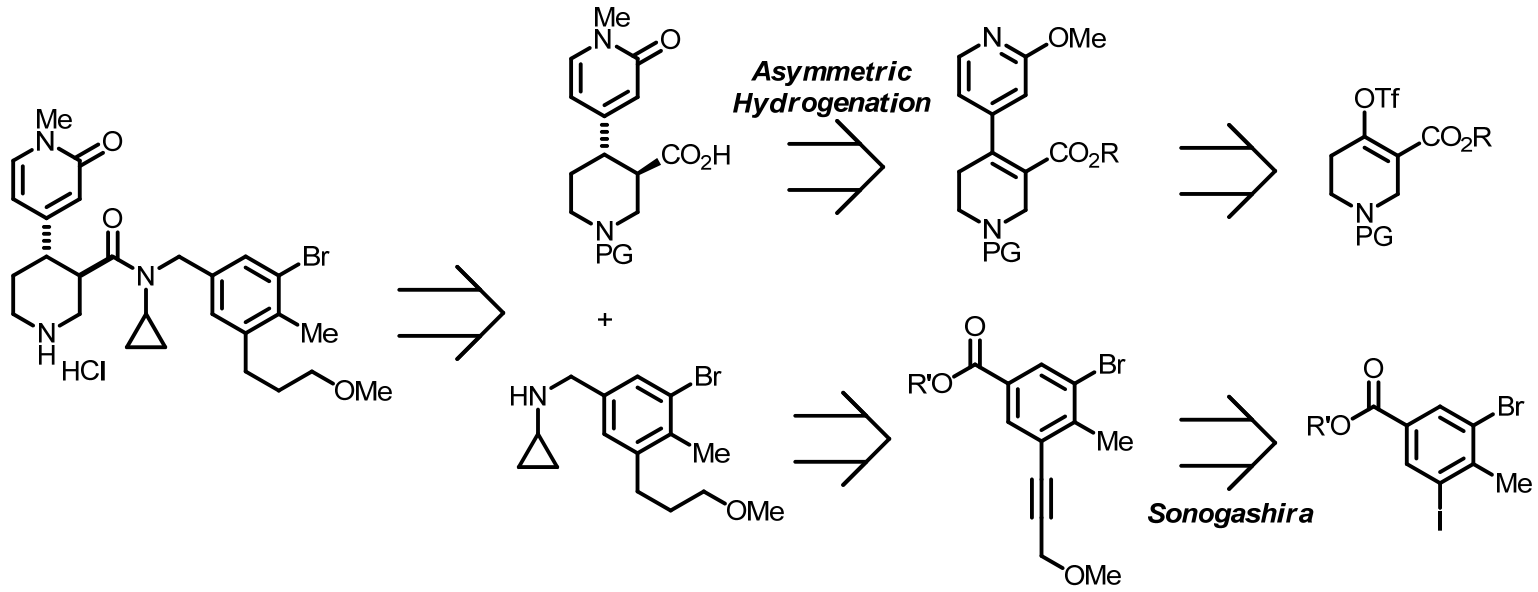
1) Amine Fragment
HATU, DIPEA, DMF
2) HCl, dioxane



MERCK SHARP & DOHME
Research Laboratories

1st GMP Delivery: Goals & Retrosynthetic Strategy

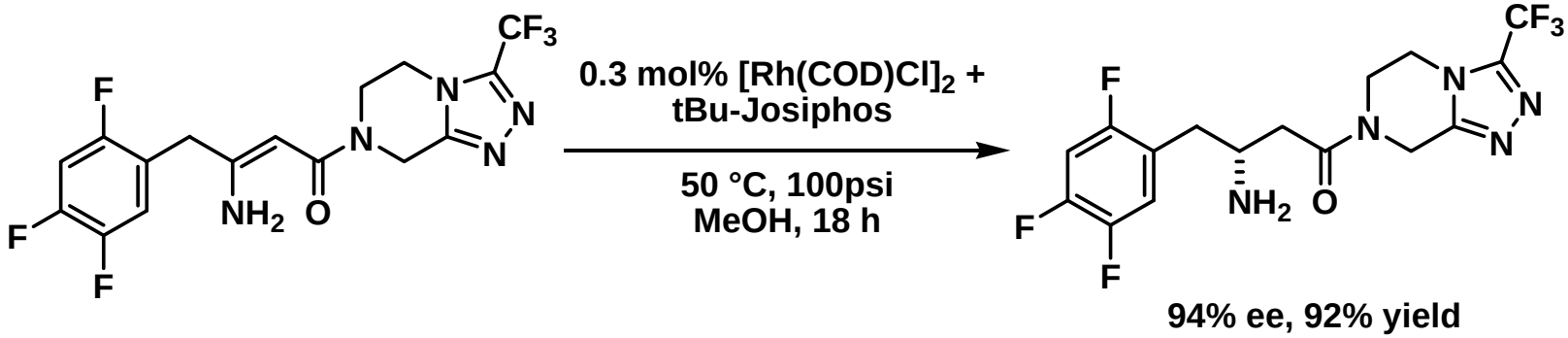
- Goals:
  - Deliver 2.5 kg of API within 16 weeks
  - Provide assessment of chemistry for future deliveries



MERCK SHARP & DOHME
Research Laboratories

Early Success in Asymmetric Hydrogenation

Sitagliptin (Januvia™, Janumet™)

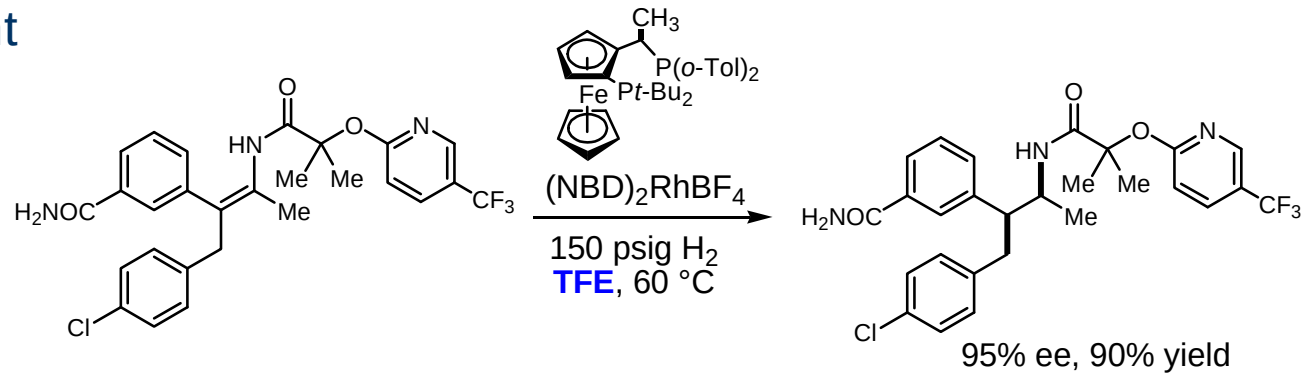


- Asymmetric hydrogenation process: 6 steps, 63% overall yield
- Implemented at factory scale (> 20 MT produced to date)
- Four-fold reduction in waste, 100% removal of aqueous waste streams
- Winner 2005 IChemE Astra-Zeneca and 2006 EPA Presidential Green Chemistry awards

Hsiao, et al. *JACS*, **2004**, *126, 9918;* Hansen, et al. *JACS* **2009**, *131, 8798*

