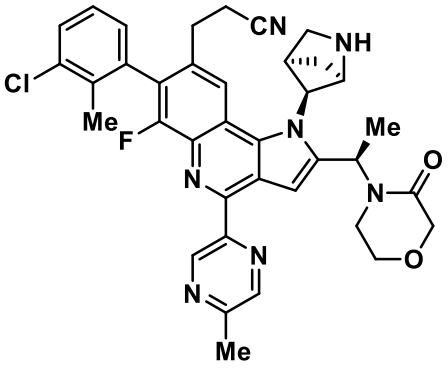
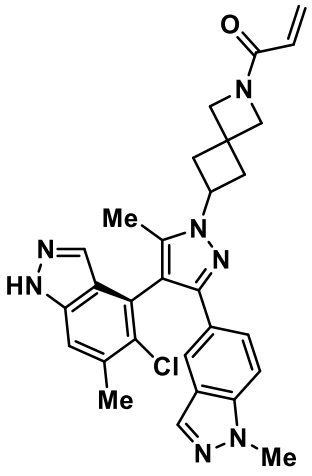
Retrosynthesis of KRAS inhibitors 20.02.2025

Art Vandelay
https://seinfeld.fandom.com/wiki/George_Costanza

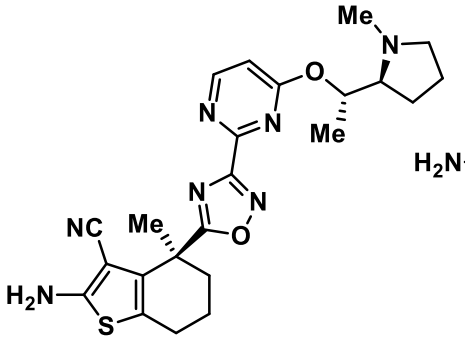
Prompt: You are being interviewed by *Art Vandelay* the CEO of *Vandelay Industries*, a prestigious (but not real) pharmaceutical company. *Vandelay Industries* has an interest in **KRAS inhibitors** and wants you and your team to provide feasible retrosynthesis pathways for target molecules below.



