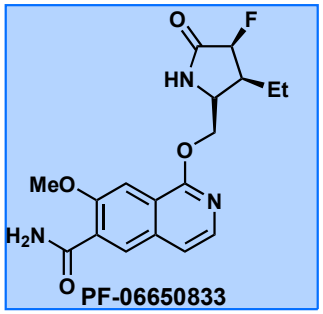
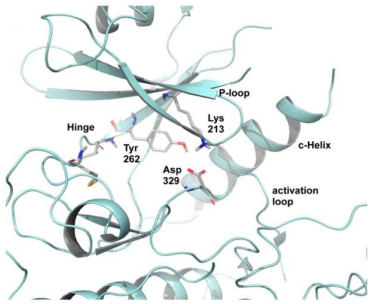
# POTW: PF-06650833




**An interleukin-1 Receptor Associated Kinase 4 (IRAK4) inhibitor currently in clinical development**

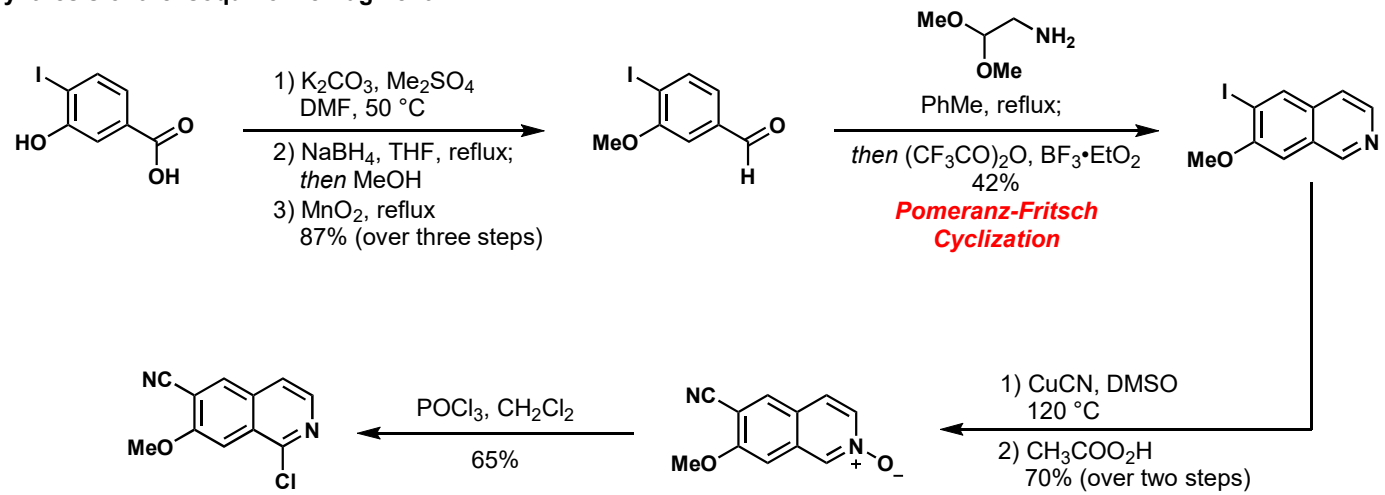



**Active site of IRAK-4 Receptor**

- Tricky to access because of Tyr262, Lys213, Asp329

