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

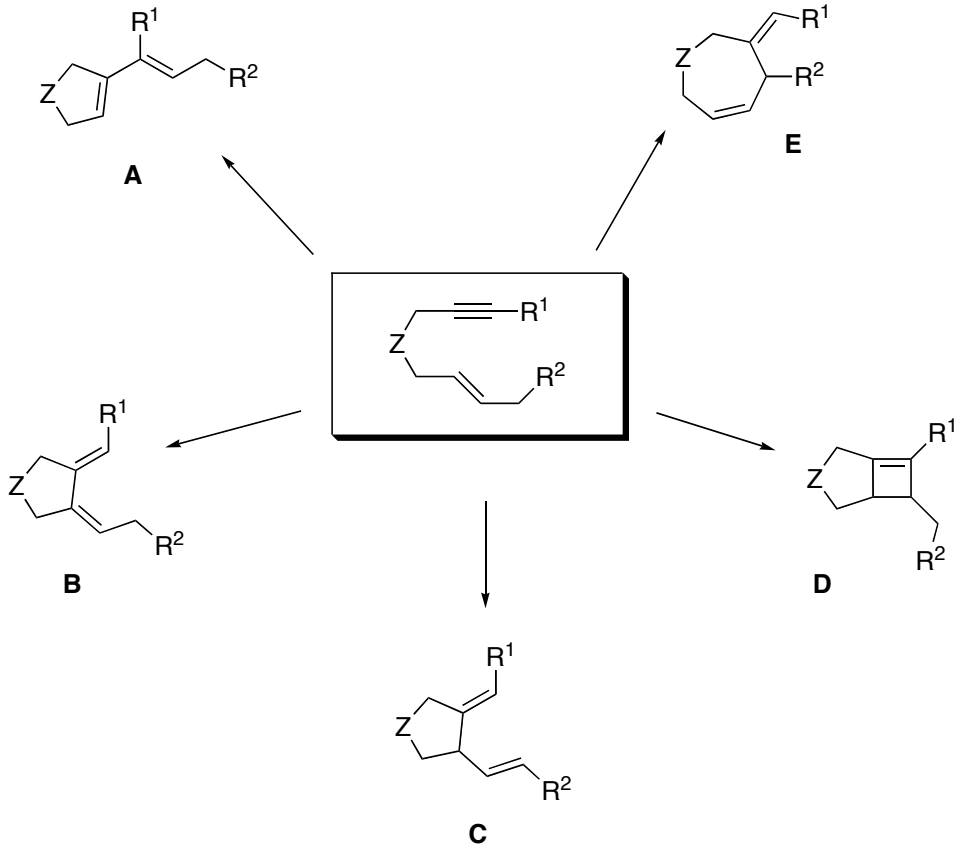
Julia Vargas

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

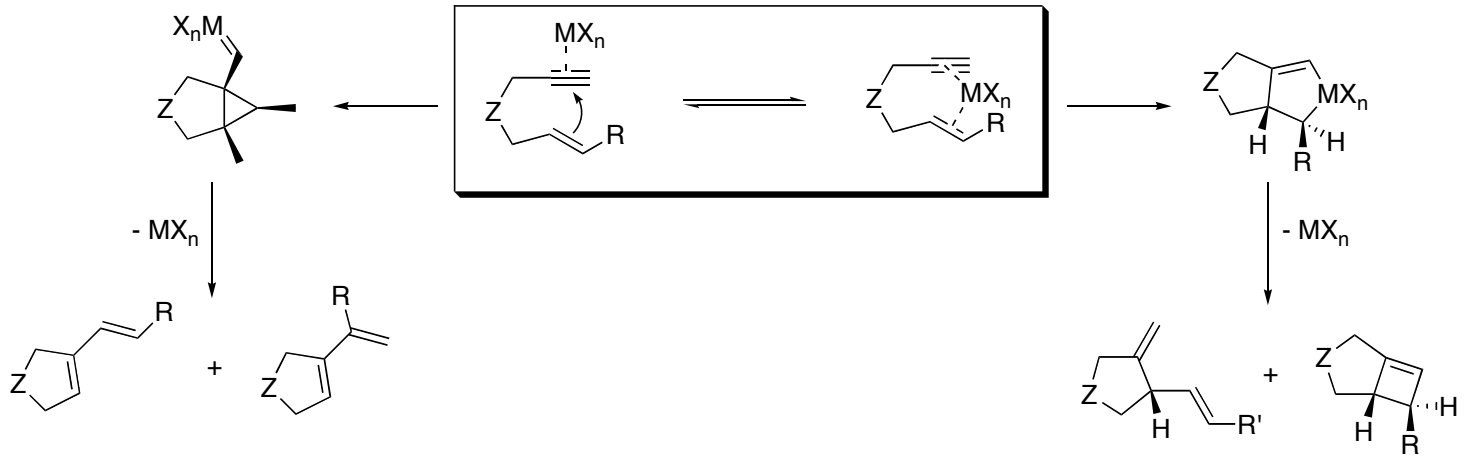
Bruneau, *ACIE*, **2005**, *44*, 2328

- D: Oxidative coupling followed by reductive elimination to give cyclobutenes
- E: Coupling involving π-allyl-metal intermediates to give nonconjugated dienes

