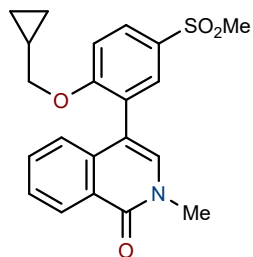


Background



BMS-986378
(CC-90010)

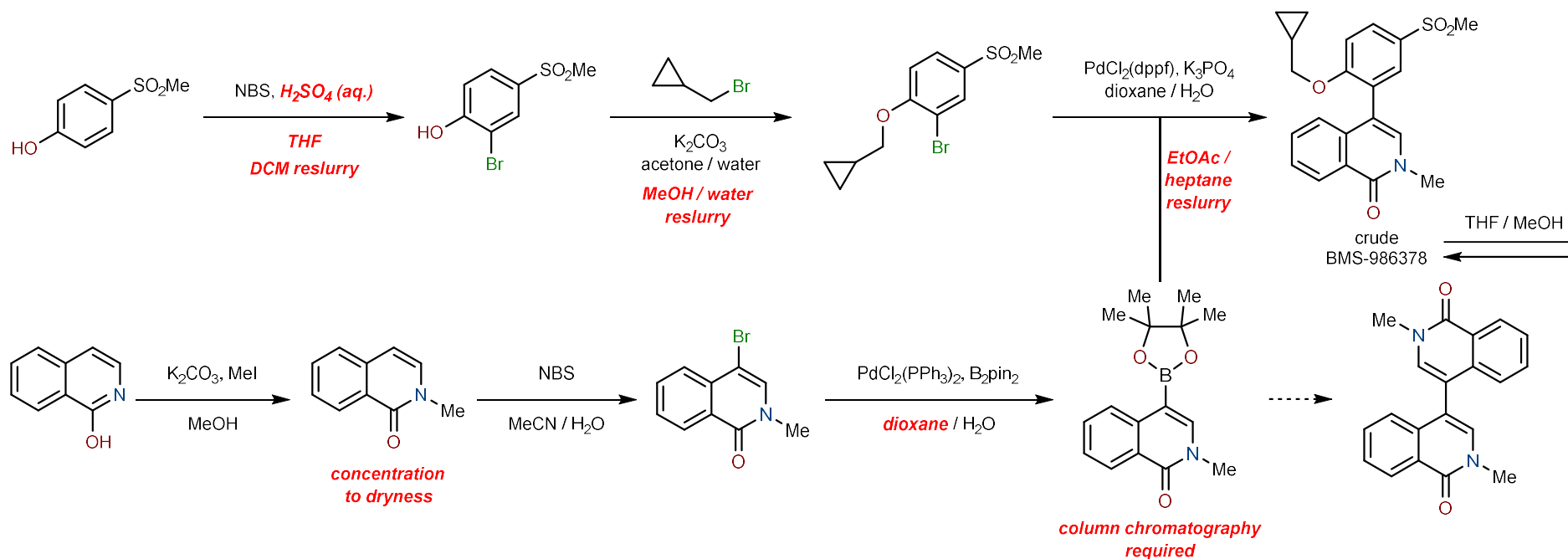
- Bromodomain and extra-terminal (BET) inhibitor
- In clinical trials for patients with solid tumors and relapsed/refractory non-Hodgkin's lymphoma



Problem Areas in Discovery Synthesis

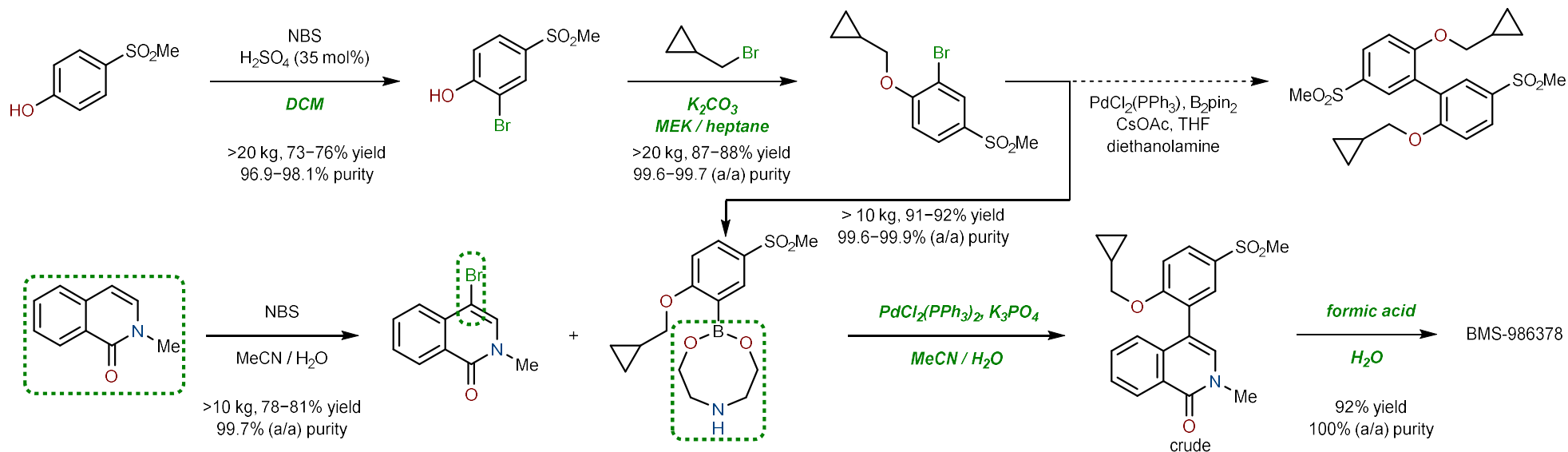
- Process safety concerns around NBS reactions
- Difficult-to-scale unit operations, such as column chromatography, hot filtrations, and distillation to dryness operations
- The use of problematic solvents, e.g., dioxane
- Pd control in the final two steps
- Poor purging of dimer impurity
- Poor stability of boronate

