An Efficient Synthetic Approach to Cyanocycline A and Bioxalomycin β2 via [C+NC+CC] coupling

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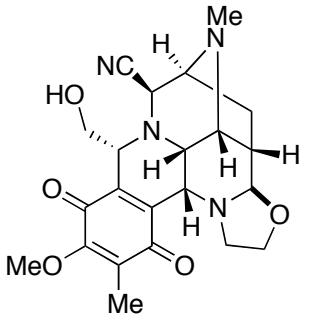
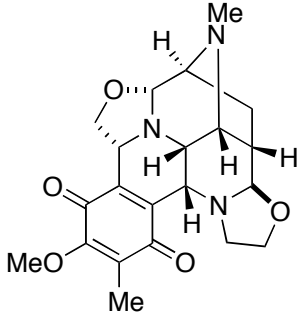
Cyanocycline A and Bioxalomycin β2

- Tetrahydroisoquinoline alkaloid family
- Exhibit wide range of biological activity:
  - antitumor, antifungal, antimicrobial

- Isolated in 1994 from *Steptomyces viridostaticus*



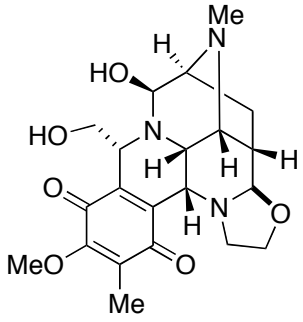
Cyanocycline A



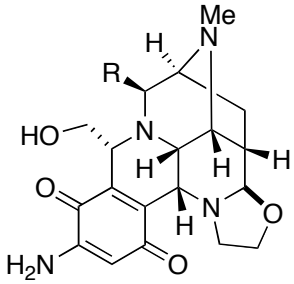
Bioxalomycin β2

- Isolated in 1970's from *Streptomyces flavogriseus*

- Isolated in 1974 from *Steptomyces lusitanus*



Naphthyridinomycin



Dnacin A_1 R = CN
Dnacin B_1 R = OH

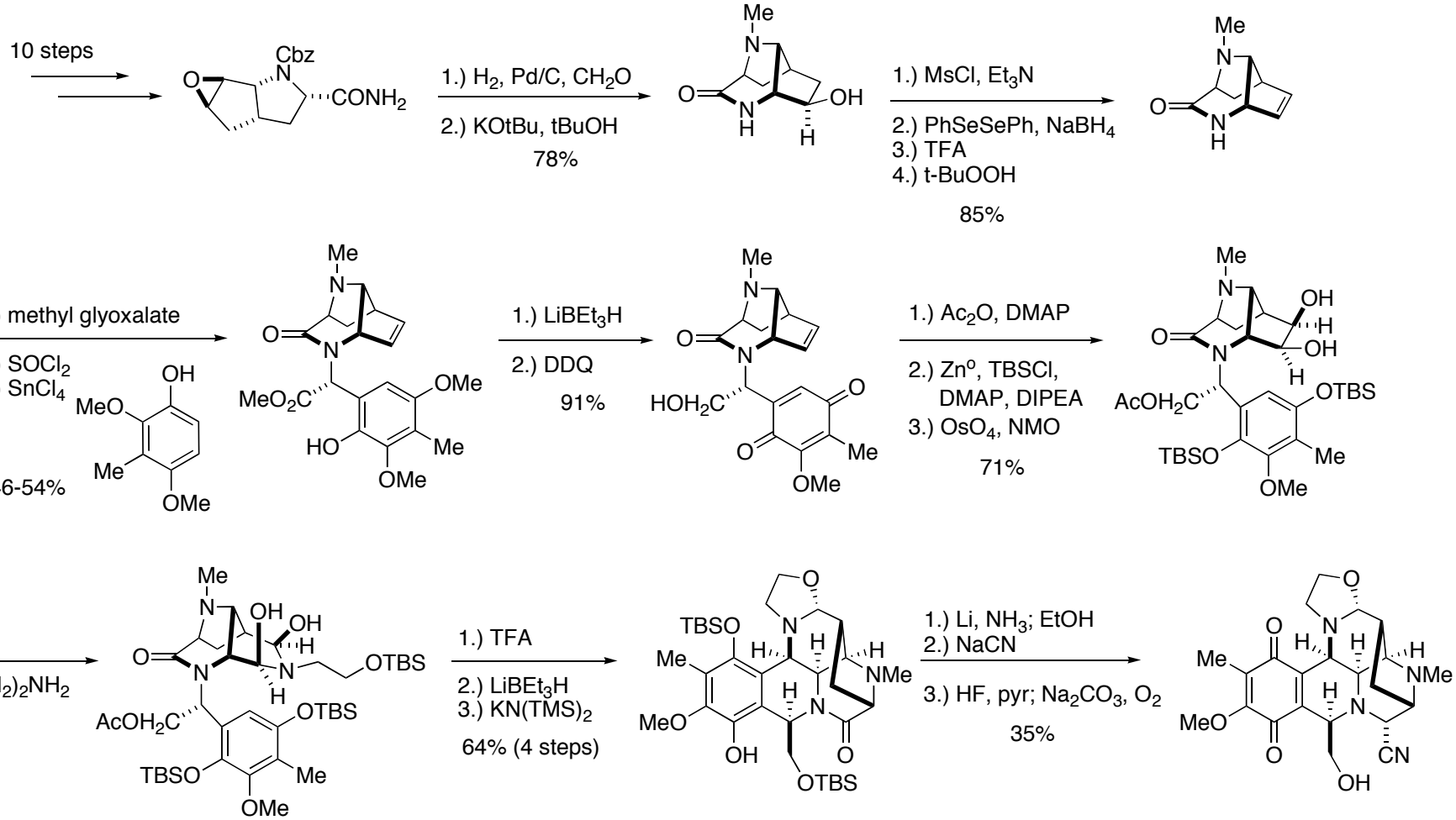
- Isolated in 1980 from *Actinosynnema pretiosum C-14482*

