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Synthesis of *ent*-Ketorfanol via a C-H Alkenylation/Torquoselective 6π-Electrocyclization Cascade

J. A. Ellman and K. N. Hauk et al., *Angew. Chem. Int. Ed.* **2015**, *54*, 12044.

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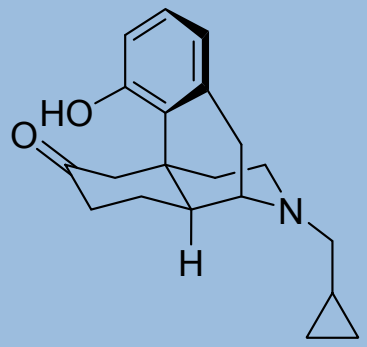

19.11.2015, Journal Club

Content

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Autors

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- Jonathan A. Ellman (Yale University)
  - *tert*-butanesulfinamide chemistry
  - catalytic conversion of C-H to C-C bonds
  - structures that interact with biological systems

- Kendall N. Houk (University of California)
  - theoretical and computational methods and programs
  - experimental research to test theoretical predictions

Opioids

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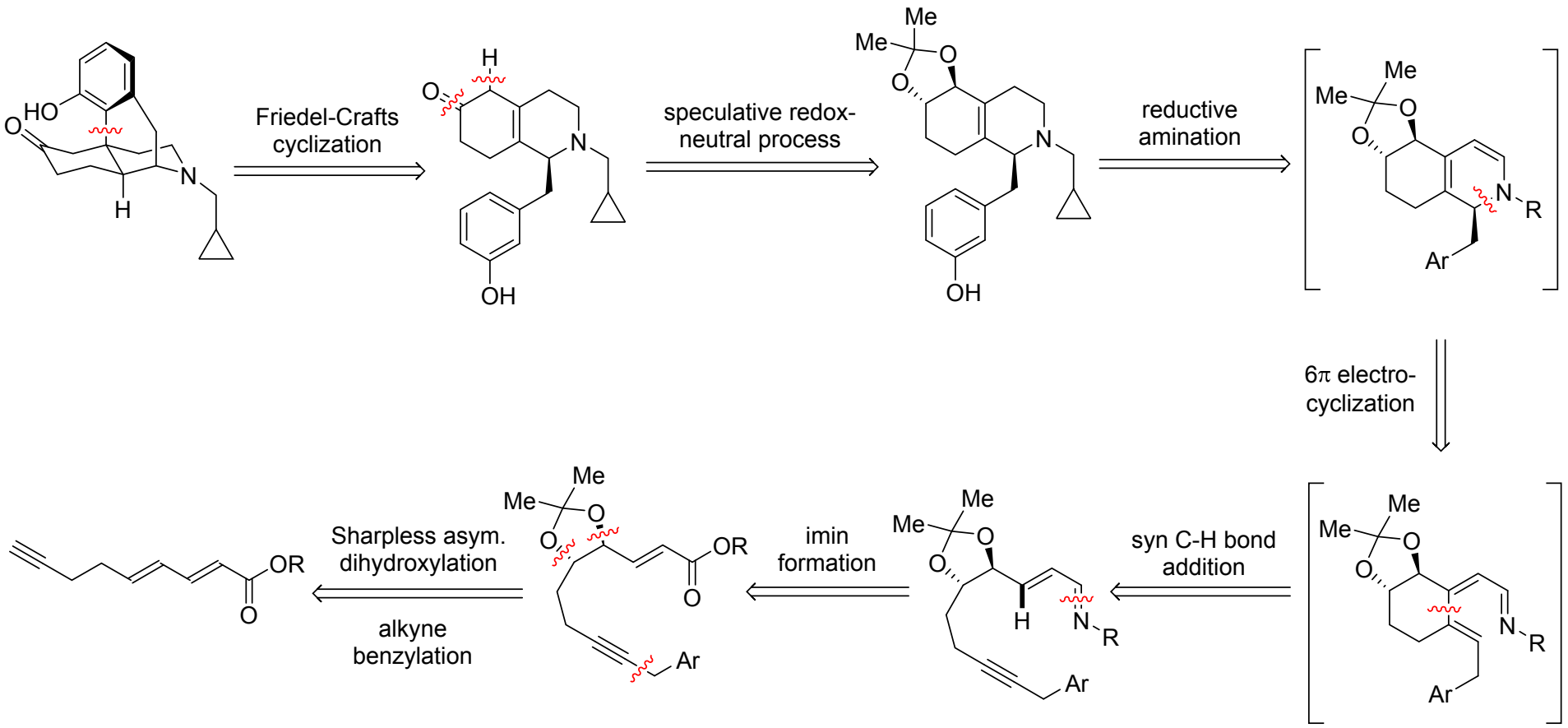
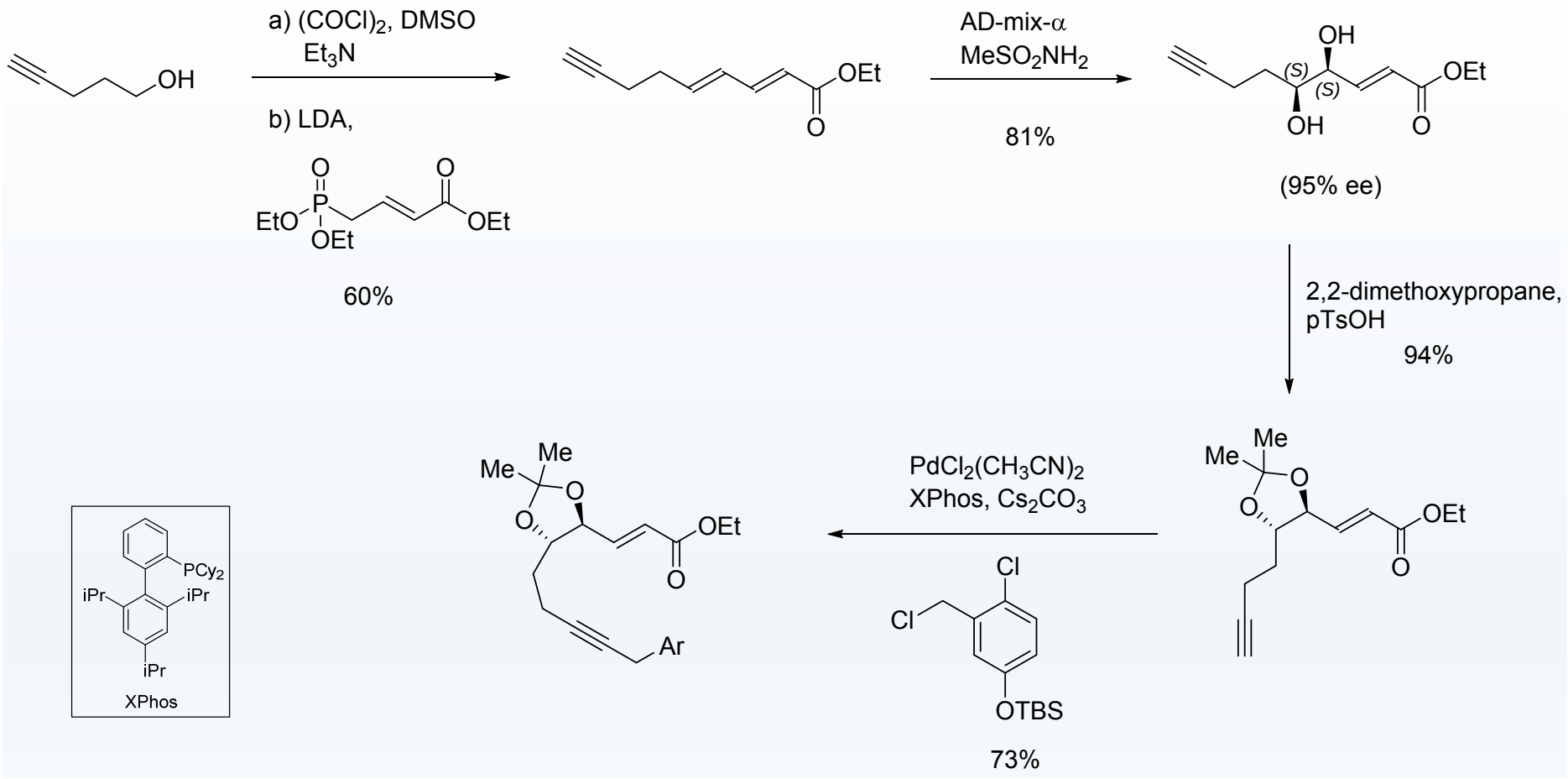
- Oxycodone and related semisynthetic opioids
  - Effective for the management of pain
  - Dependency, tolerance → higher dose → side effects
- Design of new opioid ligands with reduced drawbacks
- Ketorfanol
  - by multistep degradation of morphine and naltrexone

