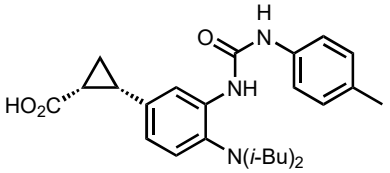
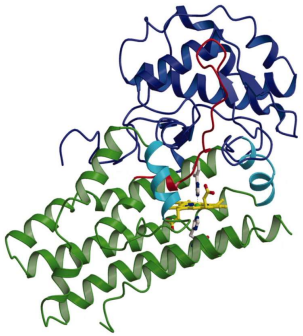
Process of the Week: BMS-978587



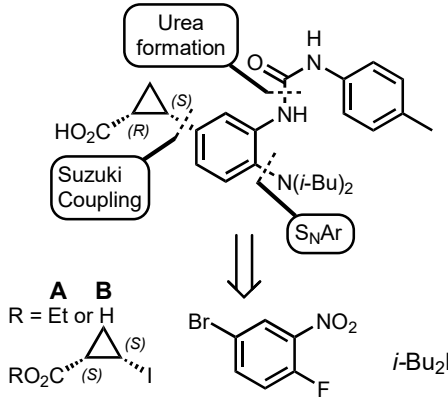
BMS-978587

Bristol-Myers Squibb



Structure of IDO with an inhibitor molecule.
Adapted from PNAS **2006**, 103 (8), 2611.

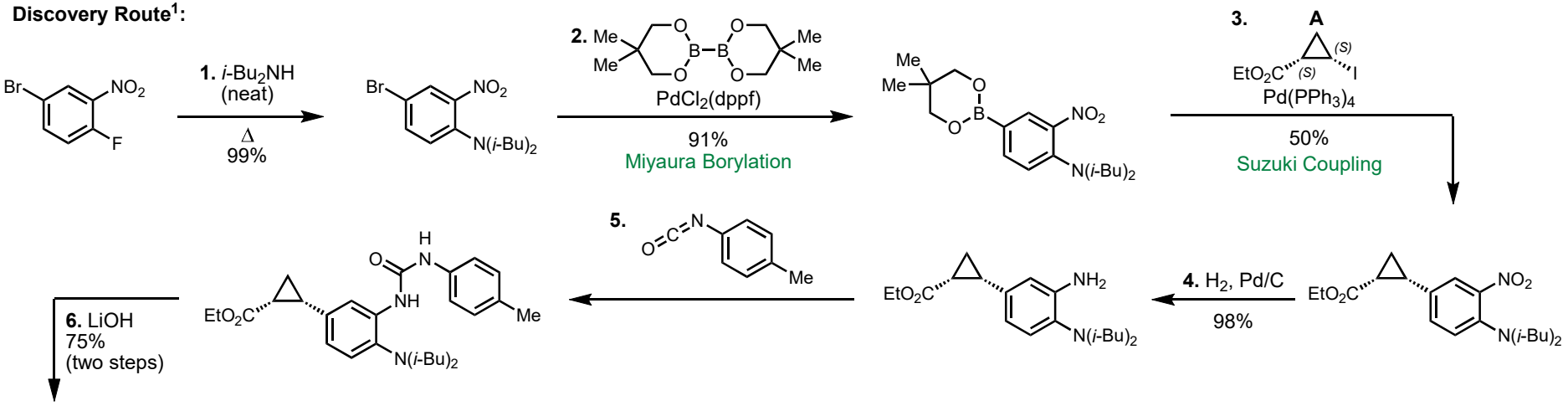
Key Retrosynthetic Disconnections:



Background[1,2]:

-BMS-978587 is a potent inhibitor of Indoleamine-2,3-dioxygenase (IDO).
-IDO is an ancient (~600 million years old) antimicrobial/immunomodulatory enzyme.
-IDO depletes tryptophan in a cell microenvironment, suppressing T-cell proliferation.

Discovery Route[1]:



BMS-978587

Overall yield: 33% over 6 steps

Limitations:

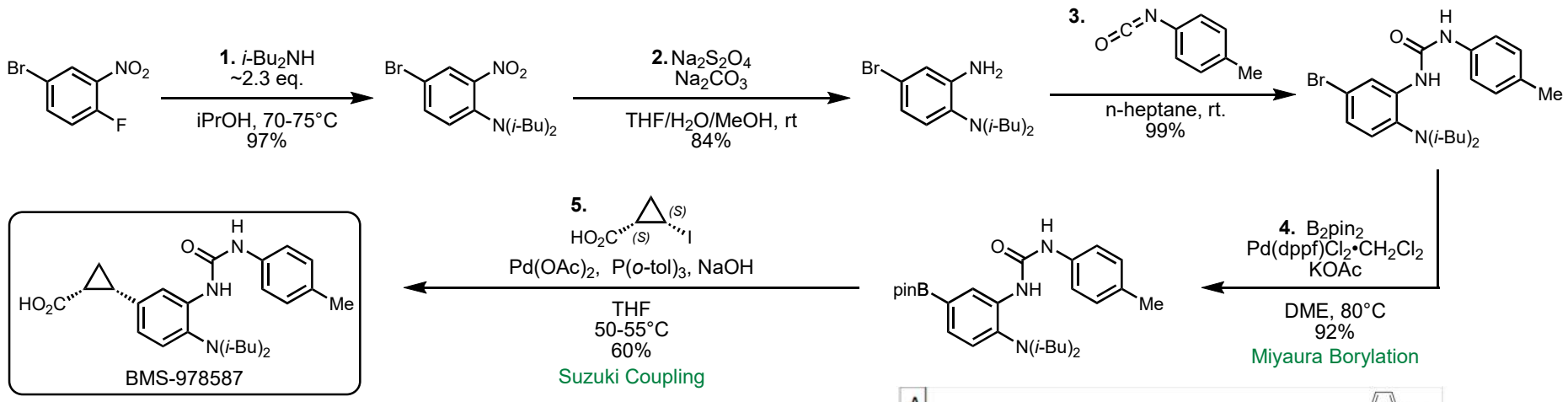
-Requires handling of potentially genotoxic nitro compounds from steps 1-4
-Enantiopure cyclopropane **A** is expensive (~$1500/g)
-Compounds 3, 4, and 5 are oils requiring chromatographic purification
-Pd/C reduction in the presence of cyclopropane gives unwanted reductive opening of ring

1.*Org. Process Res. Dev.* **2018**, *22*, 888 2. *Immunology Today* **1999**, *20*, 469.

Continued...

Process of the Week: BMS-978587

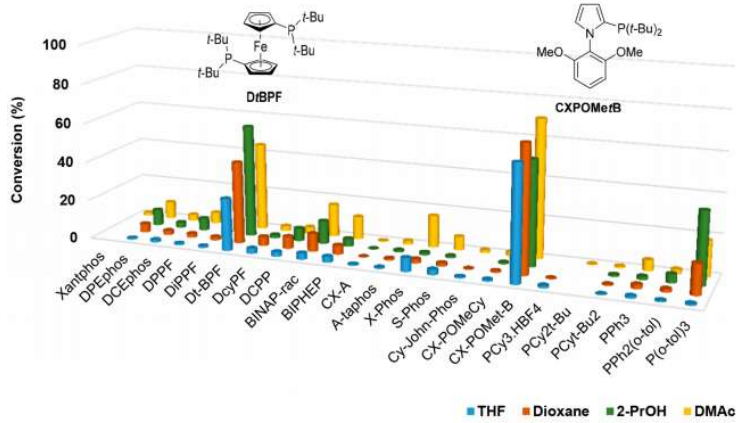
Second Generation Route[1]:



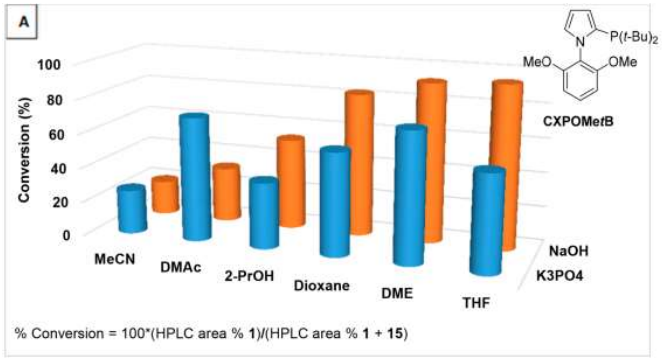
Overall yield: 42% over 5 steps

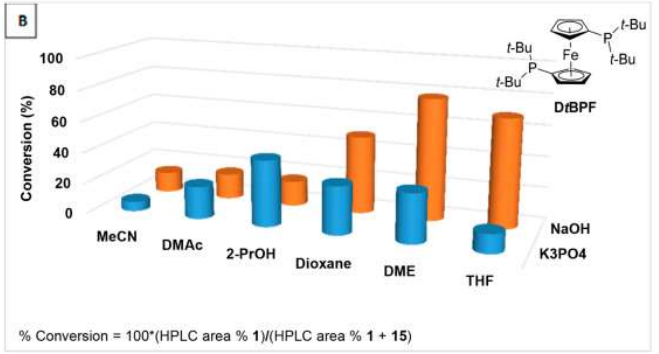
Noted improvements:

- Early reduction **2** now necessitates only two nitro compounds throughout the route
- Enantiopure solid B is commercial precursor to oil A, and significantly less expensive (~$925/g)
- Products of **3** through **5** can be crystallized using n-heptane
- B_2pin_2 is less expensive and gives comparable yield to $B_2(neop)_2$



Solvent optimization table for stereospecific Suzuki Coupling **5**





Base optimization table for **5**

Org. Process Res. Dev. **2018**, *22*, 888