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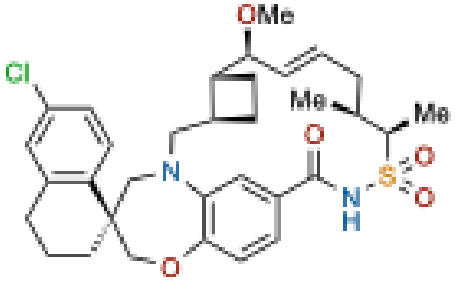
Background

- Intrinsic apoptosis is initiated by mitochondria within the cell in response to stress signals by Bcl-2 protein family
- Regulated by antiapoptotic proteins including, Bcl-2, Bcl-xL, and Mcl-1
- Cancer cells can overexpress antiapoptotic proteins leading to tumor progression
- Mcl-1 inhibitors have potential to modulate intrinsic apoptotic pathway and work in conjunction with chemotherapy or Bcl-1 inhibitors



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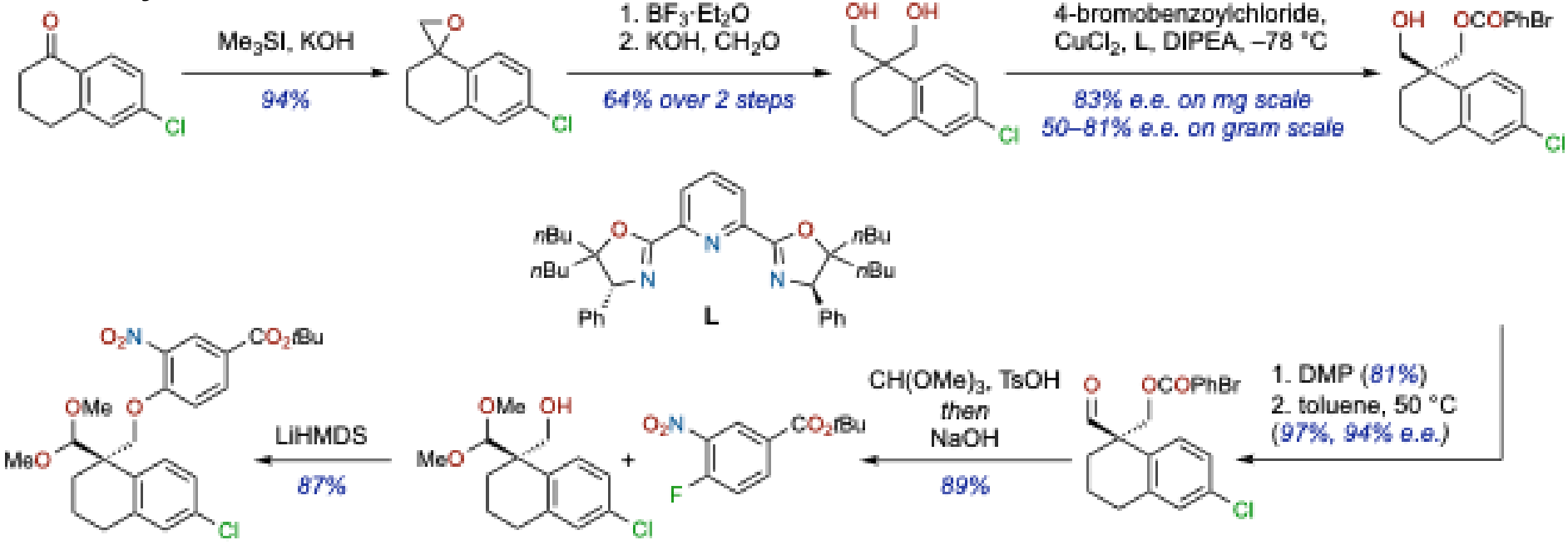
Discovery Route



