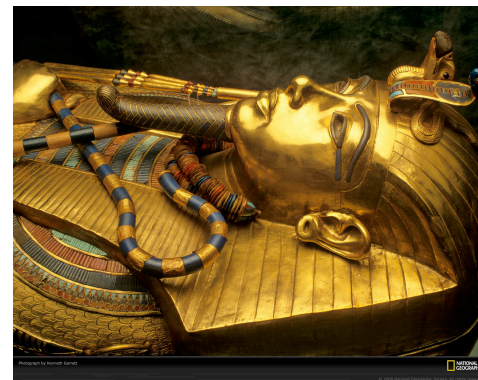
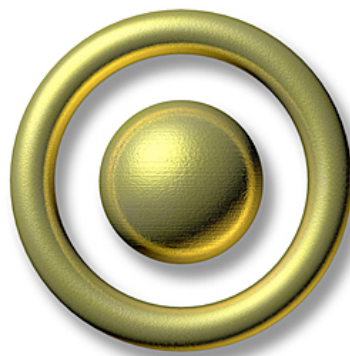
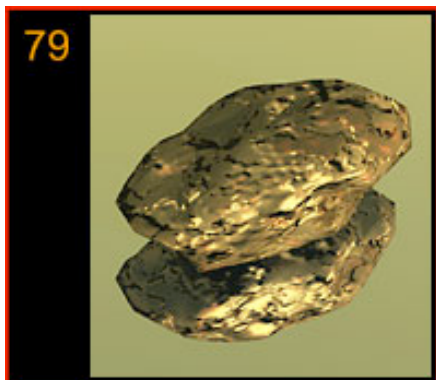


# Recent Developments in Homogeneous Gold Catalysis

*David A. Nagib*



MacMillan Group  
Literature Meeting

03.17.2010

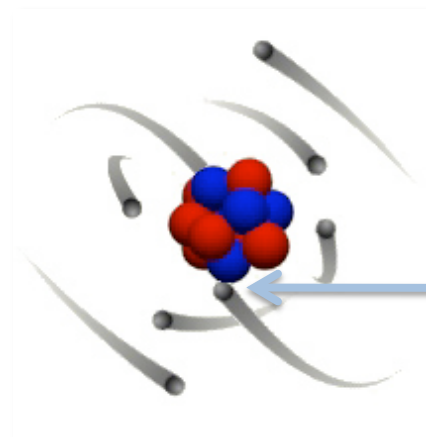
# Relativistic Effects in Gold Catalysis

*Relativistic effects* – phenomenon resulting from the need to consider velocity as significant relative to the speed of light

$$m = m_0 / \sqrt{1 - (v/c)^2}$$

### Consequences:

- Relativistic mass increases as velocity approaches c
- Increased mass results in decreased Bohr radius
- Contracted 6s orbital better shields (expands) 5d orbital

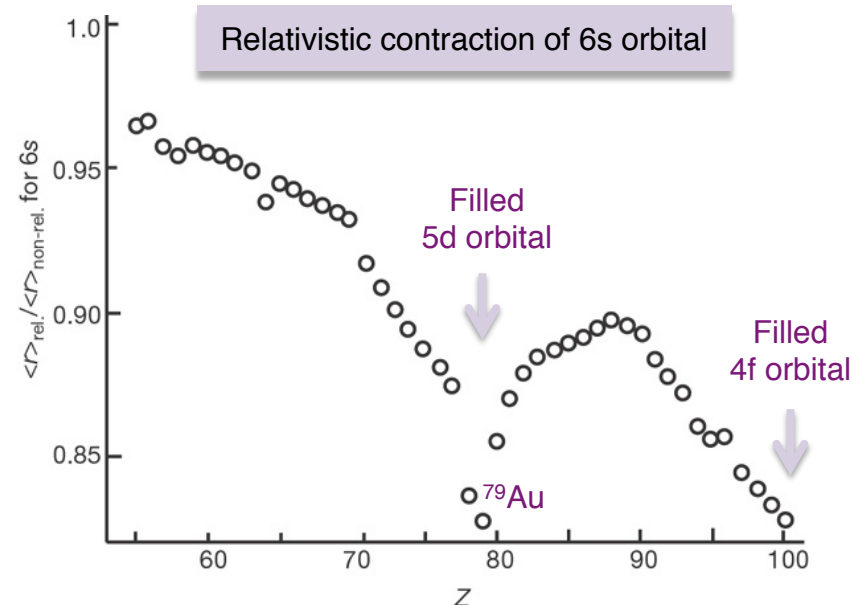


- Faster
- Heavier
- Nearer

THE PERIODIC TABLE

1 IA																	18 VIIIA																		
1 H 1.008 Hydrogen																	2 He 4.00 Helium																		
2 Li 6.94 Lithium	3 Be 9.01 Beryllium											13 B 10.81 Boron	14 C 12.01 Carbon	15 N 14.01 Nitrogen	16 O 16.00 Oxygen	17 F 19.00 Fluorine	18 Ne 20.18 Neon																		
3 Na 22.99 Sodium	4 Mg 24.31 Magnesium	3 Al 26.98 Aluminum	4 Si 28.09 Silicon	5 P 30.97 Phosphorus	6 S 32.07 Sulfur	7 Cl 35.45 Chlorine	8 Ar 39.95 Argon									9 K 39.10 Potassium	10 Ca 40.08 Calcium	11 Sc 44.96 Scandium	12 Ti 47.88 Titanium	13 V 50.94 Vanadium	14 Cr 52.00 Chromium	15 Mn 54.94 Manganese	16 Fe 55.85 Iron	17 Co 58.93 Cobalt	18 Ni 58.69 Nickel	19 Cu 63.55 Copper	20 Zn 65.39 Zinc	21 Ga 69.72 Gallium	22 Ge 72.61 Germanium	23 As 74.92 Arsenic	24 Se 78.96 Selenium	25 Br 79.90 Bromine	26 Kr 83.80 Krypton		
4 Rb 85.47 Rubidium	5 Sr 87.62 Strontium	6 Y 88.91 Yttrium	7 Zr 91.22 Zirconium	8 Nb 92.91 Niobium	9 Mo 95.94 Molybdenum	10 Tc (97.9) Technetium	11 Ru 101.07 Ruthenium	12 Rh 102.91 Rhodium	13 Pd 106.42 Palladium	14 Ag 107.87 Silver	15 Cd 112.41 Cadmium	16 In 114.82 Indium	17 Sn 118.71 Tin	18 Sb 121.76 Antimony	19 Te 127.60 Tellurium	20 I 126.90 Iodine	21 Xe 131.29 Xenon	22 Cs 132.91 Cesium	23 Ba 137.33 Barium	24 La 138.91 Lanthanum	25 Ce 140.12 Cerium	26 Pr 140.91 Praseodymium	27 Nd 144.24 Neodymium	28 Pm (145) Promethium	29 Sm 150.36 Samarium	30 Eu 151.97 Europium	31 Gd 157.25 Gadolinium	32 Tb 158.93 Terbium	33 Dy 162.50 Dysprosium	34 Ho 164.93 Holmium	35 Er 167.26 Erbium	36 Tm 168.93 Thulium	37 Yb 173.04 Ytterbium	38 Lu 174.97 Lutetium	
5 Fr 223.02 Francium	6 Ra 226.03 Radium	7 Ac 227.03 Actinium	8 Th 232.04 Thorium	9 Pa 231.04 Protactinium	10 U 238.03 Uranium	11 Np 237.05 Neptunium	12 Pu 239.05 Plutonium	13 Am 243.06 Americium	14 Cm 247.07 Curium	15 Bk 247.07 Berkelium	16 Cf 251.08 Californium	17 Es 252.08 Einsteinium	18 Fm 257.10 Fermium	19 Md 258.10 Mendelevium	20 No 259.10 Nobelium	21 Lr 262.11 Lawrencium	22 Rf 261.10 Rutherfordium	23 Db 262.11 Dubnium	24 Sg 263.10 Seaborgium	25 Bh 264.10 Bohrium	26 Hs 265.10 Hassium	27 Mt 266.10 Meitnerium	28 Unlabeled 267.10 Unlabeled	29 Unlabeled 268.10 Unlabeled	30 Unlabeled 269.10 Unlabeled	31 Unlabeled 270.10 Unlabeled	32 Unlabeled 271.10 Unlabeled	33 Unlabeled 272.10 Unlabeled	34 Unlabeled 273.10 Unlabeled	35 Unlabeled 274.10 Unlabeled	36 Unlabeled 275.10 Unlabeled	37 Unlabeled 276.10 Unlabeled	38 Unlabeled 277.10 Unlabeled	39 Unlabeled 278.10 Unlabeled	40 Unlabeled 279.10 Unlabeled
ALKALI METALS		LANTHANIDES																HALOGENS		NOBLE GASES															
EARTH METALS		ACTINIDES																																	

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Gorin, D. J.; Toste, F. D. *Nature* **2007**, 446, 395-403  
 Pyykkö, P.; Desclaux, J. P. *Acc. Chem. Res.* **1979**, 12, 276-281

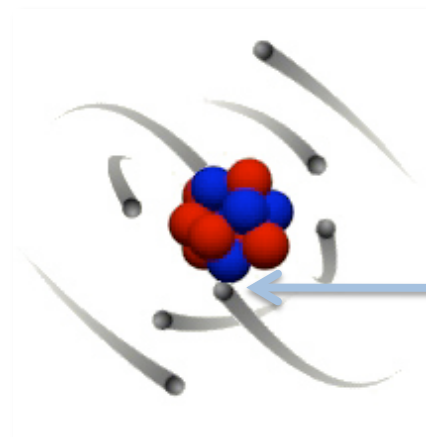
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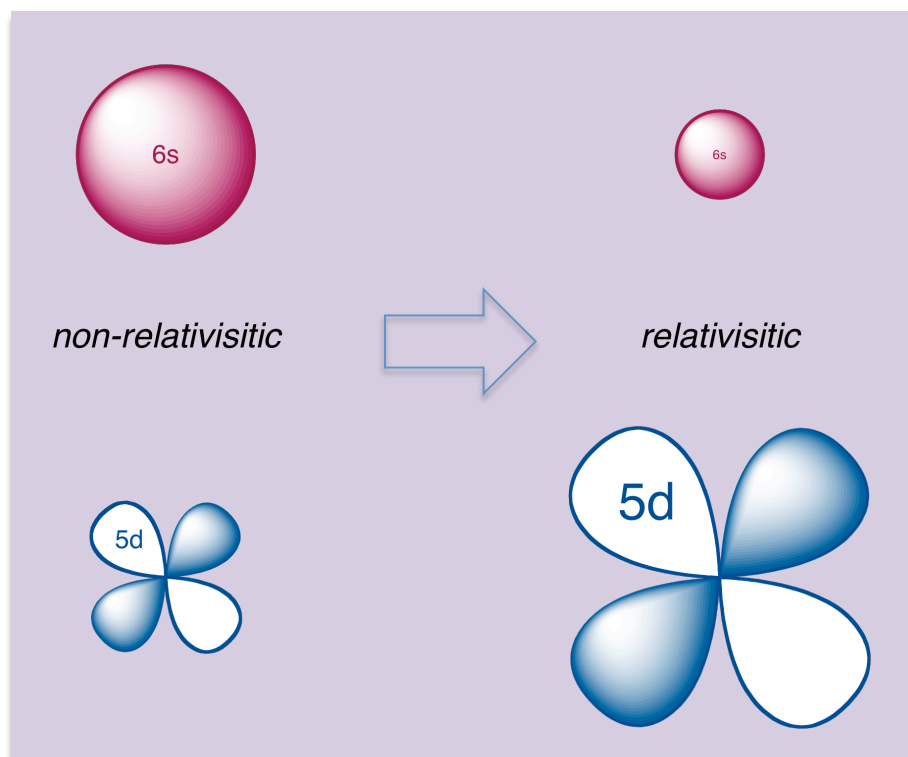
$$m = m_0 \sqrt{1 - (v/c)^2}$$

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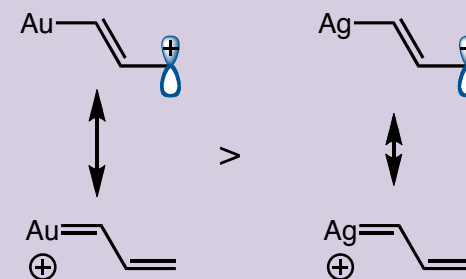
- Faster
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- Nearer



