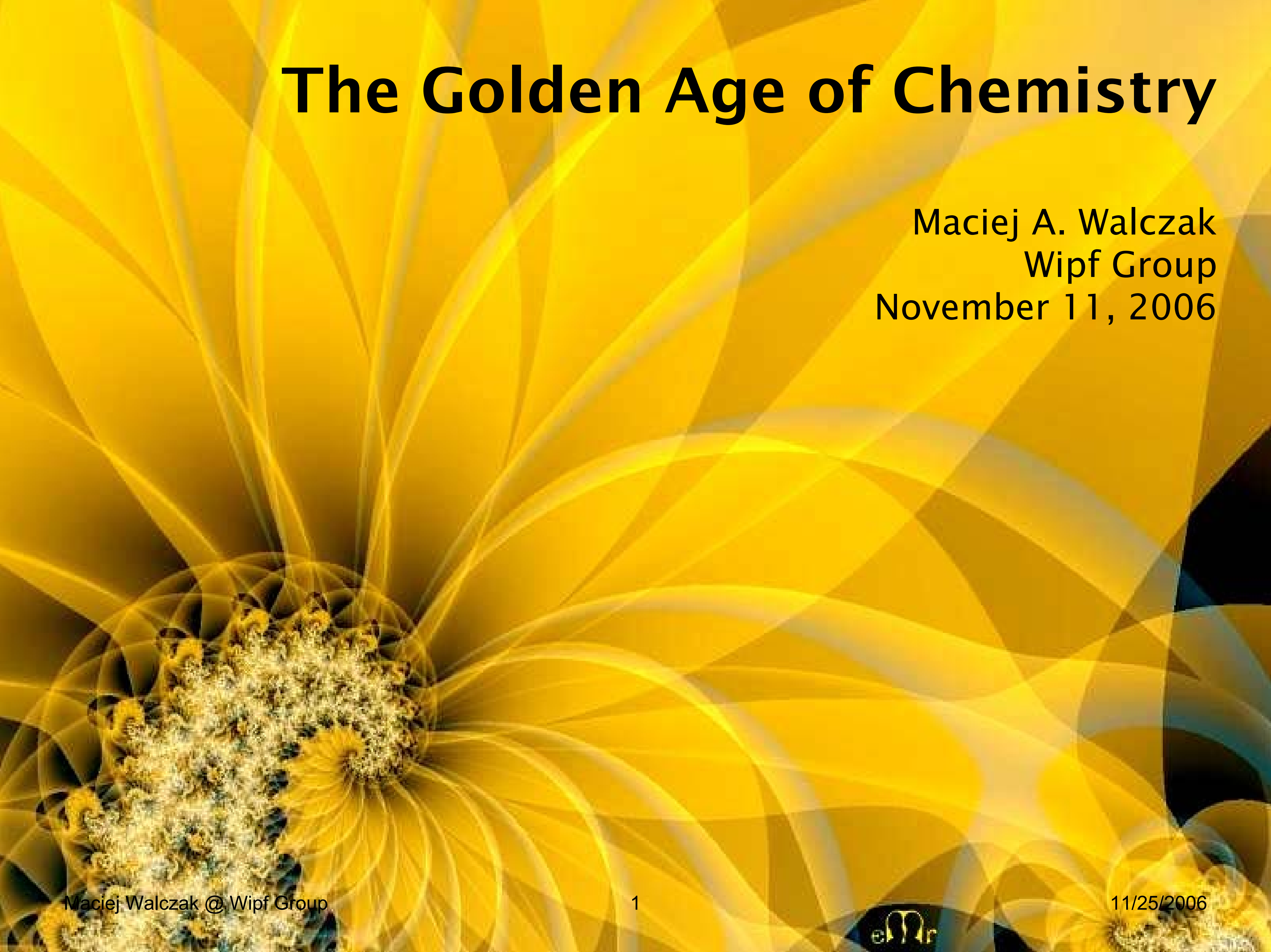


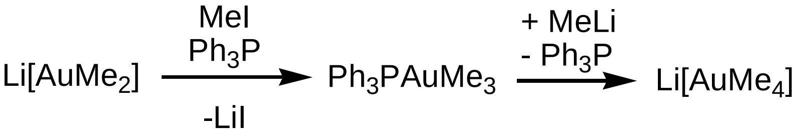
The Golden Age of Chemistry

Maciej A. Walczak
Wipf Group
November 11, 2006

Gold – Basic Facts

-Gold is known in following oxidation states: -1, **0**, **+1**, ([Xe] $4f^{14}$ $5d^{10}$), +2, **+3** ([Xe] $4f^{14}$ $5d^{8}$), +5

- Complexes of Au(I) are usually 2-coordinate, linear, 14-e species whereas Au(III) complexes are typically 4-coordinate, square-planar, 16e (compare other d^{10} and d^{8} – $[Ag(CN)_2]^-$, Ph_3PAuCl or $[Ni(CN)_4]^{2-}$, $[Rh(CO)_2Cl_2]^-$)



$$Li[AuMe_2] \xrightarrow[-LiI]{MeI,\ Ph_3P} Ph_3PAuMe_3 \xrightarrow{+MeLi,\ -Ph_3P} Li[AuMe_4]$$

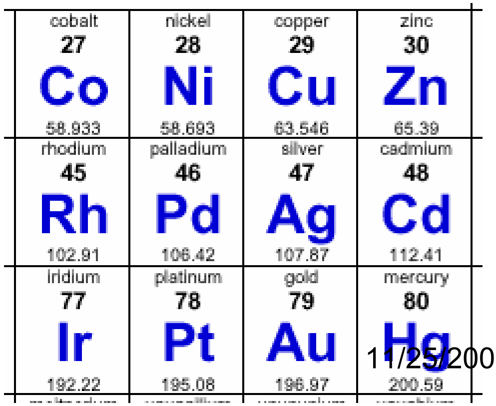
–π-complexes of Au(I) and Au(III) are thermally unstable while Cp-complexes show typically η^1-binding mode (highly fluxional at rt) – weak back-bonding is observed

-Relative stabilities of $[Me_3PAuL]^+$ complexes have been calculated

CH_2Cl_2 (+63) < **H_2O** (+44) < **HCCH** (+38) < **MeOH** (+24) < **CH_3CCH** (+18) < **CH_3CCCH_3** (0) < **Me_2S** (-18) < **PPh_3** (-114)

Teles *ACIEE* **1998**, *37*, 1415

-Among neutral $M(CH_2CH_2)$ complexes M = Cu, Ag, Au, gold is the strongest binder



cobalt 27 Co 58.933	nickel 28 Ni 58.693	copper 29 Cu 63.546	zinc 30 Zn 65.39
rhodium 45 Rh 102.91	palladium 46 Pd 106.42	silver 47 Ag 107.87	cadmium 48 Cd 112.41
iridium 77 Ir 192.22	platinum 78 Pt 195.08	gold 79 Au 196.97	mercury 80 Hg 200.59

Relativistic Effects in Gold

-Among heavy metals, gold shows largest relativistic effects

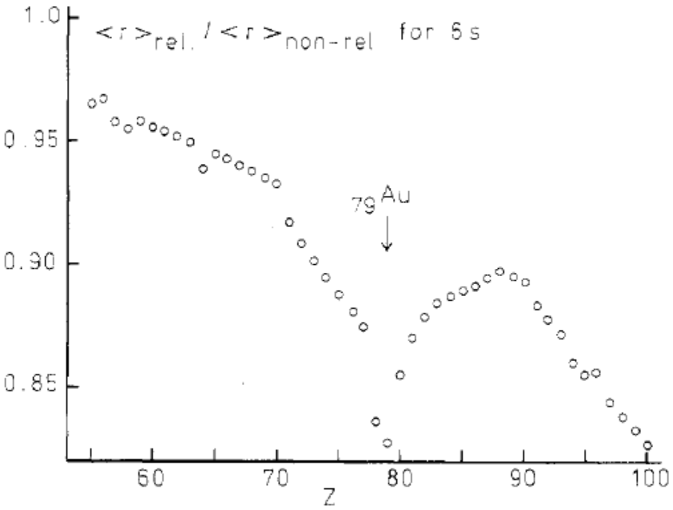
-The influence of relativistic effects can be illustrated be comparing Ag and Au

  -Energies of *s* and *p* orbitals are lowered but energy of *d* orbitals is raised

  -Gold forms shorter and more covalent bonds

  -Destabilization of 5*d* orbital in Au may explain tri- and pentavalency of Au

-Yellow color of gold can be also explained by relativistic effects



Relativistic contraction of 6*s* shell

Pyykkö *ACIEE* **2004**, *44*, 4412

Stoichiometric Reactions of Gold

- Grignard and lithium reagents undergo ligand exchange with Au(I) and Au(III) halides

$$\mathrm{AuBr_3 + 2\ EtMgBr \longrightarrow Et_2AuBr + 2\ MgBr_2}$$

-R_3Au and RAu are unstable in the absence of stabilizing ligands

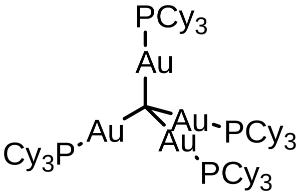
-Highly nucleophilic phosphorus ylides are able to displace almost any ligand on Au

$$\mathrm{L\ Au\ Cl\ \ +\ \ R_3PCH_2 \longrightarrow [L\ Au\ CH_2PPh_3]\ Cl}$$

-Oxidative addition of X_2 or RLi to Au(I) is a common process to obtain Au(III)

-Compounds of type R-Au-L are air and moisture stable but can be decomposed under acidic conditions

-Such exotic species as tetragoldmethane can be obtained in a stable form



-Many compounds of gold show tendency to form molecular clusters that eventually is converted into molecular metal

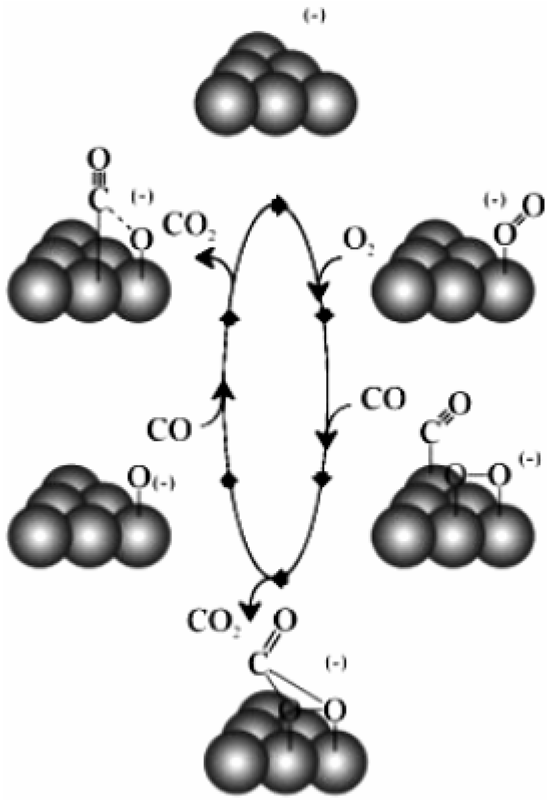
Nanoparticles in Catalysis – A New “Gold” Rush

Application of AgNP

-Catalytic Oxidation of CO to CO_2

-Removal of alkylamines (Fe_2O_3-supported AuNPs) or dioxins (La_2O_3-supported AuNPs)

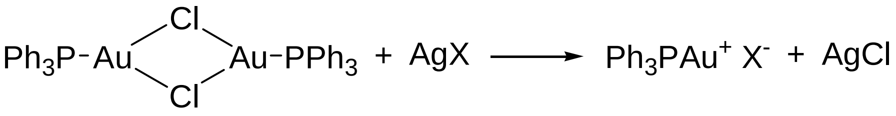
-Low-concentration sensors of H_2 and CO (Co_2O_3-supported AuNP)



Astruc *ACIEE* **2005**, *44*, 7852

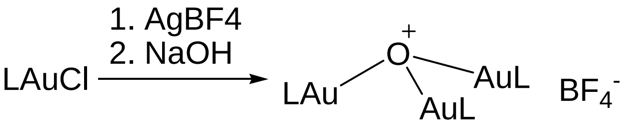
Typical Gold Catalysts

-Ph_3PAuCl (commercially available) is a common Au(I) precatalyst that can be converted into cationic gold by reactions with silver salts



X = SbF_6, BF_4, OTf, etc

- μ-Oxo-complexes of gold have also found applications in catalysis



L = phosphine

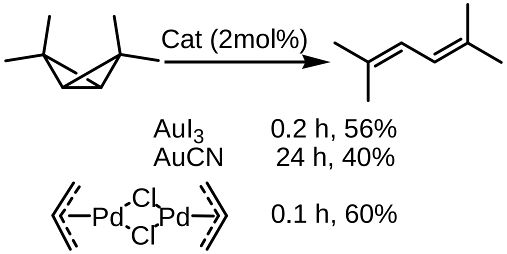
Inorg. Chem. **1993**, *32*, 1946

-Anhydrous $AuCl_3$ and $NaAuCl_4$ $2H_2O$ are common sources of Au(III)

-Various Au(I) carbene complexes are also known to be catalytically active

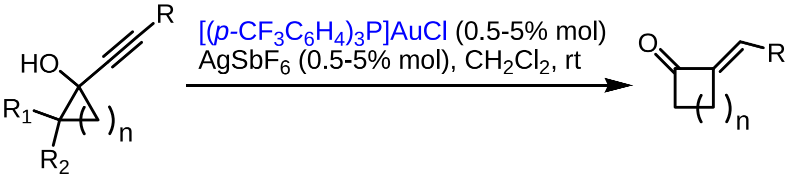
Au-Catalyzed Small Ring Rearrangements

- Early examples of strain-driven rearrangements using catalytic amounts of Au (III) involved very strained molecules (for example, Gassman *JACS* **1972**, *94*, 7741)



