

DAE Group Meeting

Au(I) and Au(III) Catalyzed Reactions by Activation of C-C multiple bonds

November 2, 2007

Hyun-Ji Song



Selected Reviews :

- 1) Toste, *Nature* **2007**, 446, 395-403.
- 2) Hashmi, *CR* **2007**, 107, 3180-3211.
- 3) Fürstner, *ACIE* **2007**, 46, 3410-3449.
- 4) Hashmi & Hutchings, *ACIE* **2006**, 45, 7896-7936.

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I. Introduction

II. Activation of Alkynes

III. Activation of Allenes

IV. Activation of Alkenes

V. Summary

Relativistic Effects

-Acidity of Au

Coordination Chemistry of Au

Advantages of Au catalysts

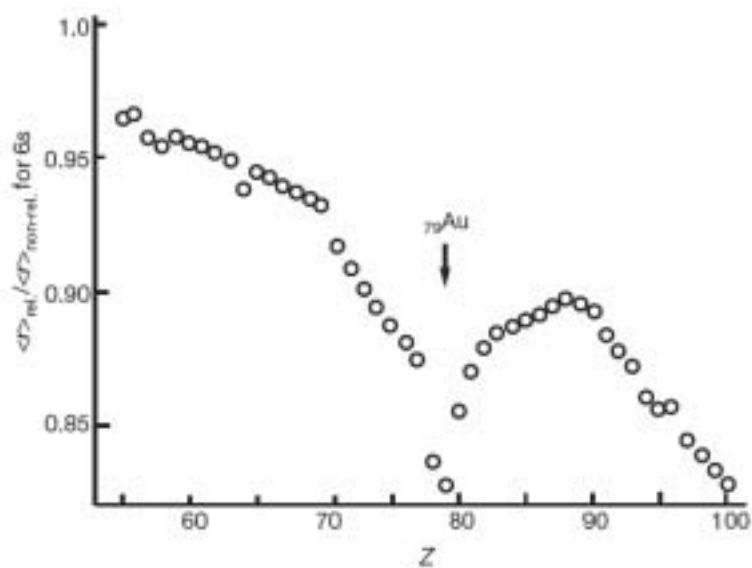
General Features of Gold Catalysis

- In aqueous solution, without stabilizing ligands, Au(I) **disproportionates** to Au(III) and Au(0) spontaneously.
- **Maximum relativistic effect** : Au(I) smaller than Ag(I) in complex.
- ^{79}Au has **only one isotope** and thus lacks a characteristic isotope pattern in MS.
- The nuclear spin of Au is $3/2$, but because of a very low sensitivity and a quadrupole moment, only a few ^{79}Au NMR spectra in an highly symmetric environment have been reported.
- The **diamagnetic** character of both Au(I) and Au(III) conveniently allows the monitoring of catalysis reactions by NMR.

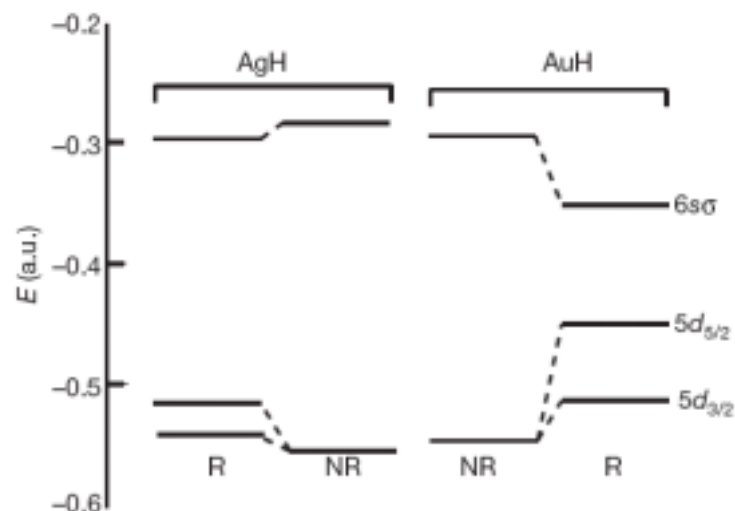
Hashmi, *CR* **2007**, *107*, 3180-3211. and references therein.

Relativistic Effects

- any phenomenon resulting from the need to consider velocity (v) as significant relative to the speed of light (c). $m_r = m_o / [1 - (v/c)^2]$ (m = mass)
- The relativistic **contraction of the s and p orbitals** effectively shields the electrons occupying the d and f orbitals, thus **more diffused d and f orbitals**.



Calculated relativistic contraction of the 6s orbital
(Pt, Au and Hg are markedly influenced)



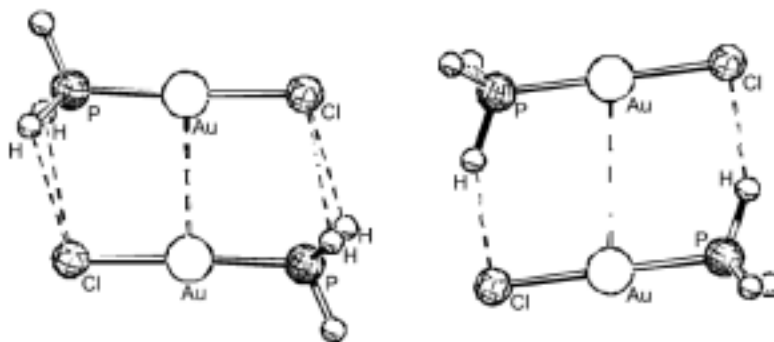
Comparison of AuH and AgH bond energies
R : relativistic , NR : non-relativistic

Toste, *Nature* **2007**, 446, 395-403.
Pyykkö, *ACR* **1979**, 12, 276-281.

Result of Relativistic Effects

Case Study on Au

- The relativistic contraction of 6s orbital results in **greatly strengthened Au-L**.
- **Aurophilicity** : the tendency of Au-Au interactions, on the order of H-bonding.



- **Redox Stability** : The high held Au 5d orbital resulting in less nucleophilic organo-Au(I) species that do not tend to undergo oxidative addition. Also reductive elimination from $LR_3Au(III)$ complexes has been shown disfavored as well. This is consistent with the broadly observed reactivity of Au(I) and Au(III) complexes, which do not readily cycle between oxidation states.

Toste, *Nature* **2007**, 446, 395-403. and references therein.

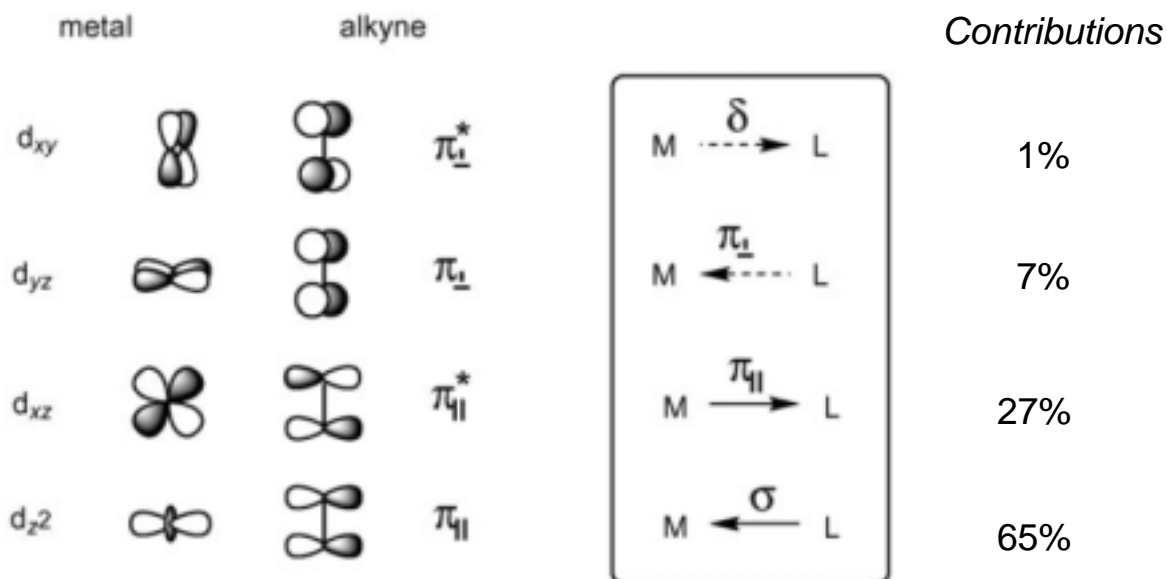
-Acidity of Au

- Relativistic contraction of valence 6s and 6p orbitals : **Low-lying LUMO**, thus strong Lewis acidity and **high electronegativity** (2.4, highest among metal)
- As a large diffuse cation, Au(I) is **soft Lewis acid**, preferentially activating 'soft' Lewis base such as π -system. Compared with Au(I), hard Au(III) exhibits a thermodynamic preference for ketone moiety coordination over alkyne coordination by 21.3 kJ/mol while also being capable of catalysing reaction through alkyne-activation pathways.
- **Au⁺-ethylene** vs **Au⁺-ethyne** : the Au⁺-ethylene complex is more stable by ~10 kcal/mol . The apparent Au(I) selectivity for alkyne over the other π systems may be due to lower LUMO of the Au-alkyne complex for the addition of a nucleophile than an analogous Au-alkene complex.

Toste, *Nature* **2007**, 446, 395-403. and references therein.

FMO Interactions of Au- Complex

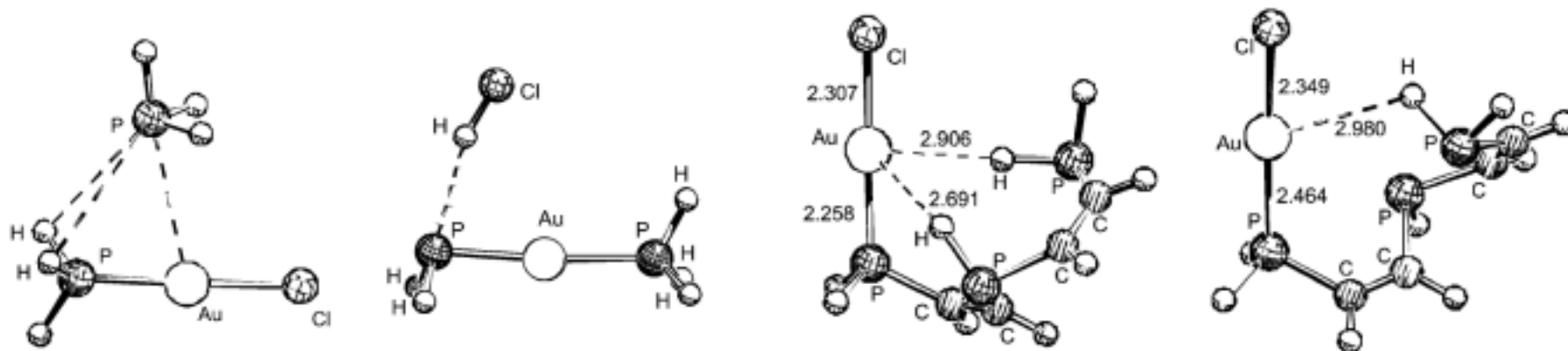
- Alkynes (as well as alkenes) are strong two-electron donors but fairly weak acceptors toward Au(I). This **larger loss of π -electron density** than the gain through back-bonding makes the **Au- complexes** even **more electrophilic**.
- Computational analyses for $[M^+(C_2H_4)]$ and $[M^+(C_2H_2)]$ ($M = Cu, Ag, Au$) indicate that approximately half of the total bonding force is actually electrostatic in nature.



Fürstner, *ACIE* **2007**, 46, 3410-3449. and references therein.

Coordination Chemistry of Au

- Au(I) predominantly adopts a **linear, bicoordinate** geometry unlike the prevalence of tricoordinate and tetracoordinate Cu(I) and Ag(I) complexes.



- *The practical consequence :*

- 1) the general **need to abstract a ligand** from neutral bicoordinate Au(I) species to induce catalytic activity, by the abstraction of Cl⁻ from LAuCl by AgX or by the protonolysis of LAuCH₃ with acid
- 2) difficulty to chelate bidentate ligands to a single gold atom and thus **scarcity of effective chiral catalysis**

Füerstner, *ACIE* **2007**, 46, 3410-3449. and references therein.

Advantages of Au catalysts in Synthetic Applications

- **Price** : Au is **less expensive** than Pt, Pd, Rh and Ir. (the price of catalyst is often dominated by the ligand rather than by the metal)
- **Redox Stability** : the resistance toward oxidation or reduction eliminates the requirement for **reprocessing**.
- **Chemoselectivity** : **tolerance** to oxygen-bearing functional groups simplifies the wider synthetic routes and impart **step-economy** in the context of target-oriented synthesis.
- **Reaction Profile** : from simple starting materials to products of significantly increased **complexity**
- **Miscellaneous** : operationally safe, simple, and practical to perform, tolerance to both oxygen (**air-stable**) and acidic protons (**moisture-stable**)

I. Introduction

II. Activation of Alkynes

III. Activation of Allenes Nitrogen Nucleophiles : Hydroamination
Schmidt reaction

IV. Activation of Alkenes Oxygen Nucleophiles : Hydration
Hydroalkoxylation

V. Summary Carboalkoxylation
Carbonyl Oxygens

Sulfur Nucleophiles : Carbothiolation

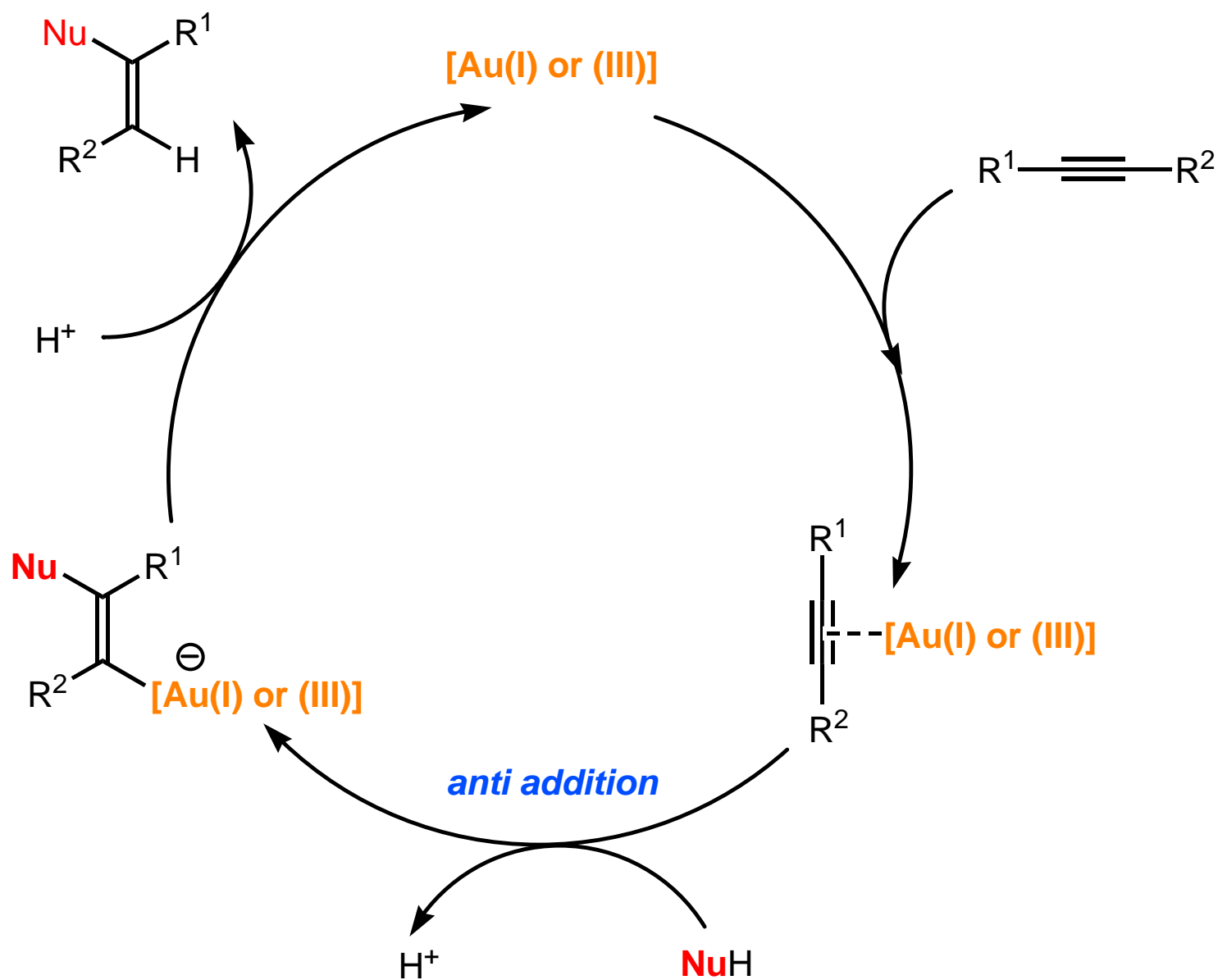
Carbon Nucleophiles : Enolates and Enolethers
Hydroarylation

Enyne Cycloisomerization : 1,6- and 1,5-Enynes

Propargyl Esters : 1,2- and 1,3-Migrations

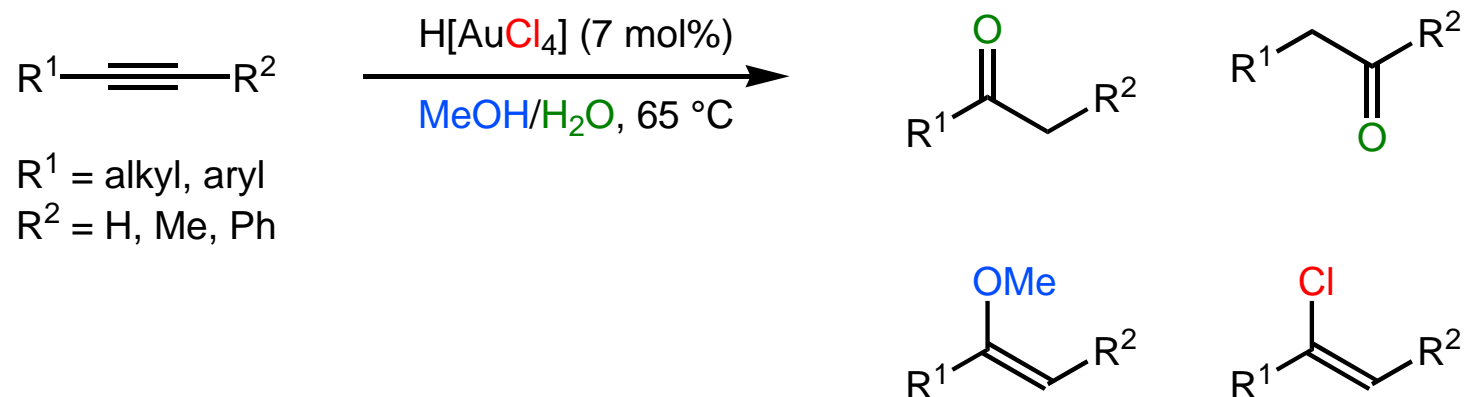
General Mechanism for the Simple Nucleophiles

Activation of Alkynes



Addition of Nucleophile

Early Studies



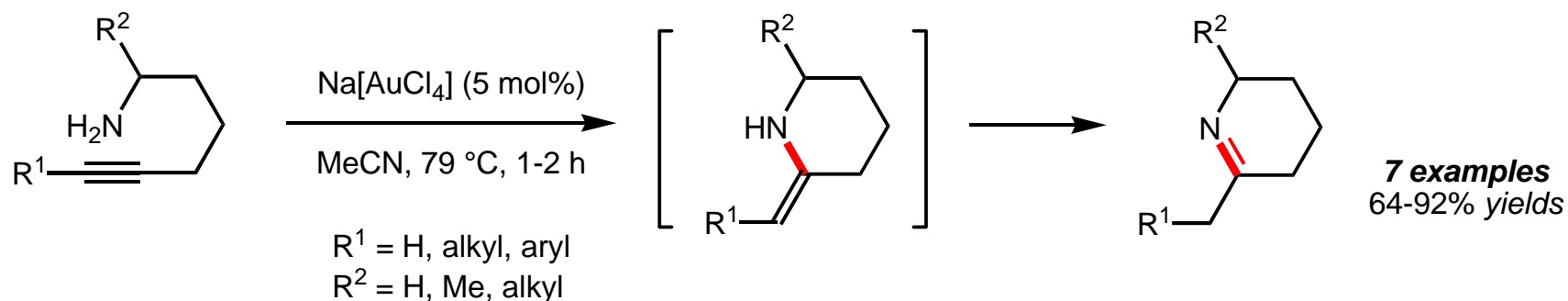
Markovnikov addition of H_2O : major product
 MeOH, Chloride addition : less than 5 % yields

Thomas *JCS PT 1*, **1976**, 1983.

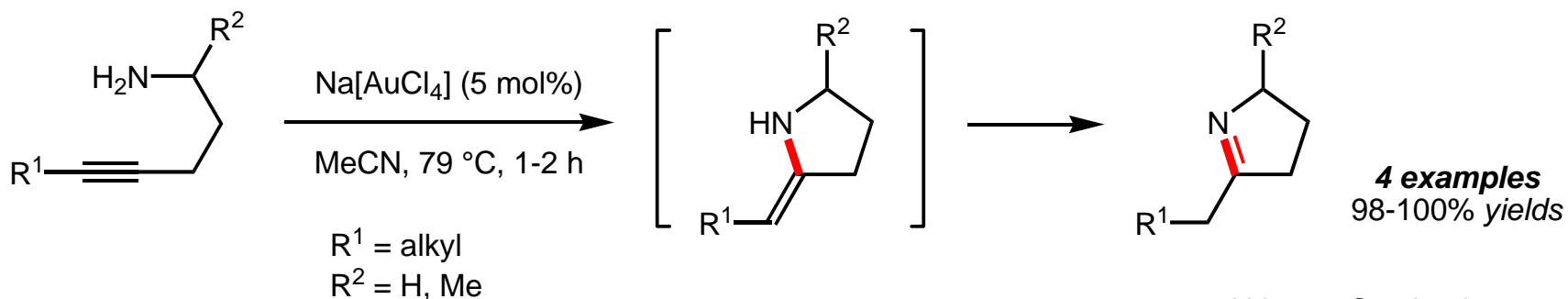


Hutchings *J. Cat.* **1985**, 96, 292.

