

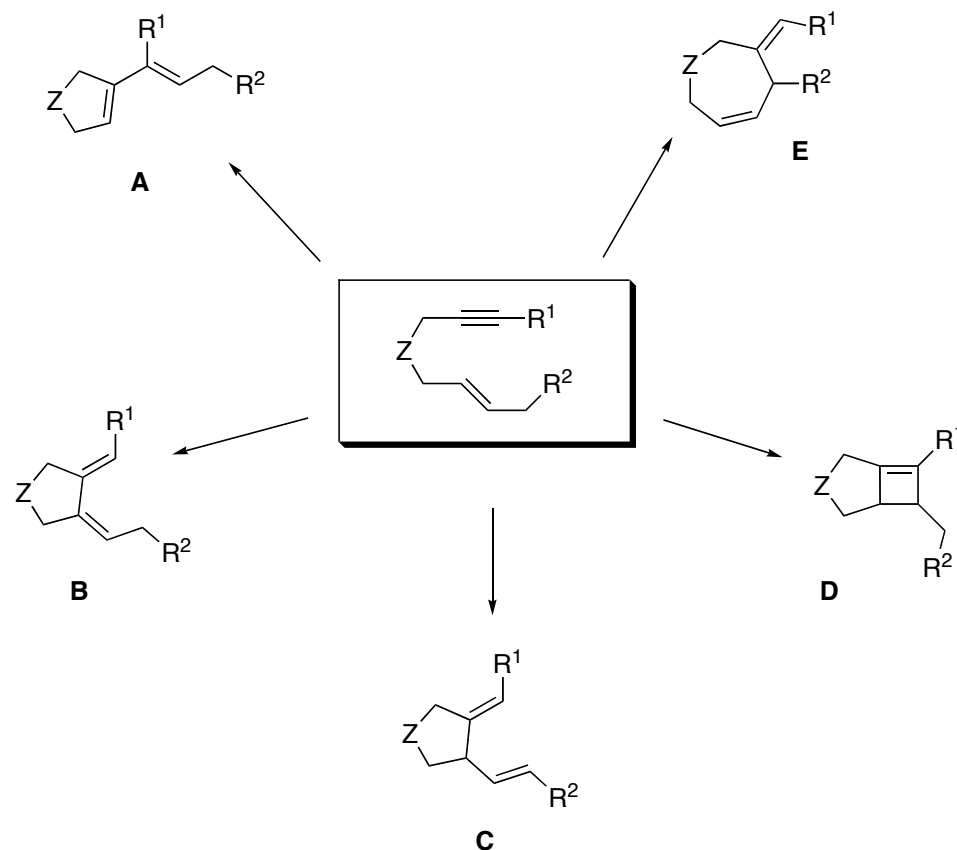
Gold(I)-Catalyzed Cycloisomerization of 1,7- and 1,8-Enynes: Application to the Synthesis of a New Allocolchicinoid

Francois-Didier Boyer, Xavier Le Goff, and Issam Hanna
JOC 2008, 73, 5163-5166

Julia Vargas
Current Literature
June 28, 2008

Cycloisomerization

Overview



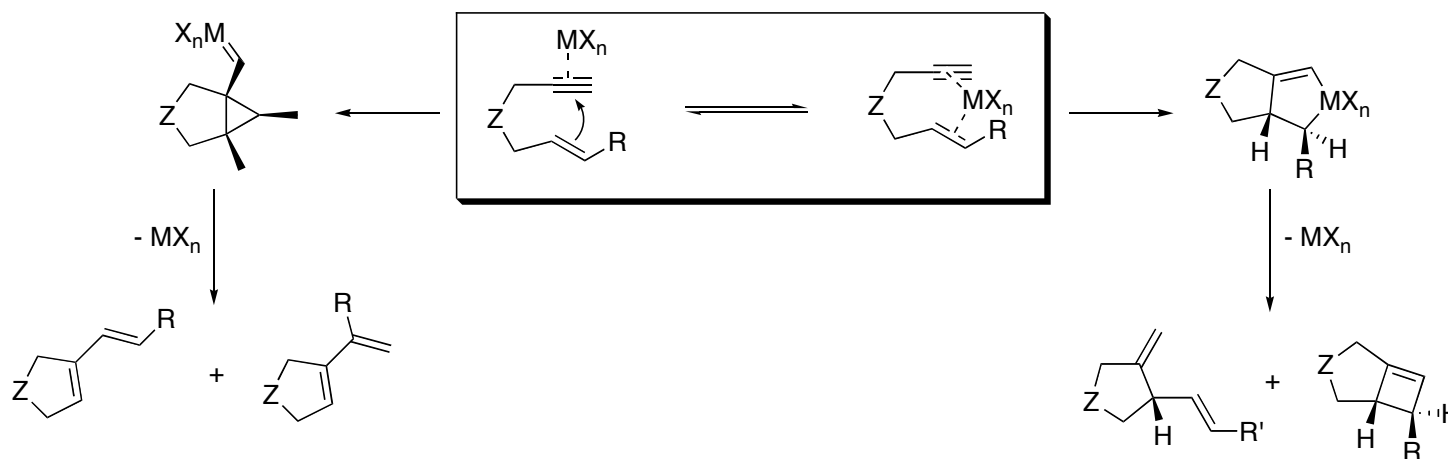
- A: metathesis of M-carbene active substrate leading to vinylcycloalkenes
- B & C: oxidative cyclometalation followed by β -elimination to give exo-1,3 or 1,4-dienes
- D: Oxidative coupling followed by reductive elimination to give cyclobutenes
- E: Coupling involving π -allyl-metal intermediates to give nonconjugated dienes