AuI_3	0.2 h, 56%
AuCN	24 h, 40%
(Pd complex)	0.1 h, 60%

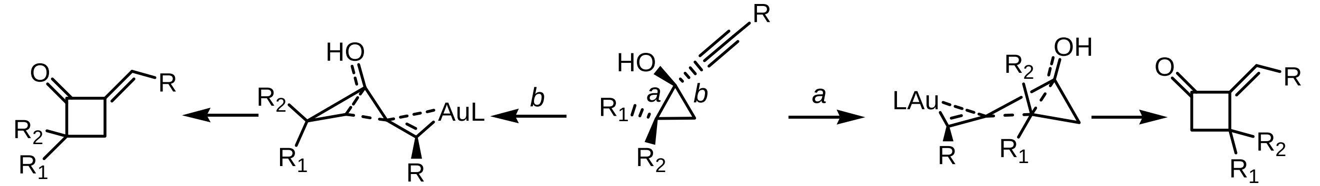
- Recently, a highly efficient rearrangement of alkynylcyclopropanols amd cyclobutanols was described (Toste *JACS* **2005**, *127*, 9708)



n = 1, 2
R = H, alkyl, aryl, I
R_1 = H, (a)cyclic aliphatic substituent

Yields: 66-98%

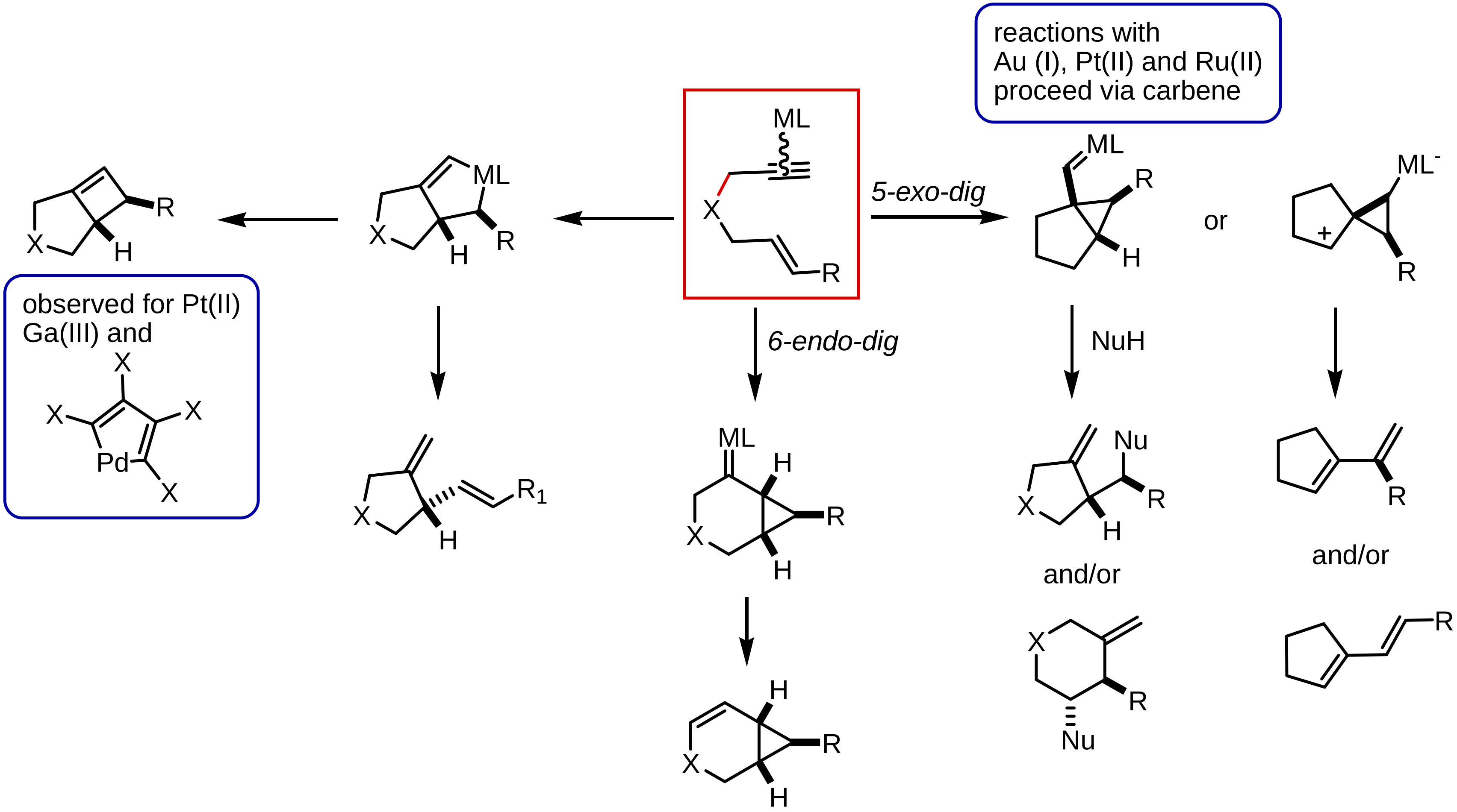
- Reaction proceeds via 1,2-alkyl shift mechanism where the $A^{1,3}$ strain interactions control the migratory preference



R = Ph, R_1 = *i*-Pr, R_2 = H, 91%

R = H, R_1 = H, R_2 = *i*-Pr, 80%

Gold-Catalyzed Rearrangements of Enynes – a Mechanistic Puzzle

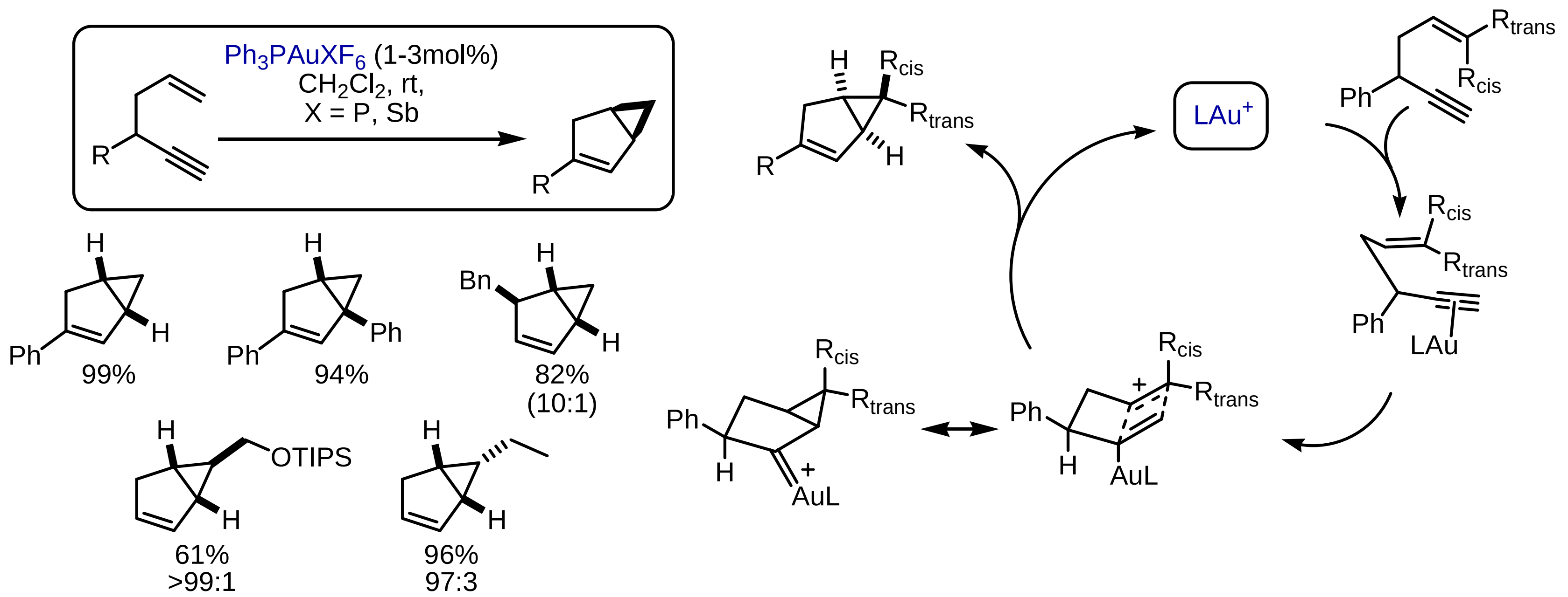


reactions with
Au (I), Pt(II) and Ru(II)
proceed via carbene

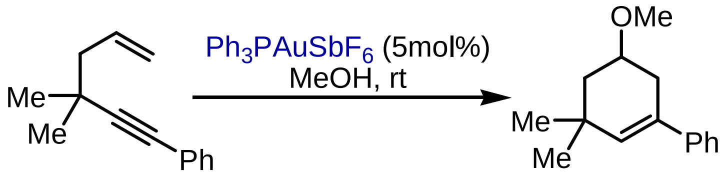
observed for Pt(II)
Ga(III) and

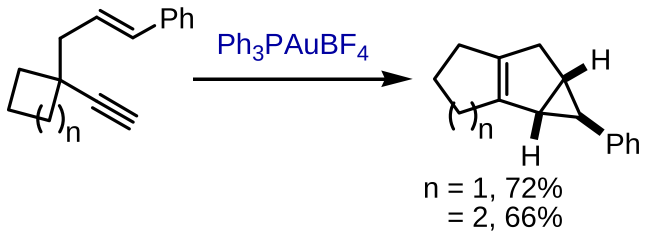
Echavarren *Chem. Eur. J.* **2006**, *12*, 5916

Au-Catalyzed Cycloisomerizatin of Alkynes



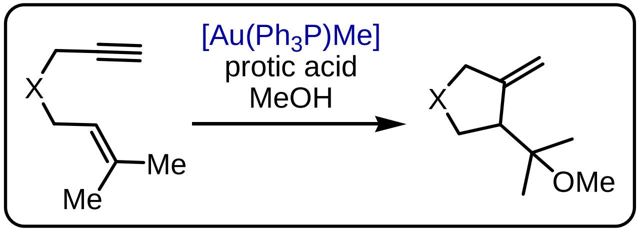
Putative carbocation X can be either trapped intramolecularly or can undergo 1,2-alkyl shift