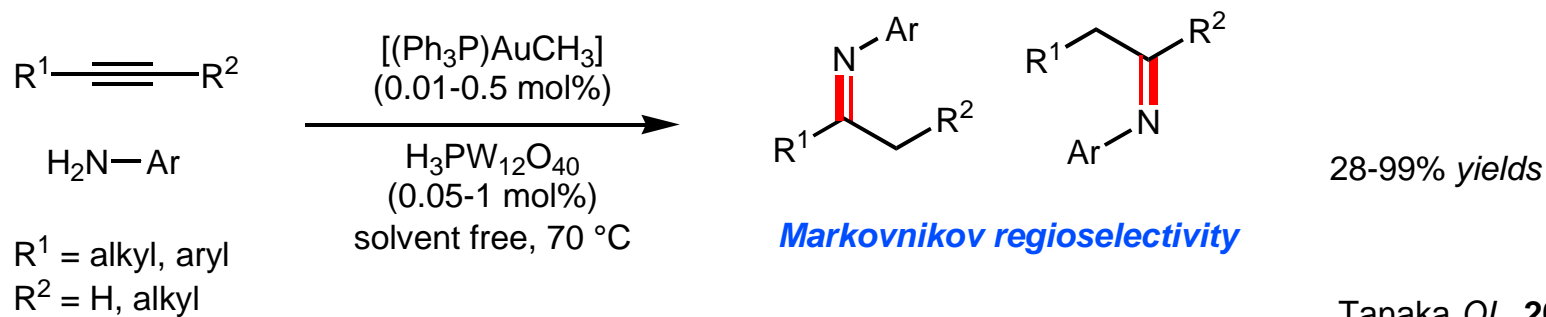
Intra- and Intermolecular Hydroamination



Utimoto *Heterocycles* **1987**, 25, 297.



Utimoto *Synthesis* **1991**, 975.

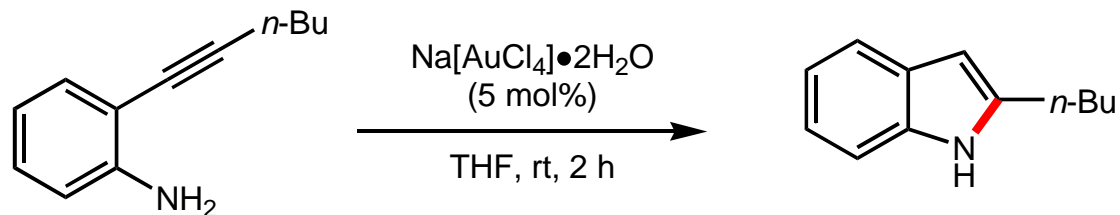


Markovnikov regioselectivity

Tanaka *OL* **2003**, 5, 3349.

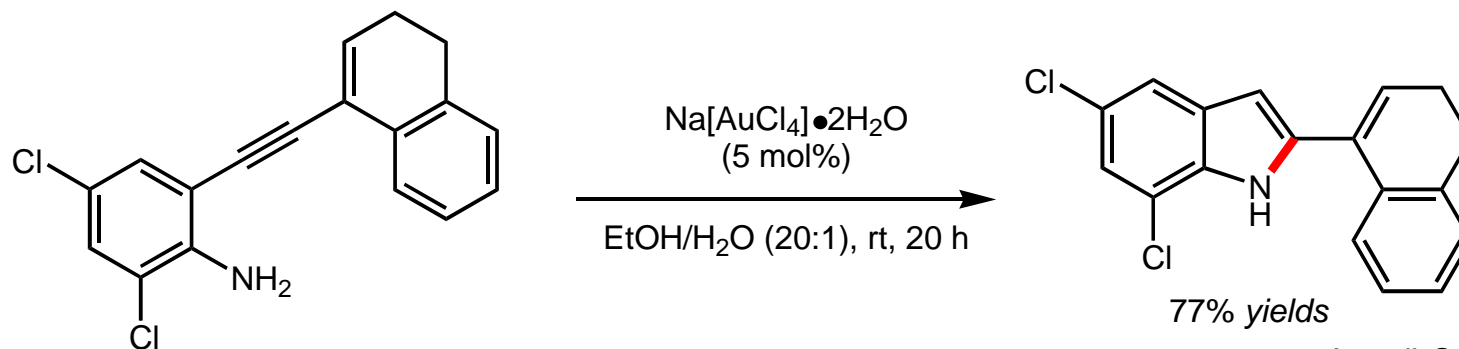
Intramolecular Hydroamination : Indole and Pyrrole

Activation of Alkynes



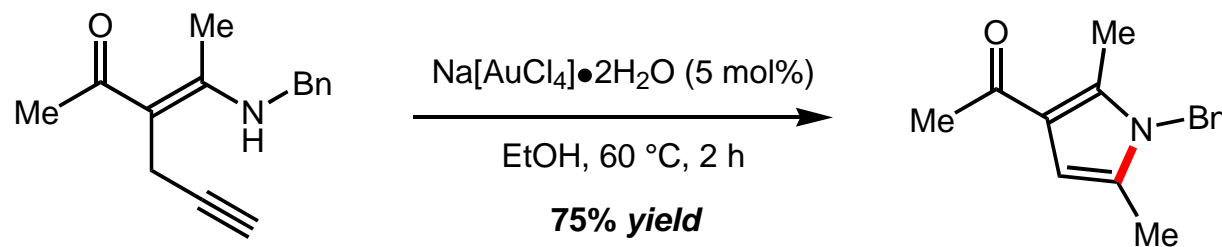
87% yields

Utimoto *TL* **1988**, 29, 1799.

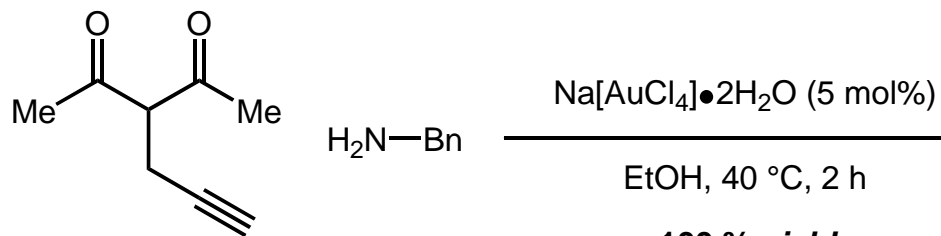


77% yields

Arcadi *Synthesis* **2004**, 610.



75% yield



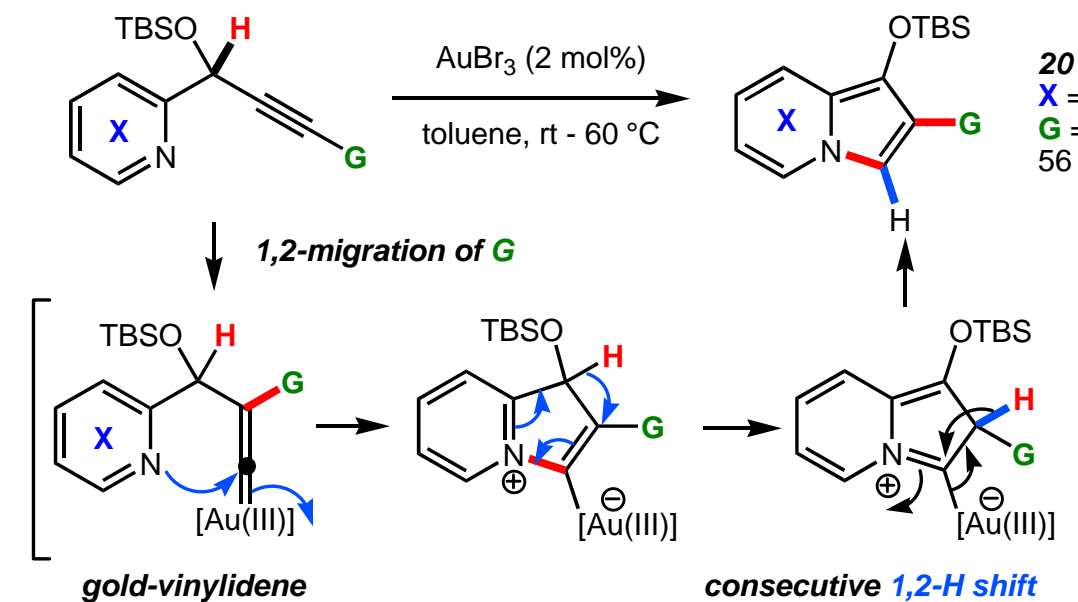
100 % yield

After the indole cyclization,
1) Au(III)-catalyzed intermolecular conjugate addition onto α,β -unsaturated ketones :
Arcadi *JOC* **2005**, 70, 2265.
2) Au(III)-catalyzed intermolecular addition onto terminal alkynes :
Li *OL* **2007**, 9, 627.

Arcadi *Adv. Synth. Catal.* **2001**, 343, 443.
Arcadi *T:A* **2001**, 12, 2715.

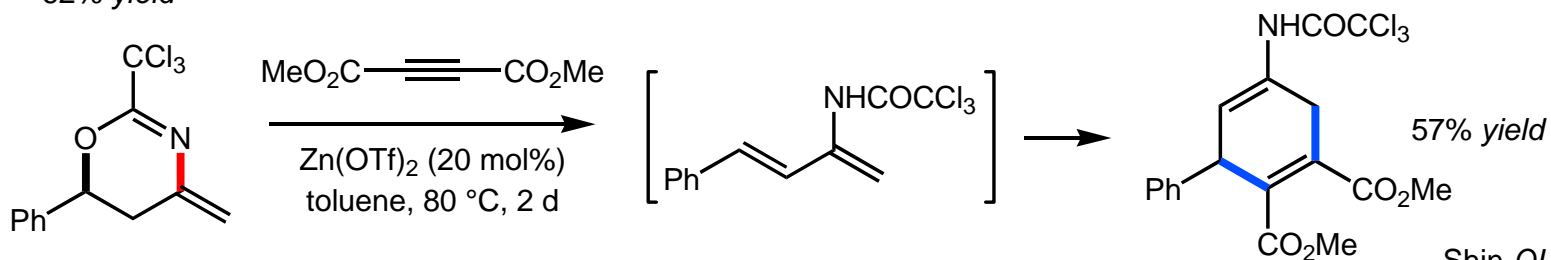
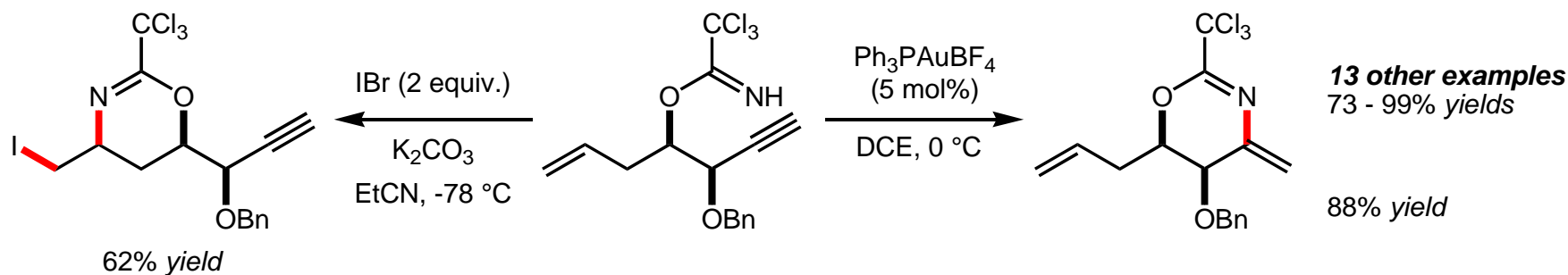
Intramolecular Hydroamination

Activation of Alkynes



Gevorgyan *JACS* **2006**, 128, 12050.

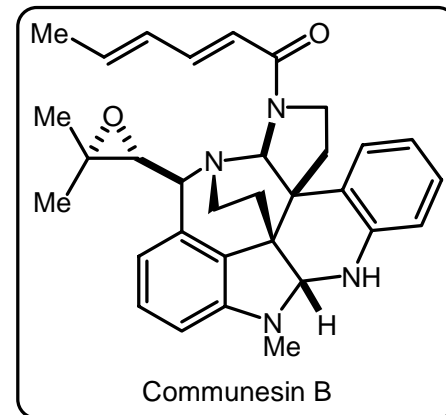
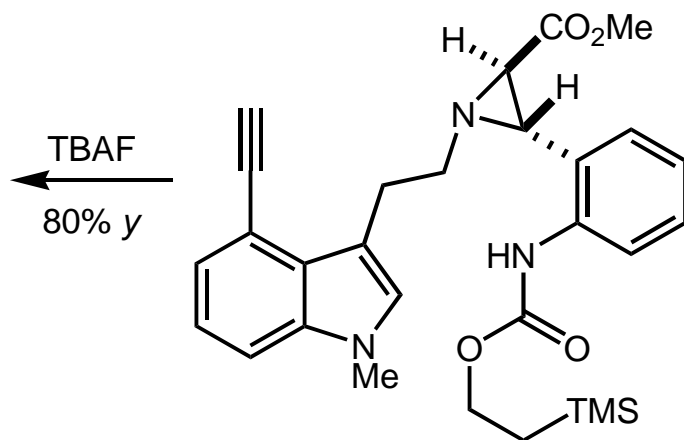
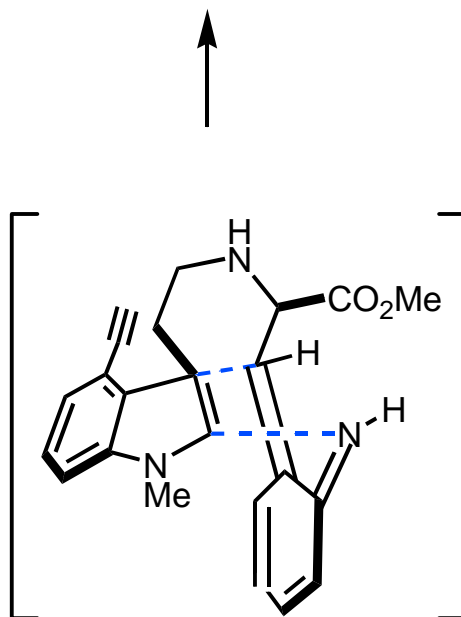
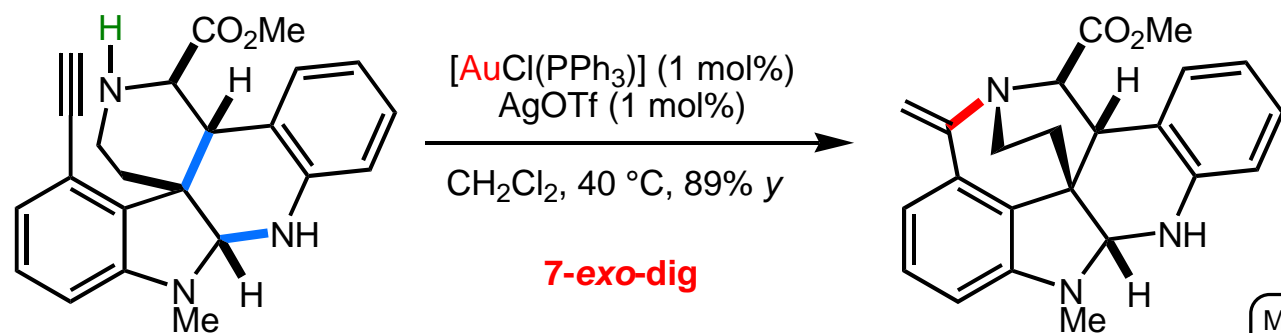
Au(III)-catalyzed three component coupling of aldehyde, amines and alkynes to aminoindolizines
Liu *OL* **2007**, 9, 4323.



Shin *OL* **2006**, 8, 3537.

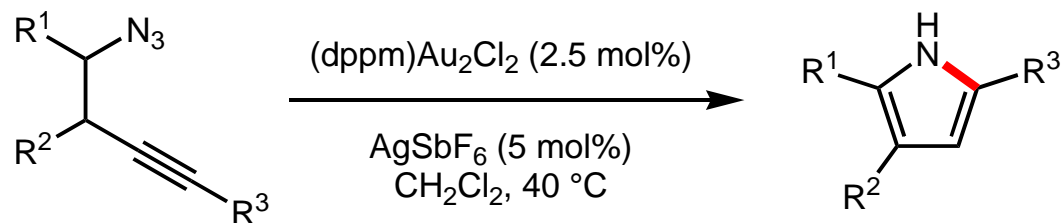
Application of Intramolecular Hydroamination *Communesin* (2006)

Activation of Alkynes



Intramolecular Acetylenic Schmidt Reaction

Activation of Alkynes

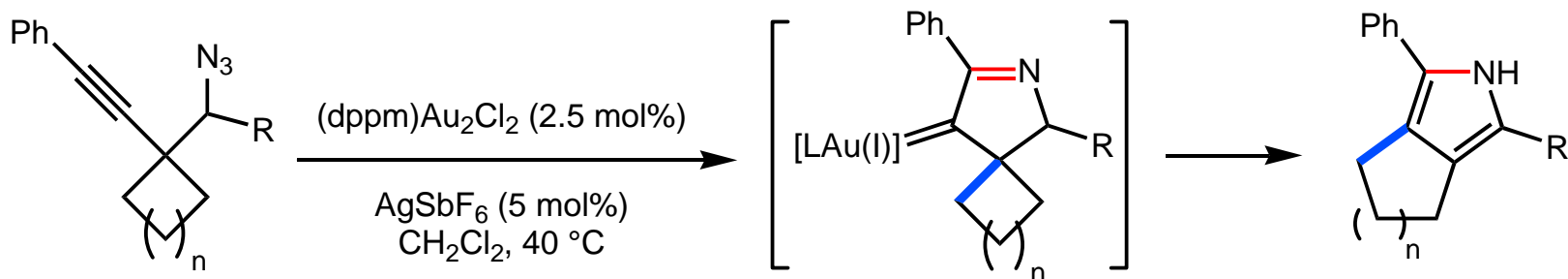
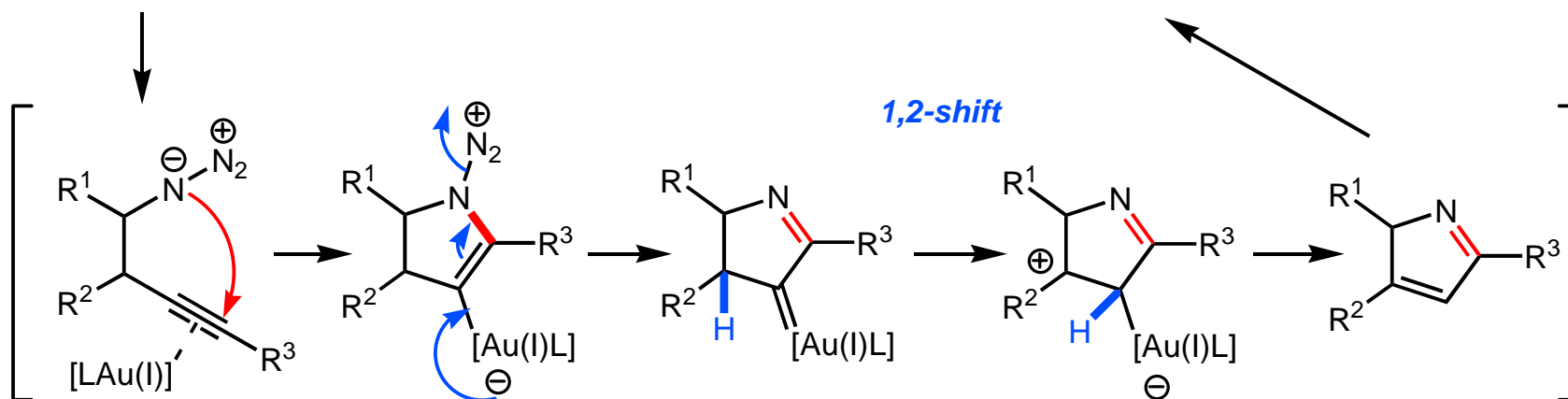


10 examples

$\text{R}^1 = \text{H}$, alkyl, cycle w/ R^2

$\text{R}^3 = \text{alkyl}$, aryl, furanyl, cyclopropyl

41-93% yields



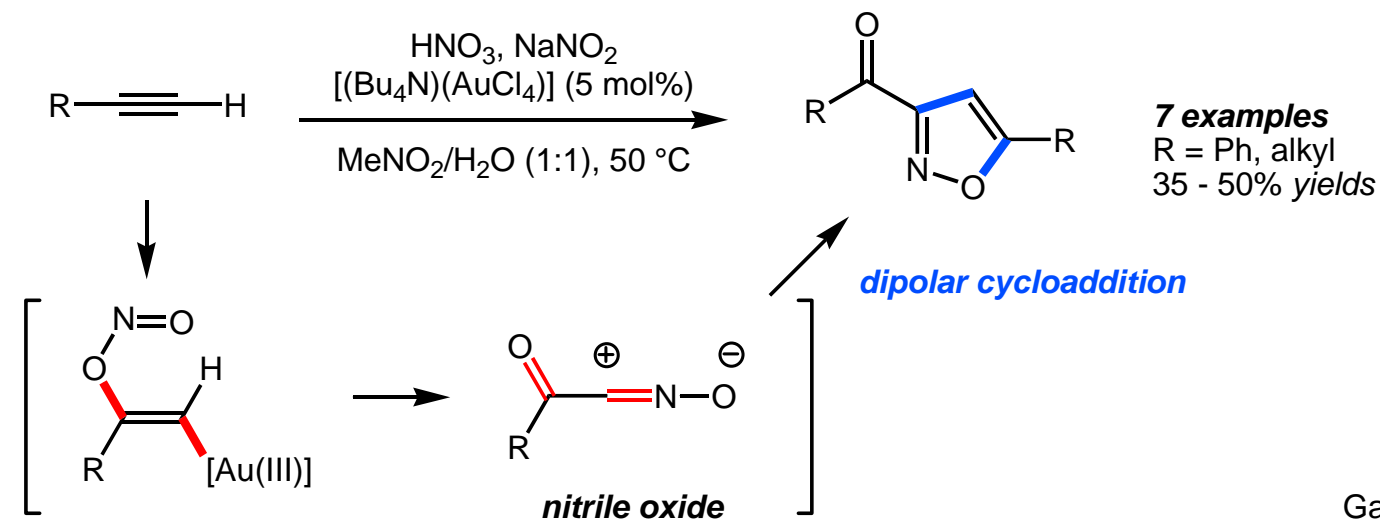
$n = 1$, $\text{R} = \text{H}$, 80% yield

$n = 2$, $\text{R} = \text{Ph}$, 84% yield

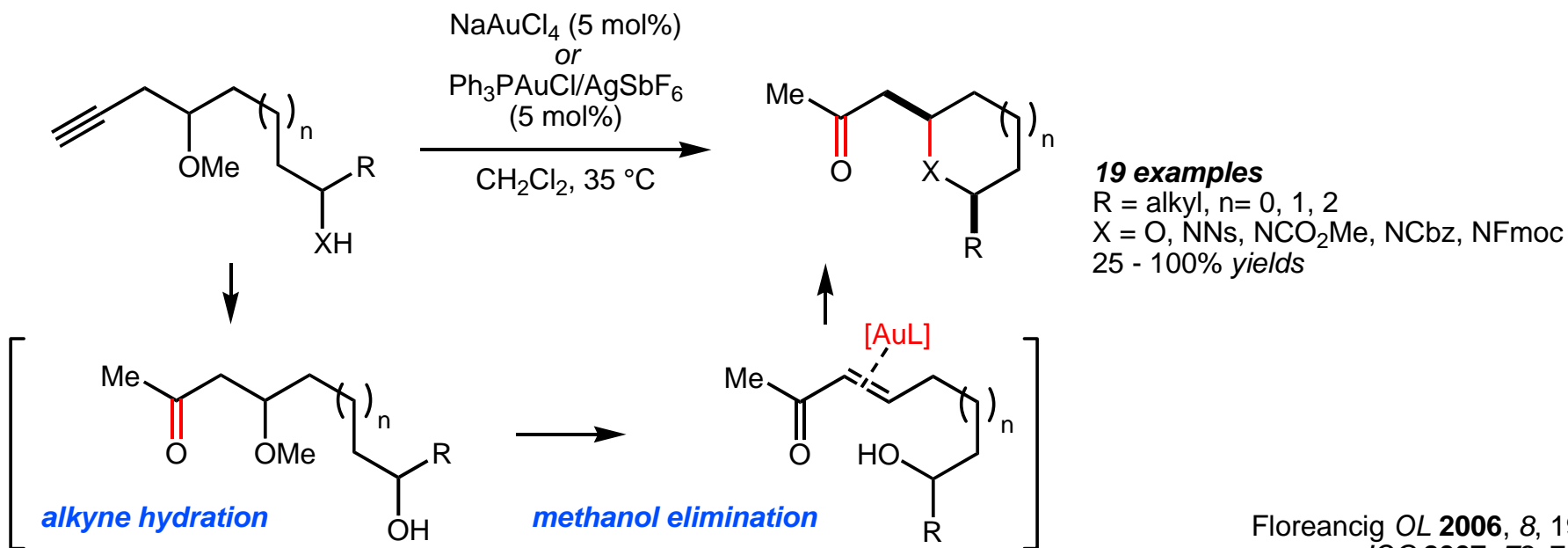
Toste *JACS* **2005**, 127, 11260.