Bruneau, *ACIE*, **2005**, *44*, 2328

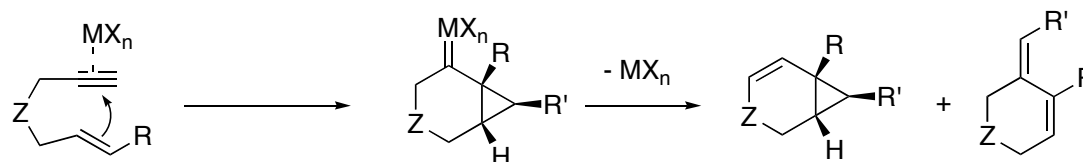
Cycloisomerization

Mechanistic possibilities

5-*exo-dig* cyclizations



6-*endo-dig* cyclizations



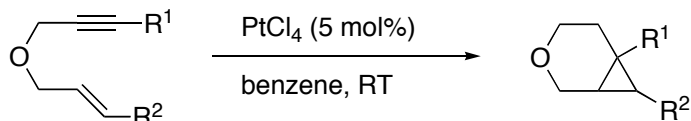
Echavarren, *Chem. Eur. J.*, **2006**, *12*, 5916

Cycloisomerization

A brief history...

Bruneau, *ACIE*, **2005**, *44*, 2328

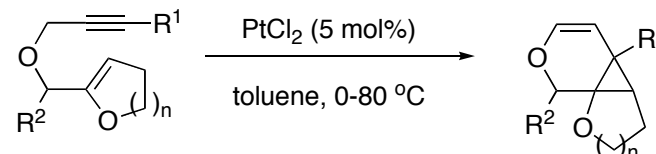
Blum et al. (1995)



Formation of
3-oxabicyclo[4.1.0]hept-4-enes

R¹ = Ph, R² = H, 20%
R¹ = Ph, R² = Ph, 97%
R¹ = Me, R² = Ph, 27%

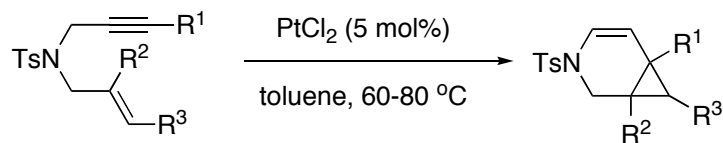
Echavarren et al. (2004)



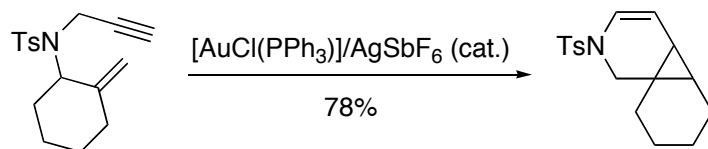
n = 1,2
R¹, R² = alkyl, aryl

54-97%

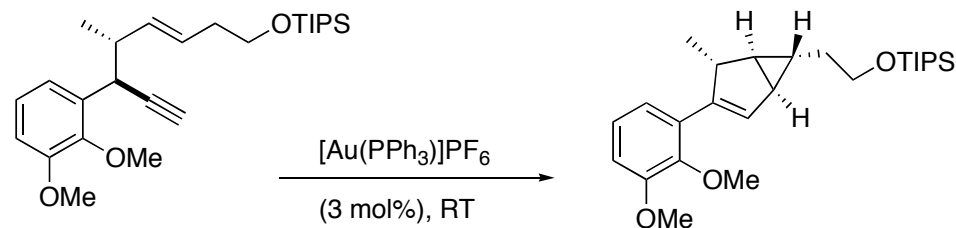
Fürstner et al. (2001)



R¹ = H, R² = CH₂TMS, R³ = H: 73%
R¹ = Me, R² = R³ = H: 59%
R¹ = Ph, R² = R³ = H: 78%
R¹ = Me, R² = H, R³ = CH₂TMS: 59%



Toste et al. (2004)