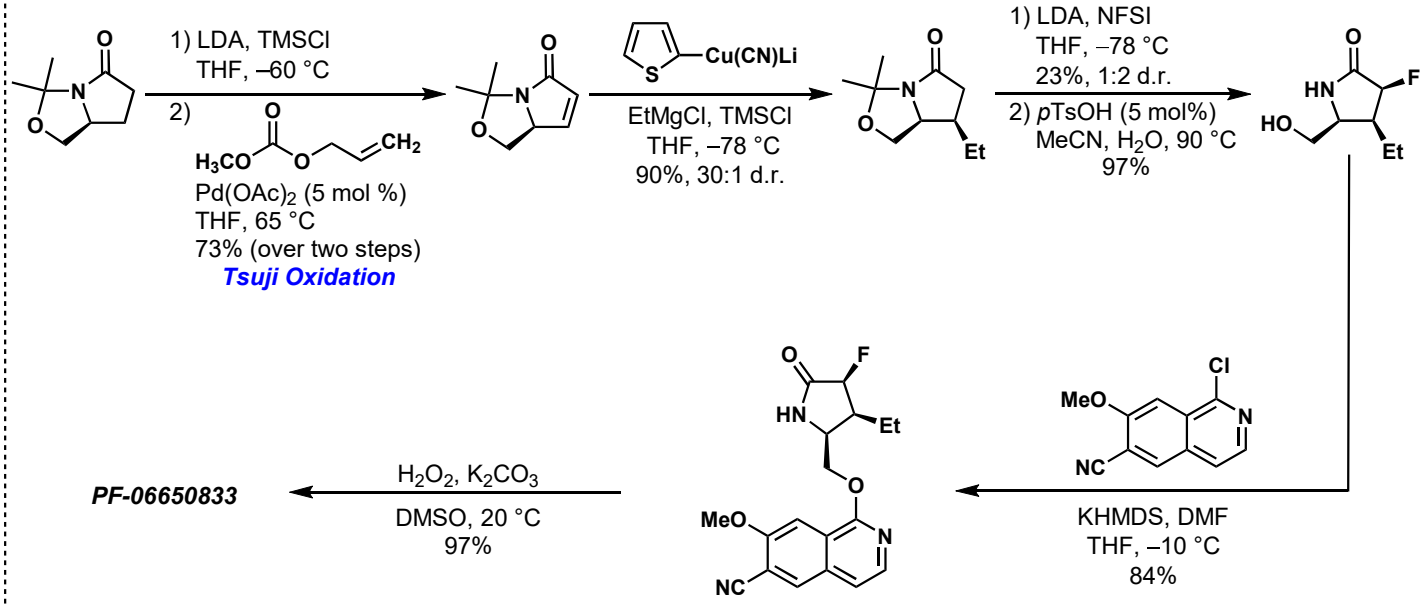
*J. Med. Chem.* **2017**, *60*, 5521-5542.

## Synthesis of the Isoquinoline fragment




WO 2015/150995 Al

## Discovery Route

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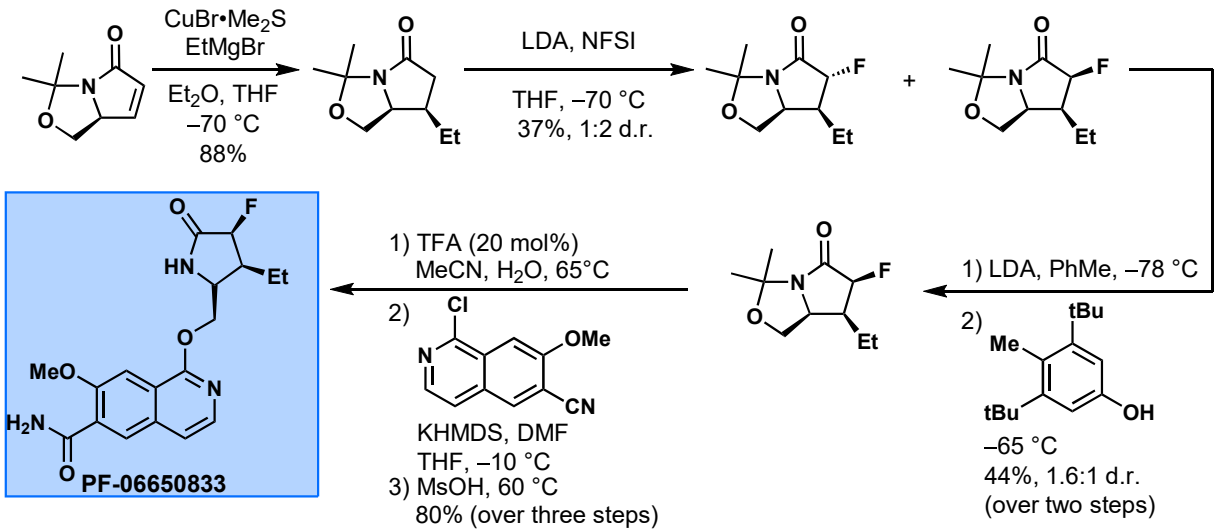
# *POTW: PF-06650833*

