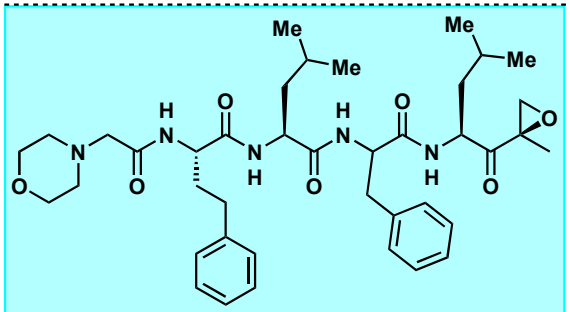
# POTW: Carflizomib, Part 2



***Carfilzomib (Kyprolis)***
***An FDA-approved drug for Multiple Myeloma***

**Mechanism of Action:**

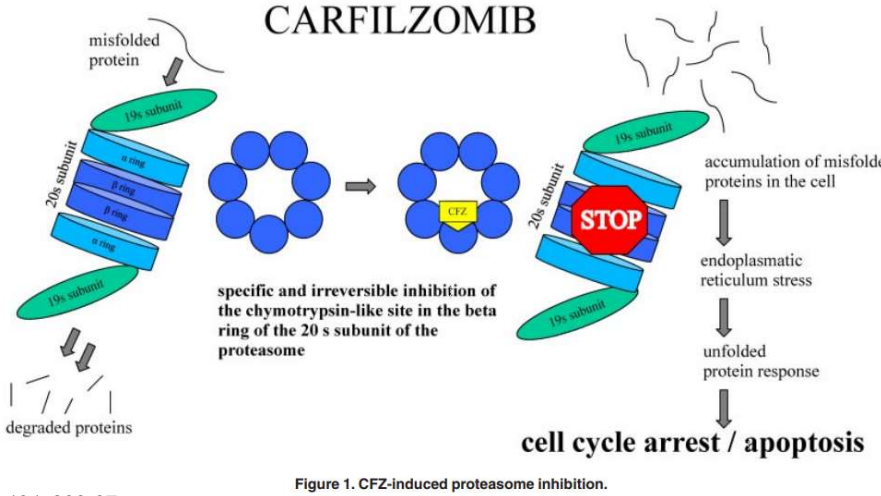
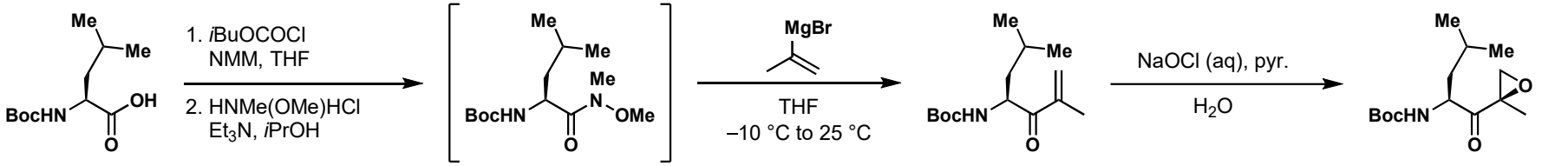
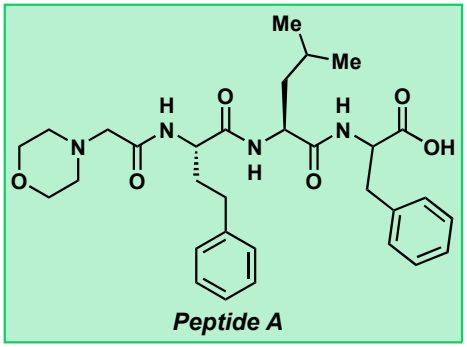



Figure 1. CFZ-induced proteasome inhibition.