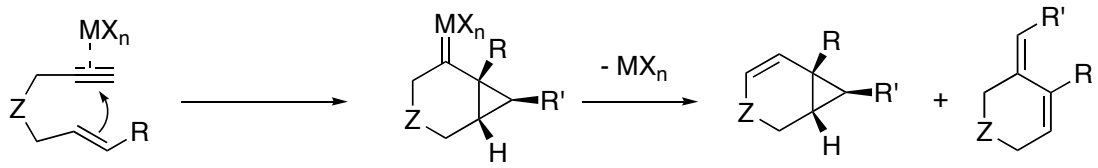
Cycloisomerization

Mechanistic possibilities

5-exo-dig cyclizations



6-endo-dig cyclizations



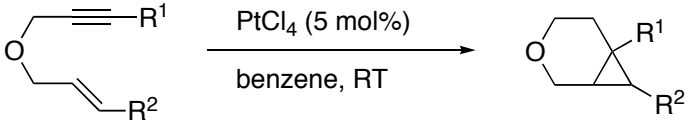
Echavarren, *Chem. Eur. J.*, **2006**, *12*, 5916

Cycloisomerization

A brief history...

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

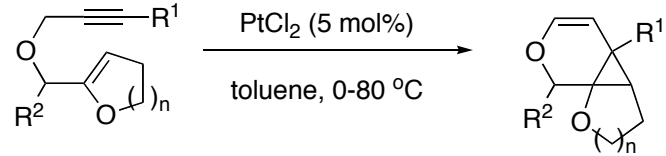
Blum et al. (1995)



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

R^1= Ph, R^2= H, 20%
R^1= Ph, R^2= Ph, 97%
R^1= Me, R^2= Ph, 27%

Echavarren et al. (2004)

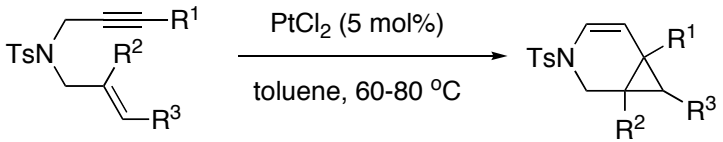


n= 1,2

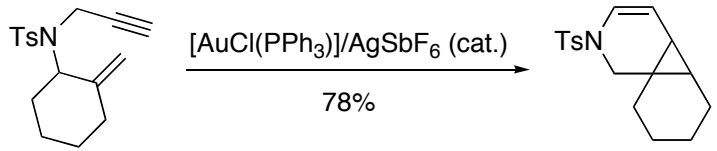
R^1, R^2 = alkyl, aryl

54-97%

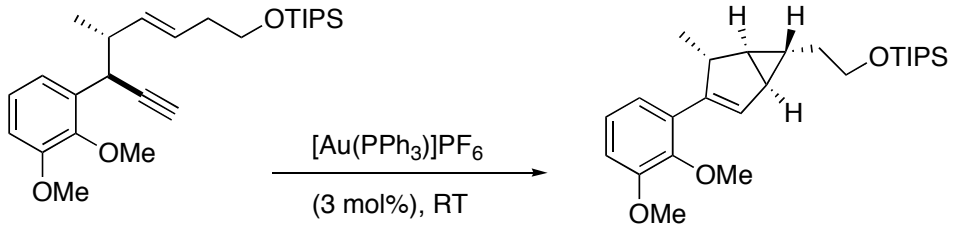
Fürstner et al. (2001)



R^1= H, R^2= CH_2TMS, R^3= H: 73%
R^1= Me, R^2= R^3= H: 59%
R^1= Ph, R^2= R^3= H: 78%
R^1= Me, R^2= H, R^3= CH_2TMS: 59%



Toste et al. (2004)