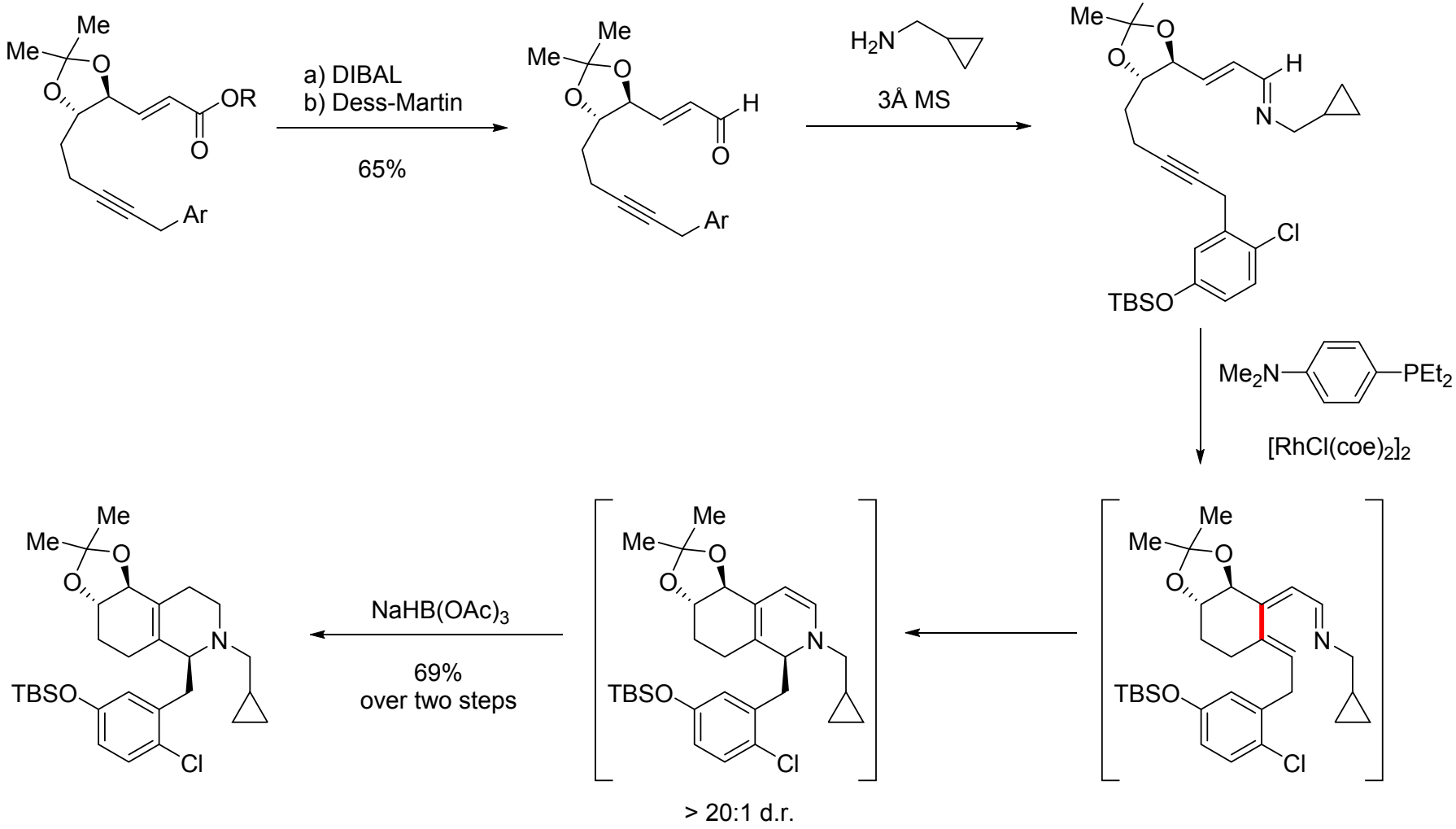
Retrosynthetic Analysis



Forward Synthesis

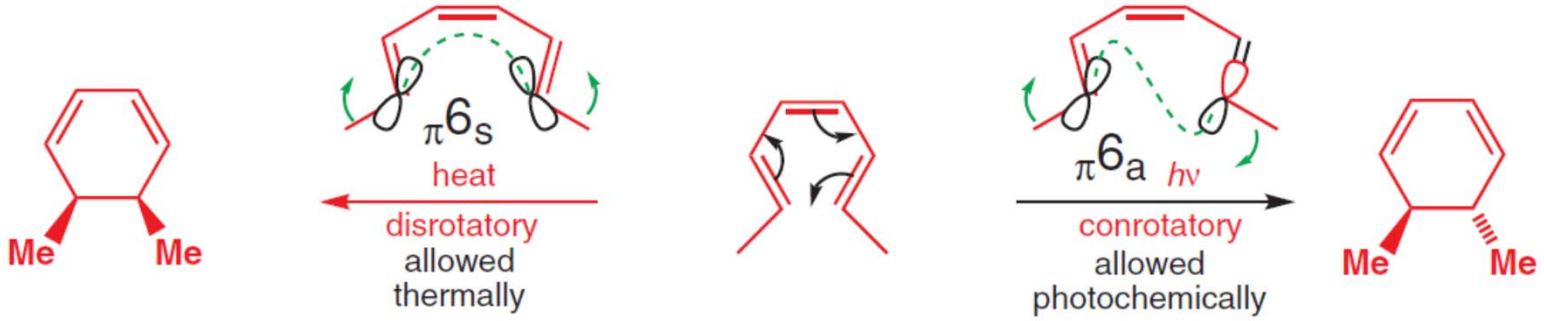


Forward Synthesis

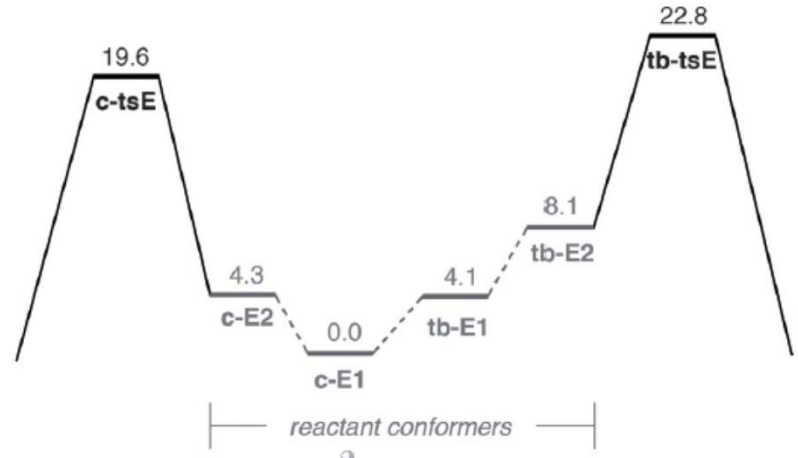


