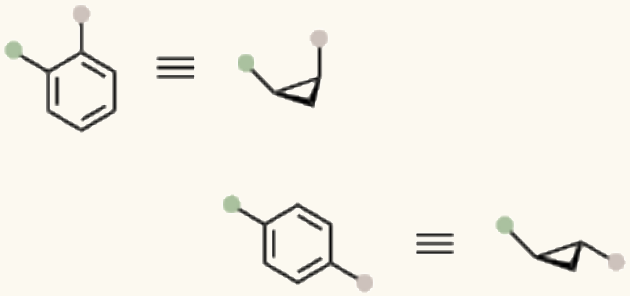
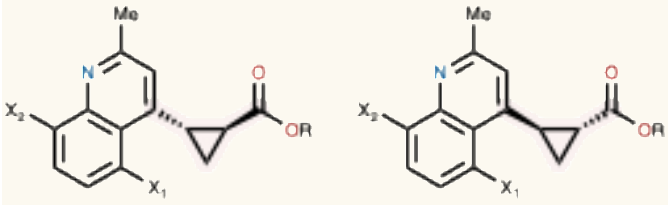
Building *trans*-Cyclopropyl Esters

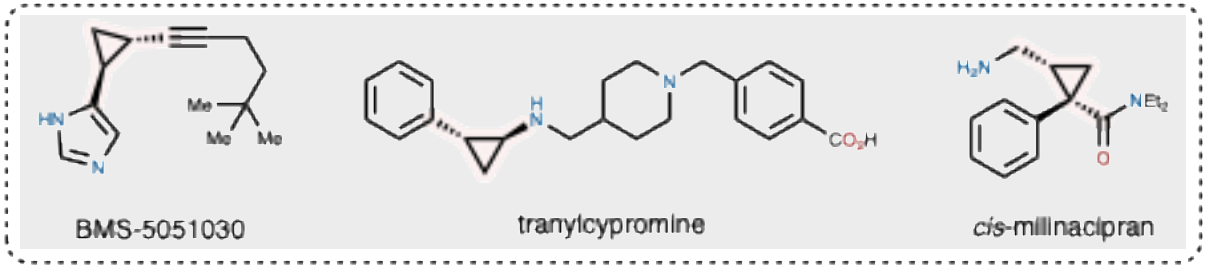
Di- and Tri-substituted Cyclopropanes in Small Molecule Drugs

- 10th most common ring in small molecule drugs
- Provides structural rigidity while decreasing metabolic stabilities
- Known to enhance pharmacokinetics in protein ligands
- Alternative to arene linkers when other arenes are too large, flexible, unstable

