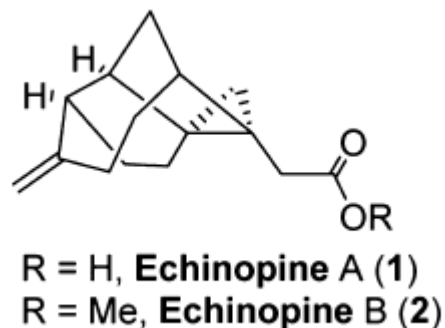


Formal Total Synthesis of Echinopines A and B via Cr(0)-Promoted $[6\pi + 2\pi]$ Cycloaddition

Saptarshi De, Shilpi Misra,* and James H. Rigby

Org. Lett. **2015**, *17*, 3230–3232





> James H. Rigby

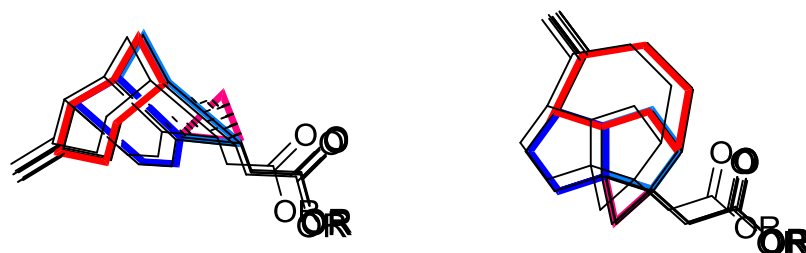
- Professor & Chair in the Organic Division at Wayne State University
- Ph.D., University of Wisconsin-Madison with Prof. B. Trost, 1973-1977
- Swiss NSF Postdoctoral Fellow, ETH-Zürich with Prof. A. Eschenmoser, 1977-1978
- NIH Post-Doctoral Fellow, Columbia University, 1978-1979

> Research Interests :

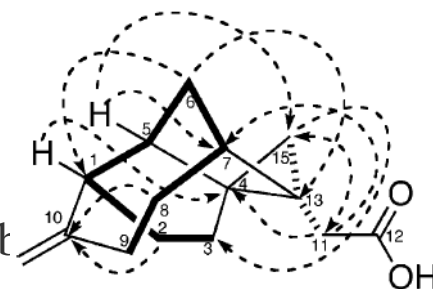
- Total synthesis of pharmacologically active natural products (Stenine, Taxol...)
- Construction of complex cyclic structures: *Via* cycloadditions ([4+2], [4+1], Cr(0)-promoted higher-order cycloaddition reactions, [6 π +4 π] and [6 π +2 π] ...)

Introduction

- > Isolated from the roots of *Echinops spinosus* by Shi and Kyota in 2008
 - From 3 kg roots 2 mg of each isomers
- > Belong to the family *Asteraceae*
(from Greek “which looks like a hedgehog”)
- > Structures unambiguously assigned as unique [3.5.5.7]
 - First example of a novel 3/5/5/7-membered ring carbon framework
 - Flat chair form for the 7 membered /ring-envelope shape for the 5 membered ring