Nirite and Water Addition onto Alkynes

Activation of Alkynes



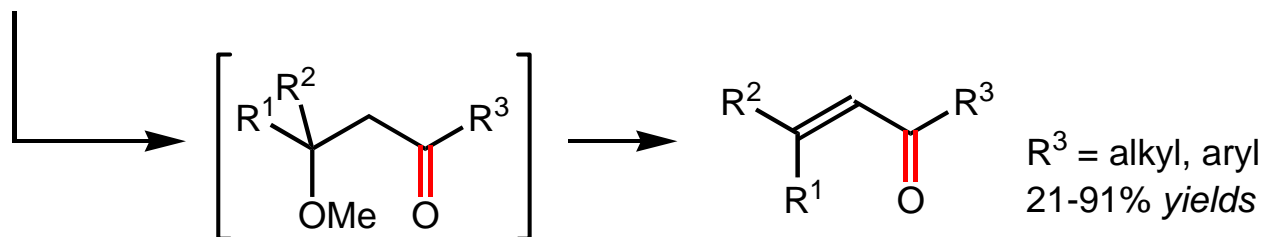
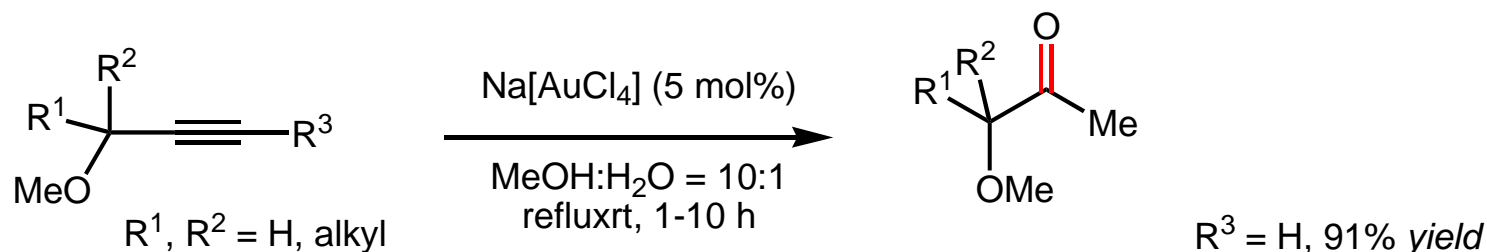
Gasparri JACS **1993**, 115, 4401.



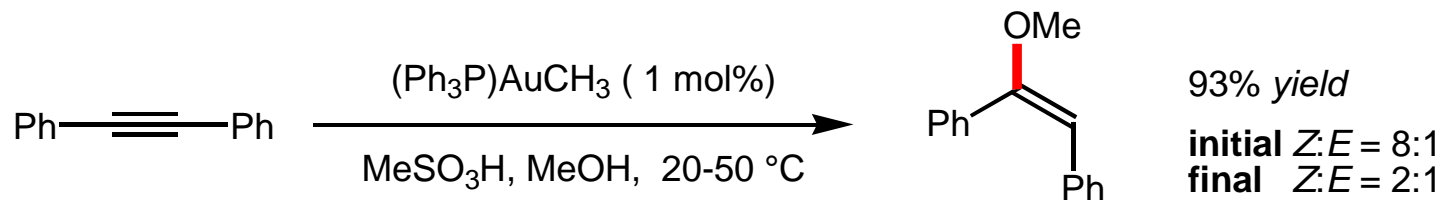
Floreancig OL **2006**, 8, 1949.
 JOC **2007**, 72, 7359.

Intermolecular Hydration and Hydroalkoxylation

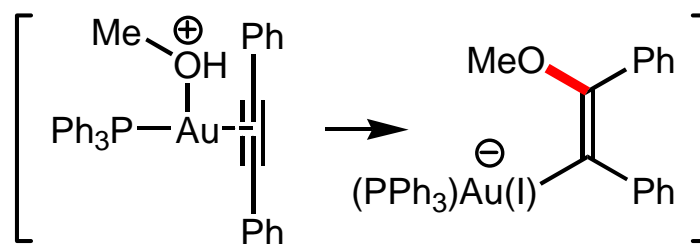
Activation of Alkynes



Utimoto *BCS Jp.* **1991**, 64, 2013.



syn oxyauration for the C-O bond-forming step



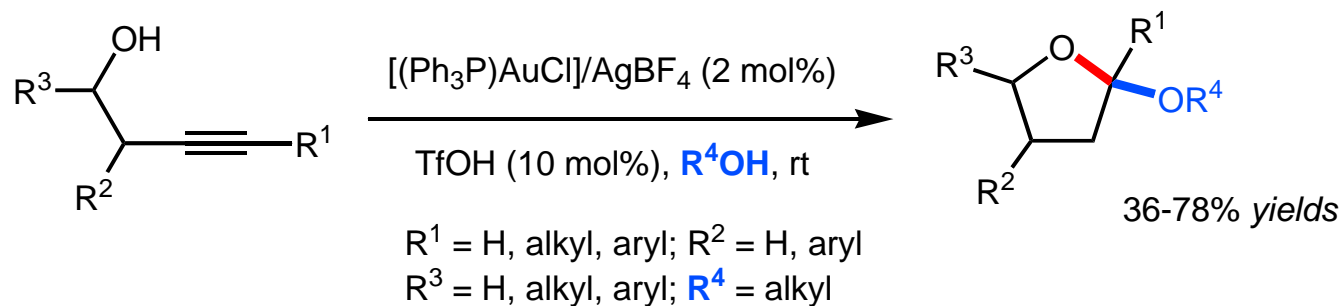
Teles *ACIE* **1998**, 37, 1415.

Intramolecular Hydroalkoxylation

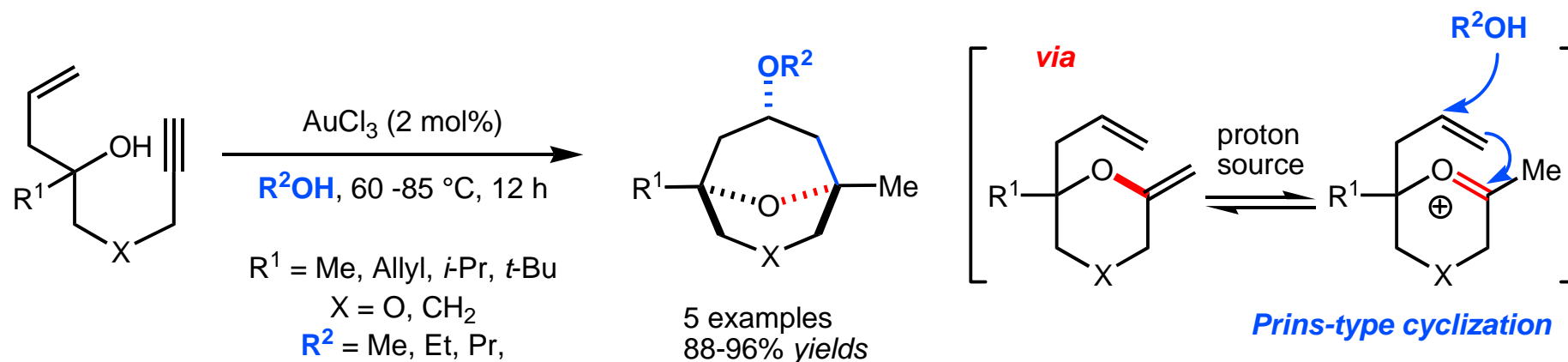
Activation of Alkynes



Genêt *JACS* **2005**, 127, 9976.



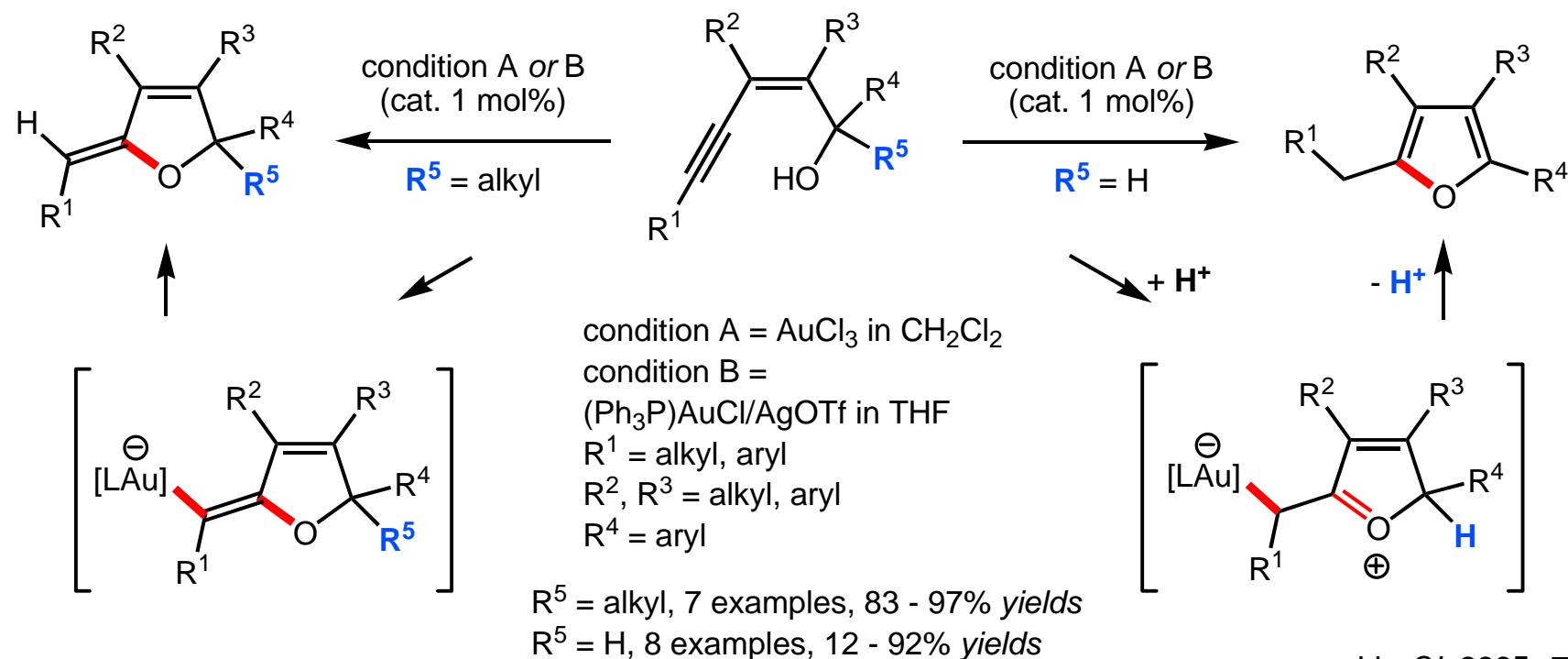
Krause *OL* **2006**, 8, 4489.



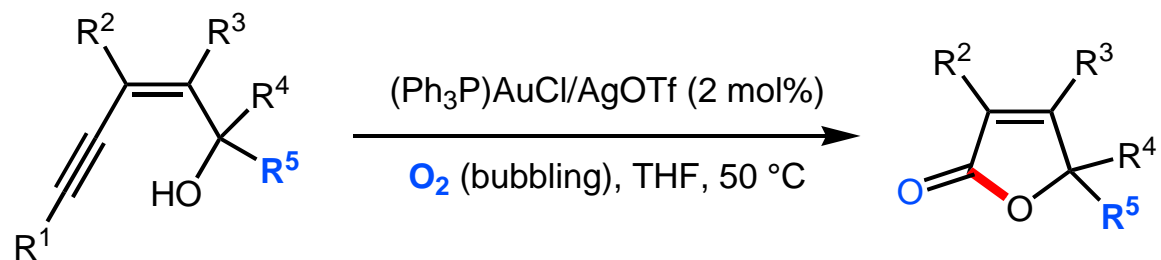
Barluenga *ACIE* **2006**, 45,2091.

Intramolecular Hydroalkoxylation

Activation of Alkynes



Liu *OL* **2005**, 7, 5409.



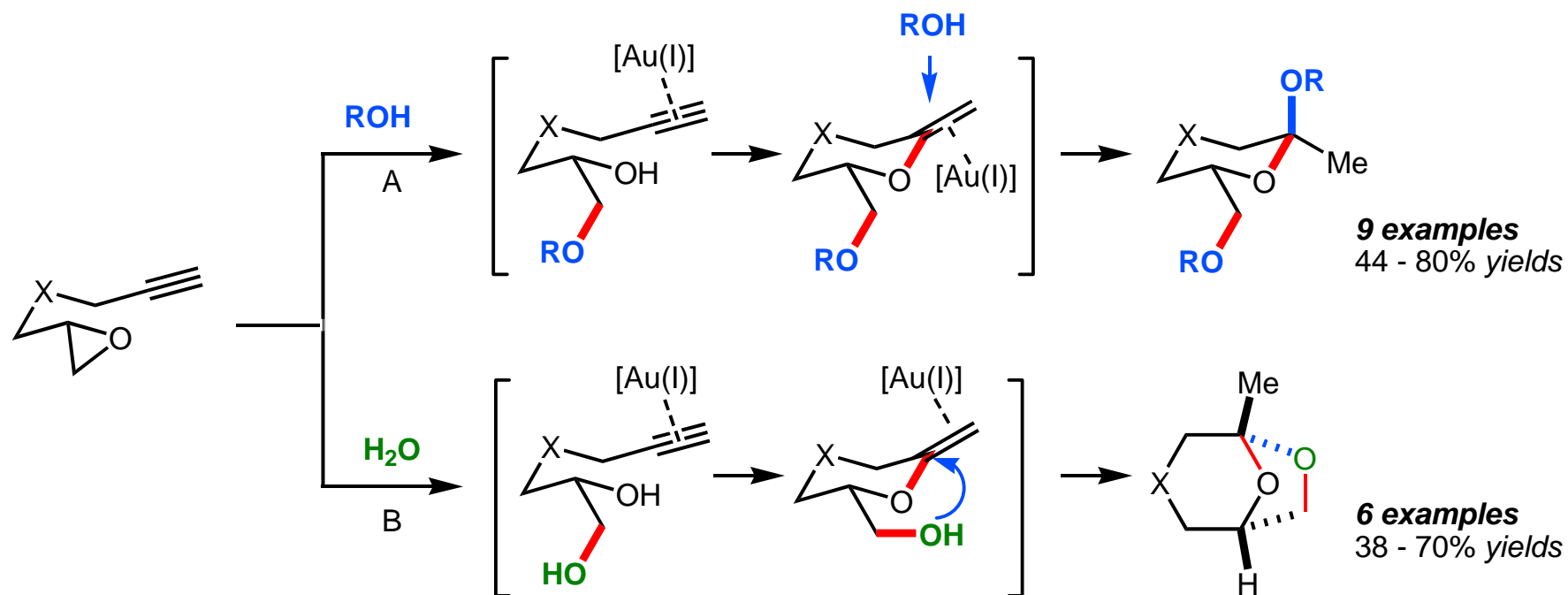
11 examples

$R^1 = \text{alkyl, aryl}$
 $R^2, R^3 = \text{alkyl, aryl}$
 $R^4, R^5 = \text{alkyl, aryl}$
 41 - 97% yields

Liu *JACS* **2006**, 128, 11332.

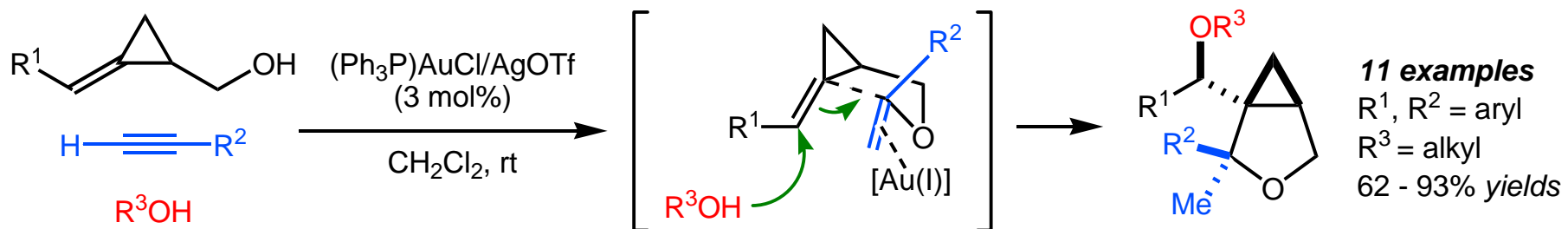
Inter and Intramolecular Hydroalkoxylation

Activation of Alkynes



condition A : (Ph₃P)AuCl/AgSbF₆ (5 mol%), ROH, *p*-TsOH, rt
 condition B : (Ph₃P)AuCl/AgSbF₆ (5 mol%), H₂O, DCE, rt

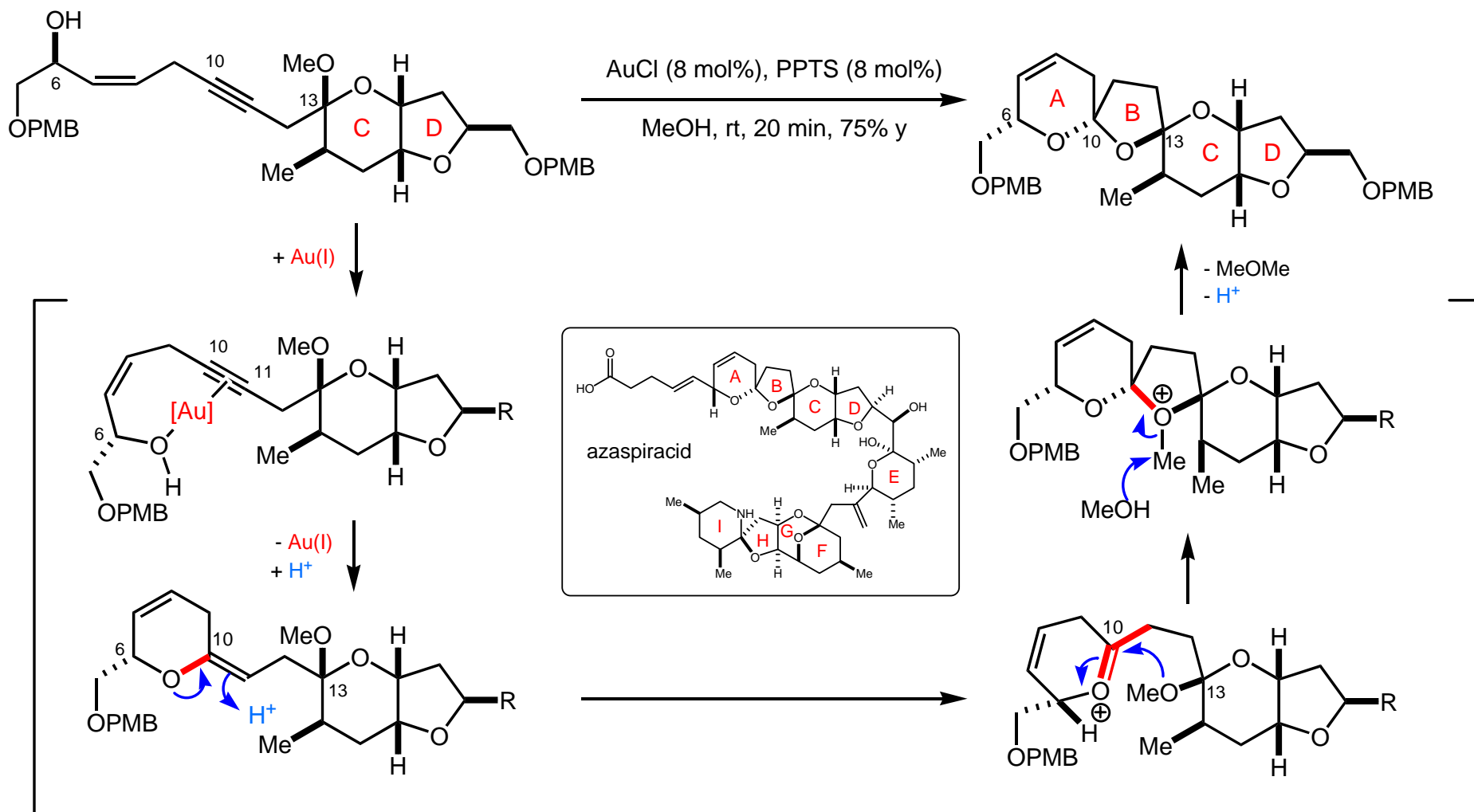
Shi *OL* **2007**, 9, 3191.