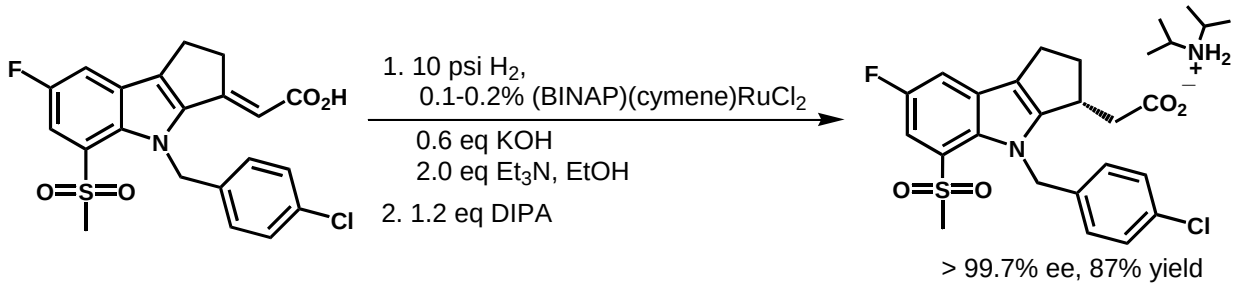
Early Success in Asymmetric Hydrogenation

Taranabant



Wallace, et al. *Org. Proc. Res. Dev*. **2009**, *13*, 84

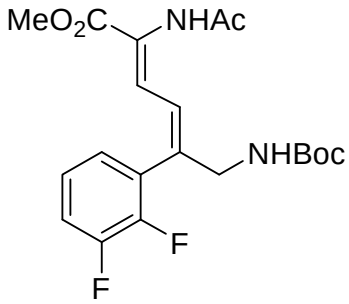
Laropiprant (Tredaptive™)



Tellers, et. al, *JACS.*, **2006,** *128,* 17063

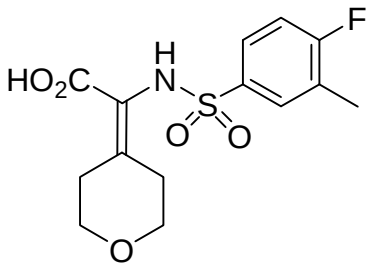
MERCK SHARP & DOHME
Research Laboratories

Asymmetric Hydrogenation in Support of Early Development Candidates



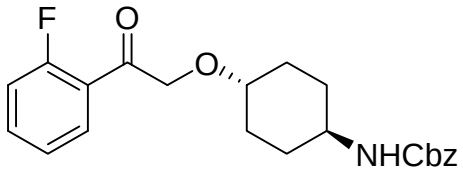
(-)-TMBTP/(COD)Ru(methallyl)$_2$
99% ee, 97% yield

Steinhuebel, et al. *Org. Lett.* **2010**, *12*, 4201



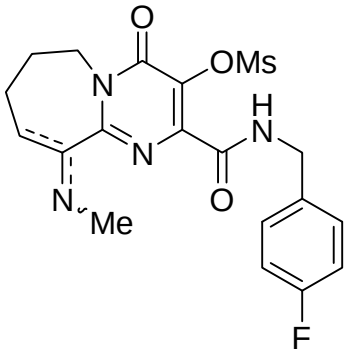
tBu-Josiphos/[Ru(p-cymene)Cl$_2$]$_2$
97% ee, 98% yield

Shultz, et al. *Org. Lett.* **2005**, *7*, 3405



SLN004-2/(PPh$_3$)$_3$RuCl$_2$
93% ee

Tellers, et al. *Tet: Asymm* **2006**, *17*, 550

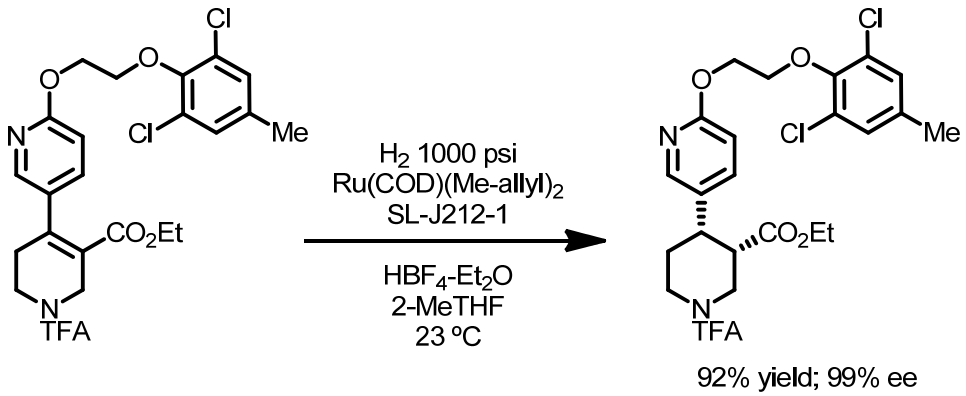


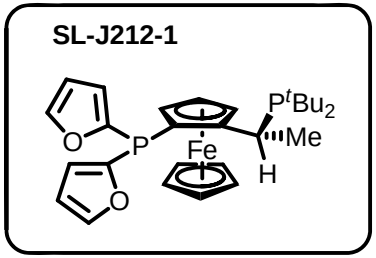
furyl/tBu-Josiphos/ [(COD)RhCl]$_2$
90% ee, 90% yield

Zhong, et al. *Org. Lett.* **2009**, *11*, 369

Asymmetric Hydrogenation of Tetra-substituted *α,β*-unsaturated esters

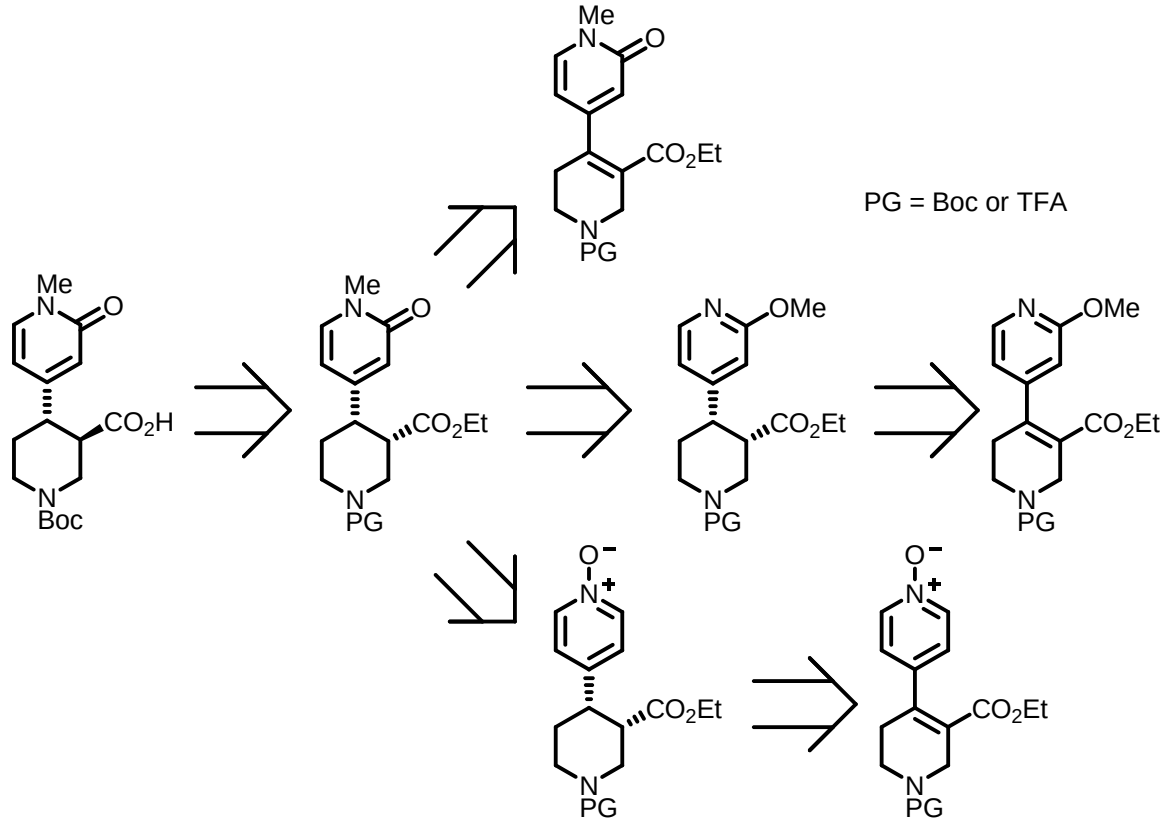
- An important precedent had been set for the synthesis of a previous compound in this program.