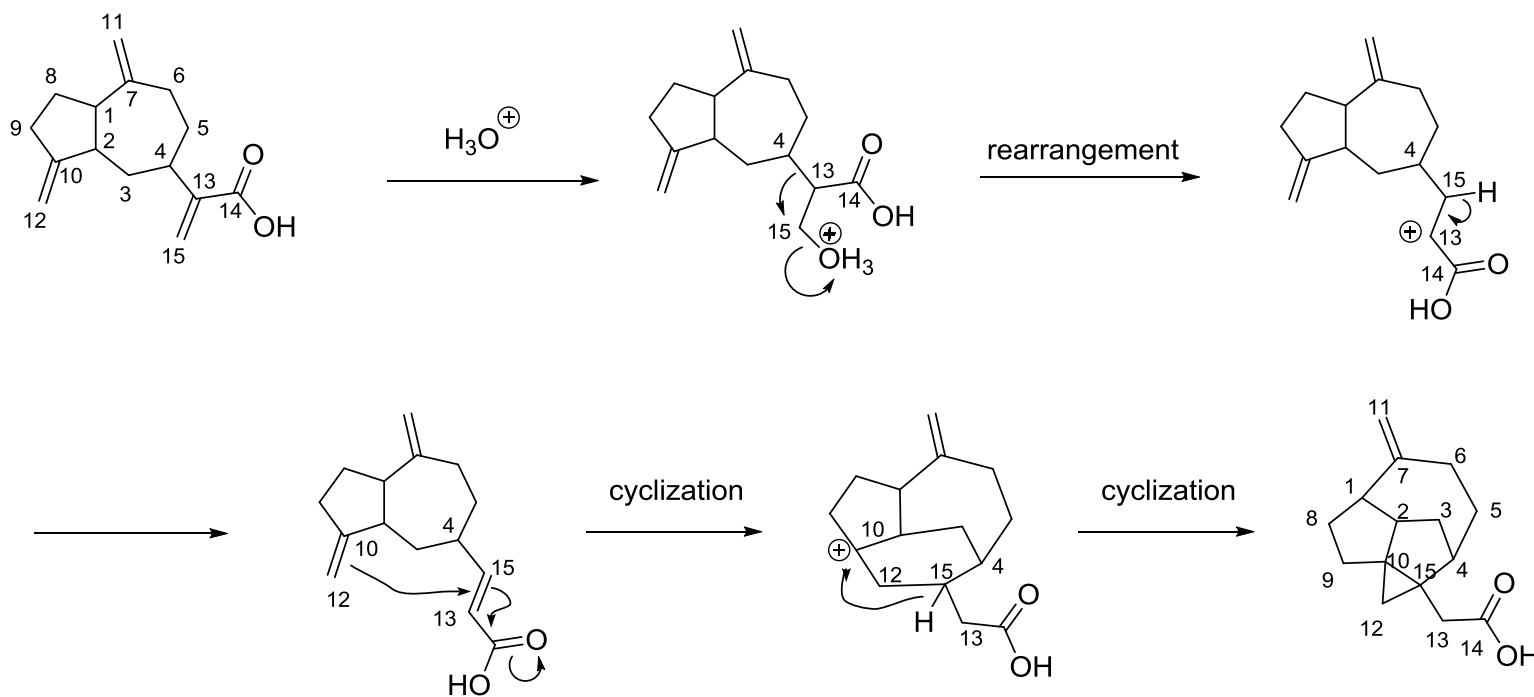


- Characterization only done with HRMS and NMR (no crystal)
- Absolute configuration in 2009: first enantioselective synthesis by workers



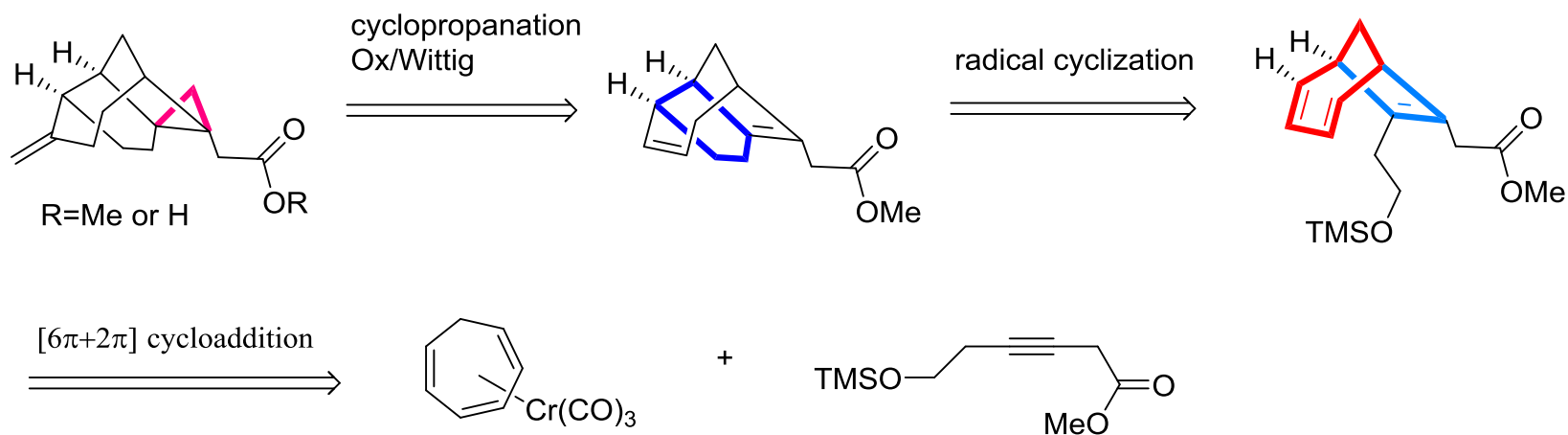
Biosynthesis

> Plausible Biosynthetic pathway from Guaiane skeleton



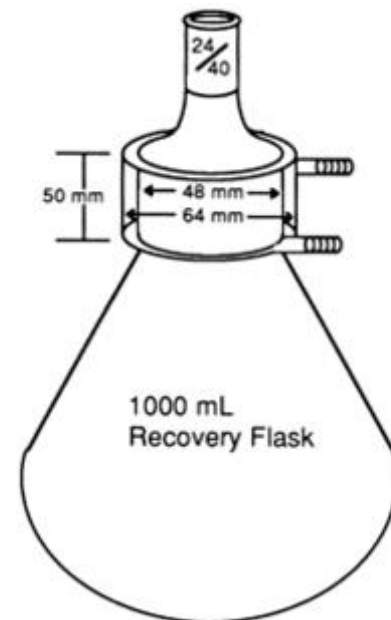
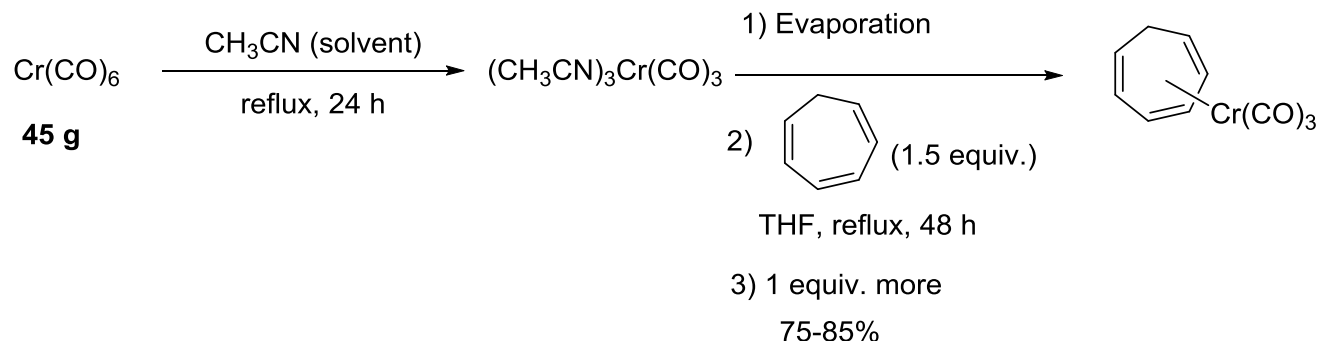
Retrosynthetic Analysis