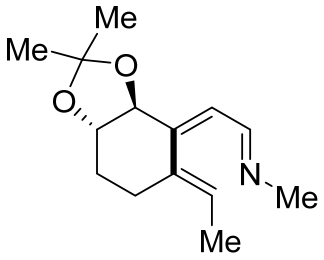
Electrocyclization

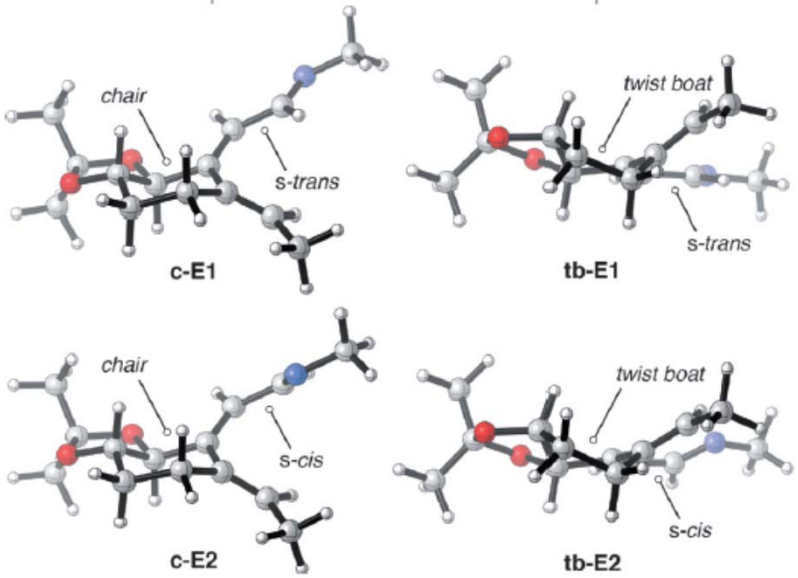
> Woodward-Hoffmann rules: suprafacial for (4n + 2) π systems under thermal conditions