Molinaro, C.; Schultz, S.; Roy, A.; Lau, S.; Trinh, T.; Angelaud, R.; O'Shea, P.D.; Abele, S.; Cameron, M.; Corley, E.; Funel, J.-A.; Steinhuebel, D.; Weisel, M.; Krska, S. *J. Org Chem.* **2011**, *76*, 1062.

Acid Fragment: Retrosynthesis

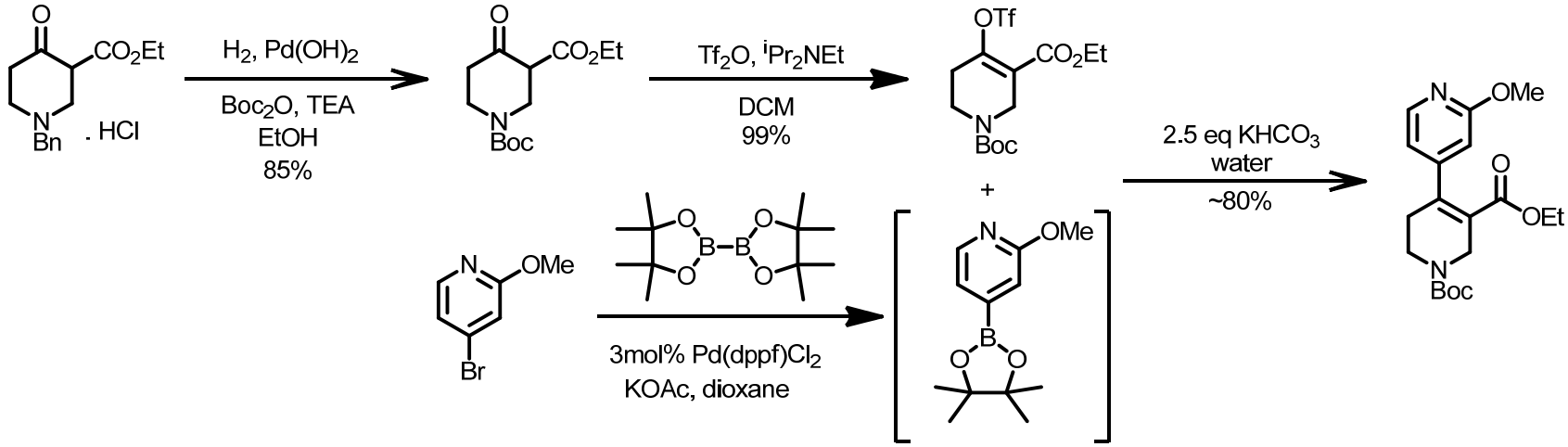


- Liabilities with *N*-oxide and pyridone reduction during asymmetric hydrogenation
- Methoxypyridine selected as best pyridone surrogate

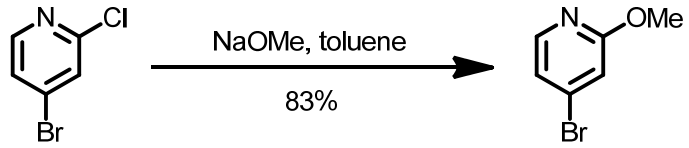
MERCK SHARP & DOHME
Research Laboratories

Preparation of the Hydrogenation Substrate

- One-pot borylation-Suzuki coupling using 4-bromo-2-methoxypyridine demonstrated on lab scale
  - 4-bromo-2-methoxypyridine not available on kg scale in suitable timeline.

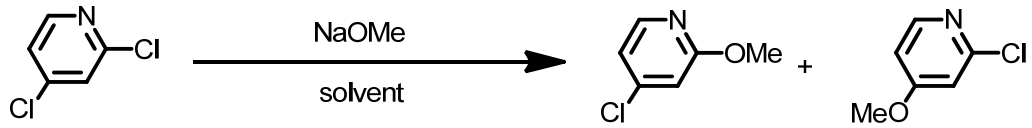


- 4-Bromo-2-chloropyridine was identified as a replacement, but also had long lead-time.

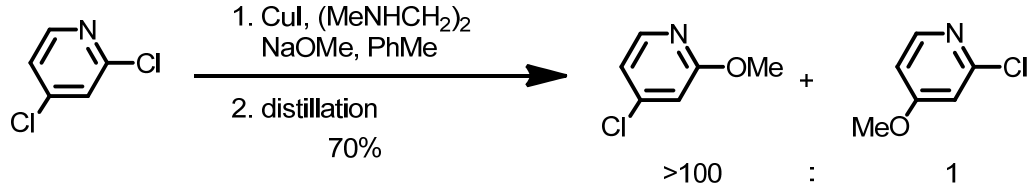


Preparation of the Hydrogenation Substrate

- 2,4-dichloropyridine was readily available and met project timelines
- S_NAr with sodium methoxide
  - High selectivity and conversion in dioxane
  - Poor conversion in toluene

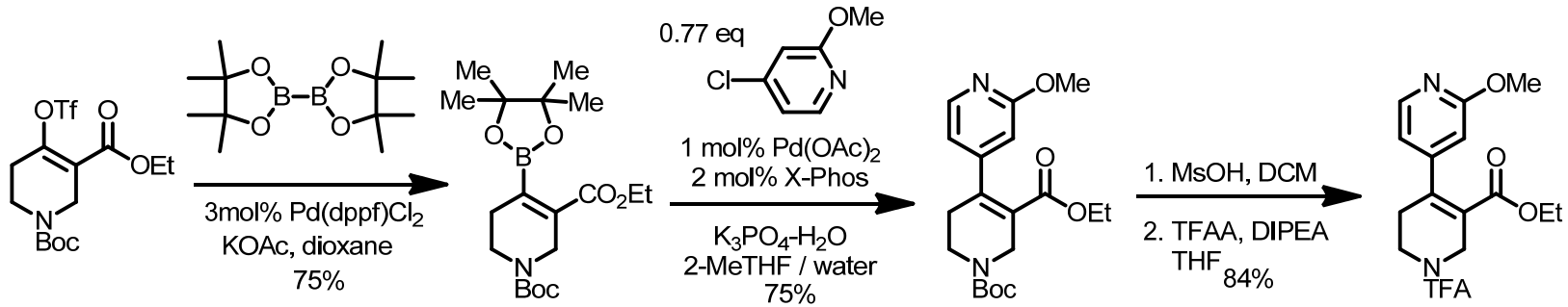


- Screen of Cu catalysts identified effective catalyst/ligand combination
  - Complete conversion in toluene in 20 h with 2 mol% catalyst

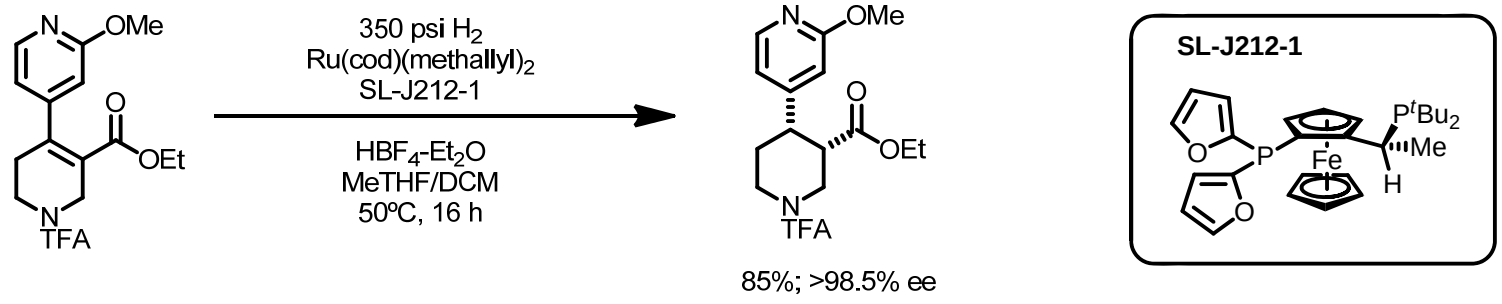


MERCK SHARP & DOHME
Research Laboratories

Preparation of the Hydrogenation Substrate & Hydrogenation

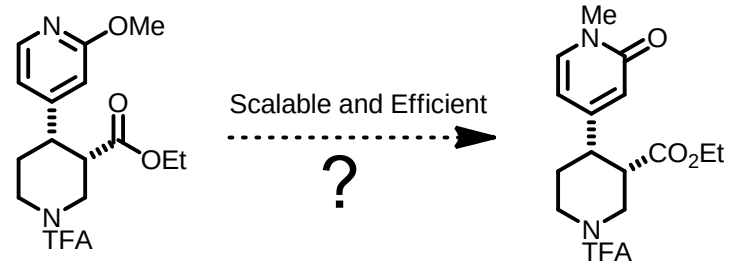


- Attempted hydrogenation of the *N*-Boc substrate resulted in partial deprotection and catalyst poisoning.
  - PG switch is a through-process without isolation of the free piperidine