Shi *OL* **2007**, 9, ASAP.

Application of Intramolecular Hydroalkoxylation Azaspiracid (2007)

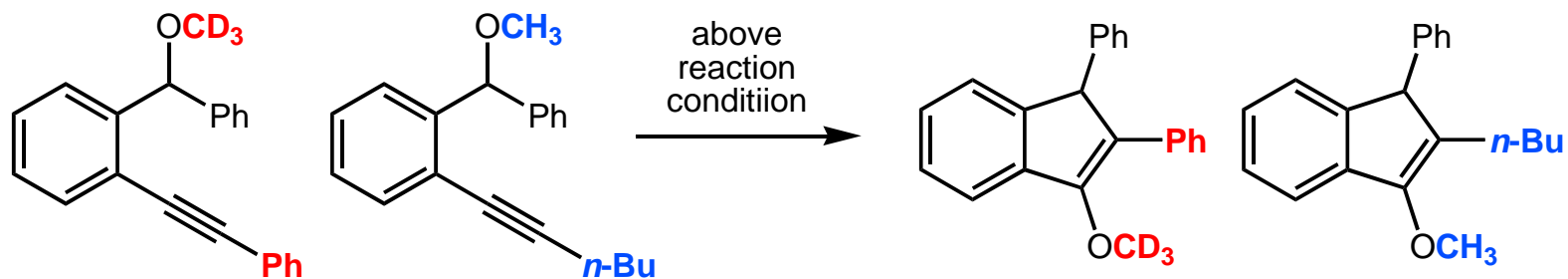
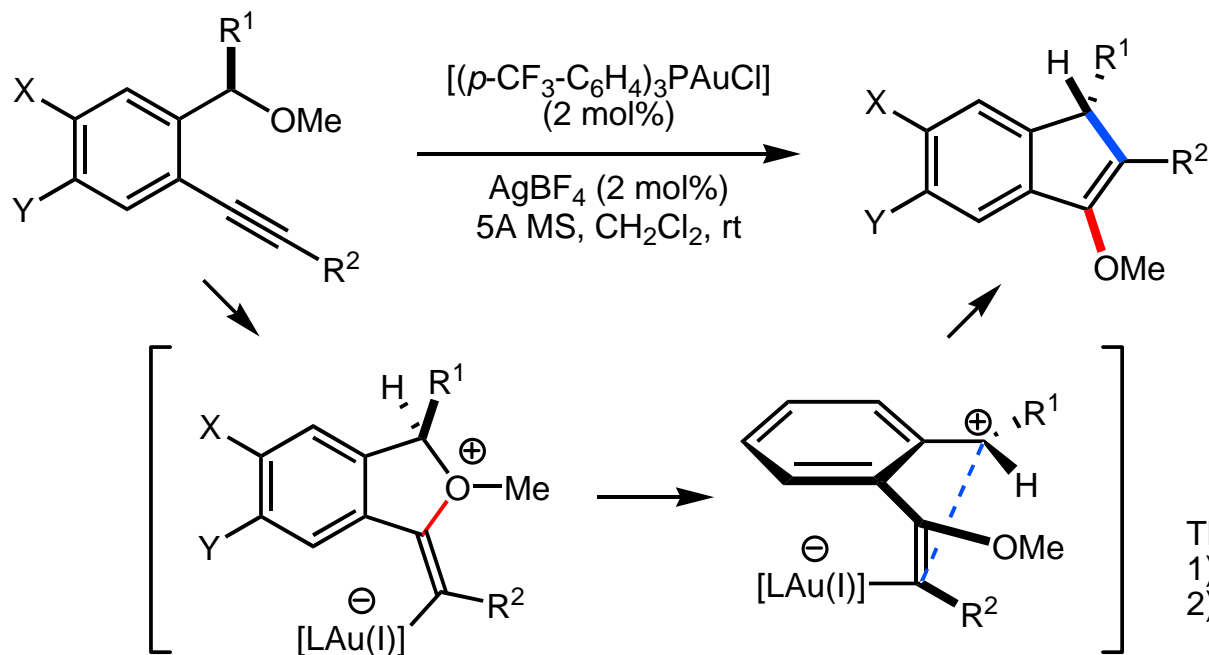
Activation of Alkynes



Forsyth *ACIE* **2007**, 46, 279.

Intramolecular Carboalkoxylation

Activation of Alkynes

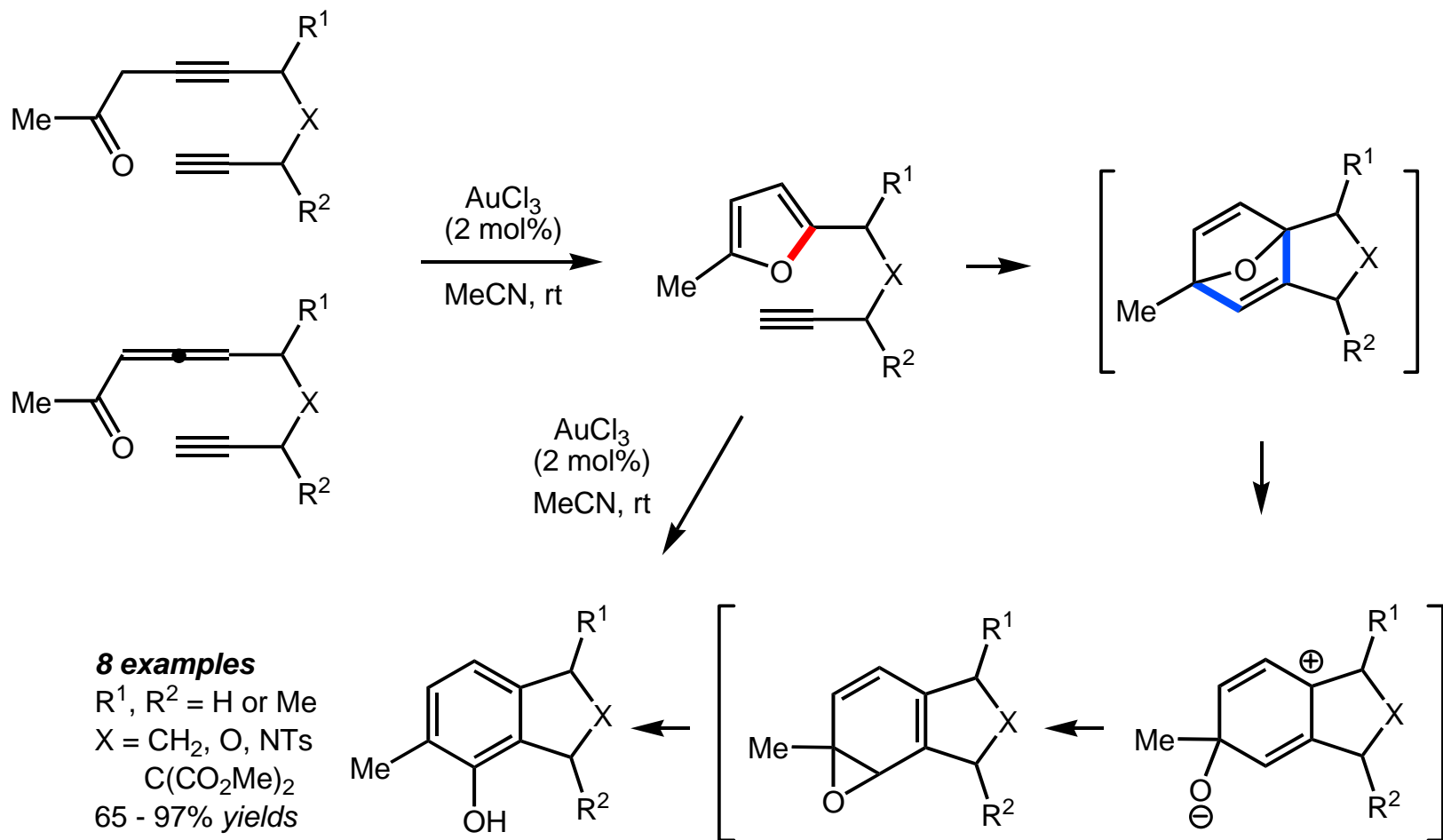


no crossover product observed

consistent with a mechanism involving alkyne activation rather than ionization of the benzylic ether

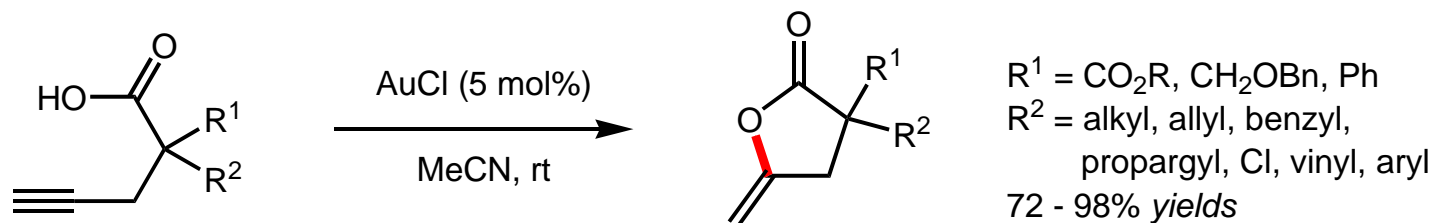
Carbonyl Oxygen as Nucleophile

Cycloaddition/Fragmentation Domino Reaction

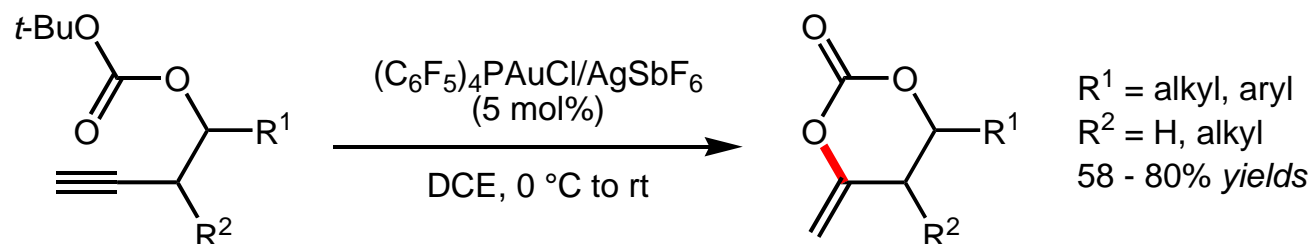
Hashmi *JACS* **2000**, 122, 11553.related follow-up study : Hashmi *ACIE*, **2004**, 43, 6545.

Carbonyl Oxygen as Nucleophile

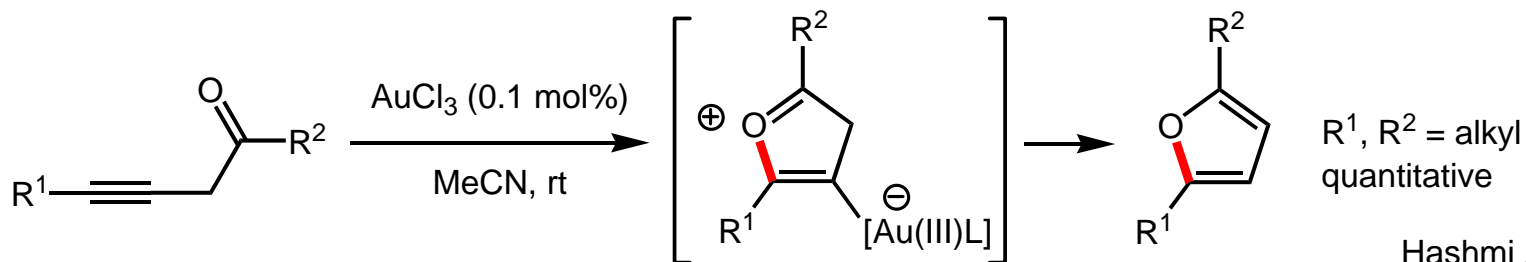
Activation of Alkynes



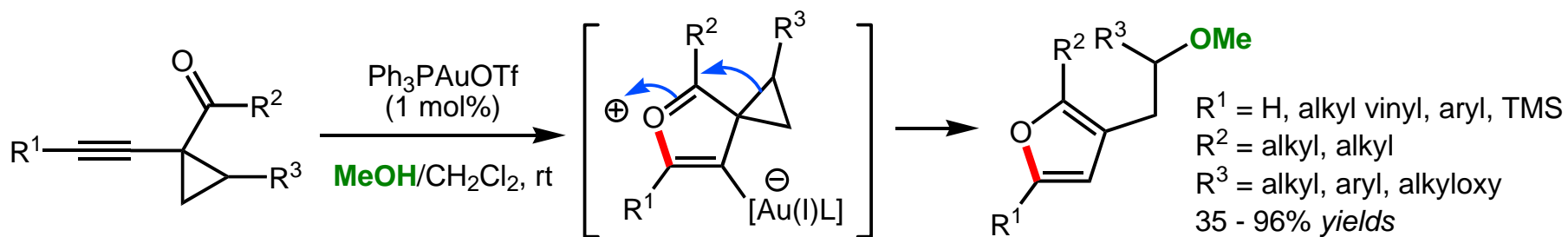
Genêt *JACS* **2006**, 128, 3112.



Shin *Synlett* **2006**, 717.
Gagosz *OL* **2006**, 8, 515.



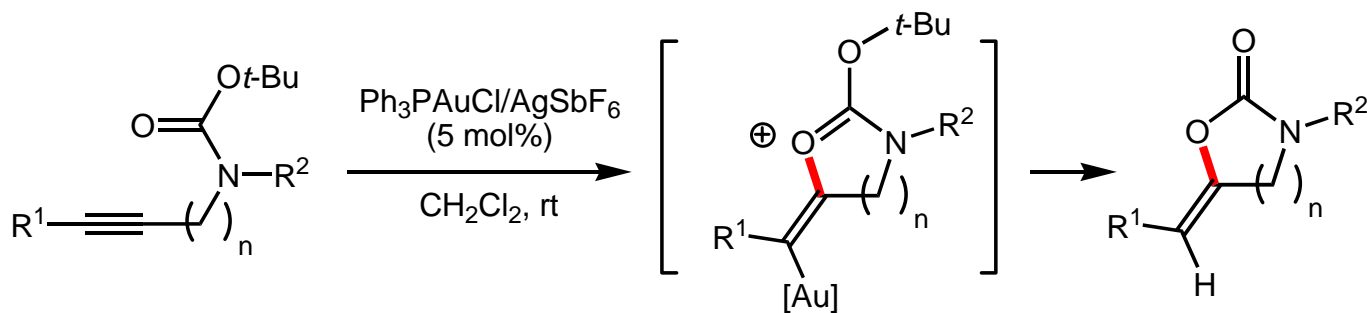
Hashmi *ACIE* **2000**, 39, 2285.



Schmalz *ACIE* **2006**, 45, 6704.

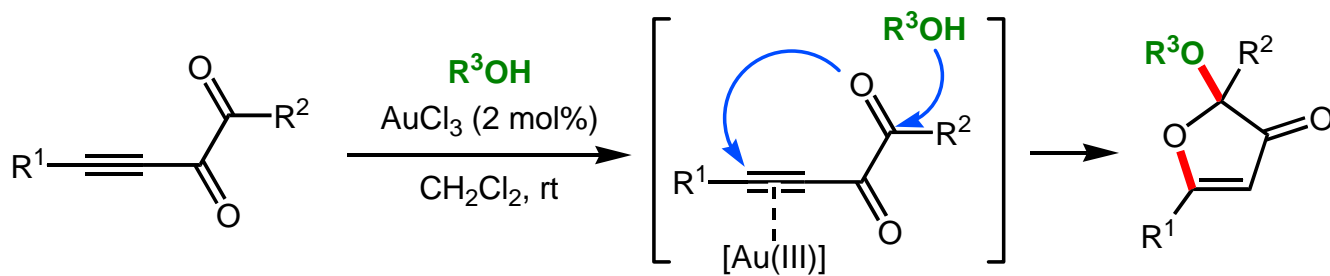
Carbonyl Oxygen as Nucleophile

Activation of Alkynes



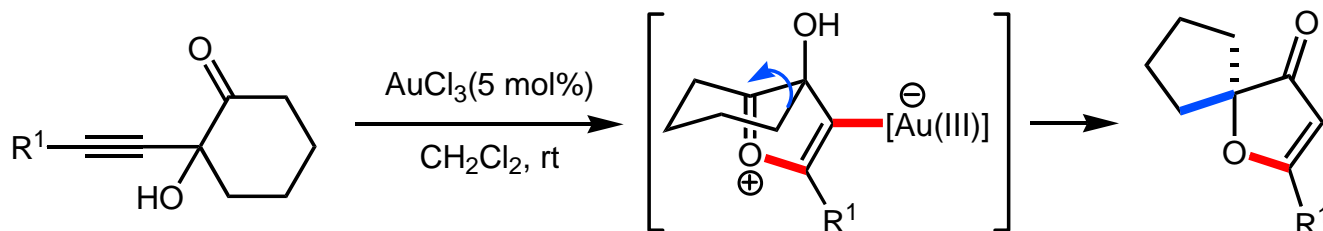
18 examples $n = 1, 2$
 $R^1 = \text{H, Me, Ph, CO}_2\text{Et}$
 $R^2 = \text{H, alkyl, aryl}$
69 - 95% yields

Adrio *JOC* **2006**, 71, 5023.



16 examples
 $R^1 = \text{alkyl, aryl}$
 $R^2 = \text{alkyl, alkynyl}$
 $R^3 = \text{Me, Et, Ph, } t\text{-Bu, } i\text{-Pr, allyl}$
42 - 88% yields

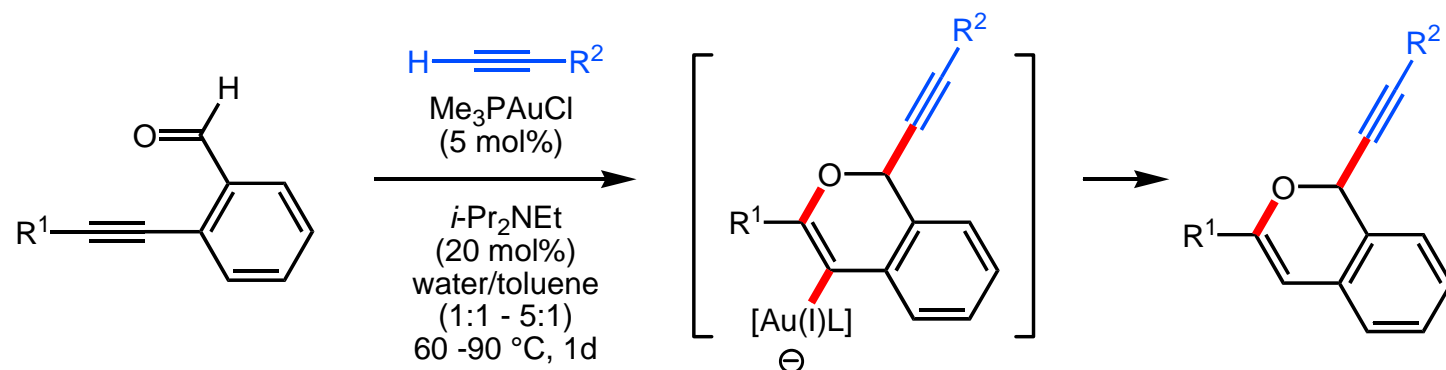
Liu *OL* **2006**, 8, 3445.



3 examples
 $R^1 = \text{aryl, alkyl}$
11 - 81% yields

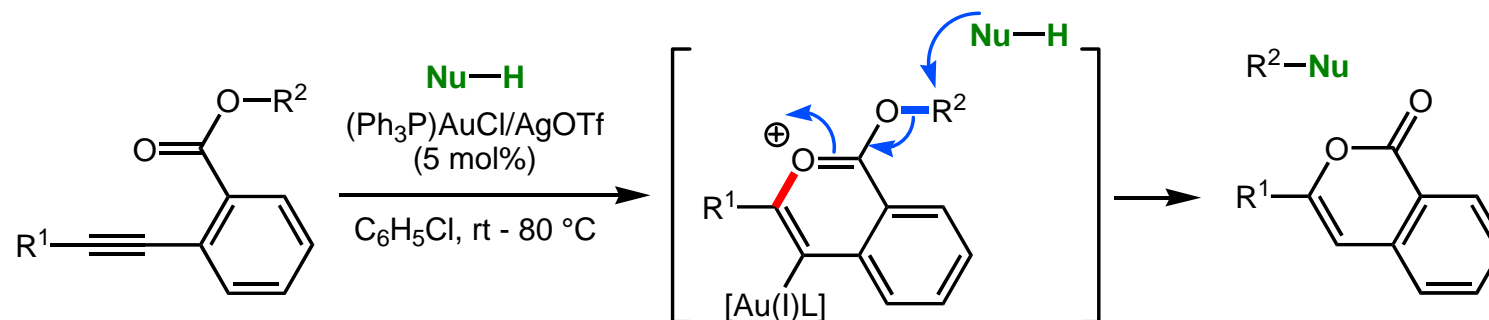
Kirsch *ACIE* **2006**, 45, 5878.