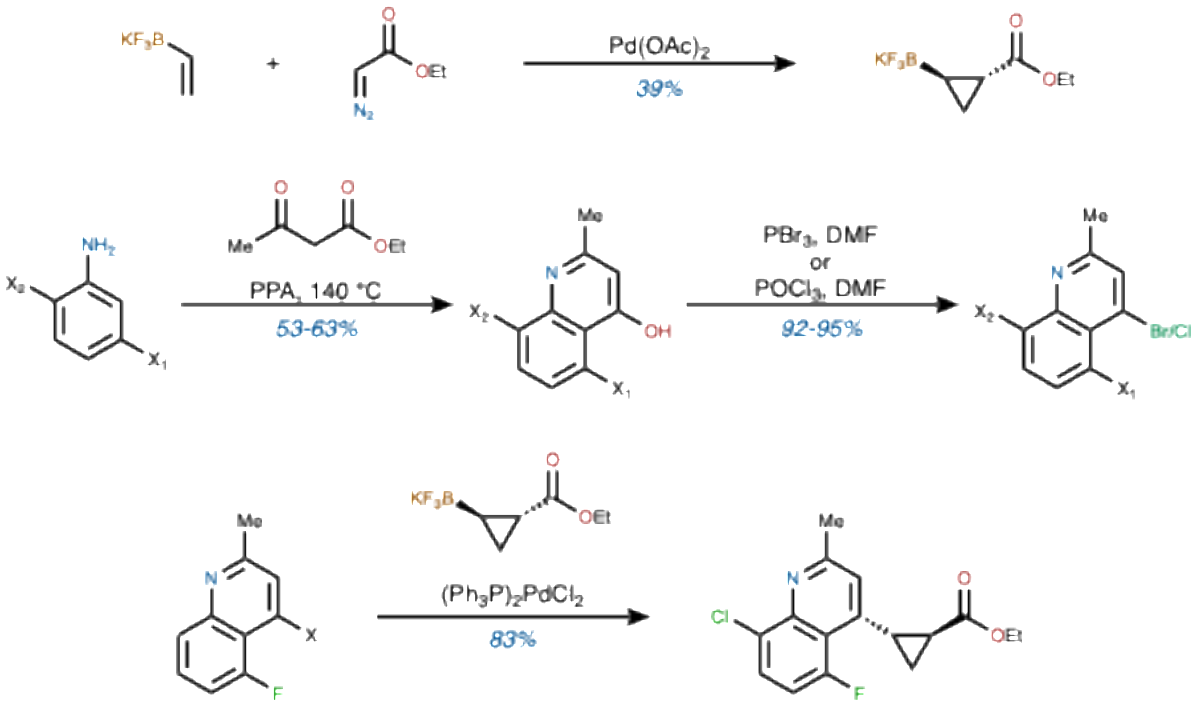


Motifs of interest:





Initial Medicinal Chemistry Strategy:



Chiral SFC used to access enantiopure cyclopropanes

Org. Process Res. Dev. 2025, XXXX, XXX, XXX-XXX, https://doi.org/10.1021/acs.oprd.5c00007.

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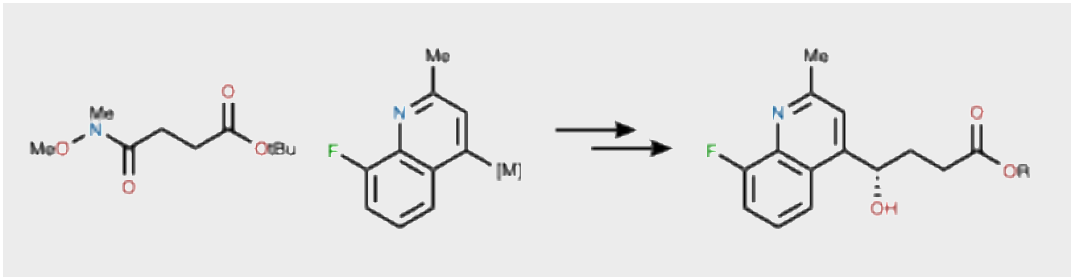
Alternative Failed Strategies

Keto-ester chiral reduction-cyclization



Strategy pitfalls:

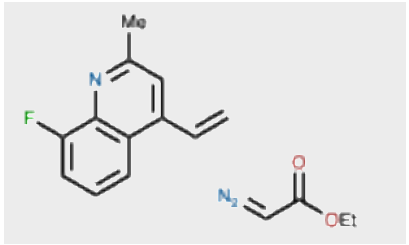
Inconclusive results

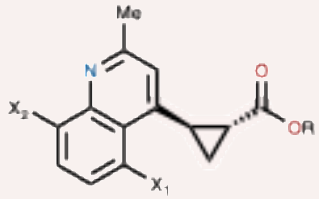
Complex mixtures

No products observed

Cost prohibitive

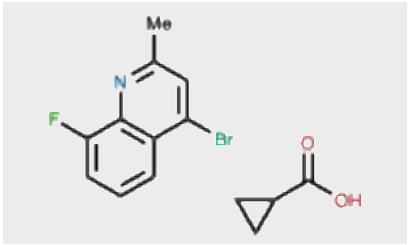
Asymmetric cyclopropanation



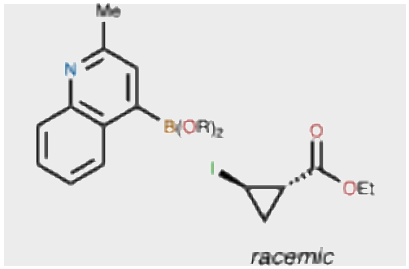


Target Motif

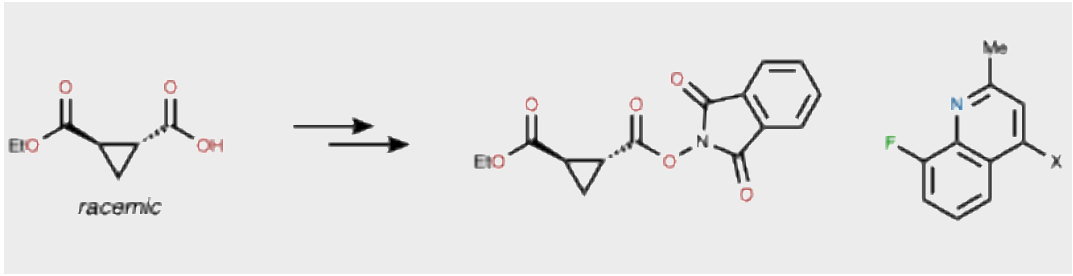
Yu C-H activated cis-coupling/epimerization