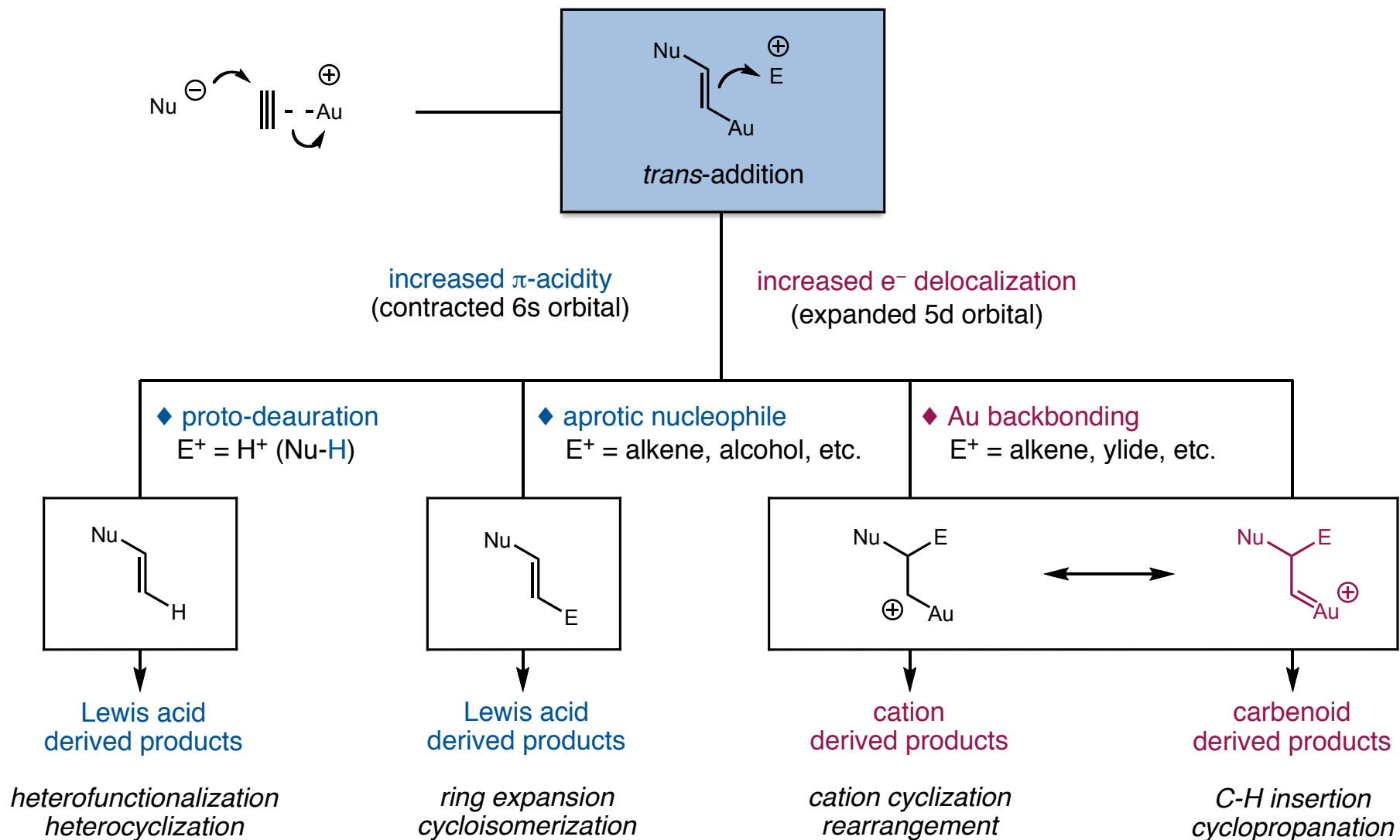
*Increased  $\pi$ -acidity*



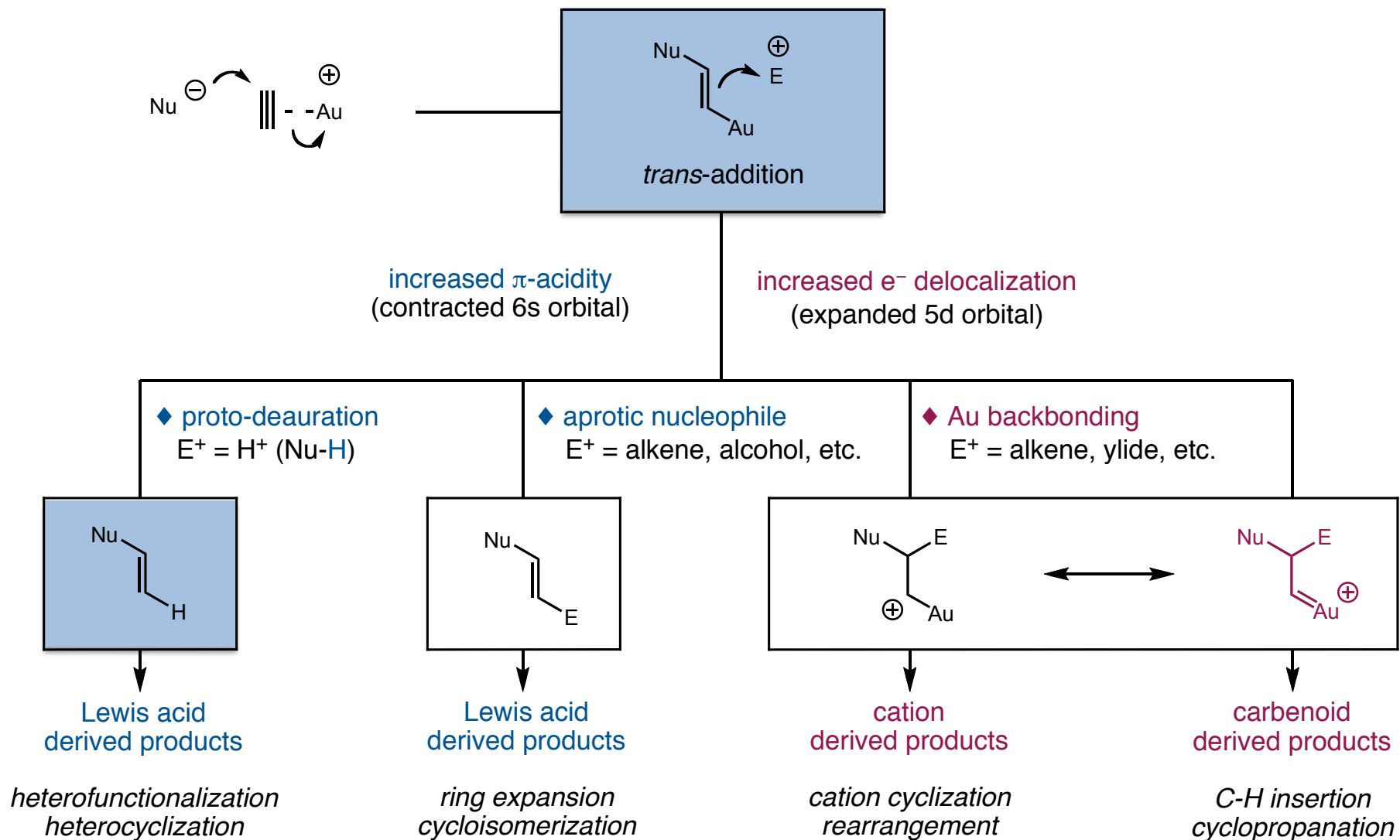
*Increased  $e^-$  delocalization (i.e. backbonding)*



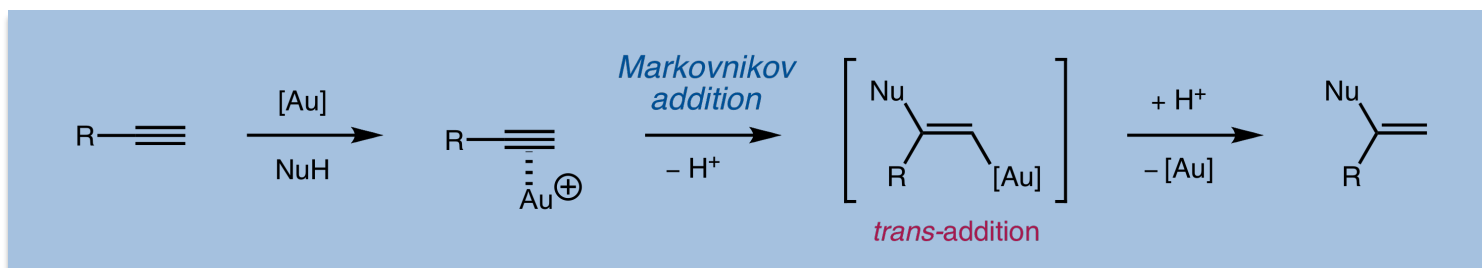
# Modes of Reactivity in Homogeneous Gold Catalysis



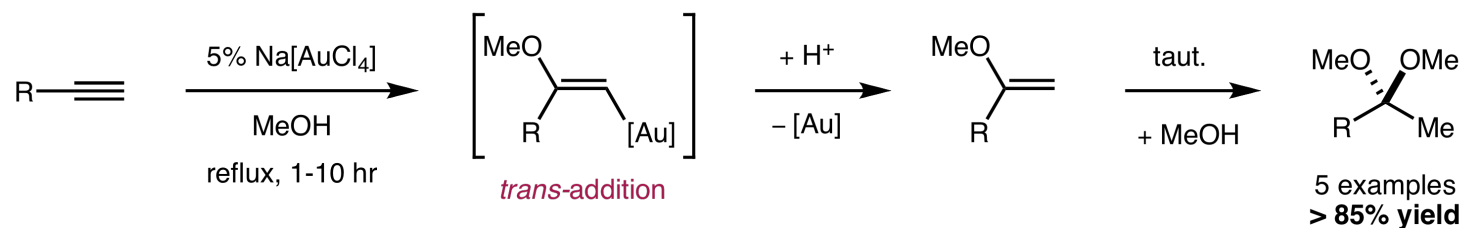
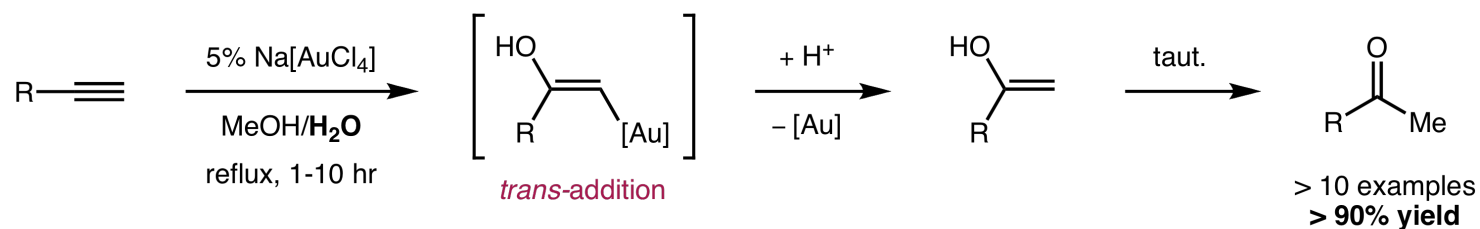
## Modes of Reactivity in Homogeneous Gold Catalysis



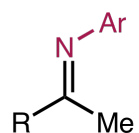
## Activation of $\pi$ -systems Towards Nucleophiles



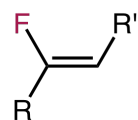
### ■ Oxygen nucleophiles



### ■ Other nucleophiles



20 examples  
> 80% yield



5 examples  
> 70% yield

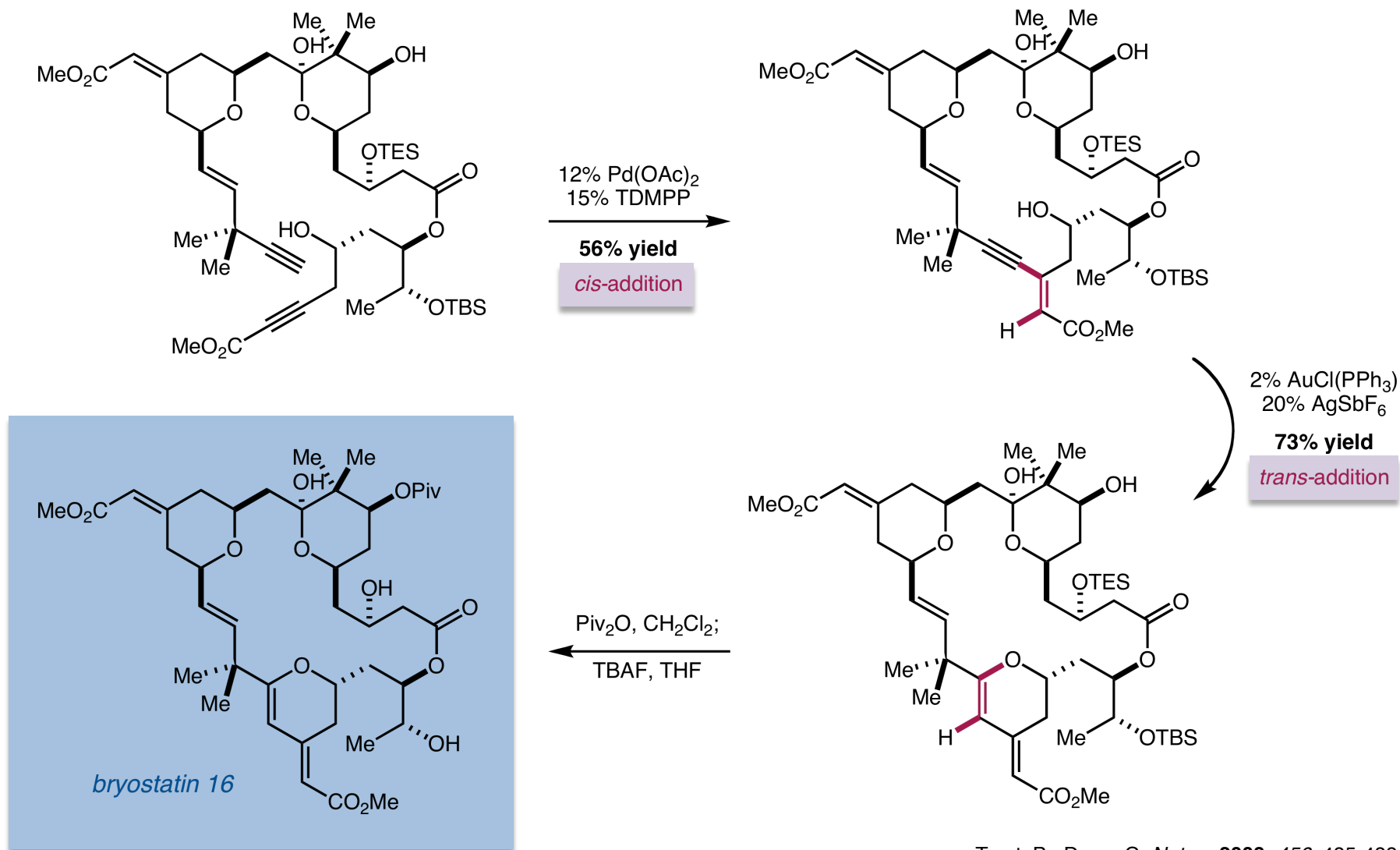
**Hydration:** Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729-3734  
Teles, J.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418

**Hydro-amination:** Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349-3352

**Hydro-fluorination:** Akana, J.; Bhattacharyya, K.; Muller, P.; Sadighi, J. *J. Am. Chem. Soc.* **2007**, *129*, 7736-7727

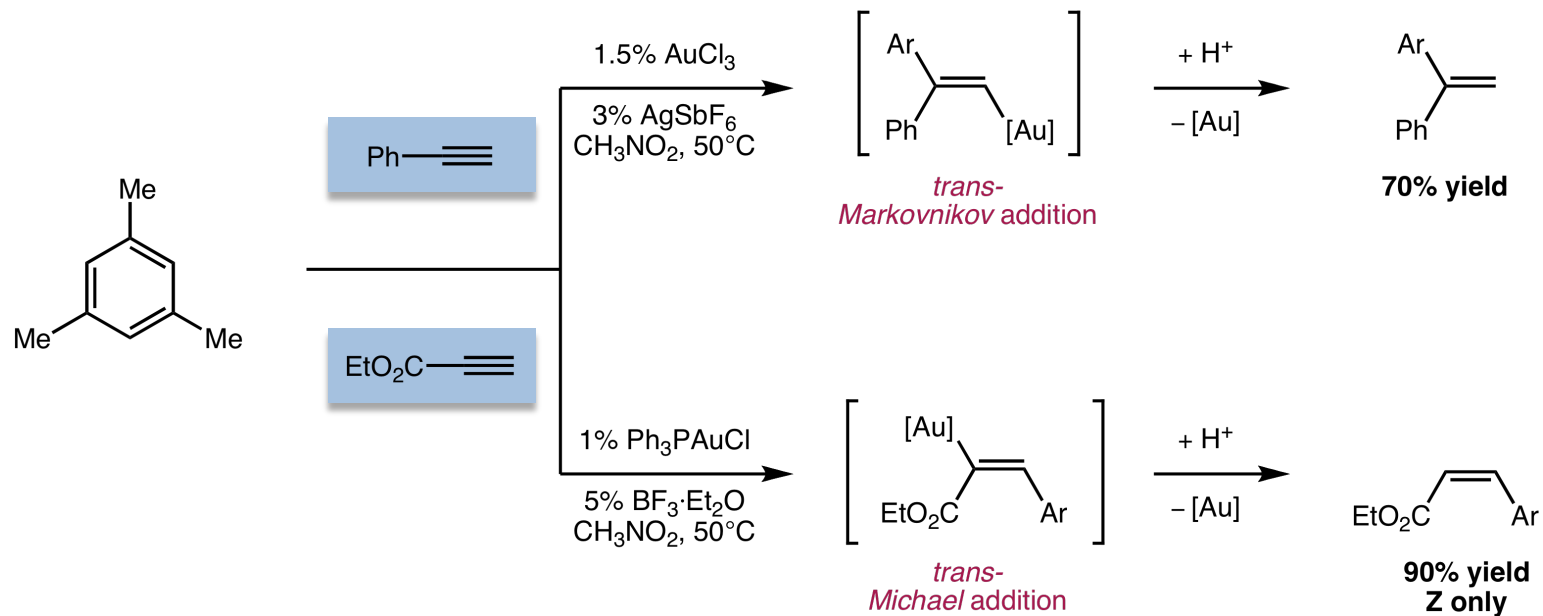
## Trost's Synthesis of Bryostatin

- Gold-catalyzed 6-endo-dig cyclization provides highly sensitive dihydrofuran C ring under mild conditions

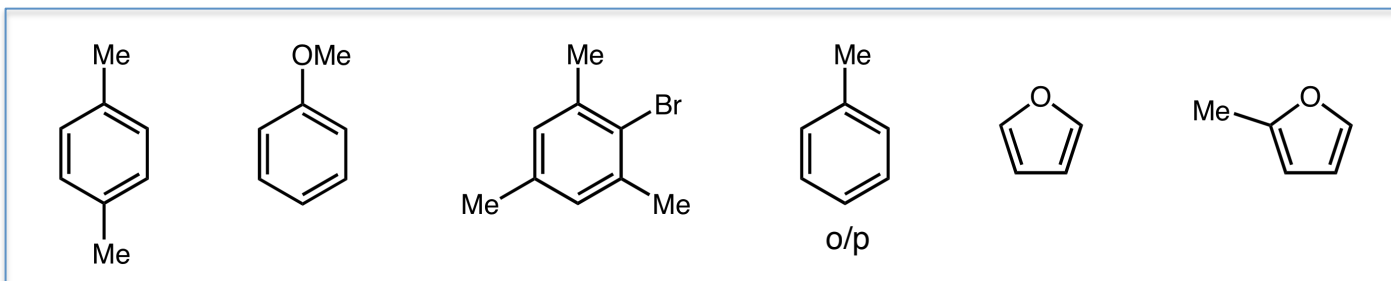


## Employing Carbon Nucleophiles: Hydroarylation

- Au(I) & Au(III)-catalysts provide complete regioselectivity in the hydroarylation of terminal alkynes