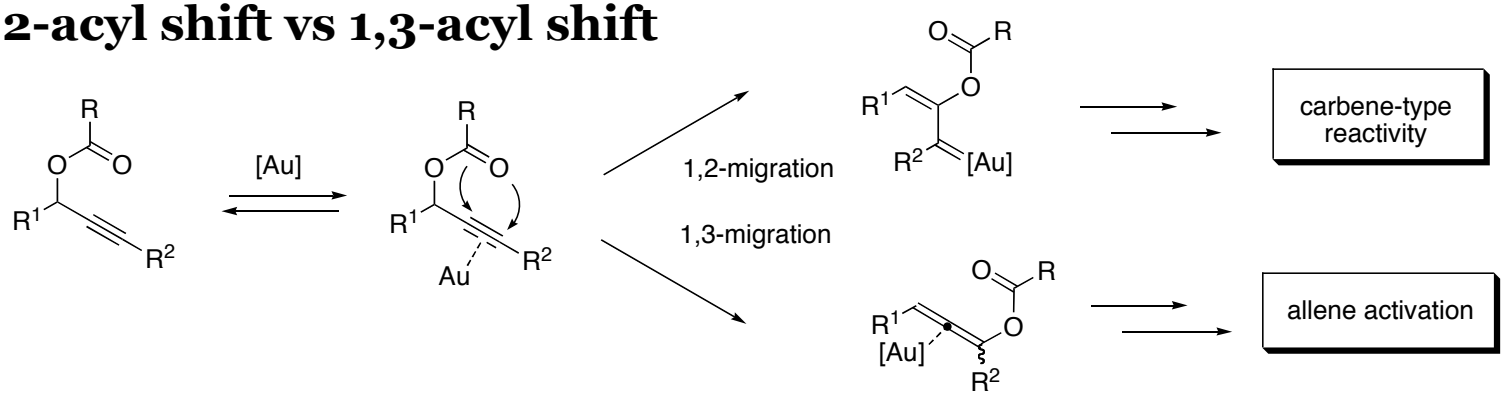


97% *ee*
98:3 d.r.

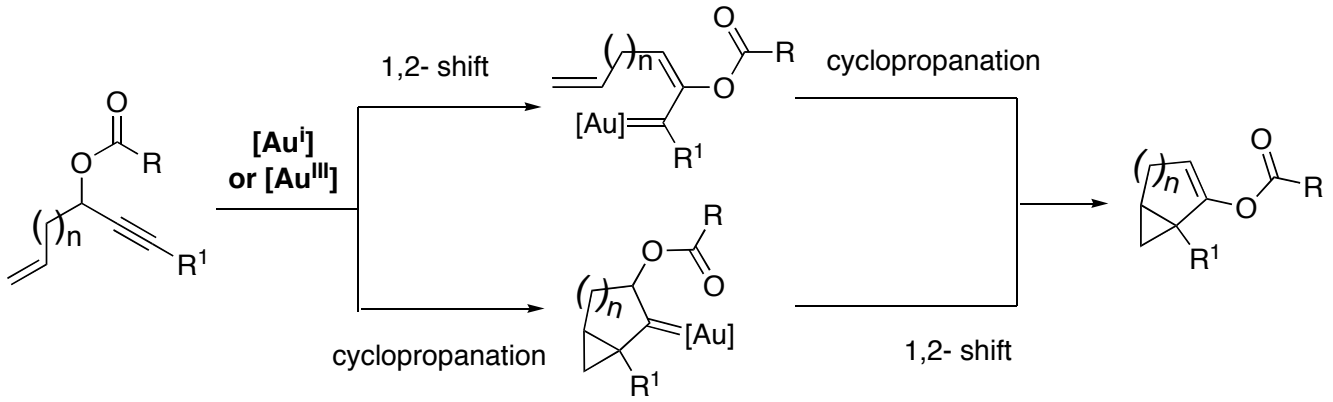
91% *ee*
99:1 d.r.

Propargylic Esters in Gold Catalysis

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



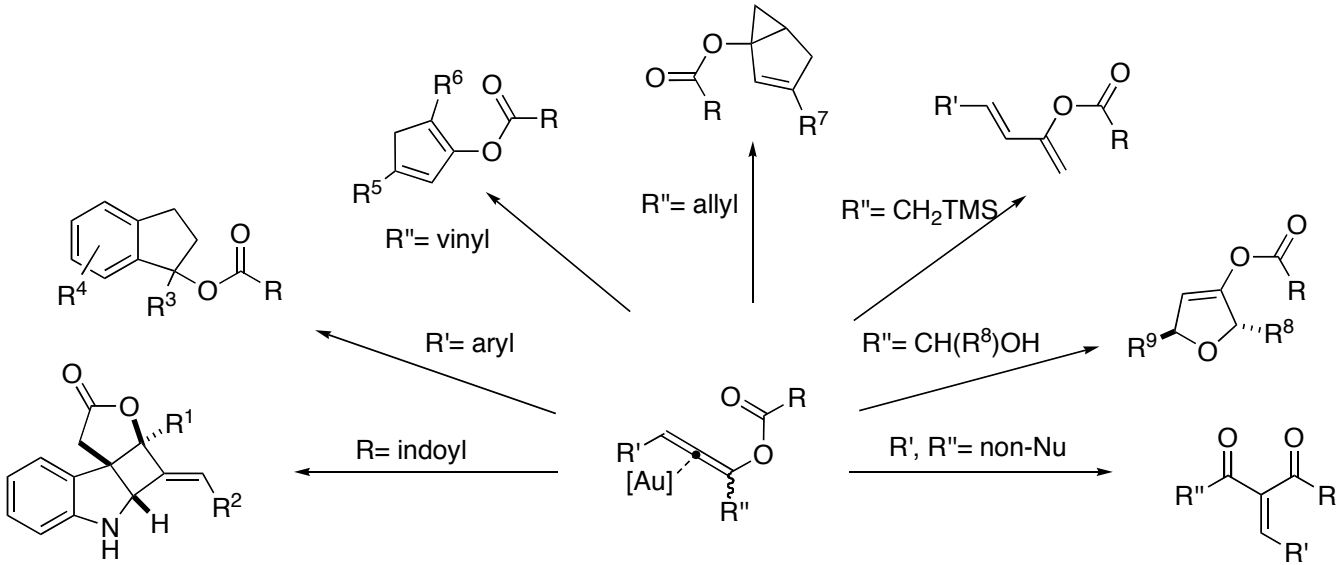
Au-catalyzed tandem 1,2-shift/cyclopropanation