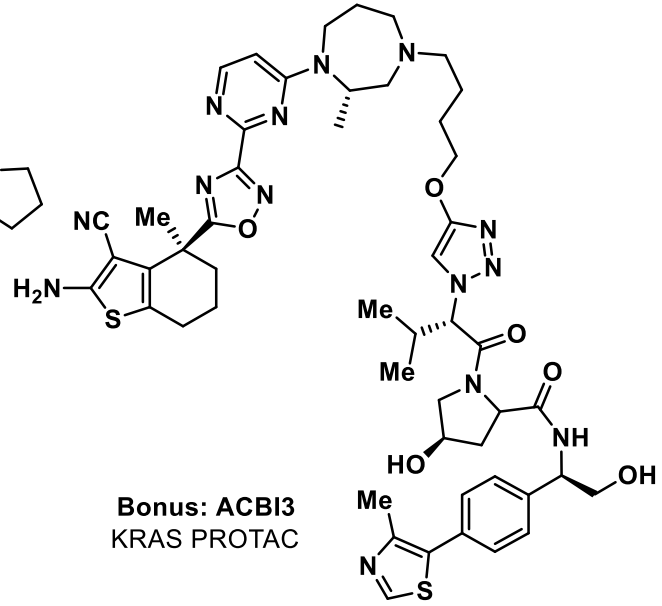
INCB159020
KRAS G12D Inhibitor



JQD443
Covalent KRAS G12C Inhibitor



BI-2865
Pan KRASi

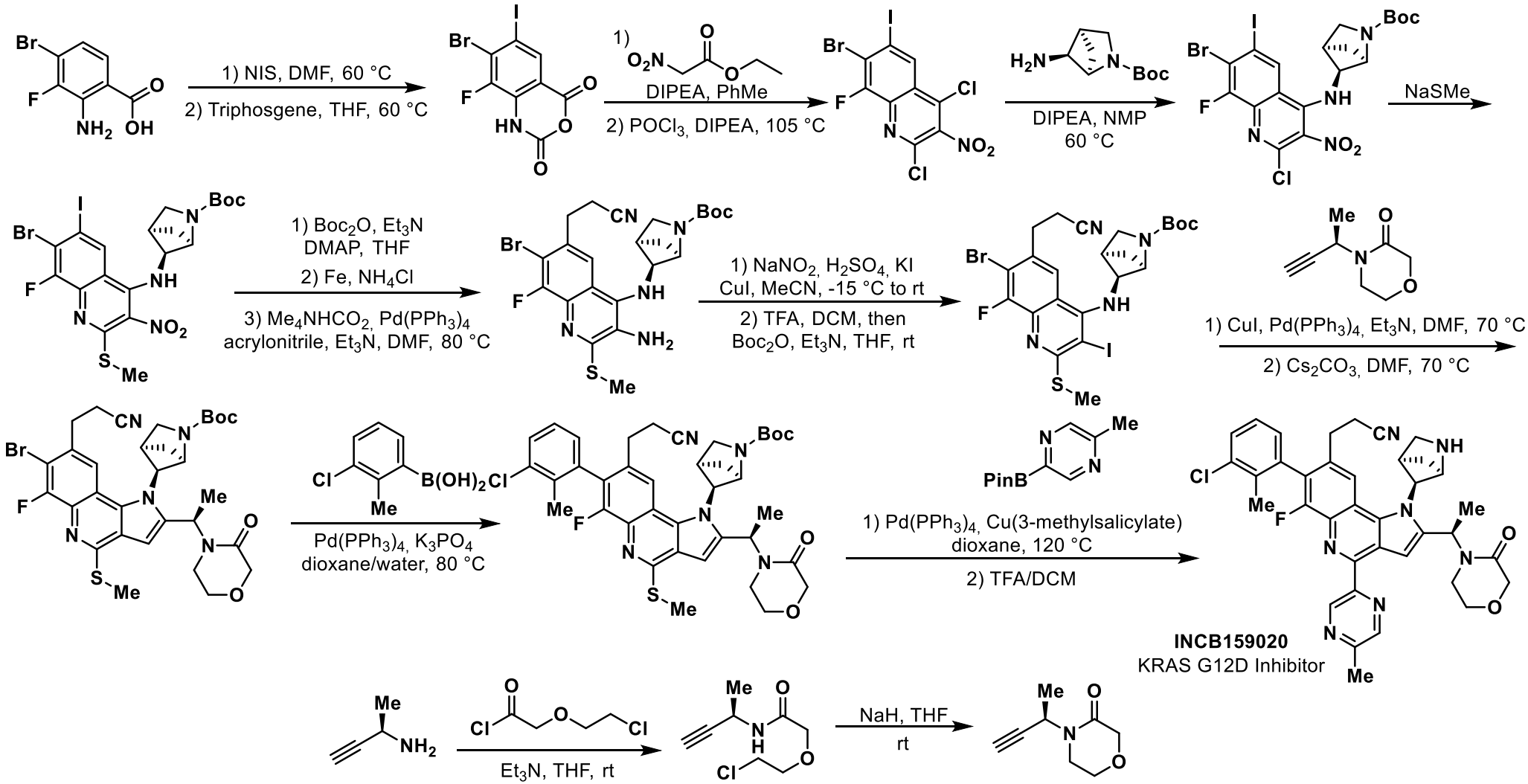


Bonus: ACBI3
KRAS PROTAC

Kirsten **RA**t **S**arcoma (**KRAS**) is a GTPase that normally binds with GDP in an inactive state, which modulates its ability to signal to the cell nucleus to control proliferation or differentiation. Several common mutations result in loss of proper functioning GTP hydrolysis, preventing KRAS deactivation, affecting important signaling pathways. These mutations are observed frequently in human cancers (~17% of solid tumours), and therefore selective KRAS mutant inhibition is an important but difficult objective!