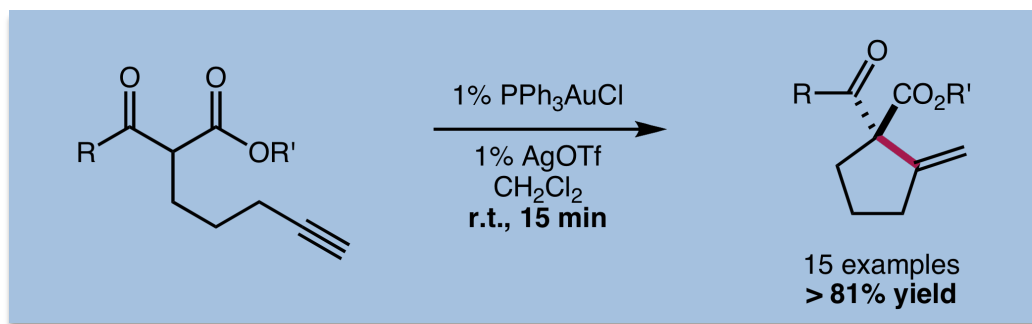
Ar =



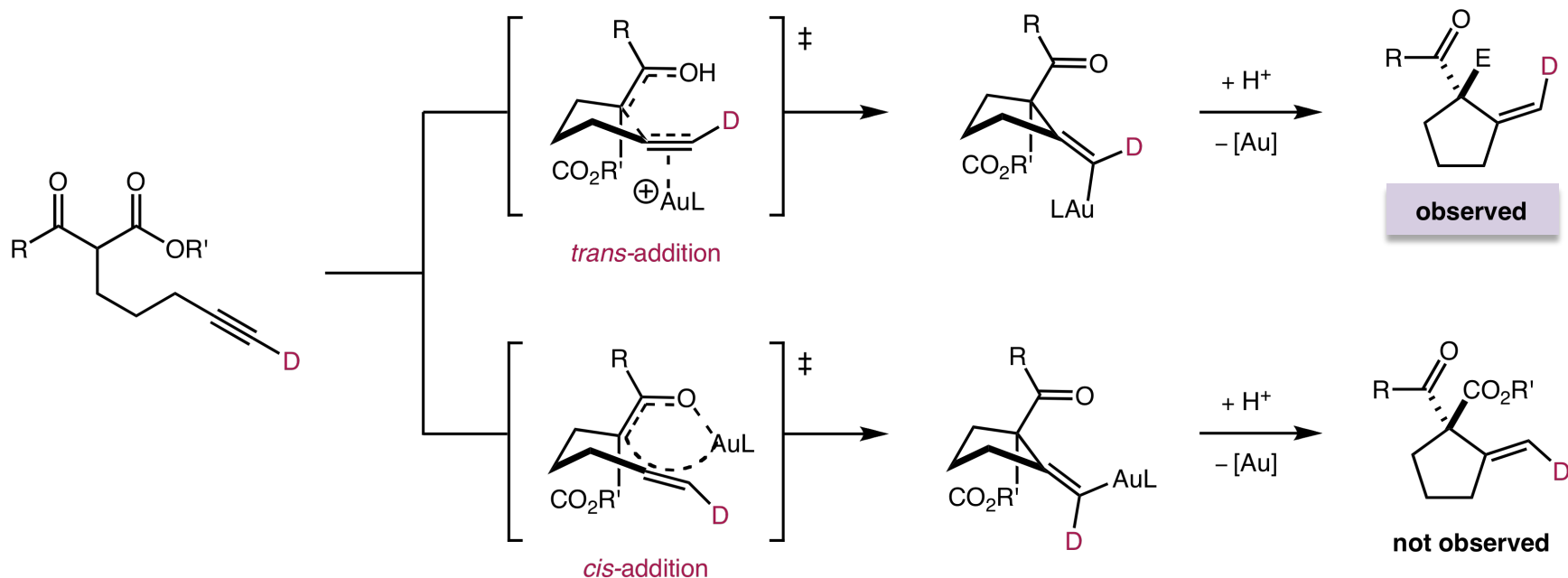


## Employing Carbon Nucleophiles: Enolate Alkylation

- A wide range of  $\beta$ -keto esters serve as efficient nucleophiles for the mild and fast hydroalkylation of *terminal* alkynes

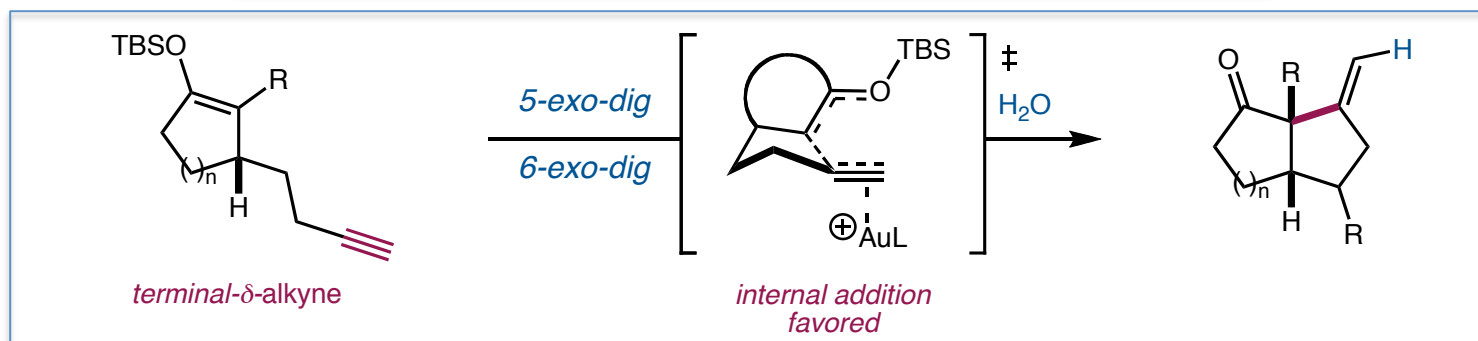
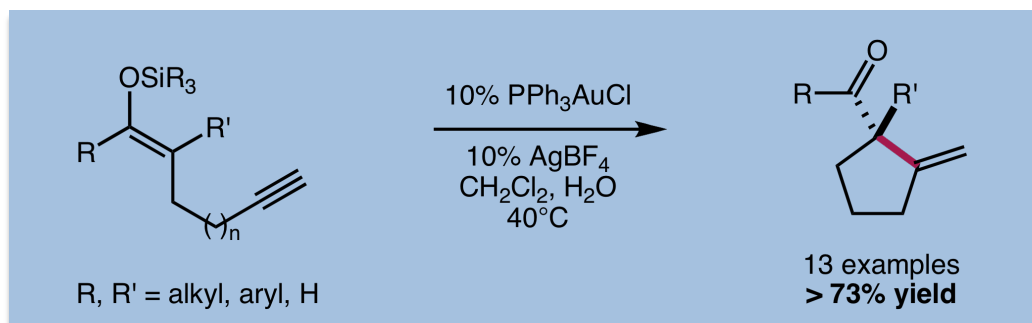


- Deuterium studies support *trans*-addition mechanism and explain limitation towards *internal* alkynes



## Cyclization of Silyl Enol Ethers

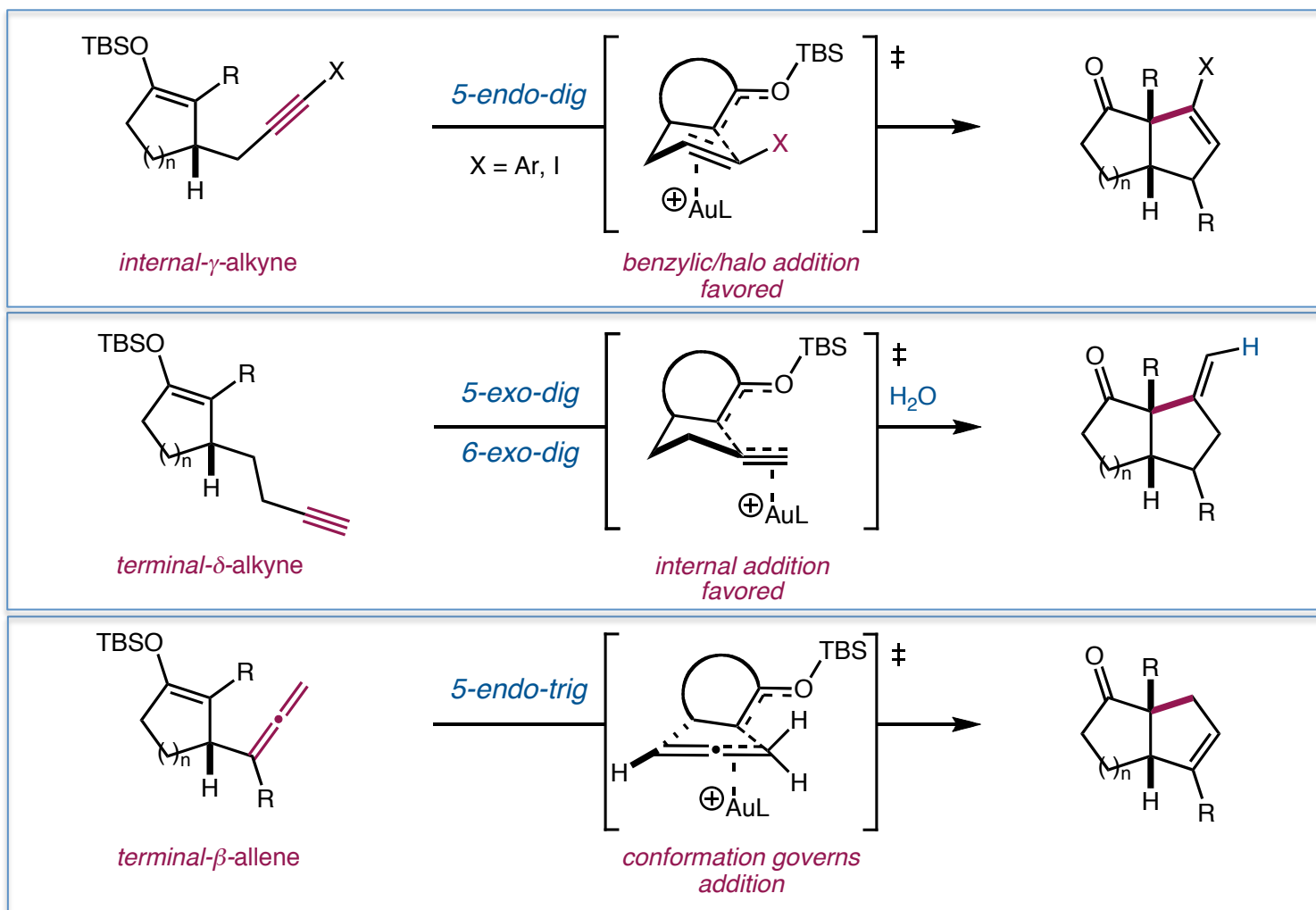
- Enol silanes are also suitable nucleophiles for quaternary (& now tertiary) carbon center construction



- Water serves as the external proton source for the final proto-deauration

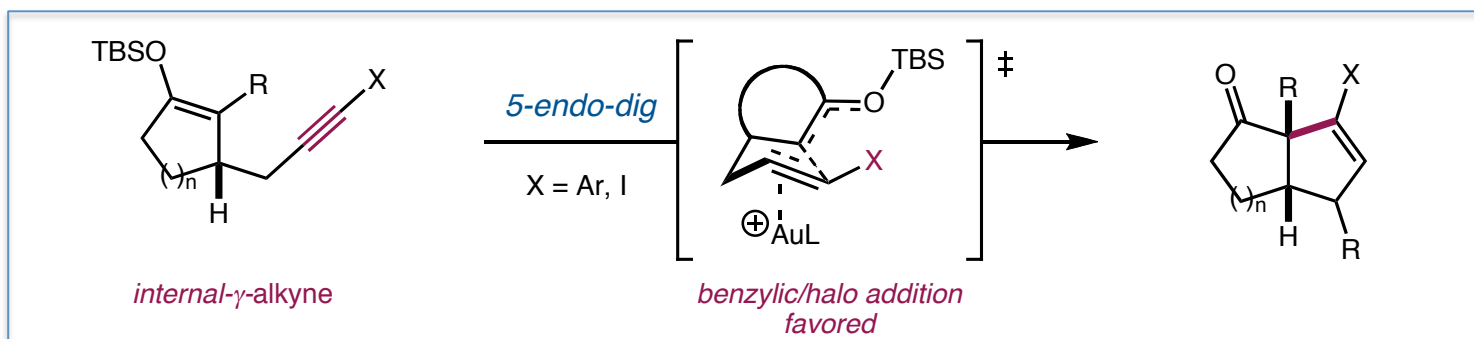
## Internal vs Terminal Alkynes

- Markovnikov addition provides access to variously substituted cyclopentenones depending on alkyne substitution

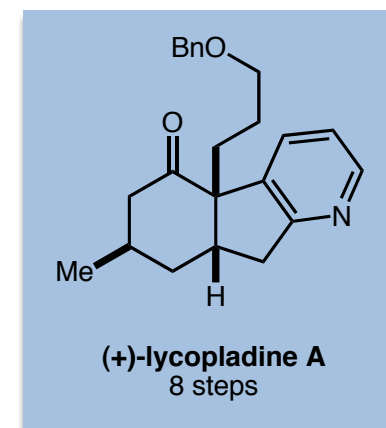
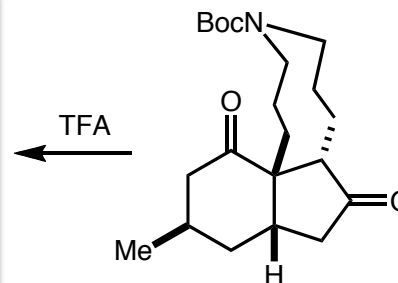
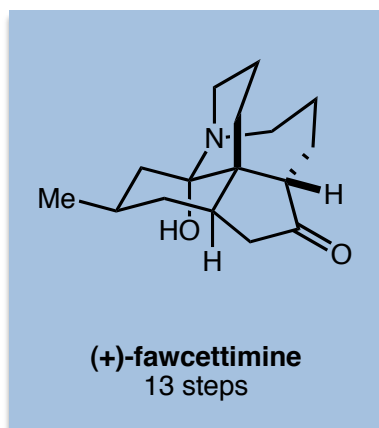
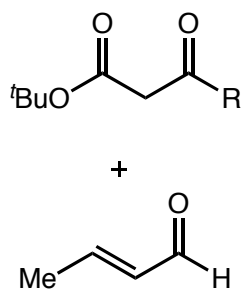


## Synthetic Applications of Cyclopentenes

- The non-ester bearing quaternary cyclopentenes allow rapid synthetic access to a variety of *Lycopodium* alkaloids.



1. Organocat.
2.  $\text{H}^+$
3.  $\beta$ -allene add'n
4. NIS



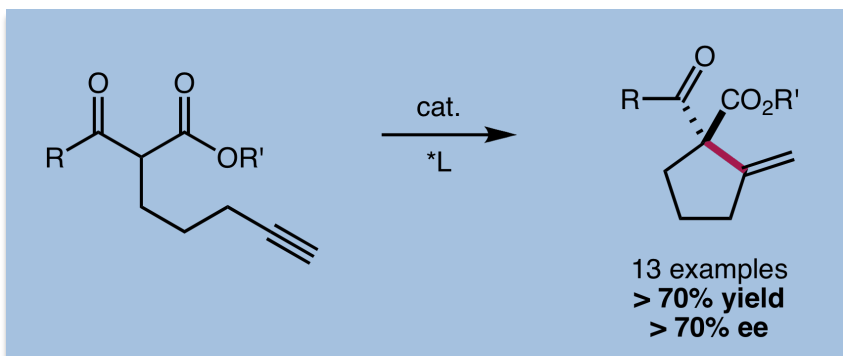
Staben, S.; Kennedy-Smith, J.; Huang, D.; Corkey, B.; LaLonde, R.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994

Linghu, X.; Kennedy-Smith, J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673

For comparison, structurally similar *Lycopodium* alkaloids synthesized in 22-24 steps: Laemmerhold, K.; Breit, B. *Angew. Chem. Int. Ed.* **2010**, ASAP

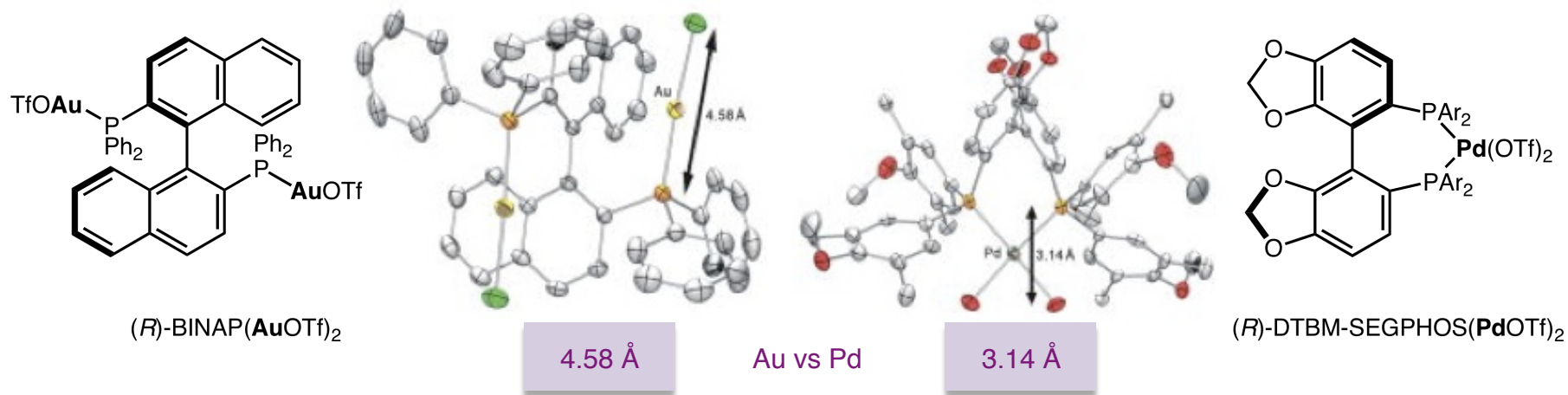
## Enantioselective Conia-Ene

- A chiral Pd-complex was preferred due to the linear geometry of the ligand and substrates across the Au-catalyst