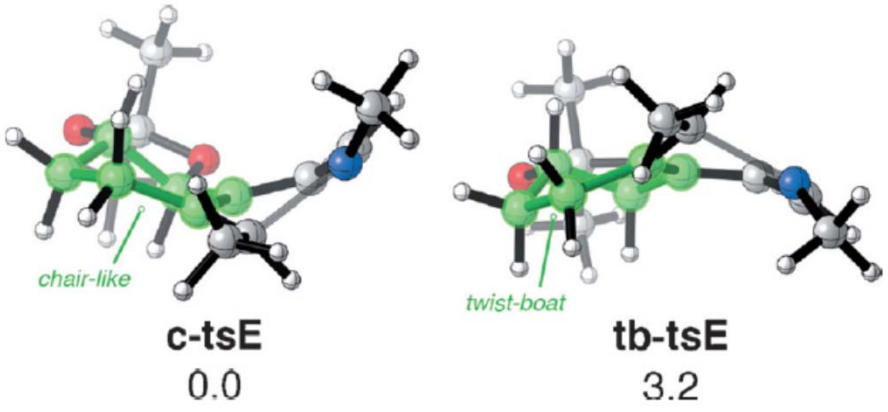


Calculations conformers and transition structures

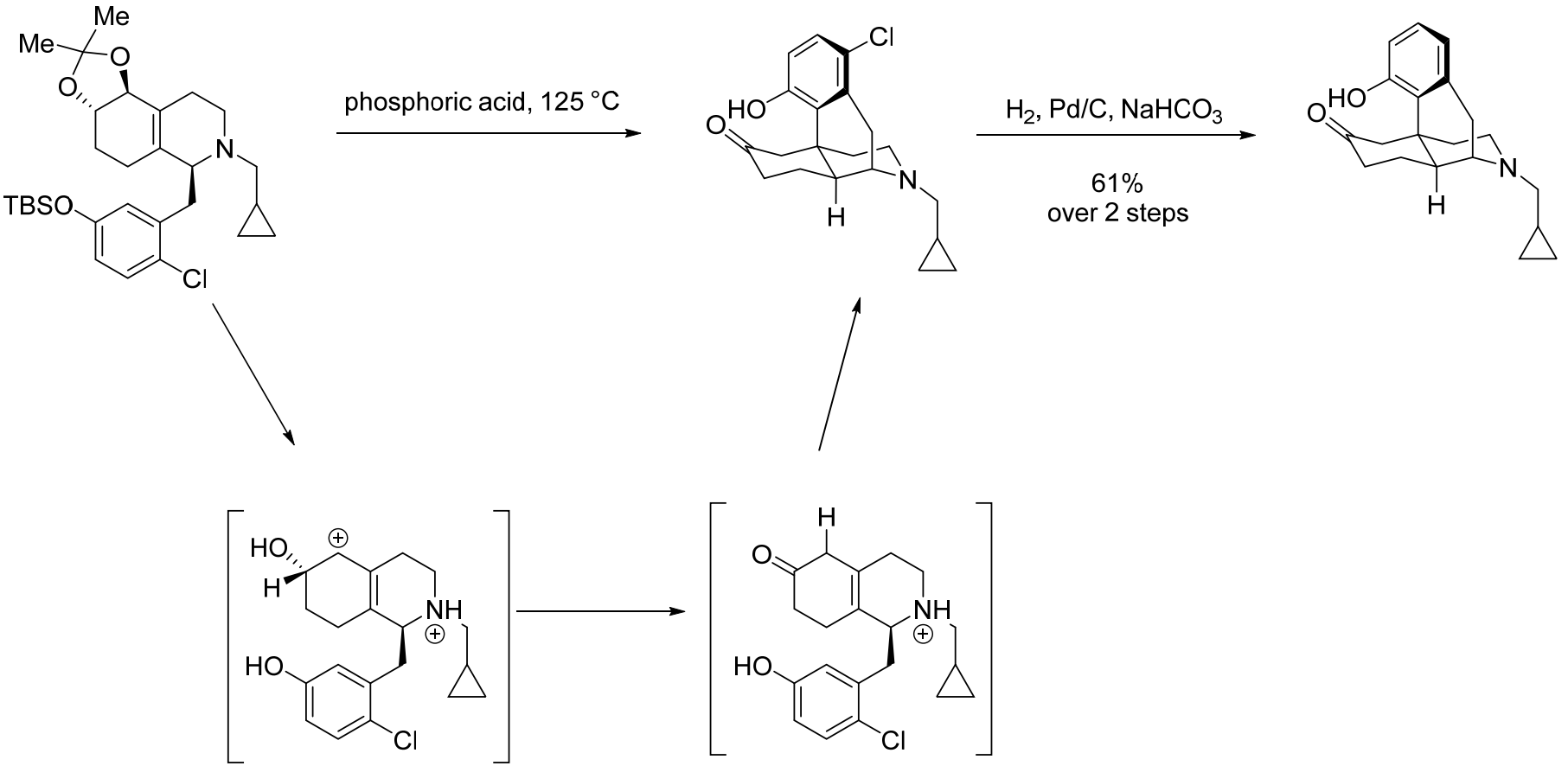