J. Med. Chem. **2019**, 62, 10258−10271; US Patent US10100063B2, **2016**

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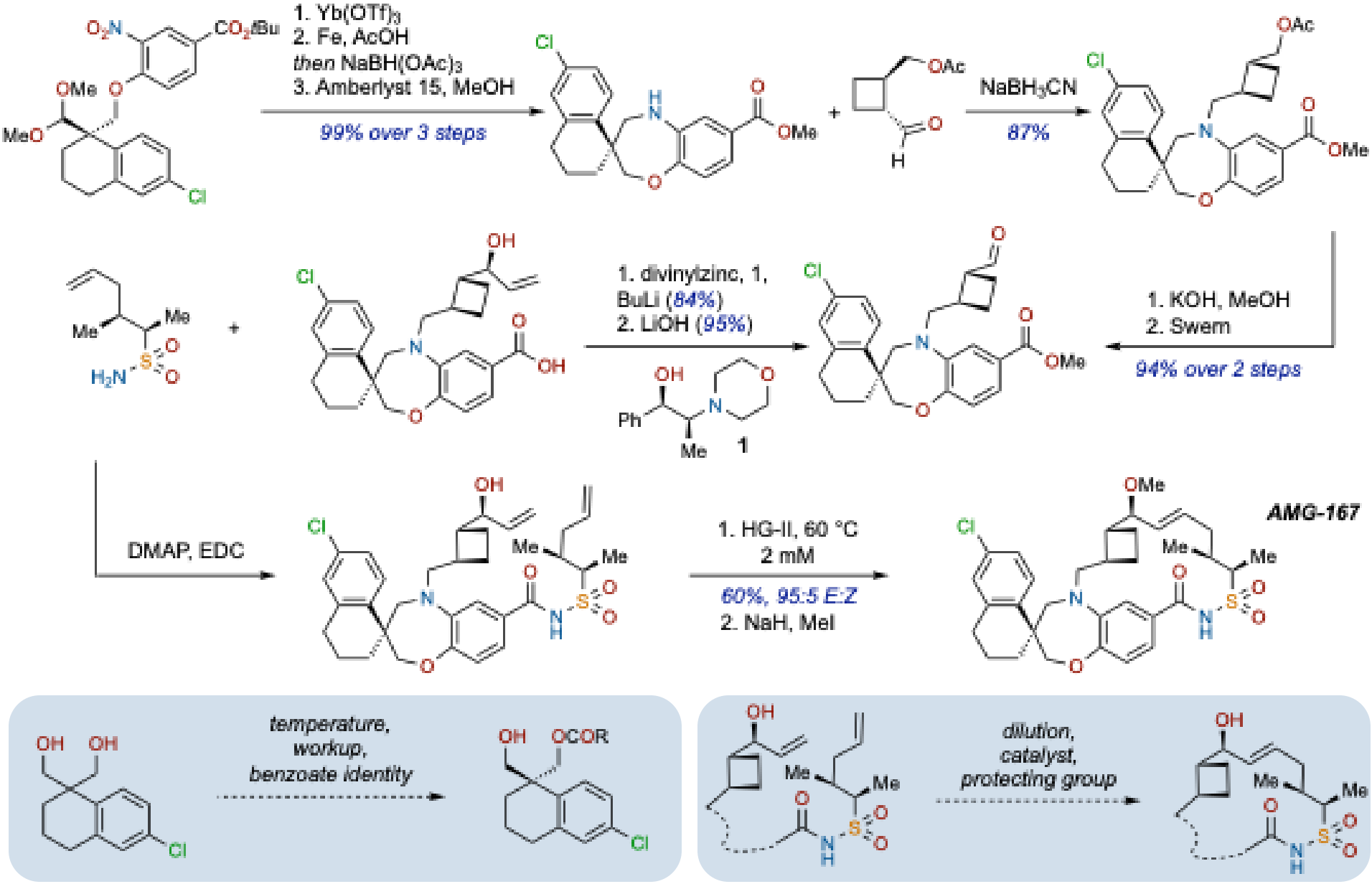