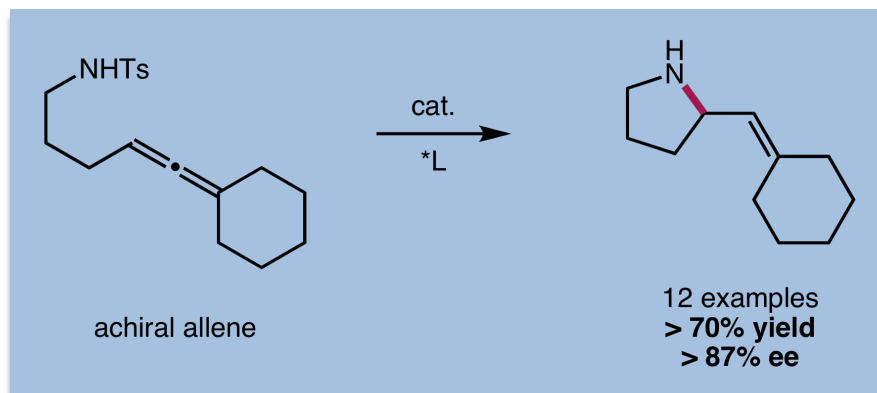
cat & *L	yield	ee
( <i>R</i> )-BINAP(AuOTf) <sub>2</sub>	85%	0%
( <i>R</i> )-BINAP(PdOTf) <sub>2</sub>	low	68%
( <i>R</i> )-DTBM-SEGPHOS(PdOTf) <sub>2</sub>	84%	89%

- X-ray structures demonstrate the distance between the ligand framework and the pro-chiral substrate



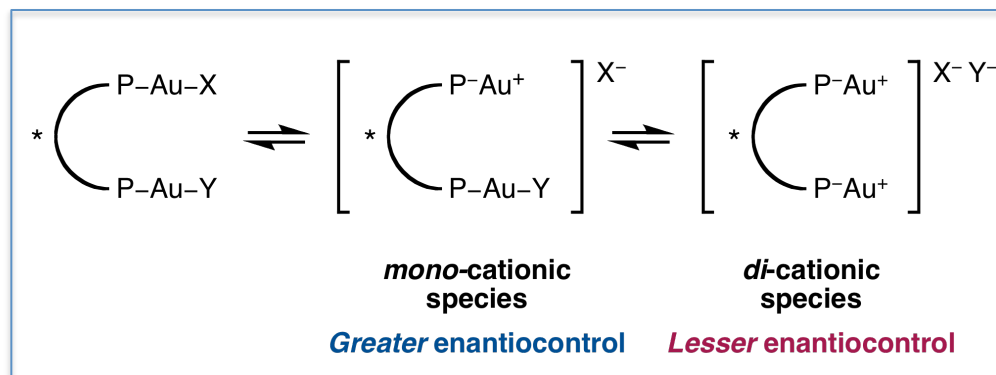
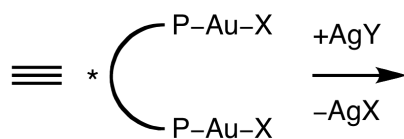
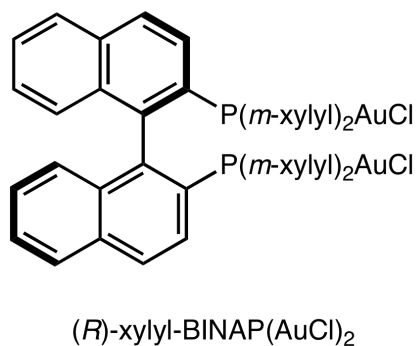
## Enantioselective Gold Catalysis

- Development of a Au(I)-catalyzed asymmetric hydroamination reaction



$*L(\text{AuX})_2 + \text{AgY}$	yield	ee
3% ( <i>R</i> )-xylyl-BINAP(AuCl) <sub>2</sub> + 6% AgBF <sub>4</sub>	82%	1%
3% ( <i>R</i> )-xylyl-BINAP(AuCl) <sub>2</sub> + 3% AgBF <sub>4</sub>	81%	51%
3% ( <i>R</i> )-xylyl-BINAP(AuCl) <sub>2</sub> + 6% AgOBz	27%	98%
3% ( <i>R</i> )-xylyl-BINAP(AuOPNB) <sub>2</sub>	88%	98%

- Coordinating counteranion provides increasing enantioselectivity due to the proposed model below

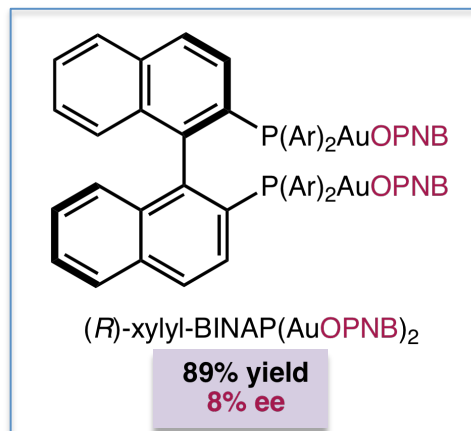
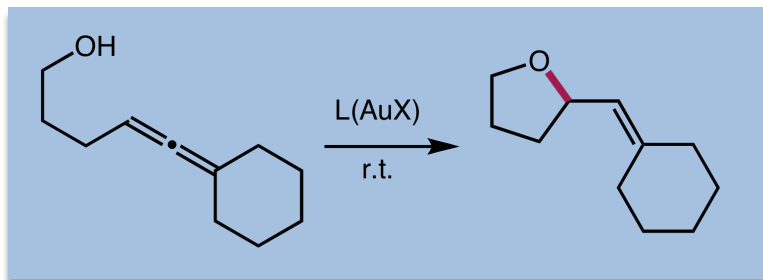


coordinating counteranion  $\rightleftharpoons$  non-coordinating counteranion

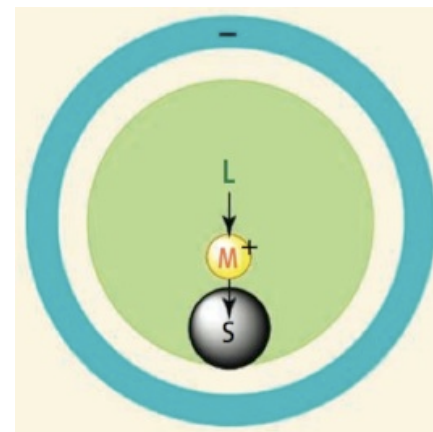
- All 3 species observed by <sup>31</sup>P NMR of 2:1 L(AuCl)<sub>2</sub>:AgBF<sub>4</sub>
- Coordinating counteranions shift equilibrium to left (higher ee)

## Chiral Counterion Catalysis

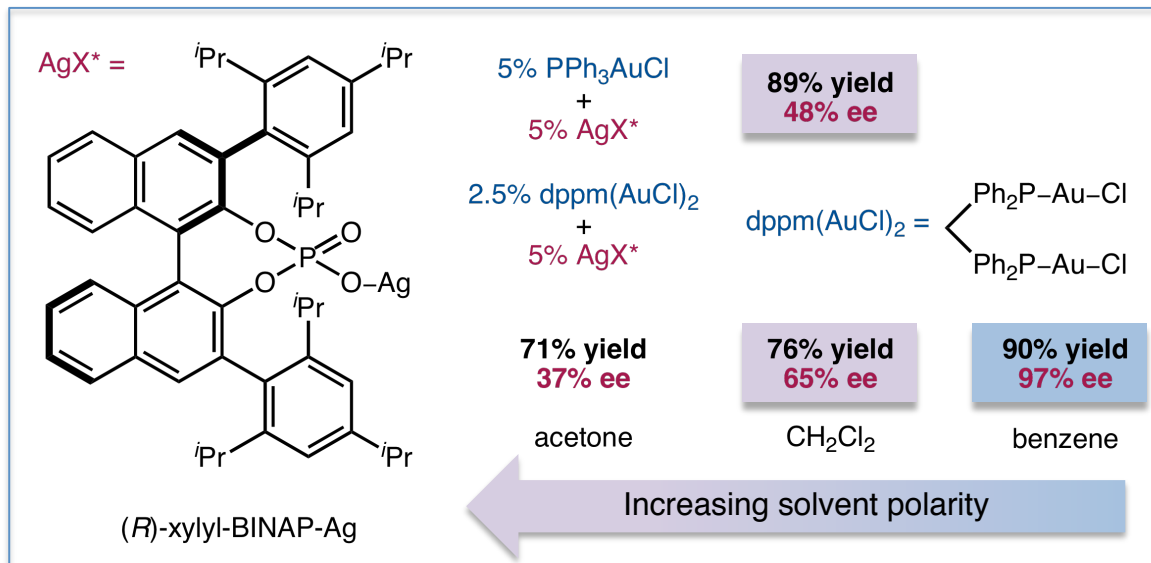
- Chiral induction still challenging due to the expense of the linear gold complex



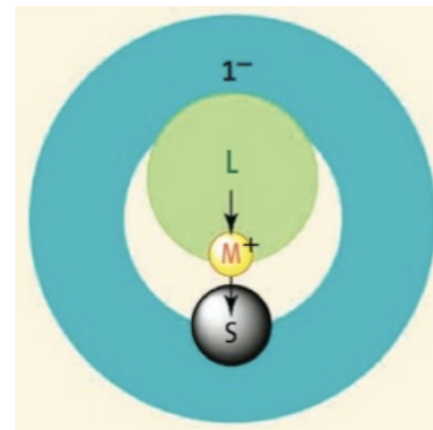
- Chiral ligand strategy



- An interesting alternative



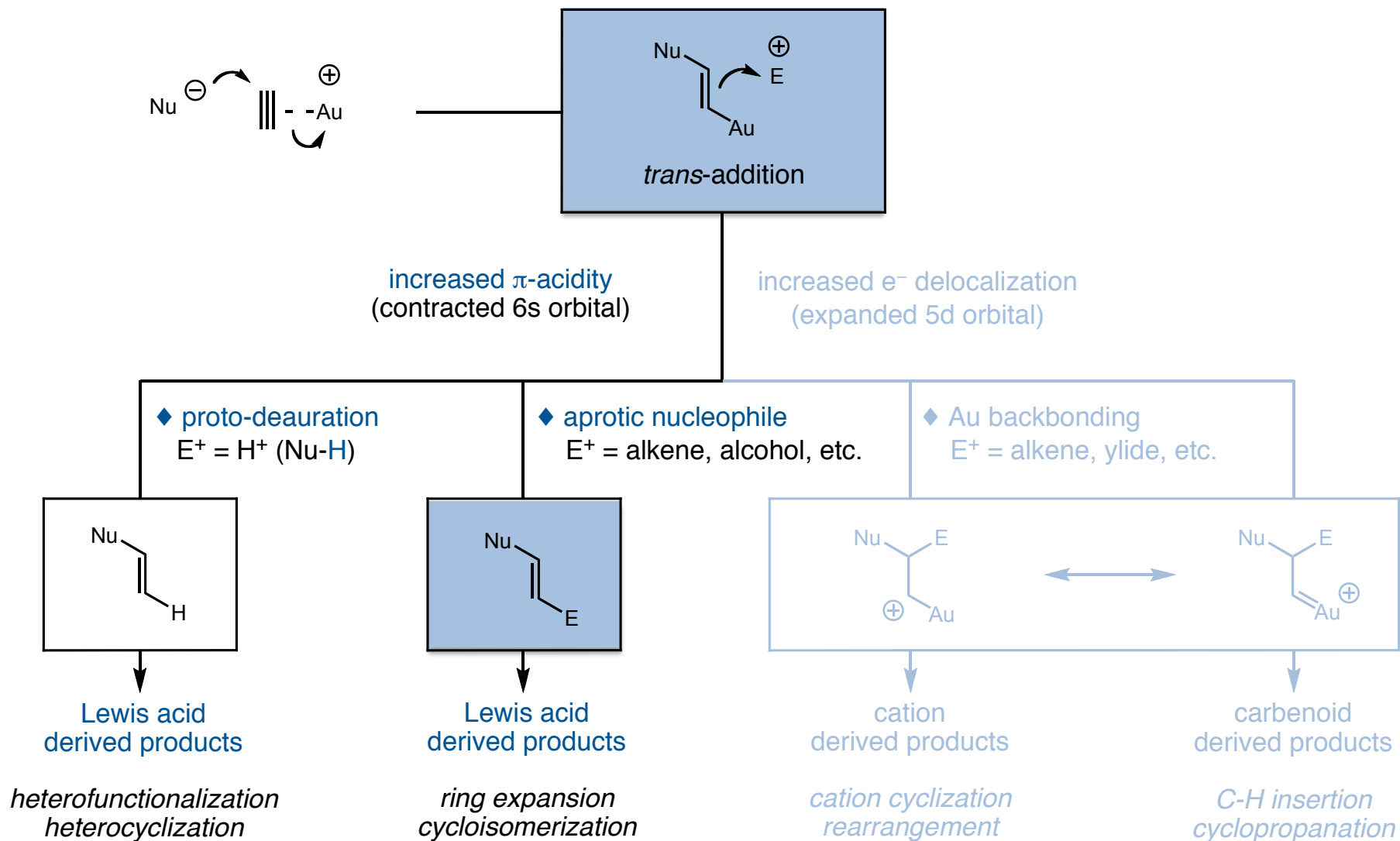
- Chiral counterion strategy



- Nucleophiles also include -NHSO<sub>2</sub>Ar & -CO<sub>2</sub>H

Hamilton, G.; Kang, E.; Mba, M.; Toste, F. D. *Science*. **2007**, *317*, 496-499  
 Perspective: Lacour, J.; Linder, D. *Science*. **2007**, *317*, 462-463

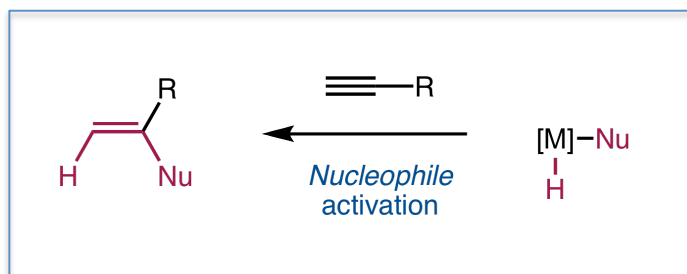
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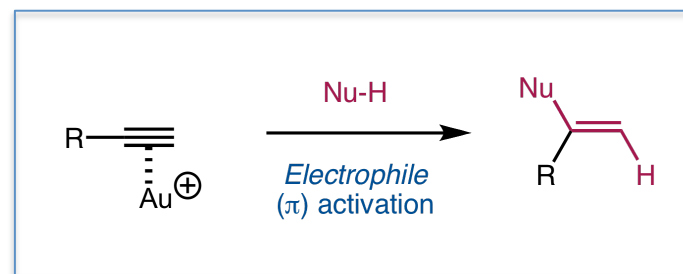


## Non-Canonical Reactivity

- Compared with *nucleophilic activation* provided by canonical metal catalysis, gold offers orthogonal *electrophilic activation*



vs

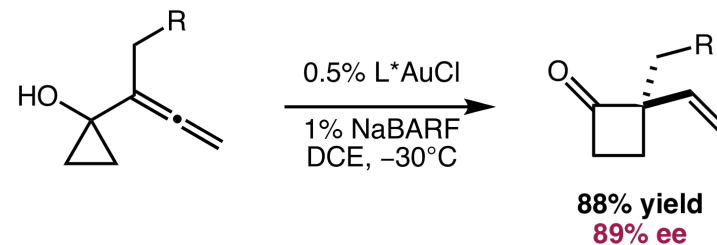
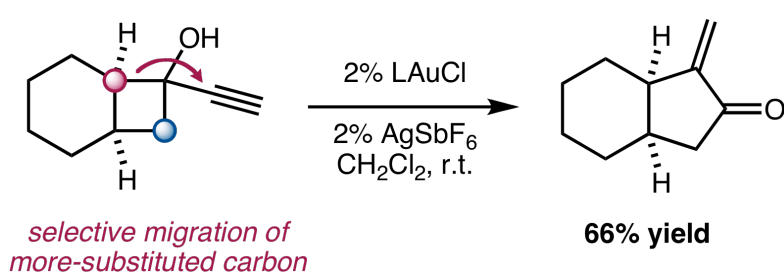
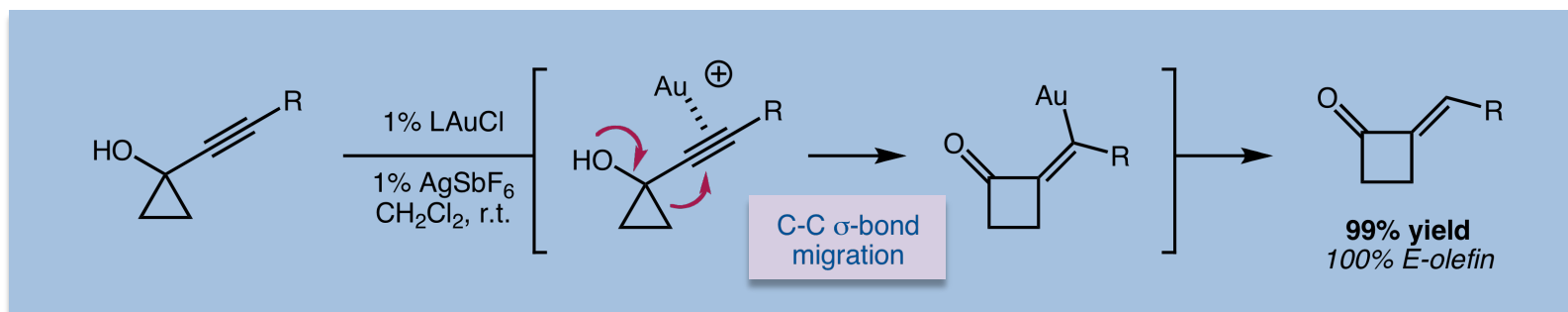