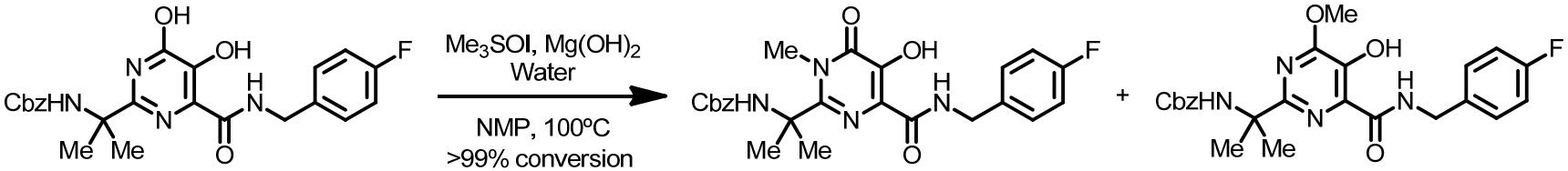


- HBF_4 protonates the pyridyl nitrogen to avoid catalyst poisoning.
- >99% conversion & 98.5% ee using 1 mol% catalyst.

Pyridine to Pyridone Conversion



- Inspired by recent breakthrough in development of a 2nd generation manufacturing route to Raltegravir Potassium.



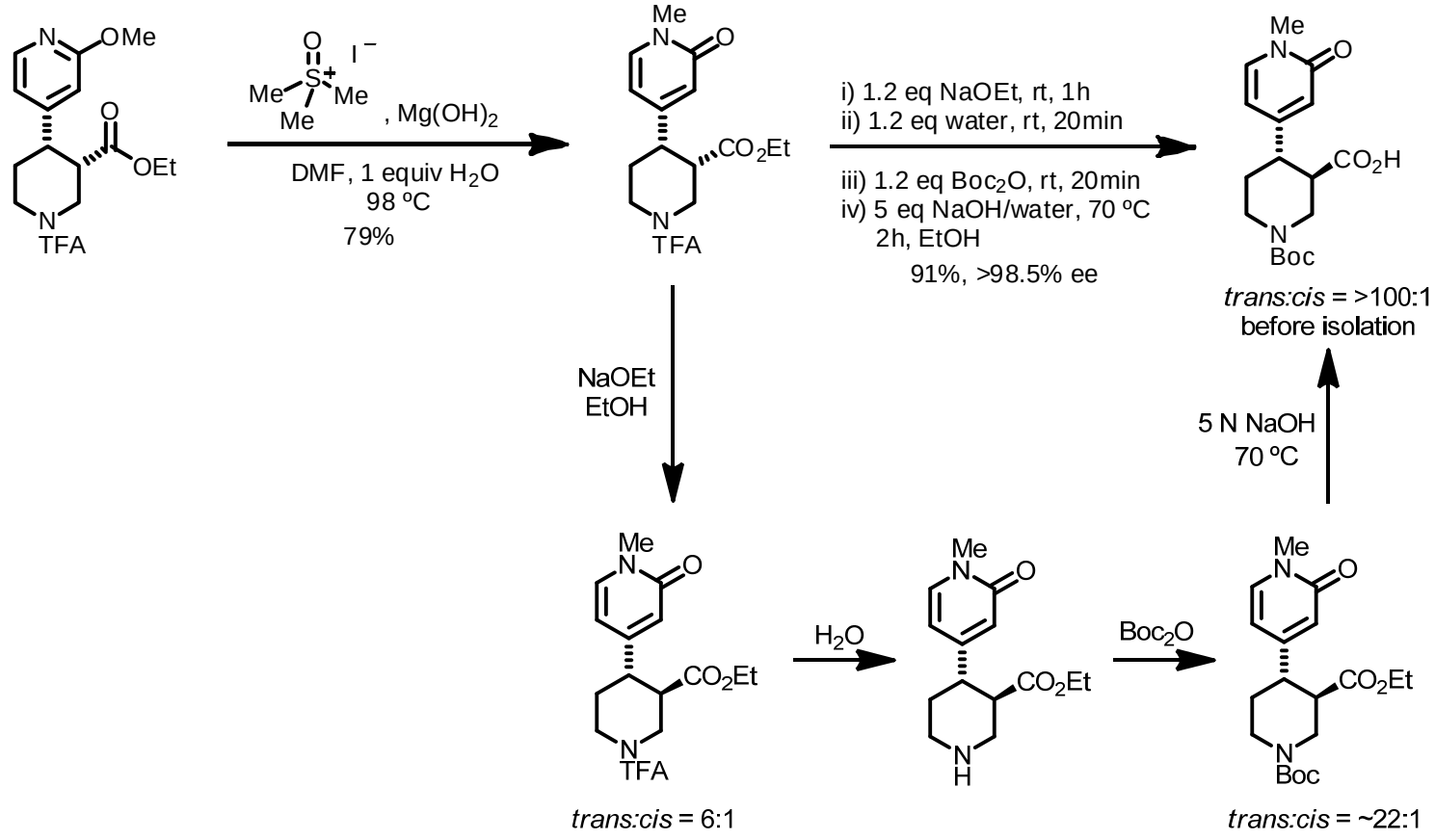
92% isolated yield

>99.9% N-Me versus O-Me

Humphrey, G. R.; Pye, P. J.; Zhong, Y.-L.; Angelaud, R.; Askin, D.; Belyk, K. M.; Maligres, P. E.; Mancheno, D. E.; Miller, R. A.; Reamer, R. A.; Weissman, S. A. *Org. Process Res. Dev.* **2011**, *15*, 73.

