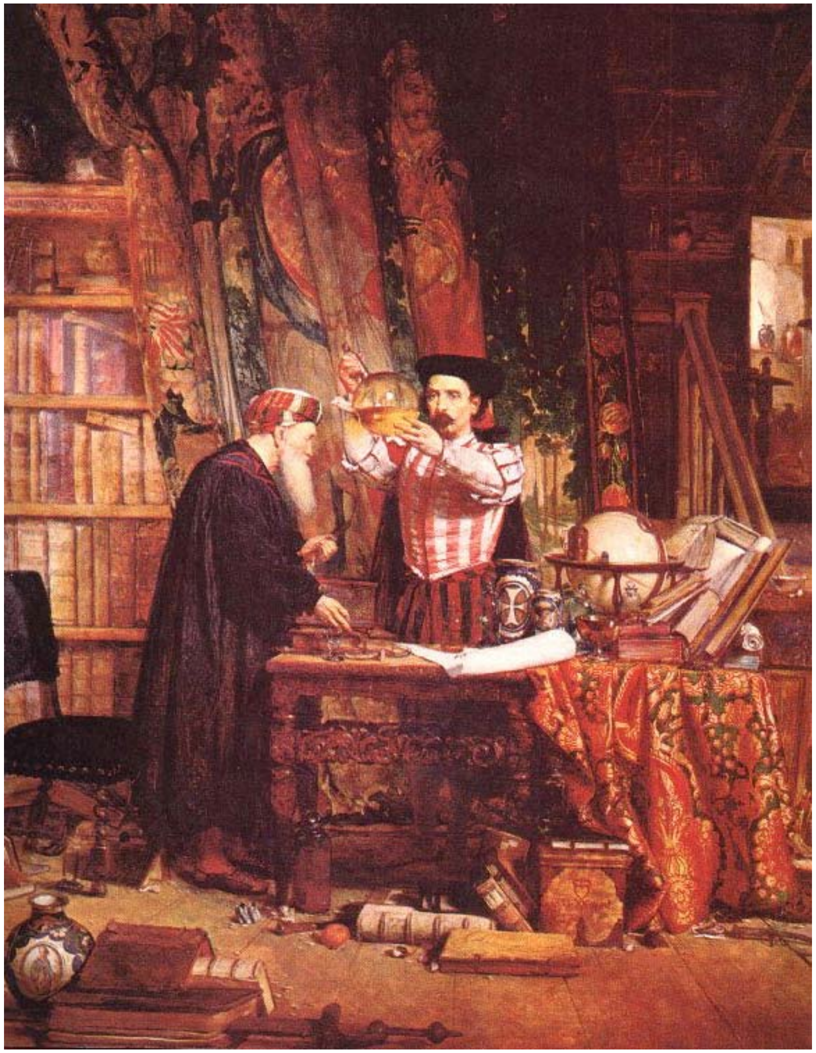
Gold in Homogeneous Catalysis

Miriam Inbar
5/22/06

Accursed thirst for gold! What dost thou not compel mortals to do?
Virgil
The Aeneid

Gold in the Development of Modern Chemistry



"The Alchemist"

Sir William Fettes Douglas

Alchemy, the forbearer to modern chemistry as we know it, was concerned with the transmutation of common metals into gold. This process was believed to be mediated by the "philosopher's stone," a mythical substance which was also believed to bestow eternal youth. The concept of the philosopher's stone may have been inspired by the chemical extraction of gold from certain alloys.

Alchemy fell out of favor in the 18^{th} century with the rise of modern chemisty.

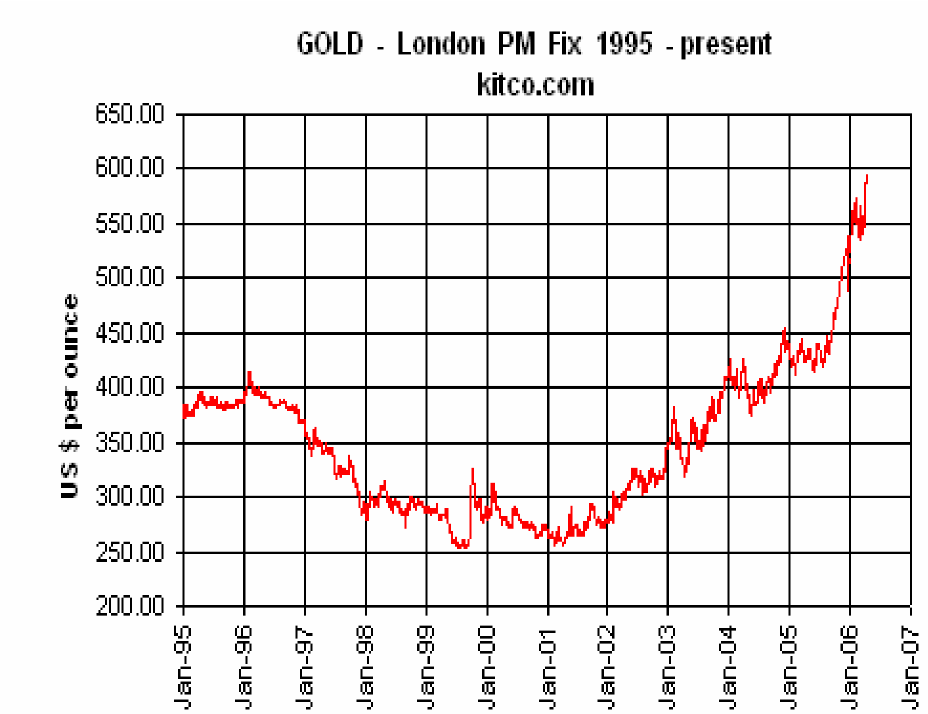
Misconceptions About Gold

Gold has traditionally been overlooked in catalysis, possibly because of preconceived notions that it is expensive and chemically inert.

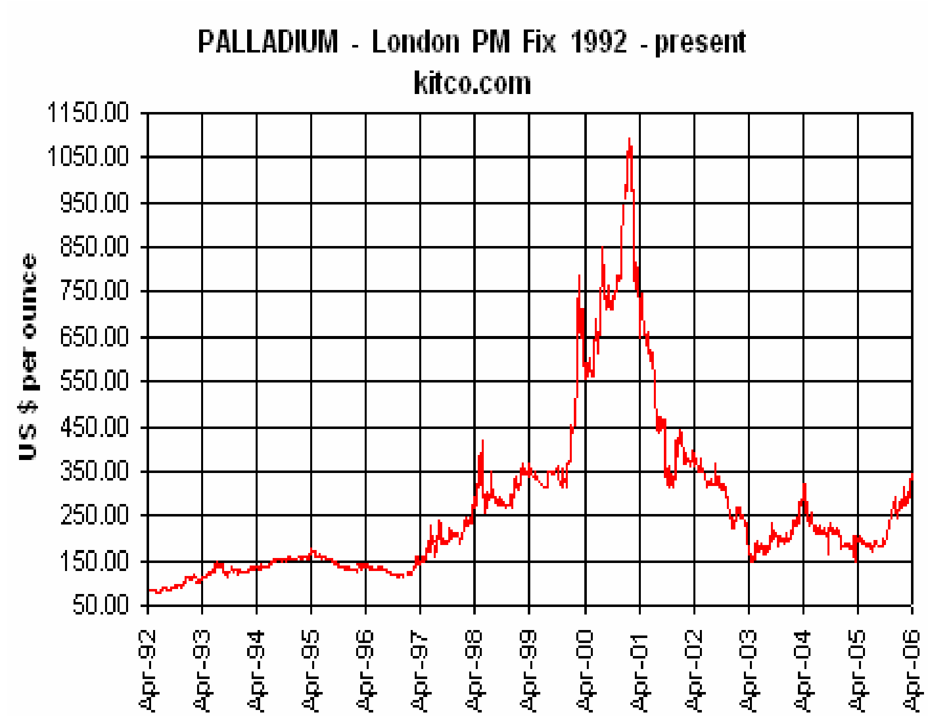
Metal	**Price ($/oz)**
Au	657
Pt	1313
Pd	352
Ru	180
Rh	6275
Ir	400