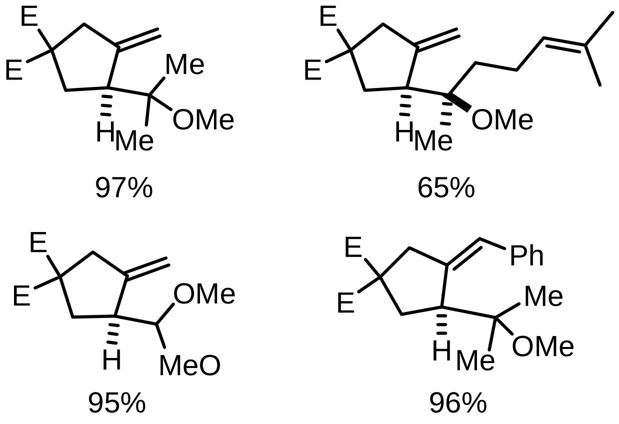


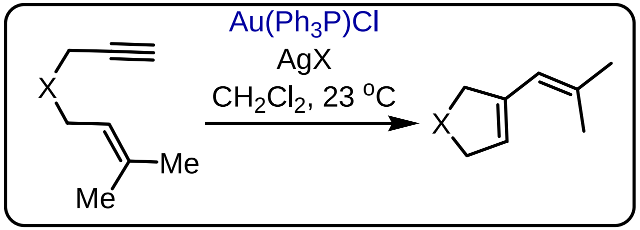


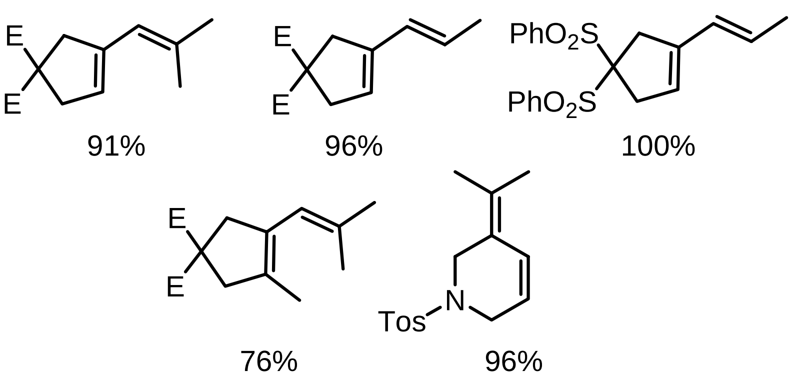
Toste *JACS* **2004**, *126*, 10858

Gold-Catalyzed Rearrangements of Enynes – a Mechanistic Puzzle





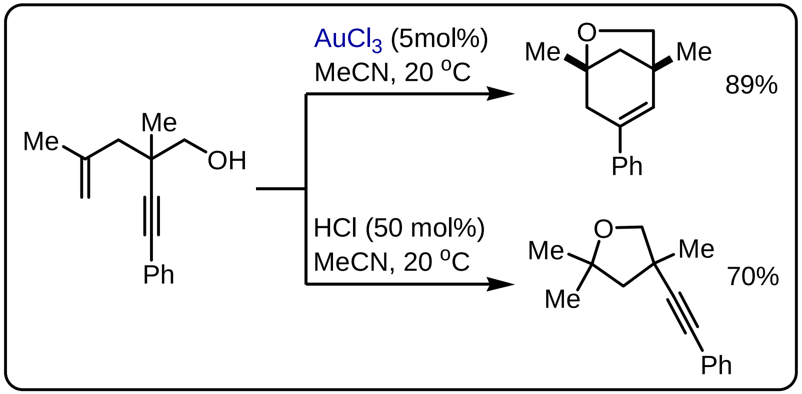


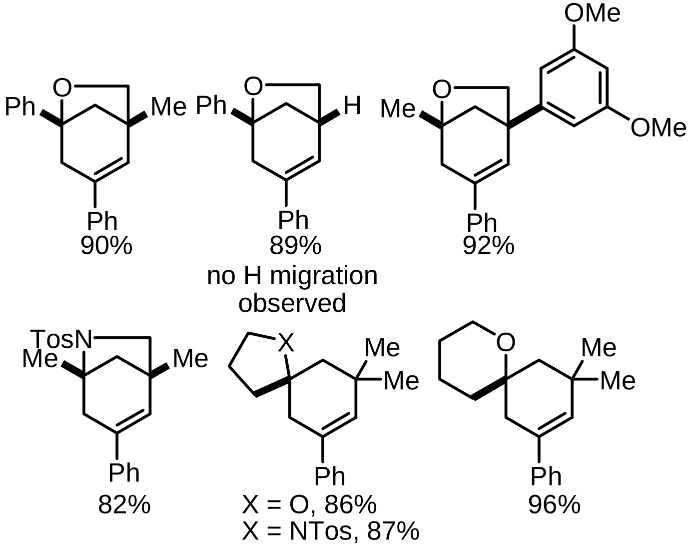


Echavarren *ACIEE* **2004**, *43*, 2402

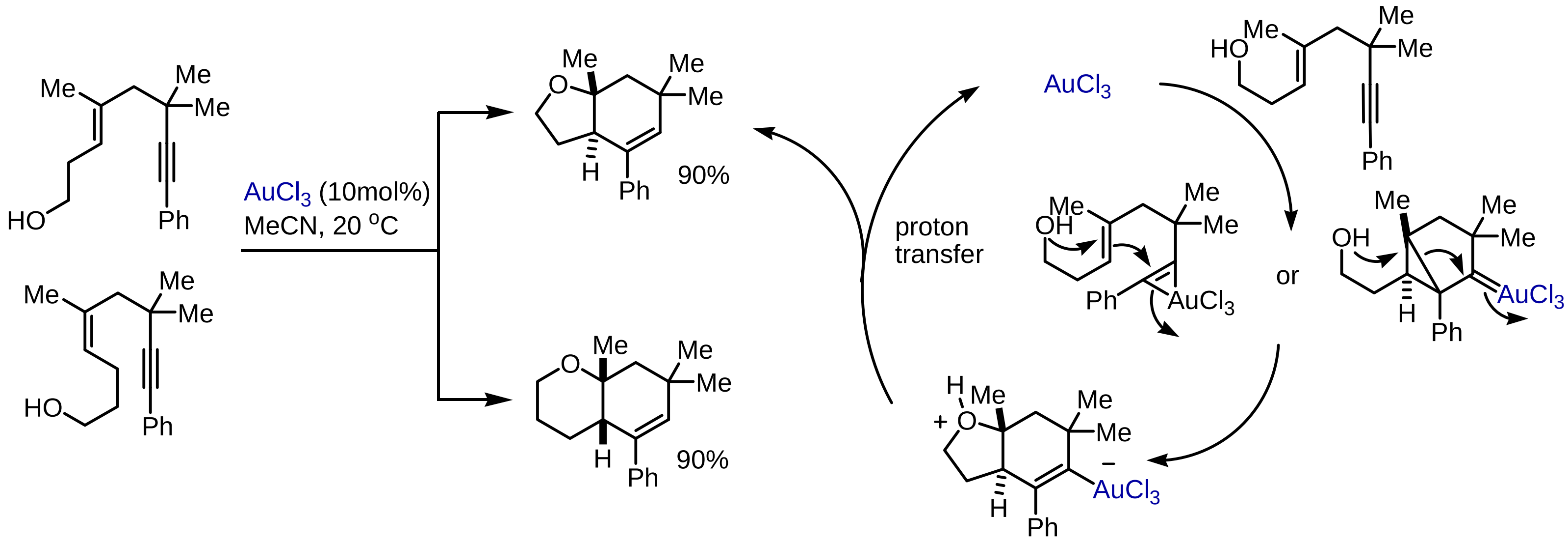
Echavarren *Chem. Eur. J.* **2006**, *12*, 1677

Nucleophilic Trapping



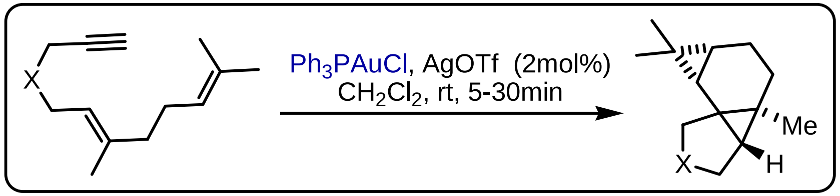


High stereospecificity was observed
in cyclization of *E*/*Z* alkenes:

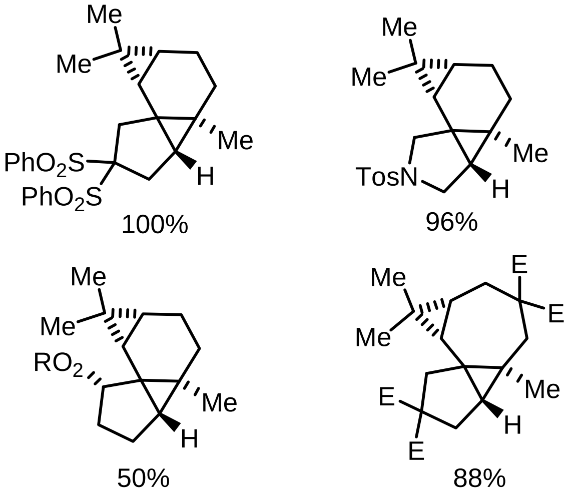


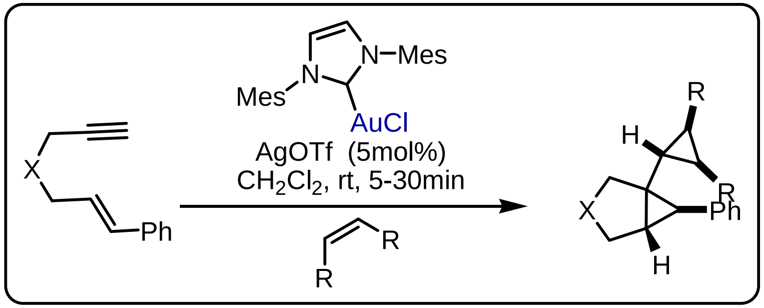
Kozmin *JACS* **2005**, *127*, 6962

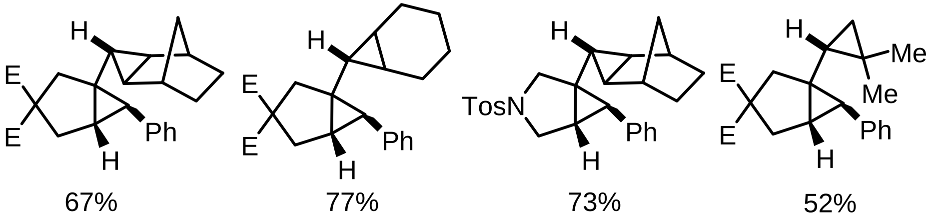
Trapping of Au-Carbene Intermediate



Echavarren *Chemistry Eur. J.* **2006**, *12*, 1694

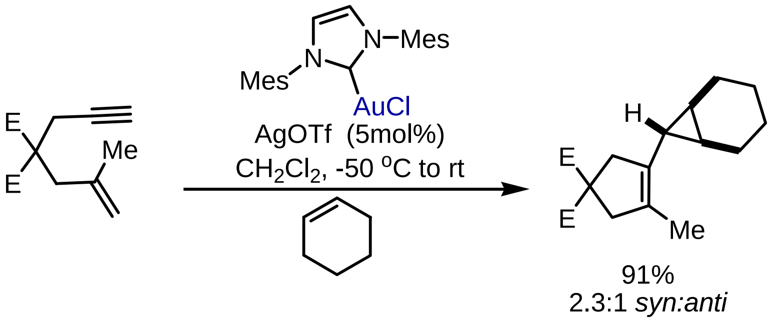




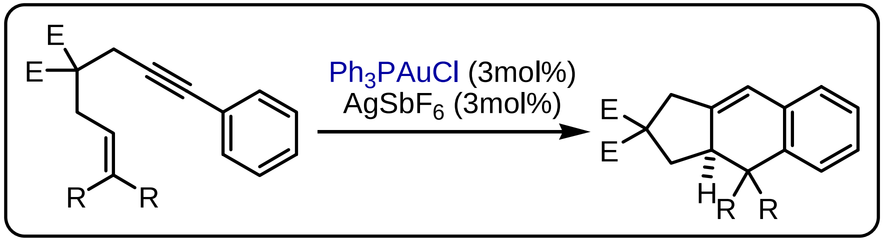


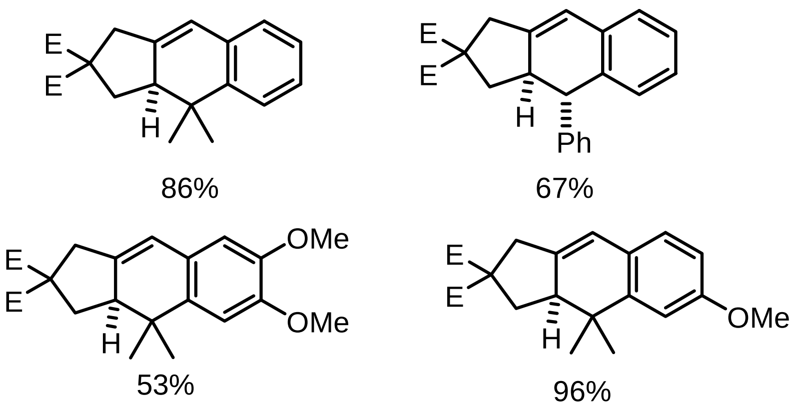
Echavarren *ACIEE* **2006**, *45*, 6029

However, additional evidence for terminal carbene can be obtained by trapping experiments



Au-Catalyzed Cycloisomerizatin

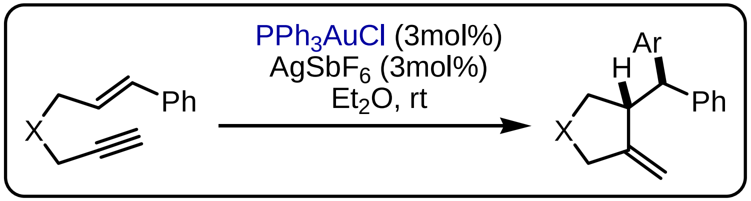


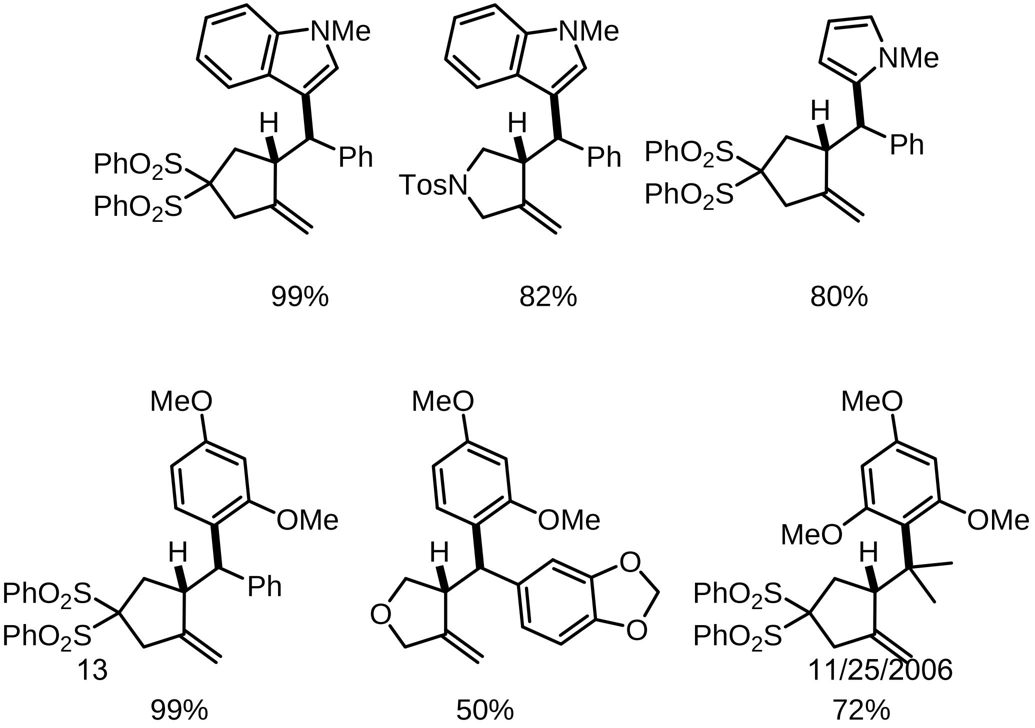


-Au(I) promotes 5-*exo*-*dig* cyclization followed by Nazarov-type cyclization

-Electron-donating groups increase yield of this transformation - an alternative pathway is formal 2+2 cycloaddition

