

## Background

- Nirmatrelvir, a SARS-CoV-2 3C-like protease inhibitor, was first synthesized by Pfizer in July 2020
- Paxlovid, a cotherapy of nirmatrelvir and ritonavir, was the first SARS-CoV-2-specific drug to receive emergency use authorization in December 2021- only 17 months from discovery!
- High demand required navigation of synthetic chemistry, supply chain, and logistical challenges as described in the following series of papers:

Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2240–2249. <https://doi.org/10.1021/acs.oprd.3c00249>

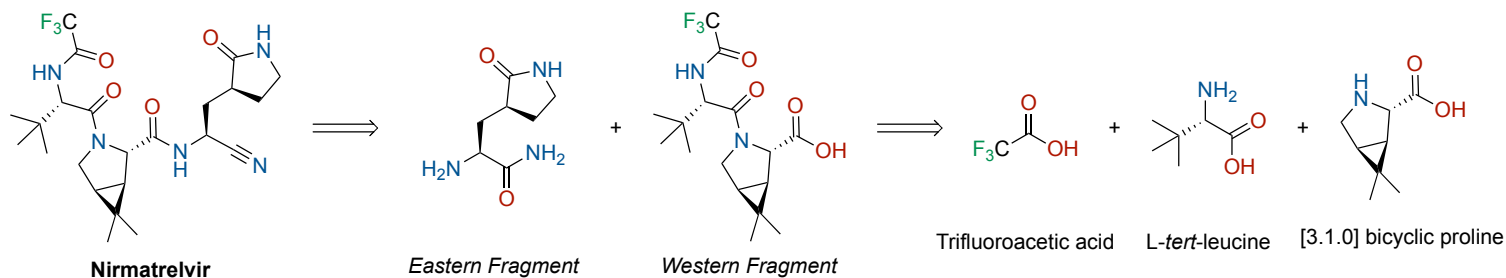
Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2250–2259. <https://doi.org/10.1021/acs.oprd.3c00250>

Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2260–2270. <https://doi.org/10.1021/acs.oprd.3c00251>

Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2271–2279. <https://doi.org/10.1021/acs.oprd.3c00252>



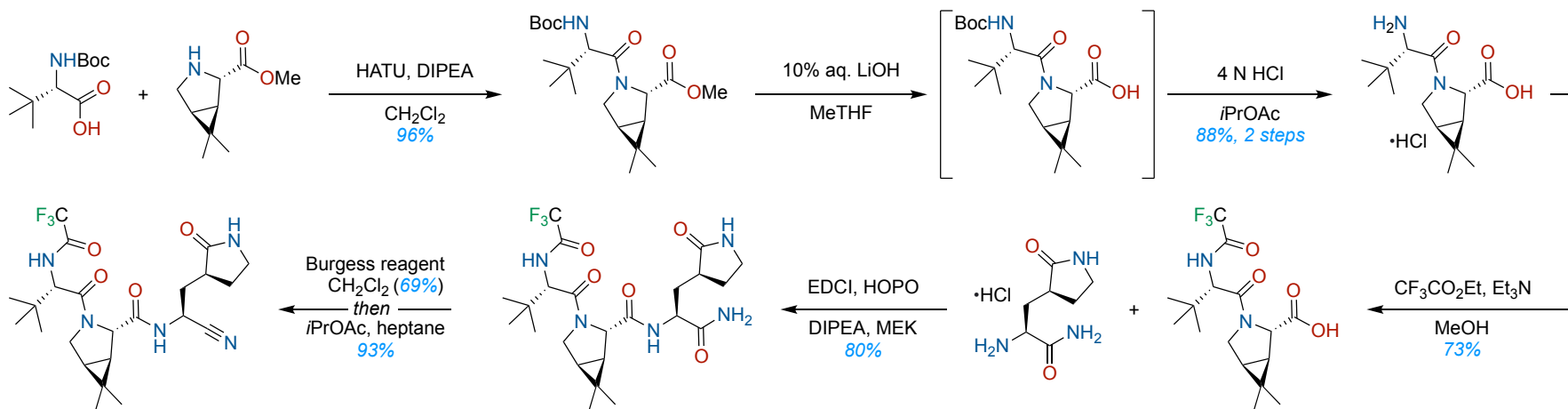
## Retrosynthesis:



- Readily available starting materials and reagents
- Robust chemistry

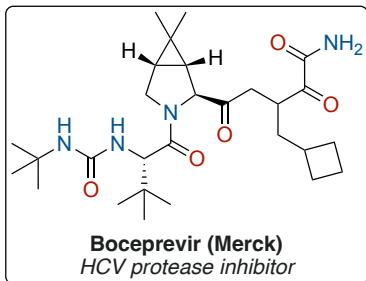
## First Kilogram-Scale Manufacturing Route:

- From milligrams to 12 kg batches in only eight months!

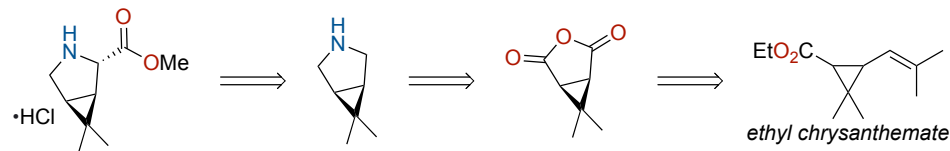


Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2240–2249. <https://doi.org/10.1021/acs.oprd.3c00249>

## [3.1.0] Bicyclic Proline: Supply Chain Considerations

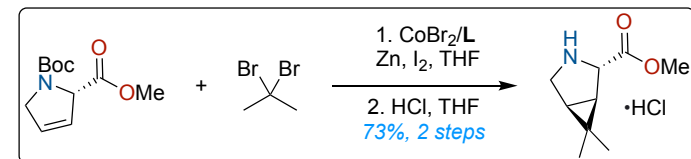
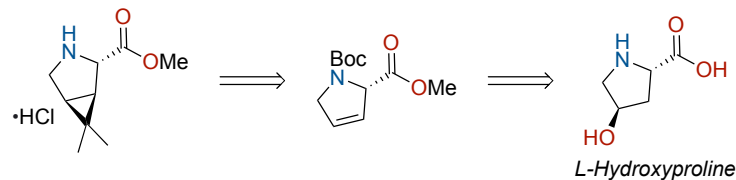


**Merck-Codexis:** A monoamine oxidase (MAO)-based strategy



Supply chains previously established for the manufacture of boceprevir provided rapid access to large quantities of the bicycle

**Uyeda's Cyclopropanation:**

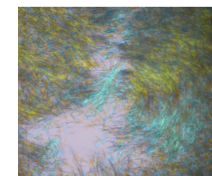
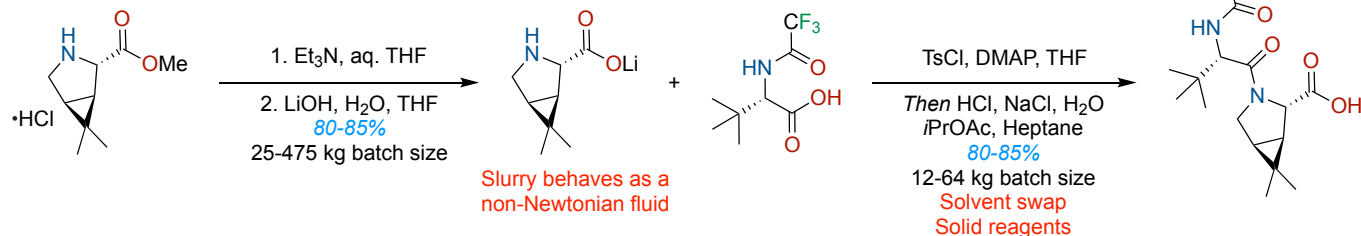