High catalytic activity of Au salts mitigates the price difference

Fluctuations in Price of Precious Metals



Gold Prices
1995-2006

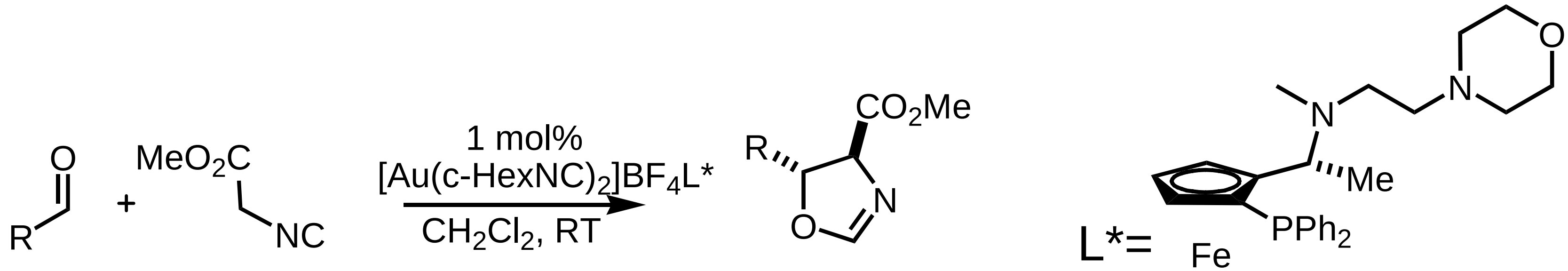


Palladium Prices
1992-2006

Characteristics of Homogenous Gold Catalysis

• Gold is a soft transition metal. It is ideally suited to activate C-C triple bonds
• Allows for the formation of C-C, C-O, C-N, C-S bonds.
• Au(I) and Au(III) are stable oxidation states
• Non-toxic
• Gold often reacts faster than other transition metals which can catalyze the same reaction.
• Au intermediates show a low tendency for β-hydride elimination
• Au intermediates undergo fast protodemetallation.
• Au compounds are easy to reduce, difficult to oxidize
• Cross-coupling chemistry difficult with Au

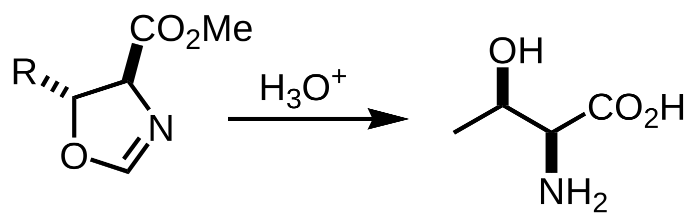
Au(I) Catalyzed Asymmetric Aldol Reaction



R= aryl, subs. aryl, alkyl

>90:10 trans:cis
86-97% ee

- First example of a catalytic asymmetric aldol reaction.
- Heteroaromatic aldehydes give low enantioselectivities
- Methodology was later expanded to include N-tosyl aldimines
- Condensations with (isocyanomethyl)phophonates also work, generating phosphonic acid analogues of amino acids

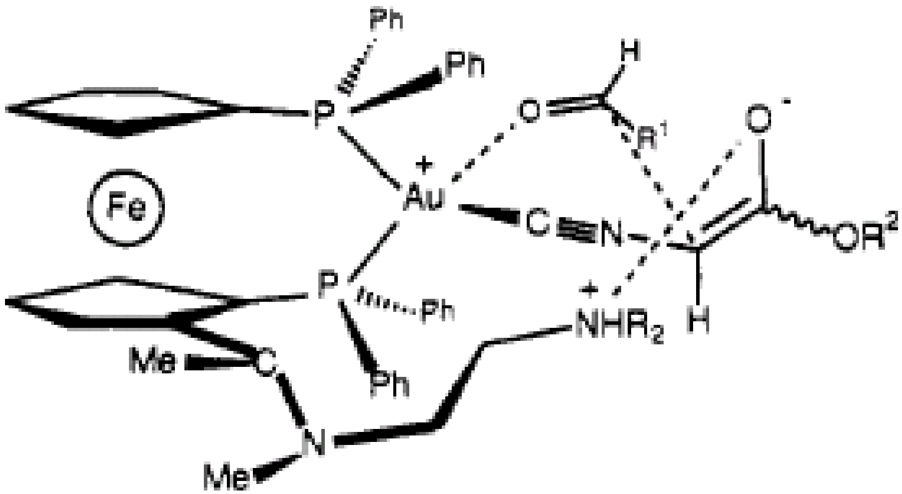


β-hydroxy amino acid

Ito, Y, Sawamura, M. *Chem. Rev*. **1992**, 92, 857.

Mechanistic Rationale of Au(I) Catalyzed Aldol

Proposed Transition State Model:

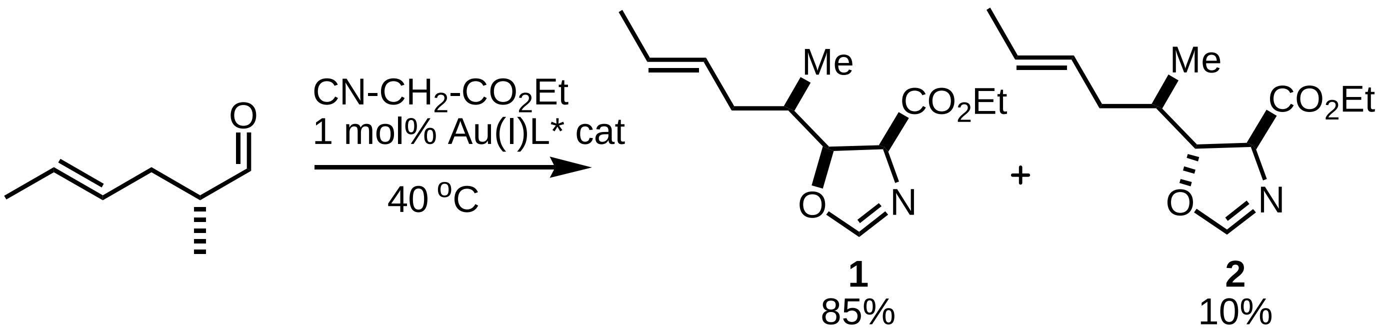


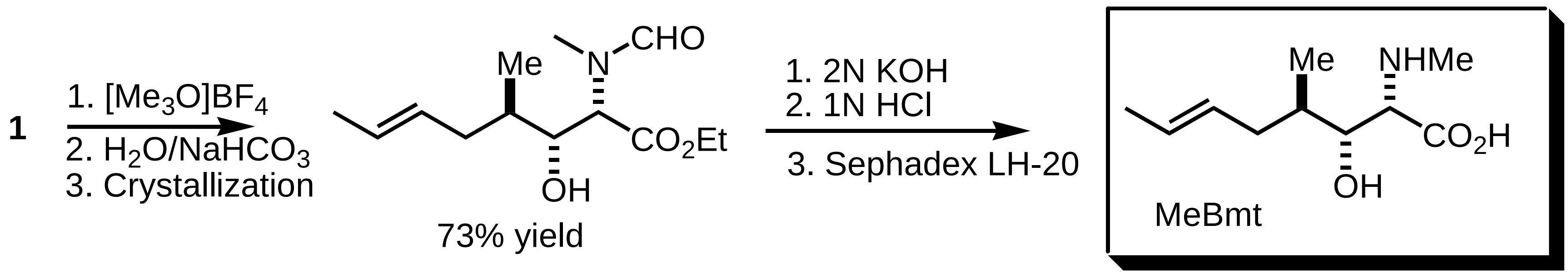
- Chiral ligand chelates to gold with phosphorous atoms
- Terminal amino group enolizes bound isocyanoacetate, forming ion pair
- Attractive interaction positions enolate and aldehyde on gold
- Enolate reacts on the *Si* face exclusively
- Substitution at the alpha position does not affect stereoselectivity

Ito, Y, Sawamura, M. *Chem. Rev*. **1992**, 92, 857.

Synthetic Applications

Stereoselective synthesis of **MeBmt** (a component of the immunosuppressant cyclosporine).



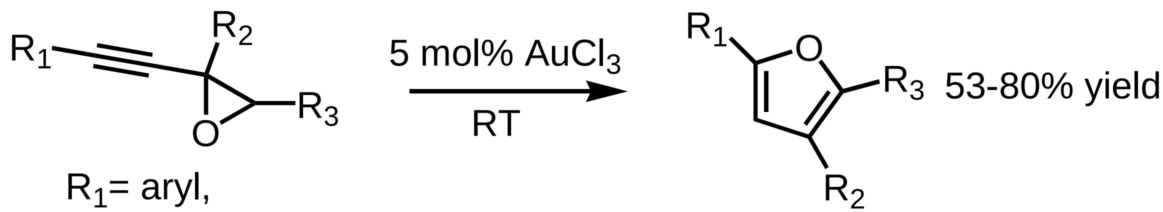


70% yield

Togni, et. al. *Helv. Chim. Acta*. **1989**, 72, 1471.