Cyanocycline A: *J, Antibiot.*, **1982**, *35*, 771
Naphthyridinomycin: *J, Antibiot.*, **1975**, *28*, 497

Bioxalomycin β2: *JOC.* **1994**, *59,* 4045
Dnacin A_1 and B_1: *J, Antibiot.*, **1980** *33*, 1443

Previous Synthesis...

- First total synthesis of (+/-) Cyanocycline A: Evans- 1986

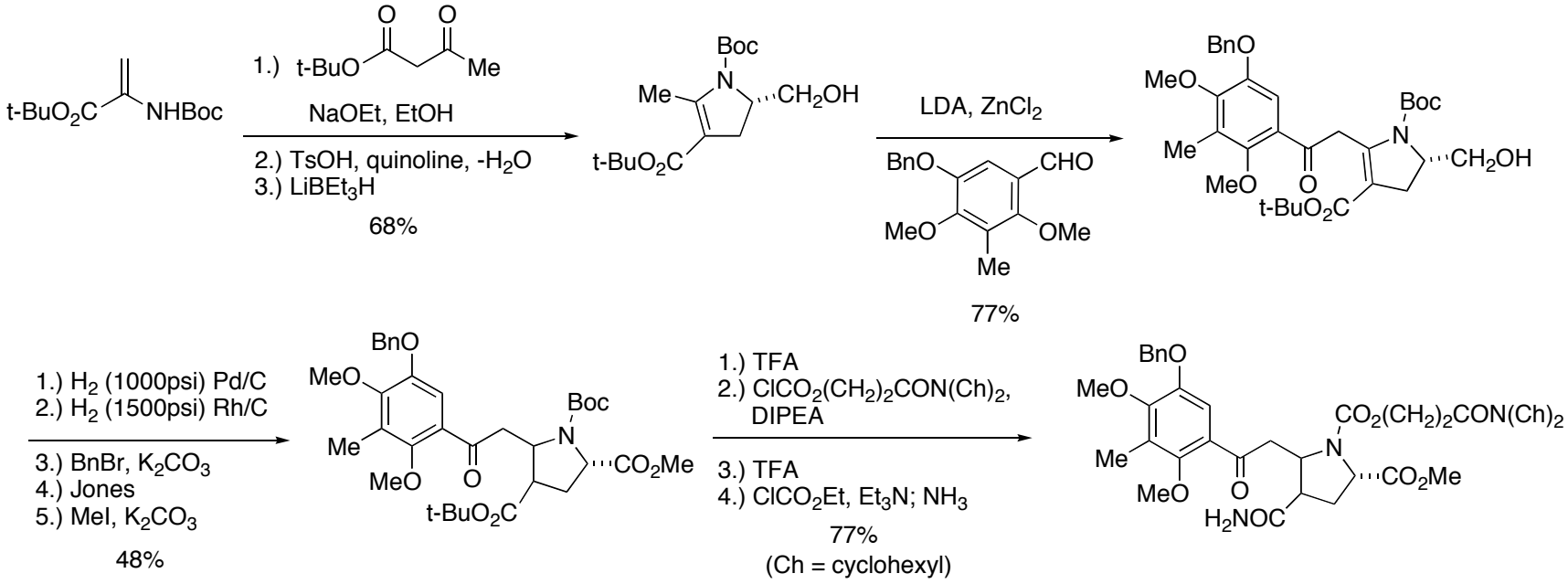


31 linear steps

JACS **1986**, *108,* 2478
Chem. Rev. **2002**, *102*, 1669

Previous Synthesis...

- Total synthesis of (+/-) Cyanocycline A: Fukuyama- 1987



JACS **1987**, *109,* 1587
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Previous Synthesis...