- > Retrosynthesis for formal and total synthesis



Synthesis of Reagents for the Cycloaddition

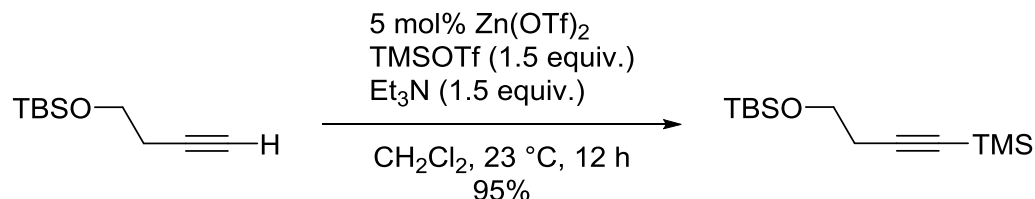
> Synthesis of Cr(0) Complex:



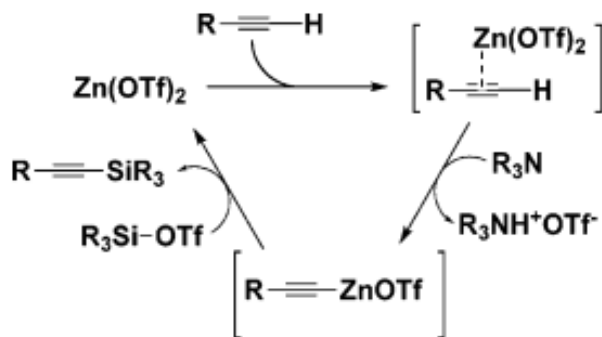
- *Warning!* Tris(acetonitrile)chromium tricarbonyl is highly pyrophoric
- Degrades rapidly when exposed to oxygen (reasonably stable in THF solution).
→ green colored [Cr(III)] decomposition product
- Reaction monitored by TLC
- Total reaction time averaged ~180 hr

Synthesis of Reagents for the Cycloaddition

- > Synthesis of substituted alkyne partners
 - Silylation of terminal alkyne for model study



- Usually: deprotonation of terminal alkynes with organolithium, or Grignard reagents → addition of a silyl electrophile

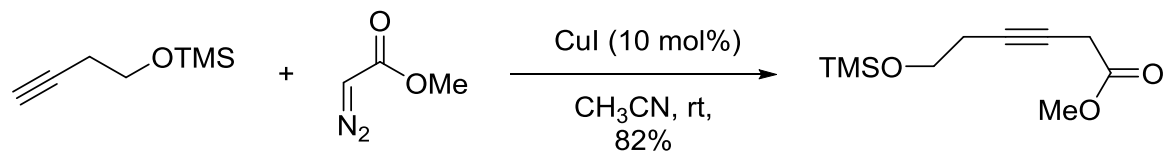


Matching the counterion of the zinc catalyst with the leaving group on silicon
 → Regeneration of Zn(OTf)_2 → Catalytic process

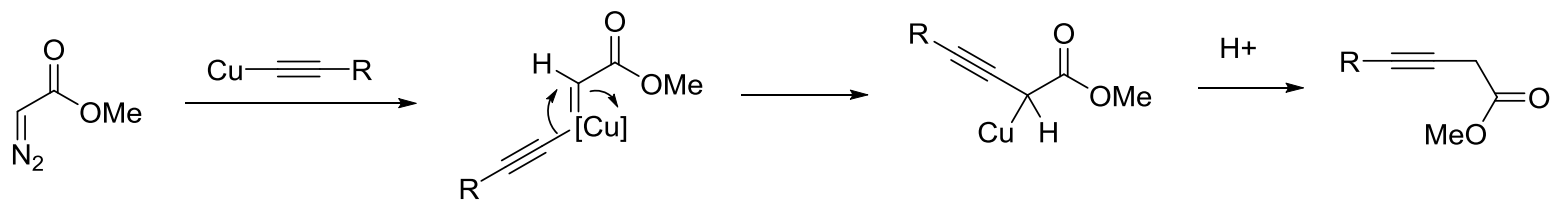
Synthesis of Reagents for the Cycloaddition

> Synthesis of substituted alkynoate

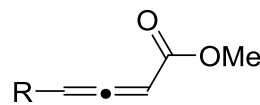
- Insertion into C_{alkynyl}-H



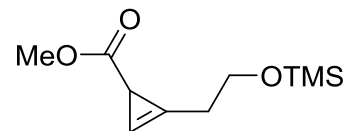
> Mechanism



- Possible side product : allene (8%)