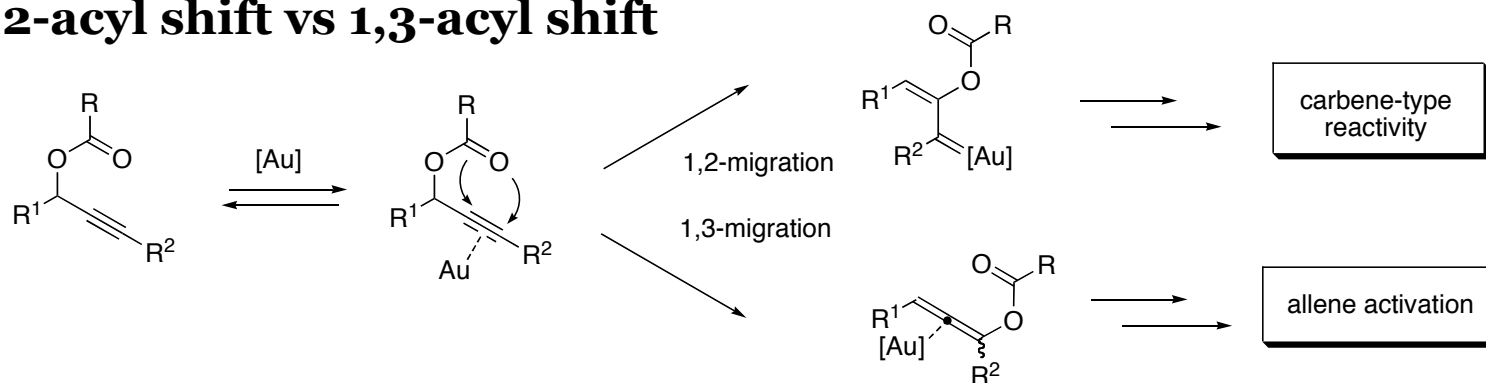


97% ee
98:3 d.r.

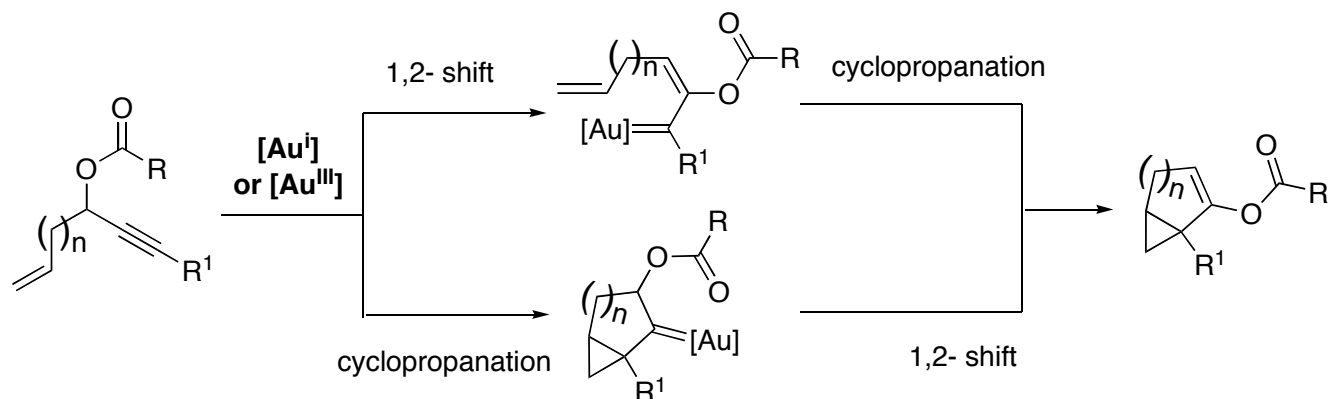
91% ee
99:1 d.r.

Propargylic Esters in Gold Catalysis

1,2-acyl shift vs 1,3-acyl shift



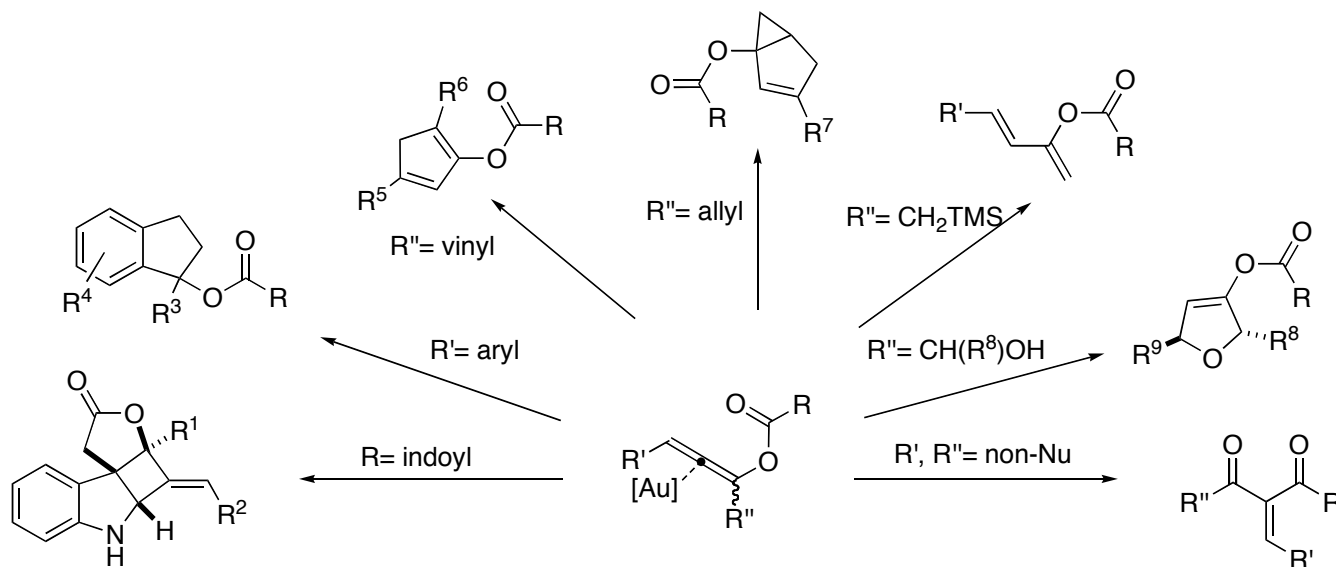
Au-catalyzed tandem 1,2-shift/cyclopropanation