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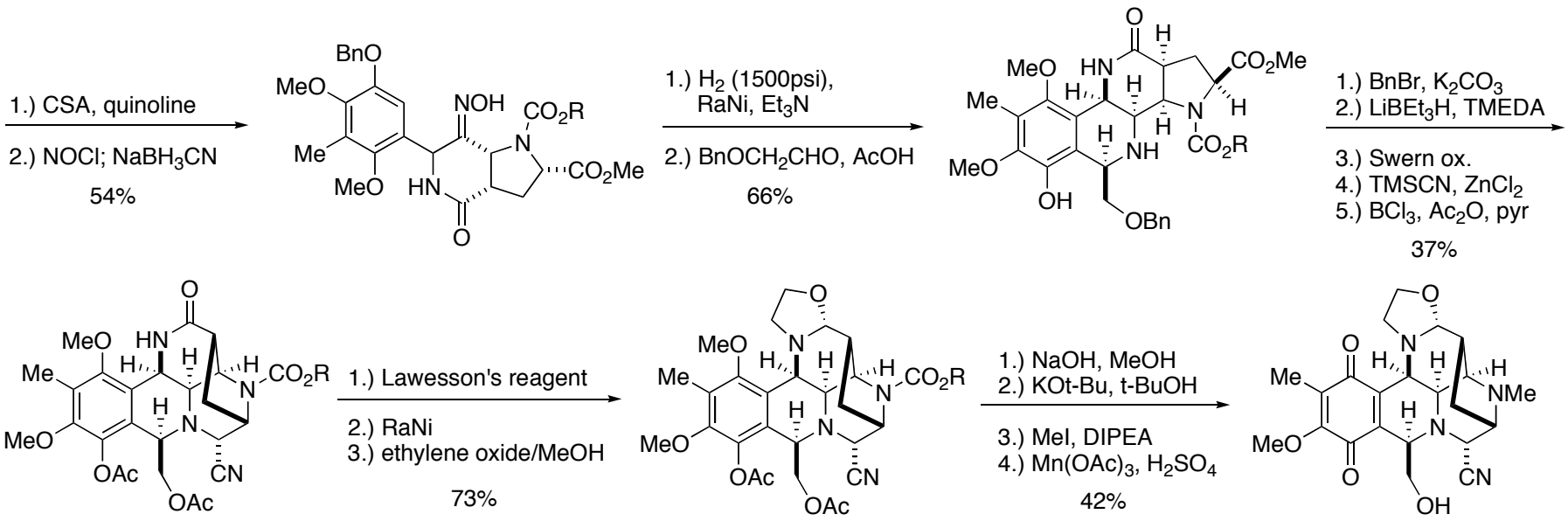
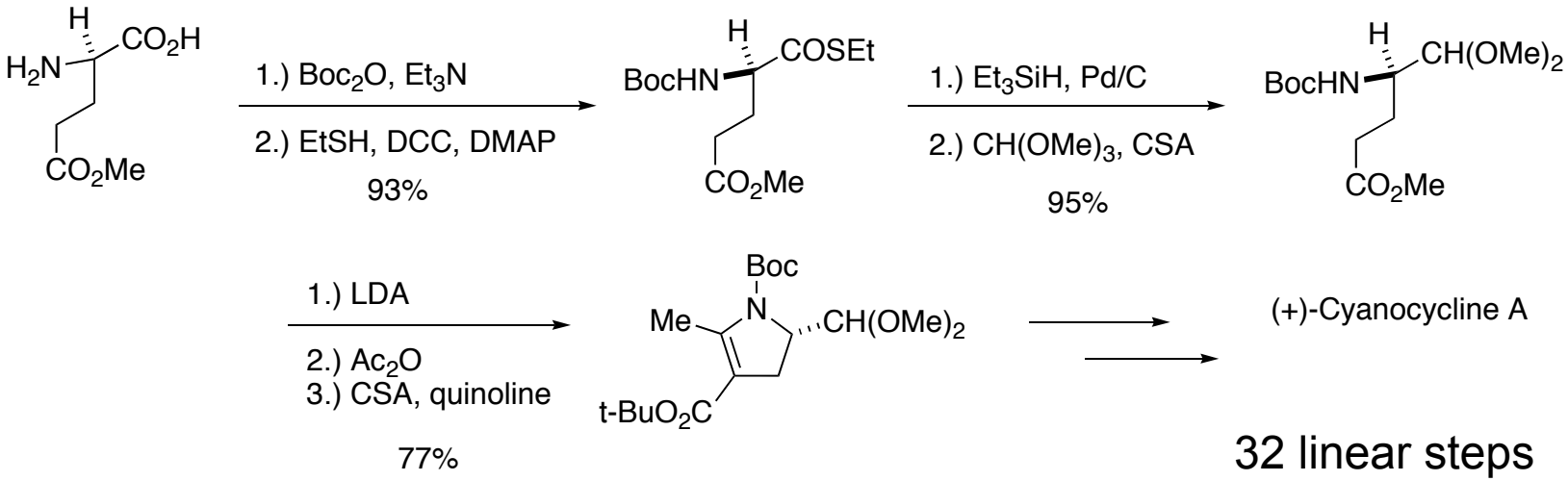


29 linear steps

JACS **1987**, *109,* 1587
Chem. Rev. **2002**, *102*, 1669

Previous Synthesis...