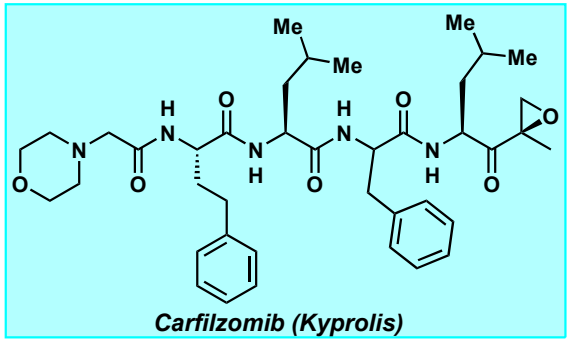
*Blood* **2013**, *121*, 893-97.

**Synthesis of Carflizomib--What we've seen so far:**



***Peptide A***



***Carfilzomib (Kyprolis)***

see *OPRD* **2020**, ASAP, https://doi.org/10.1021/acs.oprd.0c00052

*Sarlah Group*

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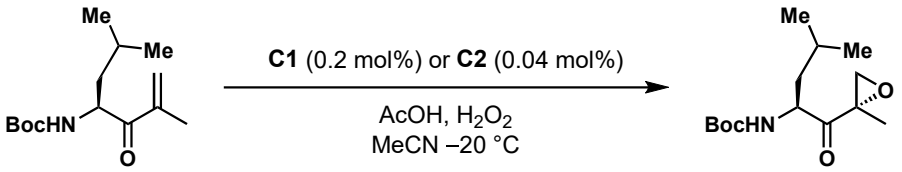
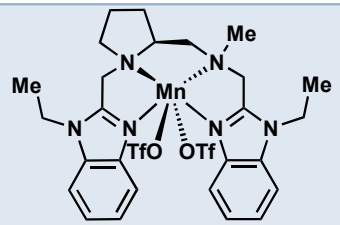
**Asymmetric optimization:**



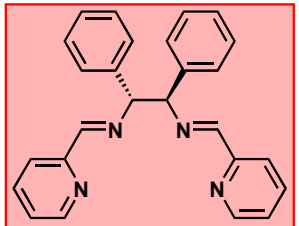

- Phase transfer catalysis unsucessful (epimerization, poor conversion)
- Iminium and lewis acid catalysis are a challenge for this substitution pattern
- Mn-bioinspired catalysts were successful. (*Chem. Eur. J.* **2012**, *18*, 6750-53)
  - Catalysts $C_1$, $C_2$, gave best conversion/*d.r.*
- However, despite significant optimization, researchers could not overide substrate bias
- Physical state of (*S,S*)-epoxyketone was different from desired (*S,R*)-epoxyketone
  -former had a signfiicantly increased melting point; enabling crystalization
- WIth this in mind, development was shifted towards a path