Echavarren *JACS* **2005**, *127*, 6178

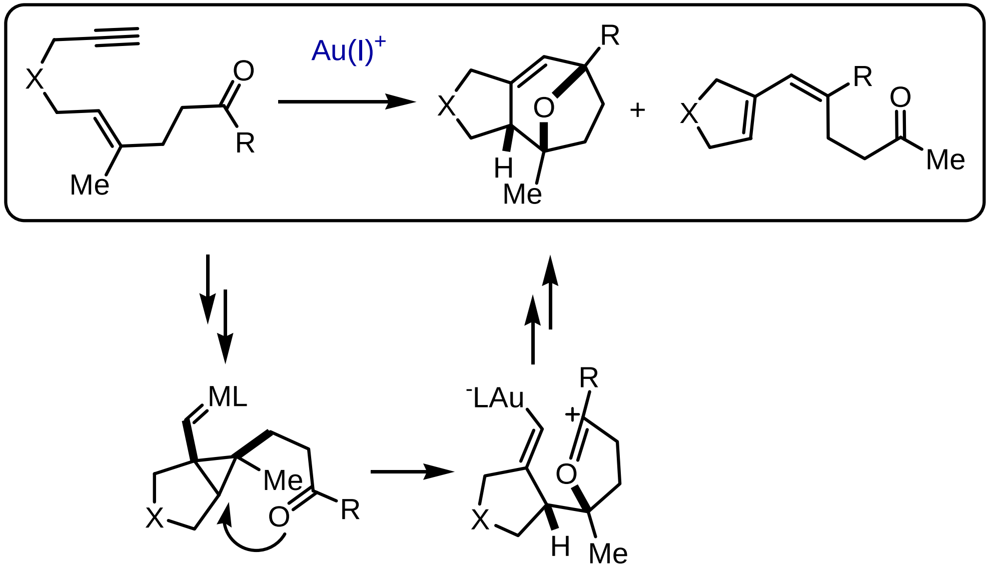




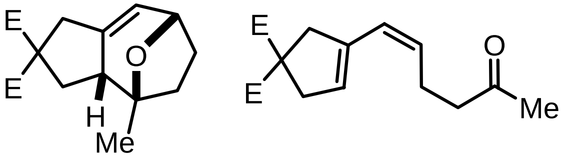
-Au-promoted cycloizomerization followed by trapping with electron-rich aromatic afforded Friedel-Crafts-type products

Genét *ACIEE* **2006**, *45*, 7427

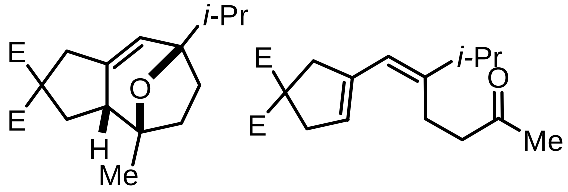
Au-Catalyzed Prins Reaction



Echavarren *ACIEE* **2006**, *45*, 5452

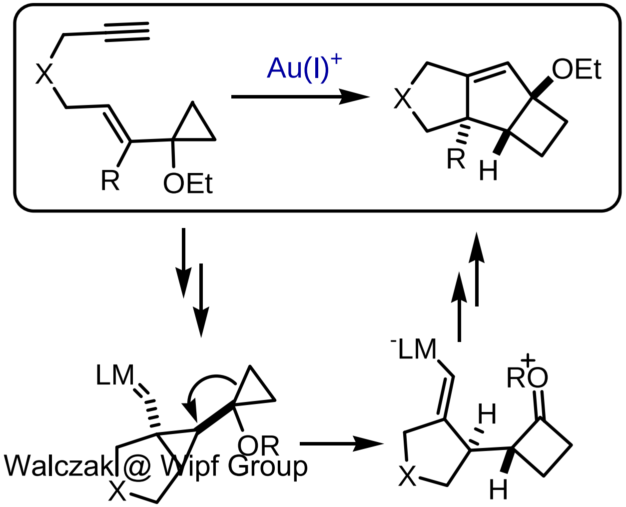


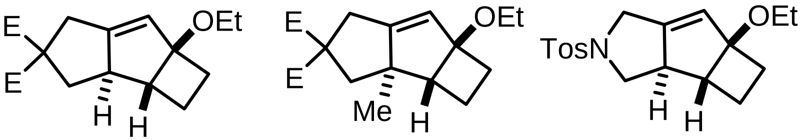
	35%	50%
Using AuCl	58%	18%



	64%	22%
Using AuCl	84%	12%

Incorporation of strained carbocycle into the substrates leads to ring-expanded product

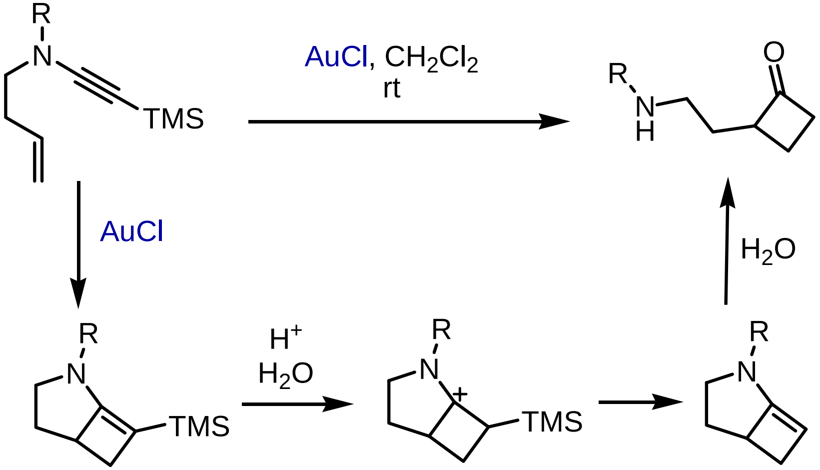




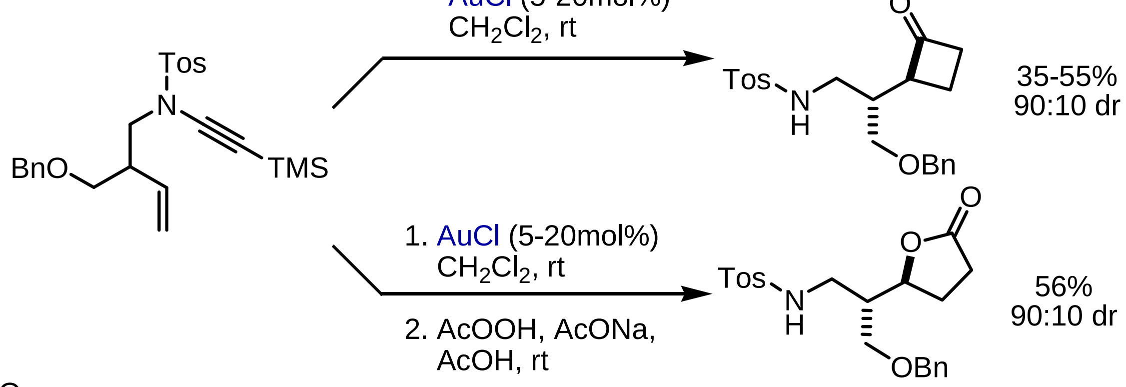
88% 60% 60%

Yields: 39-93%
dr 1:1 to 30:1

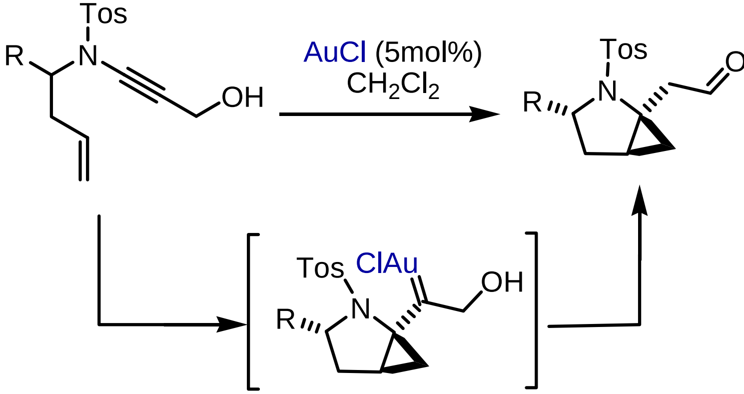
Ene-Ynamide Isomerization



R = Tos, 61%
= Cbz, 59%



Exposure of labile cyclobutanones to peracid leads to formation of γ-lactones



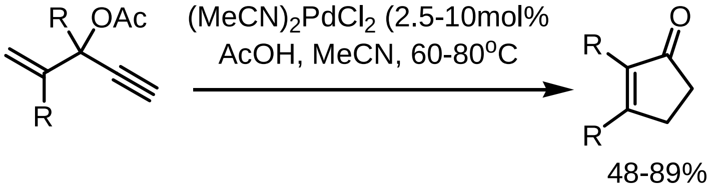
R = 61%, 95:5
= CH_2OBn, 51%, 95:5

Imidates with substituents at 2 and 3 position of homoallyl chain undergo diastereoselective rearrangements

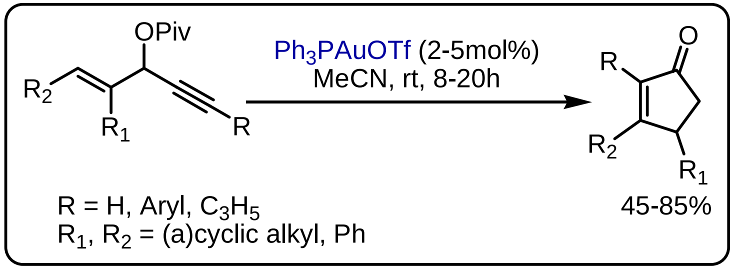
Cossy *ACIEE* **2006**, *45*, 6726

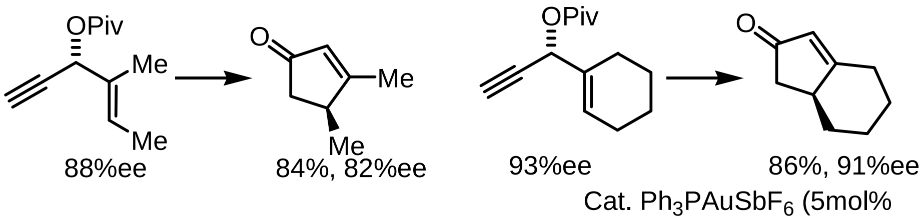
Au-Catalyzed Rautenstrauch Reaction

Vinyl propargyl esters undergo metal catalyzed rearrangement to cyclopentenones (Rautenstrauch *JOC* **1984**, *49*, 950)

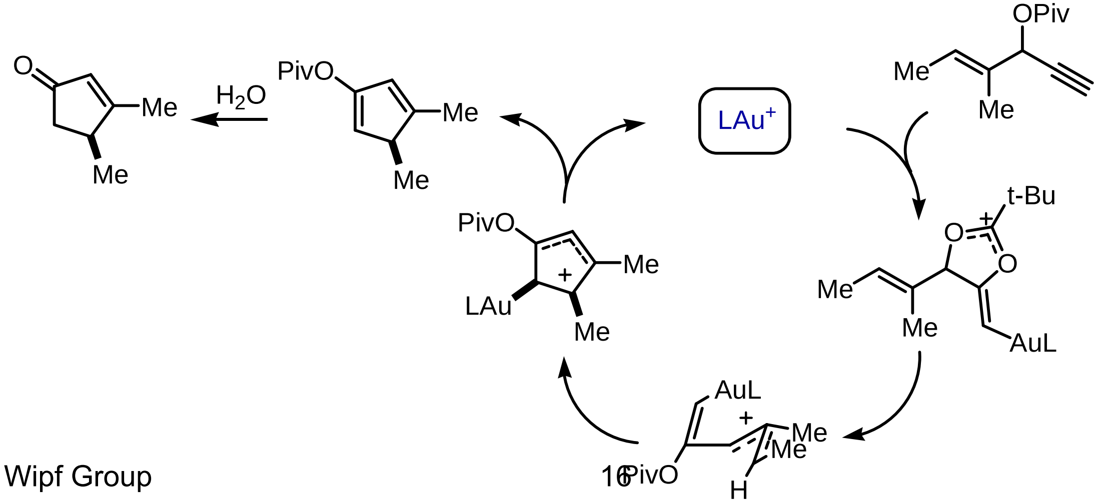


Same transformation can be carried out using gold(I) catalyst that selectively transfers chirality of non-racemic substrates to cyclopentenone skeleton Toste *JACS* **2005**, *127*, 5802



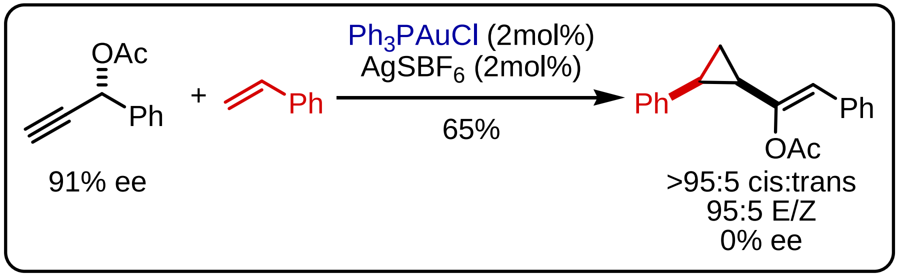


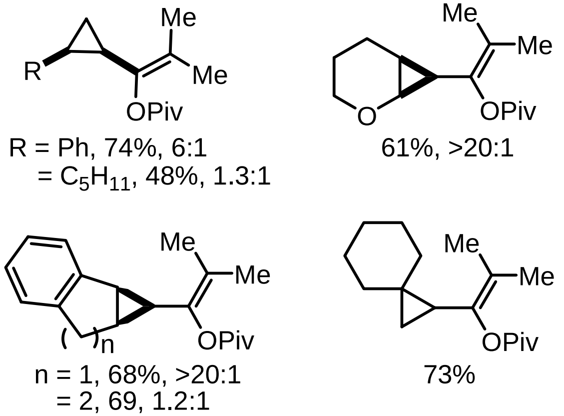
High selectivity of was atributed to heliciy of pentadienyl cation resulting from Lera *JACS* **2006**, *128*, 2434