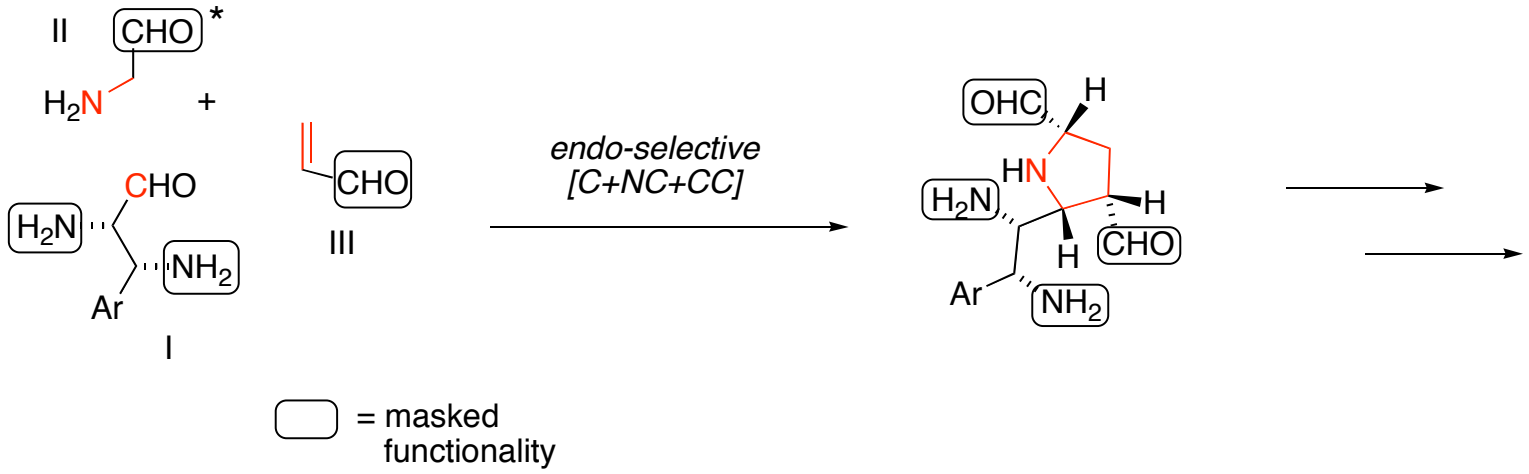
- Total Synthesis of (+)-Cyanocycline A: Fukuyama- 1987

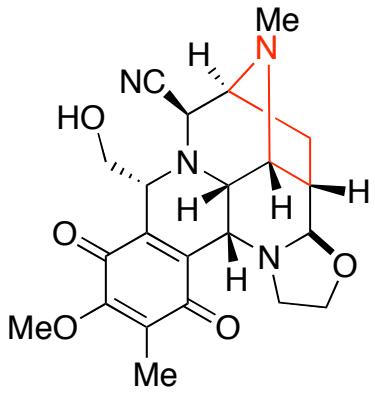


- this enantiospecific synthesis was used in the determination of the absolute stereochemistry of the natural product

Chem. Rev. **2002**, *102*, 1669
Li, L. Ph.D. Dissertation, Rice University, Houston, TX, 1989