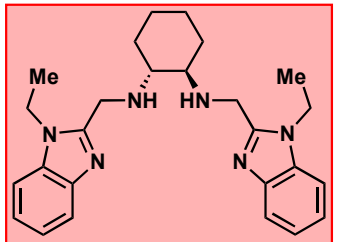

**C1:** Runtime: 2h
(*S*)-enone: >95% assay yield, 88:12 *d.r.*
(*R*)-enone: 85% assay yield, 71:29 *d.r.*


**C2:** Runtime <1h
(*S*)-enone: >95% assay yield
91:9 *d.r.*

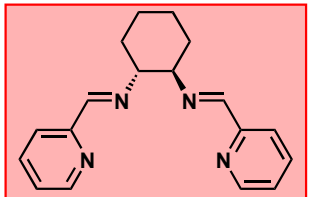
**Some other explored ligands:**



6% conversion, <1% yield



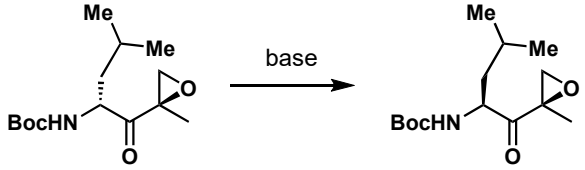

9% conversion, 2% yield
88:12 *d.r.*



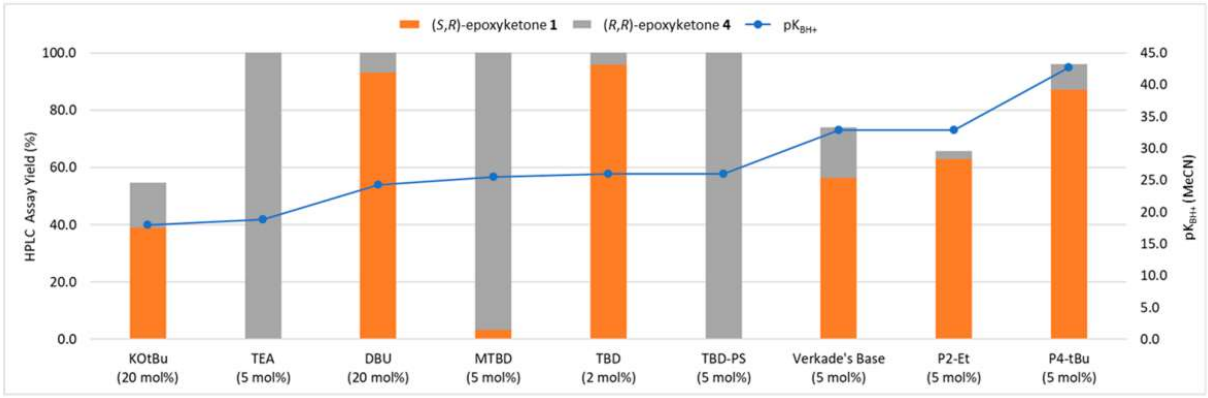
48% conversion, 40% yield
89:11 *d.r.*

**A new target: The *(R,R)*-epoxy-ketone:**

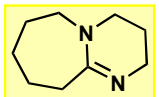
- The basic lability of the side chain was exploited to get the desired product in high selectivity.



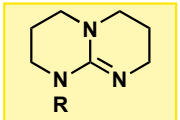

(*R,R*)-epoxyketone (*R,S*)-epoxyketone



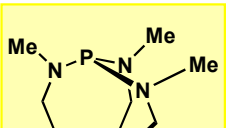

- Final optimization: DBU at 20 °C: 95:5 *d.r.* Quench of 25 wt% $NaHSO_3$. Recrystalized in IPA/$H_2O$ at 5 °C
- Allowed removal of chromatography



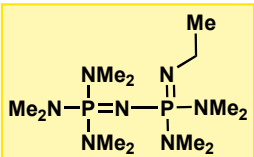
DBU



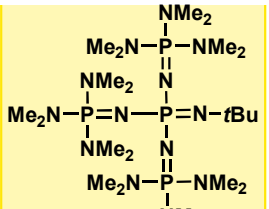

R = H: TBD
R = Me: MTBD



Verkade's Base




P2-Et




P4-*t*Bu

*Matt Bock, 2020 April 10*

*Sarlah Group*

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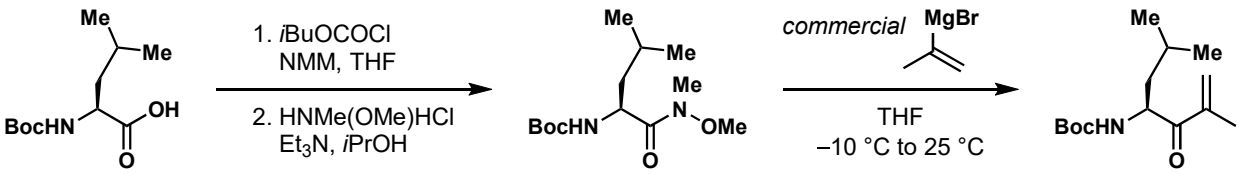
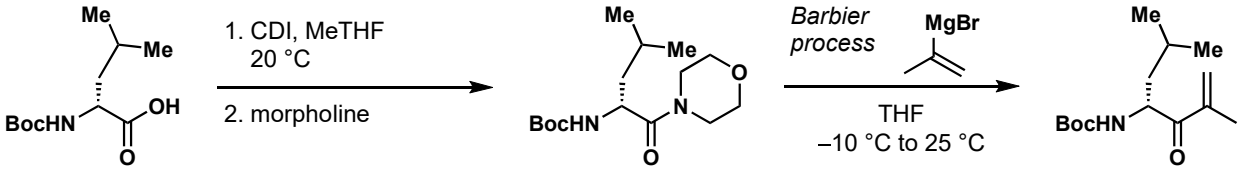
**Grignard Optimization:**