Carbonyl Oxygen as Nucleophile



15 examples
 $\text{R}^1 = \text{aryl, alkyl}$
 $\text{R}^2 = \text{aryl, alkyl}$
 16 - 89% yields

Li OL **2006**, 8, 1953.



as an efficient alkylating agent

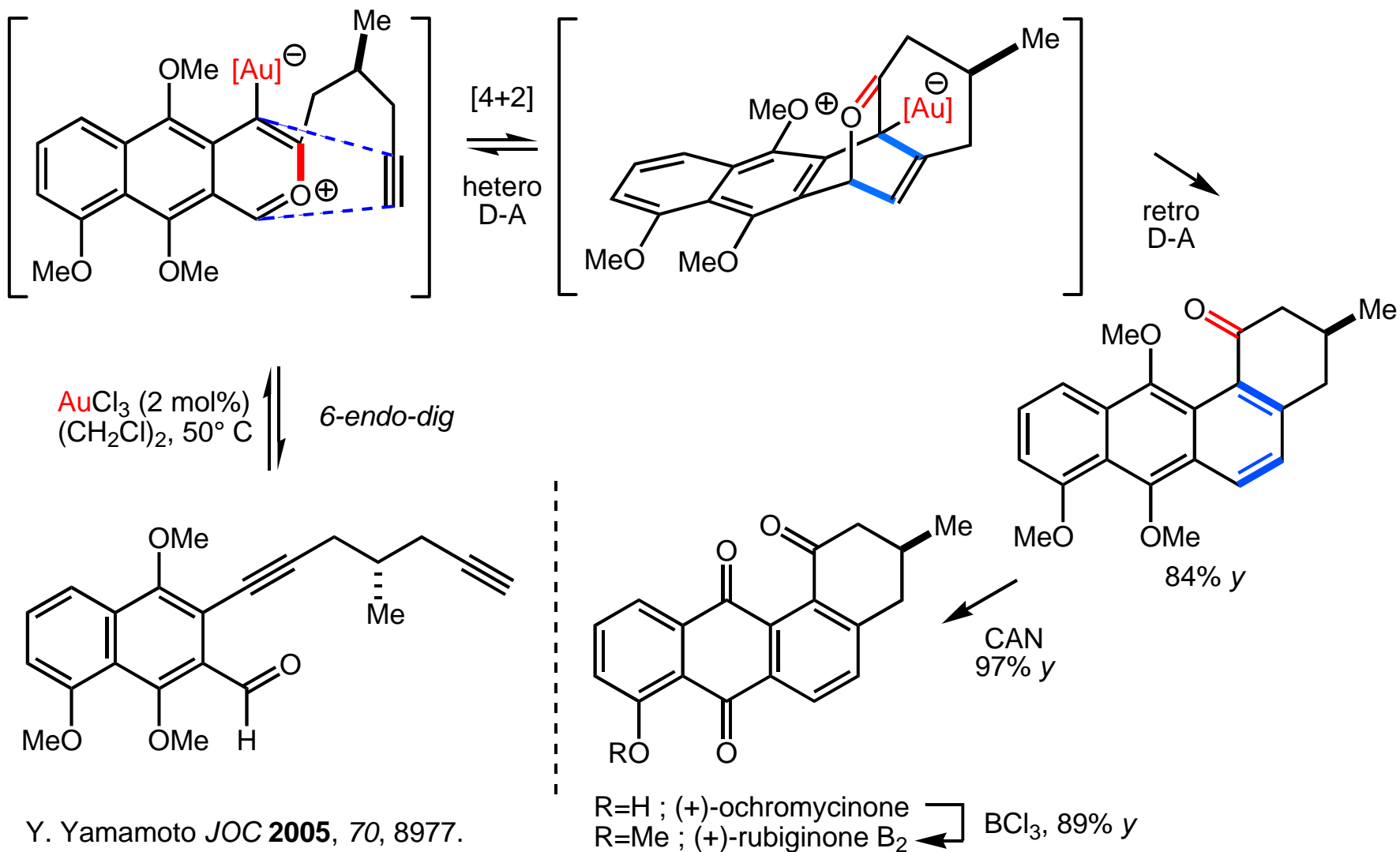
$\text{Nu}-\text{H} = \text{alkyl alcohols}$, 8 examples, 50 - 92% yields
 $\text{Nu}-\text{H} = \text{2-alkyl furan}$, 3 examples, 61 - 80% yields

Asao OL **2007**, 9, 4299.

Carbonyl Oxygen as Nucleophile

(+)-Rubiginone B₂ (2005)

Activation of Alkynes

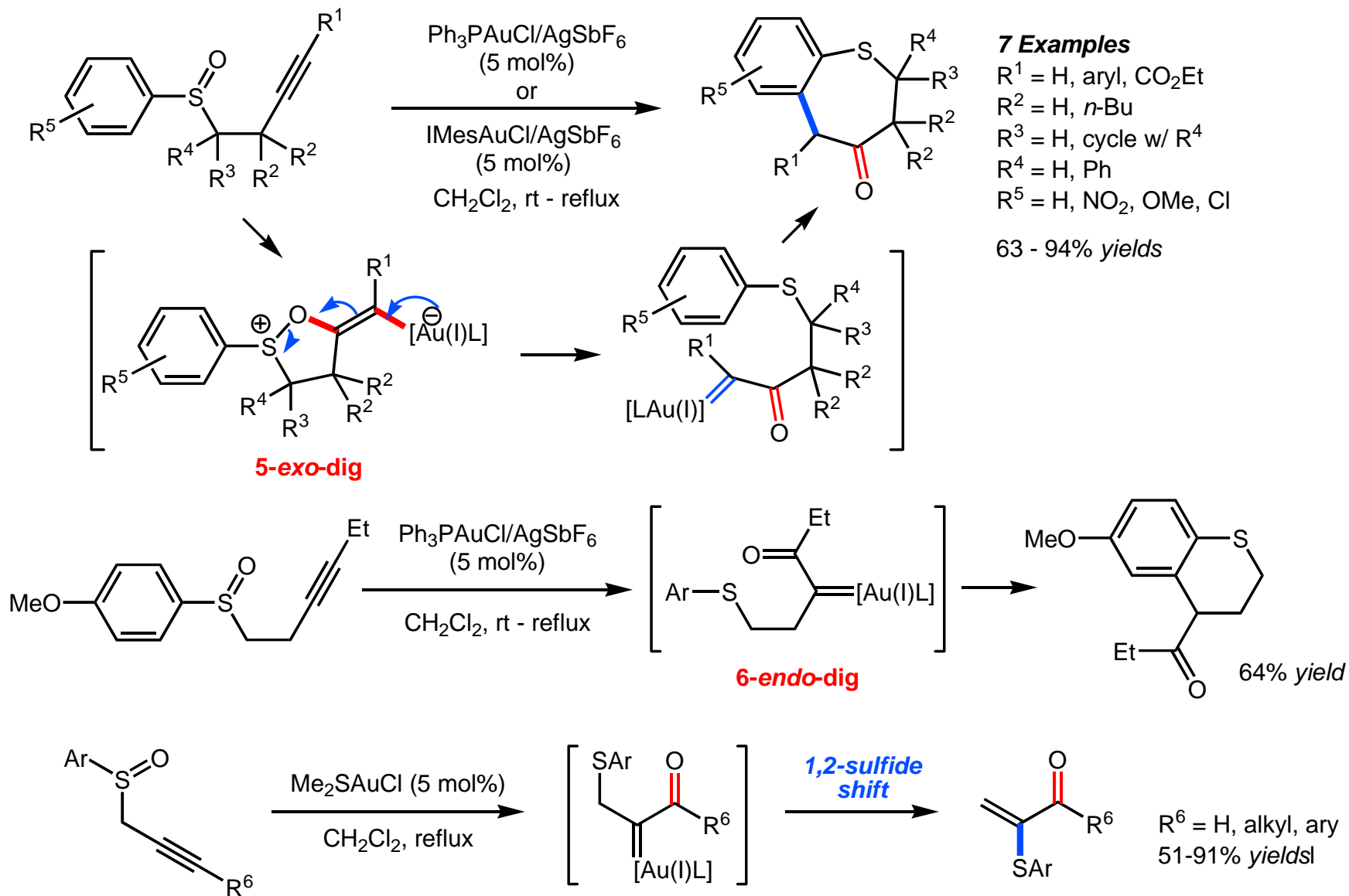


Similar application : Heliophenanthrone, Dyker *JOC* **2005**, 70, 6093.

Similar study : [3+2] dipolar cycloaddition, Oh *OL*, **2005**, 7, 5289.

Rearrangement of Alkynyl Sulfoxides

Activation of Alkynes

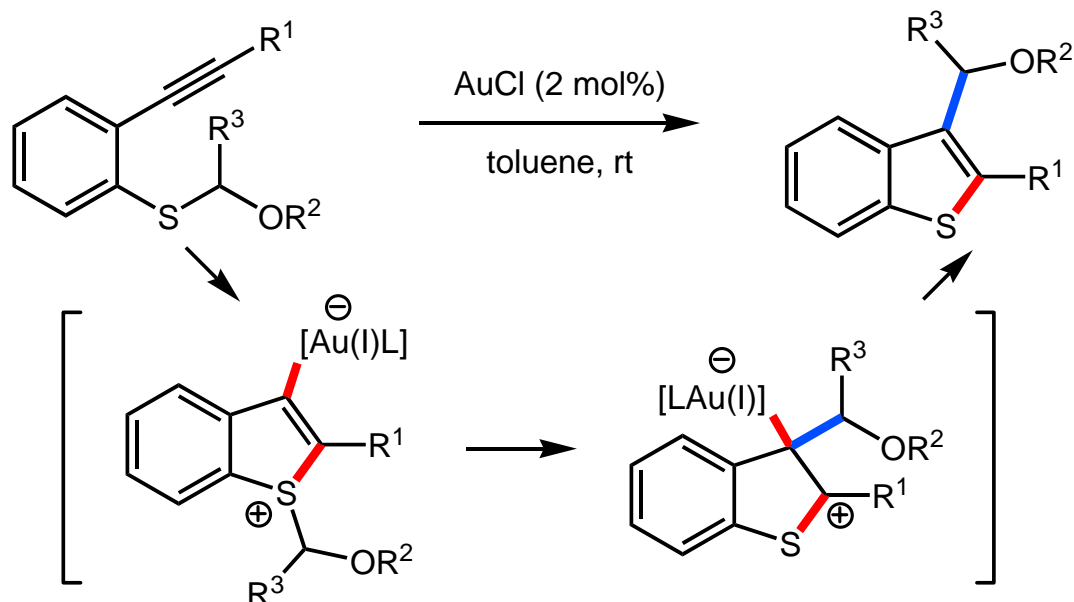


Toste *JACS* **2007**, 129, 4160.

Similar chemistry : Zhang *ACIE* **2007**, 46, 5156.

Intermolecular Carbothiolation

Activation of Alkynes



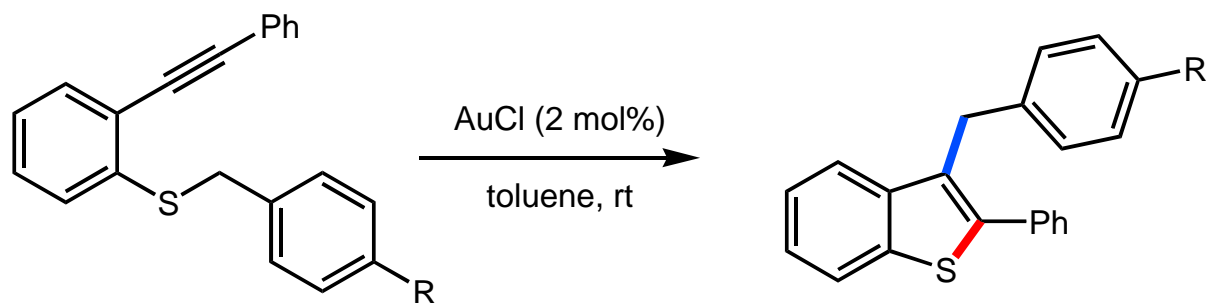
14 Examples

R^1 = alkyl, aryl

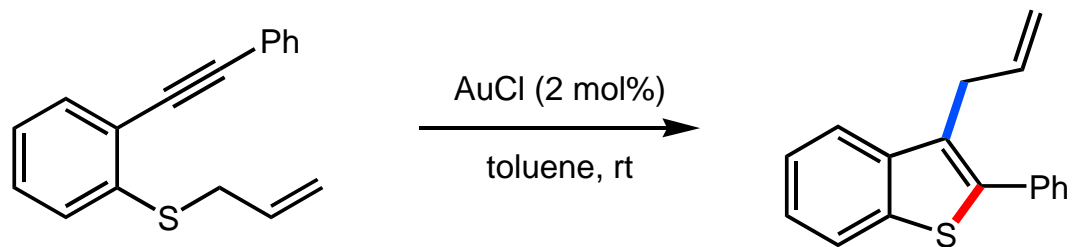
R^2 = alkyl, TBS, cycle w/ R^3

R^3 = H, Me

85 - 100% yields



R = OMe, 98% yield
 R = H, no reaction



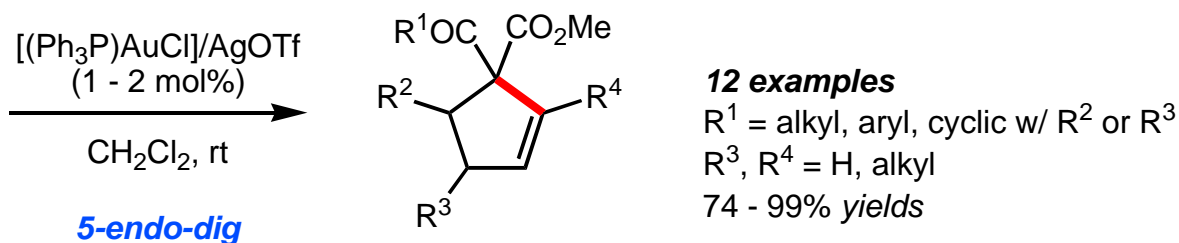
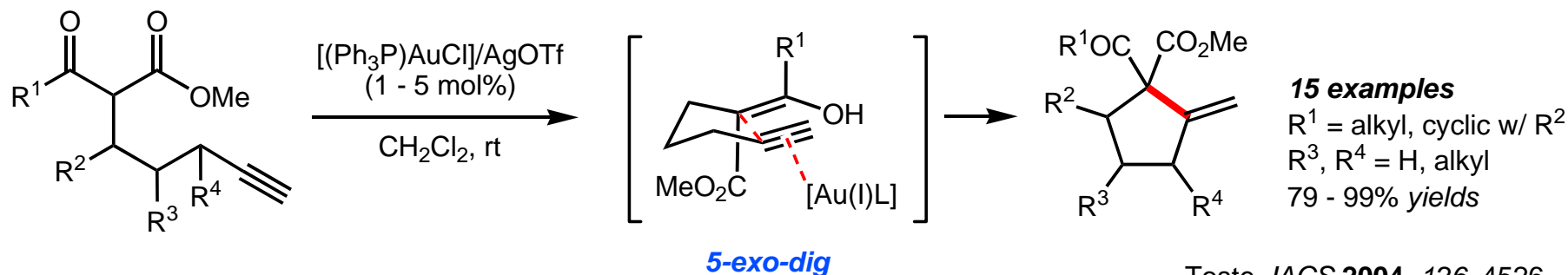
93% yield

Nakamura *ACIE* **2006**, 45, 4473.

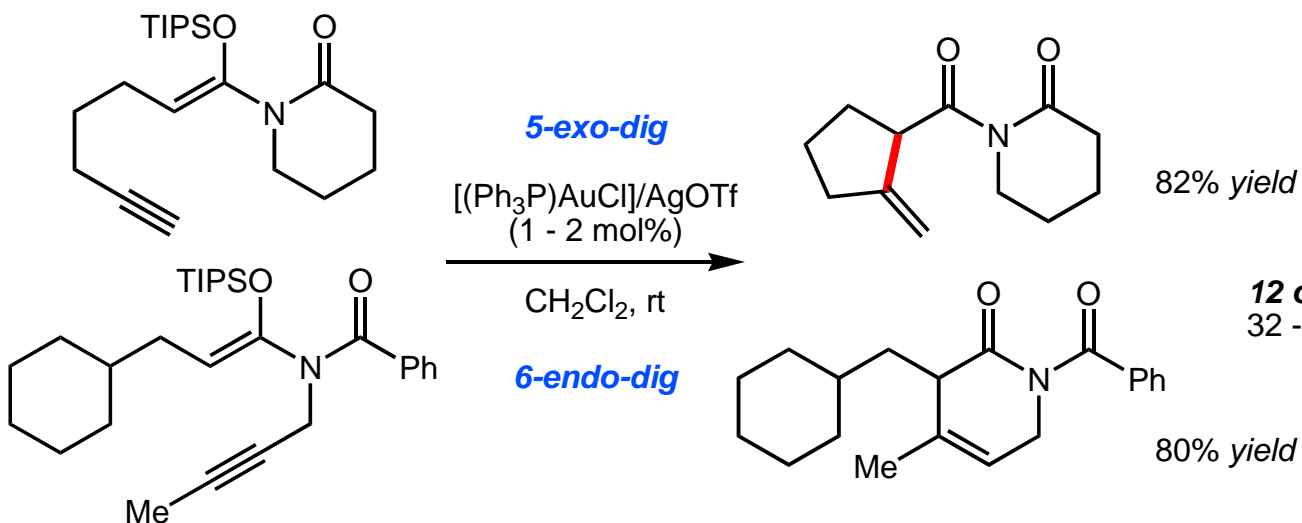
thiosilanes also successfully results in 1,3-silyl migration product. Nakamura *OL* **2007**, 9, 4081.

Enolates and Enol Ethers as Nucleophiles

Activation of Alkynes



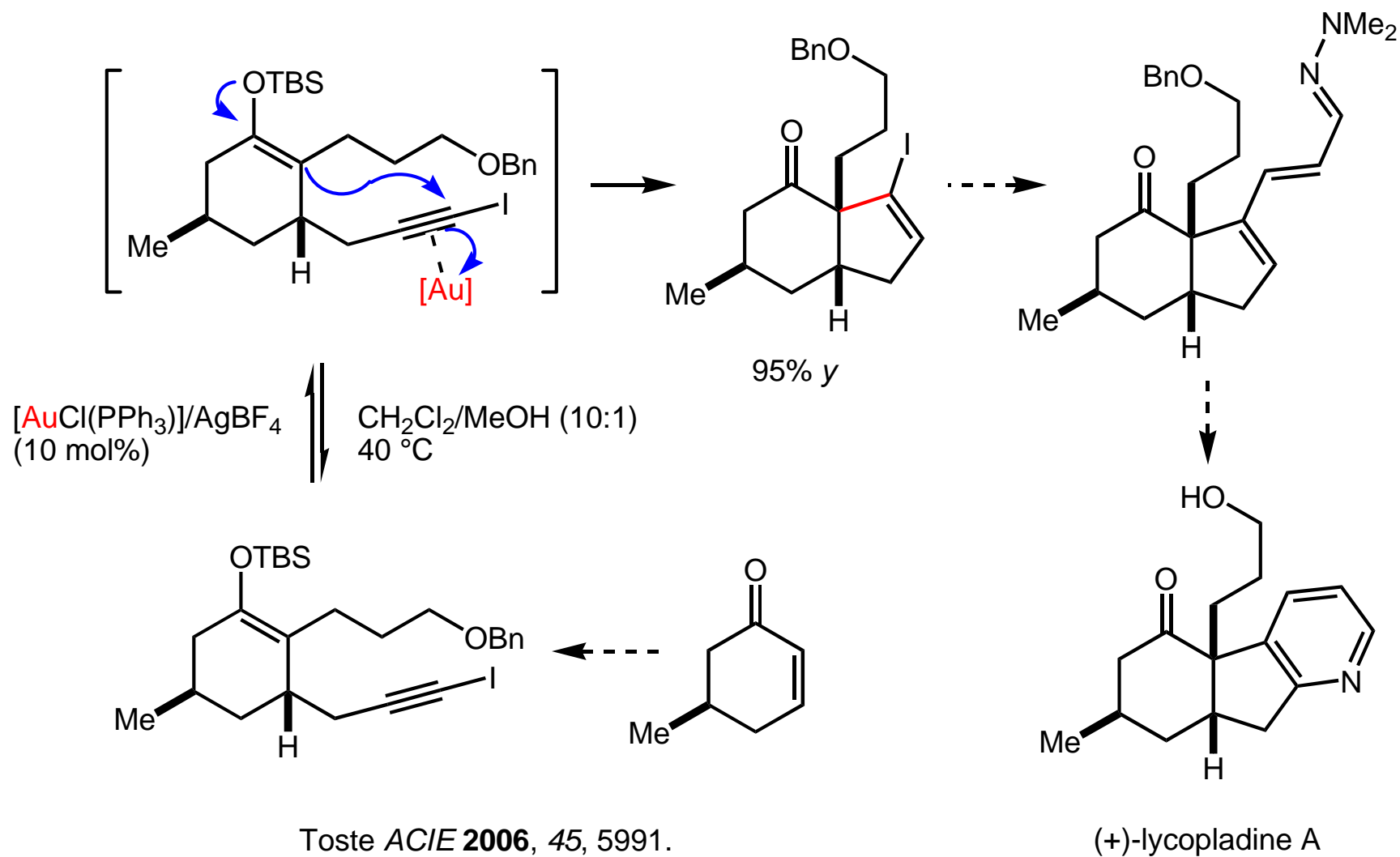
Toste *ACIE* **2006**, 43, 5350.



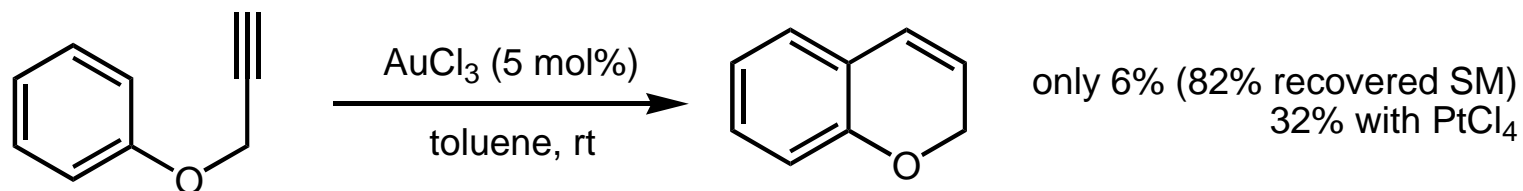
12 other examples
32 - 82% yields

Toste *JOC* **2007**, 72, 6287.