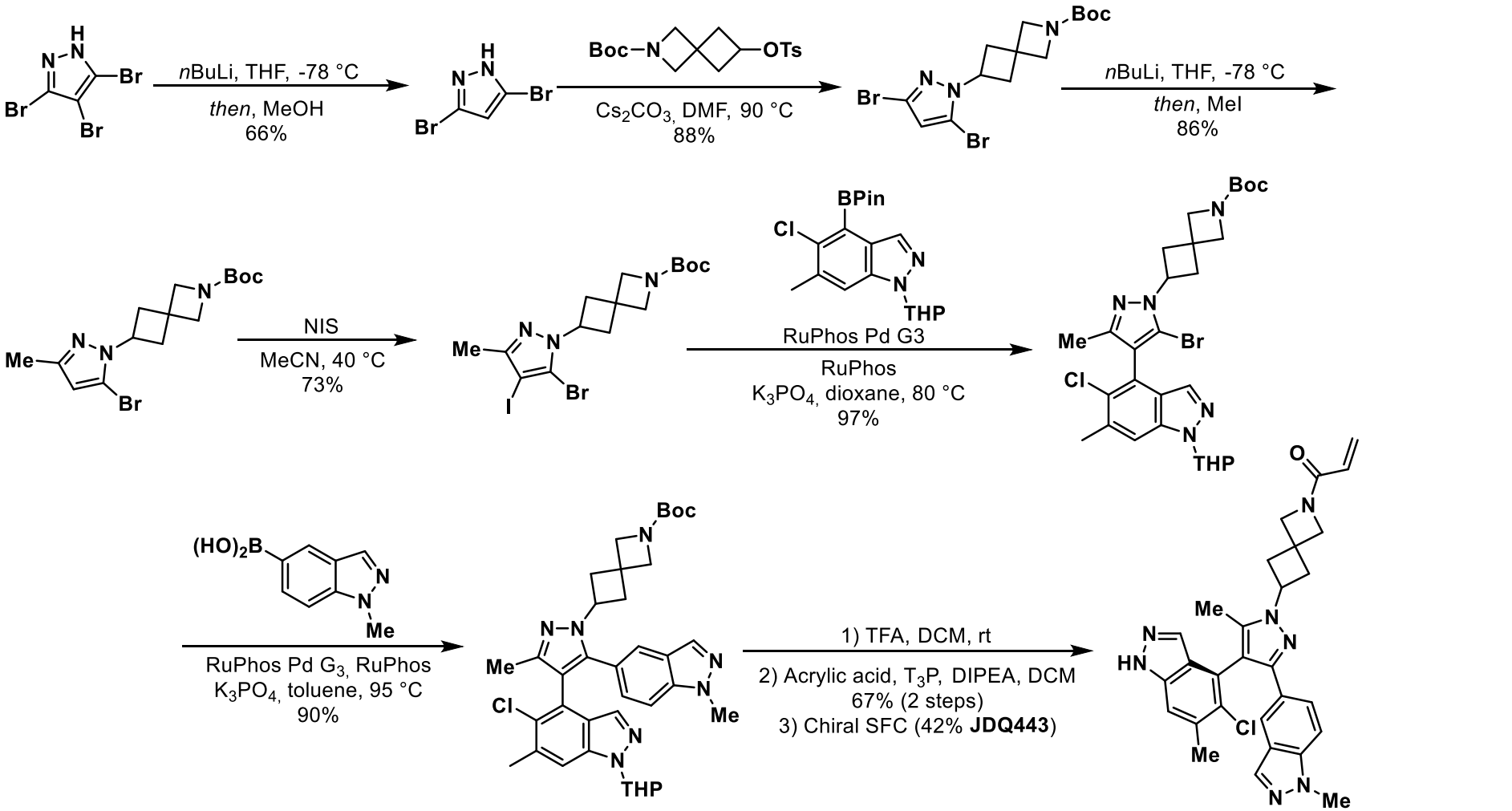
BI-2865: Kim, D.; et al. Nature, 2023, 619, 160-166.
INCB159020: Ye. Q.; et al. J. Med. Chem. 2025, 68, 1924-1939.
KRAS Reviews: Punekar, S. R.; et al. Nat. Rev. Clin. Oncol. 2022, 19, 637-655;
JQD443: Lorthiois, E.; J. Med. Chem. 2022, 65, 16173-16203
ACBI3: Popow, J.; et al. Science, 2024, 385, 1338-1347.
Parikh, K.; et al. J. Hematol. Oncol. 2022, 15, 152.