## Ring Expansions

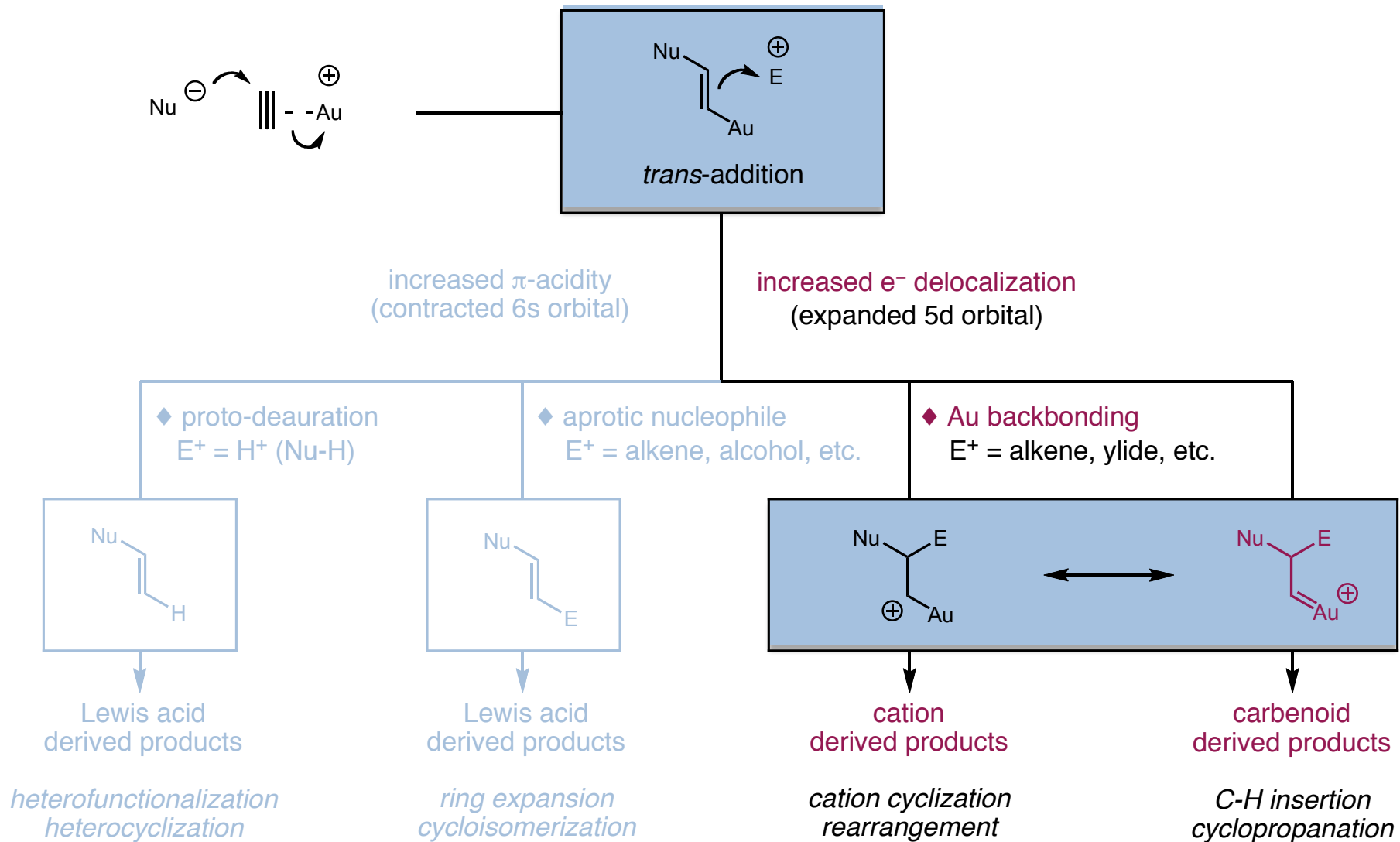
- Compared with *nucleophilic activation* provided by canonical metal catalysis, gold offers orthogonal *electrophilic activation*



- Non-canonical nucleophiles that lack metal-coordination sites (i.e. C-C  $\sigma$ -bond) are suitable partners in Au-catalysis

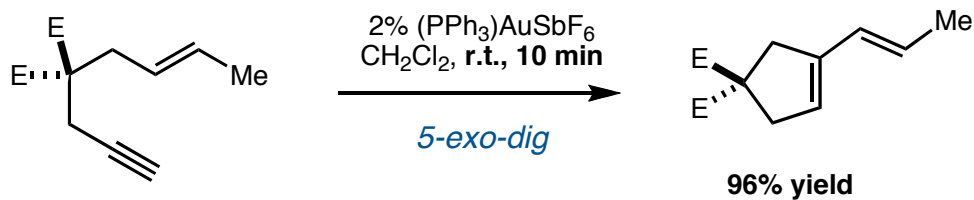


# Modes of Reactivity in Homogeneous Gold Catalysis

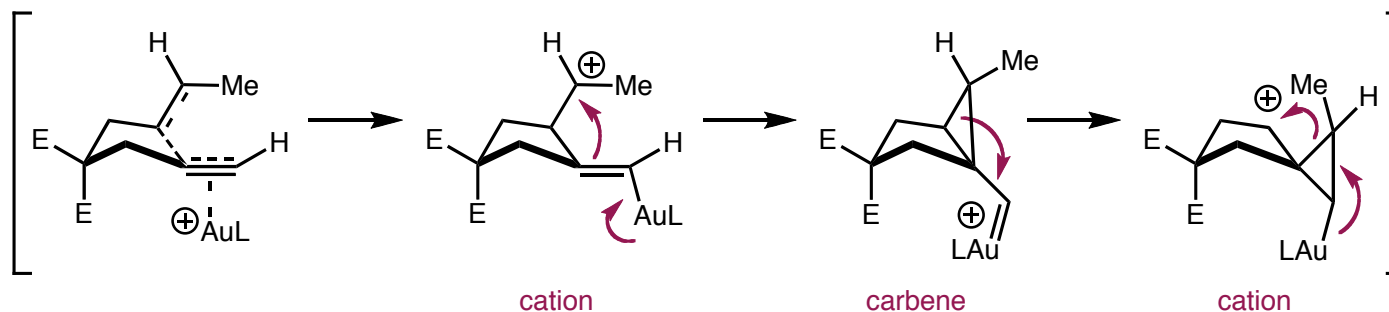


## Enyne Cycloisomerizations

- Simple olefins can also serve as nucleophiles when tethered to a  $\pi$ -activated alkyne (1,6-Enynes)



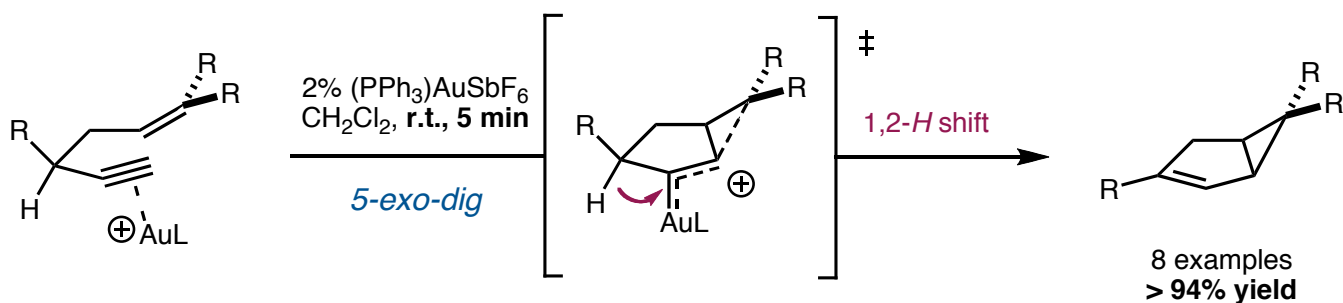
- A series of skeletal rearrangements involving carbenoid and cationic intermediates may be invoked for this transformation



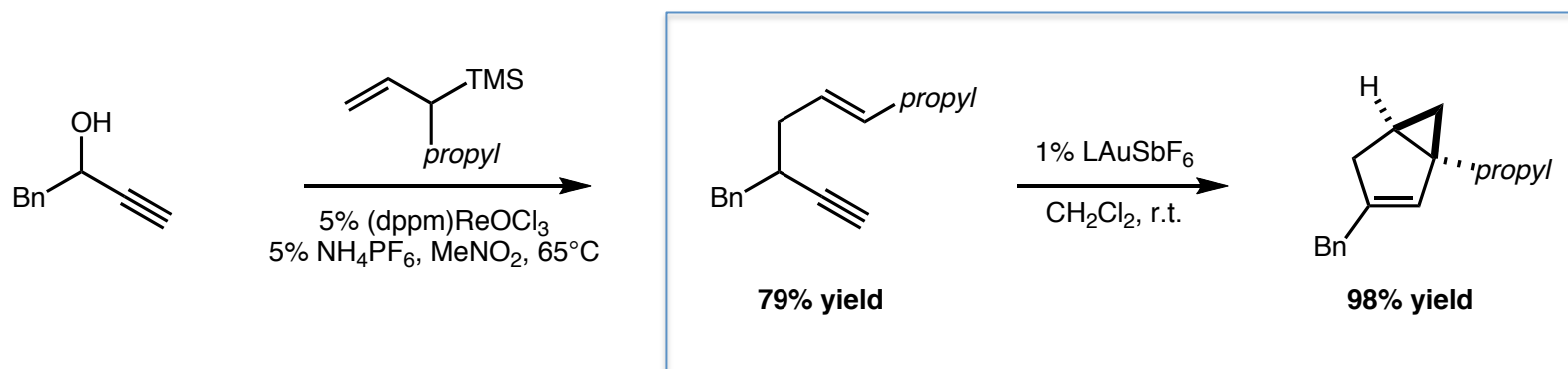
- Product selectivity is highly dependant on the substitution of the  $\alpha,\omega$ -enyne starting materials

## Enyne Cycloisomerizations Revisited

- Simple olefins can also serve as nucleophiles when tethered to a  $\pi$ -activated alkyne (1,5-Enynes)



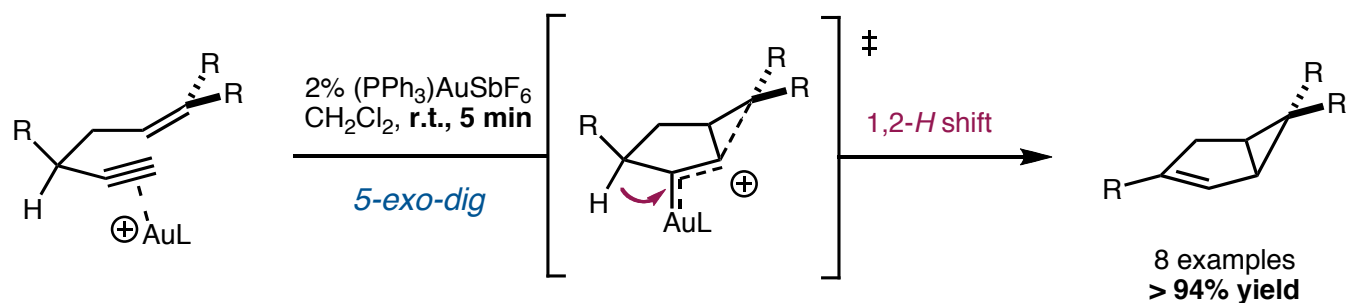
- 1,5-Enynes (from propargyl alcohols) reliably provide synthetic access to the cis-fused 3,5-ring systems



- Free alcohols can replace the benzyl substituent and provide access to propane-fused cyclopentenone

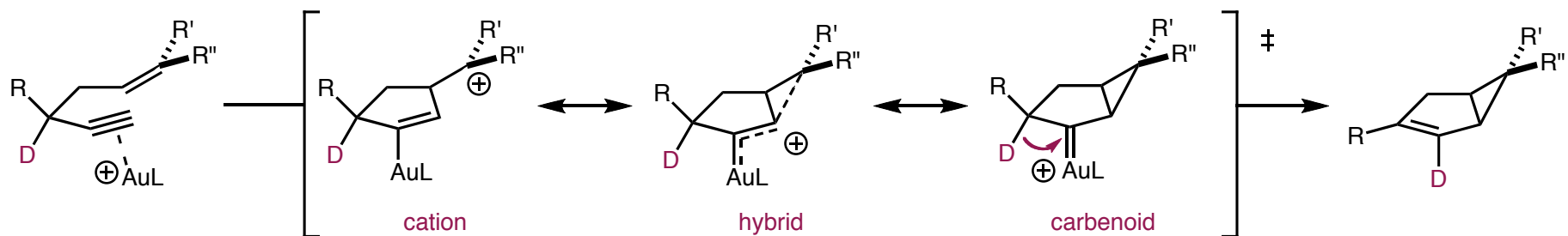
## Enyne Cycloisomerizations Revisited

- Simple olefins can also serve as nucleophiles when tethered to a  $\pi$ -activated alkyne (1,5-Enynes)



- Further mechanistic considerations

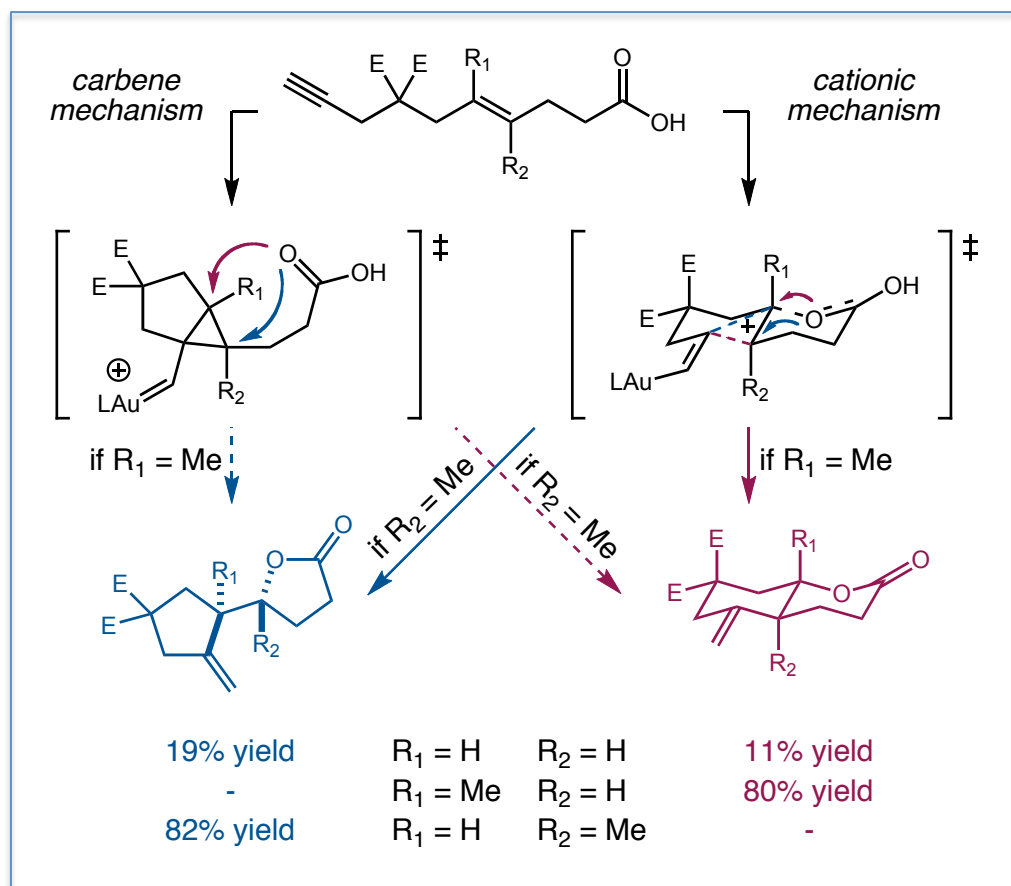
- Propargyl deuterium label is selectively incorporated in the vinyl position of the product
- 1,2-Disubstituted olefins underwent cycloisomerization stereospecifically



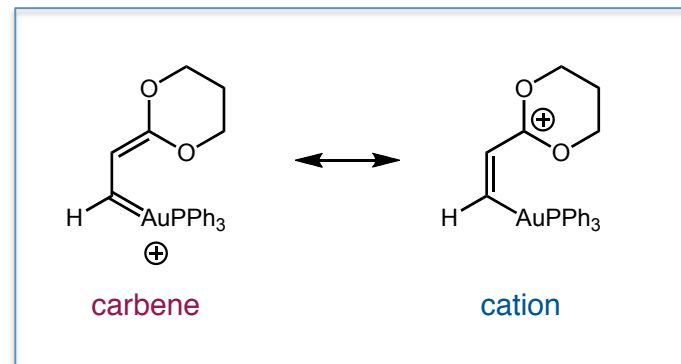
- Gold-carbenoid character is strongly suggested by these mechanistic observations ...