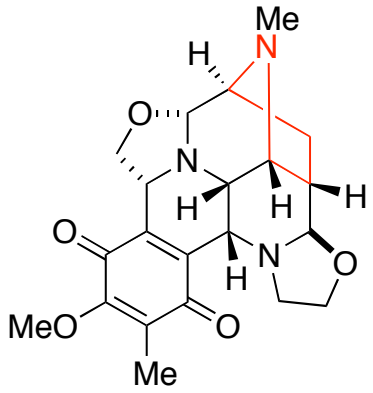
Synthetic Strategy…





Cyanocycline A

+

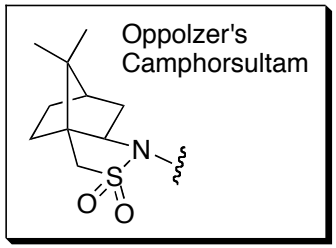


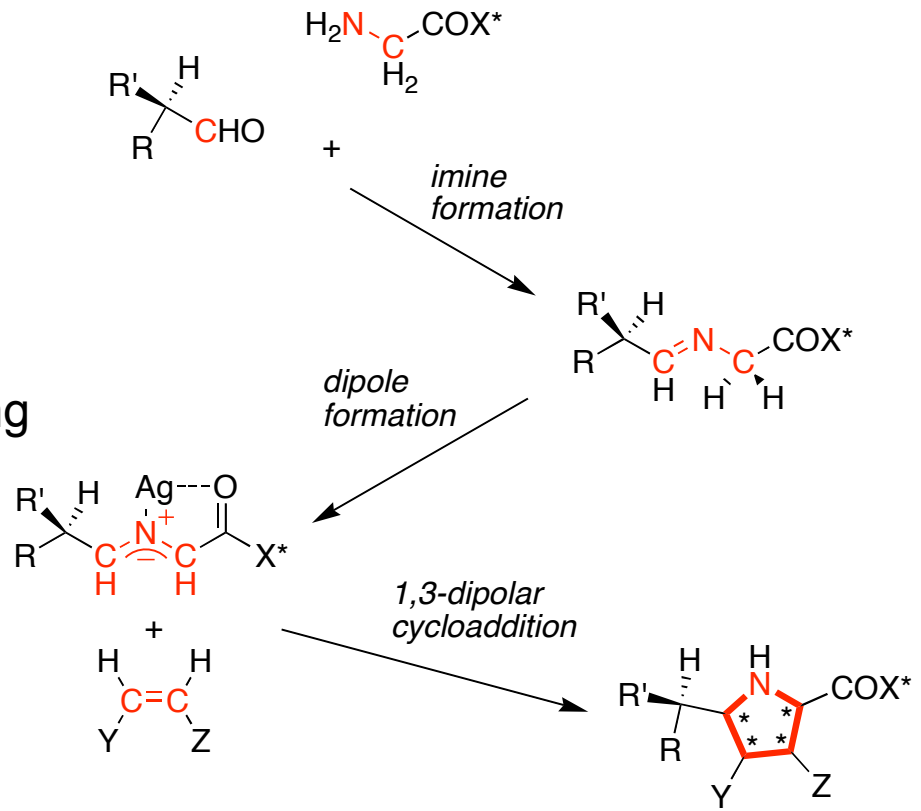
Bioxalomycin β2

The [C+NC+CC] Reaction

Ag^{I} or Cu^{I}- catalyzed Asymmetric [C+NC+CC] coupling cascade

Highlights:
- one-pot, molecular cascade featuring 1,3-dipolar cycloaddition
  - concerted process
  - 2 new C-C bonds
  - up to 4 new chiral centers
- mild, efficient, selective, high yielding
- absolute stereocontrol achieved via chiral, nonracemic substrates or auxiliaries