Au Activation of Alkynes: Synthesis of Furans

Nucleophilic attack of epoxides on activated alkynes to generate substituted furans

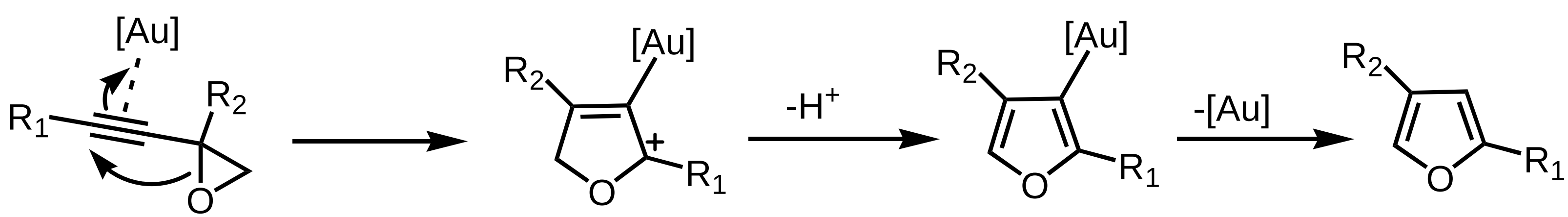


R_1= aryl,
alky, $(CH_2)_nOH$

R_2, R_3= alkyl,
$(CH_2)_nOH$

- 2-, 3-, 2,3-, 2,4-, 2,5-, 2,3,5- substitutions are all possible
- acetals deprotect in the isomerization to the furan, generating furyl aldehydes

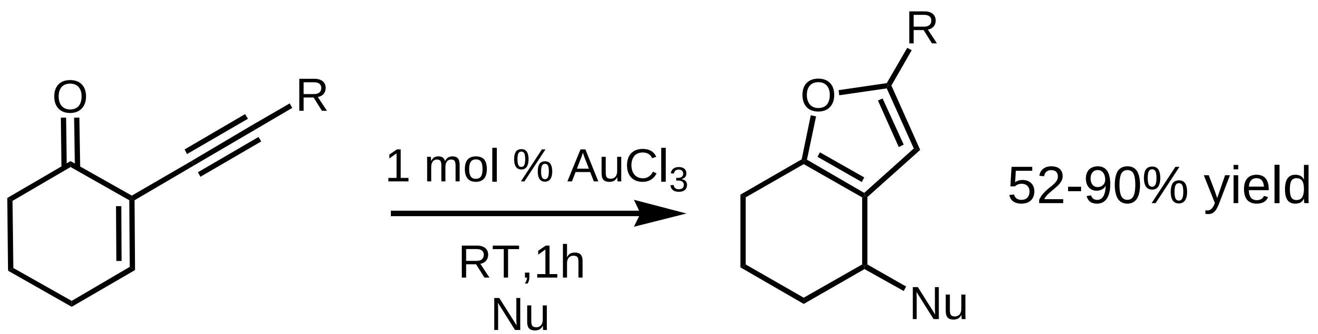
Proposed Mechanism



Hashmi et al. *Adv. Synth. Catal*. **2004**, 346, 432-438.

Au Activation of Alkynes: Synthesis of Furans

Sequential, nucleophilic domino attack on a metal-complexed alkyne



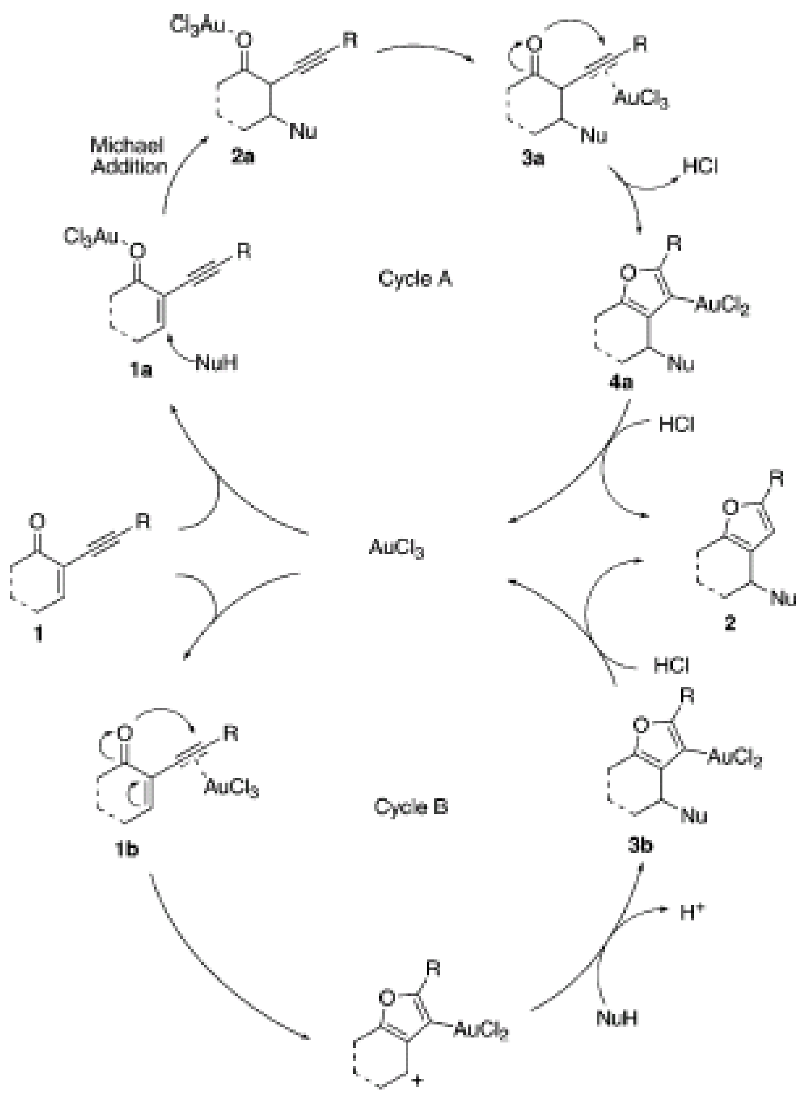
R= aryl, vinyl

- Nucleophiles: alcohols, carbohydrates, anilines, indoles, 1,3-diketones
- R= H, alkyl, or TMS doesn’t work
- Little stereoselectivity observed for substituted enones

Larock *et al. J. Am. Chem. Soc*. **2004**, 126, 11164.

Mechanism

Scheme 1



Two possible mechanisms:

Cycle A: Au(III) activates the ketone to a Michael addition followed by alkyne activation.

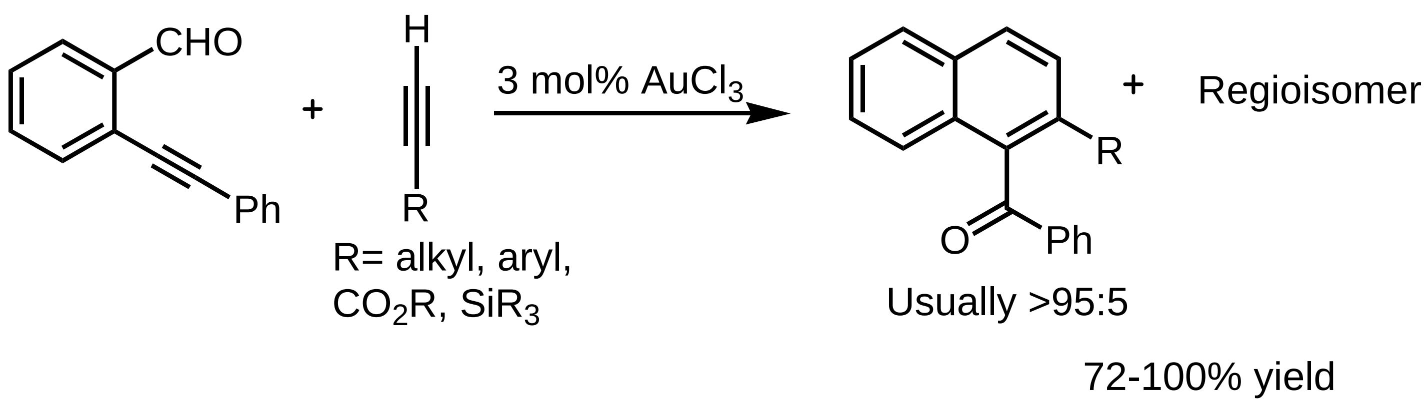
Cycle B: Au(III) activates the alkyne only

The authors concluded B was more likely.

Larock *et al. J. Am. Chem. Soc*. **2004**, 126, 11164.