- Demonstrated on commercial scale: 200 kg batch size, 10 metric tons produced
- Alternative alpha raws ensures a robust supply chain

Li, T. *J. Am. Chem. Soc.* **2012**, 134 (14), 6467–6472. <https://doi.org/10.1021/ja3010495>  
 Werth, J. *Angew. Chem. Int. Ed.* **2018**, 57 (42), 13902–13906. <https://doi.org/10.1002/anie.201807542>  
 Algera, R. F. *Process Res. Dev.* **2023**, 27 (12), 2260–2270. <https://doi.org/10.1021/acs.oprd.3c00251>

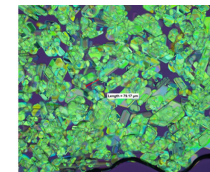
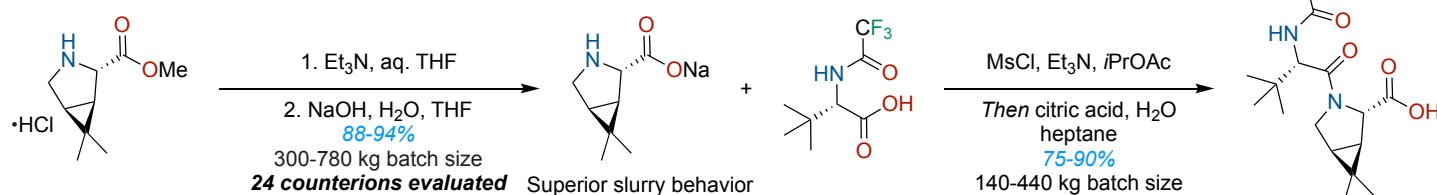
## Western Fragment Synthesis:

**First Generation:**



The lithium salt exhibits thin hair-like crystal morphology

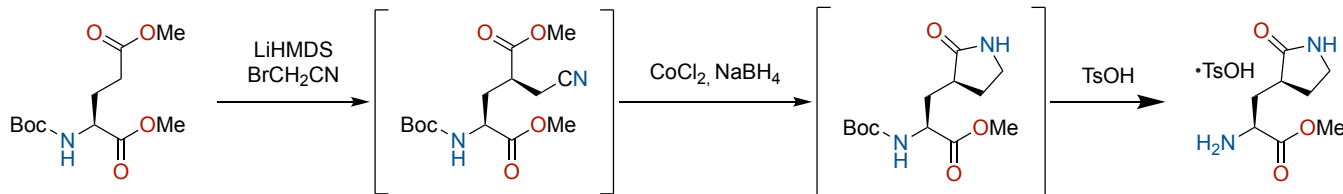
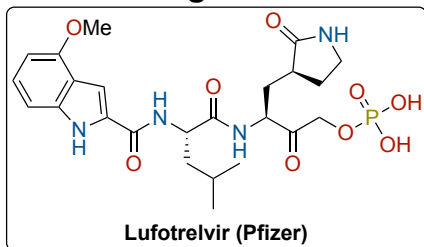
**Second Generation:**



The sodium salt exhibits block crystal morphology

Algera, R. F. *Org. Process Res. Dev.* **2023**, 27 (12), 2240–2249. <https://doi.org/10.1021/acs.oprd.3c00249>