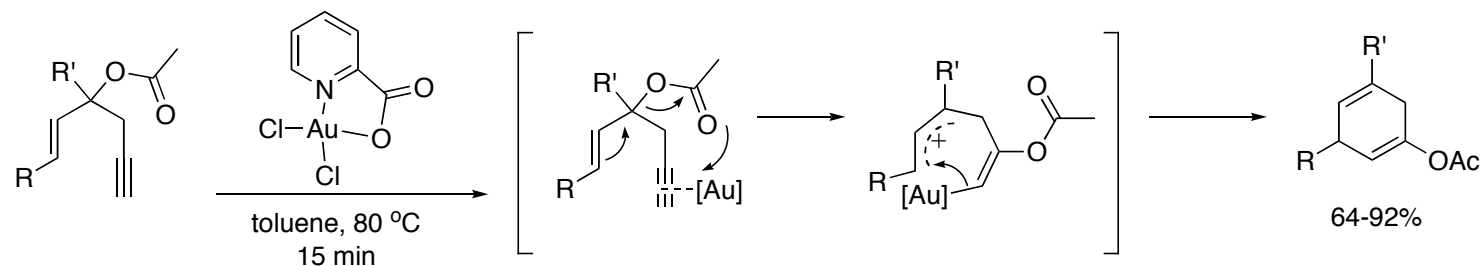
Nolan, *ACIE*, **2007**, *46*, 2750

Propargylic Esters in Gold Catalysis

Au-assisted allene activation and product diversification

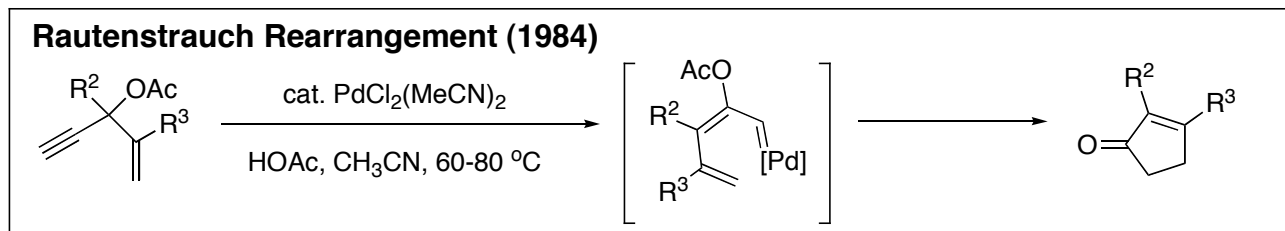


1,3- acyl shift of homopropargylic 1,5-enynes

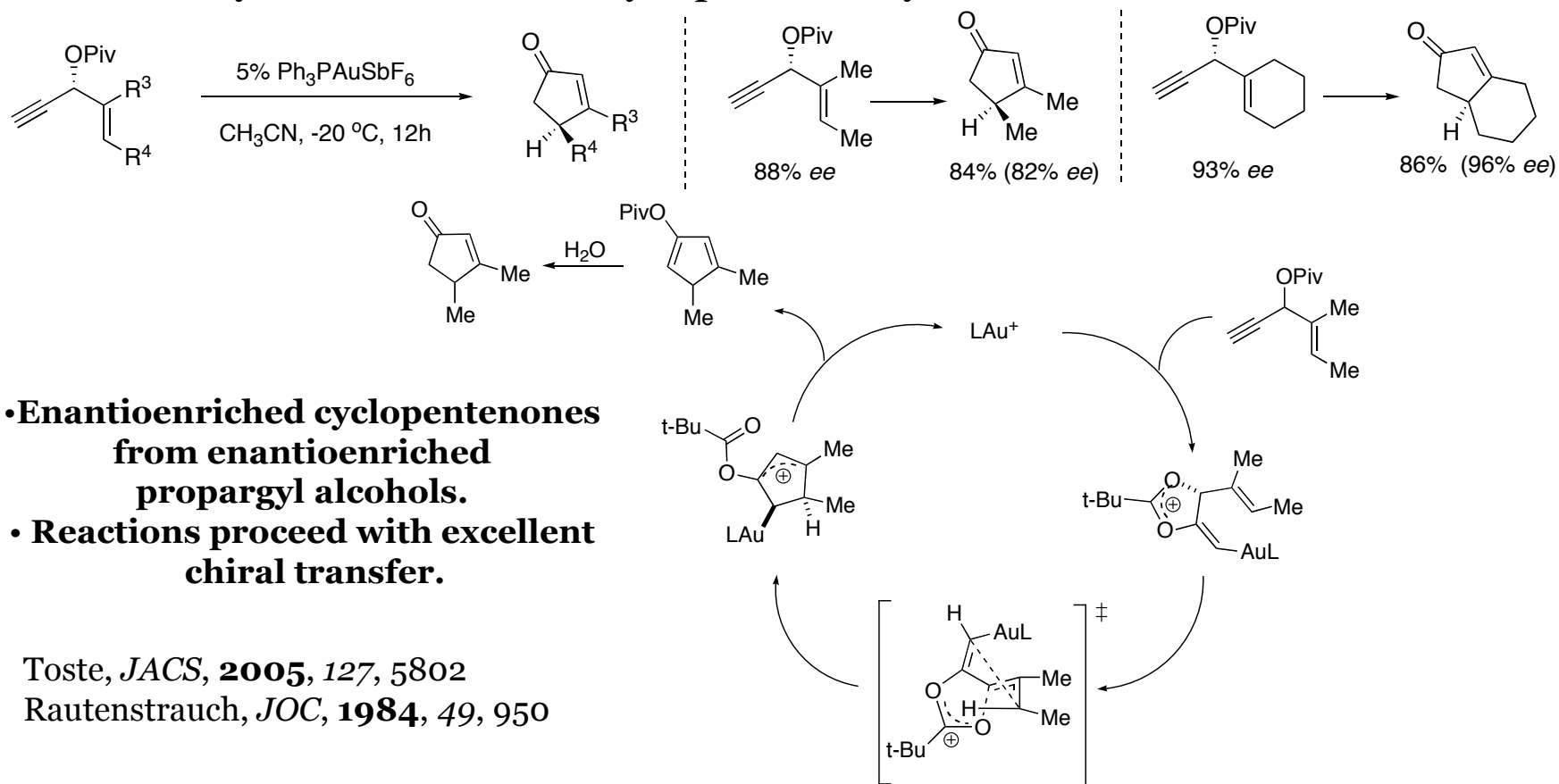


Nolan, *ACIE*, **2007**, *46*, 2750

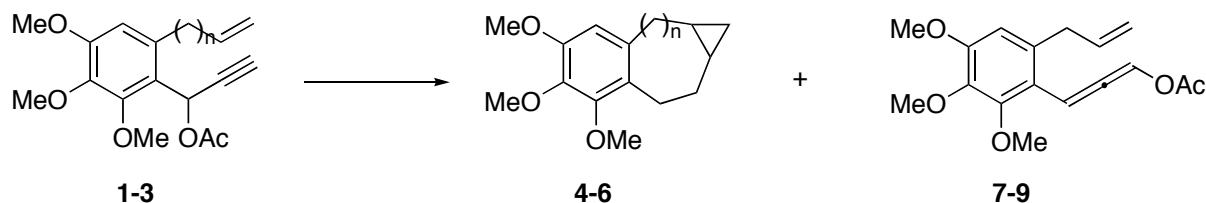
Propargylic Esters in Gold Catalysis



Au(I)- catalyzed enantioselective cyclopentenone synthesis



Gold-Catalyzed Rearrangement

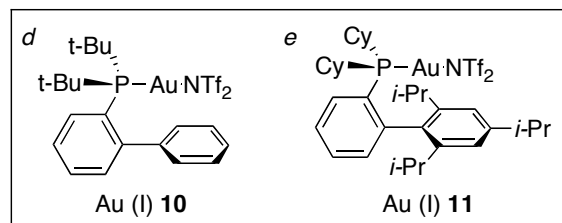


entry	enyne	catalyst (%)	product (yield) ^a	
1	1 n = 2	PtCl ₂ (5%) ^b	4 (53%)	7 (7%)
2		Au(I) 10 (1%) ^{c, d}	4 (78%)	7 (8%)
3		Au(I) 11 (1%) ^{c, e}	4 (60%) ^f	7 (16%)
4	2 n = 1	Au(I) 10 (0.5%) ^{c, d}	5 (90%)	8 (0%)
5	3 n = 3	Au(I) 10 (4%) ^{c, d}	6 (5%)	9 (32%)

^aisolated yield. ^bin toluene at 80 °C, 5 h. ^cin dichloromethane at room temperature, 2 h

- reaction most efficient with less bulky Au(I) catalyst (**d**)