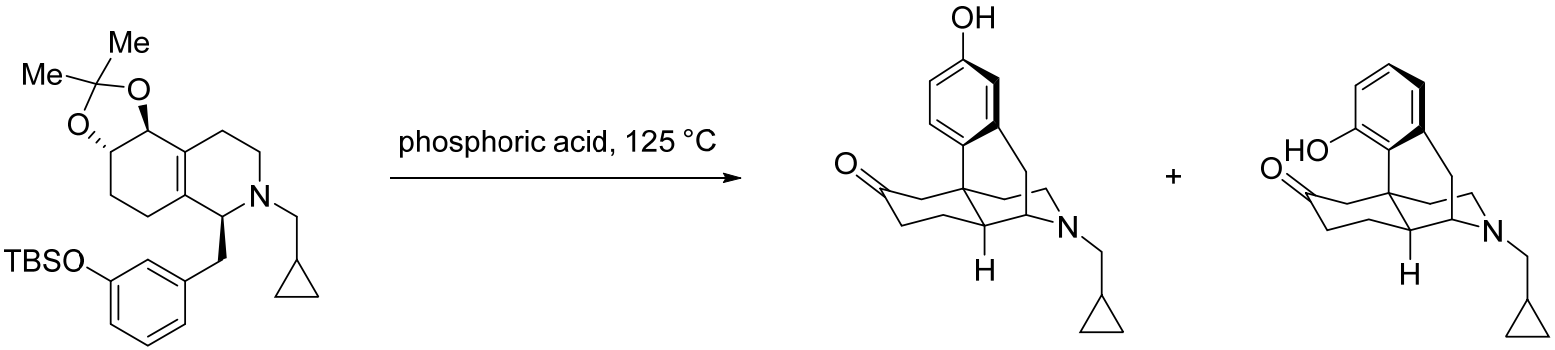




Forward Synthesis



Forward synthesis



2:1 regioisomers

Conclusion

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