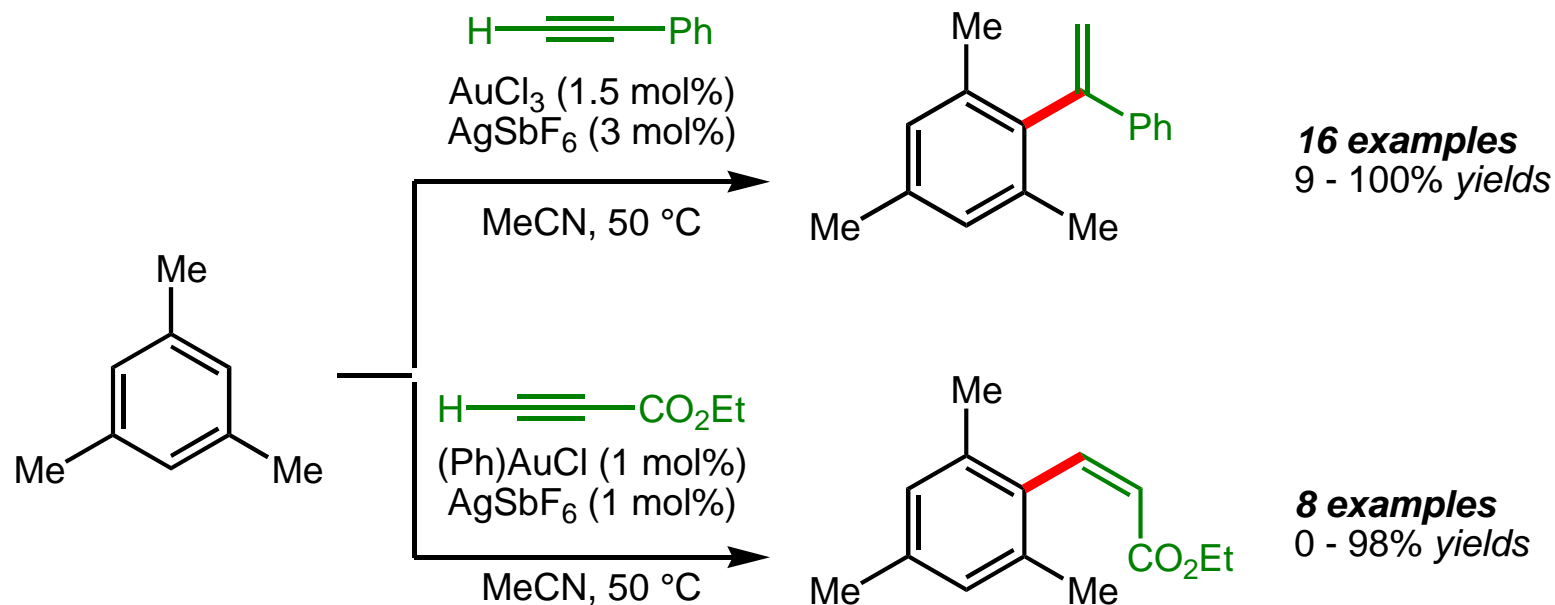
6-exo-dig and **7-exo-dig** utilizing triethynylphosphine ligands bearing bulky end caps to create a holey catalytic environment.
Sawamura *JACS* **2006**, 128, 16486.

Silylenolether as a Nucleophile*(+)-Lycopladiene A (2006)*

Hydroarylation – Early Studies

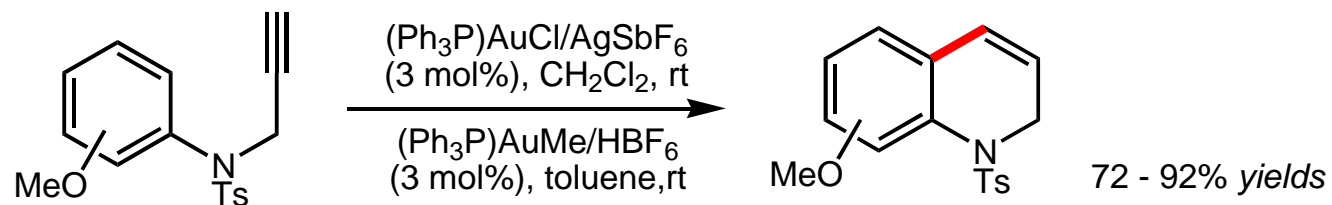
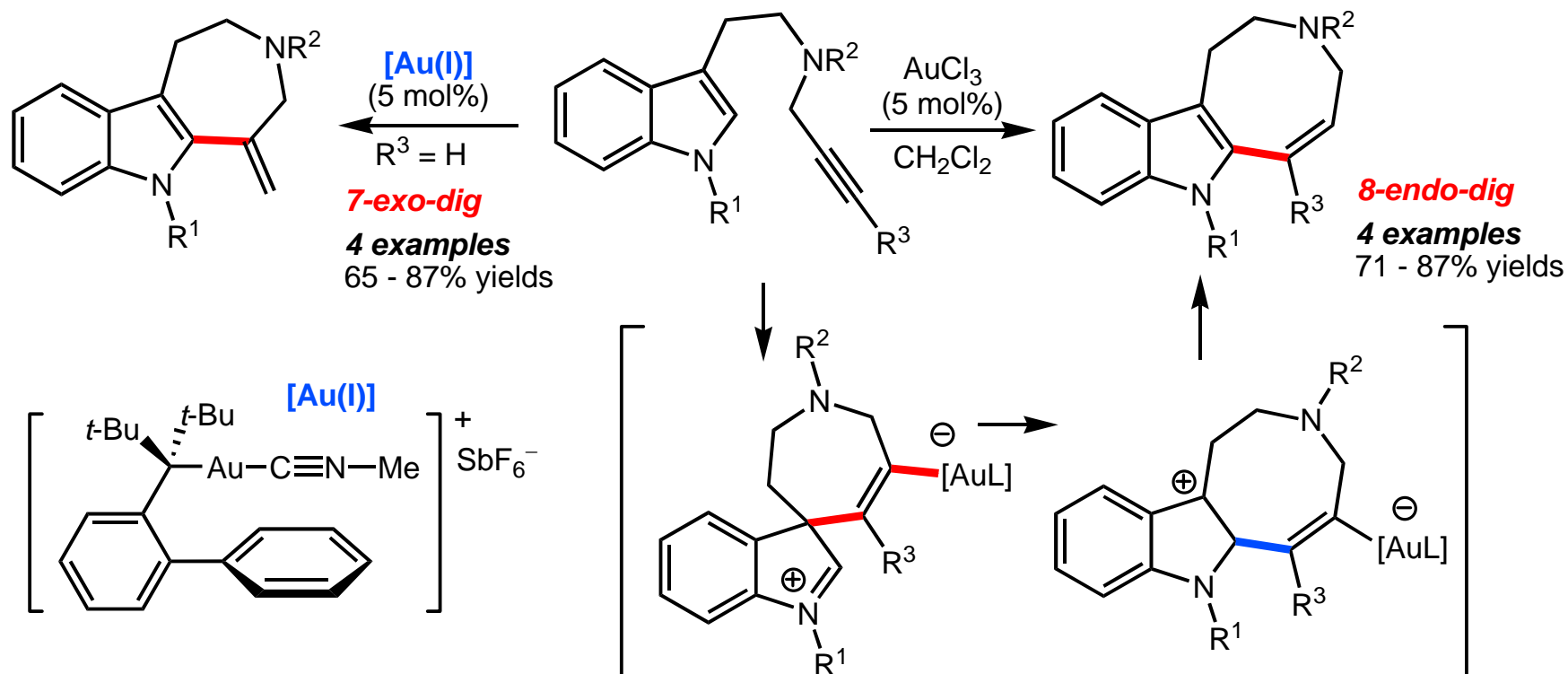


Sames *OL* **2004**, 5, 1055.



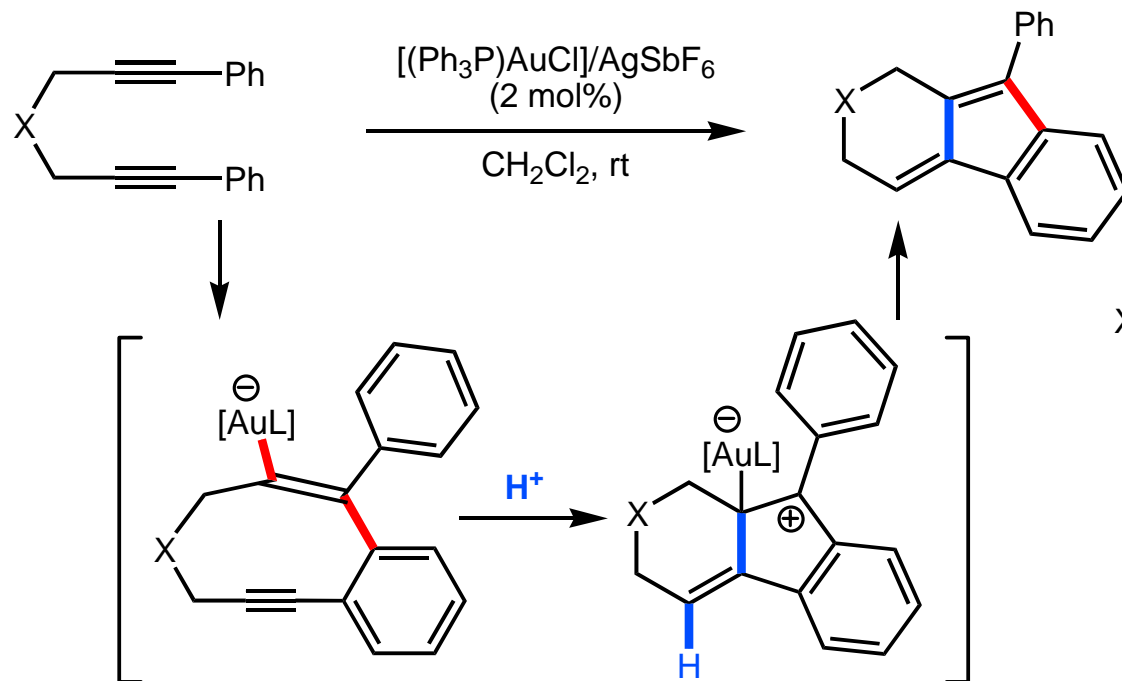
Reetz *EJOC* **2003**, 3485.

Intramolecular Hydroarylation

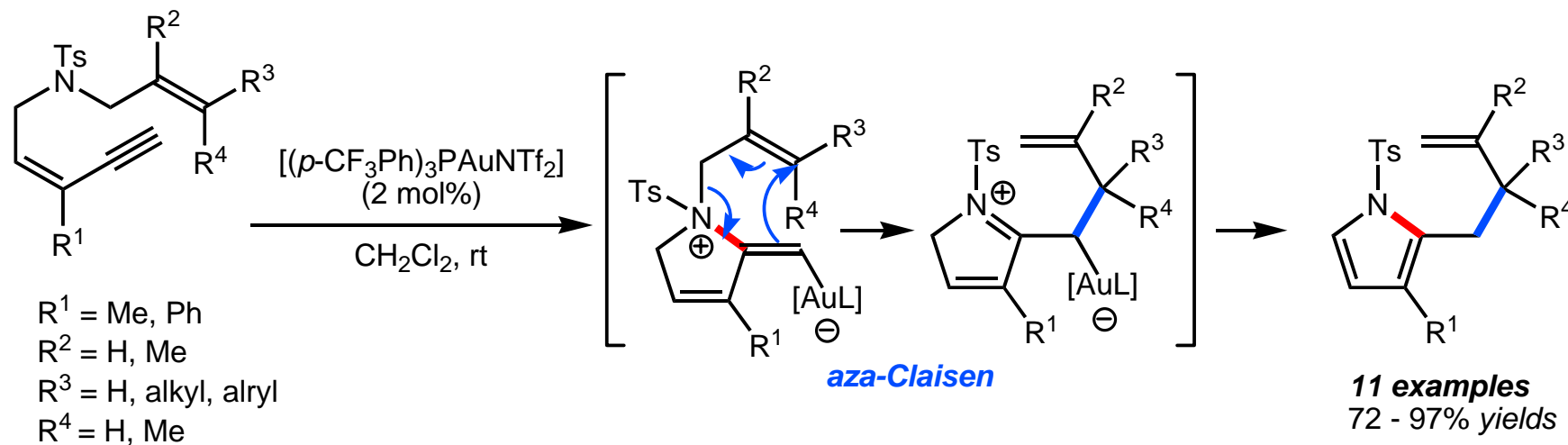
Echavarren *CEJ* **2005**, 11, 3155.Echavarren *ACIE* **2006**, 45, 1105.

[3+2] Cycloaddition / aza-Claisen Rearrangement

Activation of Alkynes



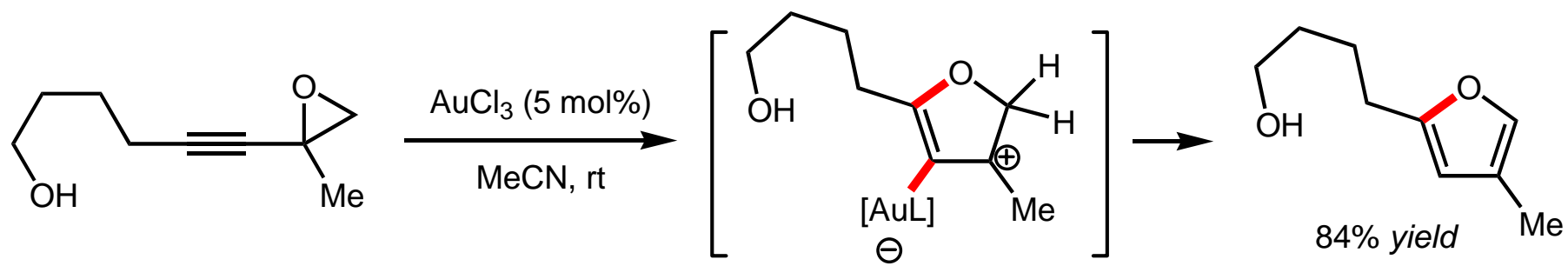
Liu *JACS* **2006**, 128, 11372.



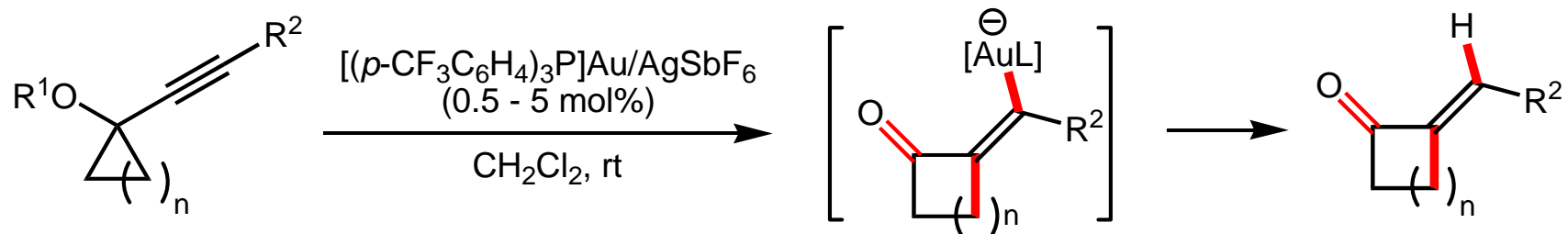
Gagosz *OL* **2007**, 9, 3181.

Ring Enlargement Reactions

Activation of Alkynes



Hashmi *Adv. Synth. Catal.* **2004**, 346, 432.



16 examples

$\text{R}^1 = \text{H}, \text{TBS}, \text{TMS}$

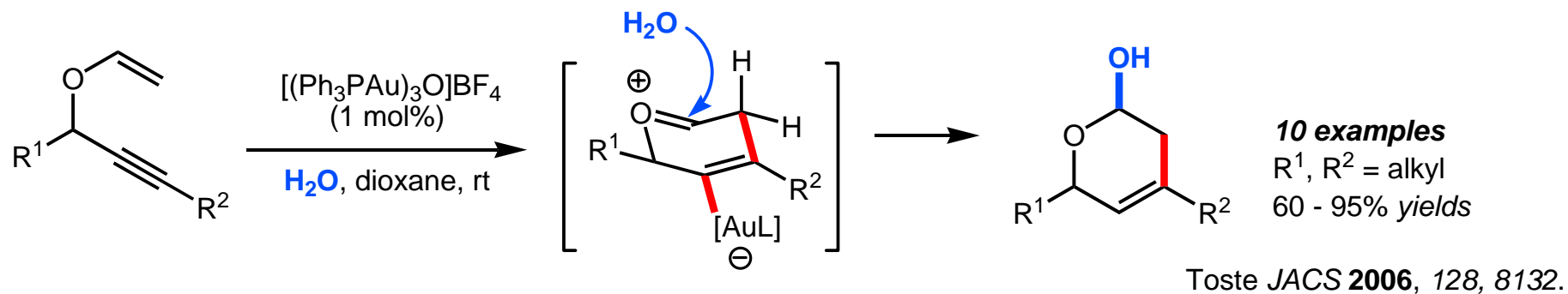
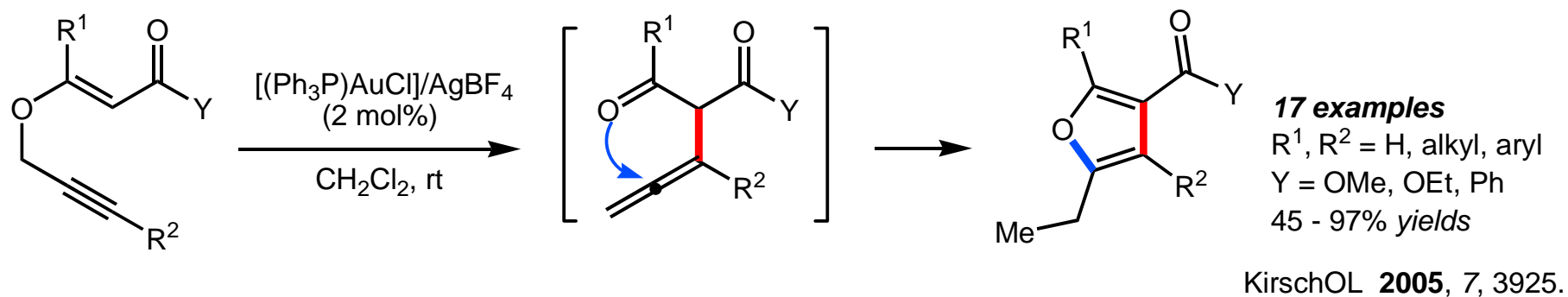
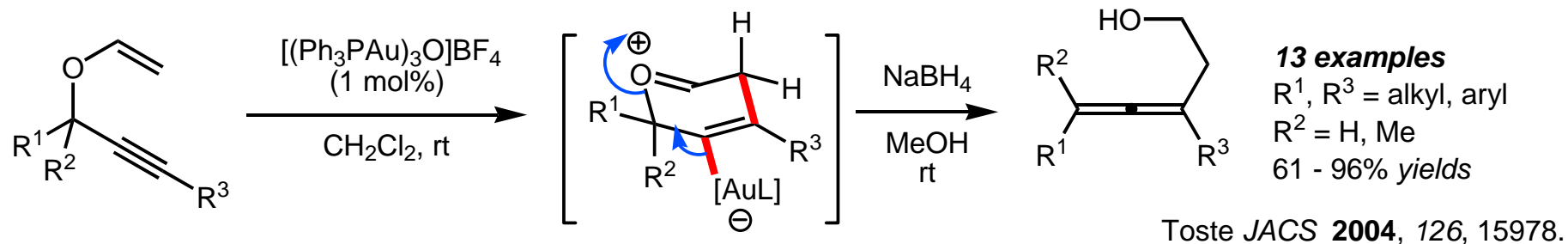
$\text{R}^2 = \text{H}, \text{alkyl}, \text{aryl}, \text{I}$

61 - 98% yields

Toste *JACS* **2005**, 127, 9708.