Activation of Alkynes: Benzannulations

Synthesis of napthyl ketones via [4+2] benzannulation

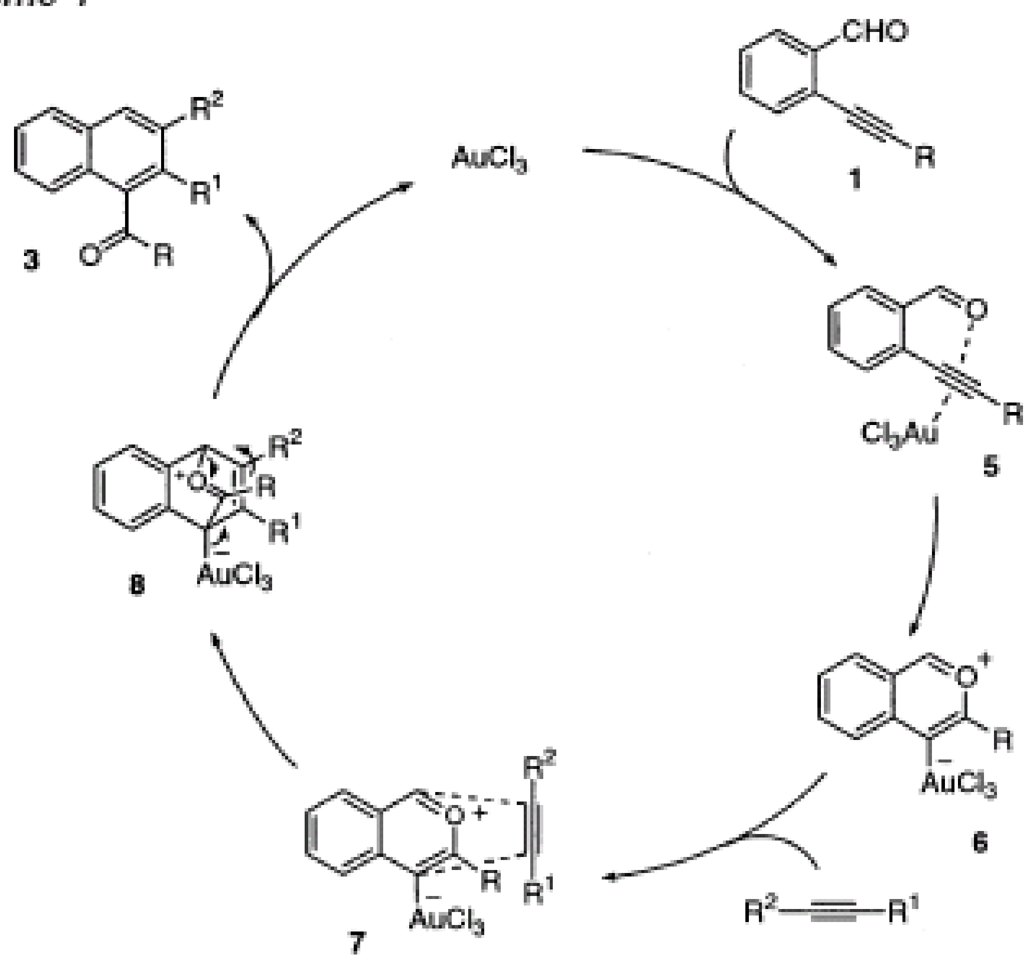


- Highly regioselective benzannulation strategy
- For alkynyl esters the other regioisomer is favored

Yamamoto et al. *J. Am. Chem. Soc*. **2003**, 125, 10921.

Proposed Mechanism of Au(III) Catalyzed Benzannulation

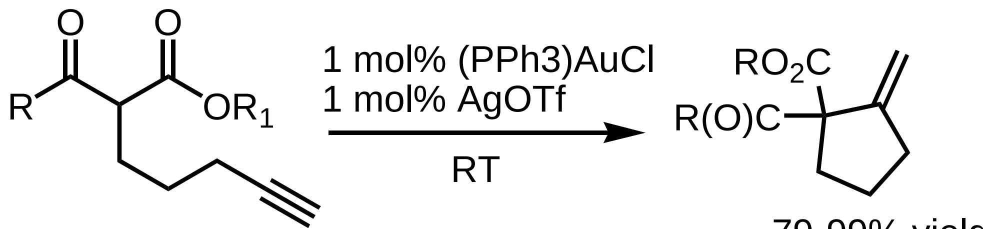
Scheme 1



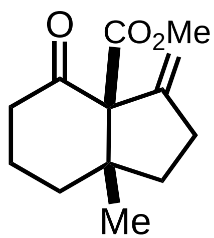
Yamamoto et al. *J. Am. Chem. Soc*. **2003**, 125, 10921.

Activation of Alkynes: Au(I) Catalyzed Conia-Ene

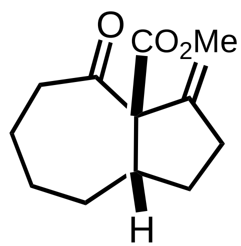
Additions of b-ketoesters to Au(I) activated alkynes



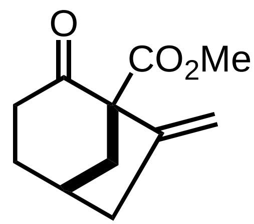
79-99% yield



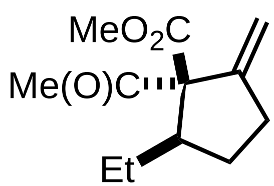
83%



86%



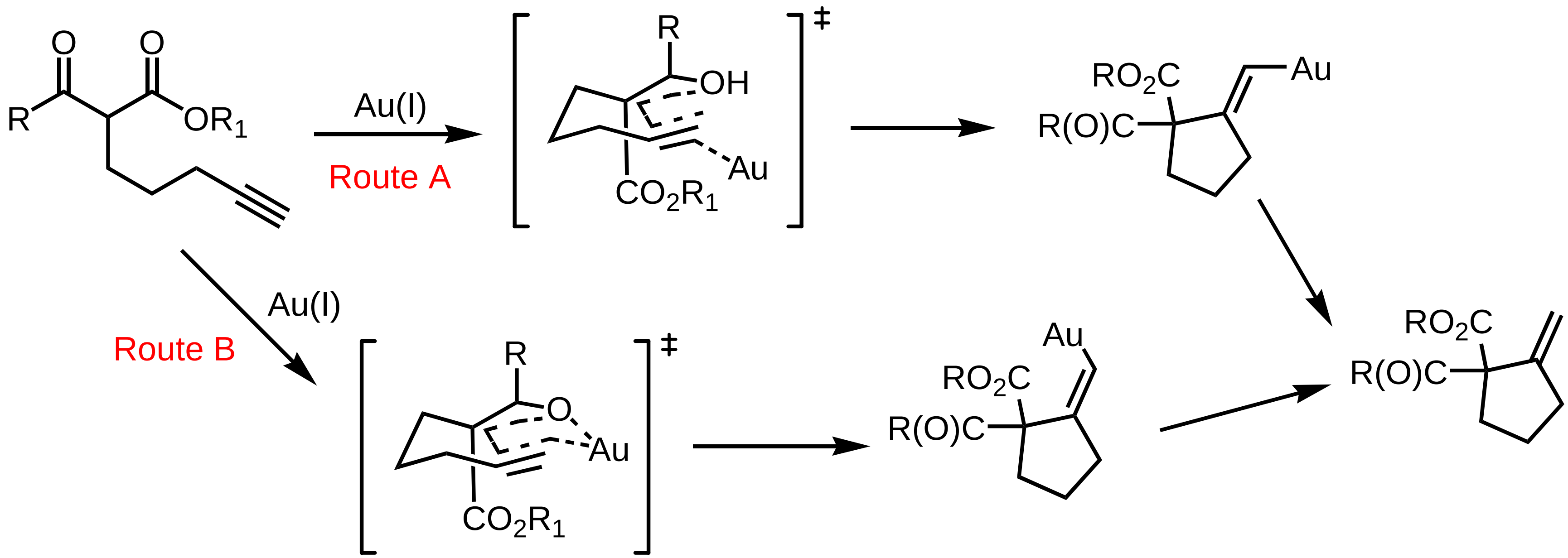
99%



95%
17:1 dr

Toste *et al. J. Am. Chem. Soc*. **2004**, 126, 4526.

Mechanism: Au(I) Catalyzed Conia-Ene Reaction

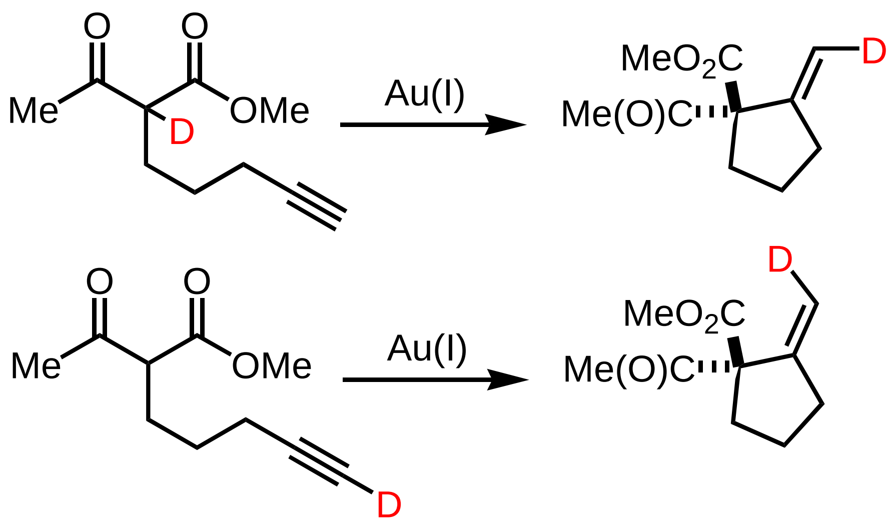


Route A: Nucleophilic attack of enol on activated alkyne
Route B: Formation of Au-enolate

Toste *et al. J. Am. Chem. Soc*. **2004**, 126, 4526.