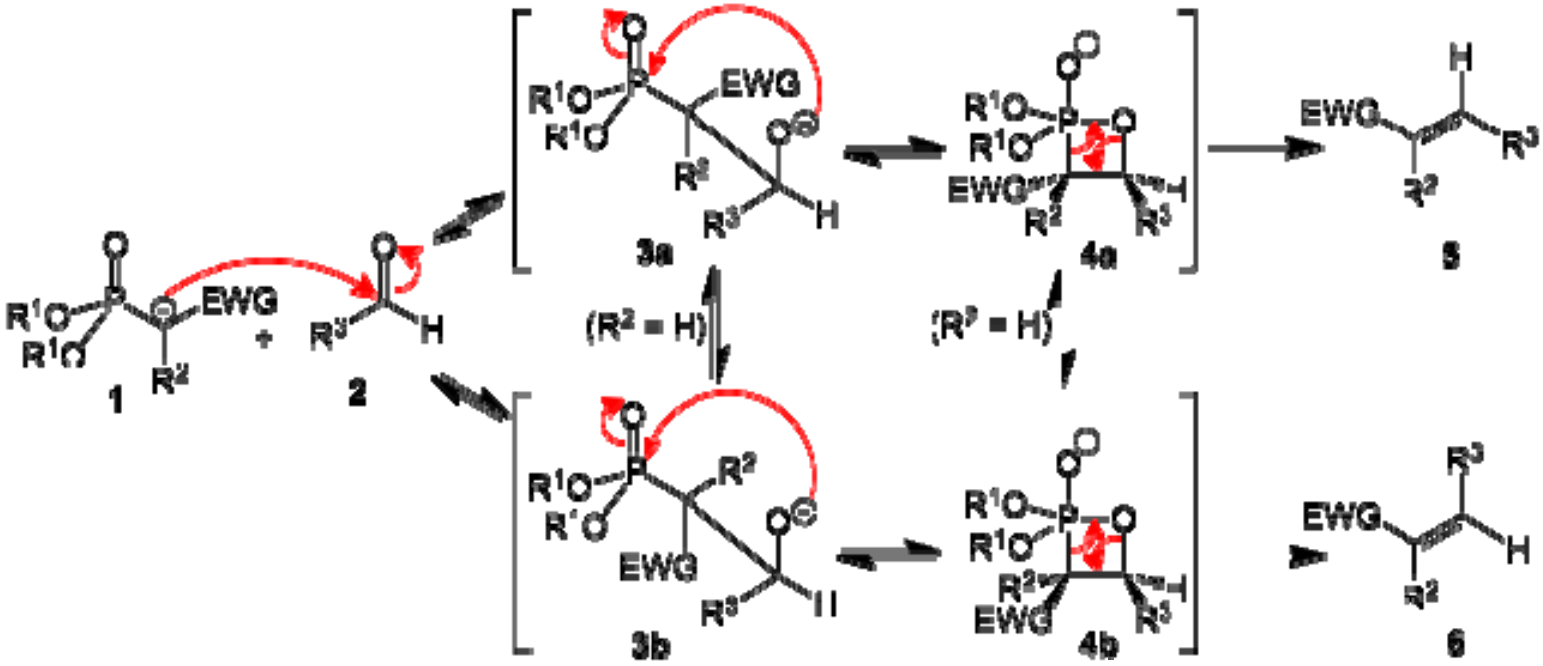
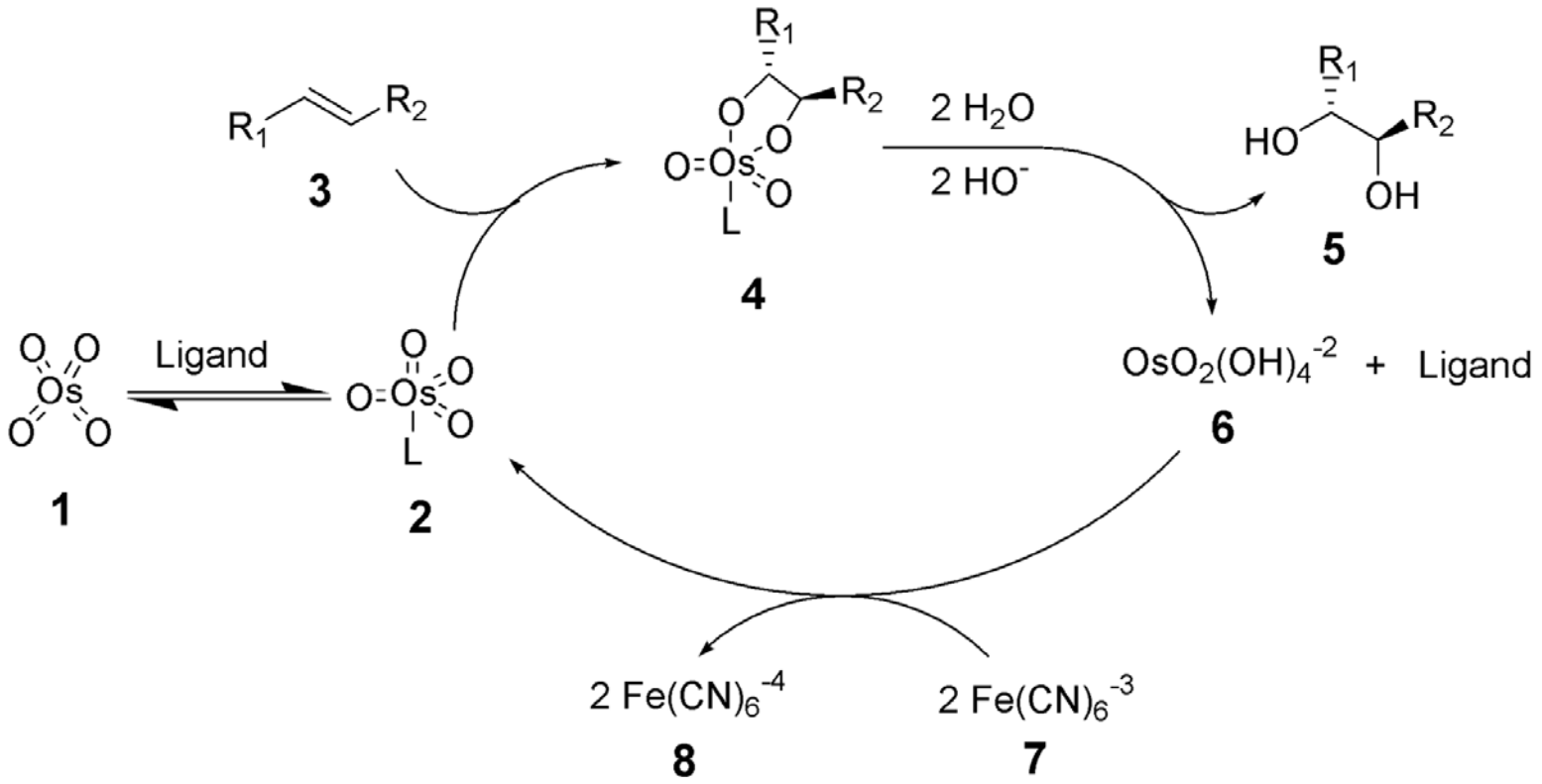
- Synthesis of *ent*-Ketorfanol: 9% yield over 11 steps