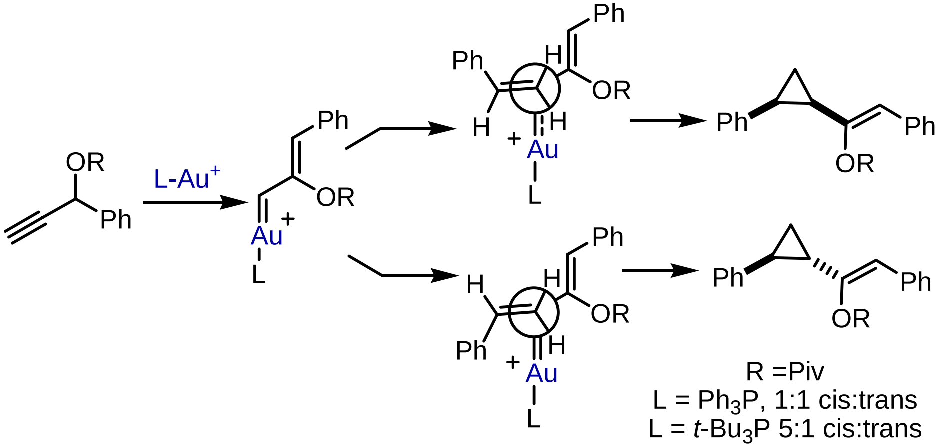
Au(I)-Promoted Rearrangement of Propargyl Esters

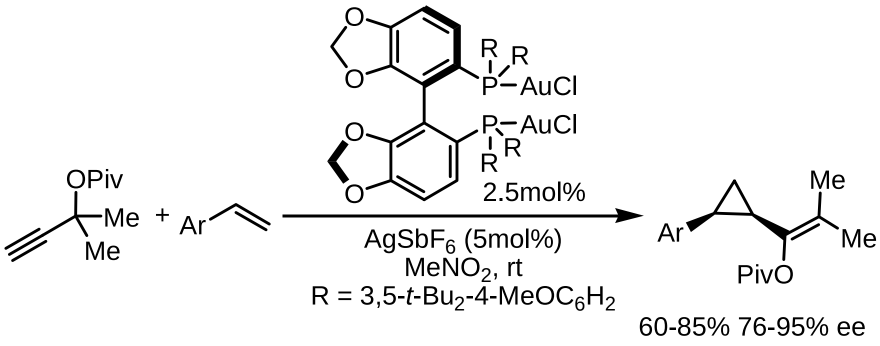
Propargyl esters undergo Au(I) promoted rearrangements followed by trapping with styrenes





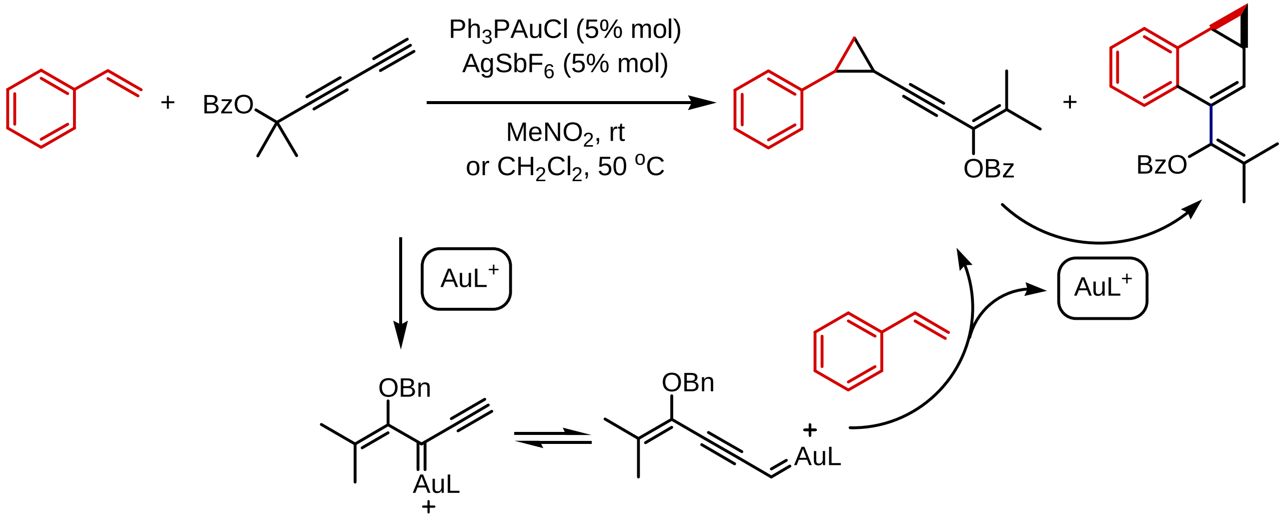
Mechanistic proposal is consistent with the pathway favoring formation of carbene



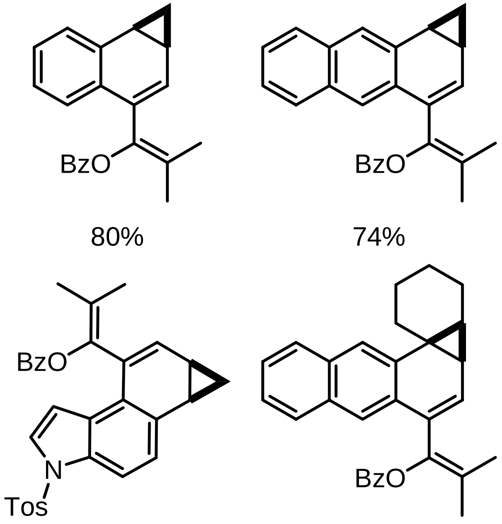


Toste *JACS* **2005**, *127*, 18002

Au(I)-Catalyzed [4+3] Annulation



Reaction Scope:



Key Features:

- Pt(II) and Ru(II) gave desired product in moderate yield
- only *trans* metylstyrenes underwent stereospecific reaction whereas *cis* gave 1:0.8 diastereomeric mixture

Toste *JACS* **2006**, *128*, 14480

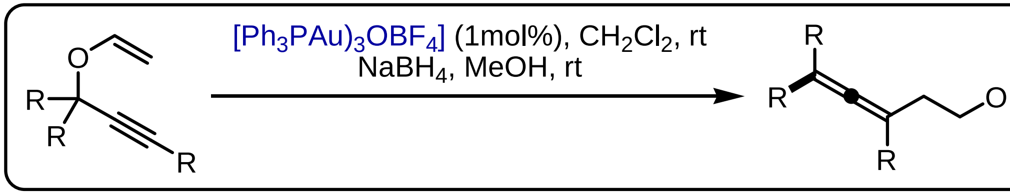
Highly-Selective Claisen Rearrangements

-Catalytic Claisen rearrangement can be promoted by hard (Al(III)) and soft (Hg(II), Pd(II)) Lewic acids

Hiersemann *Eur. J. Org. Chem.* **2002**, 1461

-No general approach to catalytic Claisen rearrangement of propargyl vinyl ethers has been developed

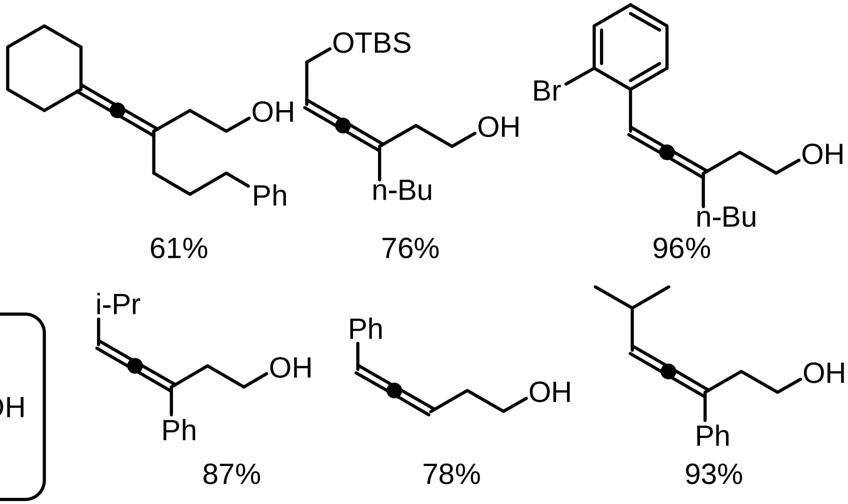
-Cationic Au(I) efficiently homoallenyl alcohols

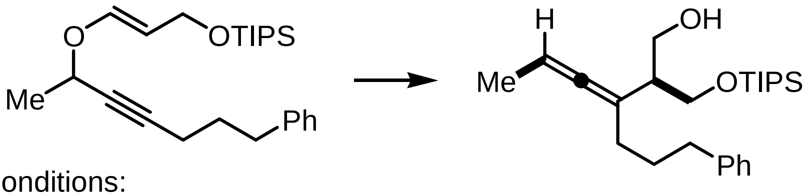


$[(Ph_3PAu)_3OBF_4]$ (1mol%), CH_2Cl_2, rt

$NaBH_4$, MeOH, rt

Reaction Scope





Conditions:

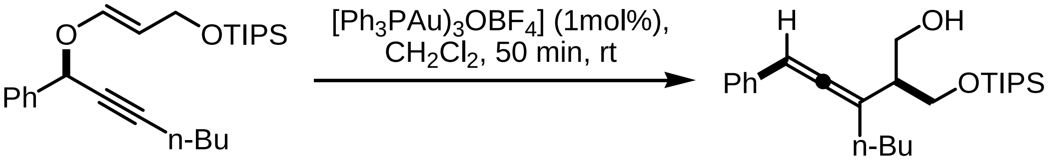
A. $[(Ph_3PAu)_3OBF_4]$ (1mol%), CH_2Cl_2, 4h, 40 ^oC 76%, >20:1

$NaBH_4$, MeOH, rt

B. PhMe, 170 ^oC, 3h; $NaBH_4$, MeOH, rt 90%, 1:1.5

-Au-catalyzed Claisen rearrnagemnt provides homoallenic alcohols in high dr and ee's

-Other catalysts ($Ph_3PAuOTf$, Ph_3PAuBF_4) afforded allylic alcohols in low ee's (racemization of the product)



$[(Ph_3PAu)_3OBF_4]$ (1mol%), CH_2Cl_2, 50 min, rt

95%ee

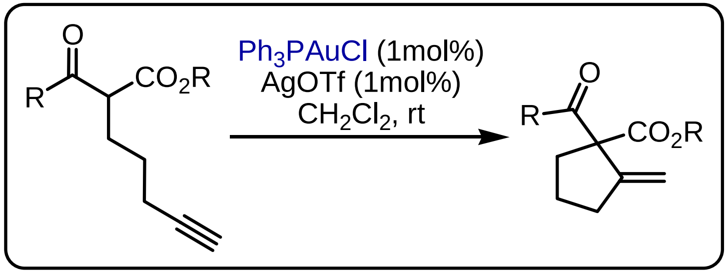
81%, 94%ee
dr >20:1

Toste *JACS* **2004**, *126*, 15978

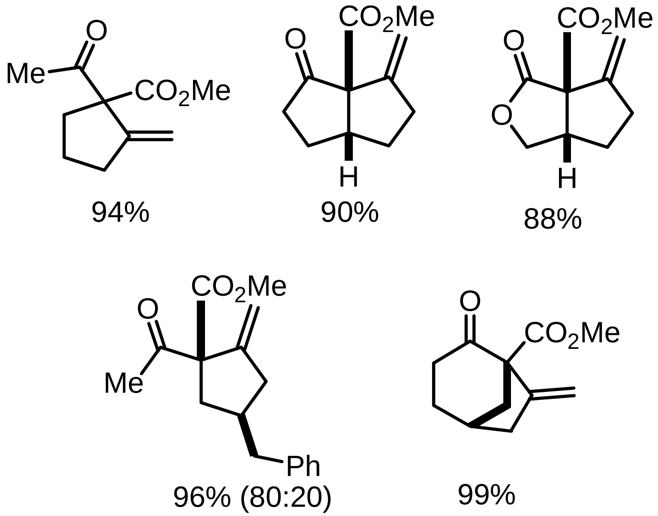
Enol – Alkyne Cyclization

- Typical conditions for Conia-ene reaction require activation by heat, strong acid or base

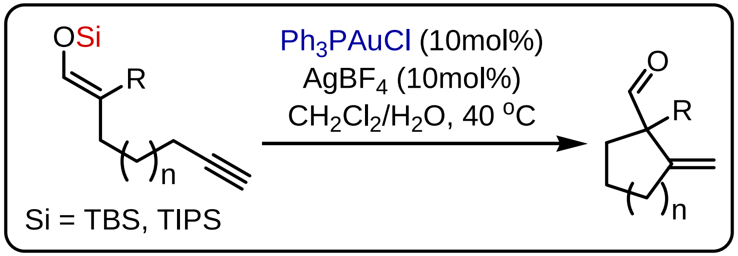
-Gold-catalyzed version of ene reaction proceeds under relatively mild conditions