**First Generation Route**



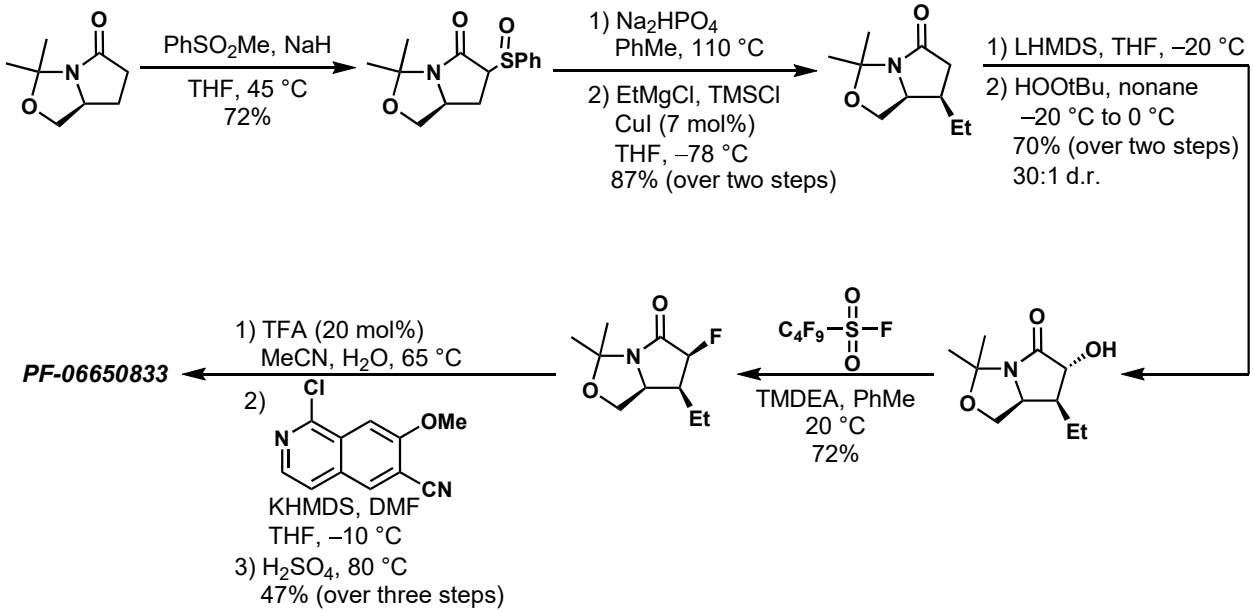

**Improvements from Discovery Route**

- Change of cuprate reagent enables reduction of waste
- Kinetic deprotonation following fluorination increases d.r.
  - -Benefit: Use of sterically hindered acid is key
  - -Cost: one more step
- Deprotection with TFA skips chromatography
- Mesic acid is more mild
  - -$H_2O_2$ can exothermically decompose into $H_2O$ and $O_2$
  - -$H_2O_2$-DMSO solution is a problem on large scales

**Issues for Synthesis Greater than 30 kg**

- Tsuji oxidation generates *i*$Pr_2NH$, LiCl
- Organocuprate addition
- Challenging flurorination
- Removal of chromatographic steps

**Second Generation Route**




**Improvements from First Gen Route**

- Sulfoxide intermediate can be crystalized
- Cuprate addition is now catalytic
  - Transformation is now cheaper, more efficient
- Desired fluoro-stereoisomer obtained directly
  - Increases step count, but increases overall yield

*ORPD*. **2018**, *22*, 1835-1845.

*Matthew Bock, January 11, 2019*