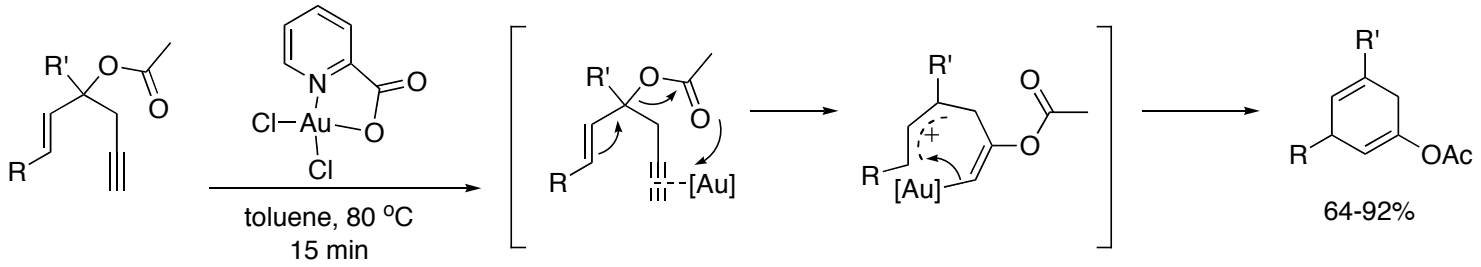
Nolan, *ACIE*, **2007**, *46*, 2750

Propargylic Esters in Gold Catalysis

Au-assisted allene activation and product diversification



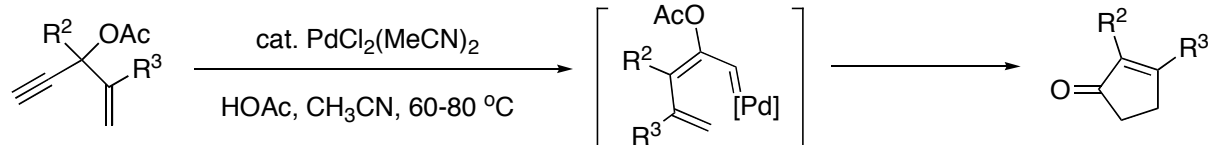
1,3- acyl shift of homopropargylic 1,5-enynes