Toste *JACS* **2004**, 126, 4526

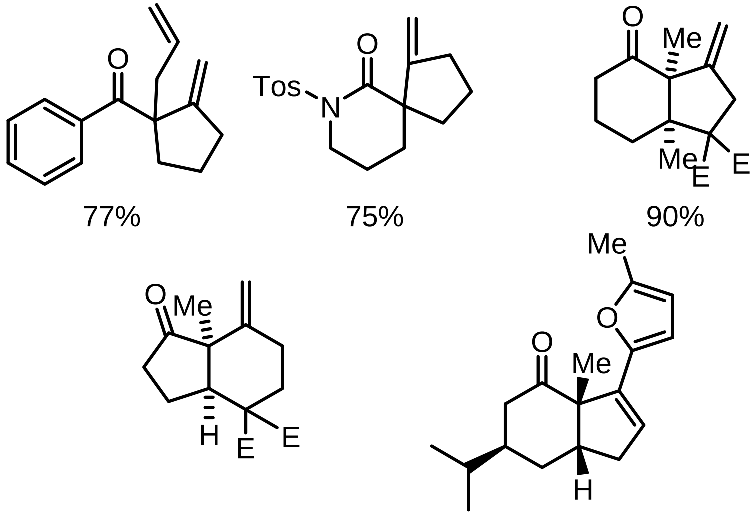


-Similarly, silyl enol ethers can participate in an yne carbocyclization



Water as well as methanol can be used as an external proton source

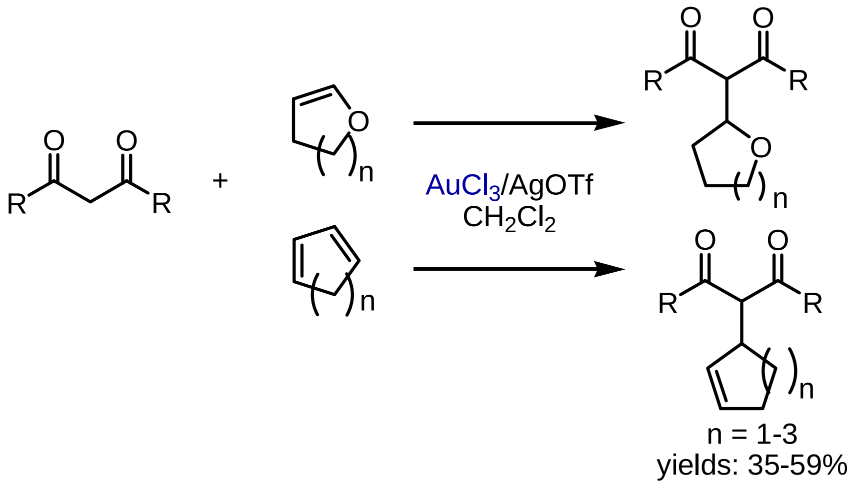
Toste *ACIEE* **2006**, 45, 5991



94%

73%

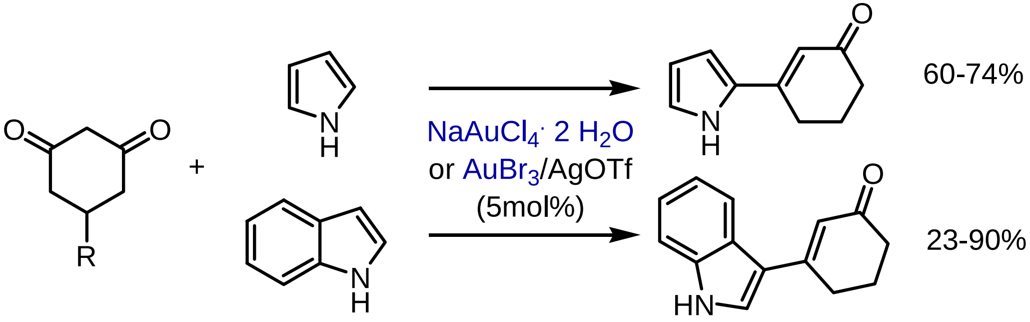
Catalytic Addition of 1,3-Dicarbonyl Compounds



-No isomerization of double bond observed

-Tentative mechanism involves activation of olefin by Au(III)

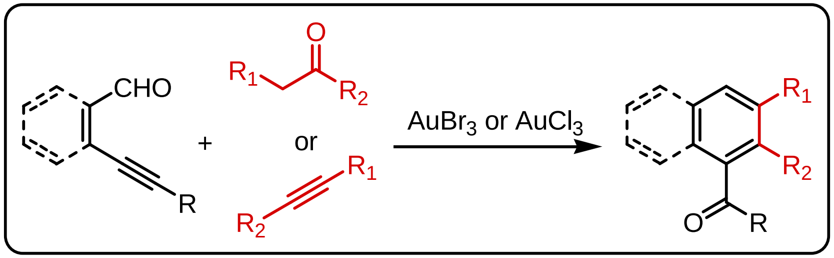
Li *OL* **2005**, *7*, 673



Marinelli *Adv. Synth. Cat.* **2006**, 331

Au(I)-Catalyzed [4+2] Annulation

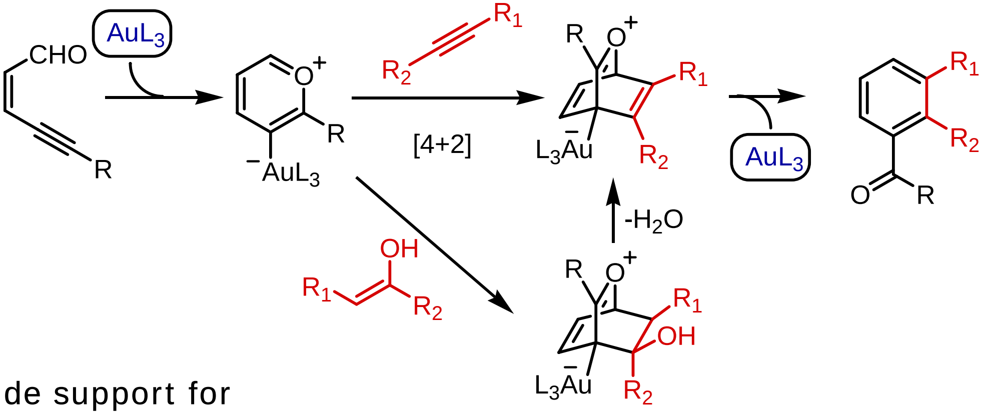
CC bond formtin forcesses followed by Trapping of oxabicyclic scaffolds



Yields: 45-90%

Intramolecular cyclization can be also carried out using $Cu(OTf)_2$

Benzannuklation reactio proceeds also with dimethylacetals (3equiv of H_2O added)

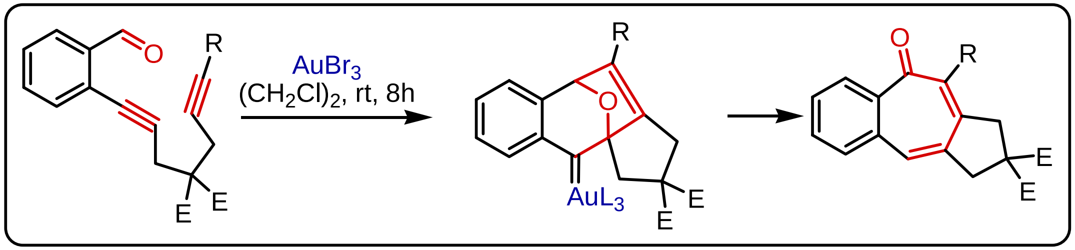


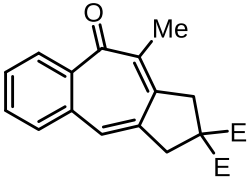
DFT calculations provide support for formation of oxonianaphtalene aurate. However, formal [4+2] cycloaddition proceeds via Huisgen [3+2] cycloaddition
Straub *Chem. Comm.* **2004**, 1726

Yamamoto *JACS* **2002**, *124*, 12650
Yamamoto *JACS* **2004**, *126*, 7458
Yamamoto *JOC* **2005**, *70*, 3682

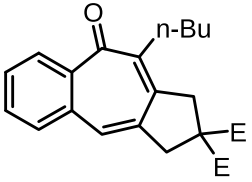
Au(I)-Catalyzed [3+2] Cycloaddition

Formal $AuBr_3$-catalyzed [3+2] cycloaddition was reported as a major pathway in reaction carried out at elevated temperatures

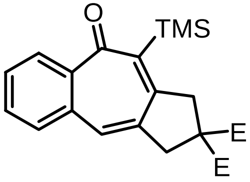




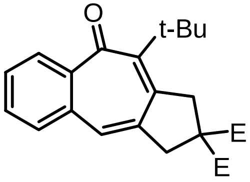
80%



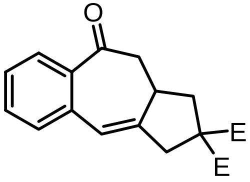
71%



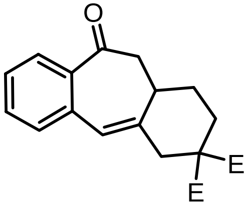
86%



0%

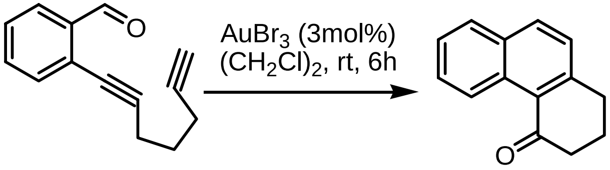


84%



64%

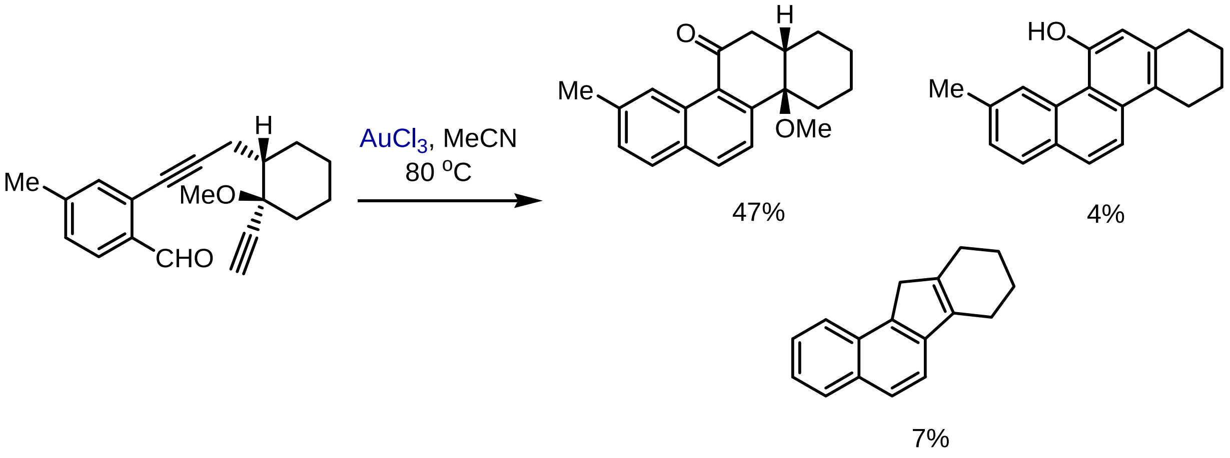
Importantly, *gem*-substituents favor formation of 5-membered rings



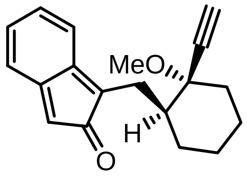
84%

Oh *OL* **2005**, *7*, 5289

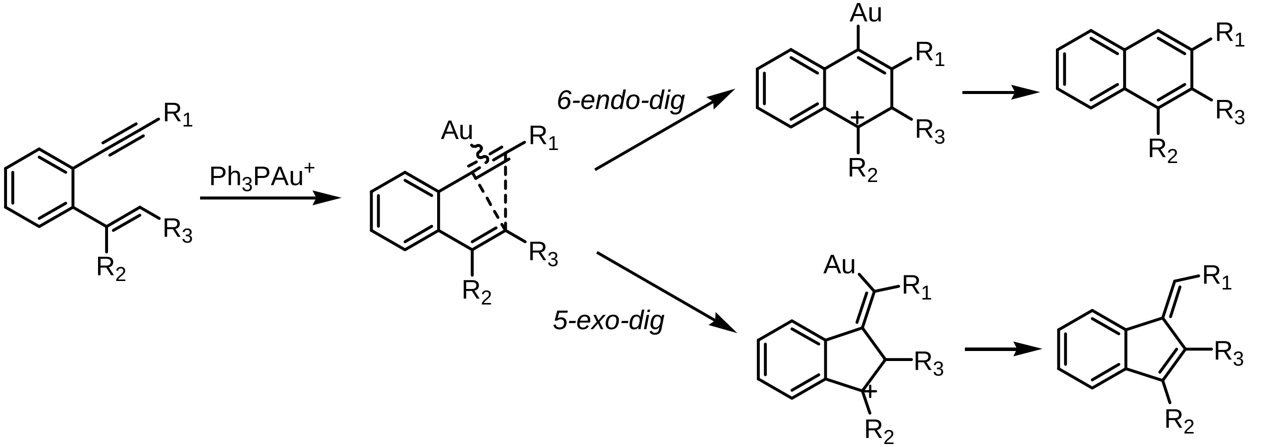
Extension of Au-Catalyzed Domino Processes



Formation of benzo[a]fluorene may proceed via *o*-quinoid ketone



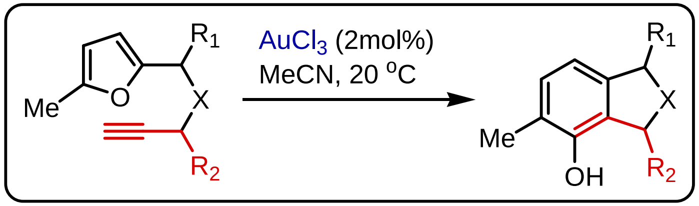
Dyker *JOC* **2006**, *71*, 6728

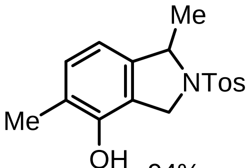


yields: 71-97%
2:1 to >20:1 ratio

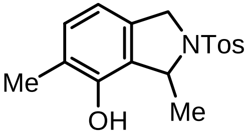
Shibata *Synlett* **2006**, 411

Au-Catalyzed Benzannulation

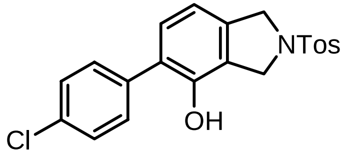




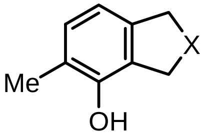
94%



93%



76%



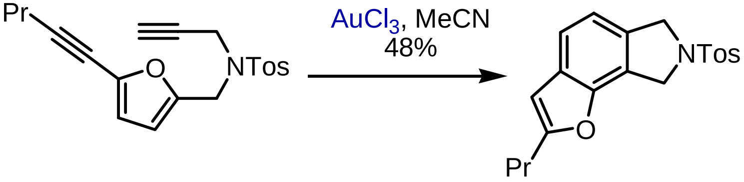
X = CH_2, 65%
= O, 69%
= NTos, 97%
= $NTosCH_2$, 81%

- Catalyst such as $AgNO_3$, $Hg(ClO_4)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3\ CHCl_3$, failed to promote this transformation
- Only terminal alkynes underwent aromatization reaction