## Carbene Controversy

- Fürstner strongly argues that these gold-catalyzed processes exhibit more non-classical carbocationic features



- Fürstner isolated and characterized a stable alkyl-gold complex that could exist as a carbene

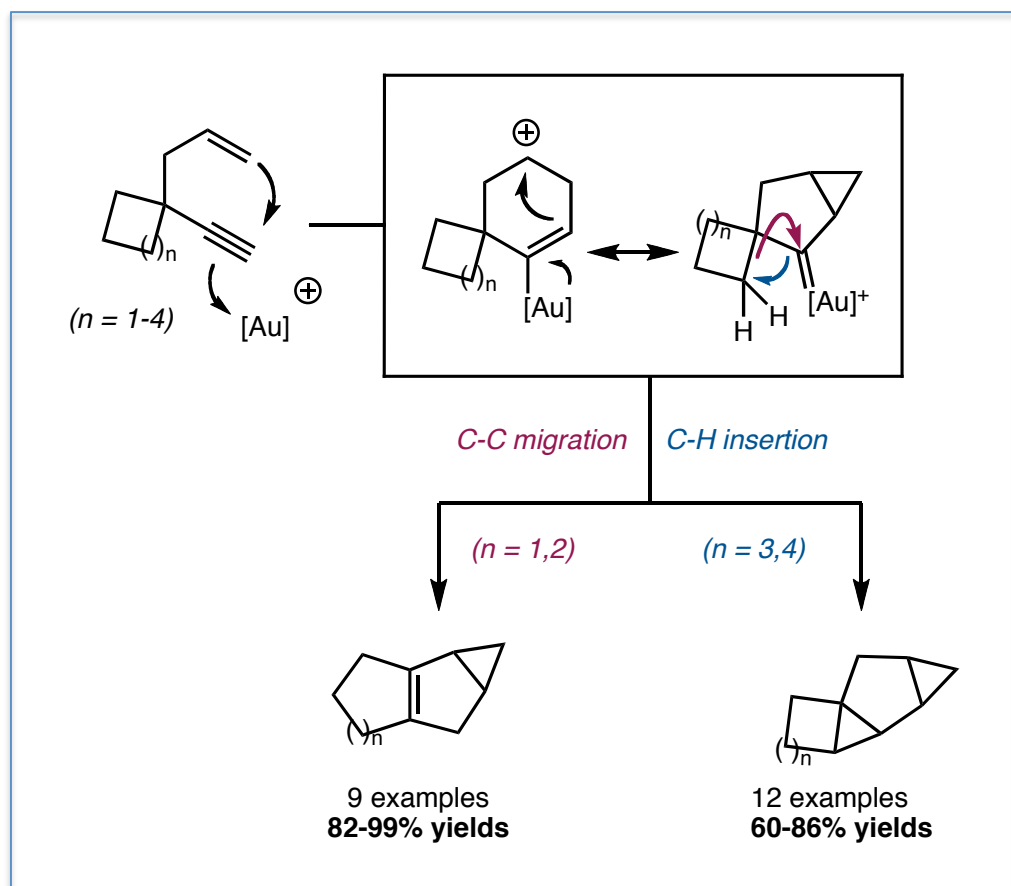


- NMR studies strongly suggest that the *cation* mesomer better represents the complex

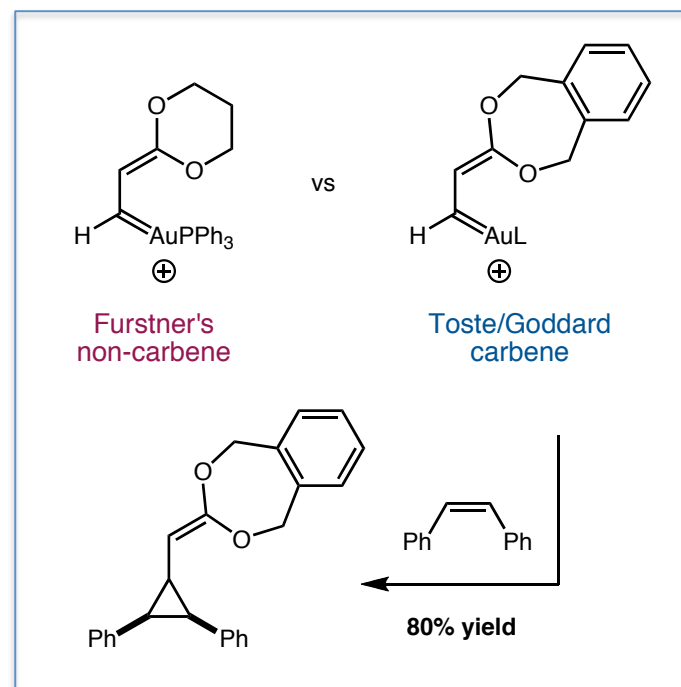
- Employing a carboxylate trap as a mechanistic probe, Fürstner demonstrated the 1,6-enynes arise from cationic mechanism

## Carbenes Defended

- Toste held that many of their methodologies strongly resembled reactivity associated with carbenic systems



- Toste & Goddard refute Fürstner's NMR experiments with bond rotation calculations and measurements of their own

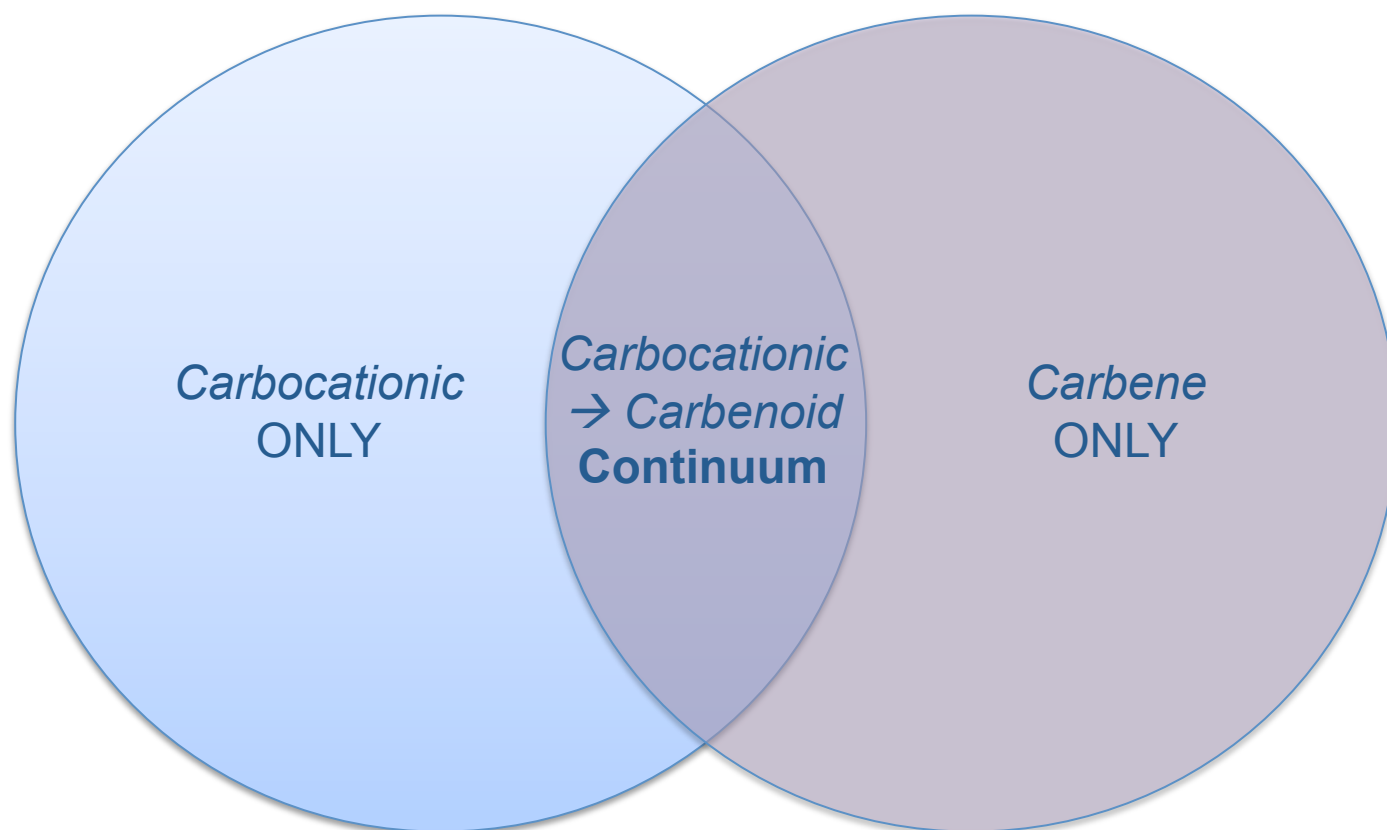


- Toste & Goddard's bonding model for gold(I) carbene complex involves both  $\sigma$ - and  $\pi$ -bonding, with a bond order  $\leq 1$



## *Carbene Controversy Concluded*

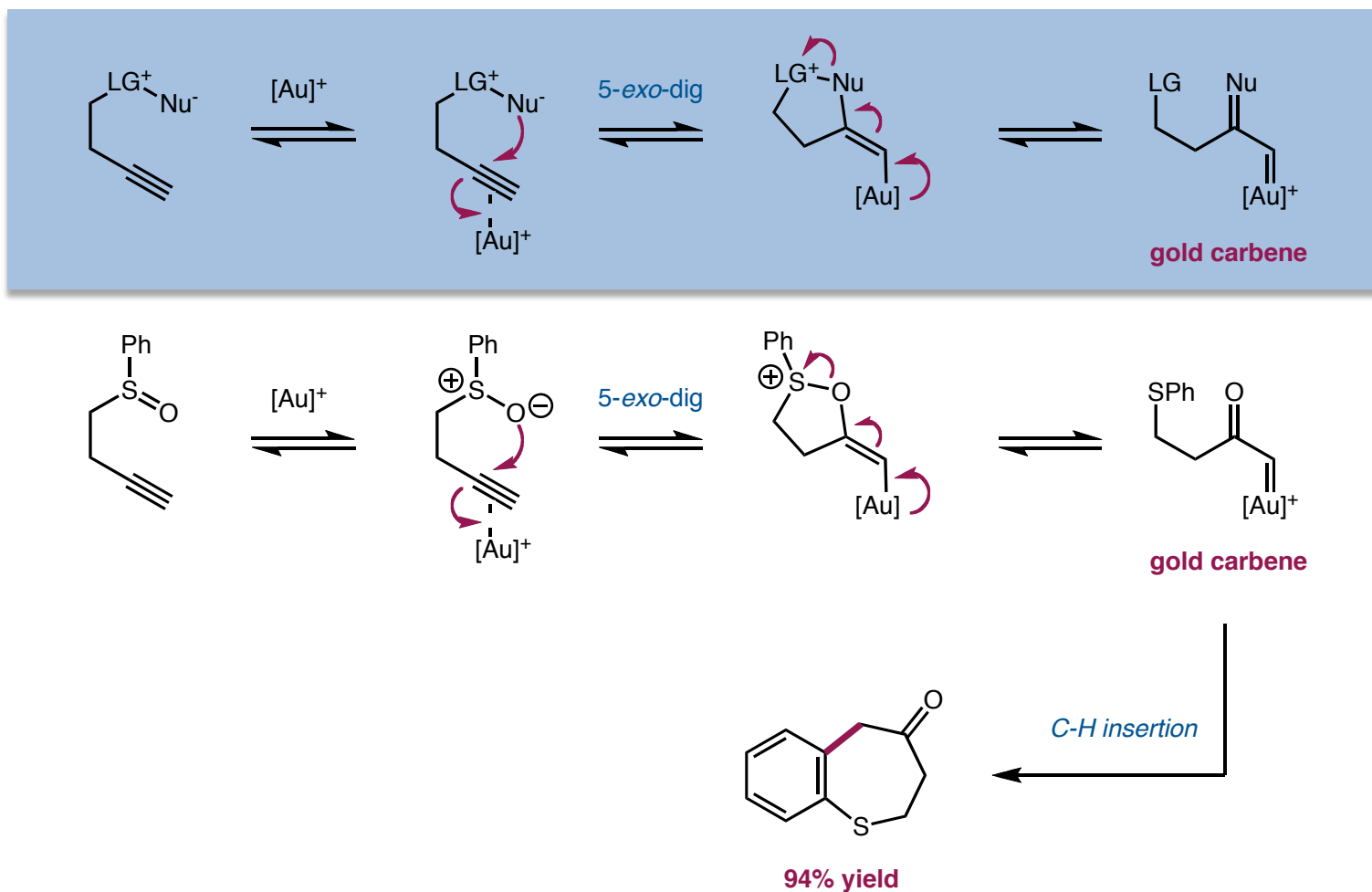
- An entire literature meeting could be devoted to this subject ...



- Ongoing debate on the *cationic* and *carbene* character of gold catalysis suggests a *continuum* of tunable reactivity
- The *carbocation-carbenoid* continuum best offers a helpful mnemonic to explain *and predict many* facets of gold catalysis

## Methods of Generating Gold Carbenes

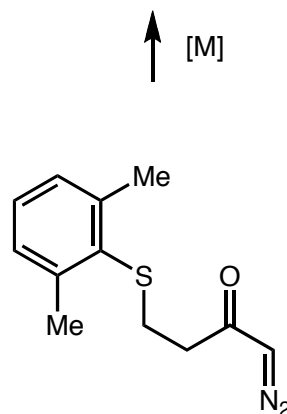
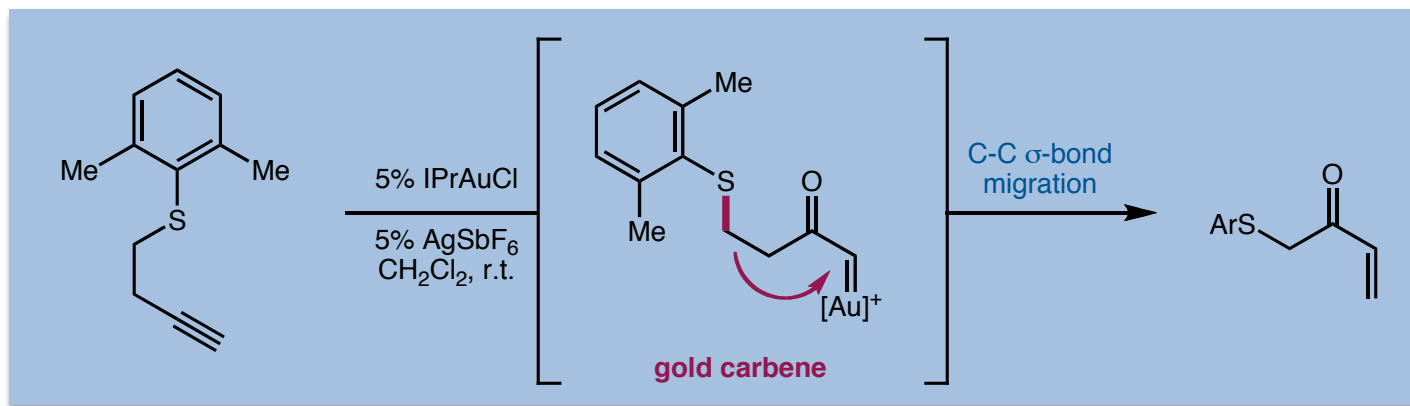
- *Gold carbenes* from alkynyl sulfoxides offer an orthogonal approach to reactivity previously associated with diazocarbonyls



