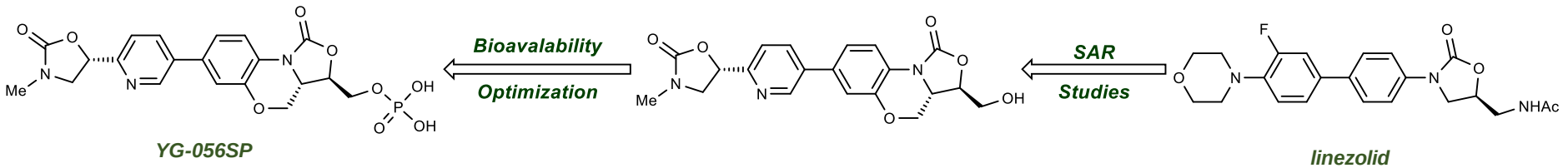
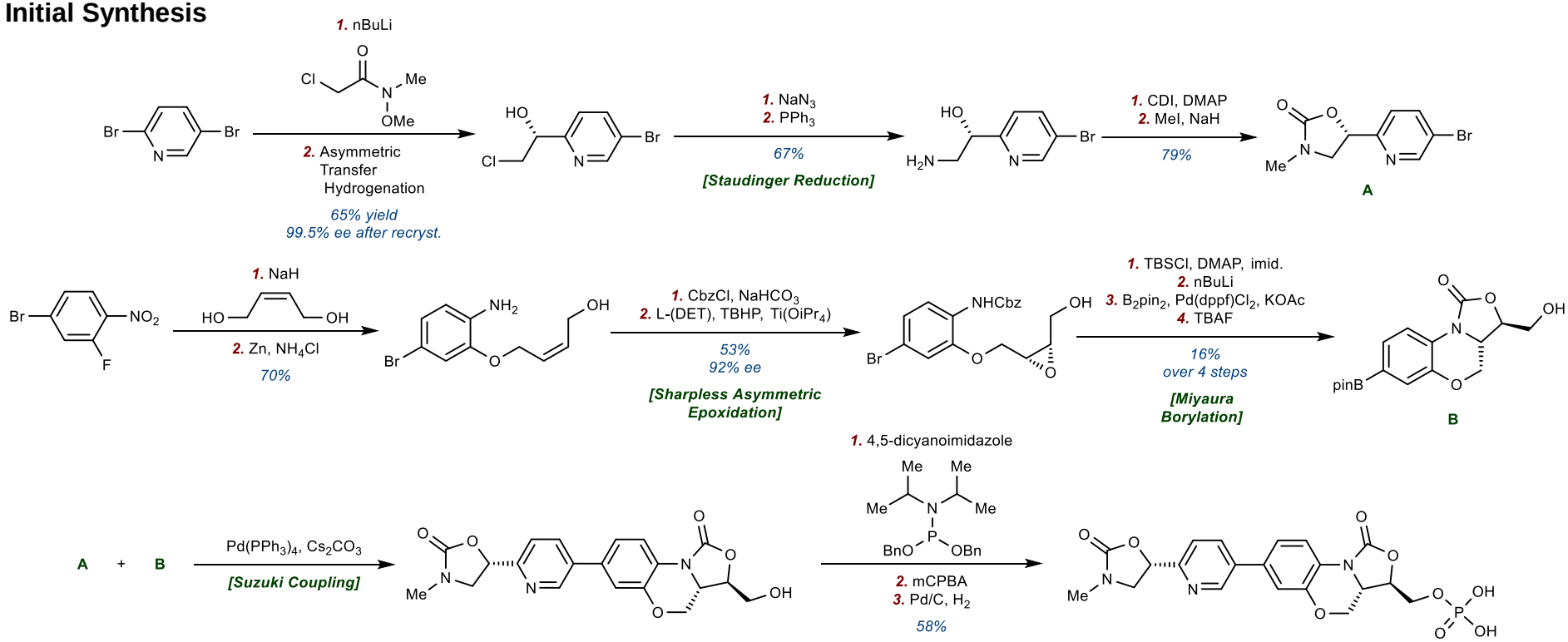
Kilogram Scale Synthesis of YG-056SP