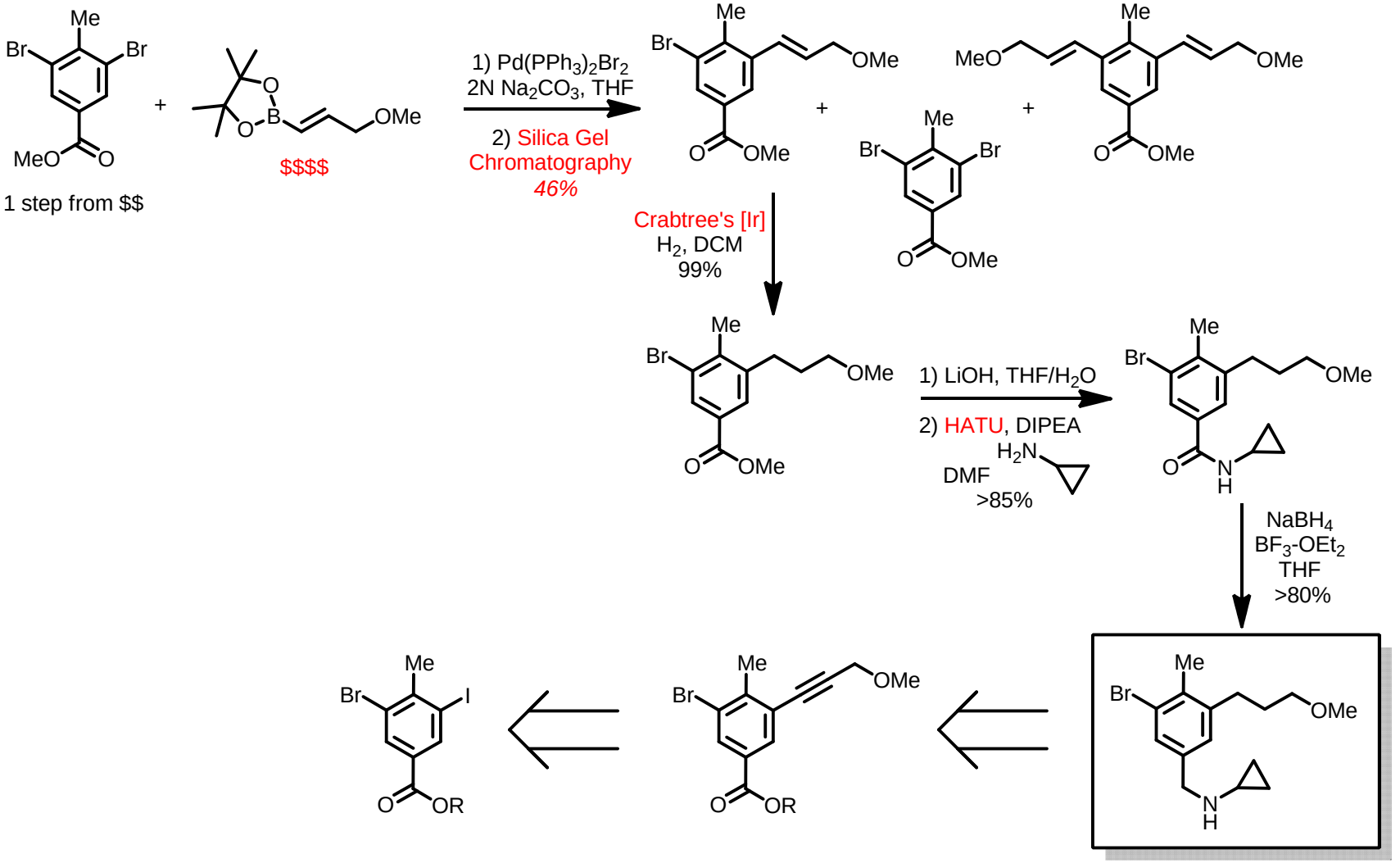
- Could this be applied to the conversion of 2-methoxypyridines?

Completing the Synthesis of the Acid Fragment



- One-pot, four-step sequence developed to convert the *cis* ester to the *trans* acid, based on earlier work from a previous compound in this program.

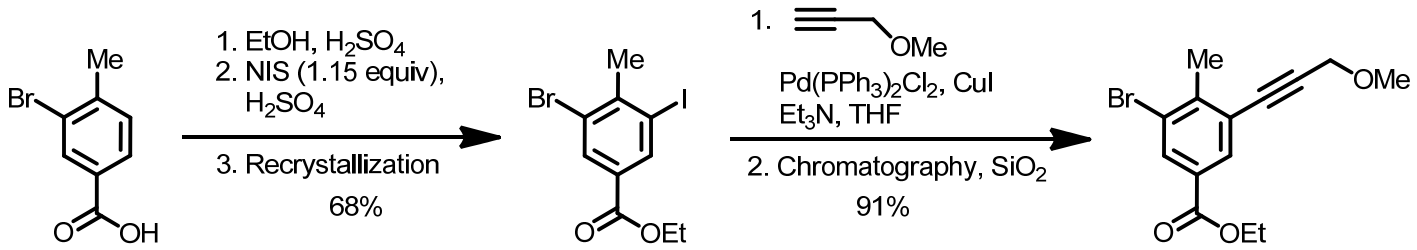
Medicinal Chemistry Route to Amine Fragment



MERCK SHARP & DOHME
Research Laboratories

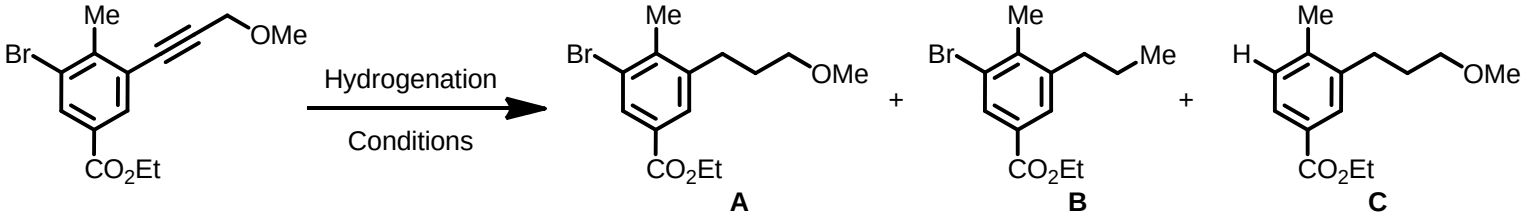
Sonogashira Approach to the Amine Fragment

- Ethyl ester substrate successfully prepared in the lab.



~5% bis-coupled product

- Two impurities generated in the hydrogenation.
  - Residual Pd from the Sonogashira increased formation of **C**.

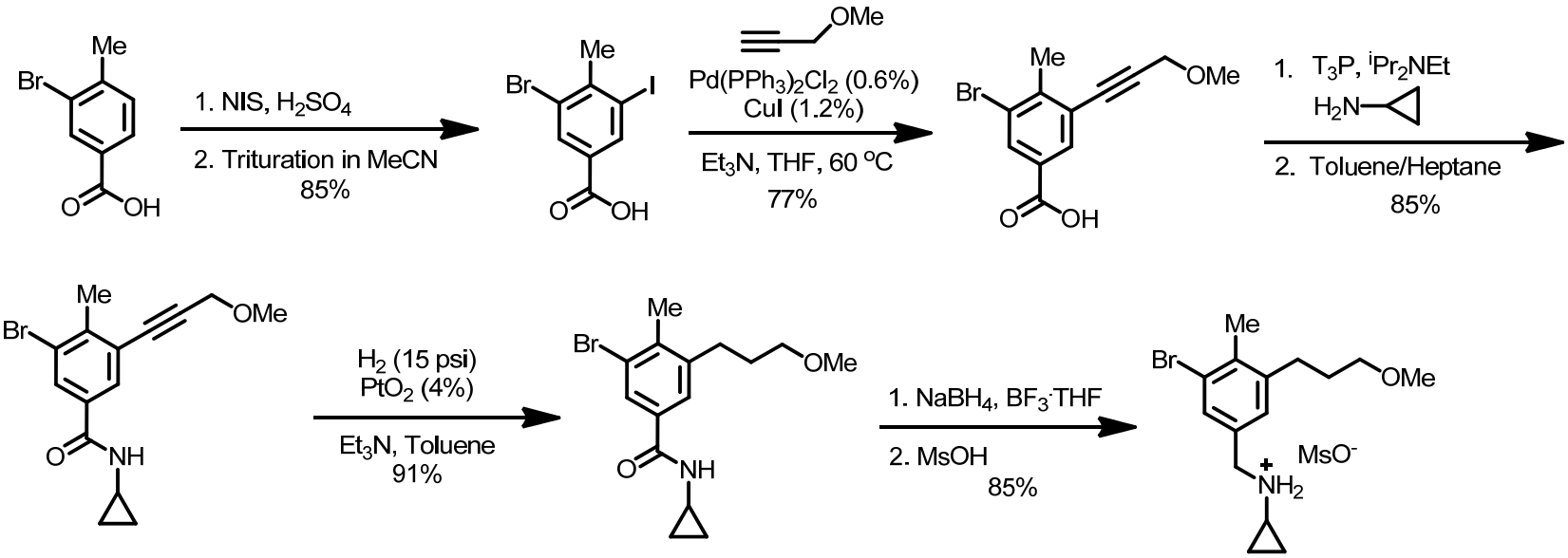


Entry	Catalyst[a]	Solvent	Additive[b]	Conversion[c]	A:B[c]	%C[c]
1	$RhCl(PPh_3)_3$	EtOAc	none	0%	-	-
2	Pd/C	EtOH	none	0%	-	-
3	Pd/C	EtOH	$MgBr_2$	100%	9:1	3.3%
4	PtO_2	EtOH	none	100%	1:1	-
5	PtO_2	PhMe	none	100%	13:1	<3%
6	PtO_2	PhMe	AcOH	100%	19:1	-
7	PtO_2	PhMe	Cs_2CO_3	100%	>50:1	1.8%