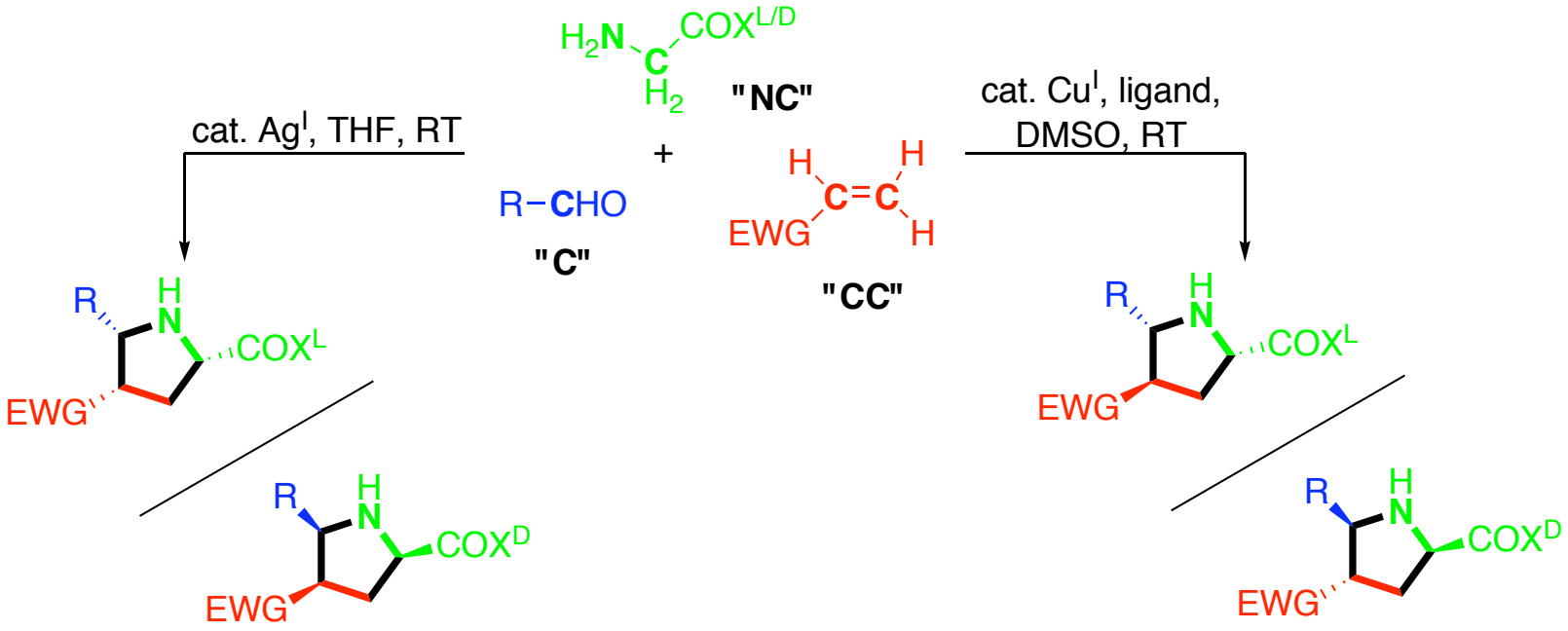
X*= oppolzer's D- or L-camphorsultam

- works well with enolizable and α-chiral aliphatic aldehydes!
- access to highly functionalized pyrrolidines

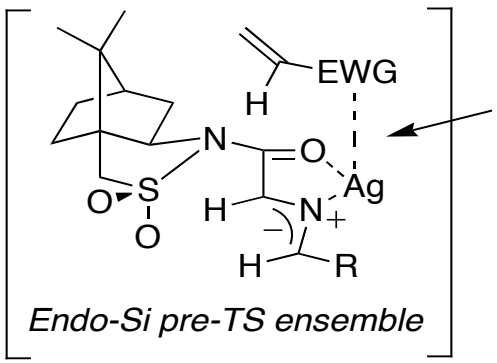
OL. **2006**, *8*, 3647
Tet. Lett., **2007**, *48*, 3867

The [C+NC+CC] Reaction

Selectivity in the [3+2] cycloaddition:



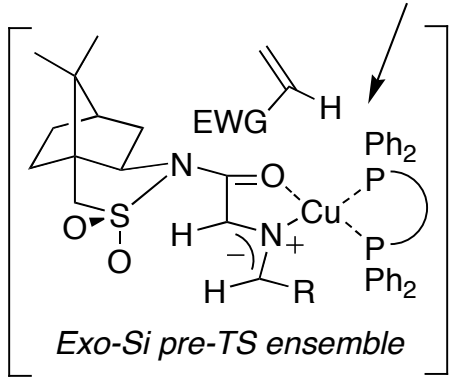
Transition State Rational



Endo-Si pre-TS ensemble

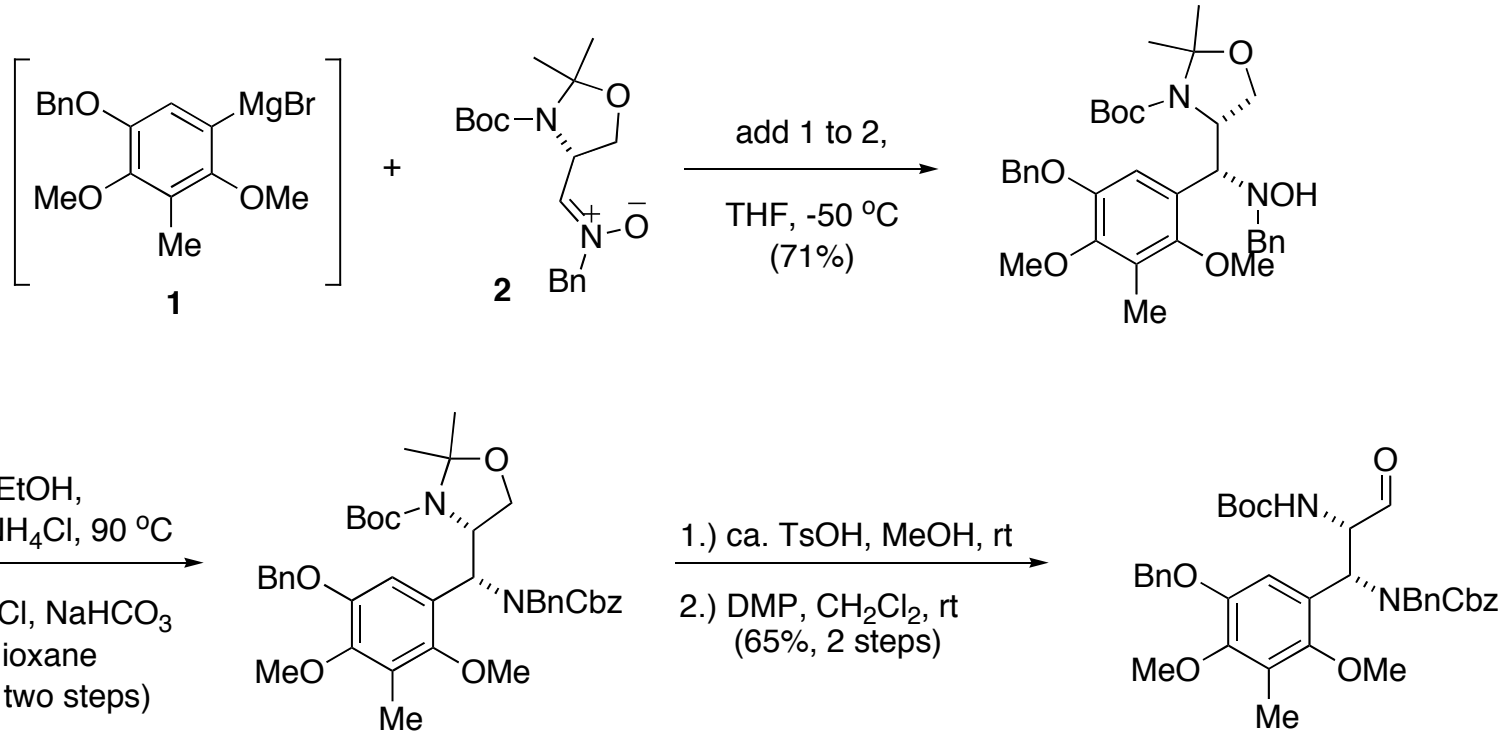
favorable coordination

Highly selective, often exclusively one stereoisomer.



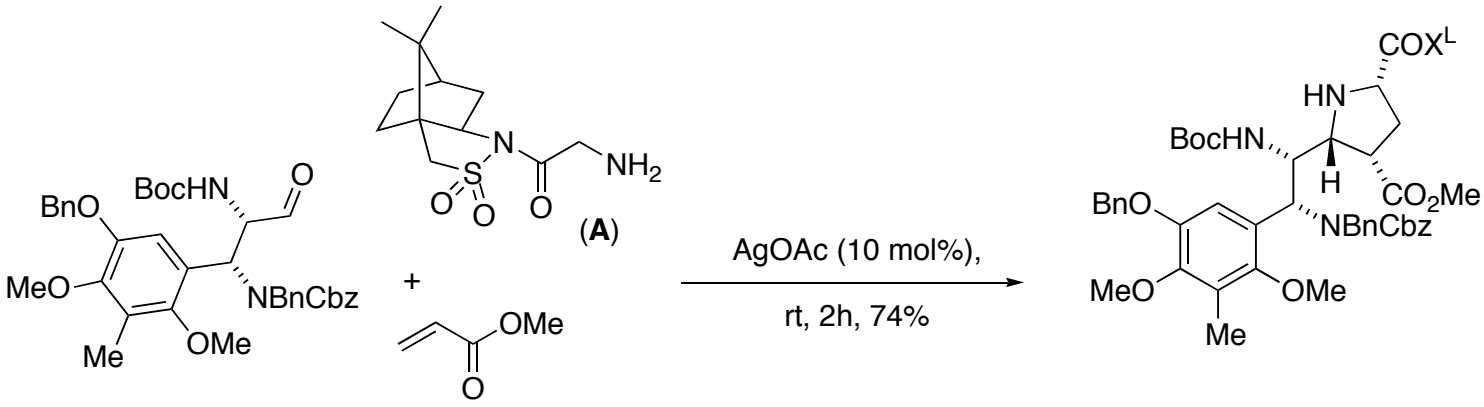
Exo-Si pre-TS ensemble

Aldehyde Synthesis



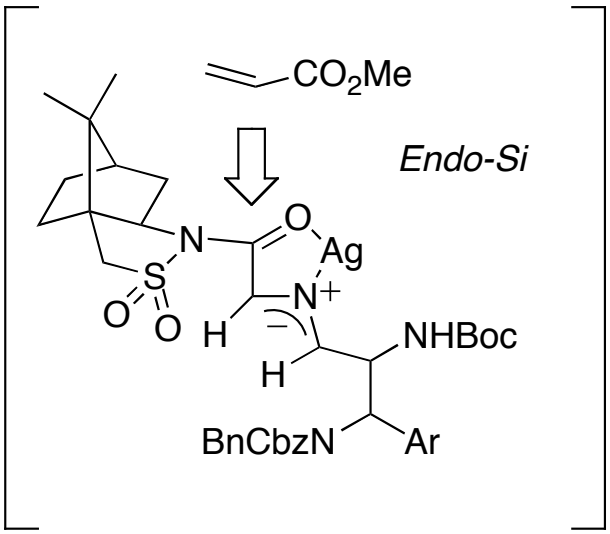
42% overall yield
from 2

Key [C+NC+CC] coupling



X^L= Oppolzer's camphorsultam (**A**)