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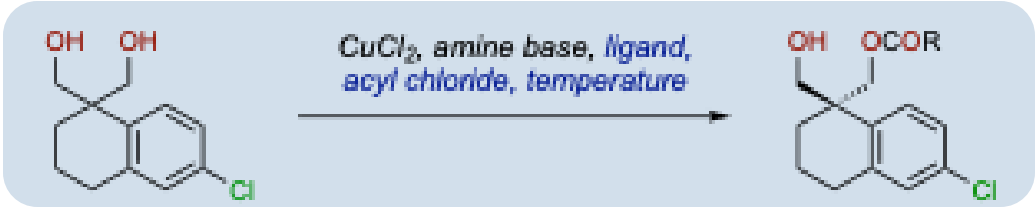
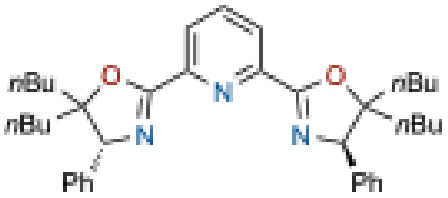
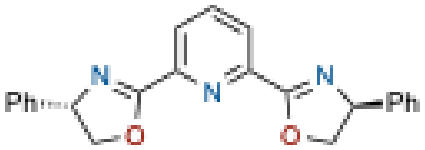


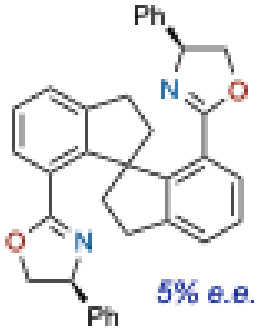
Ligand:



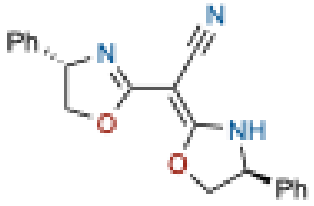
69% e.e. (S)



32% e.e. (R)

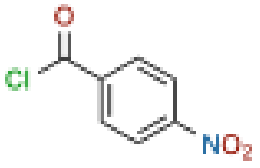


5% e.e. (R)

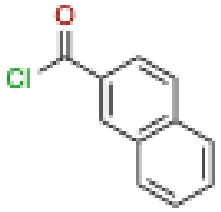


40% e.e. (R)

Acyl Chloride:

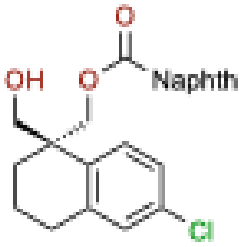


71% e.e. at –78 °C



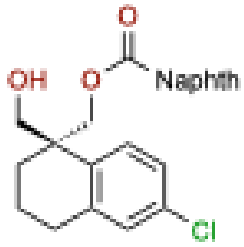
82% e.e. at –40 °C
crystalline intermediate

temperature (°C)	*e.e. (%)*	*yield (%)*
21	*47*	–
– 25	*77*	*83*
– 40	*82*	*76*

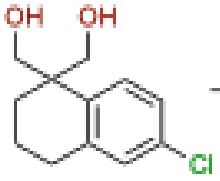


79% e.e.

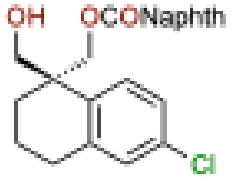
sat. aq. NH_4Cl
–40 °C to rt,
24 hours



67% e.e.