[a] 5mol% catalyst loading. [b] 20mol% additive. [c] Determined by HPLC

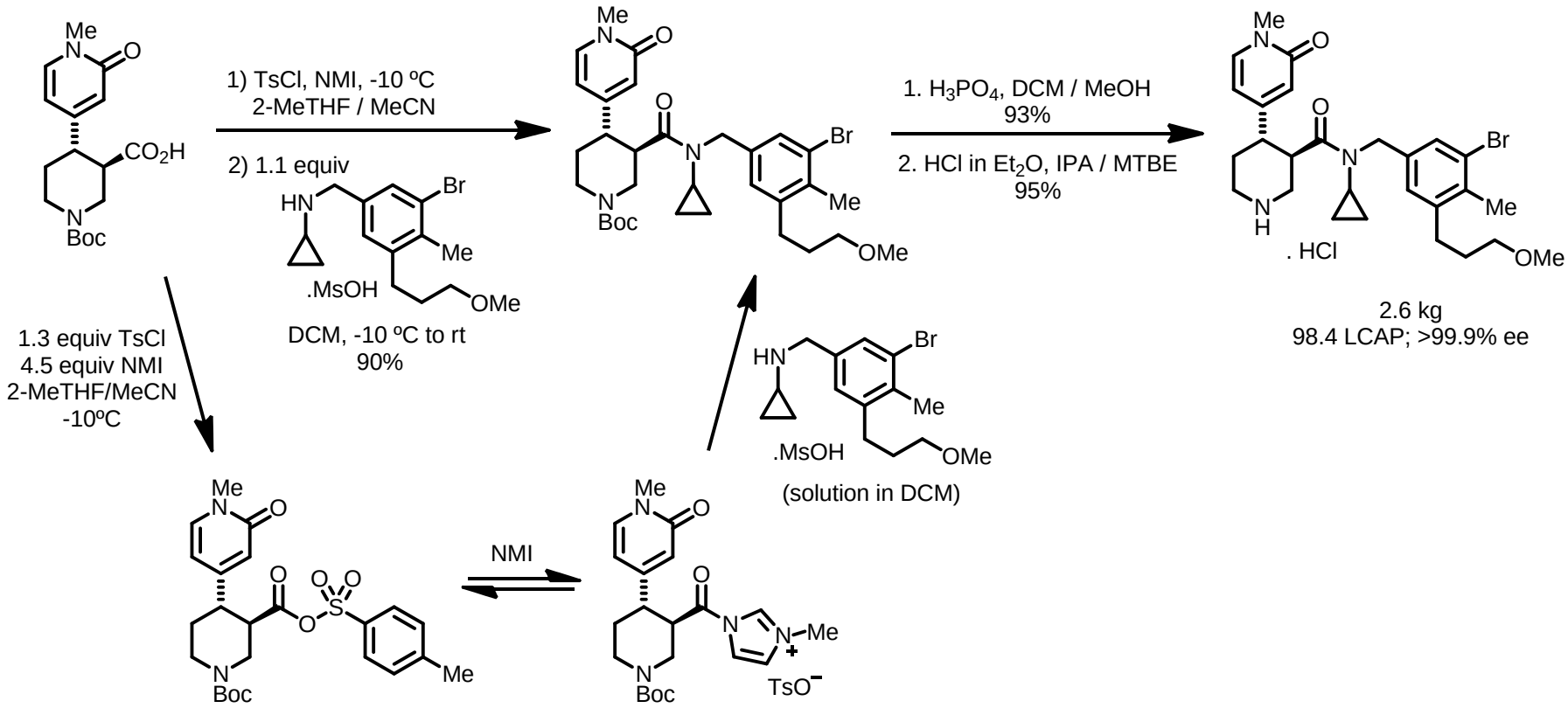
Synthesis of the Amine Fragment

- Adapted Sonogashira Approach:
  - Sonogashira coupling and hydrogenation separated by the amidation.
  - Removed the esterification step.



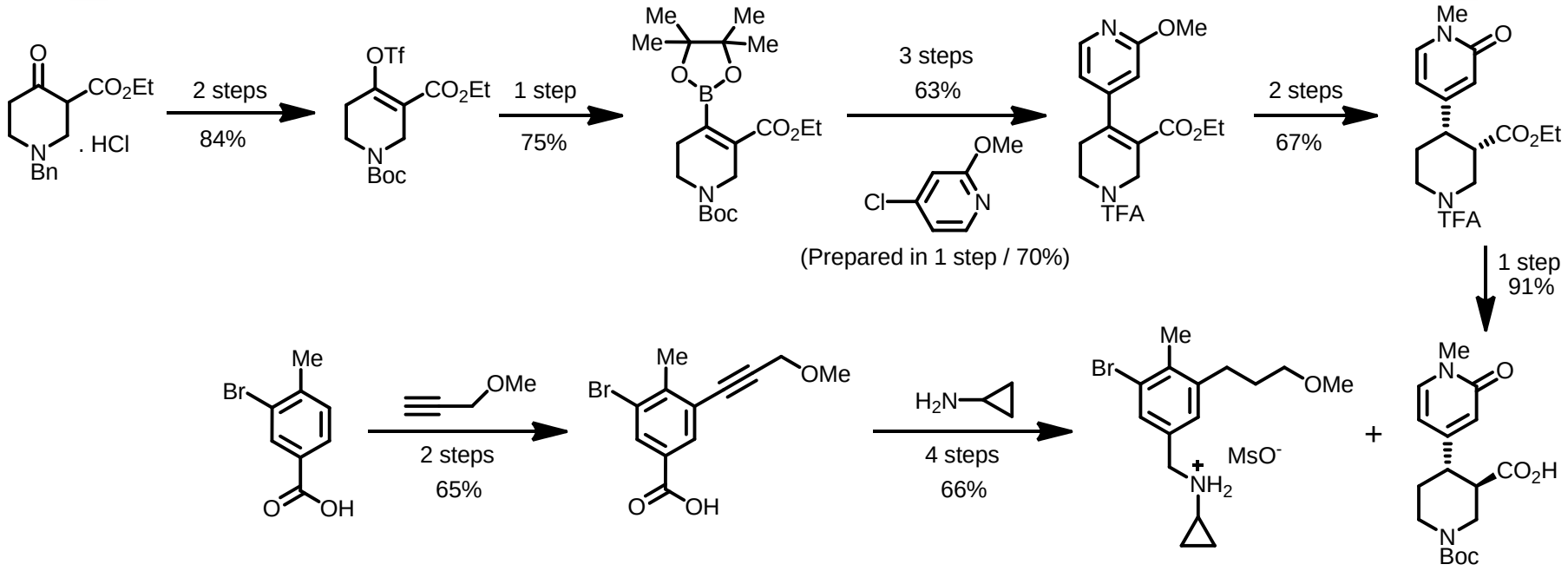
  - All intermediates are crystalline allowing for facile purification.
  - No bis-coupling observed in the Sonogashira.
  - Sonogashira product was extracted into aqueous base to reject impurities.
  - Hydrogenation substrate contained only 31 ppm Pd & 2 ppm Cu.
  - Final amine isolated as a crystalline salt.

Amide Coupling and End-Game



- Temperature of the coupling was carefully controlled in order to minimize formation of the diastereomeric amide.
  - Room temperature reaction yielded as much as 5% of *cis*-diastereomer.
  - <0.5% cis-diastereomer formed with above conditions.