Reversed palladium catalyzed Suzuki-Miyaura



Decarboxylative 1,4-Minisci or photoredox coupling



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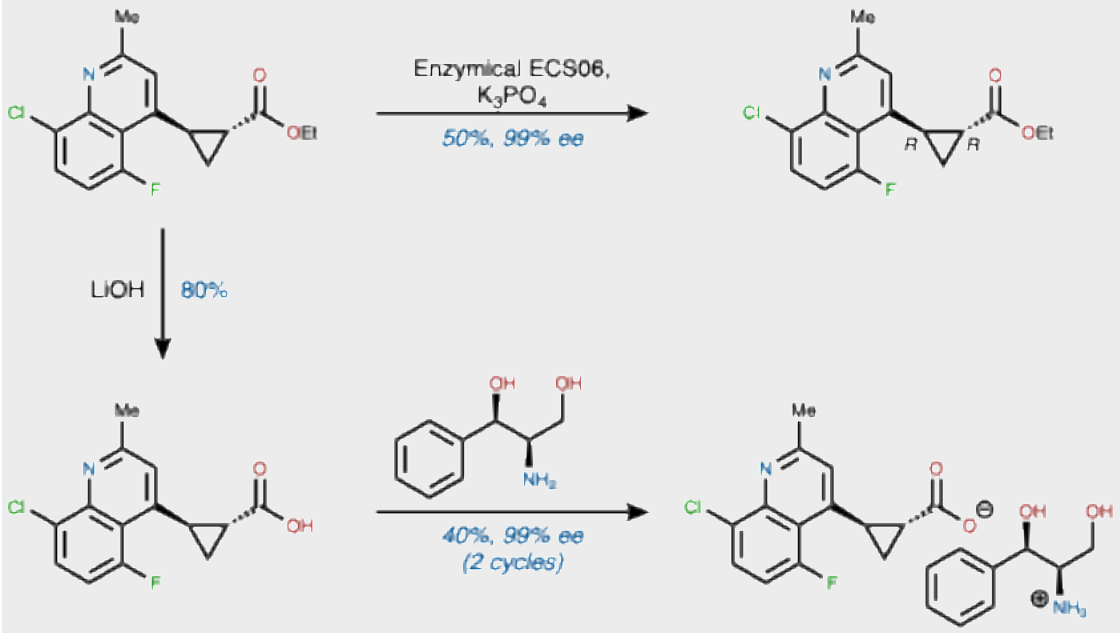
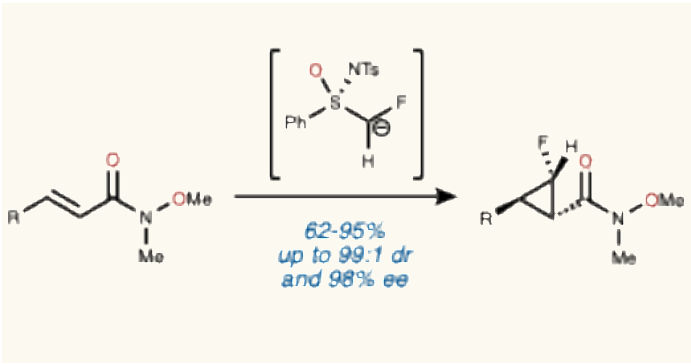
Resolution Strategies



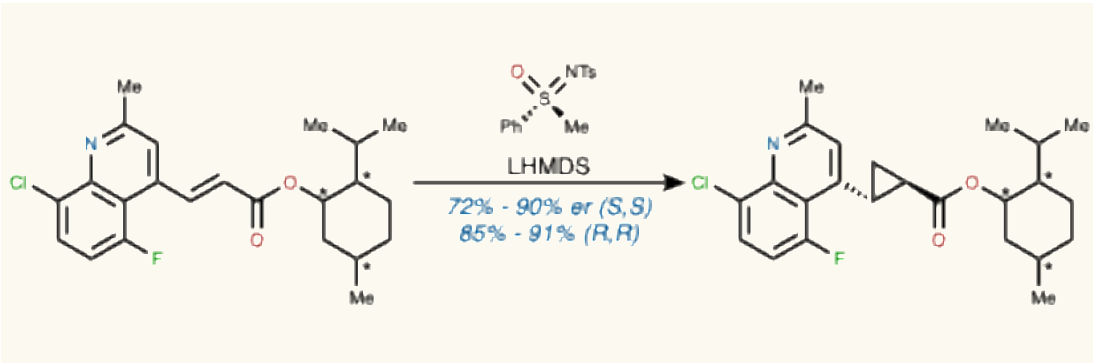
Two hits found in HTE for enzymatic resolution; however, poor aqueous solubility of substrate and limited DMSO cosolvent tolerability caused highly dilute conditions