Mechanism: Au(I) Catalyzed Conia-Ene Reaction

Deuterium Labeling Experiment

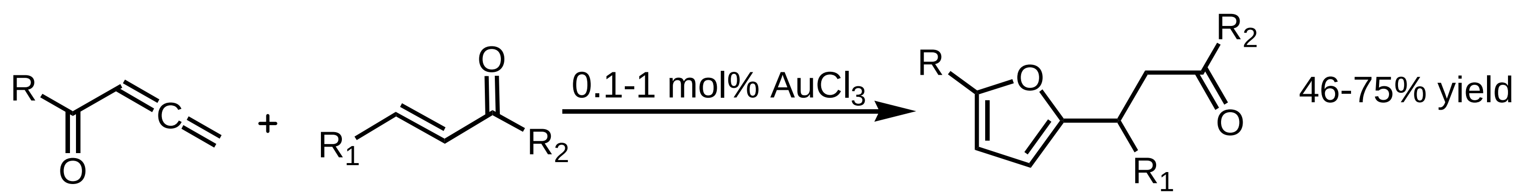


The authors concluded “Route A” was more likely.

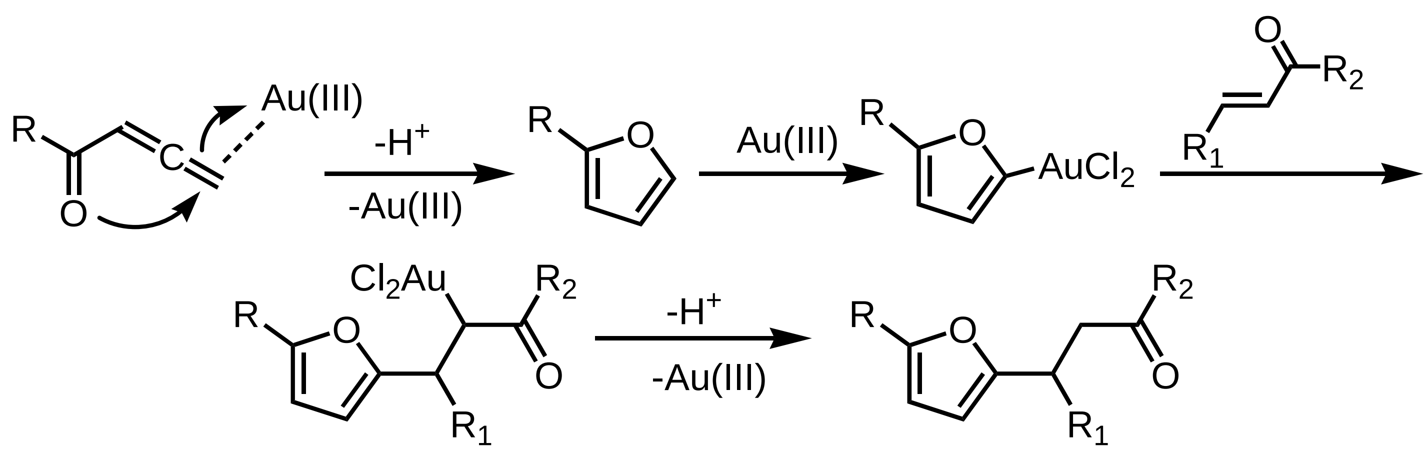
Toste *et al. J. Am. Chem. Soc*. **2004**, 126, 4526.

Activation of Allenes

Cross-dimerization of allenyl ketones and Michael acceptors



Other aurated, electron rich benzenoid aromatics may also engage in Michael additions

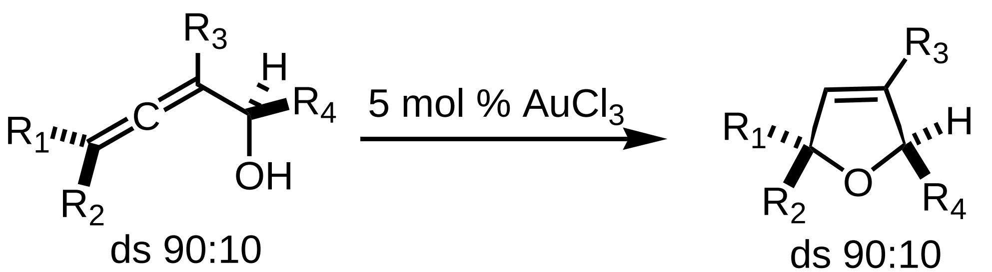


No competing β-hydride elimination observed

A. Stephen, K. Hashmi. *Angew. Chem. Int. Ed.* **2000**, 39, 2285.

Activation of Allenes

Cyclization of Hydroxyallenes to Dihydrofurans



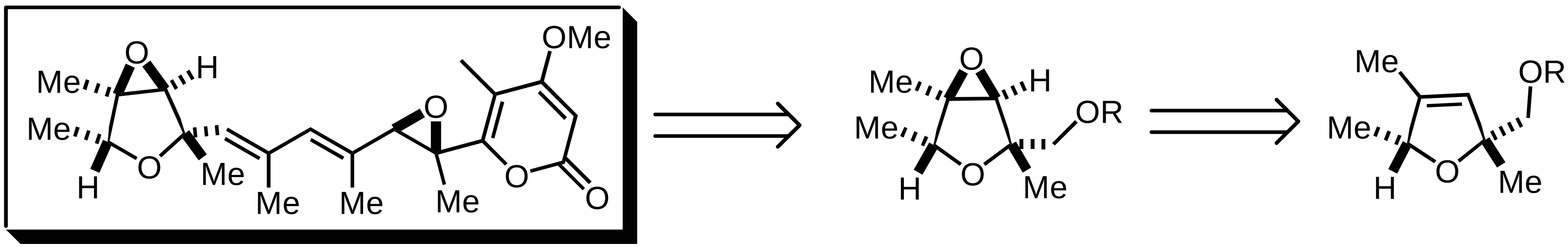
R_1= H, alkyl, alkenyl
R_2= alkyl
R_3= EE, CH_2OH, CH_2OPG

74-100% yield

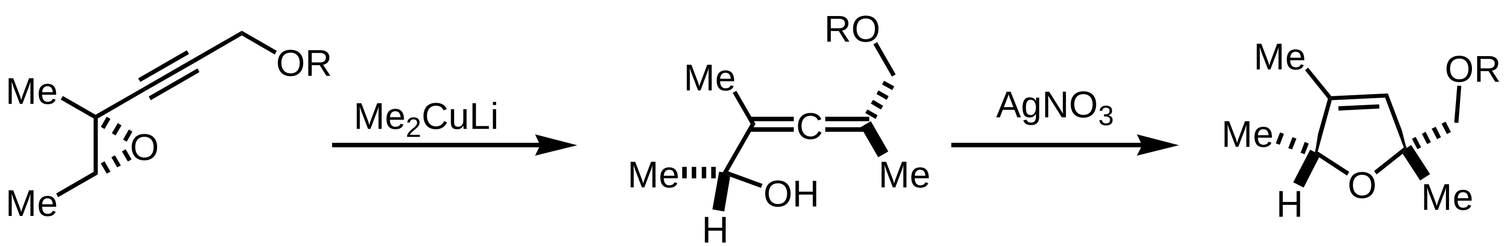
- Complete chirality transfer observed
- Reaction not influenced by substitution on allene, even with sterically demanding alkyl groups.
- Experimentally trivial: no aqueous workup required

Krause et al. *Org. Lett*. **2001**, 3, 2537.

Synthetic Application: Core of Verrucosidin



Verrucosidin

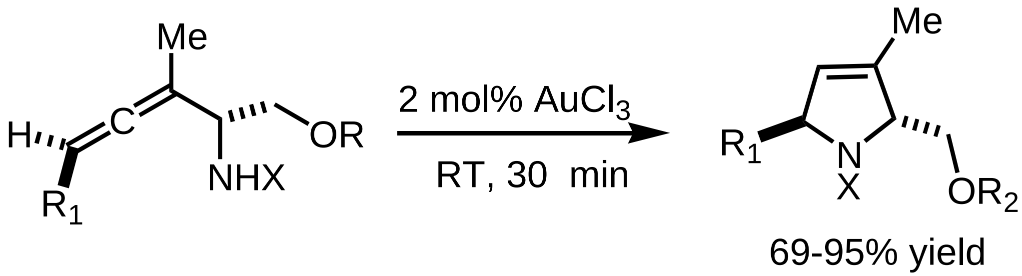


Published synthesis with Ag(I) cyclization requires long reaction times.

Marshall, J. and Pinney, K.G. *J. Org. Chem.* **1993**, 58, 7180..