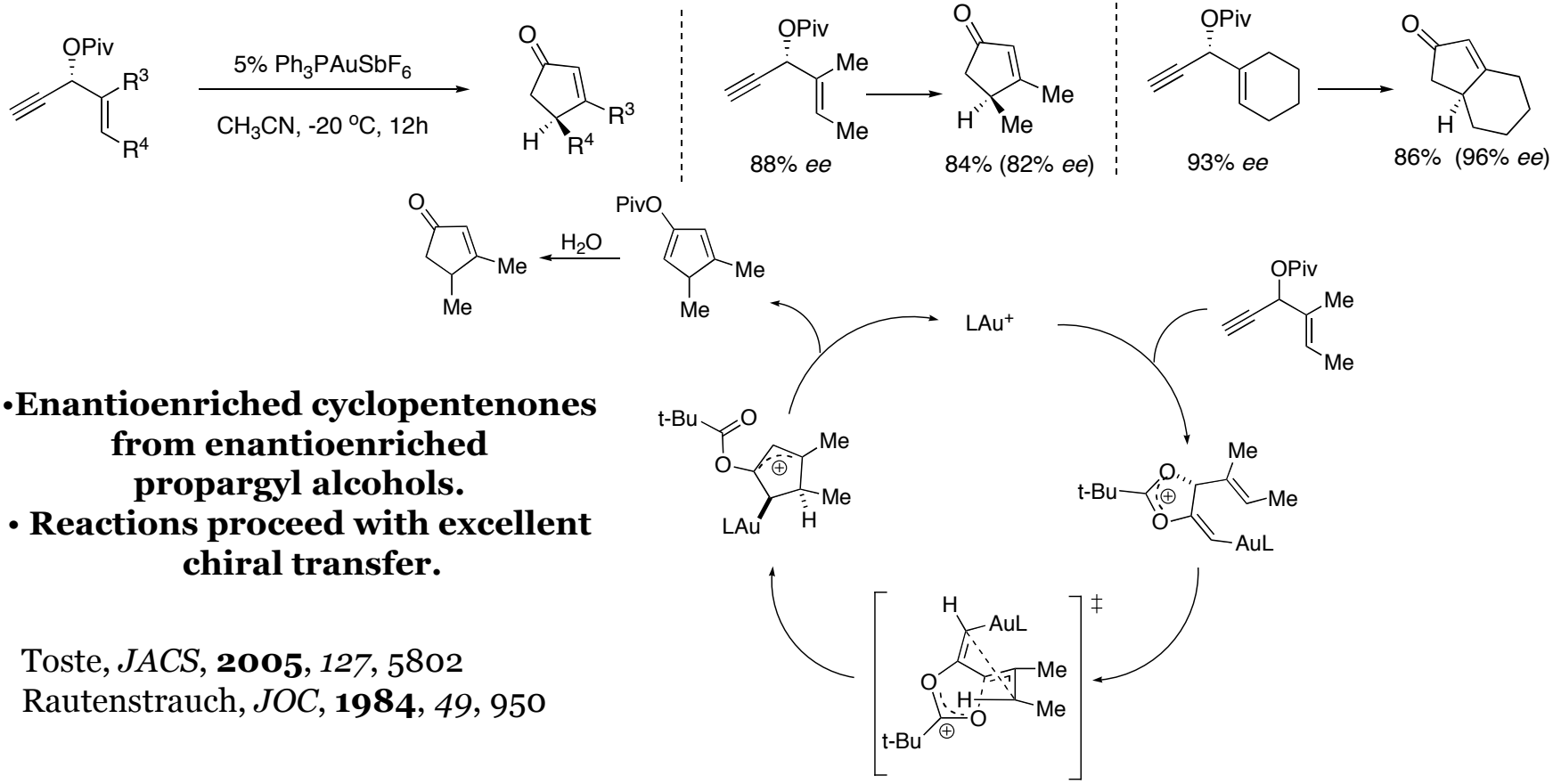
Nolan, *ACIE*, **2007**, *46*, 2750

Propargylic Esters in Gold Catalysis

Rautenstrauch Rearrangement (1984)



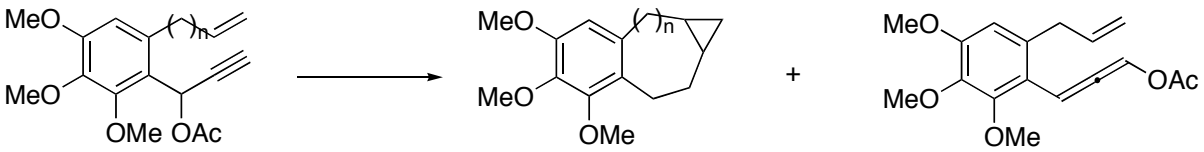
Au(I)- catalyzed enantioselective cyclopentenone synthesis



•Enantioenriched cyclopentenones from enantioenriched propargyl alcohols.
• Reactions proceed with excellent chiral transfer.

Toste, *JACS*, **2005**, *127*, 5802
Rautenstrauch, *JOC*, **1984**, *49*, 950

Gold-Catalyzed Rearrangement

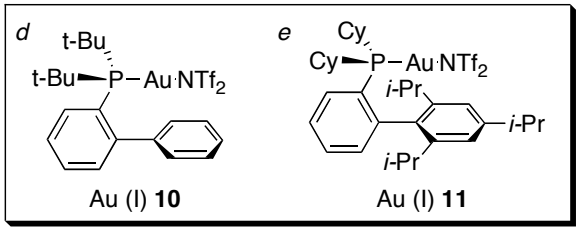


1-3 **4-6** **7-9**

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%)

[a]isolated yield. [b]in toluene at 80 °C, 5 h. [c] in dichloromethane at room temperature, 2 h