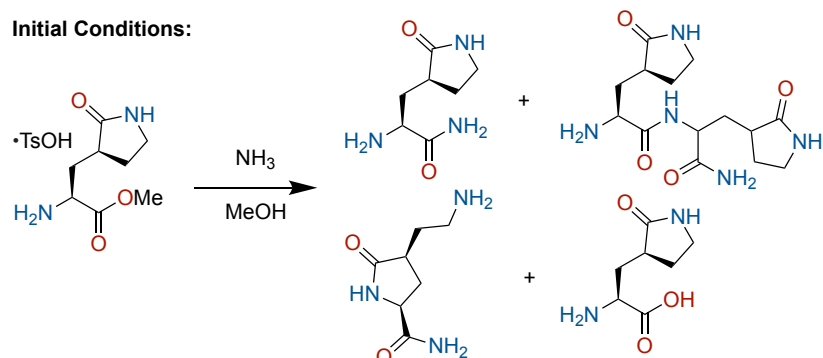
## Eastern Fragment:



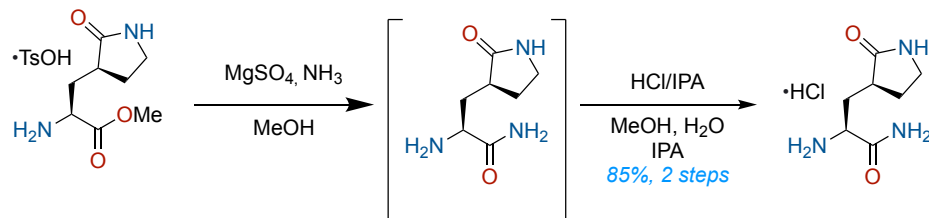
*A previously established supply chain provided ready access to a key lactam intermediate*

Allais, C. *Org. Process Res. Dev.* **2023**, *27* (12), 2223–2239. <https://doi.org/10.1021/acs.oprd.2c00375>

## Initial Conditions:



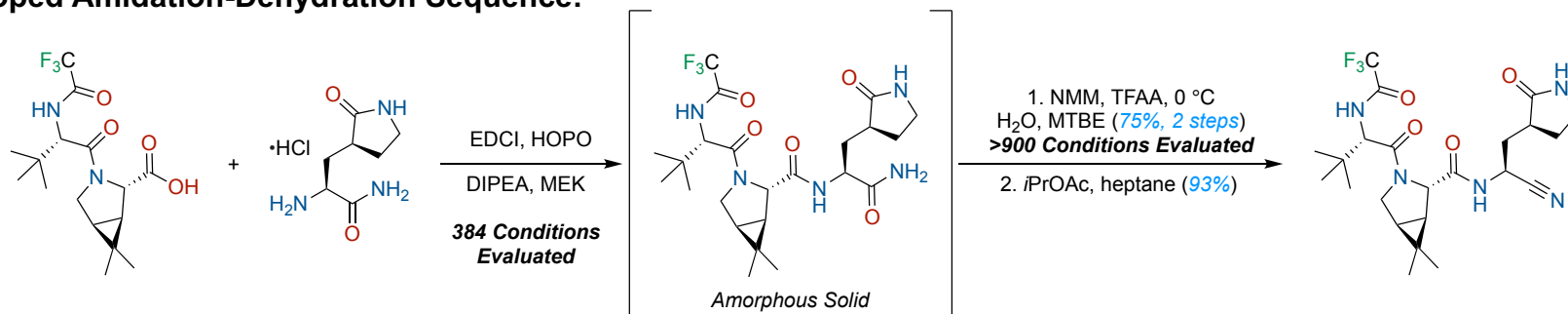
## Optimized Conditions:



*MgSO<sub>4</sub> accelerates aminolysis and suppresses formation of impurities*

Algera, R. F. *Org. Process Res. Dev.* **2023**, *27* (12), 2271–2279. <https://doi.org/10.1021/acs.oprd.3c00252>

## Telescoped Amidation-Dehydration Sequence:



*Burgess reagent limitations (cost, availability, stability, and byproduct removal) were resolved with HTE evaluation of dehydration conditions*

Algera, R. F. *Org. Process Res. Dev.* **2023**, *27* (12), 2250–2259. <https://doi.org/10.1021/acs.oprd.3c00250>

**Pfizer's commercial route has supported production of >100 metric tons of nirmatrelvir!**