**- Problems with this route:**
- Step 1: contained ICBF as a limiting reagent required multiple washes and distillations
- Step 2: Multiple washes, distillations, silica plug very dilute grignard reagent, cycling

**Modified route:**




*Total heat released during process:*
*–1182 kJ/mol (203 °C adiabatic temp rise)*

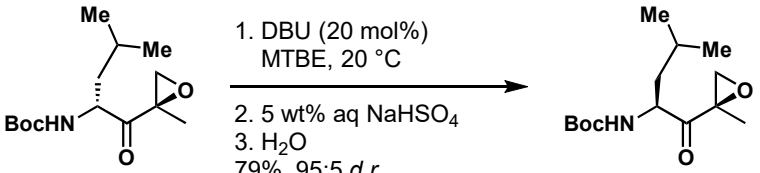
**Improvements:**
1. 2 eq of CDI allowed direct use of starting material without any pre-drying

2. Continuous stirred tank reactors enable grignard process to be done safely and consistently

3. Multiday continous process only required 6.0 g of mg for activation, while batch required 1 kg.

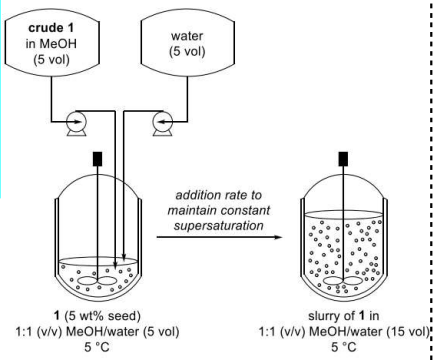
Two steps: 89% yield, >99.9% purity

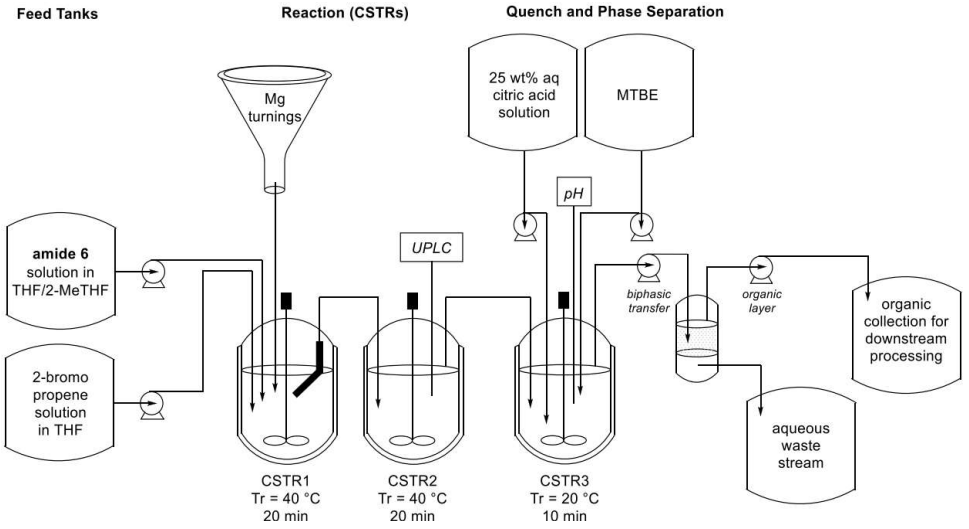
**Final Optimization:**




0.89kg in one batch
52.5% overall yield
E factor: 304 (previous 2639)

- Isolation issues:
  - (*S,R*)-epoxyketone has a tendency for oiling
  - $MeOH/H_2O$ at 5 °C identified as a system
  - seeded batch coaddition process enables efficient crystalization of this final intermediate
  - Monitoring water content and supernatent concentration are critical for process success--if not kept constant, oiling of the epoxyketone occurs.




*Matt Bock, 2020 April 10*