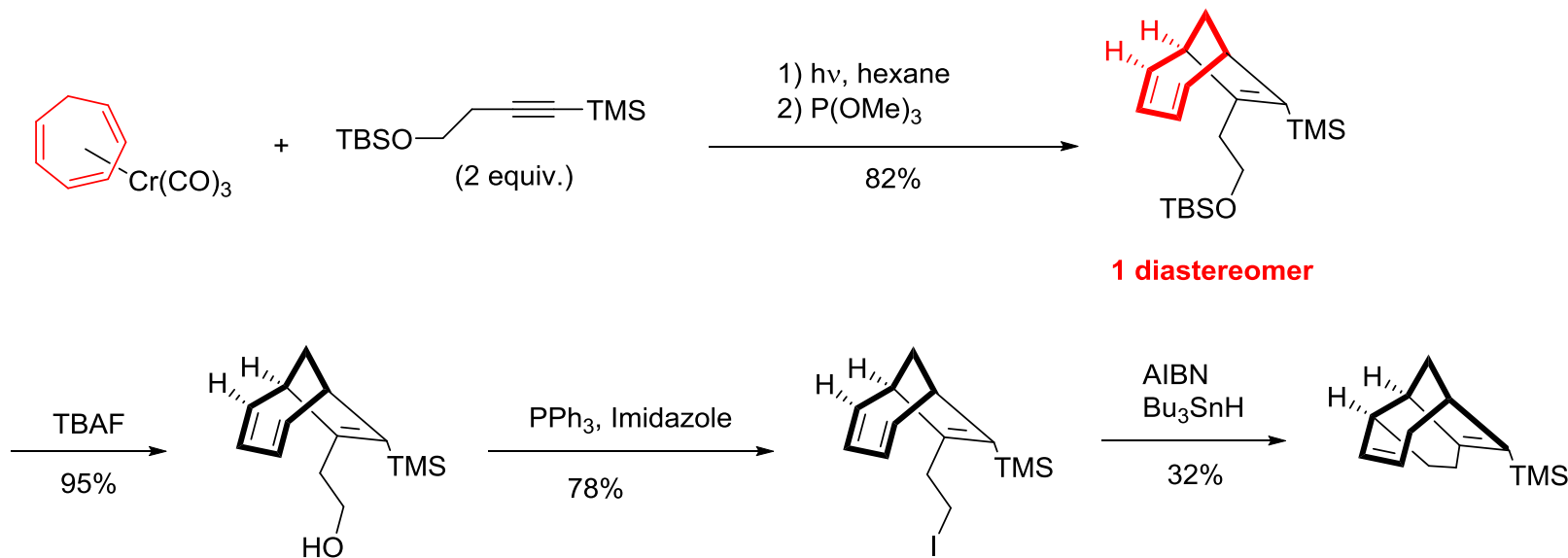


- Without catalyst, with Rh complexes or Cu:



Synthesis of bicyclo[4.2.1]nonane substructure

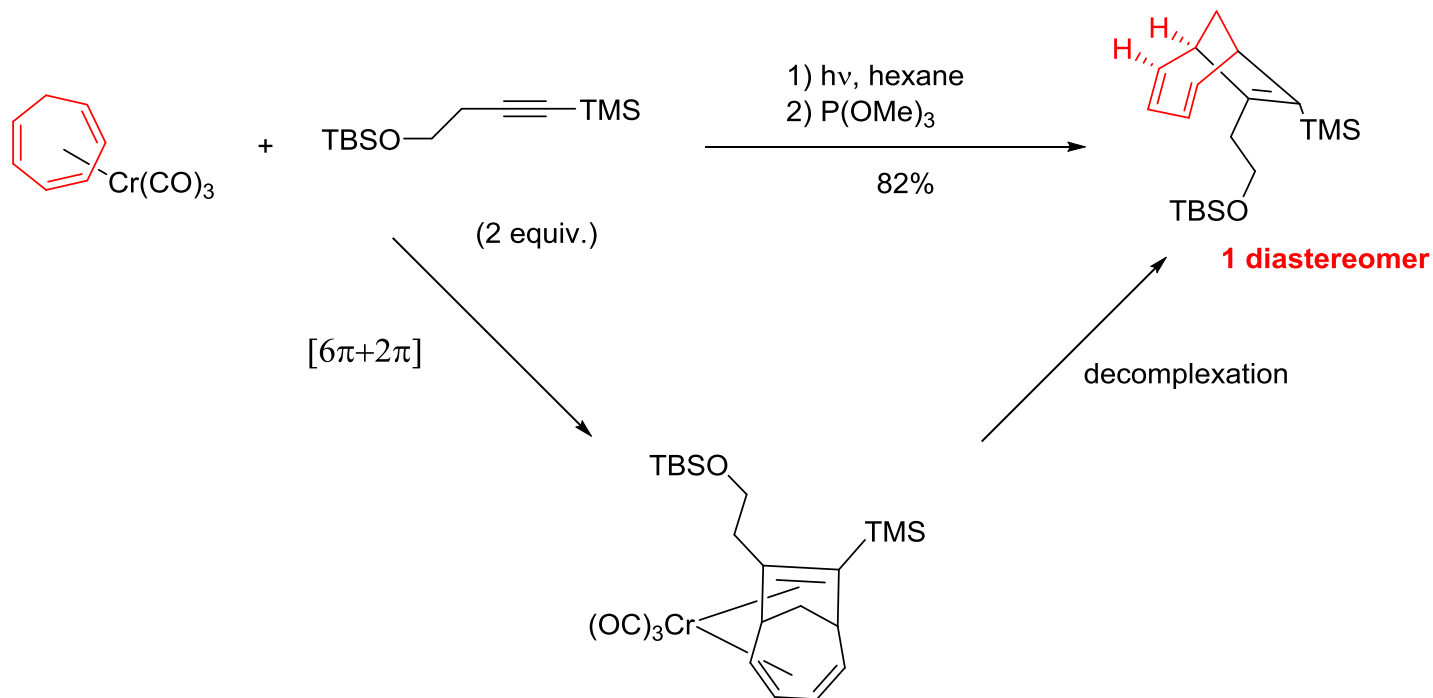
> Model study (Known final product)



- Not really optimized (I vs Xanthate, addition of AIBN/ Bu_3SnH)
- Other starting material not complicated to do?
- Just to attribute every H or C by NMR.