INCB159020



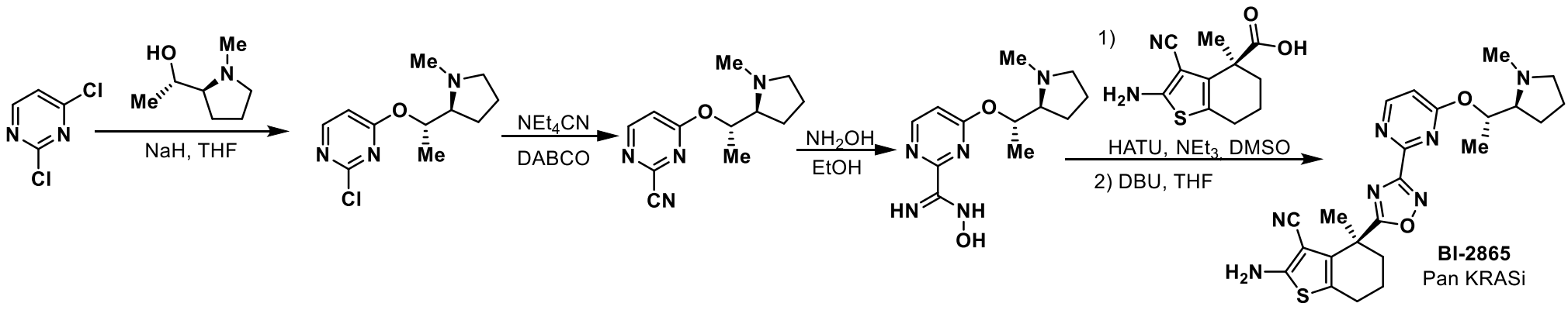
INCB159020: Ye. Q.; et al. J. Med. Chem. 2025, 68, 1924-1939.

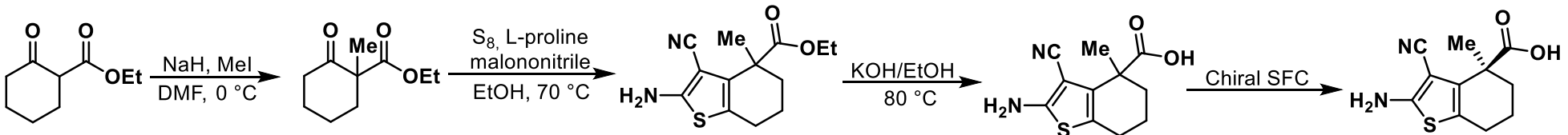
JQD443



JQD443: Lorthiois, E.; J. Med. Chem. 2022, 65, 16173-16203
Azetidine: Meyers, M. J.; et al. Org. Lett. 2009, 11, 3523-3525

