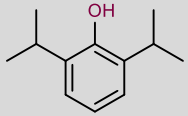
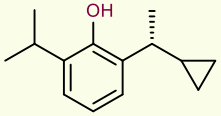
Cipepofol

Discovery and Precedent:

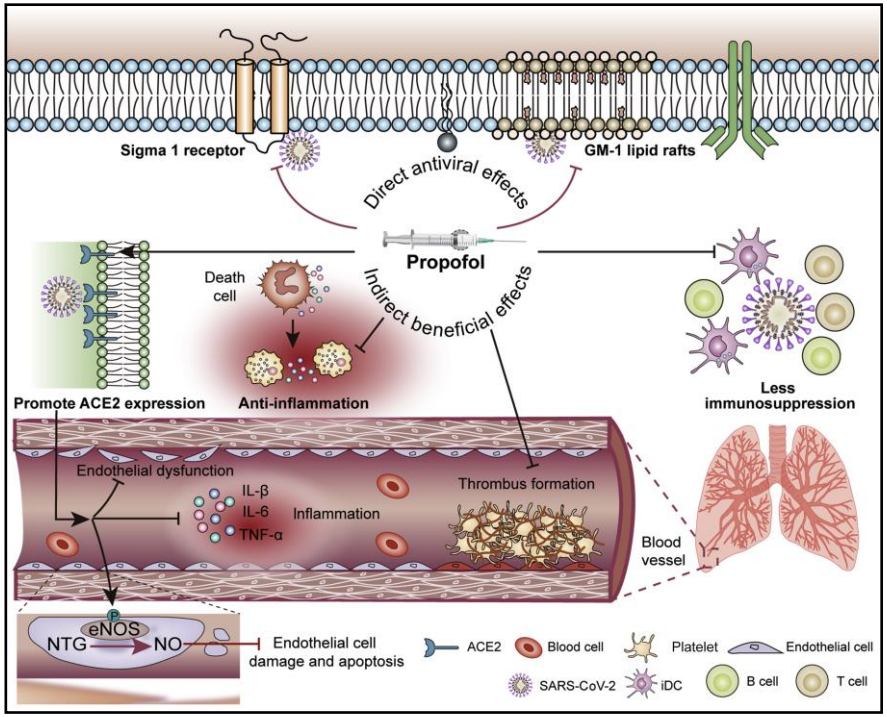


Propofol (Approved 1989)



Cipepofol (Phase III Clinical Trials)

Mechanism of Action:



Propofol is a $GABA_A$ receptor agonist which is used as an intravenous anesthetic in clinical usage.

$GABA_A$ ion channels are responsible for mediating inhibitory neurotransmission
in the CNS.

Propofol decreases the rate of dissociation of GABA from the receptor, affording more time for the chloride channel to be open, resulting in the hyperpolarization of the post synaptic membrane. This ultimately results in functional inhibition of the post synaptic membrane.

Cipepofol has been found to match the efficacy of propofol while simultaneously reducing side effects of propofol such as:

- injection pain
- respiratory depression
- drops in blood pressure

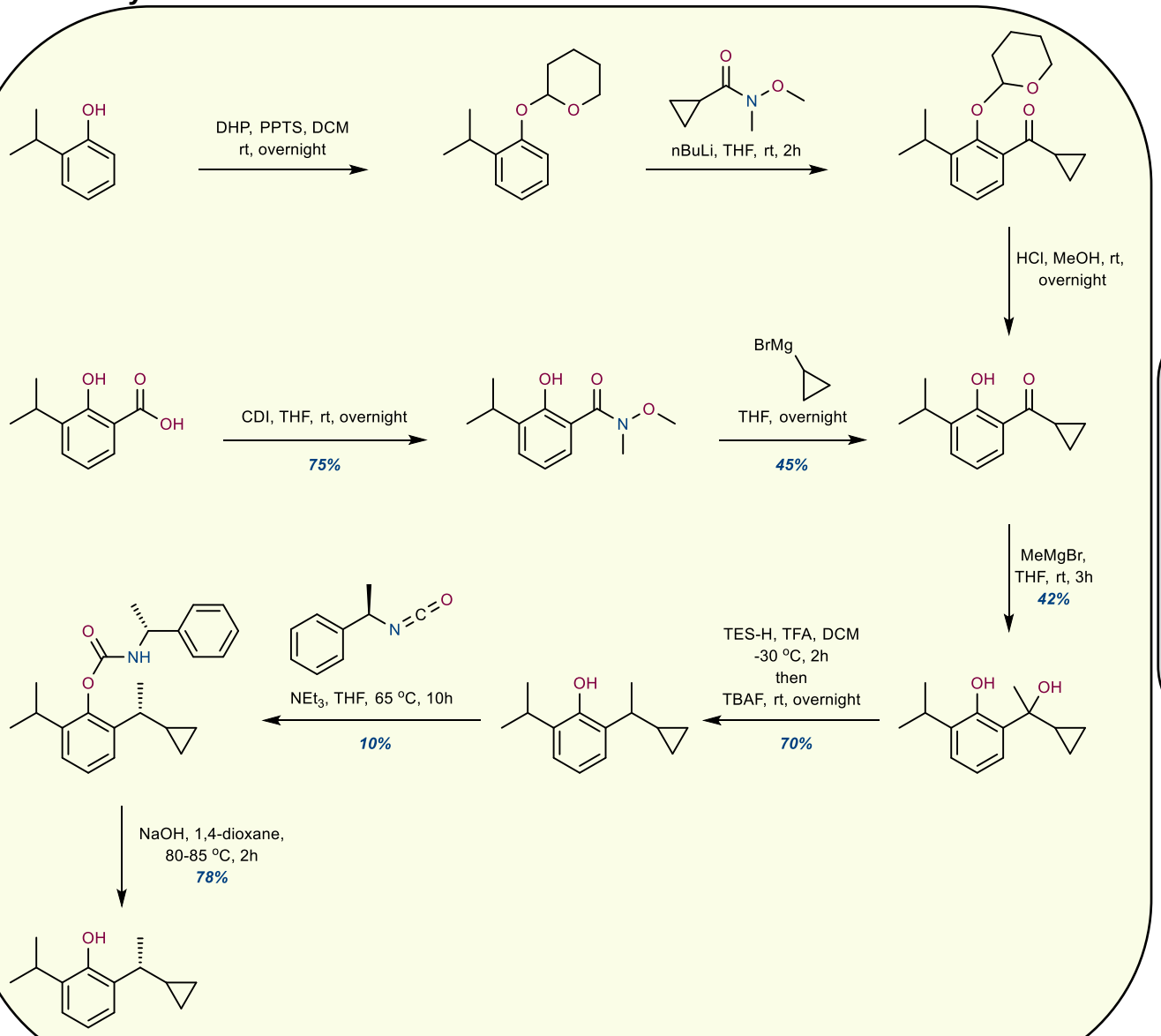
Cipepofol is currently in phase III clinical trials.

Wei, P. *British Journal of Anaestesia.* **2021**, 1*26, 5, 188-191.* https://doi.org/10.1016/j.bja.2021.02.006

Zhang, X. *Org. Process Res. Dev.* **2022**, *26, 4, 1054–1062.* https://doi.org/10.1021/acs.oprd.1c00306

Nefopam (Fenazoxine)

Discovery Route:



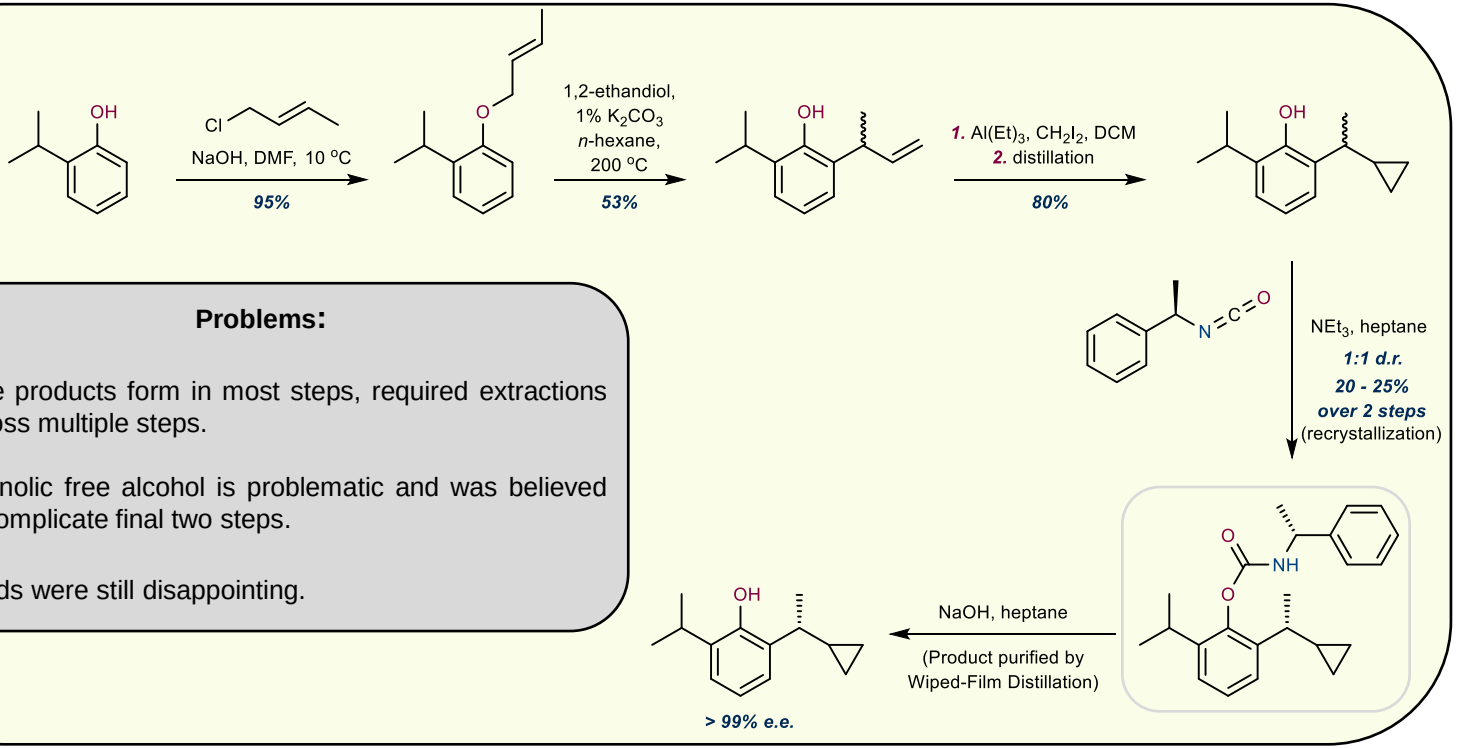
Zhang, X. *Org. Process Res. Dev.* **2022**, *26, 4, 1054–1062.* https://doi.org/10.1021/acs.oprd.1c00306

Problems:

- nBuLi and other organometallics are not ideal for kilogram scales due to safety.
- PPTS toxicity adds additional risks to quality control.
- This route required multiple column chromatography steps.
- Yields were overall disappointing.

Nefopam (Fenazoxine)

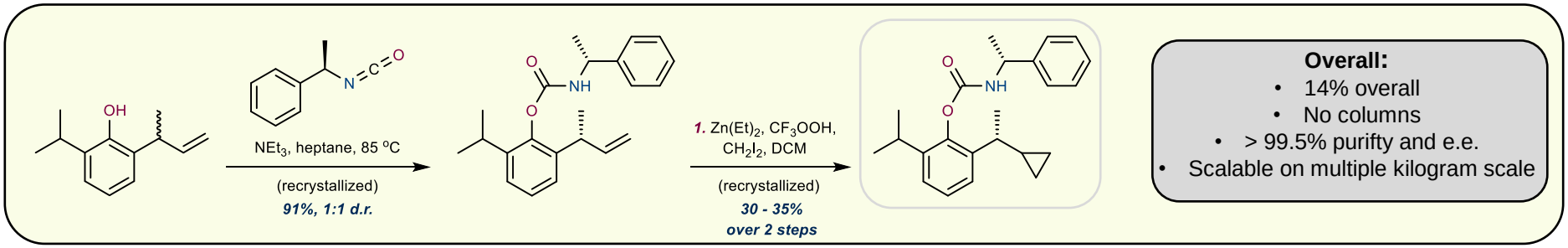
Second Generation Synthesis:



Problems:

- Side products form in most steps, required extractions across multiple steps.
- Phenolic free alcohol is problematic and was believed to complicate final two steps.
- Yields were still disappointing.

Third Generation Synthesis:



Overall:

- 14% overall
- No columns
- > 99.5% purifty and e.e.
- Scalable on multiple kilogram scale

Final sequence uses the chiral carbamate as a protecting group to improve yield and efficiency

Zhang, X. *Org. Process Res. Dev.* **2022**, *26, 4, 1054–1062.* https://doi.org/10.1021/acs.oprd.1c00306