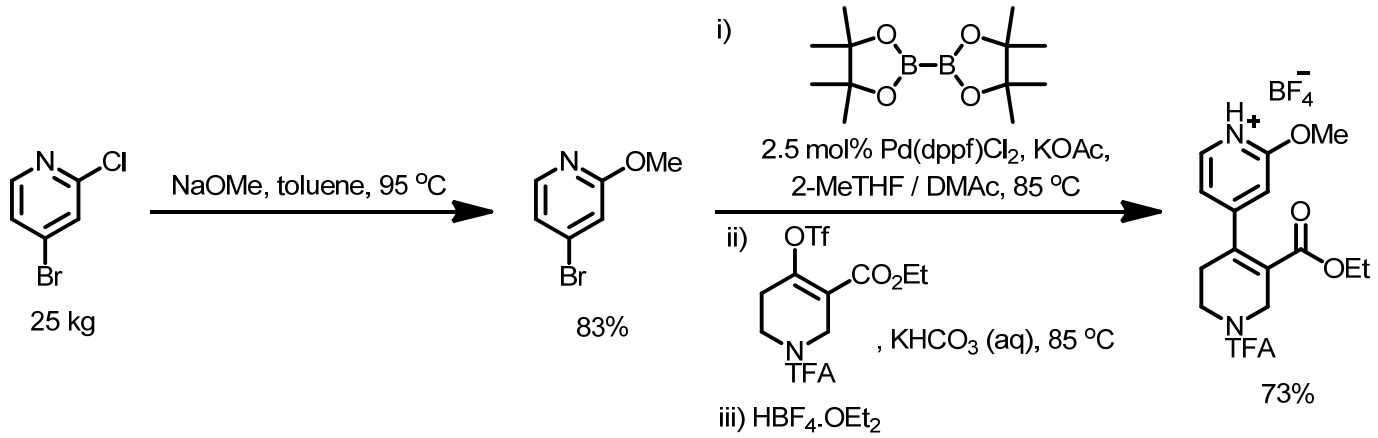
1st GMP Delivery Summary



- First GMP Delivery Summary:
  - Total of 18 steps.
  - The longest linear sequence is 11 steps (19% yield).
  - 2.6 kg of API HCl salt isolated via this process.
- Second GMP Delivery Goal:
  - Deliver 13 kg of API.

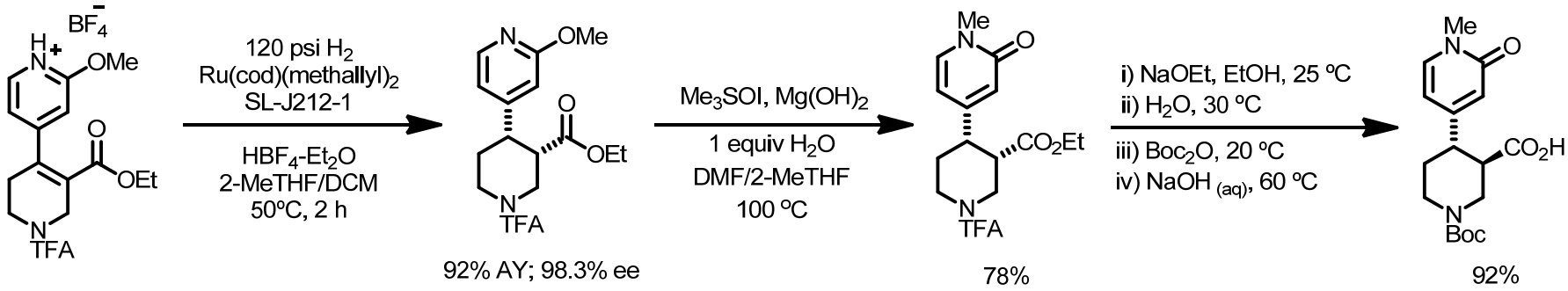
2nd Delivery: Preparation of the Acid Fragment

- Used 4-bromo-2-chloropyridine for this delivery
  - 98:2 selectivity for 2- vs. 4-methoxy with 99% conversion after 40 h.



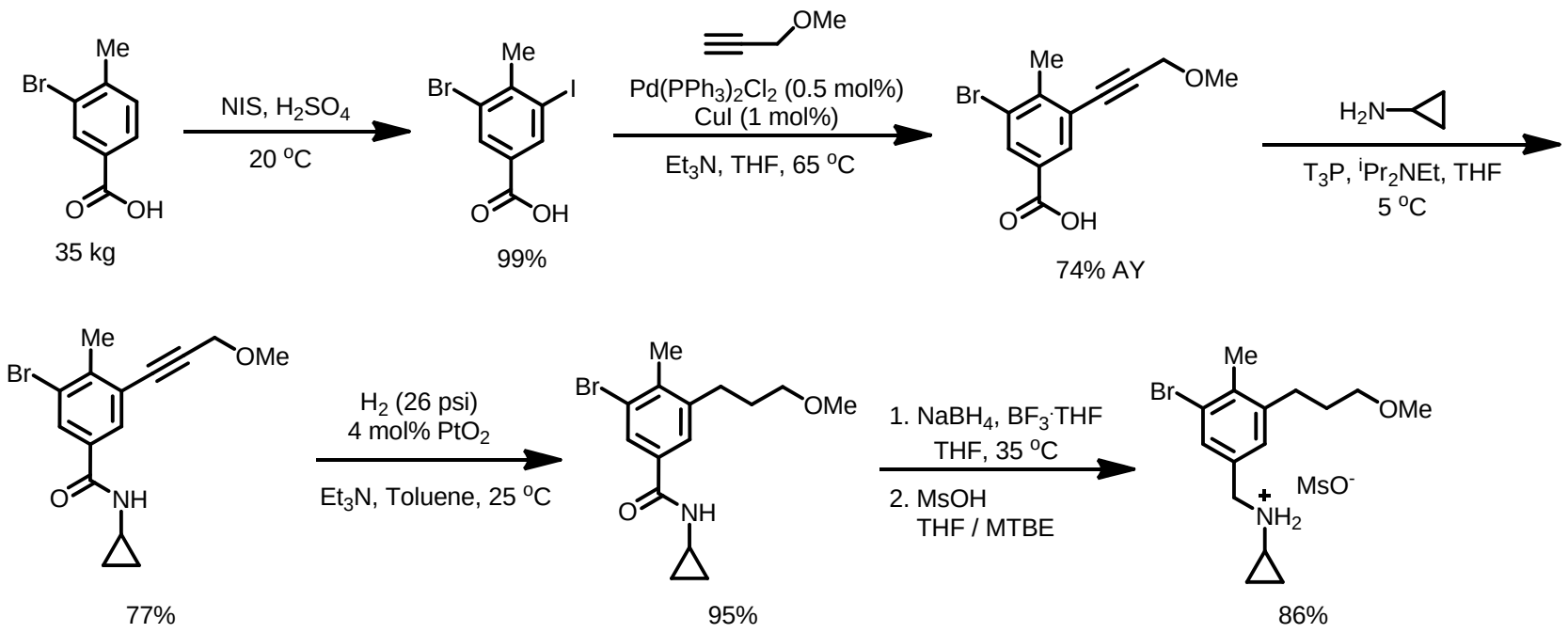
- TFA protected vinyl triflate used in the Suzuki coupling.
  - 45 kg prepared in 2 steps & 86% yield.
- Process developed for the one-pot borylation-Suzuki coupling:
  - Dioxane replaced with 2-MeTHF.
  - DMAc added to ensure reproducible conversion and rate.
  - Product isolated as a crystalline HBF_4 salt.