BI-2865

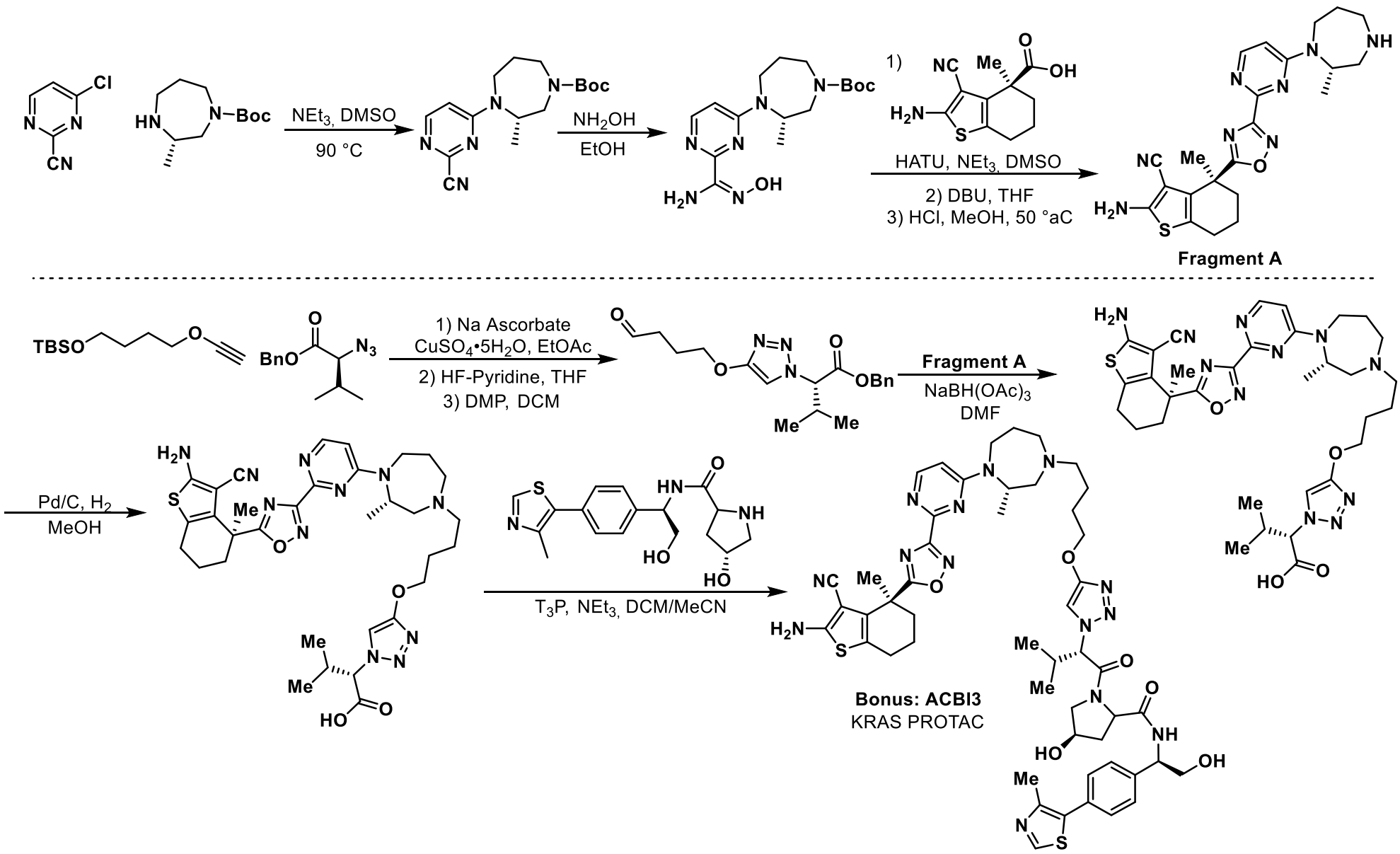




Bröker, J.; et al. *J. Med. Chem*. **2022**, *65*, 14614-14629

BI-2865: Kim, D.; et al. Nature, 2023, 619, 160-166.

ACBI3



ACBI3: Popow, J.; et al. Science, 2024, 385, 1338-1347.