Background



- YG-056SP is a potent gram positive antibiotic currently being investigated for efficacy in clinical trials in China
- Phosphate group identified as a key for bioavailability
- Identified as a lead compound after extensive SAR studies with linezolid

Initial Synthesis



- Steppy synthesis of two aromatic building blocks
- Inefficient Miyaura borylation/Suzuki coupling sequence
- nBuLi as base for carbamate formation (towards B) led to large amounts of dehalogenation
- Weinreb amide requires in-house synthesis

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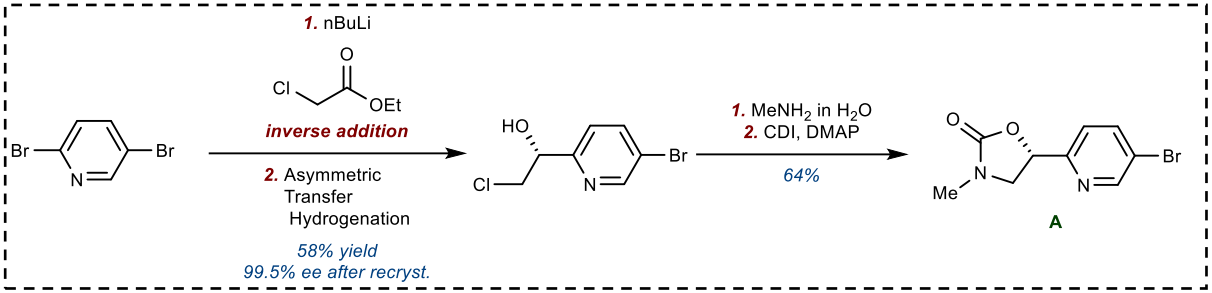
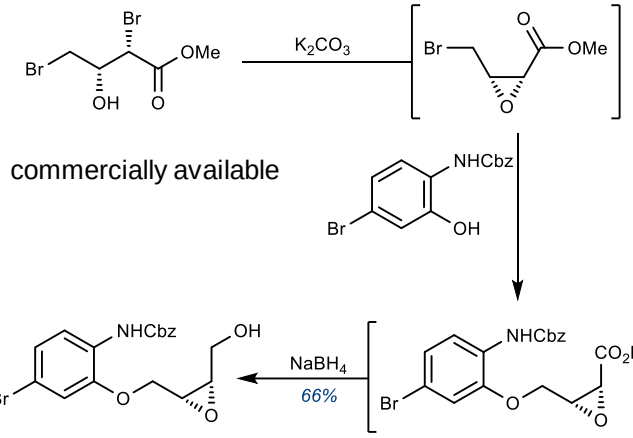
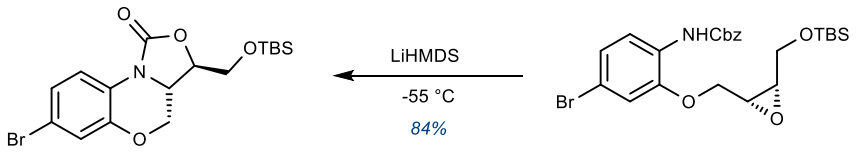
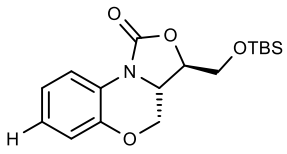






Entry	Temp. (° C)	Base	Eq.	Ratio (R-Br to R-H)	Yield
1	-78 to 20	nBuLi	1.5	11:5	N.D.
2	-55 to 20	nBuLi	1.5	11:5	N.D.
3	-55 to 20	nBuLi	1.2	75:12	N.D.
4	-55 to 20	nBuLi	1.0	82:7	76%
5	-55 to 20	LDA	1.0	81:0.4	77%
6	-55 to 20	LiHMDS	1.0	87:0.6	84%



major side product

Process Improvements:

- Efficient building block synthesis
  - Direct installation of methylamine
  - Chiral pool strategy for epoxide formation
- Use of LiHMDS instead of nBuLi to prevent dehalogenation
- Improved one-pot borylation and coupling sequence
- Late stage phosphate deprotection avoids Pd impurities
- 270 kg made in a single pass