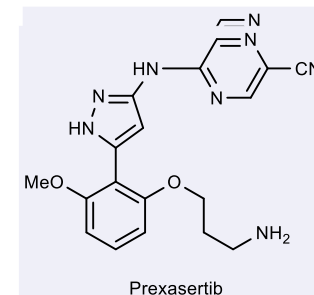




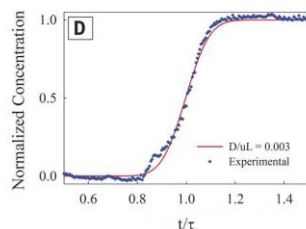
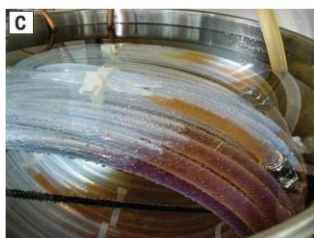
- Developed by Eli Lilly and Company
- Checkpoint kinase 1 (CHK1) and 2 (CHK2) inhibitor.
- Regulates DNA replication and the repair of damaged DNA.
- Hopefully, Prexasertib blocks CHK1 leading to tumor cell death
- Under Phase 2 clinical trials for various adult and pediatric cancers including for patients with a BRCA1/2 mutation associated breast, ovarian, or prostate cancer
- First CHK1 inhibitor to exhibit objective clinical responses as a monotherapy
- Administered via infusion so water solubility is important



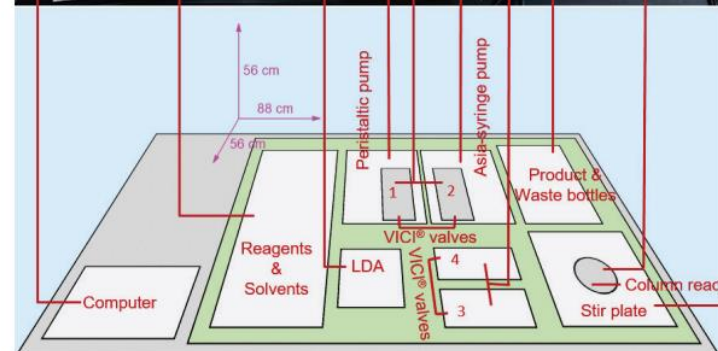
## Continuous Flow Synthesis

Stancato, L.F. *Clinical Cancer Research*. 2019. 25, 2278. <https://doi.org/10.1158/1078-0432.CCR-18-2728>

- Large batch pharmaceutical manufacturing ill-equipped for the decreased quantity of drugs with increased potency compared to historical needs
- Small-volume continuous manufacturing allows for small batches of active pharmaceutical ingredients (APIs) to be manufactured in fume hoods and can easily be switched between different reactions or the apparatus can easily be disposed of and cheaply replaced
- Less exposure to hazardous materials
- Allows for gram-scale synthesis of API derivatives