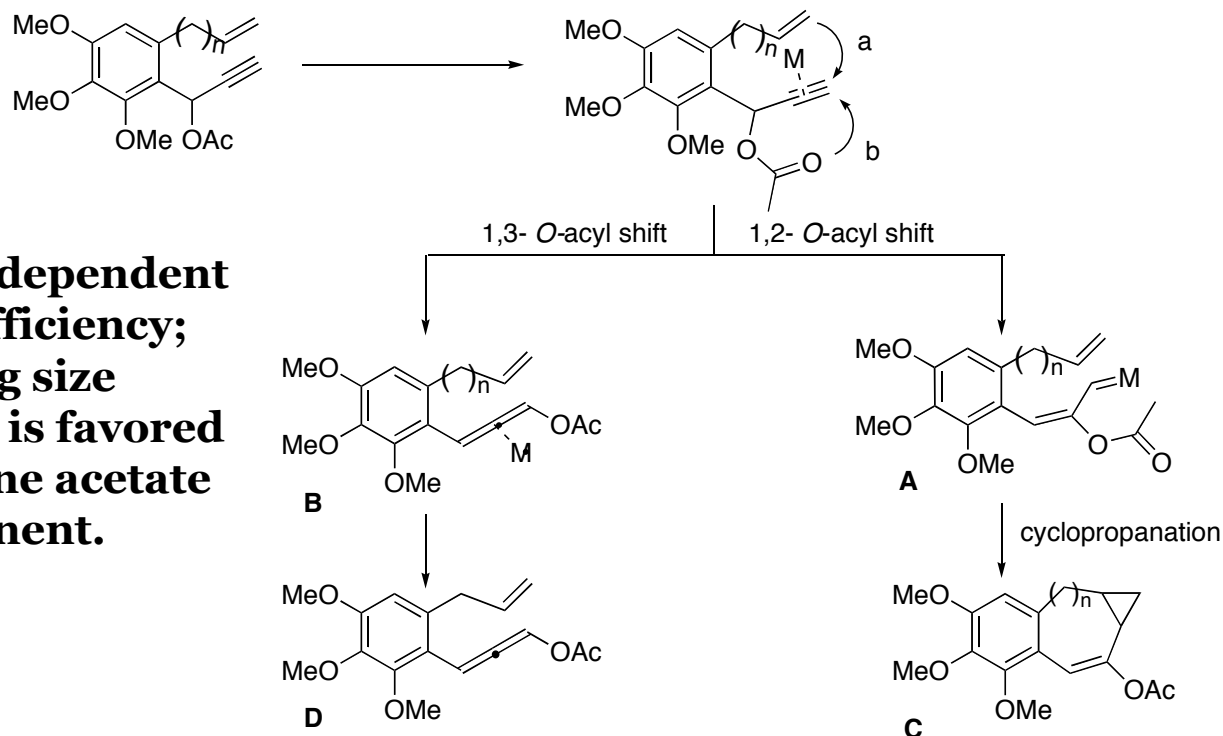
- exclusive formation of tricyclic product, where n=1, high yielding



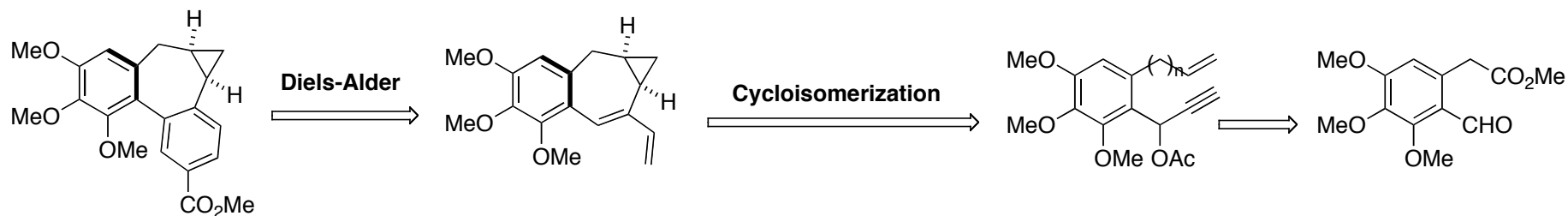
Applying methodology to total synthesis

Proposed Mechanism

D/C product ratio dependent on cyclization efficiency; related to ring size
For n=1, tricycle C is favored
For n=2 or 3, allene acetate more prominent.