Extension to Aminoallenes

Synthesis of pyrrolines

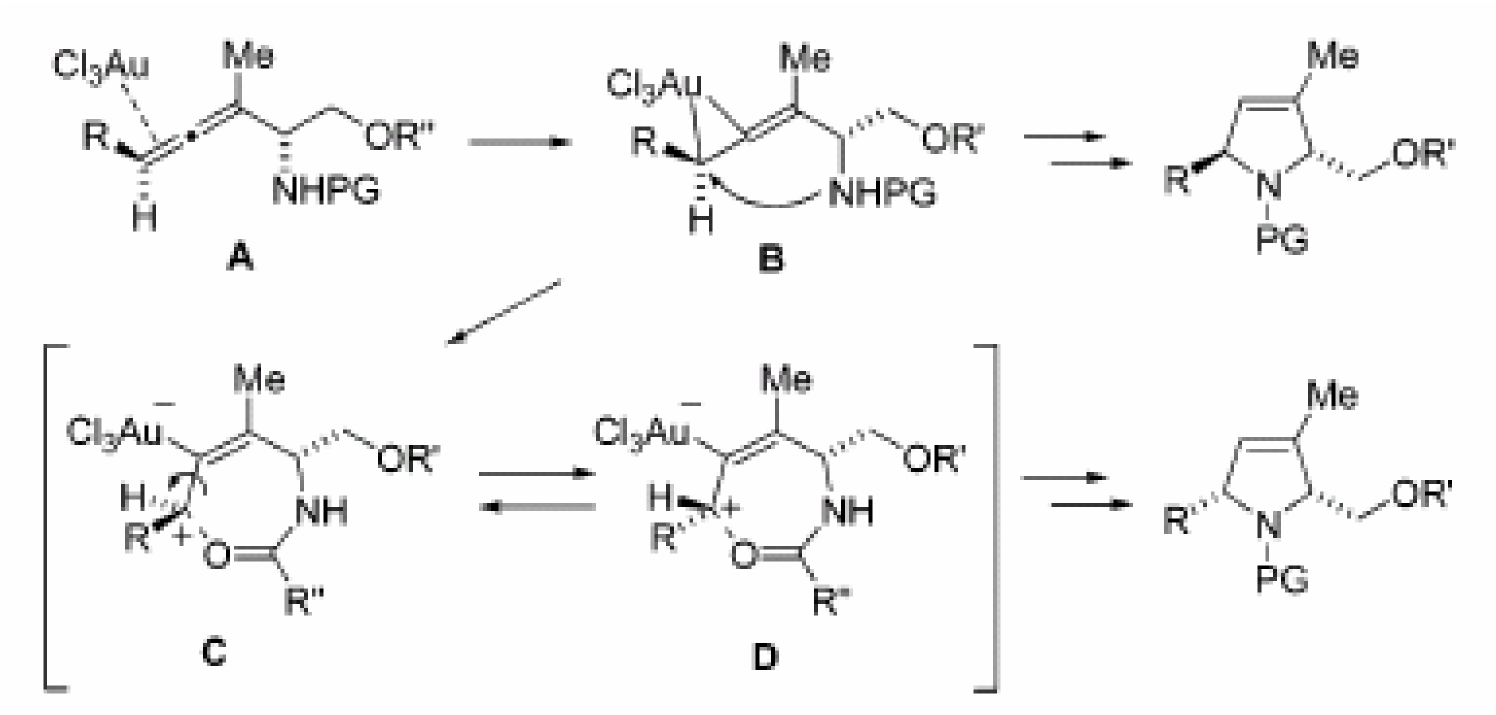


X	**dr SM**	**dr Pdt**
H	99:1	99:1
Ts	99:1	95:5
Ac	99:1	70:30
BOC	99:1	46:54

Depending on the nature of the protecting group, erosion in chirality transfer is observed.

Krause et al. *Org. Lett*. **2004**, 6, 4121.

Explanation for Erosion of Chirality Transfer



Oxygen atom of the protecting group stabilizes complex **C**. Bond rotations results in isomerization.

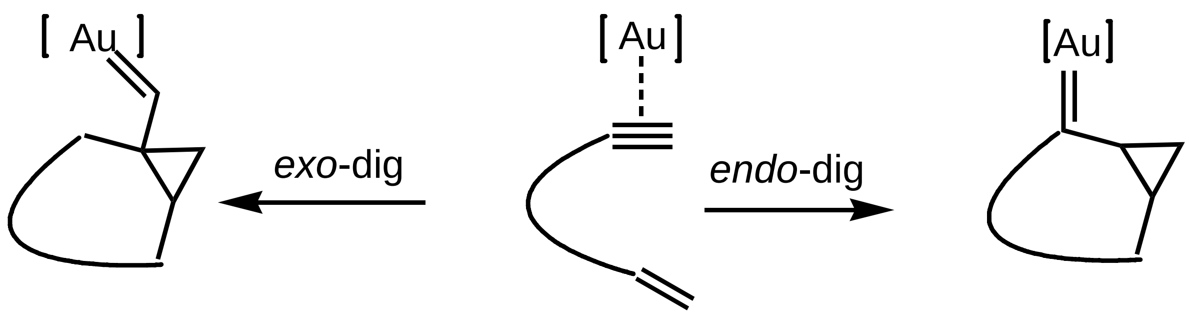
Krause et al. *Org. Lett*. **2004**, 6, 4121.

Au(I) Catalyzed Enyne Cyclizations

• Recent reports cite evidence of Au carbenes in enyne cyclizations

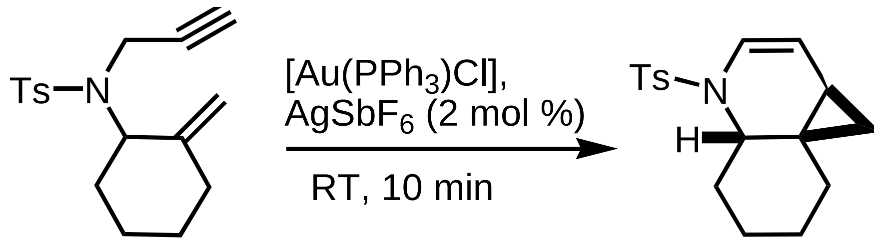
• Activation of alkyne followed by nucleophillic attack of olefin and generation of cyclopropylcarbene-metal intermediate

• Both *exo* and *endo* cyclizations observed

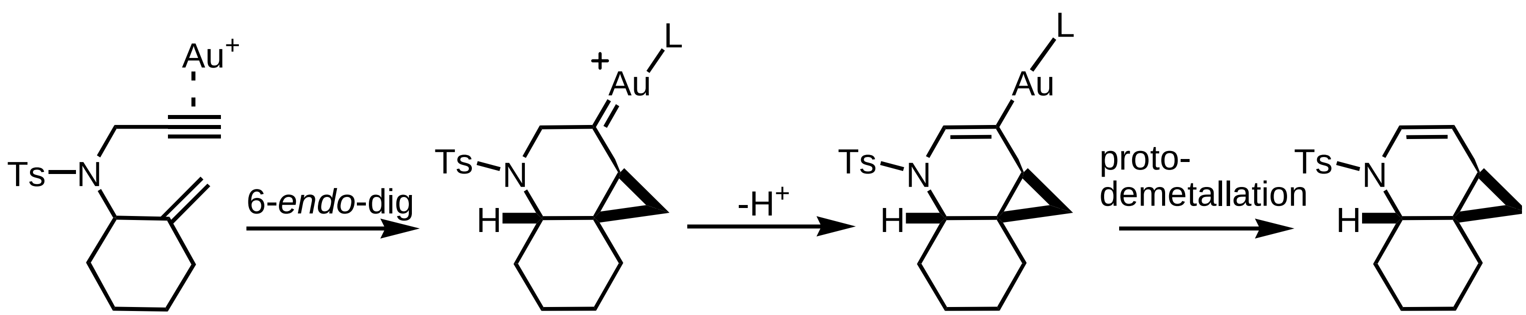


For a Review See: Bruneau, *Angew. Chem. Int. Ed*. **2005**, 44, 2328.

Au(I) Catalyzed 1,6-Enyne Cyclization

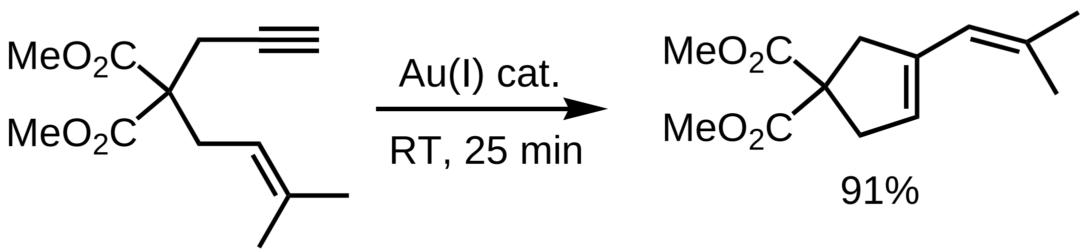


• 1,6-enynes with a heteroatom at the allylic position undergo 6-*endo*-dig cyclizations under mild conditions with short reaction times to give cyclopropanes
• Heteroatom required, otherwise 5-*exo*-dig cyclization and subsequent skeletal rearrangement is observed.



