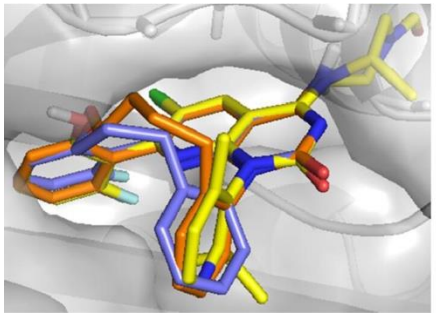
MK-1084

Background:

- Recent development in small-molecule inhibition of *KRAS* mutations
- RAS family of genes play an important role in cell growth and proliferation
- Mutations in RAS proteins account for ~ 30% of tumors; *KRAS* account for 85% of these mutations
- Focus has been on developing small molecules and macrocyclic peptides to target a variety of binding pockets
- Utilized modeling to predict the optimal macrocyclic linker length



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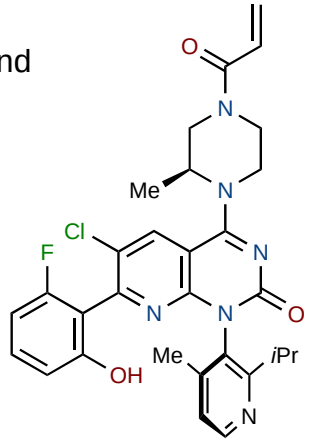
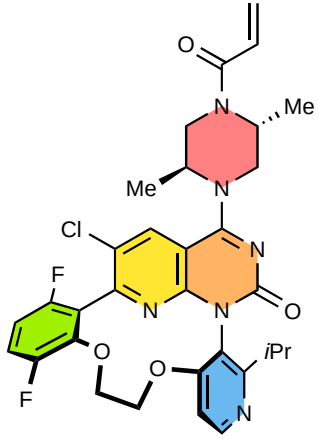
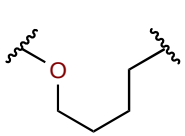


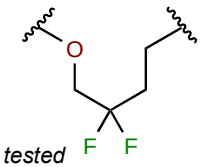
previous KRAS inhibitor
(AMG-10)

1. Predicted macrocycle would reinforce active conformation
2. Docking revealed 4 or 5 atom linker length would potentially be optimal
3. Removing phenol could decrease metabolic lability and H-bonding interaction that lowered potency



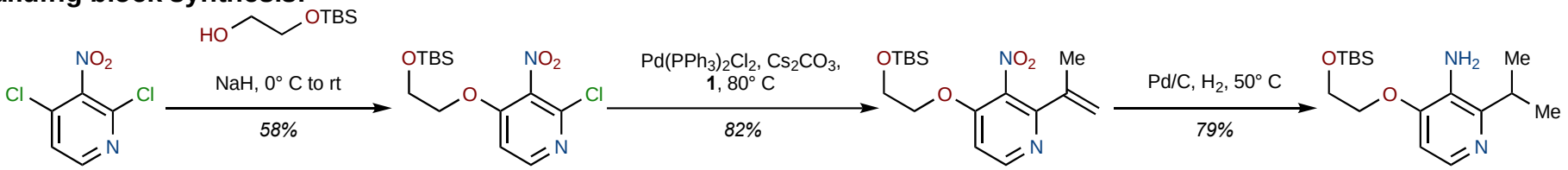
MK-1084

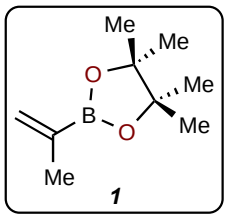


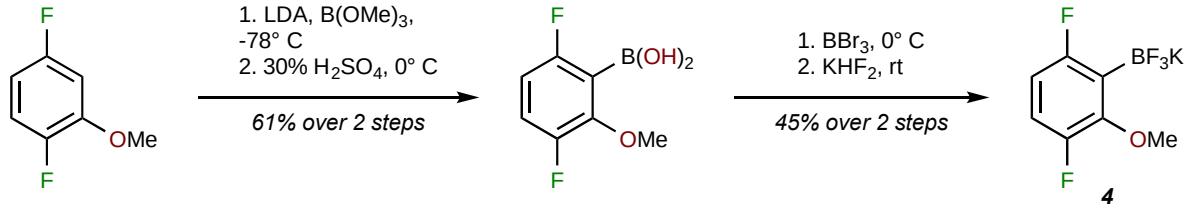


other linkers tested

Building block synthesis:



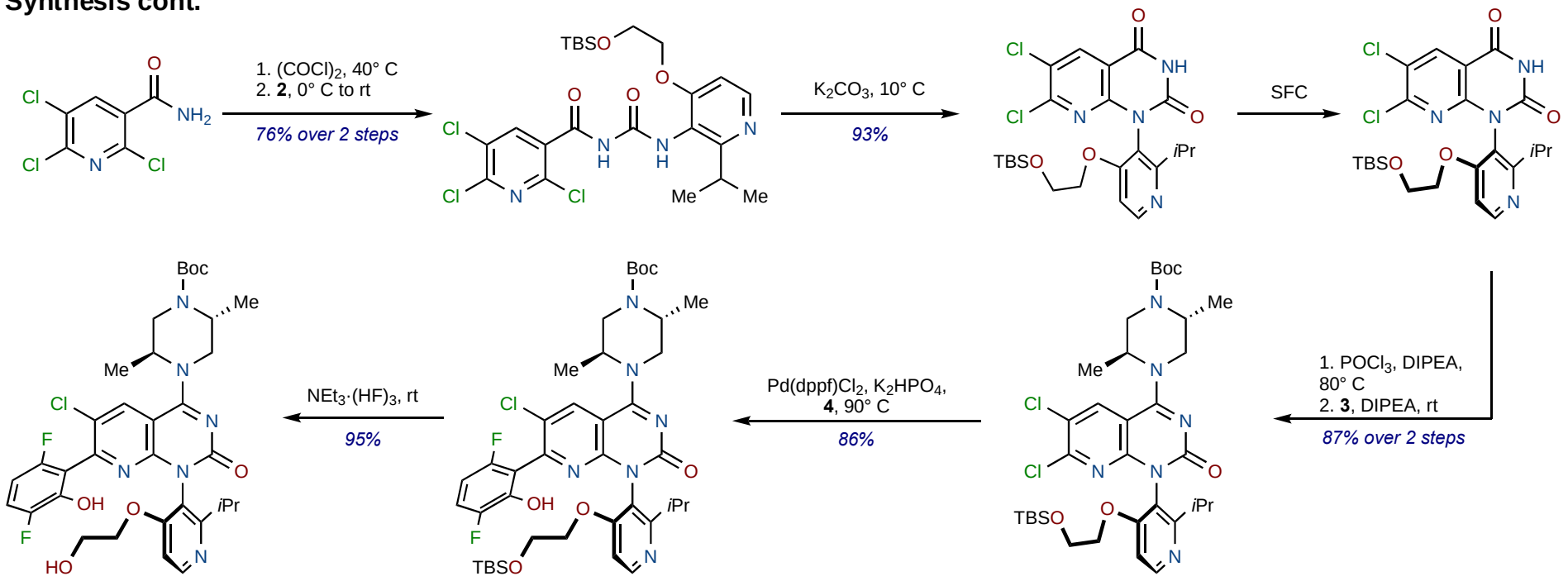


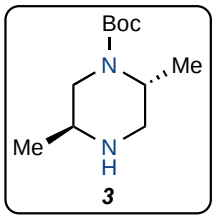


J. Med. Chem. **2024**, 67, 11024−11052

MK-1084

Synthesis cont.





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