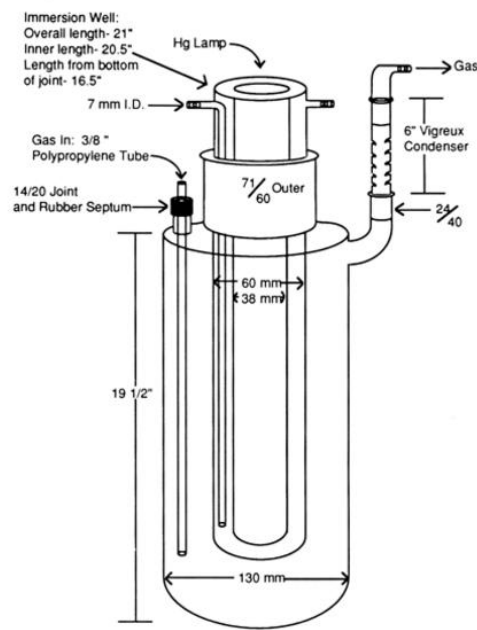
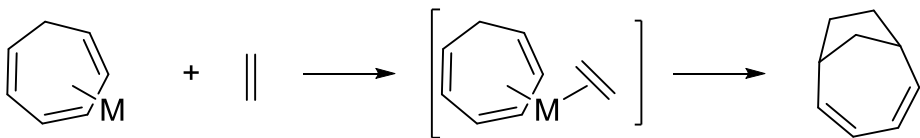
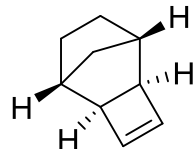
Synthesis of bicyclo[4.2.1]nonane substructure

> Photochemical cycloaddition (key step)



Synthesis of bicyclo[4.2.1]nonane substructure

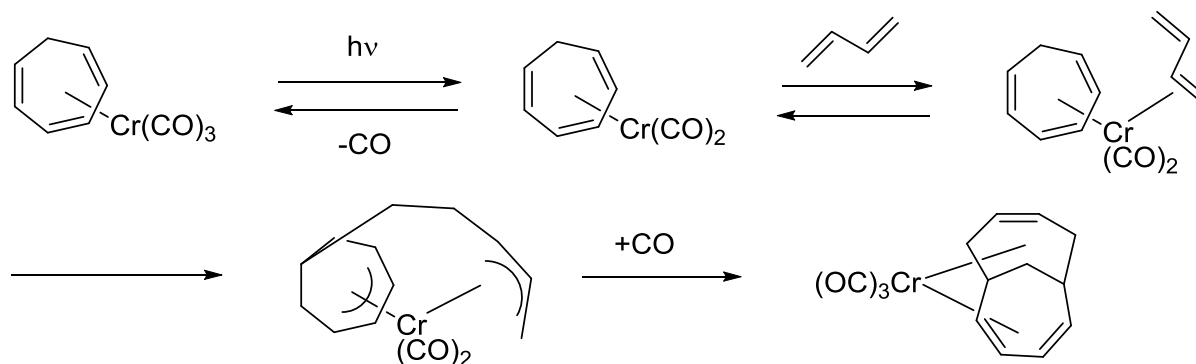
- > Photochemical cycloaddition: methodology beyond
 - Aim : produce bicyclo[4.2.1]nonane carbon skeleton
→ Creation of several C-C bonds and stereocenters one pot.
 - Problem usually: competitive pathway, low periselectivity level
 - How? Irradiation (450-W Canrad-Hanovia medium pressure Hg vapor lamp, Pyrex filter)
 - Use of Pyrex filter (cut off) to avoid
 - Result: metalfree bicyclo- [4.2.1]nonadiene adducts (g)
→ Orientation with Cr



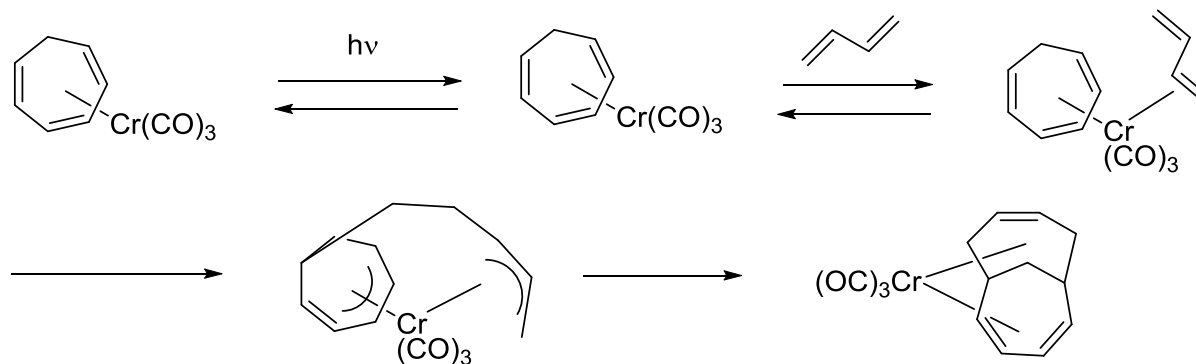
Synthesis of bicyclo[4.2.1]nonane substructure