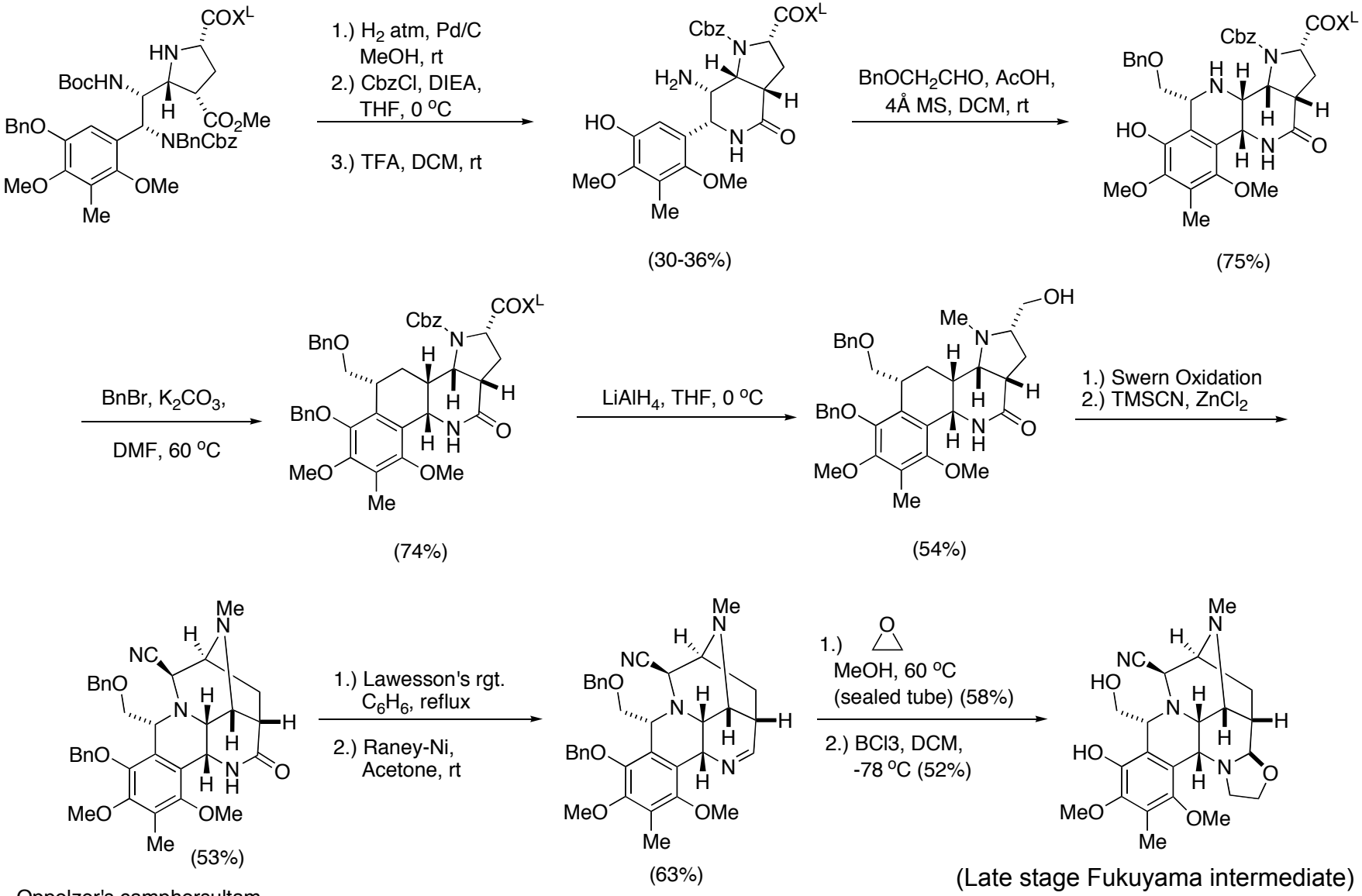
Proposed Pre-TS model:



- Stereochemical outcome predicted based on previous [3+2] cycloaddition studies
- Difficulty in confirming relative configurations by NMR at this stage
- Later determined by NOE studies of advanced, rigid intermediate

- Achieving this intermediate represents most ambitious application of the asymmetric [C+NC+CC] coupling manifold to date

End Game



X^L= Oppolzer's camphorsultam

In summary…

- A formal total synthesis of Cyanocycline A was accomplished in 22 linear steps from commercial material

- Cyanocycline A had previously been converted to Bioxalomycin β2, thus making this an efficient formal synthesis of it as well.
  (see: J*OC*, **1994**, *59*, 4045; Adv. Heterocycl. Chem, **1992**, *2*, 189)

- The [C+NC+CC] coupling methodology afforded the desired target, reducing the total steps by one-third of that of previous syntheses

- The successful application of the [C+NC+CC] coupling technology has now provided access to these complex natural product scaffolds and can provide access to similar members of the Tetrahydroisoquinoline family

- The [C+NC+CC] reaction manifold has great potential for introducing structural diversity in natural products and should become a valuable tool in both target and diversity oriented synthesis