Hashmi *JACS* **2000**, *127*, 6962
Hasmi *Cat. Today* **2002**, *72*, 19

In the presence of intramolecular alkyne acceptor, benzofurane scaffold can be obtained

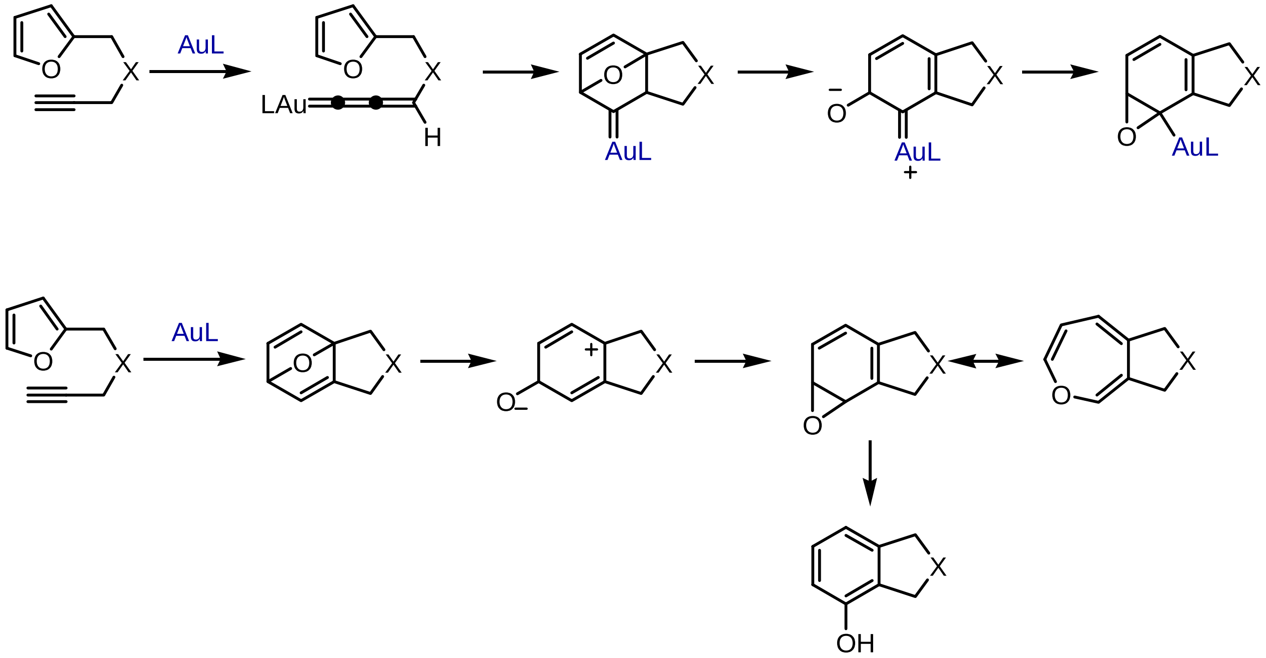
Hashmi *OL* **2001**, *3*, 3769



Mechanistic Proposal

Low-temperature ^{1}H NMR as well as trapping experiments indicated intermediacy of arene oxide

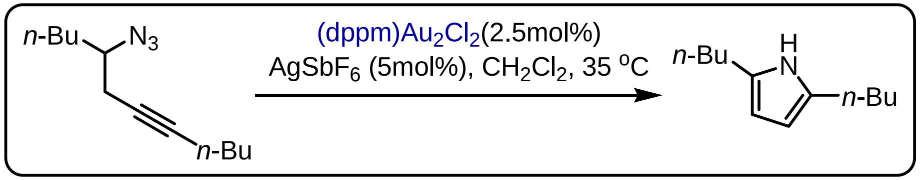
Hashmi *ACIEE* **2005**, *44*, 2798

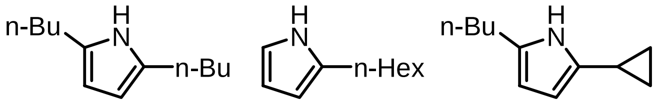


According to DFT calculations, **Diels-Alder** pathway is **thermodynamically** favored whereas **carbene** mechanism is **kinetically** favored

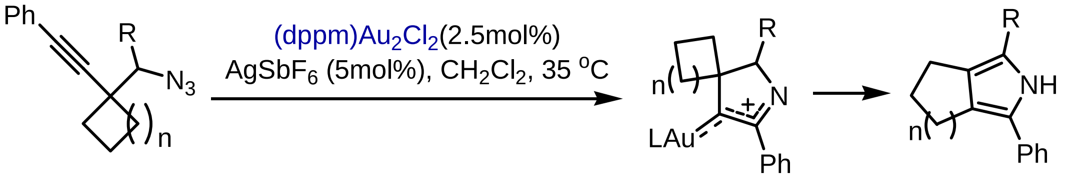
Hashmi *Int. J. Quant. Chem.* **2007**, *107*, 359

Synthesis of Nitrogen-Containing Heterocycles

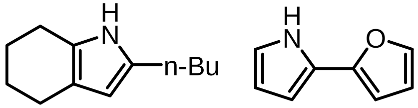




82%　76%　78%

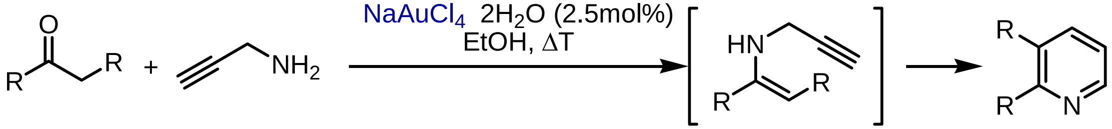


n= 1, R = H, 80%
n = 2, R = Ph, 84%



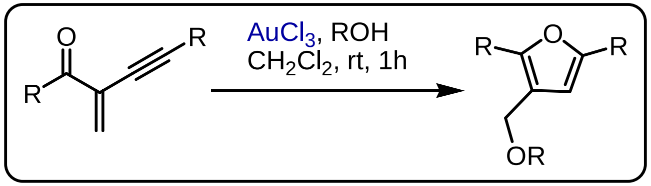
73%　61%

Toste *JACS* **2005**, *127*, 11260

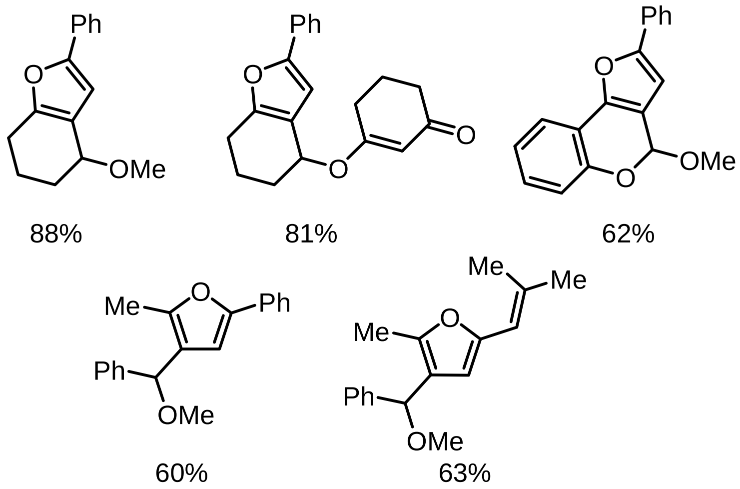


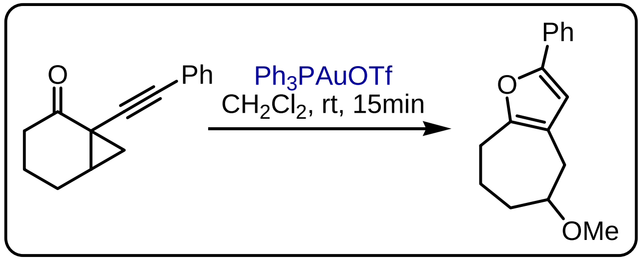
Yields: 15-98%
Arcadi *JOC* **2000**, *68*, 6959

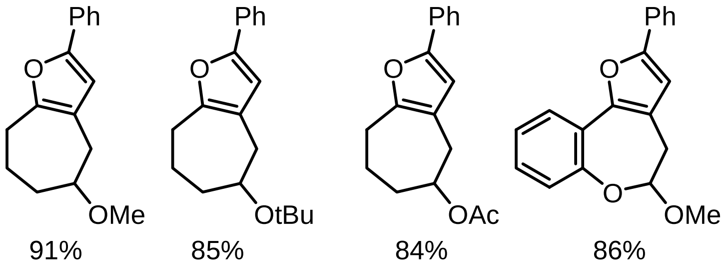
Synthesis of Furans



Larock *JACS* **2004**, *126*, 11164



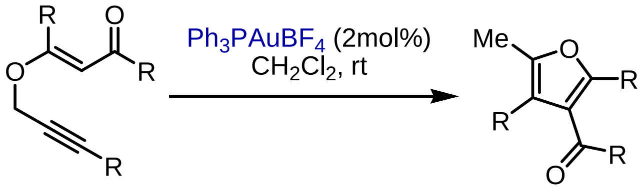




Schmalz *ACIEE* **2006**, *45*, 6704

Au(I) has proven to be superior to catalysts such as Cu(I), Ag(I) or lanthanide salts

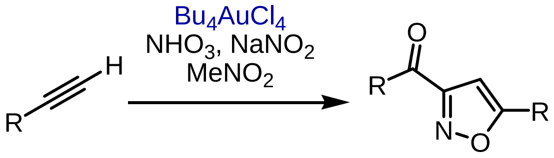
Synthesis of Oxazoles and Furans



Aromatic and aliphatic substituents are tolerated

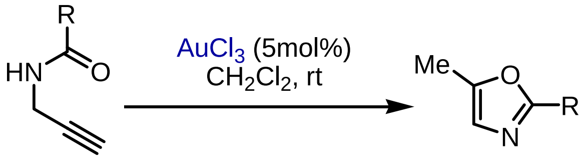
Mostly esters and ketones are suitable substrates

Kirsch *OL* **2005**, *7*, 3925



“Dimerization” of terminal alkynes can be carried out on substrates with alkyl, ether and ester functionalities (yields 35-50%)

Gasparrini *JACS* **1993**, *115*, 4401



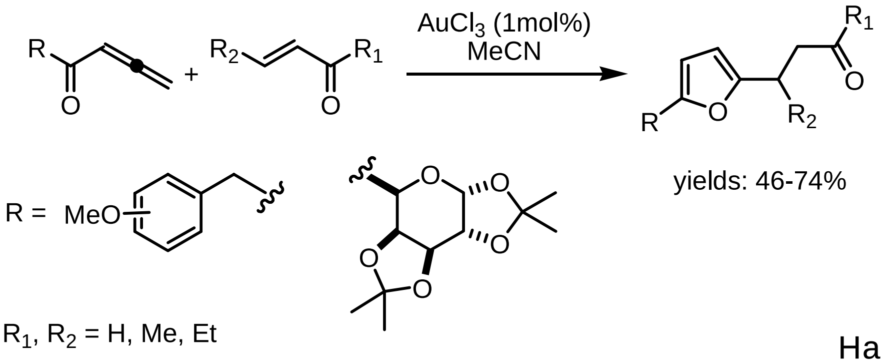
Only terminal alkynes are suitable substrates

Aromatic and aliphatic ketones furnished oxazoles in good yields (48-95%)

Hashmi *OL* **2004**, *6*, 4391

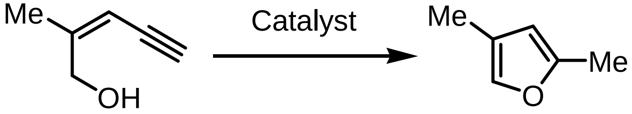
Au-Catalyzed Arene Synthesis – CH Activation

Au (III) is capable to promote electrophilic activation of allenyl ketones followed by CH insertion and addition to enones



Hashmi *ACIEE* **2000**, *39*, 2285

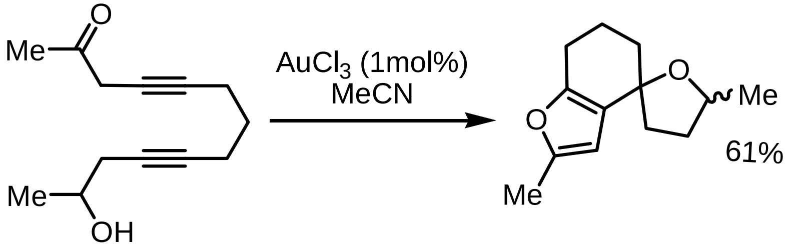
-Gold is a superior catalyst in cycloisomerization reactions



Catalyst:
(*p*-Cymene)$RuCl_2PPh_3$ (1mol%), 60 °C, 1h
Dixneuf *T* **1995**,*51*, 13089

$AgBF_4$ (20mol%), rt, 2h
Marshall *JOC* **1995**, *60*, 5966

-Putative furyl-gold intermediate can be trapped in an intramolecular reactions with alkocohol



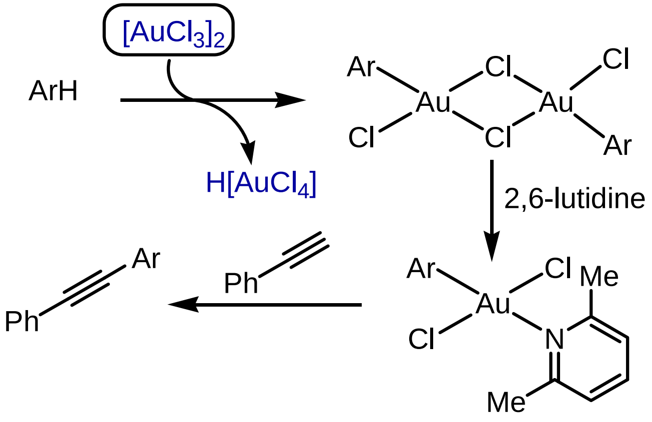
-β-Hydride elimination is rarely observed in Au-catalyzed reactions