> Photochemical cycloaddition: mechanism

■ First proposition

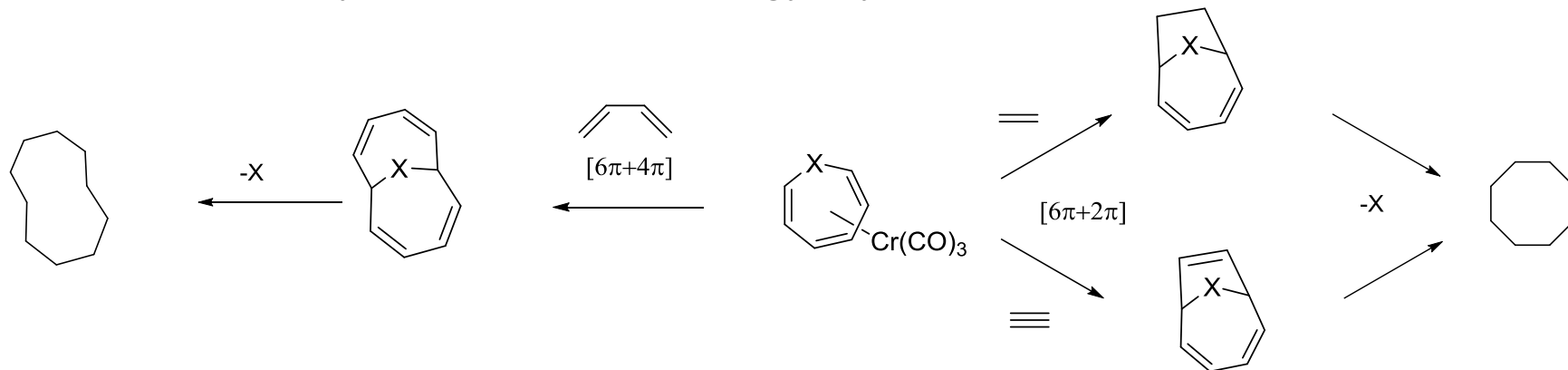


■ Alternative pathway

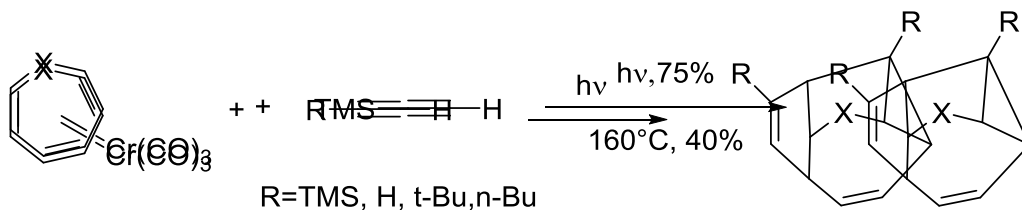
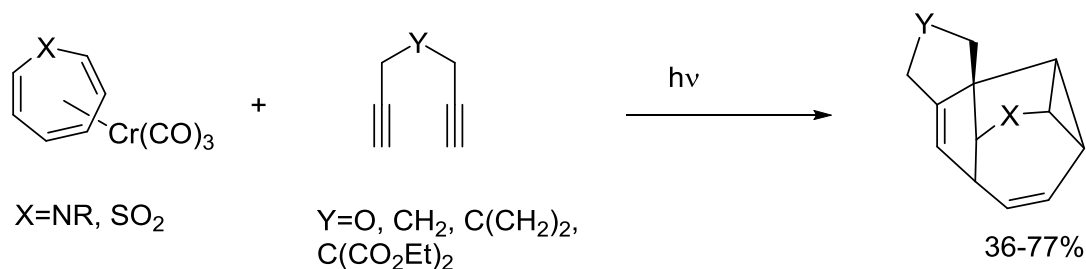