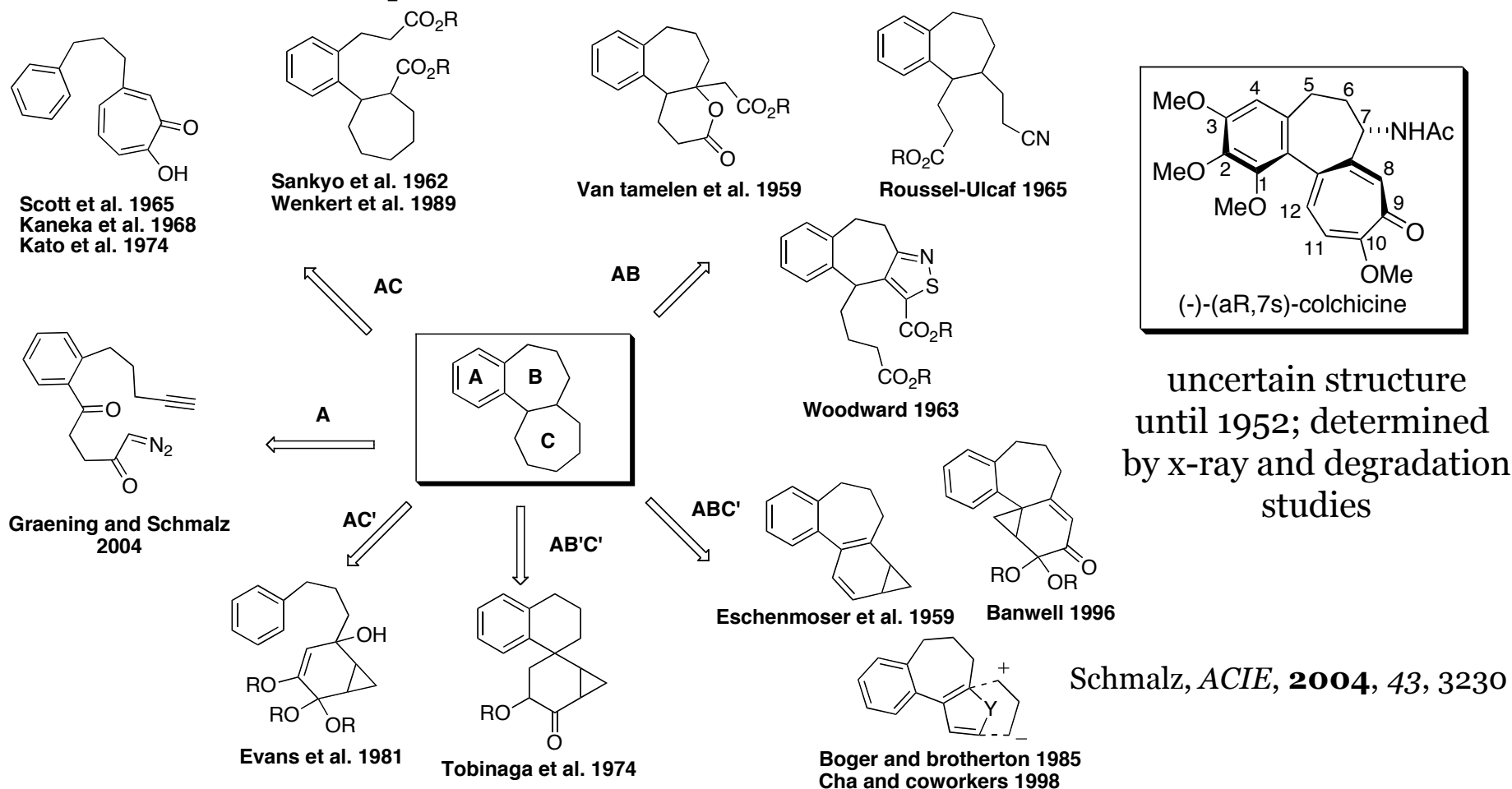
Retrosynthesis



Colchicine Alkaloids

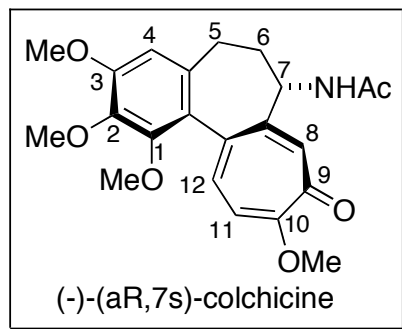


- Discovered by Pelletier and Caventou in 1820
- poisonous meadow saffron; autumn crocus
- found in Europe and North Africa



uncertain structure until 1952; determined by x-ray and degradation studies

Colchicine Alkaloids: Biology

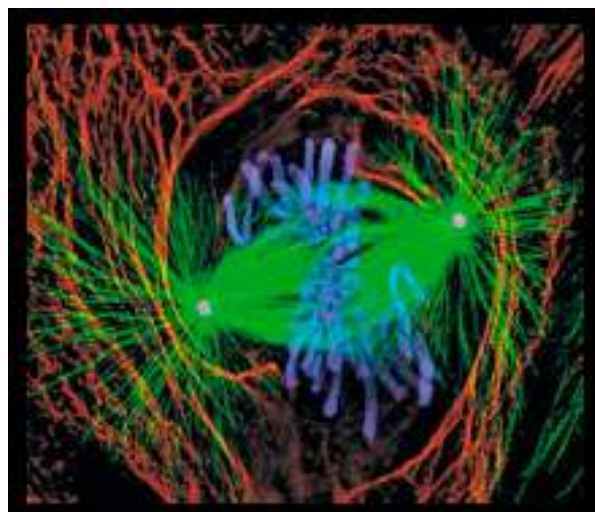


- **Bioactive compound**
- **To date, only treatment for acute gout and familial Mediterranean fever**
- **Antimitotic agent; Binds Microtubules**

- **Microtubules - long protein fibers, 12-13 protofilaments, alternating α and β -tubulin units; exists in dynamic equilibrium with tubulin dimer**