Discovery Synthesis (33% yield in total)

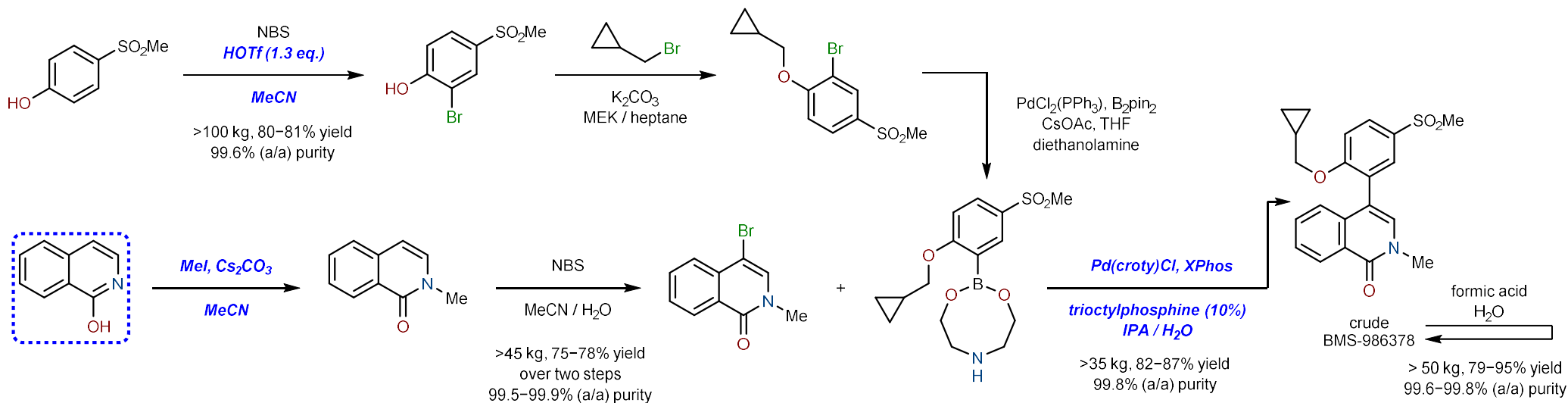


Primer, D. N.; Yong, K.; Ramirez, A.; Kreilein, M.; Ferretti, A. C.; Ruda, A. M.; Fleary-Roberts, N.; Moseley, J. D.; Forsyth, S. M.; Evans, G. R.; Traverse, J. F., *Org. Process Res. Dev.* **2022**, 26 (5), 1458 <https://doi.org/10.1021/acs.oprd.2c00057>

Process Synthesis A (>45% yield in total)



Process Synthesis B (>49% yield in total)



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Org. Process Res. Dev. **2022**, 26 (5), 1458 <https://doi.org/10.1021/acs.oprd.2c00057>

Routes Comparison

Discovery Route	Process Route A	Process Route B
NBS-H ₂ SO ₄ -THF & DCM Reslurry	NBS-H ₂ SO ₄ -DCM & Recrystallization	NBS-HOTf-MeCN & Simpler Recrystallization
	Continued use of DCM & Solid charges of NBS	
Acetone Distillation & MeOH / H ₂ O Reslurry	MEK-Heptane & Recrystallization	
Concentration to Dryness for Methylation	Use of Commercial Methylated S.M.	One Step back up & Two Steps in One Pot
	Inconsistent Quality	
Dioxane for Borylation & Unstable Boronate & Unpurgeable Impurity	THF for Borylation & Switch of Coupling Partner & Use of Diethanolamine	Reoptimized Reaction Condition
	Difficulty at Scale	
Pd Control: Hot Filtration in THF /H ₂ O	Pd Control: Spontaneous Precipitation of Pd(0) in HCO ₂ H & H ₂ O	Acid / H ₂ O Ratio Adjustment
	Kinetic Solvated Product	