Synthesis of bicyclo[4.2.1]nonane substructure

> Photochemical cycloaddition: methodology beyond

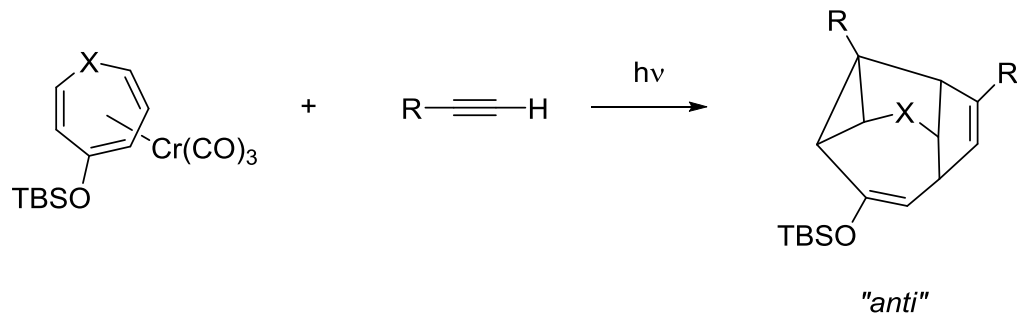
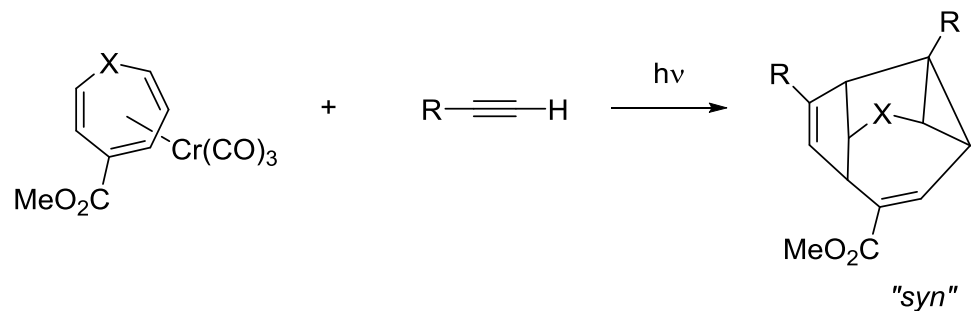


■ Exemple of polycycles with alkynes (3-component)



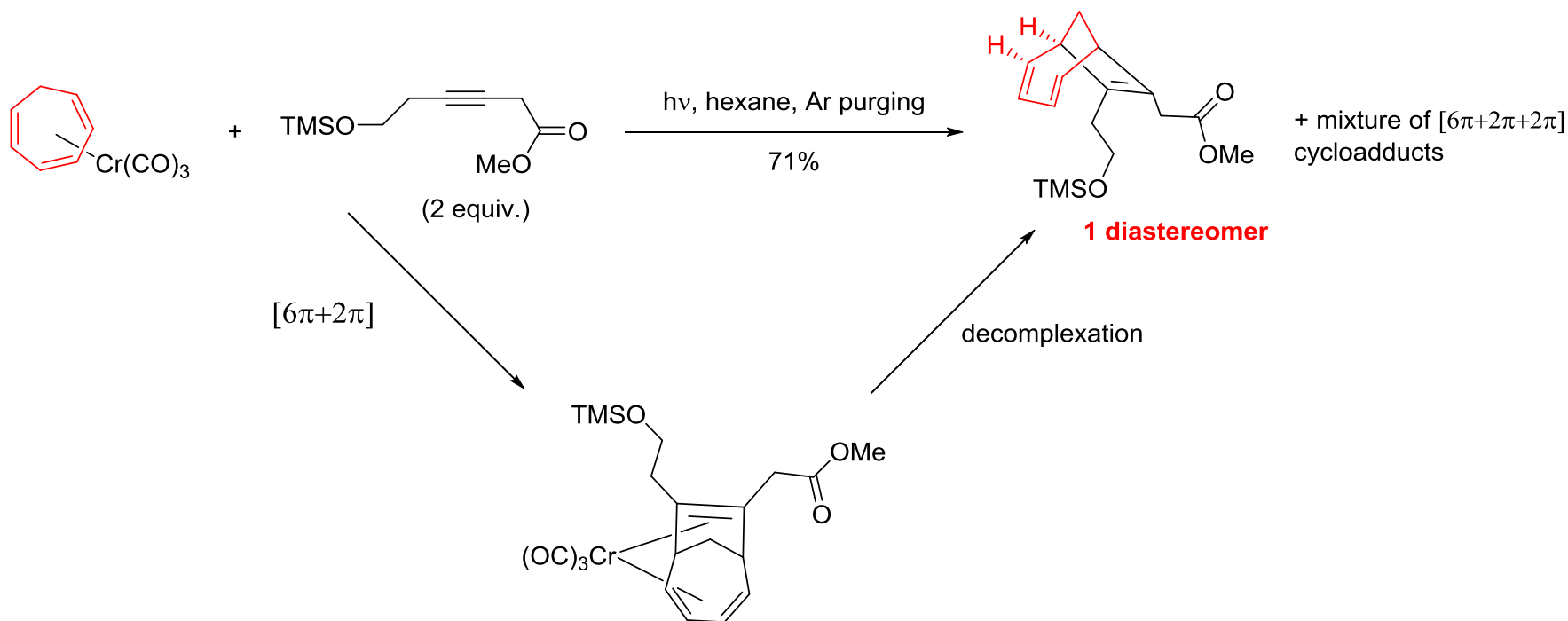
Synthesis of bicyclo[4.2.1]nonane substructure