Only the indicated diol with ethyl acetate resulted in crystal formation and allowed enrichment after two recrystallizations

Key Precedent



Chiral Sulfoximine and Menthyl Ester Auxiliary



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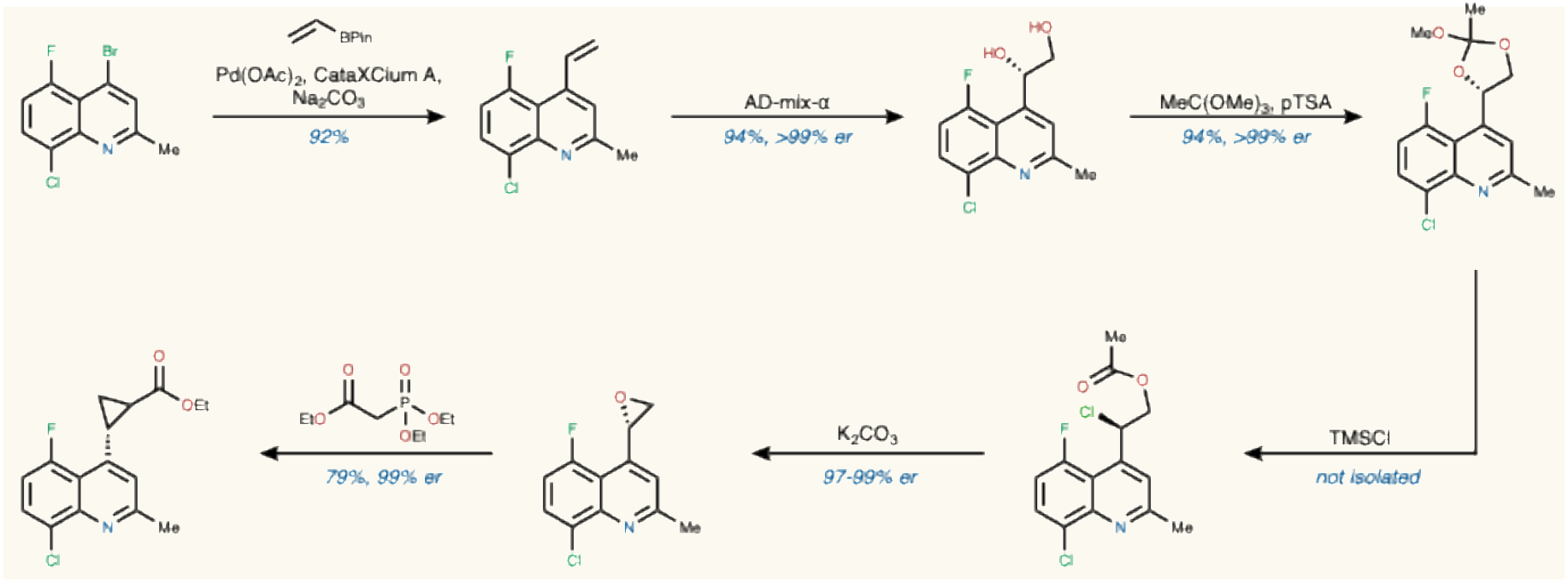
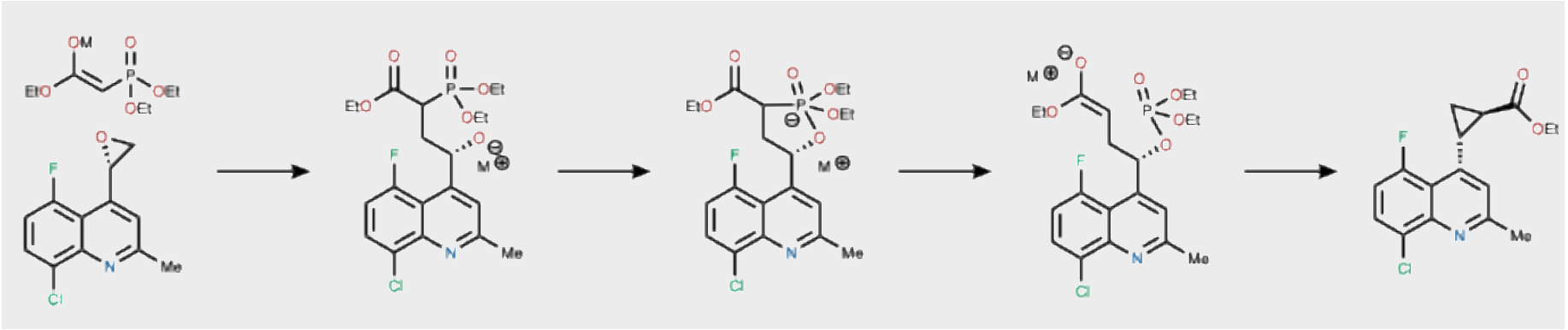
Third Generation Route – Earlier Installation of Chiral Purity