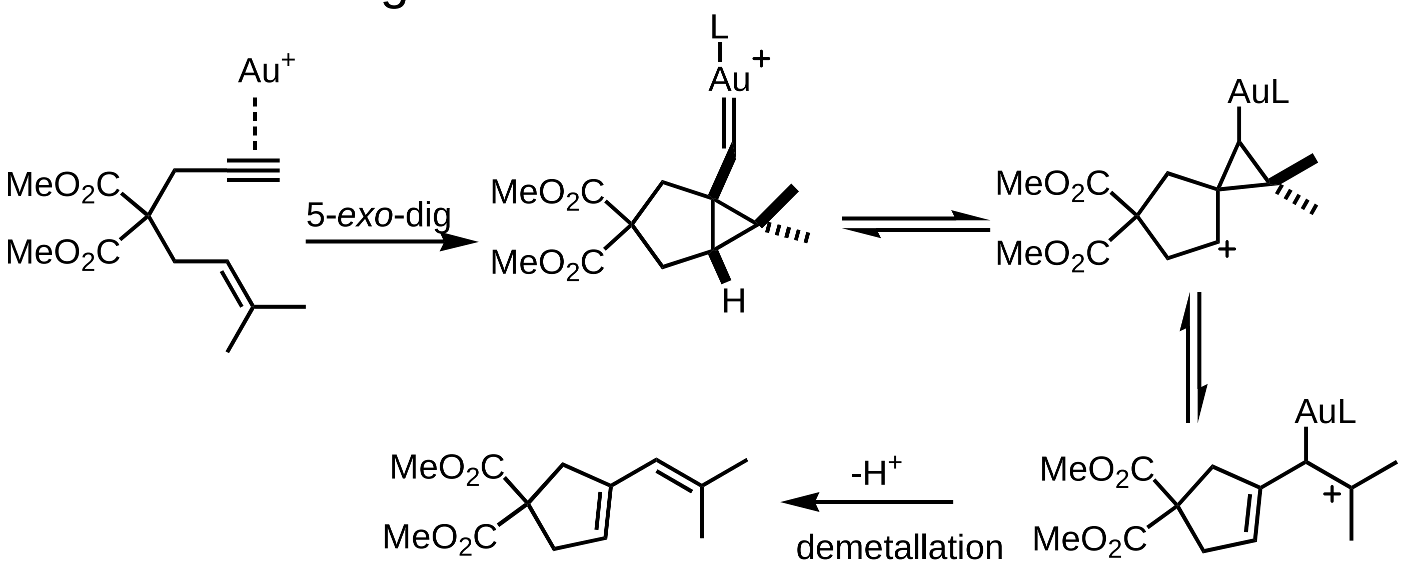
Echavarren *et al. Angew. Chem. Int. Ed*. **2004**, 43, 2402

Lack of Heteroatom Results In Skeletal Rearrangement



Rearranged product only!

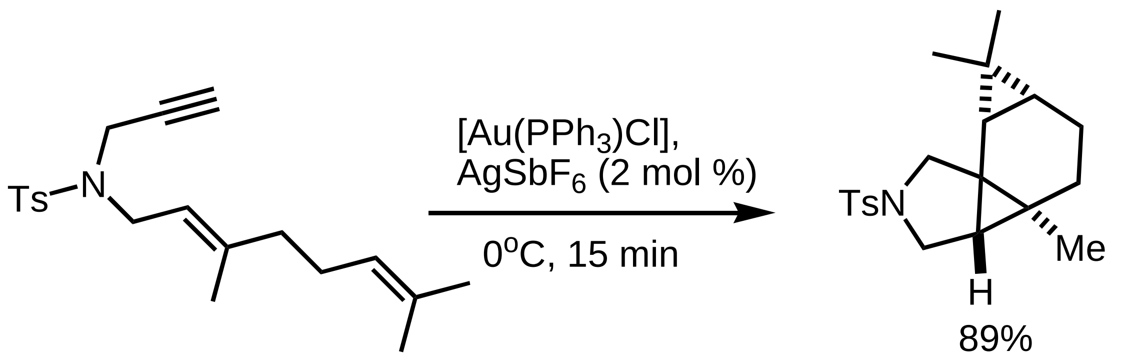
Mechanism for Rearrangement:



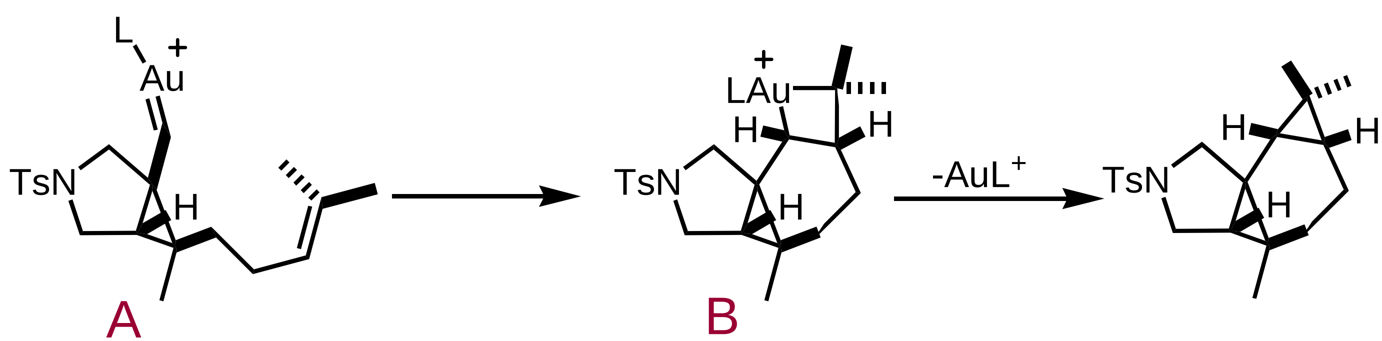
Angew. Chem. Int. Ed. **2004**, 43, 2402

Tandem Cyclopropanations of Dienynes

Dienynes may undergo two successive cyclopropanations. Reactivity is exclusively *exo.*



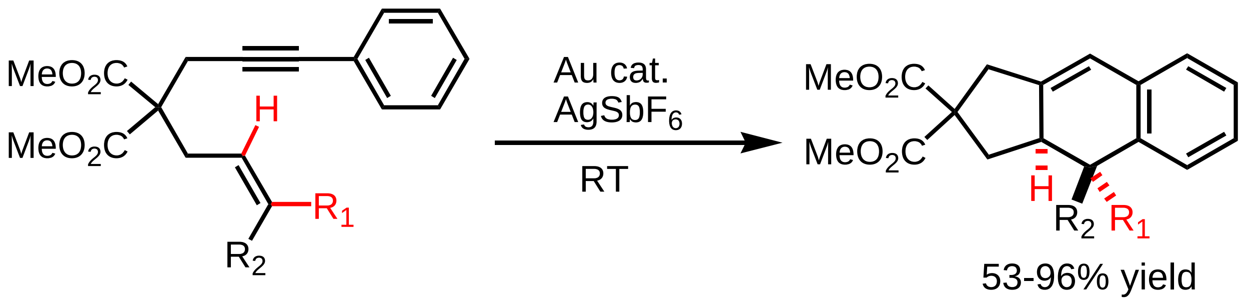
Stereoselectivity of the second cyclopropanantion due to kinetically controlled trapping of A where metal carbene and cyclopropane are antiperiplanar.



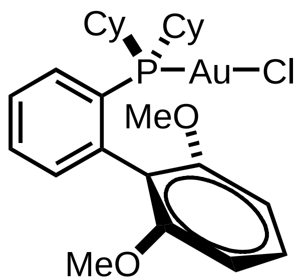
Angew. Chem. Int. Ed. **2004**, 43, 2402

Au(I) Catalyzed Cyclopropanation Followed by [4+2]

- •Cyclization via 5-exo-dig pathway to a cyclopropyl intermediate followed by [4+2] ring expansion
- •Reaction proceeds stereospecifically.
- •Alkenes, rather than aryl groups, work as well