1. L*, $CuCl_2$, $EtNiPr_2$, –40 °C
2. 1-naphthoyl chloride
3. Si-Thiol *then* filter
4. aq. $NaHCO_3$
5. swap to toluene, 80 °C
6. cool to 20 °C *then* filter



63%, 96% e.e.
produced > 100 kg total

Synthesis **2023**, 55, 2397–2405

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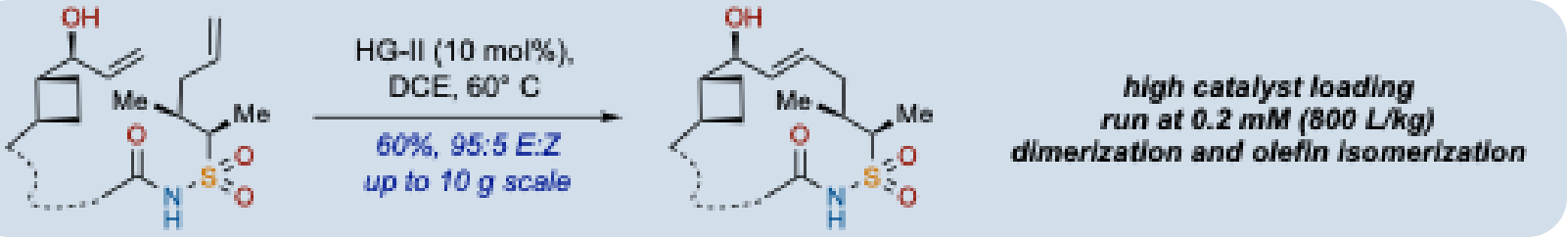
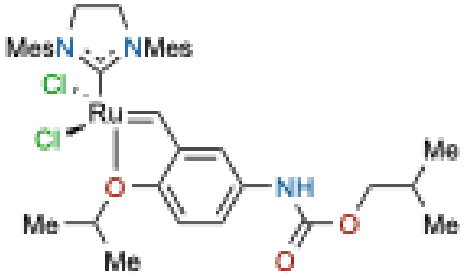
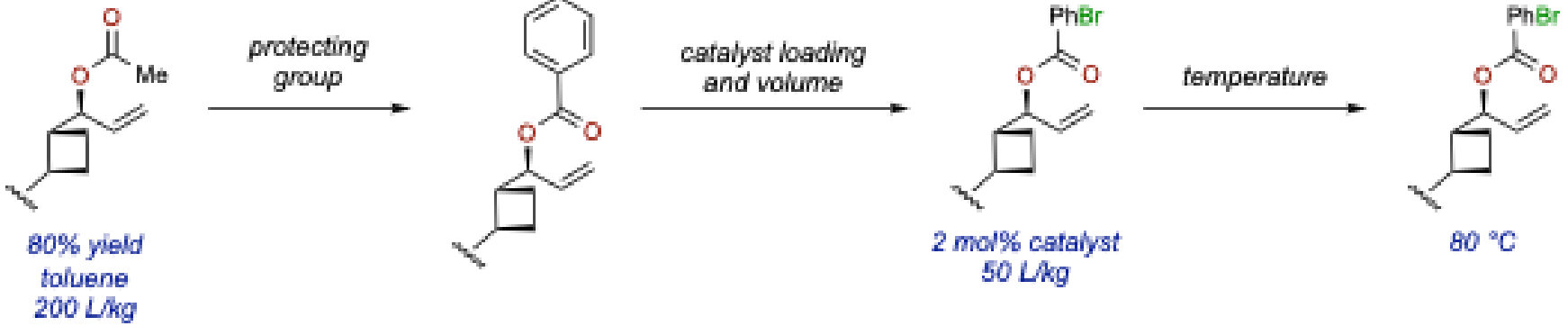




M73-SIMes

protecting group	*effective molarity (M)*
Piv	*0.012*
Ac	*0.049*
Bz	*0.12*
4-BrBz	*0.17*

High-throughput screening:



M73-SIMes
Toluene (50 L/kg)
80 °C
400 Torr vacuum

92% yield
45 kg scale
16-fold increase in concentration

Org. Process Res. Dev. **2021**, 25, 442−451