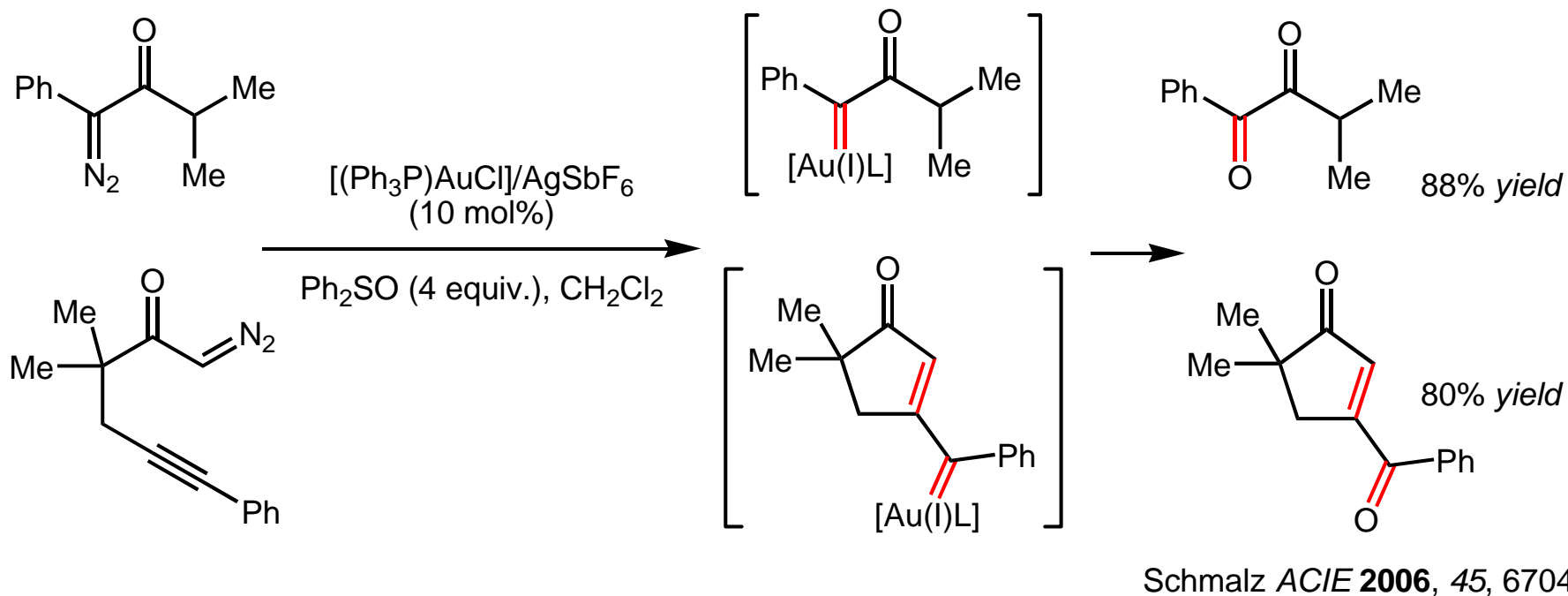
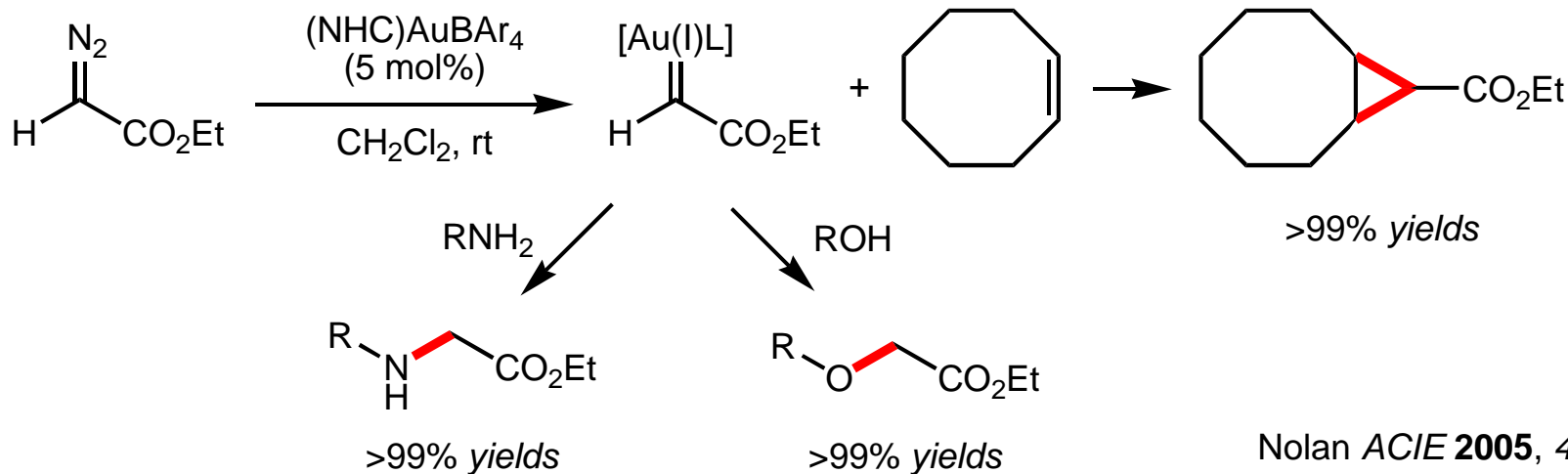
Propargyl Vinyl Ethers

Activation of Alkynes

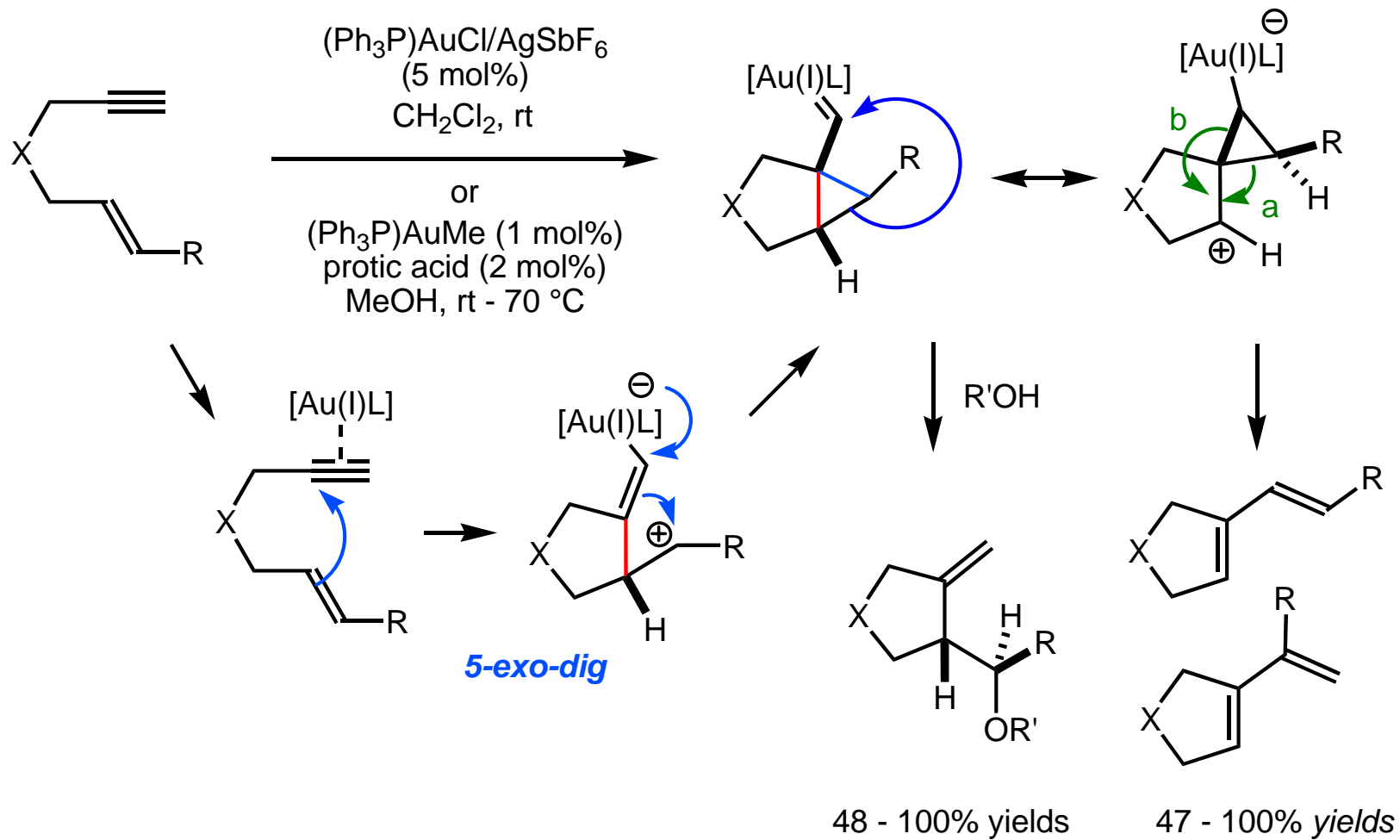


Gold Carbenoid

Activation of Alkynes



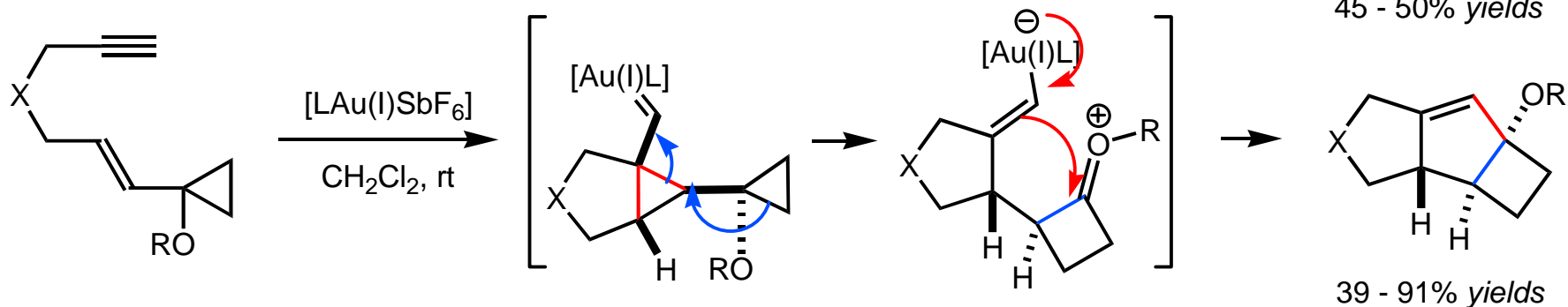
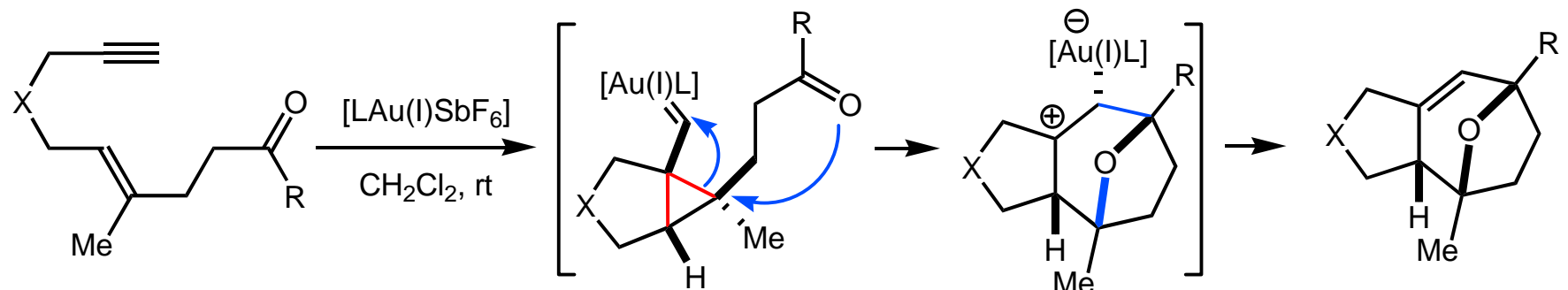
1, 6-Enyne Cyclizations



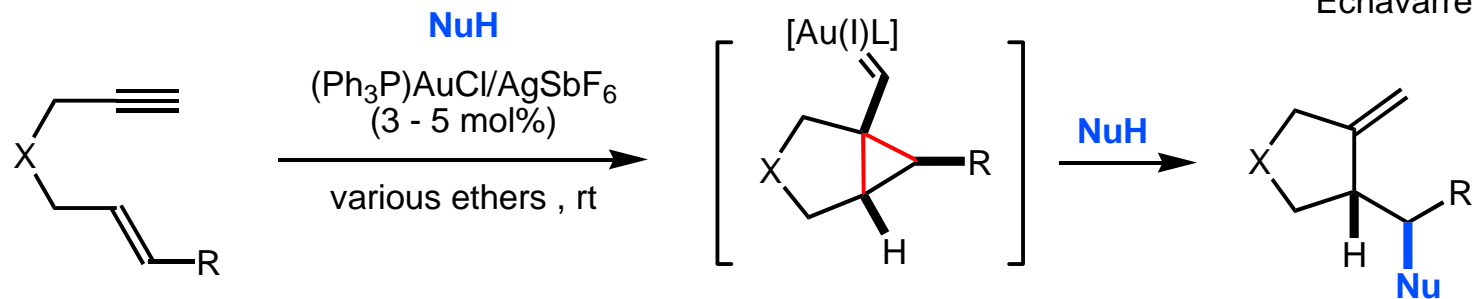
Echavarren *ACIE* **2004**, 43, 2402.
OM **2005**, 24, 1293.
CEJ **2006**, 12, 1677.

1,6-Enyne Cyclizations

Activation of Alkynes



Echavarren *ACIE* **2006**, 45, 5452.

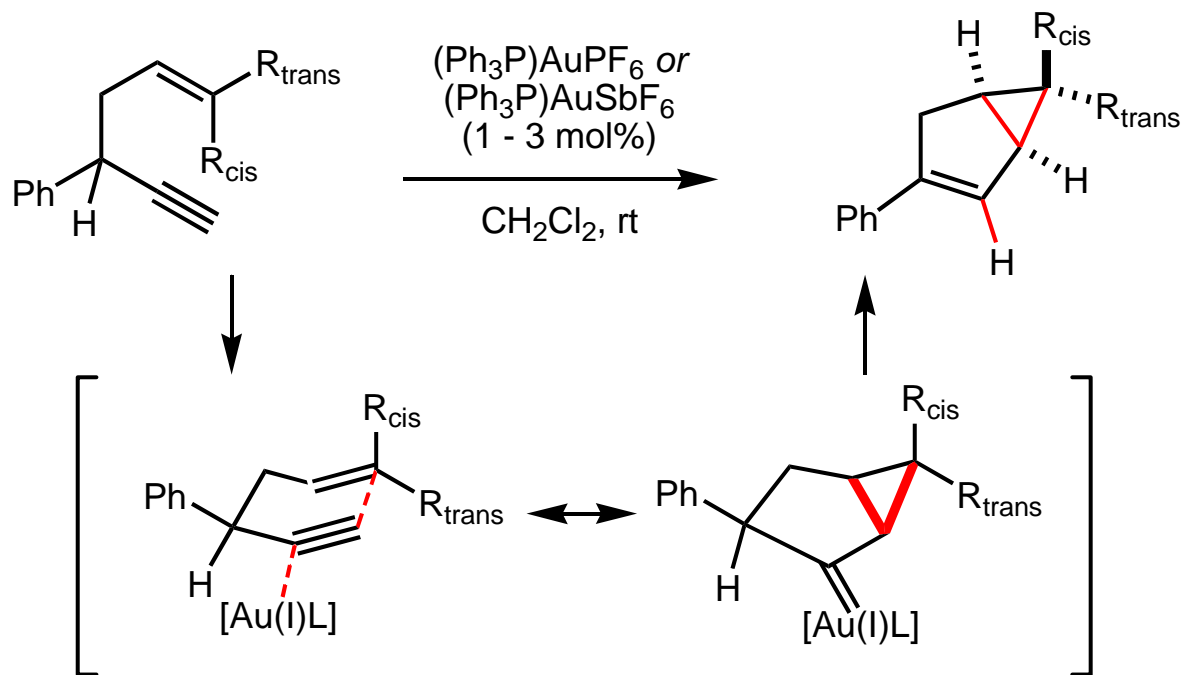


NuH = indoles, pyrroles, e-rich benzene rings
alcohols, amines

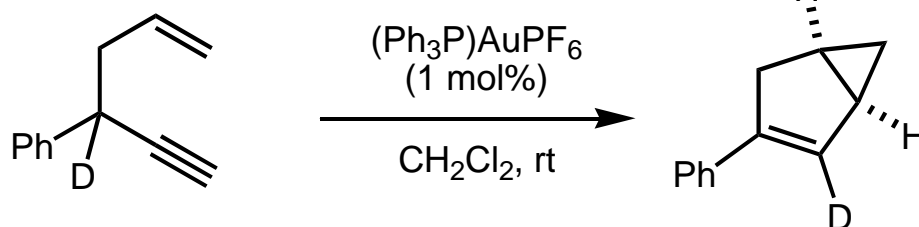
Genêt *ACIE* **2006**, 45, 7427.
OL **2007**, 9, 4049.

Cycloisomerization of 1,5-Enyne

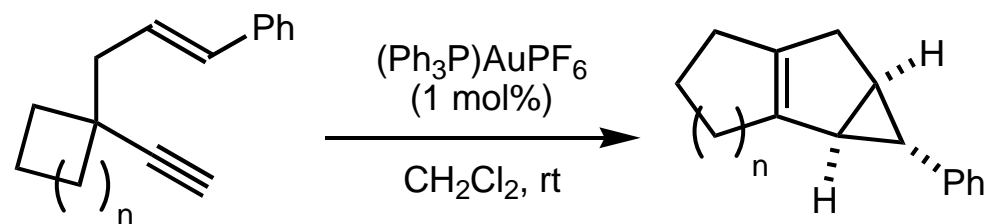
Activation of Alkynes



Deuterium-Labeling
Experiment supporting
the 1,2-H Shift



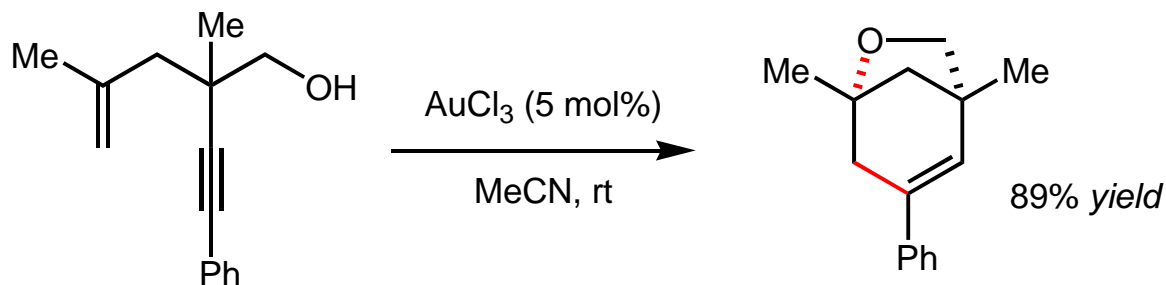
Ring-Enlargement
by the 1,2-C Shift



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

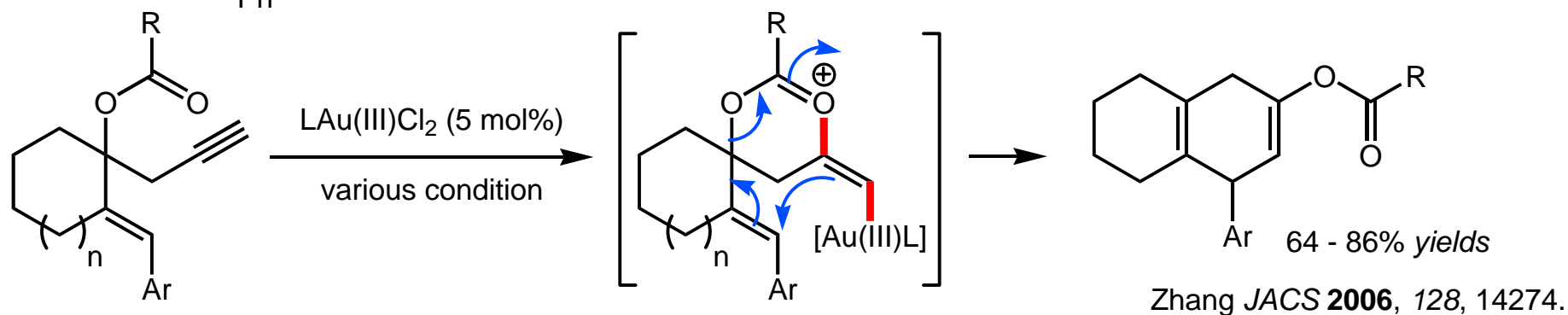
More 1,5-Enyne Cyclizations

Activation of Alkynes

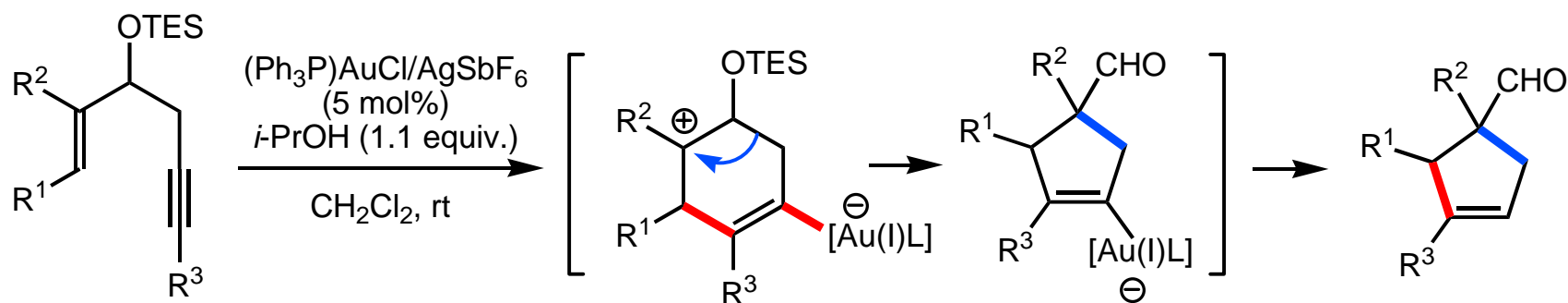


7 examples
82 - 96% yields

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



Zhang *JACS* **2006**, 128, 14274.