Outer diameter = 24 nM
Forms hollow cylinder

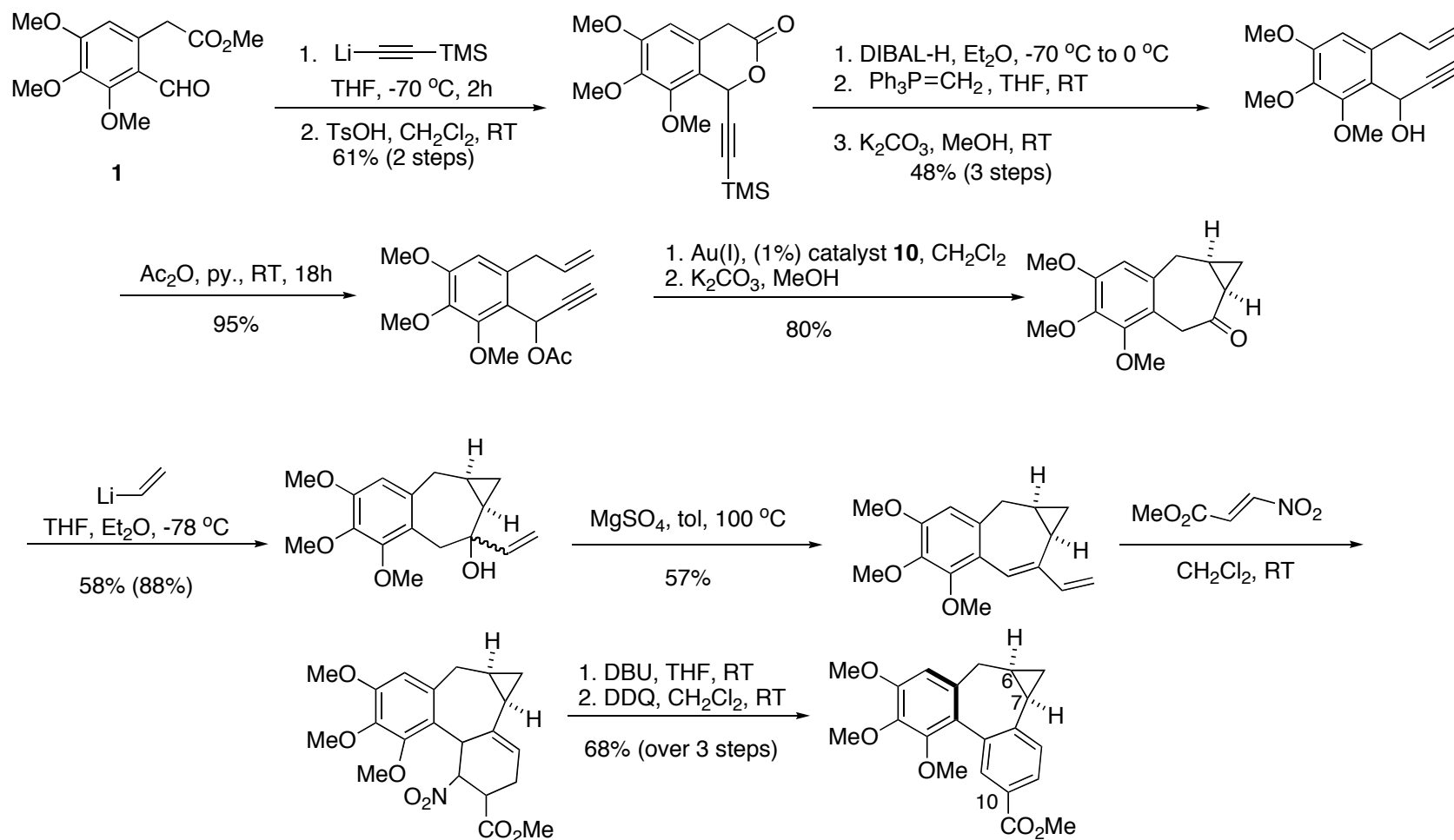


Schmalz, *ACIE*, **2004**, *43*, 3230
Jordan, *Nat. Rev. Caner*, **2004**, *4*, 253

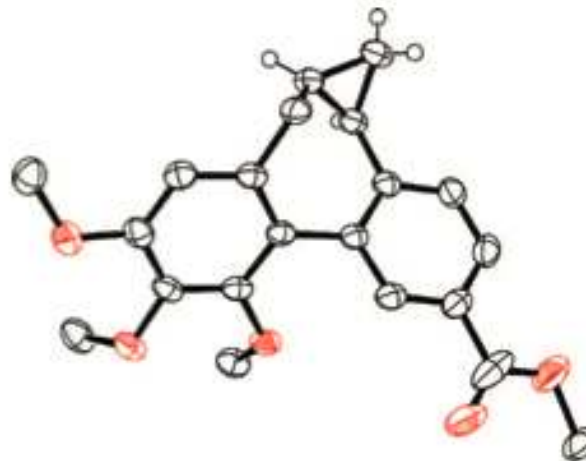
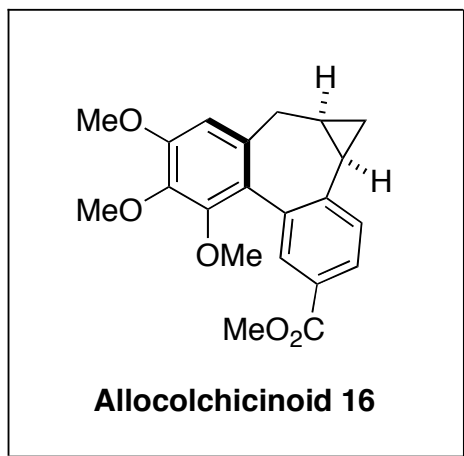
- **Cellular Functions:**
 - **mechanically stabilize cellular structures**
 - **“highways” for cell signaling and transport**
 - **formation of mitotic spindle during mitosis**

**Binding Tubulin dimer distorts
tubulin/microtubule
equilibrium
leads to cell cycle arrest**

Applying methodology to total synthesis



In Summary...



- **The synthesis of a new allocolchicinoid was achieved in 13 steps from aldehyde 1, 7.6% overall yield.**
- **The synthesis featured a cycloisomerization of 1,7-enyne to form the 7-membered ring fused to the cyclopropane ring. Further elaboration via a diels alder/aromatization furnished the aromatic C ring.**
- **The relative stereochemistry at C-6 and C-7 was confirmed by x-ray analysis. Characteristic of allocolchicinoids, the compound displays molecular asymmetry due to the noncoplanar arrangement of rings A and C (torsion angle 45 °C).**
- **Tubulin binding assays are currently underway for the evaluation of this compound as a potential antimitotic agent.**