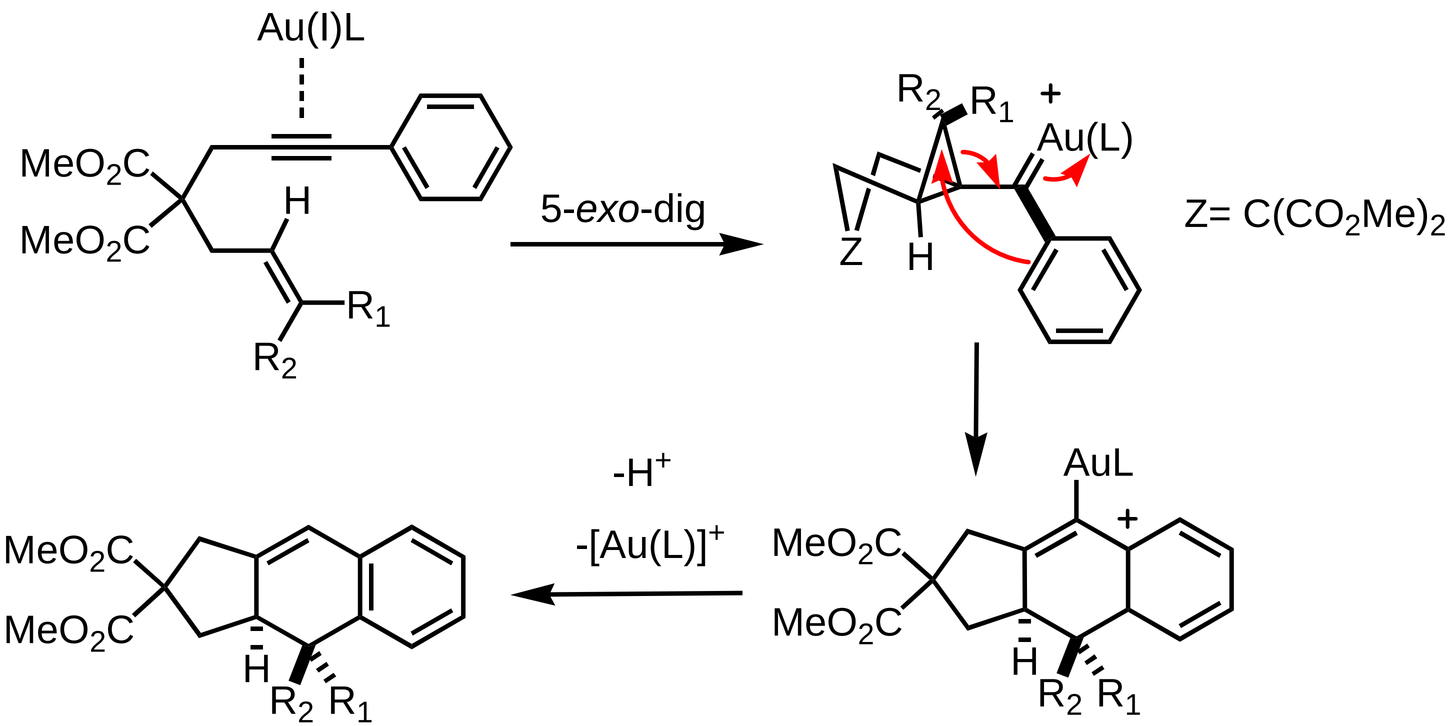


Au cat =



Echavarren *et al. J. Am. Chem. Soc*. **2005**, 127, 6178

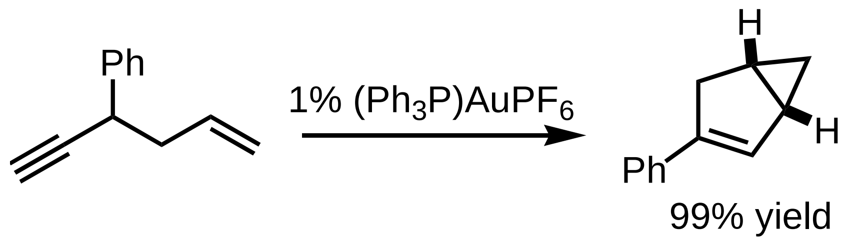
Mechanism



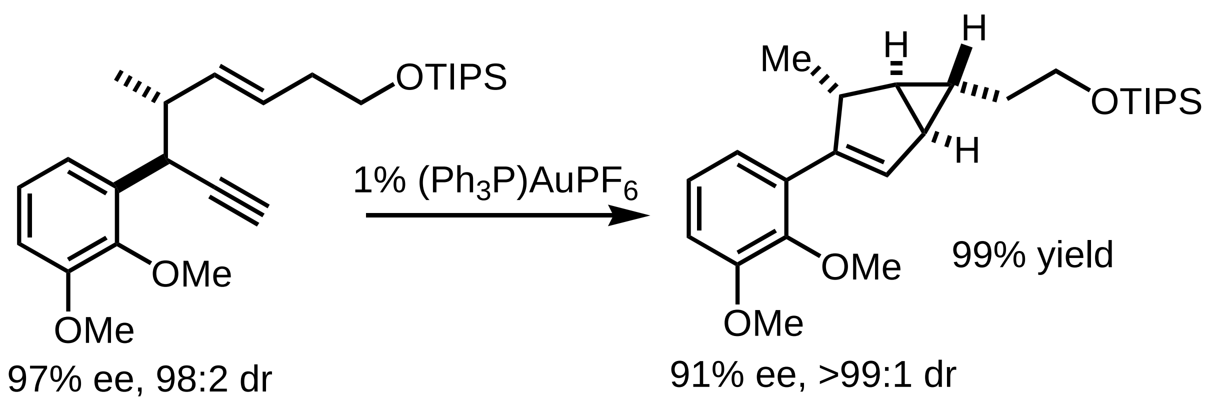
The cyclopropyl carbene intermediate may also be trapped by the addition of MeOH, which supports the proposed mechanism.

Echavarren *et al. J. Am. Chem. Soc*. **2005**, 127, 6178

Au(I) Catalyzed Cyclizations of 1,5 Enynes



- No 5-exo-dig product observed.
- Equally effective with non-terminal acetylenes

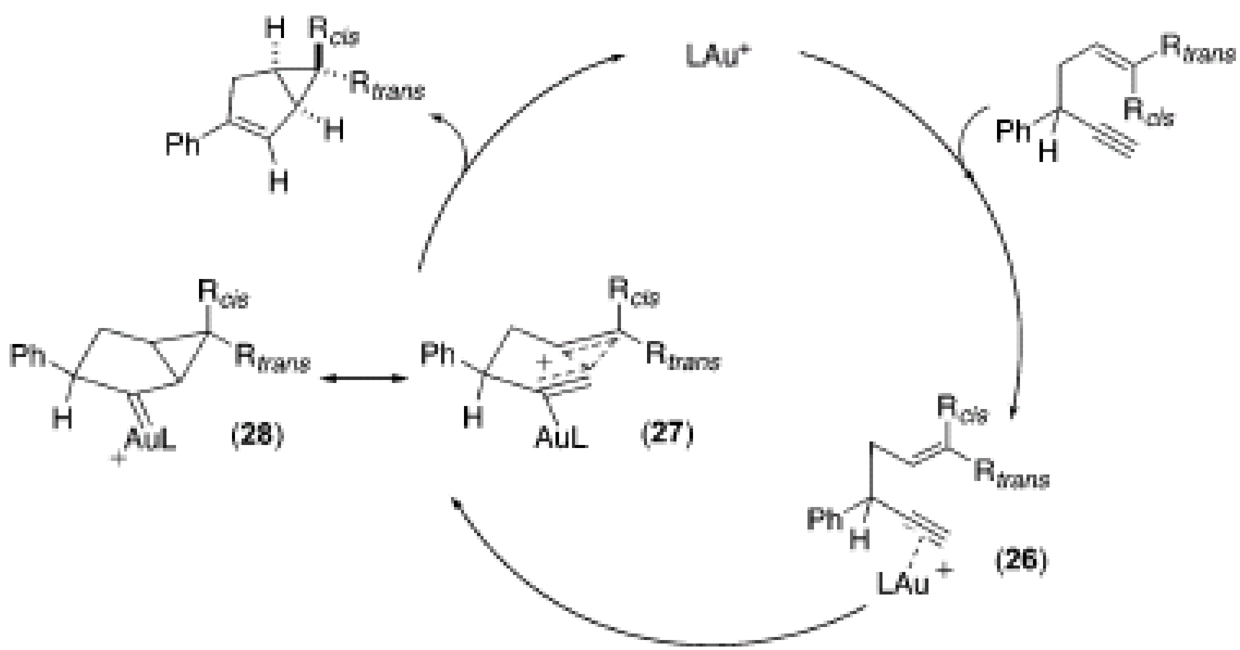


- Reaction with disubstituted olefins is stereospecific
- Excellent chirality transfer observed.

Toste *et al. J. Am. Chem. Soc*. **2004**, 126, 10858

Au(I) Catalyzed Cyclizations of 1,5 Enynes

Scheme 1. Mechanistic Proposal for Au(I)-Catalyzed Cycloisomerization



Large groups occupy pseudoequatorial positions in half-chair transition states.

Toste *et al. J. Am. Chem. Soc*. **2004**, 126, 10858

Conclusions

• Homogenous Gold catalysis is a burgeoning field with numerous applications in organic synthesis.

• Au catalysts are experimentally friendly: air/moisture tolerant, non-toxic, mild reaction conditions

• Most Au catalysis occurs via activation of “soft” C-C bonds, such as alkynes or allenes. Some Au catalyzed reactions occur via Au carbene intermediates

• Asymmetric Au catalysis is not common since Au complexes are usually linear.

Gold Reviews

A. Stephen, K. Hashmi. Homogeneous Catalysis by Gold. *Gold Bulletin* **2004**, 37, 51-65.

Hoffmann-Roder, Anja, Krause, Norbert. The Golden Gate to Catalysis. *Org. Biomol. Chem*. **2005**, 3, 387-391.

Arcadi, Di Giuseppe, S. *Curr. Org. Chem*. **2004**, 8, 795.

Dyker, Gerald. An Eldorado for Homogeneous Catalysis. *Angew. Chem. Int. Ed*. **2000**, 39, 4237-4239.

Bruneau, Christian. Electrophillic Activation and Cycloisomerization of Enynes: A New Route to Functional Cyclopropanes. *Angew. Chem. Int. Ed.* **2005**, 44, 2328-2334.

The End