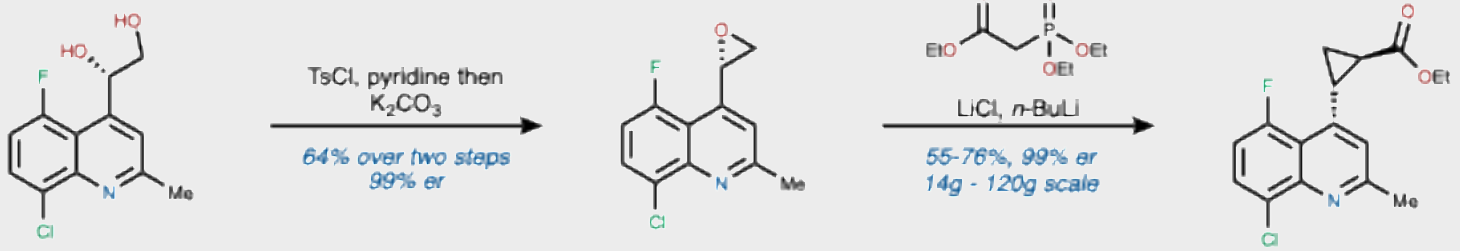
Cyclopropanation Proposed Mechanism



Org. Process Res. Dev. 2025, XXXX, XXX, XXX-XXX, https://doi.org/10.1021/acs.oprd.5c00007.

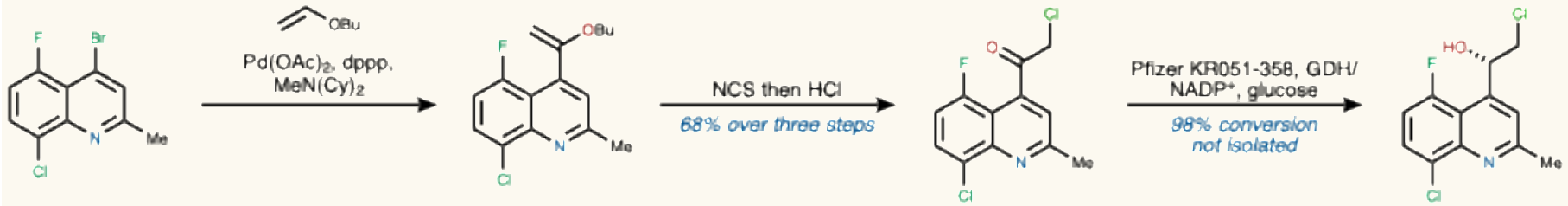
Building *trans*-Cyclopropyl Esters

Improved Route to From Diol to Cyclopropane



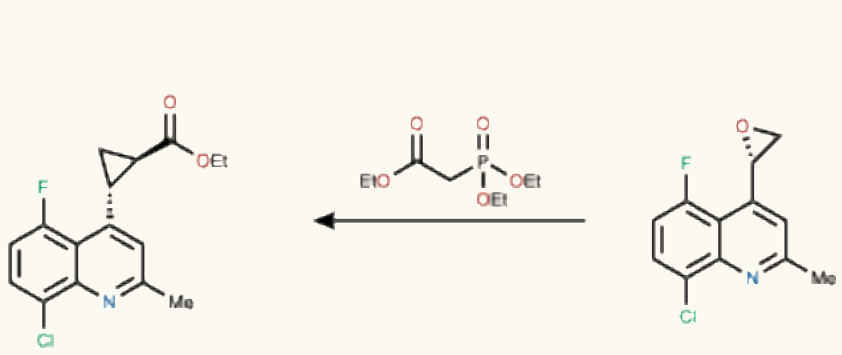
Under previous conditions minor drops in enantipurity due to lability of benzylic chloride

Improved Route to Chiral Epoxide



Mizoroki-Heck → Sharpless dihydroxylation → and epoxidation could be scaled to over 100 g

Replacing Sharpless dihydroxylation avoided use of toxic osmium reagents and allowed for greener biocatalysis



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