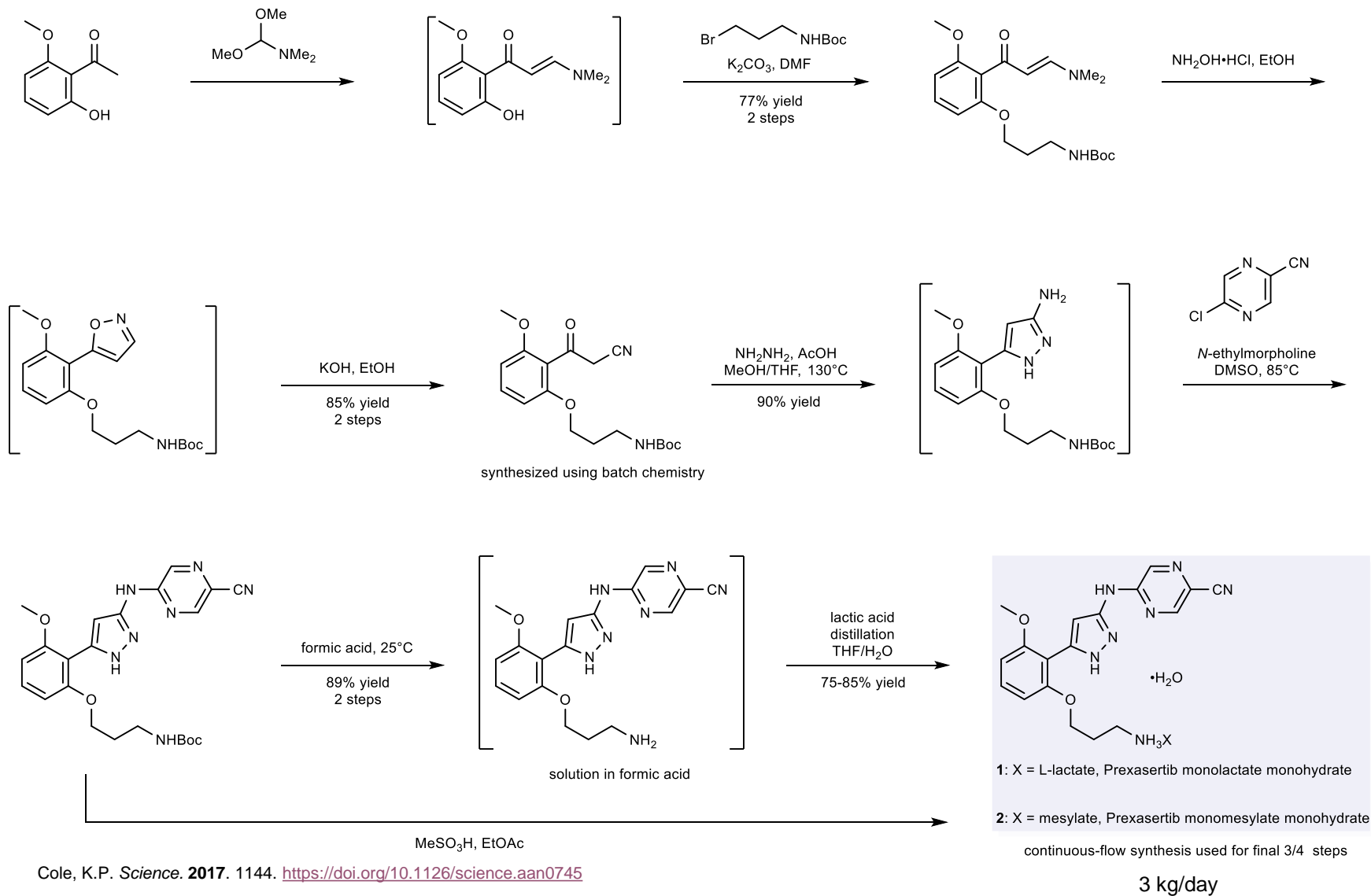


Automated continuous flow synthesis



Automated solid-phase synthesis flow system

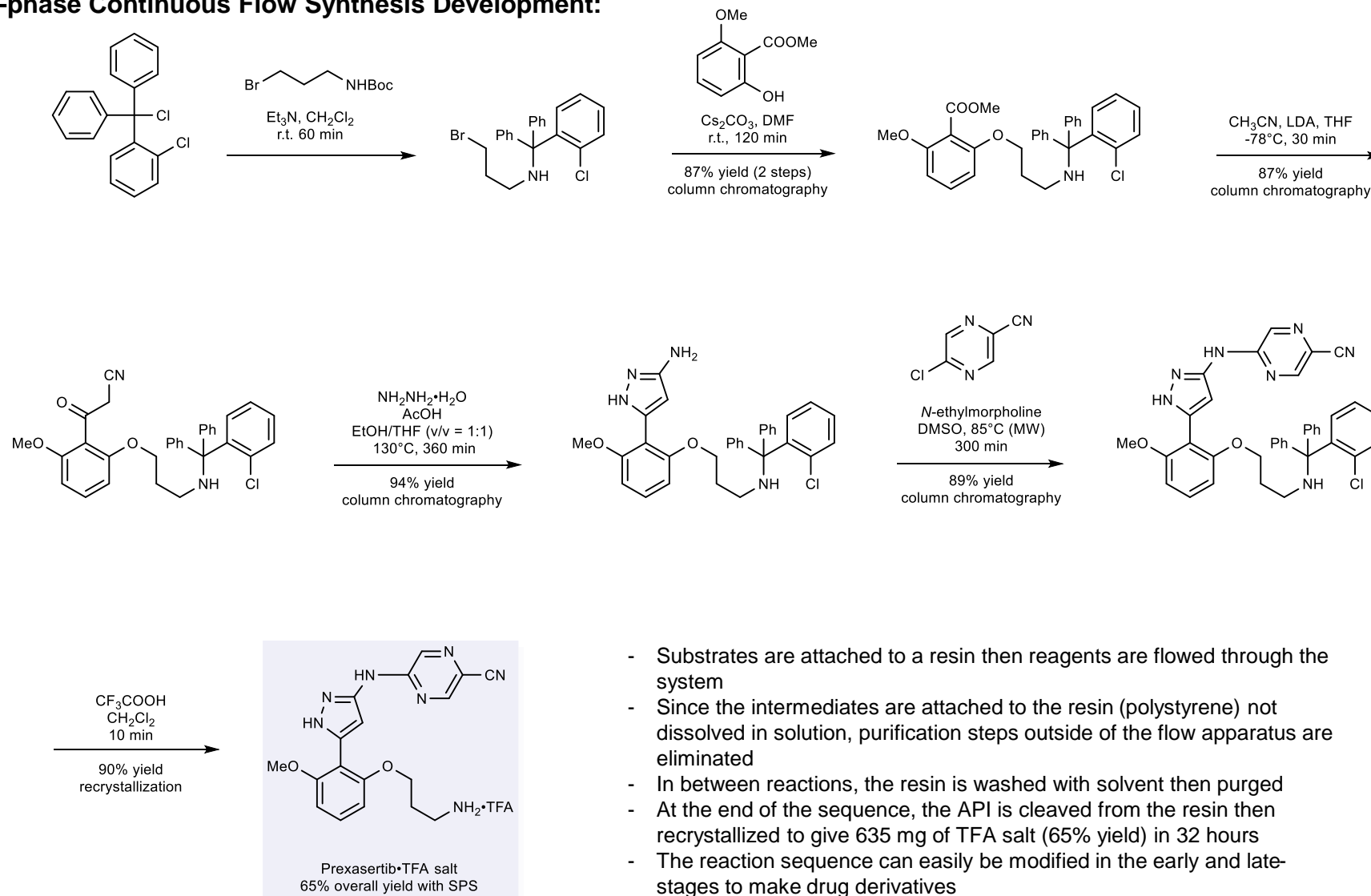
## Continuous Manufacturing Using Good Manufacturing Practices



Cole, K.P. *Science*. 2017. 1144. <https://doi.org/10.1126/science.aan0745>

3 kg/day

## Solid-phase Continuous Flow Synthesis Development:



- Substrates are attached to a resin then reagents are flowed through the system
- Since the intermediates are attached to the resin (polystyrene) not dissolved in solution, purification steps outside of the flow apparatus are eliminated
- In between reactions, the resin is washed with solvent then purged
- At the end of the sequence, the API is cleaved from the resin then recrystallized to give 635 mg of TFA salt (65% yield) in 32 hours
- The reaction sequence can easily be modified in the early and late stages to make drug derivatives