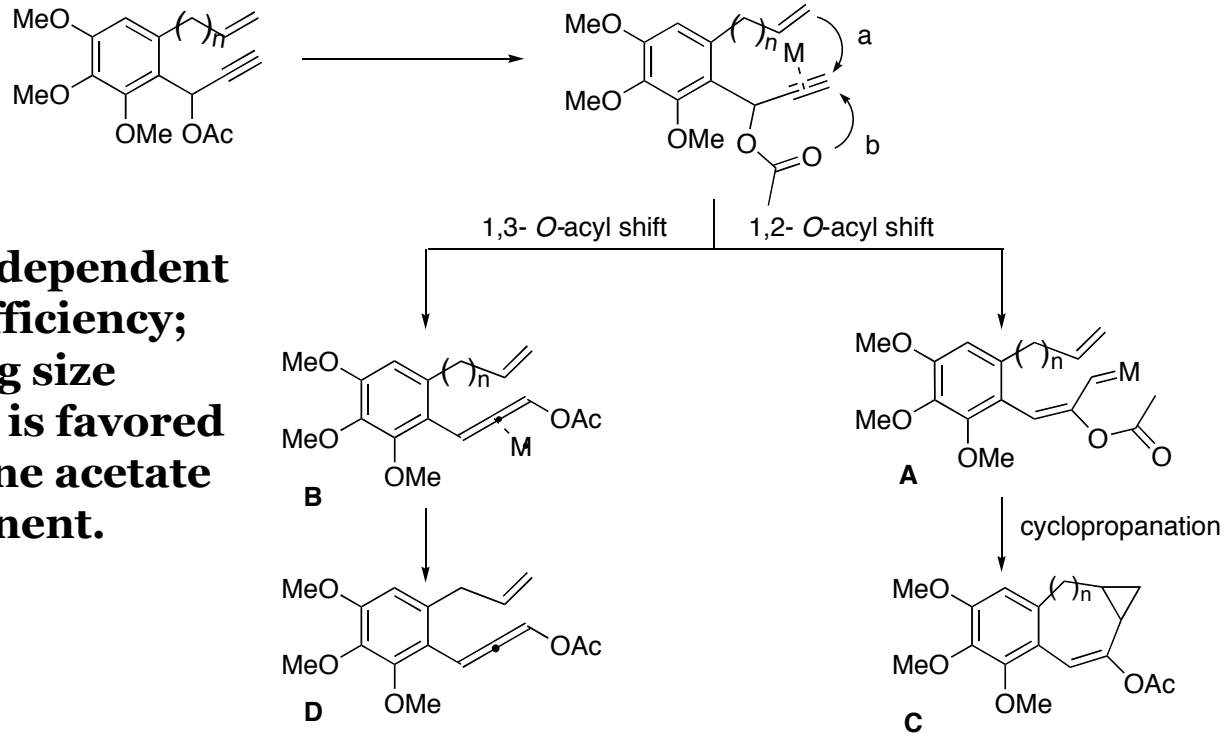
- **reaction most efficient with less bulky Au(I) catalyst (d)**
- **exclusive formation of tricyclic product, where n=1, high yielding**



Au (I) **10** Au (I) **11**

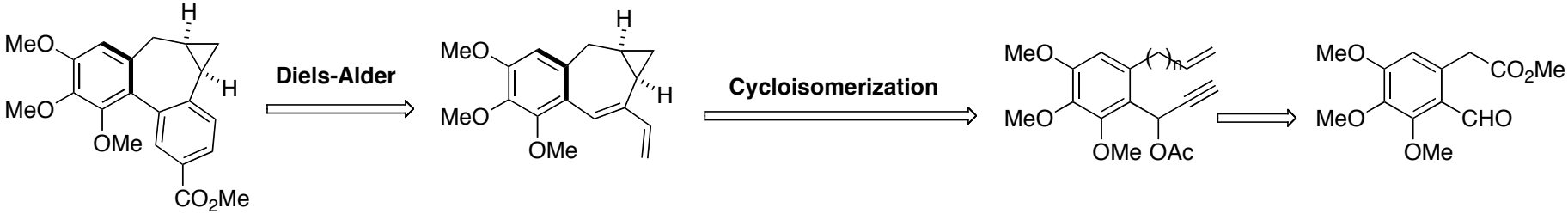
Applying methodology to total synthesis

Proposed Mechanism



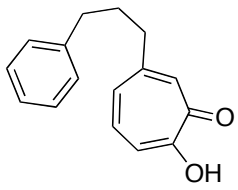
D/C product ratio dependent on cyclization efficiency; related to ring size
For n=1, tricycle C is favored
For n=2 or 3, allene acetate more prominent.

Retrosynthesis

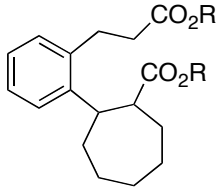


Colchicine Alkaloids

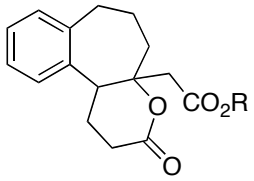
-Discovered by Pelletier and Caventou in 1820
- poisonous meadow saffron; autumn crocus
- found in Europe and North Africa



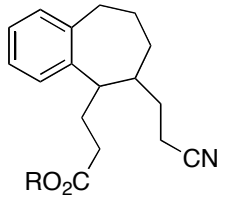
Scott et al. 1965
Kaneka et al. 1968
Kato et al. 1974