- Azides are analogous carbene precursors

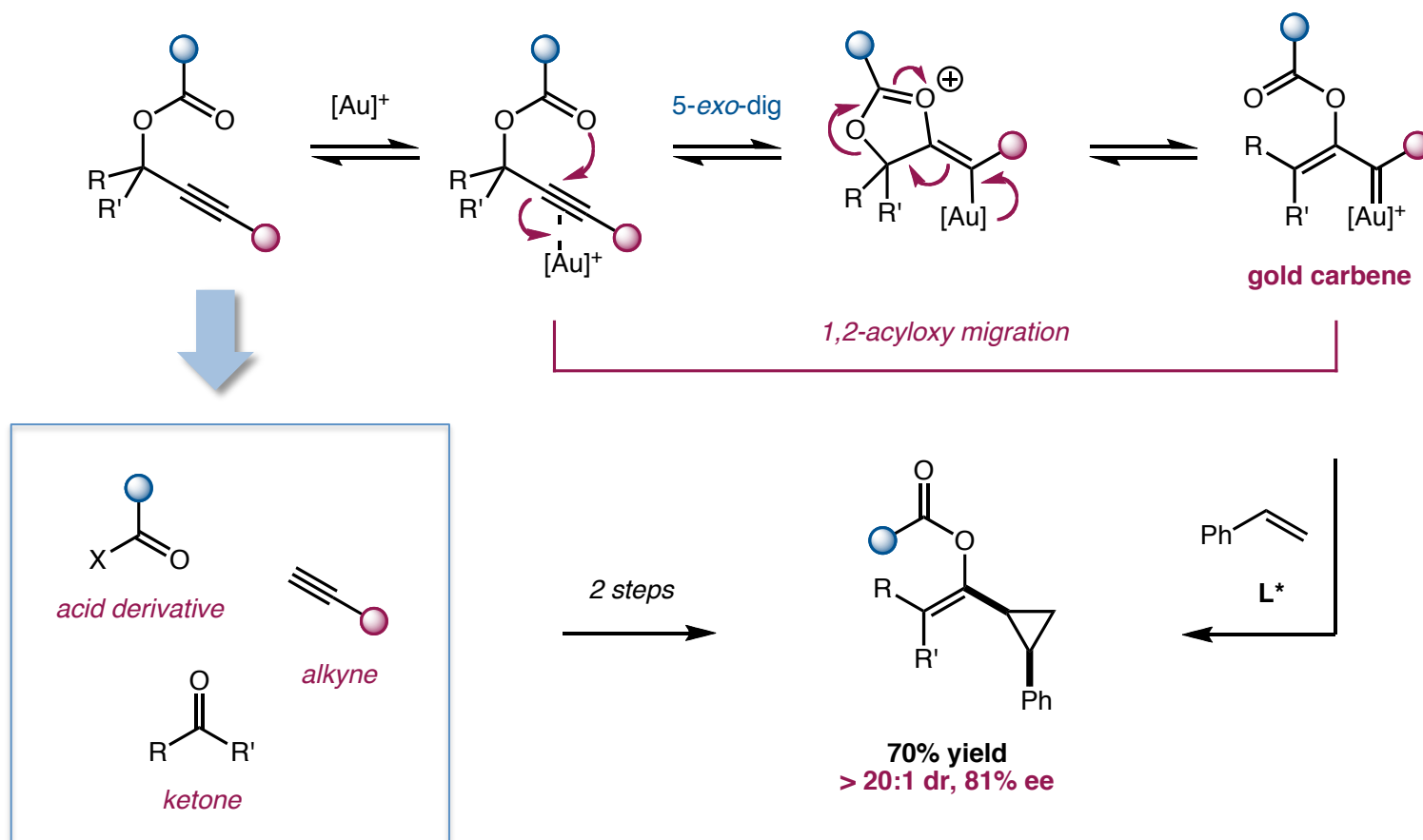
## Methods of Generating Gold Carbenes

- *Gold carbenes* from alkynyl sulfoxides offer an orthogonal approach to reactivity previously associated with diazocarbonyls



## Another Method of Generating Gold Carbenes

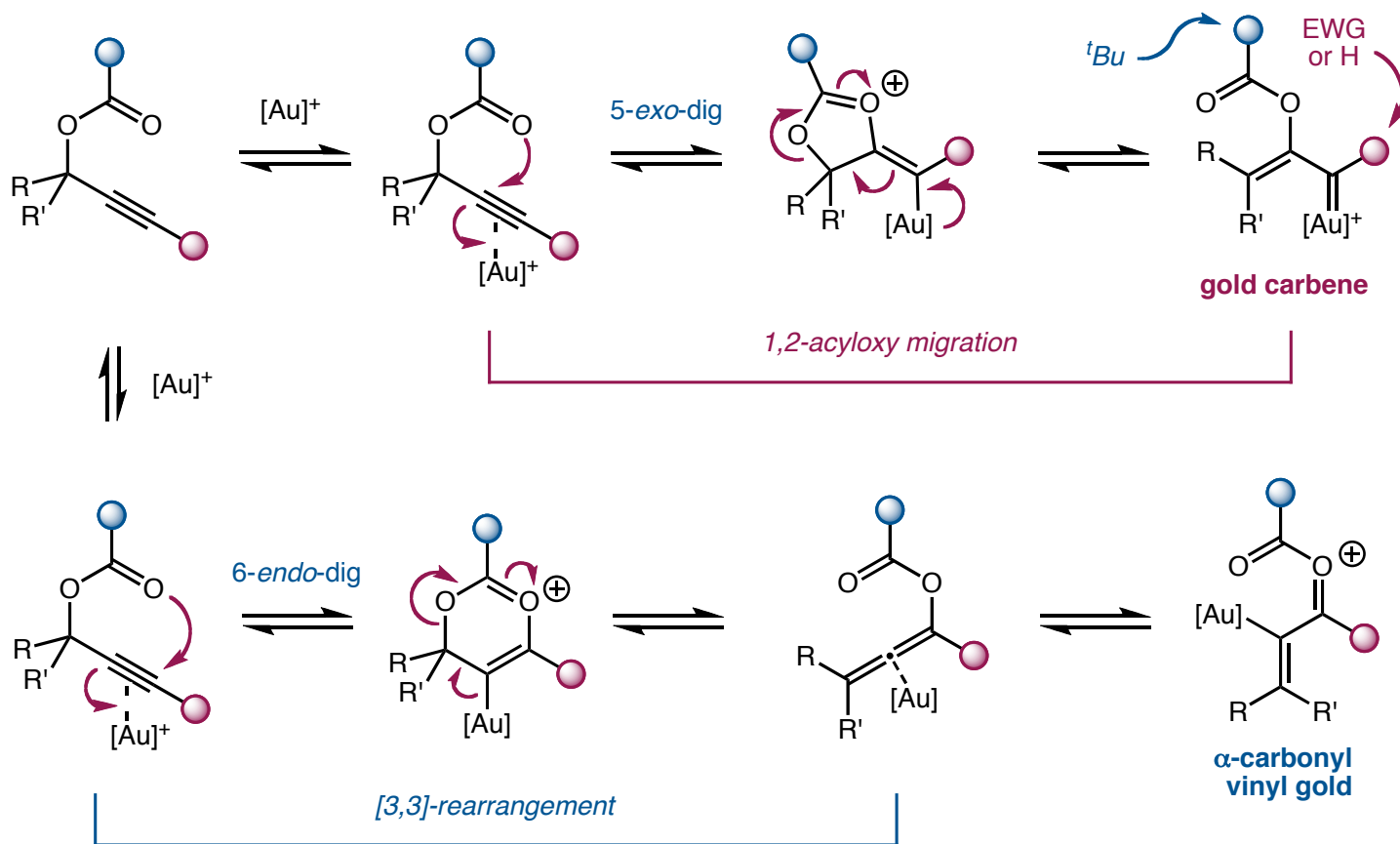
- Propargyl carboxylates allow synthetically facile access to *gold carbenes* via a 1,2-acyloxy migration



- Modular synthesis of propargyl carboxylates coupled with *gold carbene* pathways allow for rapid complexity generation

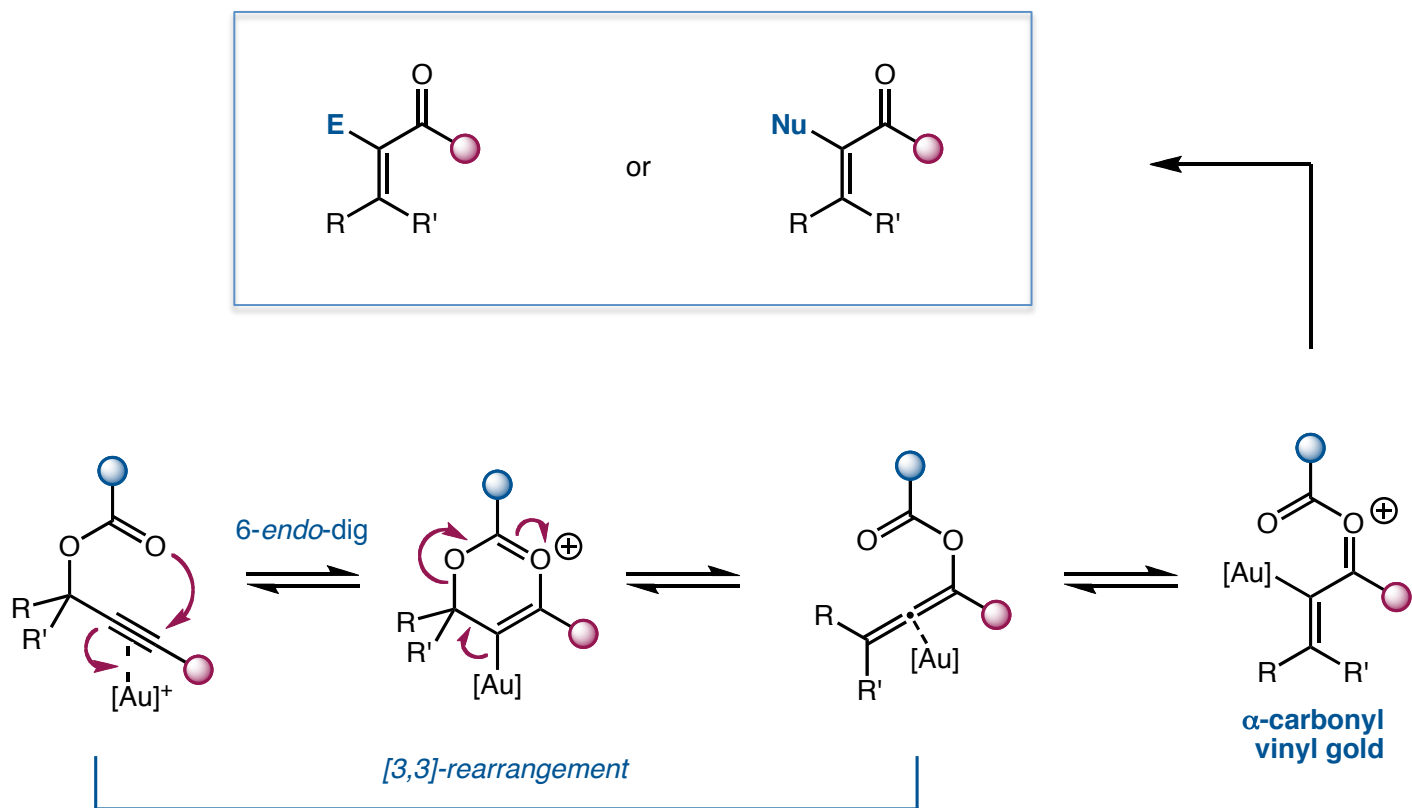
## Propargyl Carboxylate Reactivity

- Substitution patterns dictate formation of *vinyl gold* versus *gold carbene* species



## Vinyl Gold Intermediate

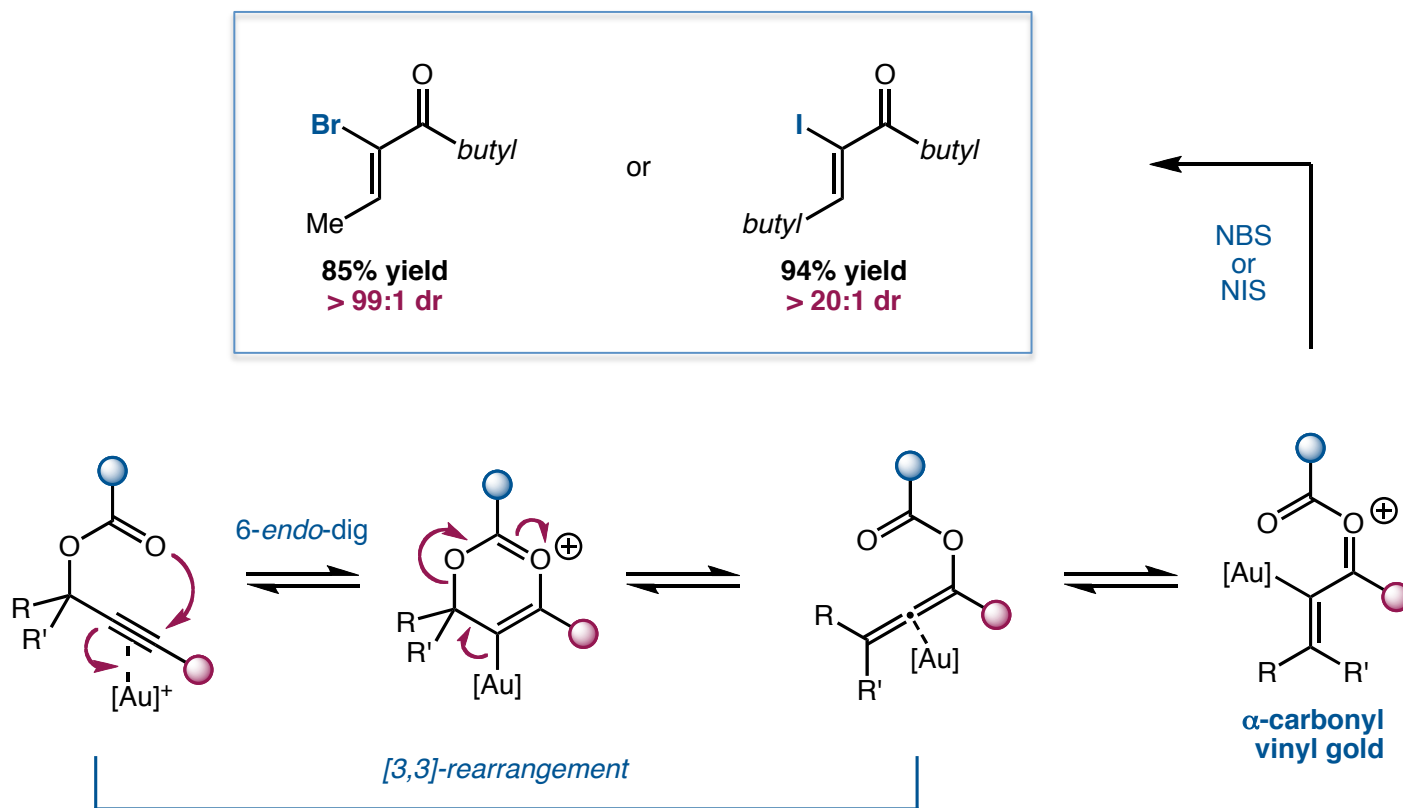
- Substitution patterns dictate formation of *vinyl gold* versus *gold carbene* species



- Vinyl gold* species can also be exploited in a variety of rapid complexity generating transformations

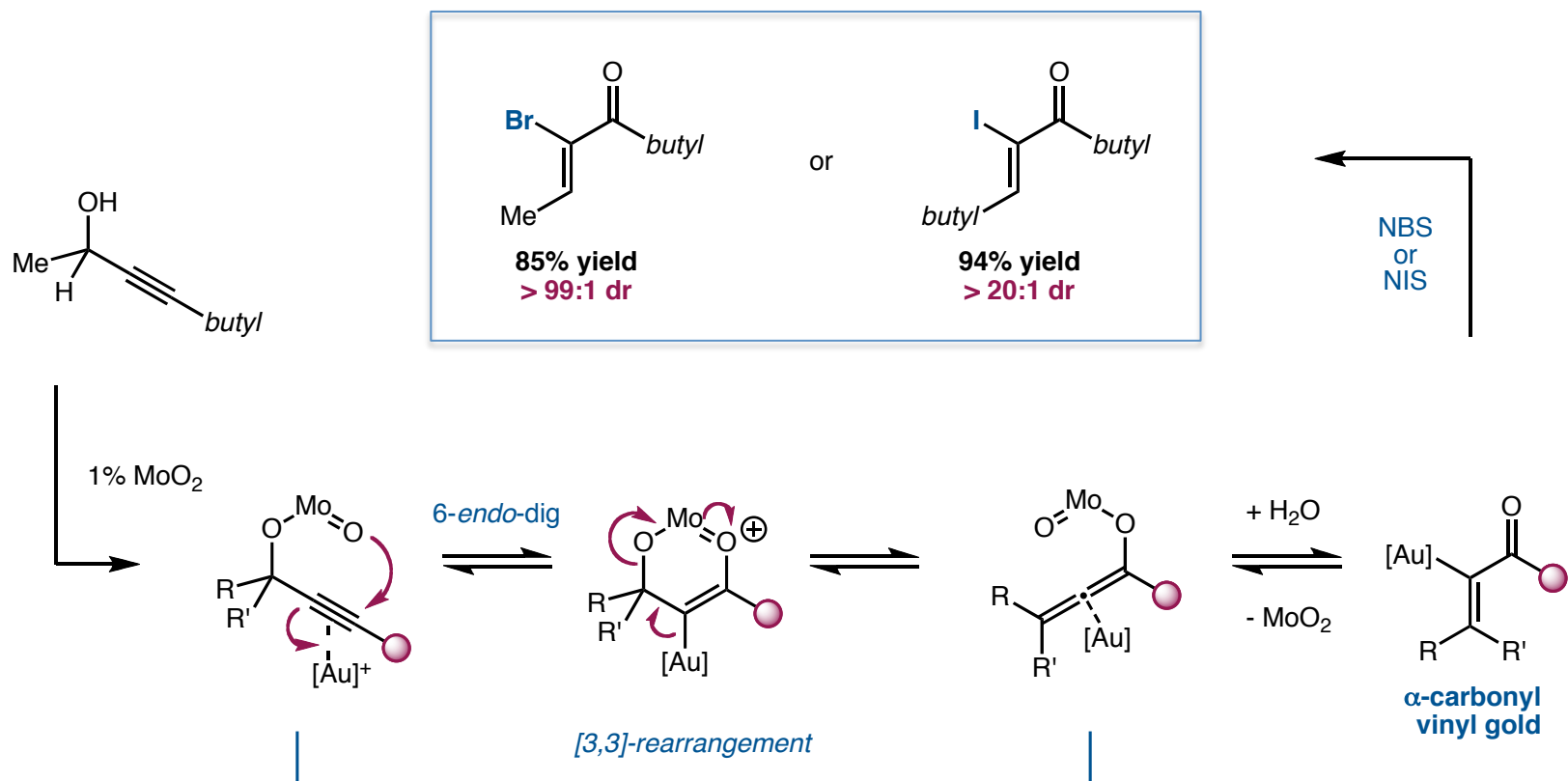
## Electrophilic Trapping of Vinyl Gold

- Electrophilic trapping by N-halo-succinimides affords  $\alpha$ -halo -enones and -enals from propargyl acetates