- **Key steps**
  - intramolecular C-H alkenylation/torquoselective 6π electrocyclization cascade
  - Redox-neutral rearrangement of a vicinal diol → ketone then intramolecular Friedel-Crafts alkylation

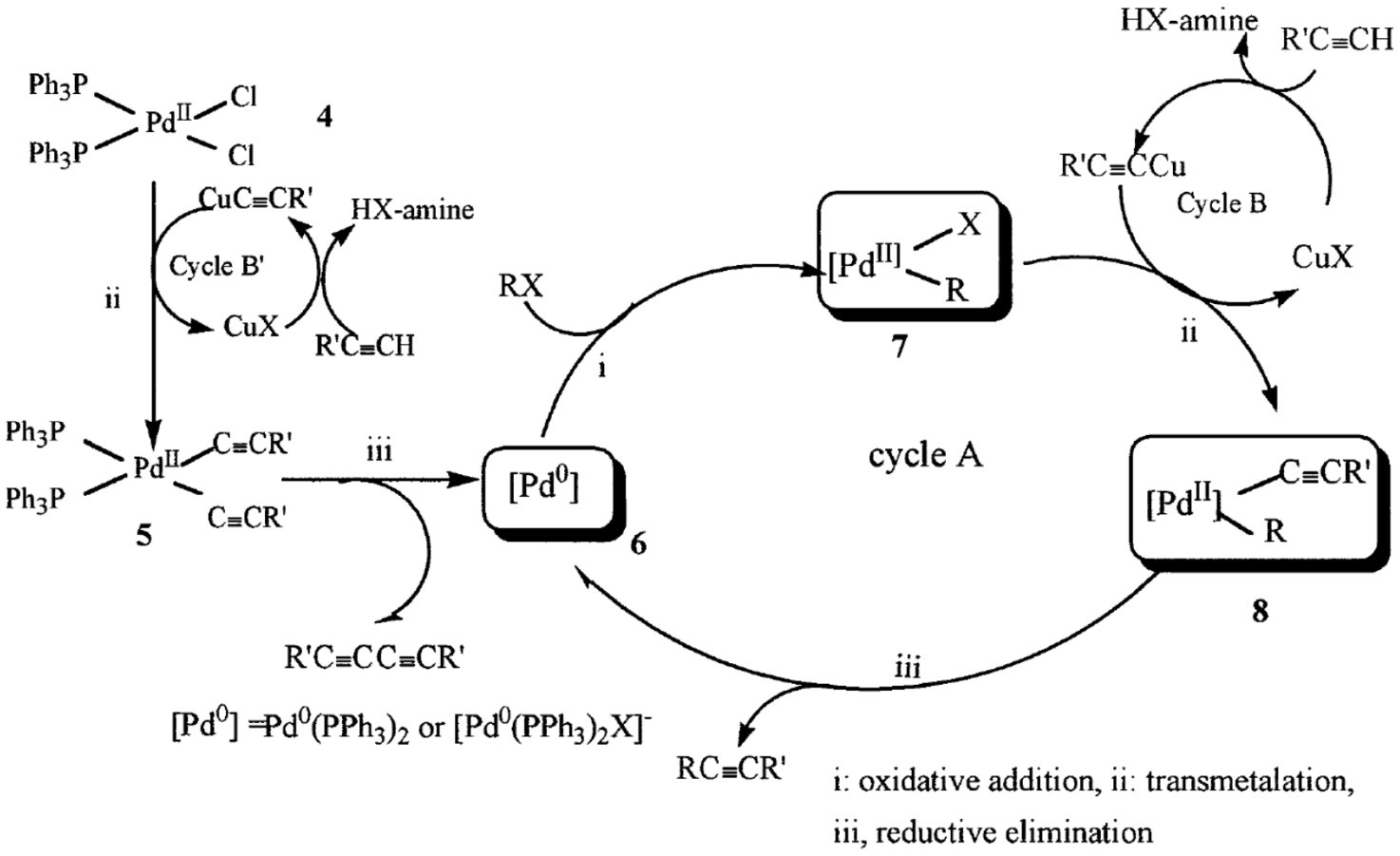
Horner-Wadsworth-Emmons



Sharpless asymmetric dihydroxylation



Palladium-Catalyzed Heck alkynylation of benzyl chlorides



CH-functionalization/6π electrocyclization cascade