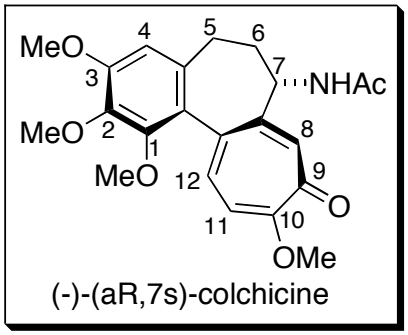
Sankyo et al. 1962
Wenkert et al. 1989



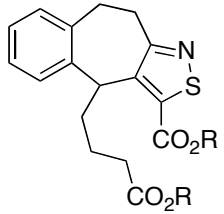
Van tamelen et al. 1959



Roussel-Ulcaf 1965



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



Woodward 1963

AC

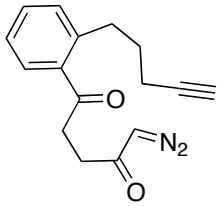
AB

A

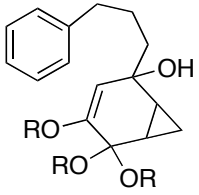
AC'

AB'C'

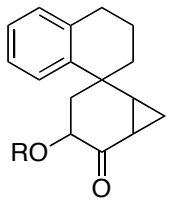
ABC'