## Electrophilic Trapping of Vinyl Gold

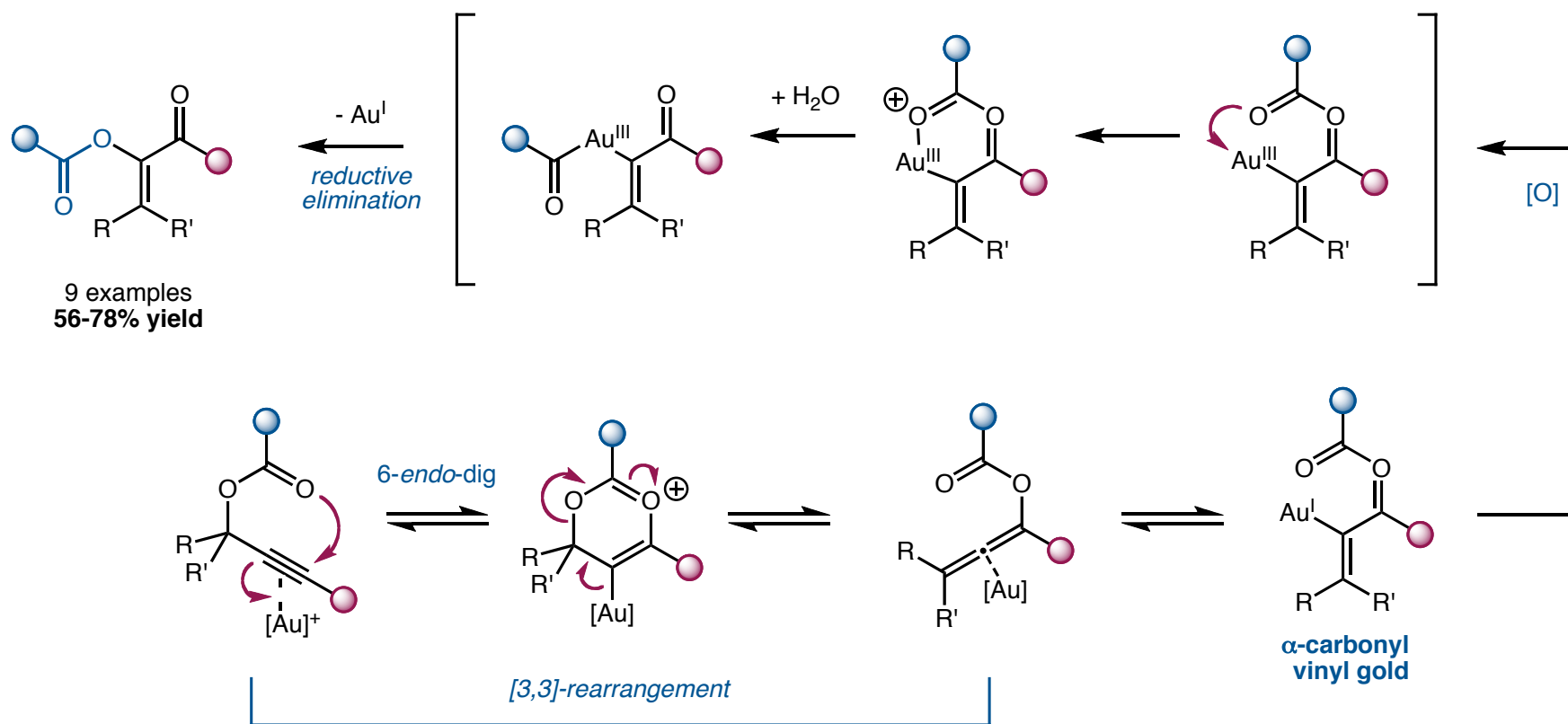
- Catalytic molybdenum oxide allows for the use of propargyl alcohols in addition to propargyl carboxylates





## Nucleophilic Trapping of Vinyl Gold

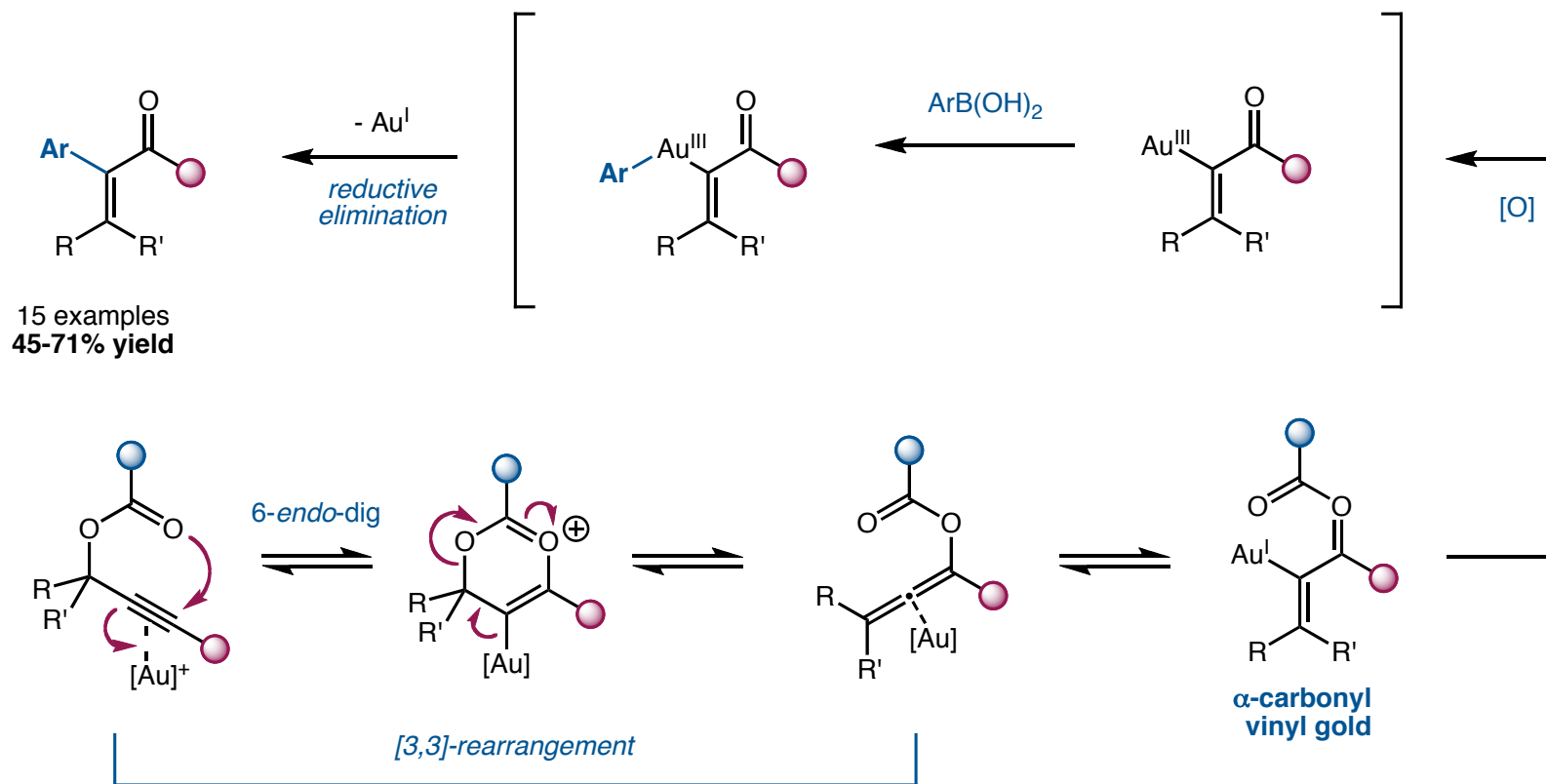
- Oxidation of the *vinyl gold* intermediate allows access to Au(III) oxidation state and corresponding nucleophilic trapping



- A variety of intermolecular nucleophilic functionalizations can be envisioned to access  $\alpha$ -substituted enones and enals

## Gold Cross-Coupling

- Addition of boronic acids under semi-aqueous conditions readily provides  $\alpha$ -aryl enones and enals

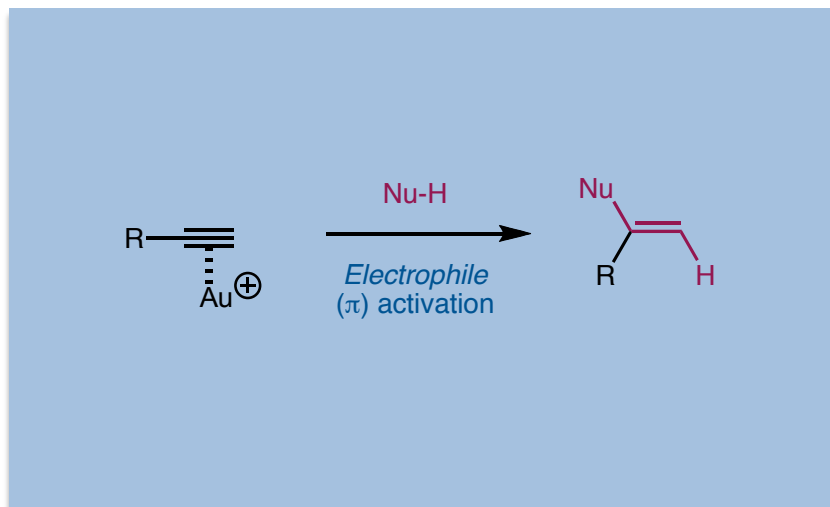


Zhang, G.; Peng, Y. Cui, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2009**, *121*, 3158-3161

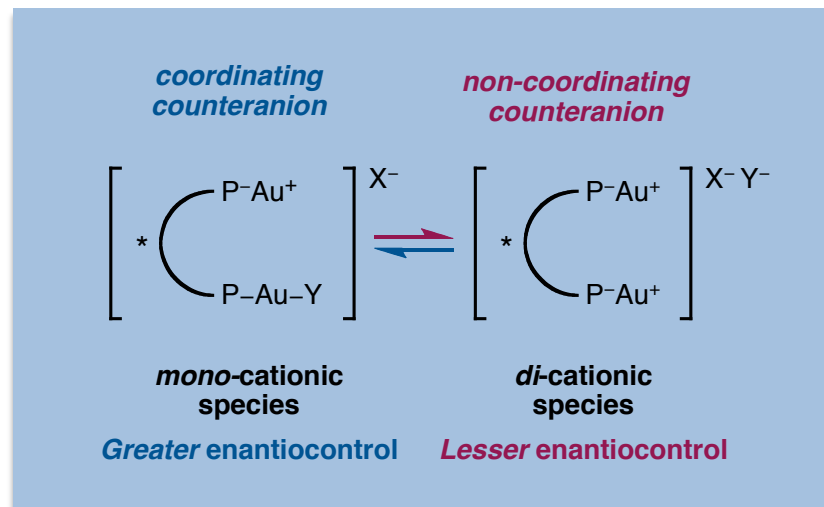
**Related transformation for homo-allylic alcohols:** Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474-1475

## Major Milestones in Homogeneous Gold Catalysis

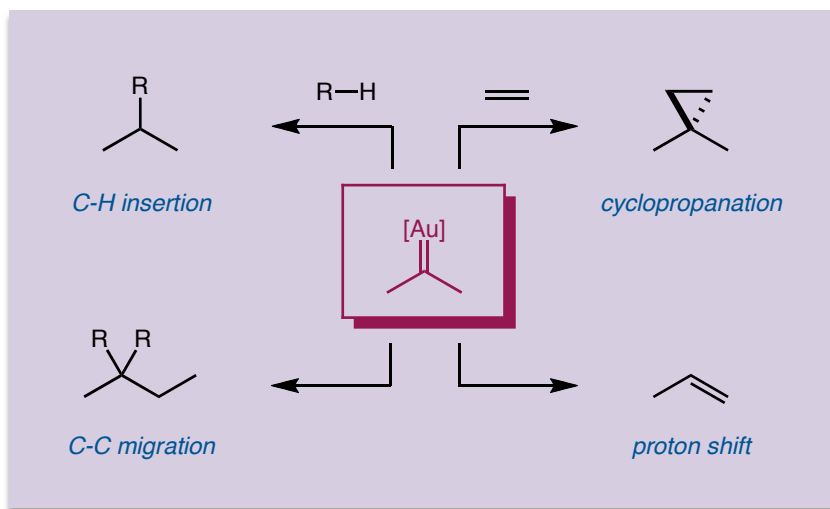
### Alkynophilic $\pi$ -activation toward nucleophiles



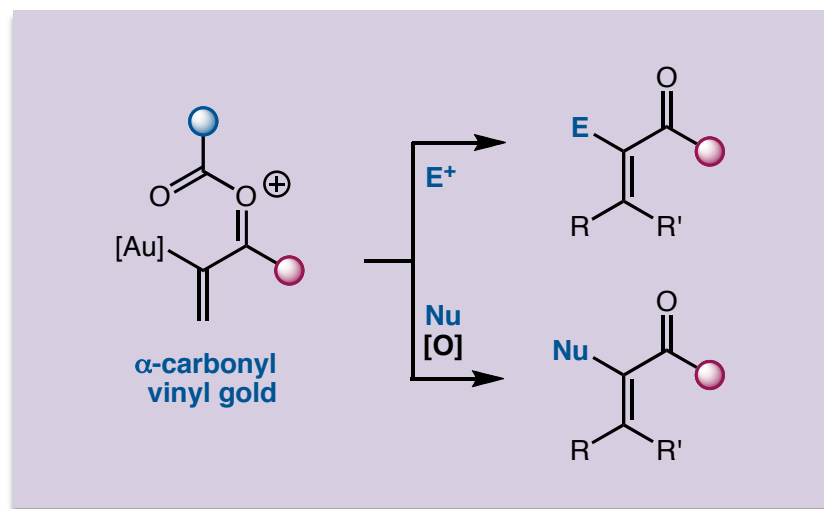
### Asymmetric catalysis; counteranion control



### Investigating & harnessing carbenoid character



### Novel propargyl carboxylate reactivity



## Recent Reviews on Homogeneous Gold Catalysis

### Synlett '10 Accounts



#### A Reactivity-Driven Approach to the Discovery & Development of Gold-Catalyzed Organic Reactions

Shapiro, N. D.; Toste, F. D.

*Synlett.*, 2010, 5, 675-691

#### Gold-Catalyzed Reaction of Propargylic Carboxylates via an Initial 3,3-Rearrangement

Wang, S.; Zhang, G.; Zhang, L.

*Synlett.* 2010, 5, 692-706

### Chem Rev - Special Issue '08 Coinage Metals in Organic Synthesis



#### Gold-Catalyzed Organic Reactions

Stephen, A.; Hashmi, K.;

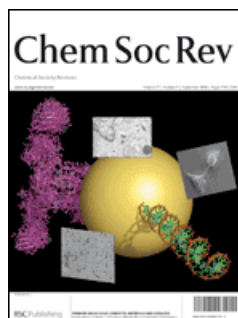
*Chem. Rev.* 2007, 7, 3180-3211

#### Gold-Catalyzed Organic Transformations

Li, Z.; Brouwer, C.; He, C.

*Chem. Rev.* 2008, 8, 3239-3265

### Chem Soc Rev - Special Issue '08 GOLD: CHEMISTRY, MATERIALS & CATALYSIS



#### Gold catalysis in total synthesis

Stephen, A.; Hashmi, K.; Rudolph, M.

*Chem. Soc. Rev.* 2008, 37, 1766-1775

#### N-Heterocyclic carbenes in Au catalysis

Marion, N.; Nolan, S.

*Chem. Soc. Rev.* 2008, 37, 1776-1782

#### Alternative Synthetic Methods through New Developments in Catalysis by Gold

Arcadi, A.

*Chem. Rev.* 2008, 8, 3266-3325

#### Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective

Jiménez-Núñez, E.; Echavarren, A.

*Chem. Rev.* 2008, 8, 3326-3350

#### Ligand Effects in Homogeneous Au Catalysis

Gorin, D.; Sherry, B.; Toste, F. D.

*Chem. Rev.* 2008, 8, 3351-3378

and many more ...