- Modification on the triene



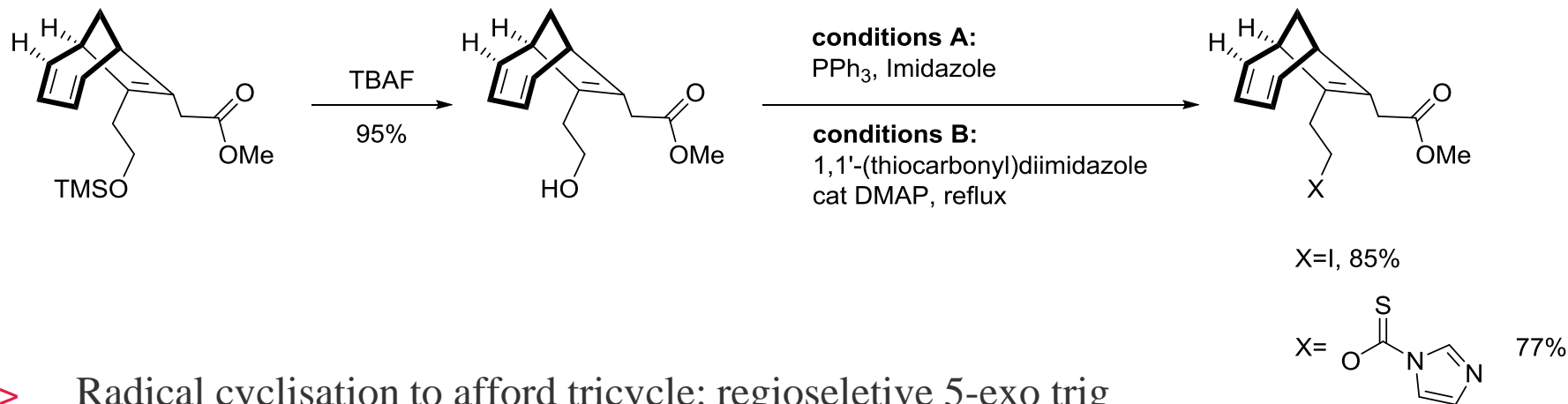
Synthesis of bicyclo[4.2.1]nonane substructure

- > Photochemical cycloaddition applied to the synthesis (key step)

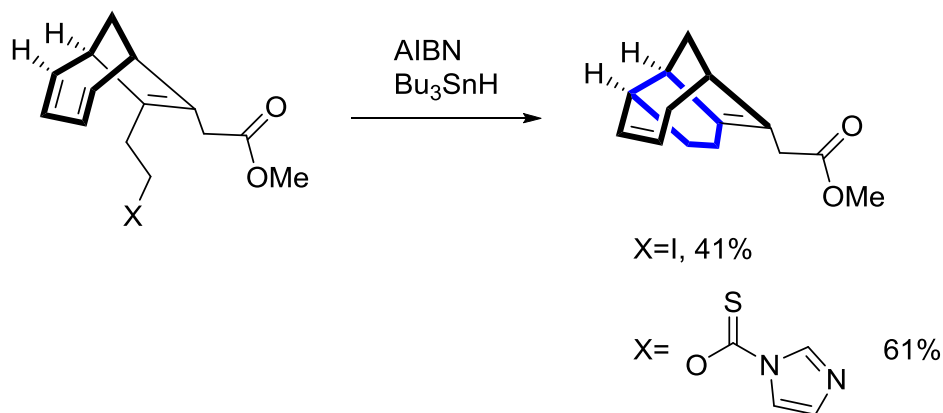


Synthesis of [5,5,7]tricyclic core

> Preparation of radical precursors

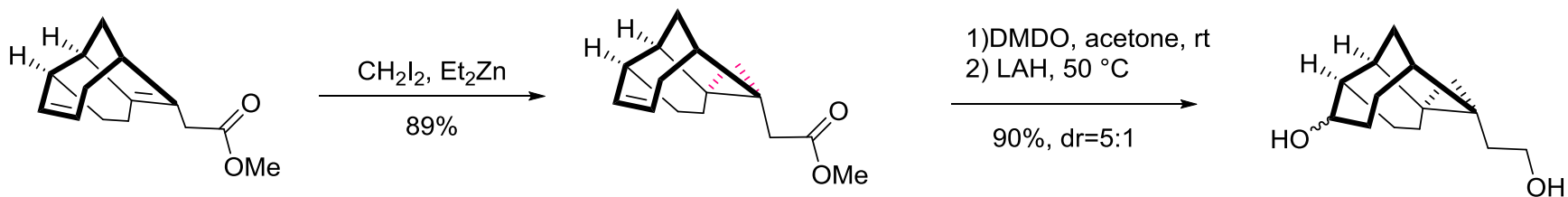


> Radical cyclisation to afford tricycle: regioselective 5-exo trig



Final Part

> Completion of the Synthesis from Magauer and coworkers (2009)

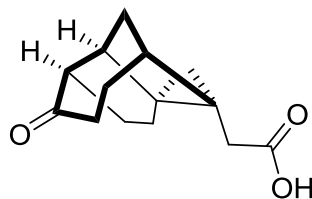


Furukawa Simmons Smith

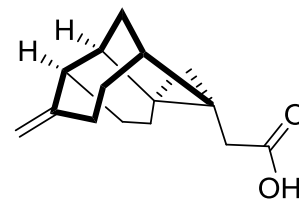
IBX, DMSO
then NaClO₂, NaH₂PO₄,
2-methyl-2-butene

72%

Pinnick

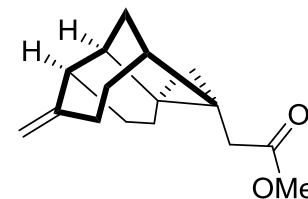


MePPh₃,
t-BuOK
62%



Echinopine A

CH₂N₂
99%



Echinopine B

- > Formal synthesis of Echinopine A and B in 5 steps, 26% overall yield
- > Efficient process : 10 steps if total synthesis compared to previous syntheses (more than 20 steps)
- > Cr(0)-promoted photoinduced $[6\pi + 2\pi]$ cycloaddition as the key step
- > Novel intramolecular radical cyclization step involving an inactivated cyclic diene

Thank you for your attention!