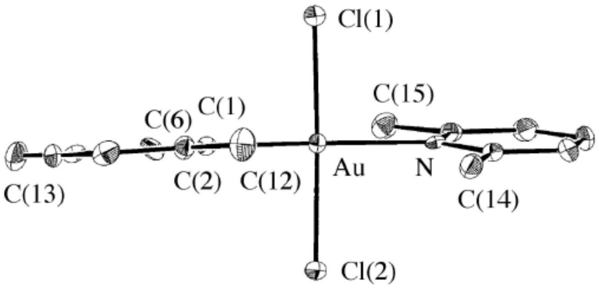
Direct Activation of Aromatic CH Bonds

-Kharasch showed that anhydrous $AuCl_3$ can promote electrophilic exchange of H in various benzene derivatives

Kharasch *JACS* **1931**, *53*, 3053

-Introduction of stabilizing ligands (2,6-lutidine) led to isolation of stable complexes

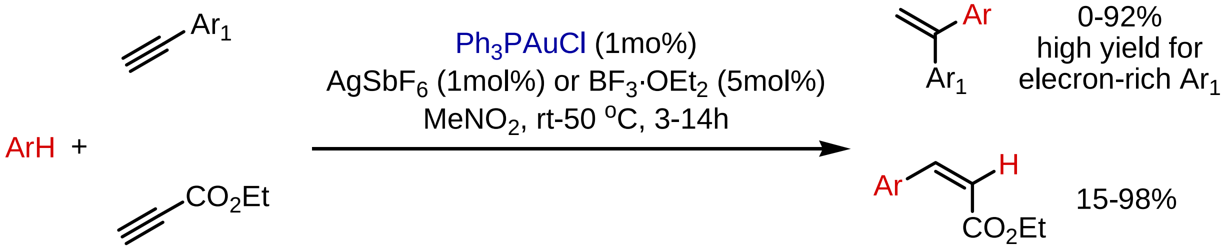




Yasutake *J. Chem. Soc. Dalton Trans.* **2001**, 2330

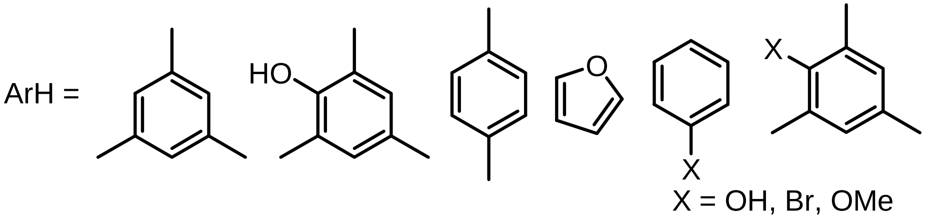
-Reetz reported A-catalyzed hydroarylation of unactivated ane electron-defficient alkynes

Reetz *EJOC* **2003**, 3485



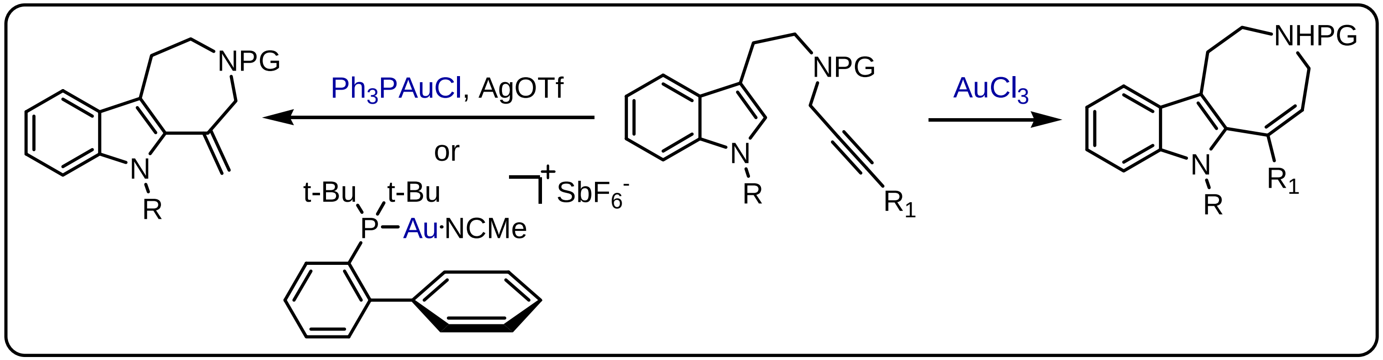
Inter and intramolecular catalytic addition of electron-rich arenes to electron-deficient alkynes using $AuCl_3/AgOTf$ has also been reported

JOC **2004**, *69*, 3669

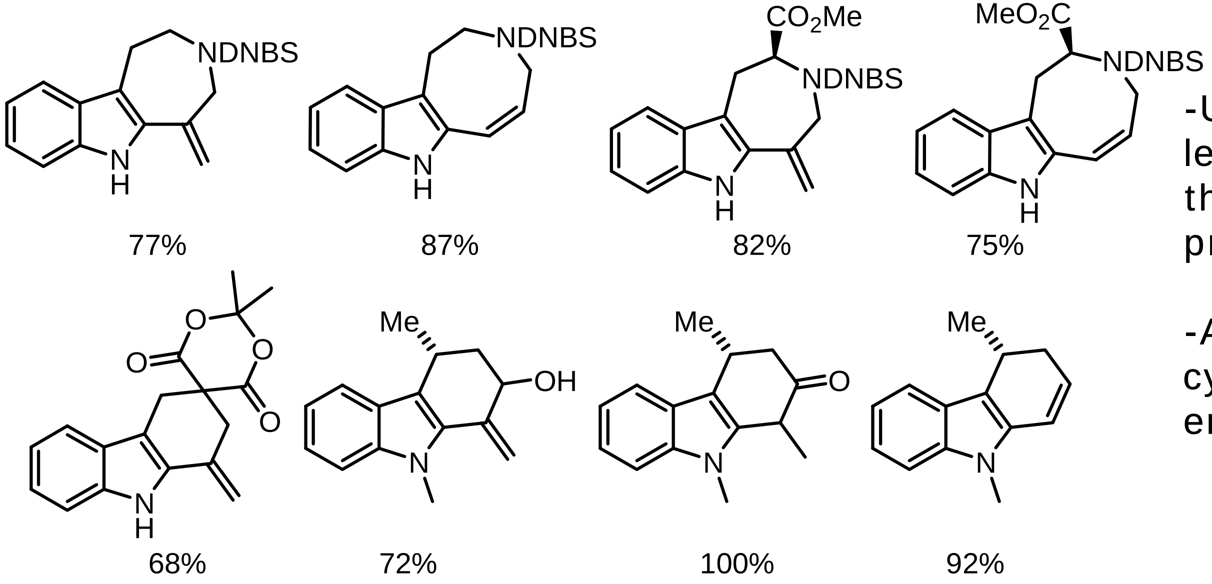


Ar_1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

Activation of Indole CH Bonds



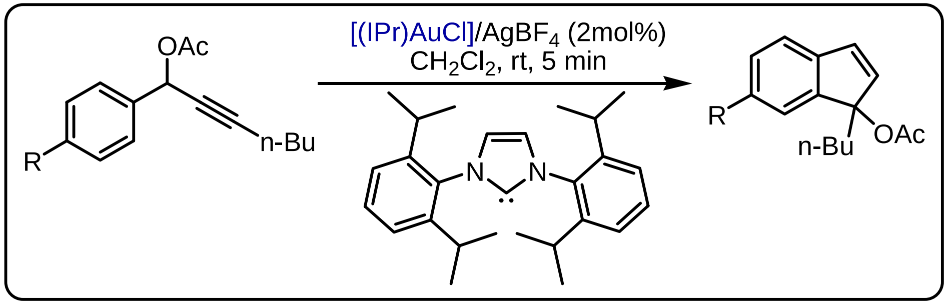
Echavarren *ACIEE* **2006**, *45*, 1105

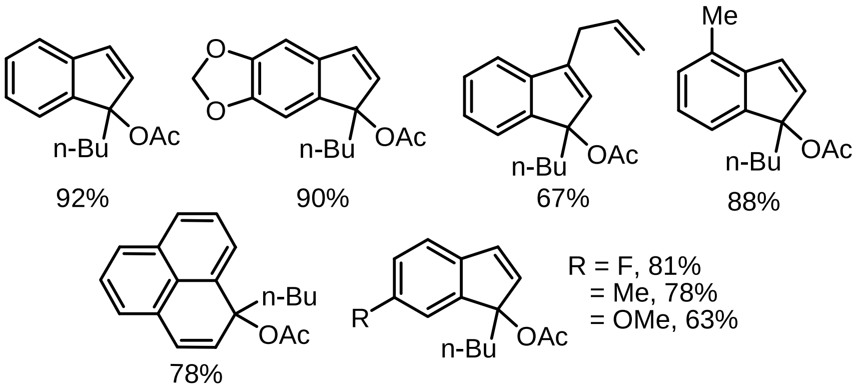


-Use of more electrophilic AuCl$_3$ leads to formation of thermodynamically less stable products

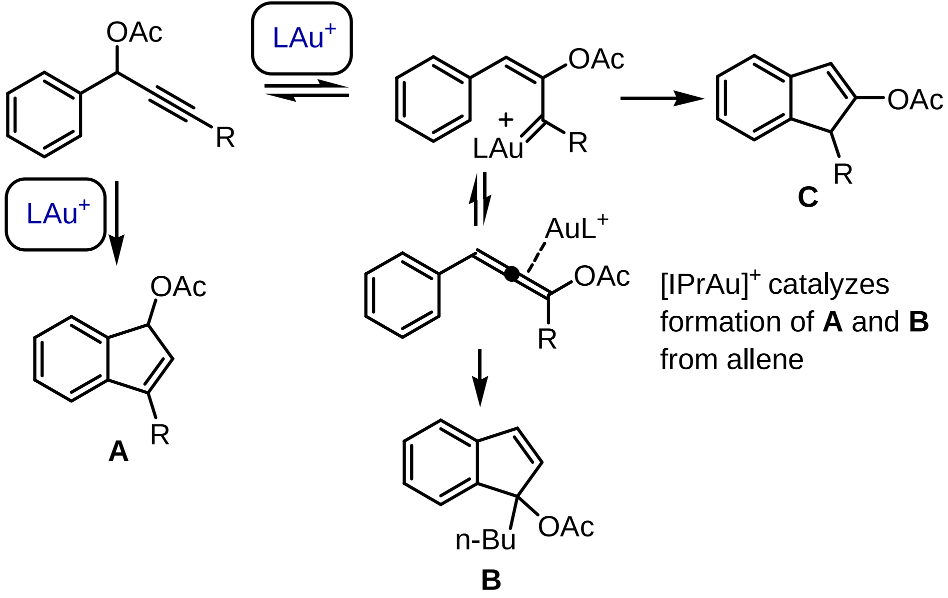
-Alkenylation via Friedel-Crafts cyclopropyl carbene mechanism are energetically accessible pathways
Chem. Eur. J. **2005**, *11*, 3155

Au-Catalyzed CH Activation



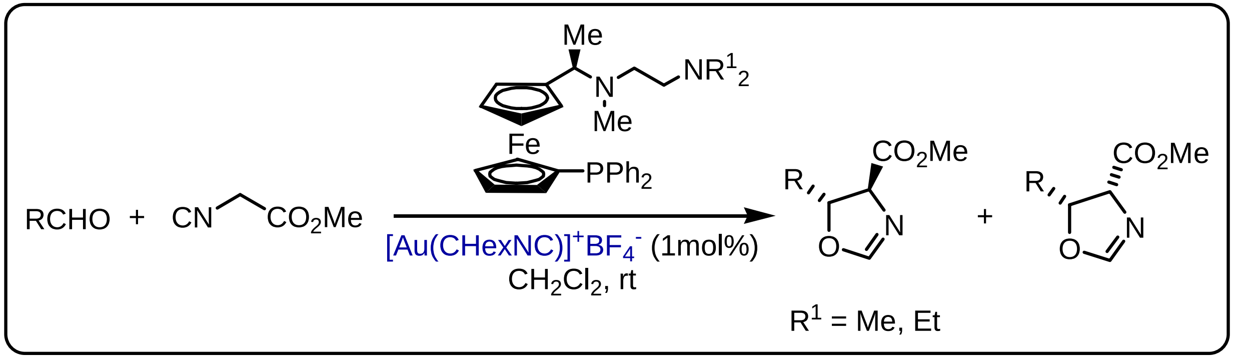


Nolan *ACIEE* **2006**, *45*, 3647



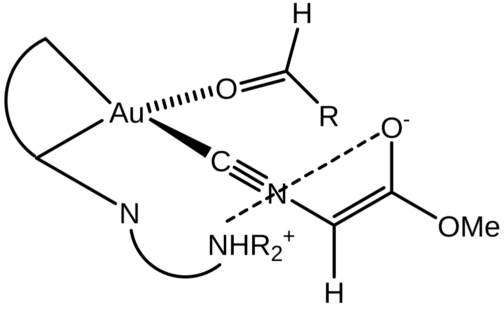
[IPrAu]$^+$ catalyzes formation of **A** and **B** from allene

Catalytic Enantioselective Reactions of Au



91-100%
81-96%ee

Plausible TS



Hayashi *JACS* **1986**, *108*, 6406

Summary

High binding of gold to alkyne promotes various skeletal rearrangement reactions.

Gold shows low tendency to undergo “classical” 2-electron redox reactions and both Au(I) and Au(III) show similar reactivity.

Unlike many transition metals, gold in its common oxidation states shows low propensity for hydride elimination. However, typically for the late transition metals (XI, XII), easy protodemetallation is often observed.

In the presence of hard nucleophiles, gold acts as soft Lewis acid.