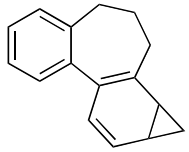
Graening and Schmalz 2004



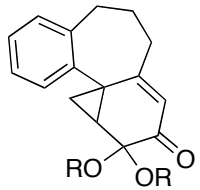
Evans et al. 1981



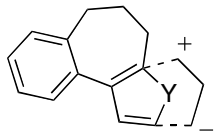
Tobinaga et al. 1974



Eschenmoser et al. 1959



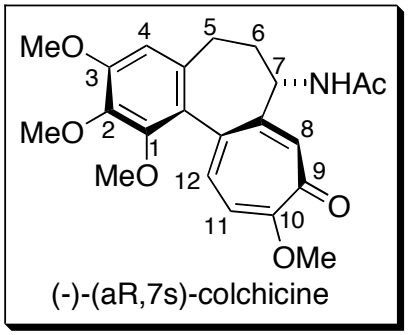
Banwell 1996



Boger and brotherton 1985
Cha and coworkers 1998

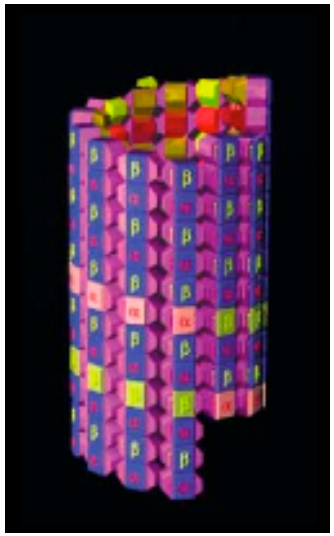
Schmalz, *ACIE*, **2004**, *43*, 3230

Colchicine Alkaloids: Biology



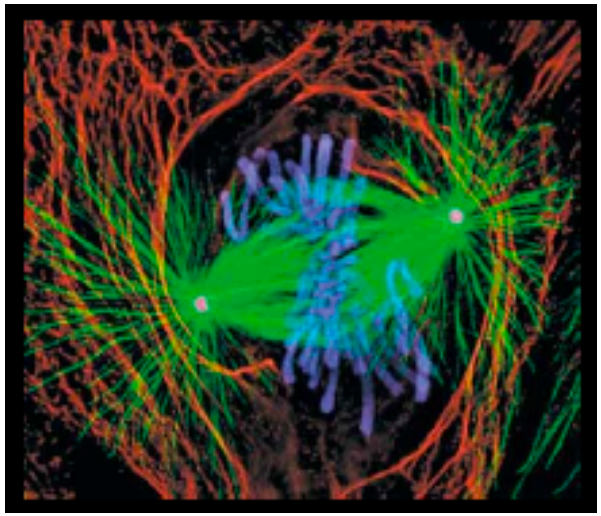
(-)-(aR,7s)-colchicine

- **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



- **Cellular Functions:**

- mechanically stabilize cellular structures

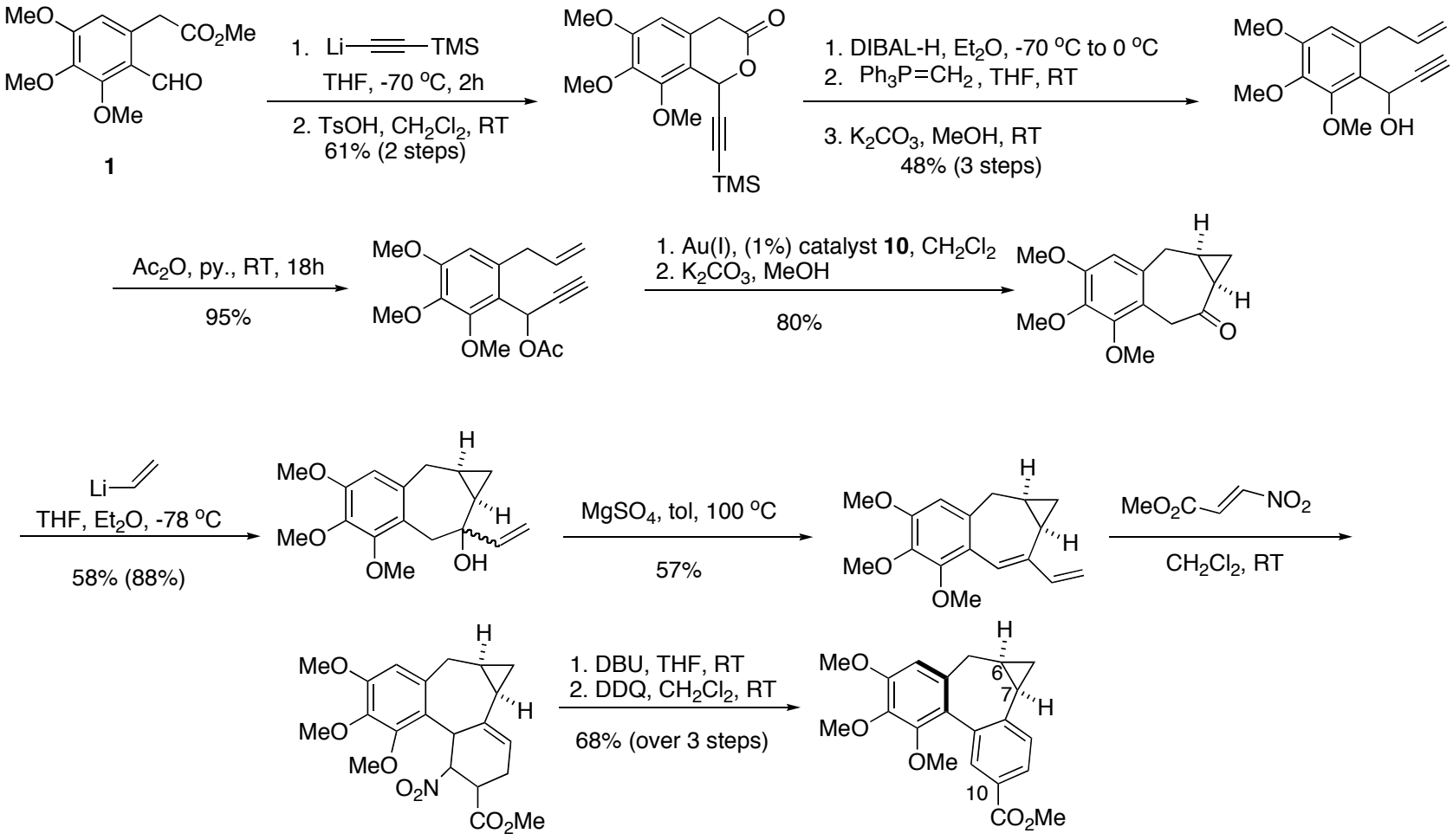
- "highways" for cell signaling and transport

- formation of mitotic spindle during mitosis

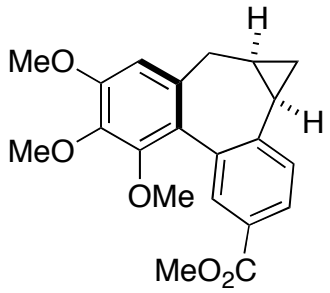
Binding Tubulin dimer distorts tubulin/microtubule equilibrium leads to cell cycle arrest

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

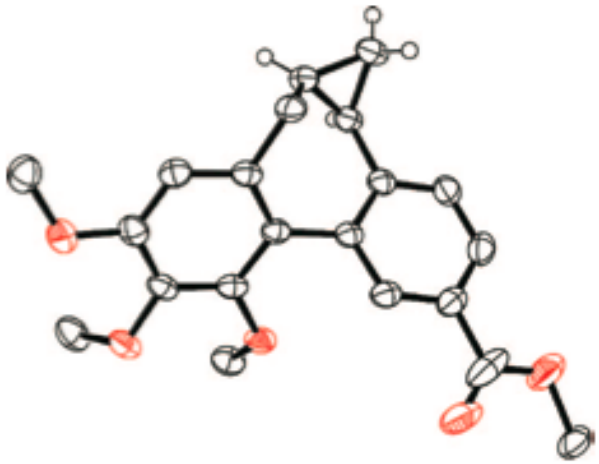
Applying methodology to total synthesis



In Summary…



Allocolchicinoid 16



- **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.**