2nd Delivery: Preparation of the Acid Fragment



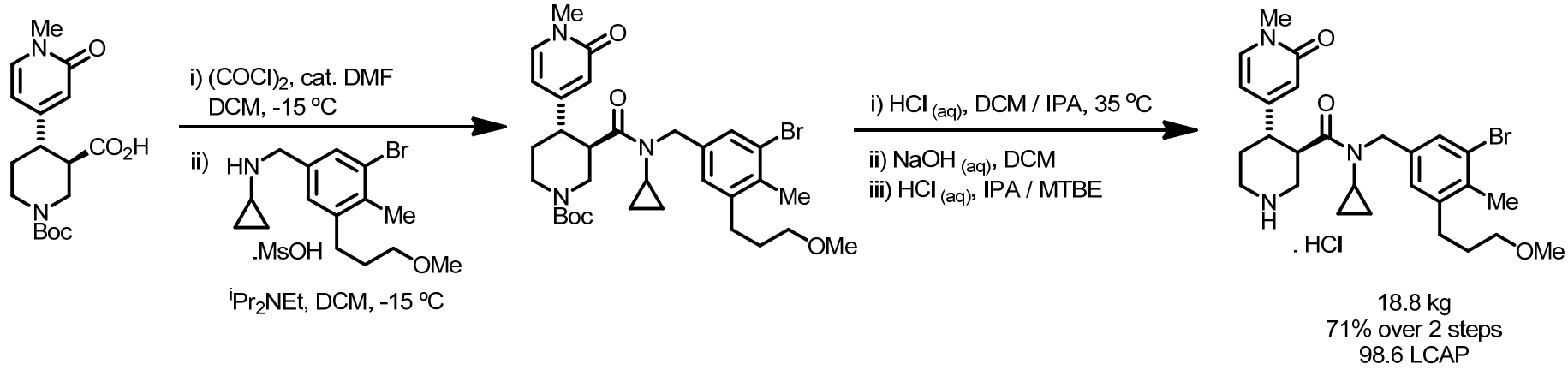
- Small amount of HBF_4 required to activate the hydrogenation catalyst.
  - Reaction complete in 2 h with 1 mol% catalyst (at lower pressure).
- Carbon treatments incorporated before and after the rearrangement.
  - Facilitated crystallization of the *N*-Me pyridone.
  - Reduced residual metal content (2 ppm Pd; 31 ppm Ru; 14 ppm Fe).
- Streamlined work-up & isolation of the *trans*-acid developed.
  - Isolated solid contained <0.1 A% of the *cis* diastereomer.

2nd Delivery: Synthesis of the Amine Fragment



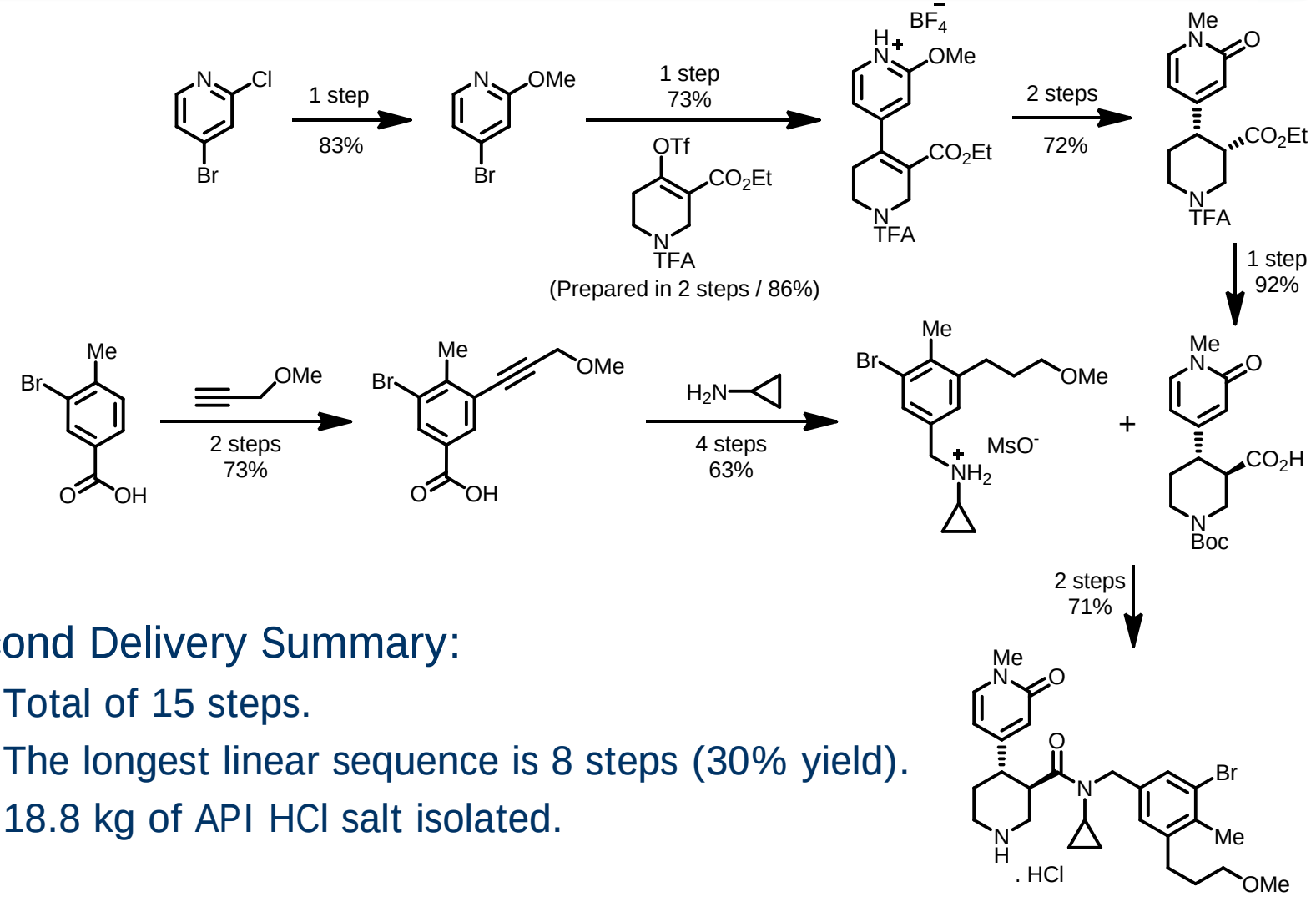
- Iodination didn't work with 5 equiv of acid in a co-solvent, or with weaker acids (AcOH or TFA).
- Carbon treatment after the Sonogashira used to remove residual Pd.
- "Saturated" amide was crystallized to ensure high purity amine MsOH salt was obtained.

2nd Delivery: End-game



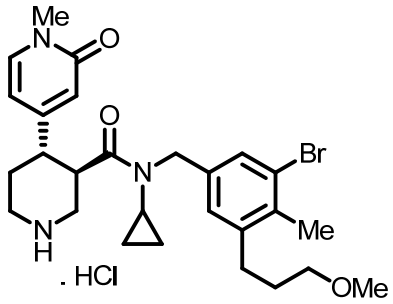
- Amide coupling run via formation of the acid chloride.
  - Couplings with CDI, EDC, or T_3P gave minimal product.
  - Slight undercharge of the amine used (0.9 equiv) – acid easier to reject.
- Simplified deprotection procedure with HCl was used.
  - DCM solution of the penultimate taken directly into the deprotection.
  - API HCl salt extracted from reaction mixture into water, then neutralised and re-extracted into DCM, to upgrade purity.
  - API HCl salt was crystallized from IPA by addition of conc. HCl.

2nd GMP Delivery Summary



- Second Delivery Summary:
  - Total of 15 steps.
  - The longest linear sequence is 8 steps (30% yield).
  - 18.8 kg of API HCl salt isolated.

Summary



- A highly convergent synthesis of a novel Renin inhibitor was developed to support kilogram deliveries of API.
- Key steps include an asymmetric hydrogenation of a tetra-substituted alkene, efficient rearrangement of a methoxypyridine to the N-Me pyridone, and the Sonogashira coupling to selectively install the methoxypropyl chain.
- This route supported a 2.6 kg delivery of API.
- Further improvements shortened the route by 3 steps, increased overall yield from 19% to 30%, and supported a 18.8 kg delivery.
- Asymmetric hydrogenation of prochiral olefins is outstandingly powerful technology for the asymmetric synthesis of pharmaceuticals