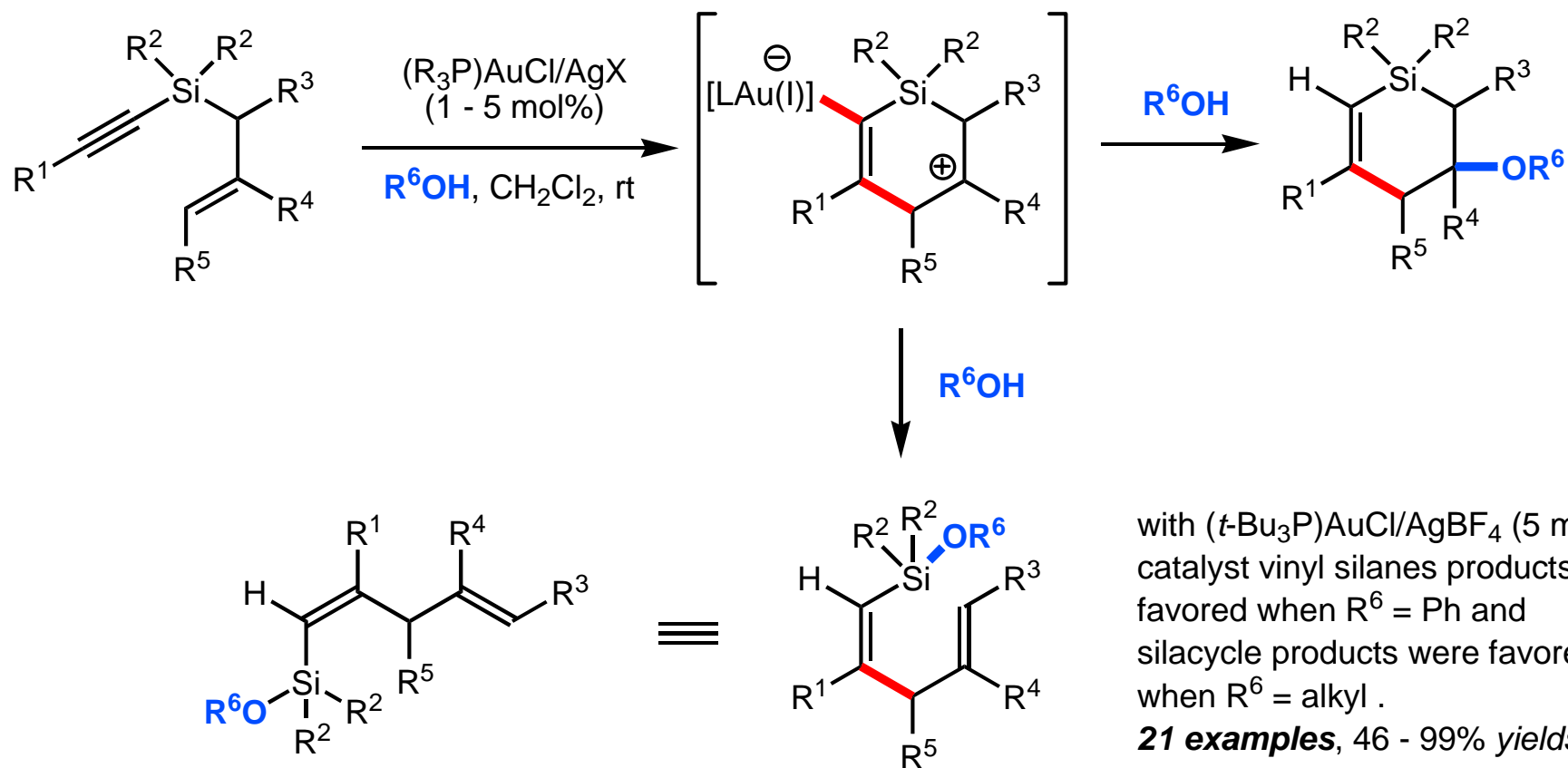
12 examples, 28 - 83% yields

Zhang *JACS* **2006**, 128, 14274.

More Examples of 1,5-Enyne Cyclizations :
Shin *OL* **2007**, 9, 3539.
Fürstner *JACS* **2004**, 126, 8654.

Alkynyl Allyl Silanes

Activation of Alkynes



with $(t-Bu_3P)AuCl/AgBF_4$ (5 mol%) catalyst vinyl silanes products were favored when $R^6 = Ph$ and silacycle products were favored when $R^6 = alkyl$.

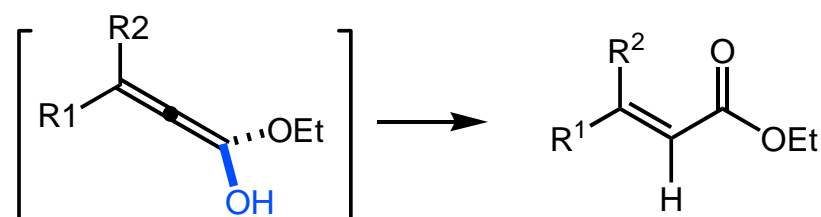
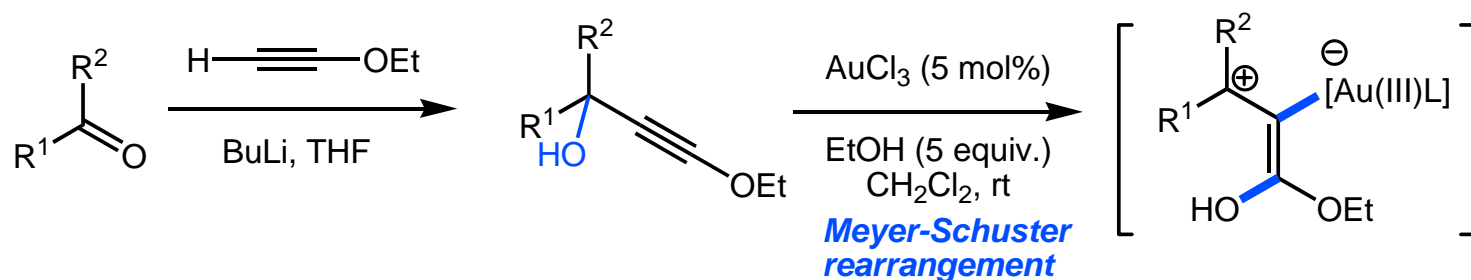
21 examples, 46 - 99% yields
Toste *JACS* **2006**, 128, 11364.

with $(Ph_3P)AuCl/AgSbF_6$ (1 mol%) catalyst and $R^6 = alkyl$, only vinyl silanes products were observed.

16 examples, 55 - 89% yields
Lee *JACS* **2006**, 128, 10664.

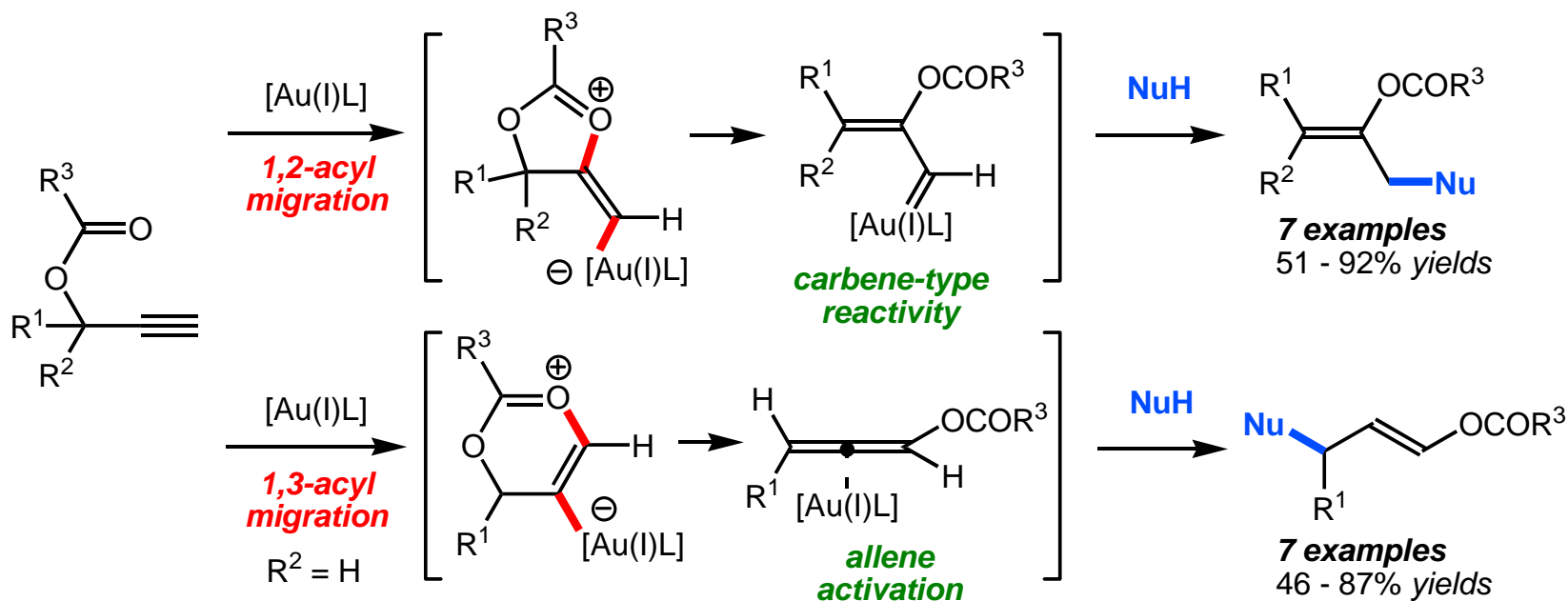
Migration of Propargyl Functional Groups

Activation of Alkynes



This approach was successfully applied for the olefination of hindered ketones.
6 examples
 68 - 99% yields

Dudley OL **2006**, 8, 4027.



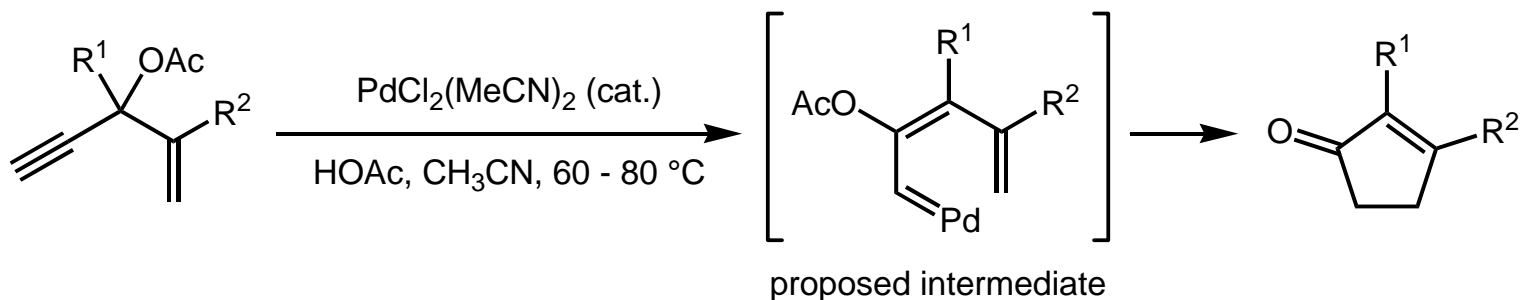
results depending on the ligands on catalysts and substrates

Echavarren OL **2007**, 9, 4021.

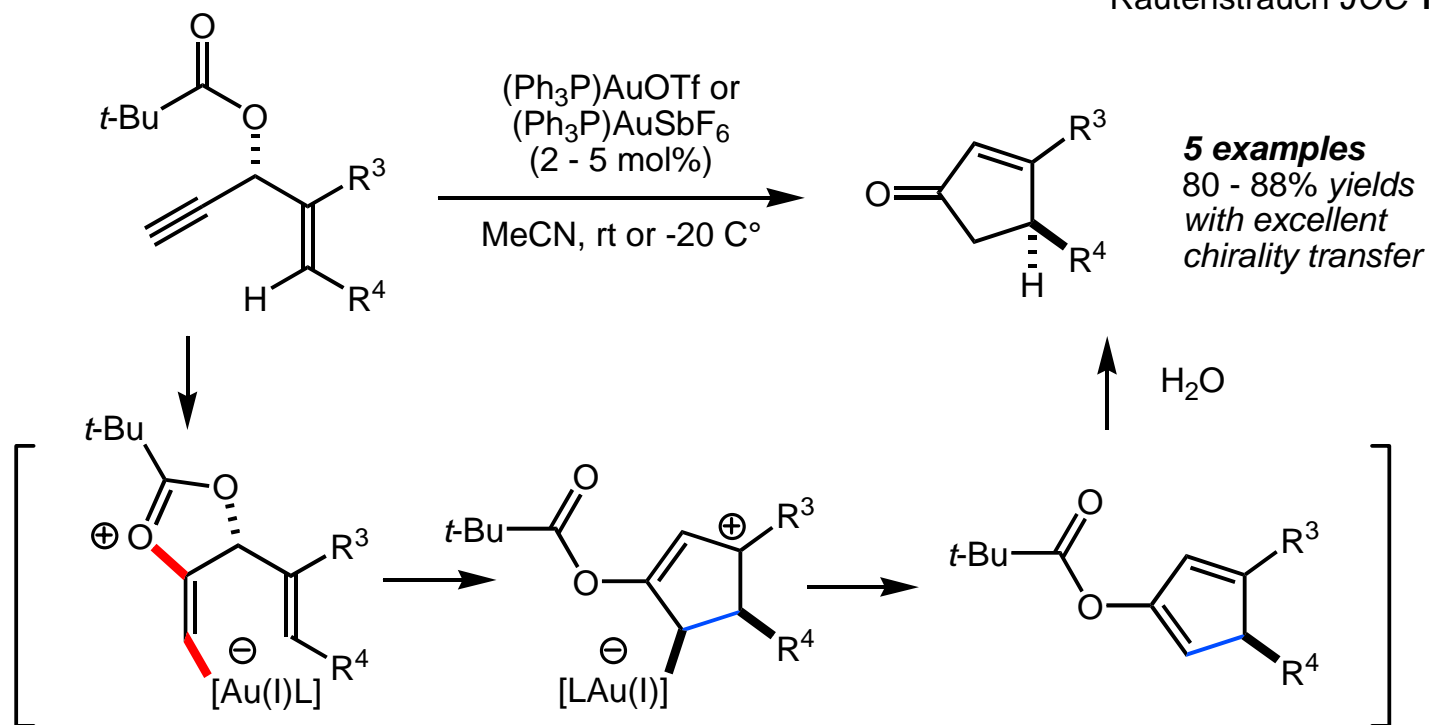
Reactions of Propargylic Esters

Rautenstrauch Reaction

Activation of Alkynes



Rautenstrauch *JOC* **1984**, 49, 950.

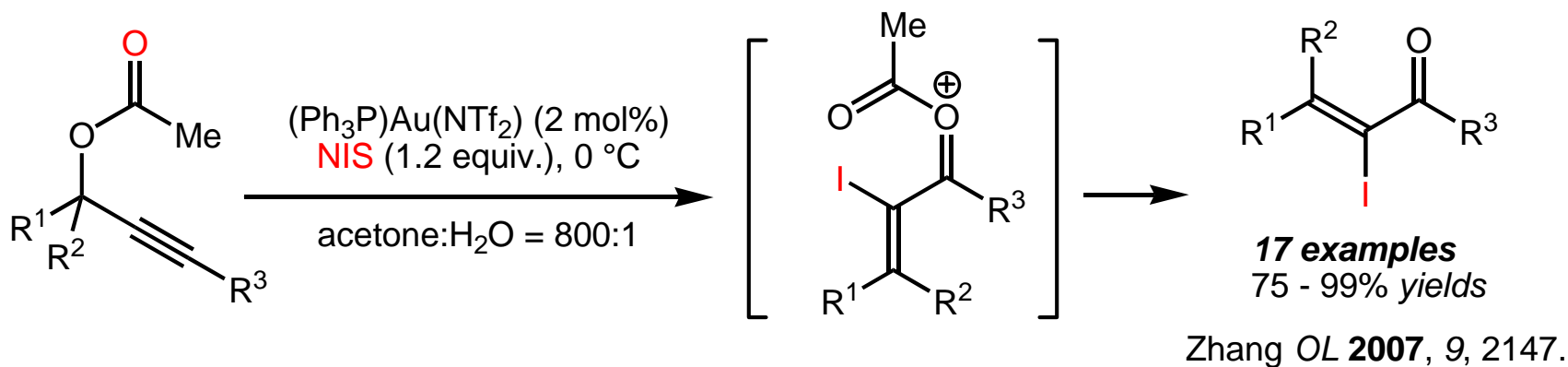
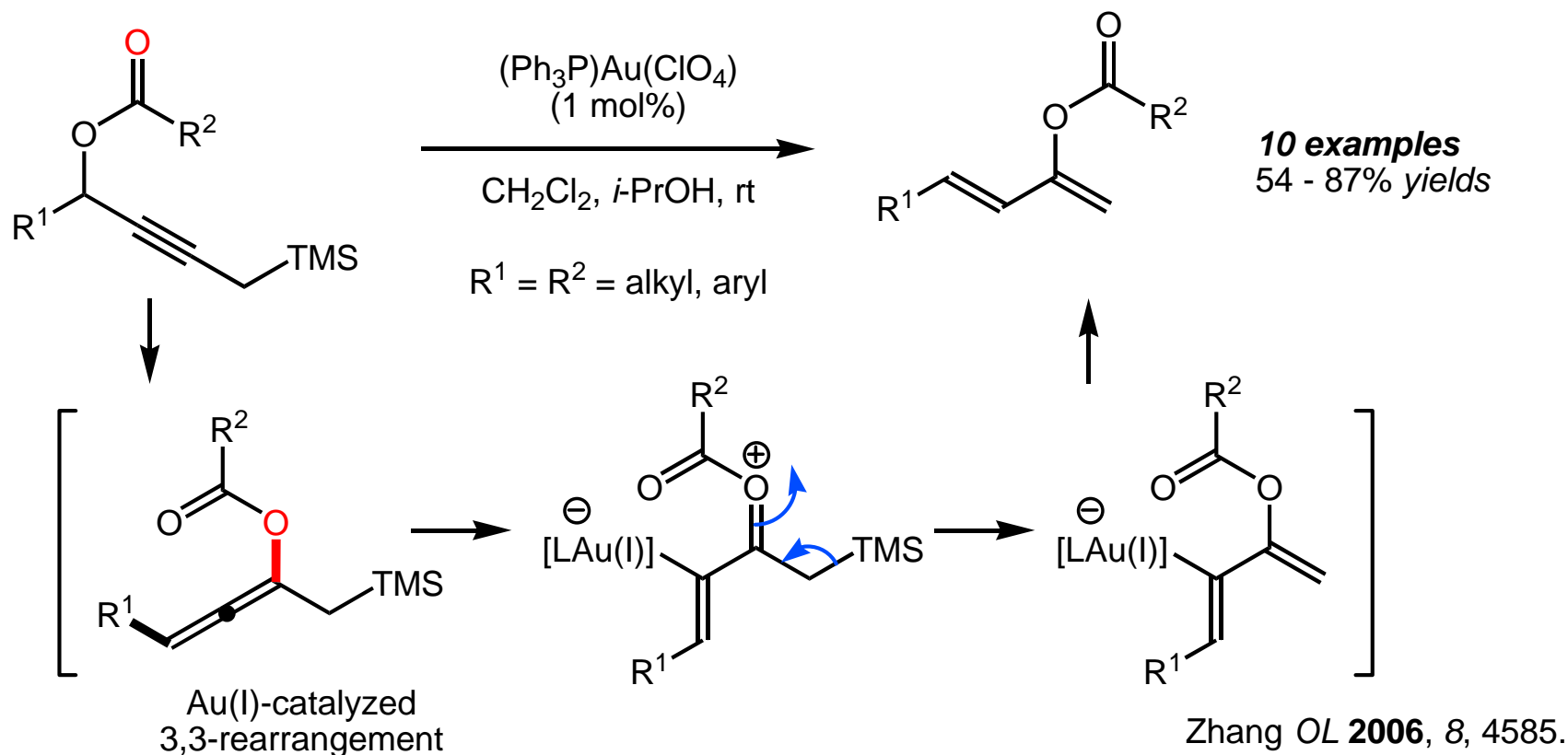


Toste *JACS* **2005**, 127, 5802.

Mechanistic studies for center-to-helix-to-center chirality transfer : de Lera *JACS* **2006**, 128, 2434.

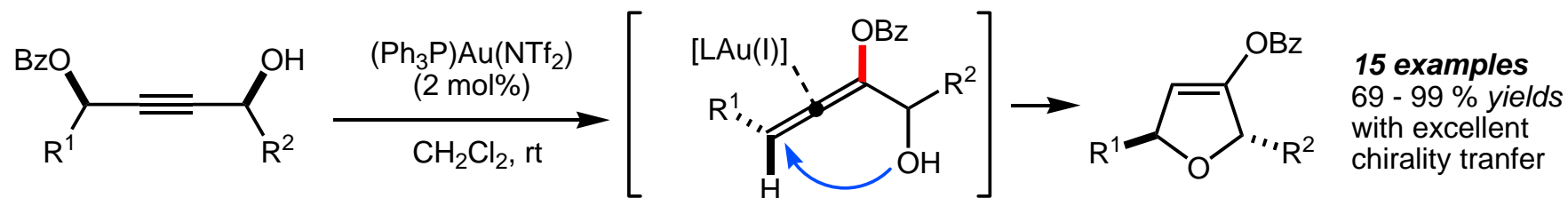
Reactions of Propargylic Esters

Activation of Alkynes

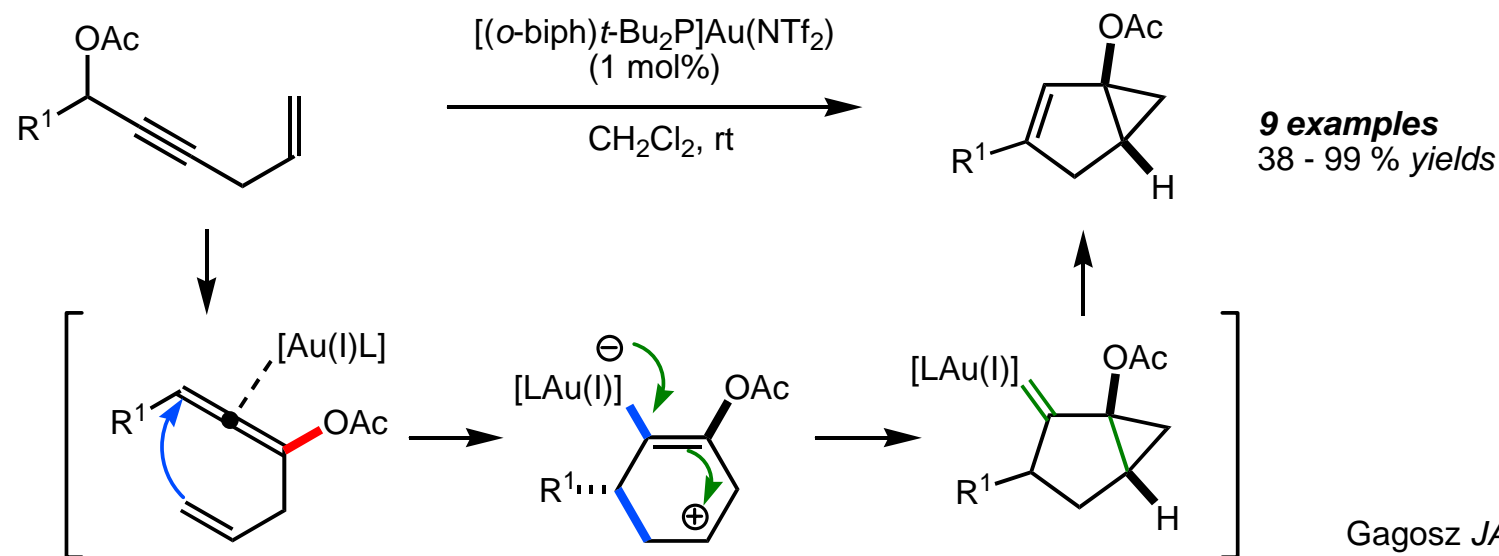


Reactions of Propargylic Esters

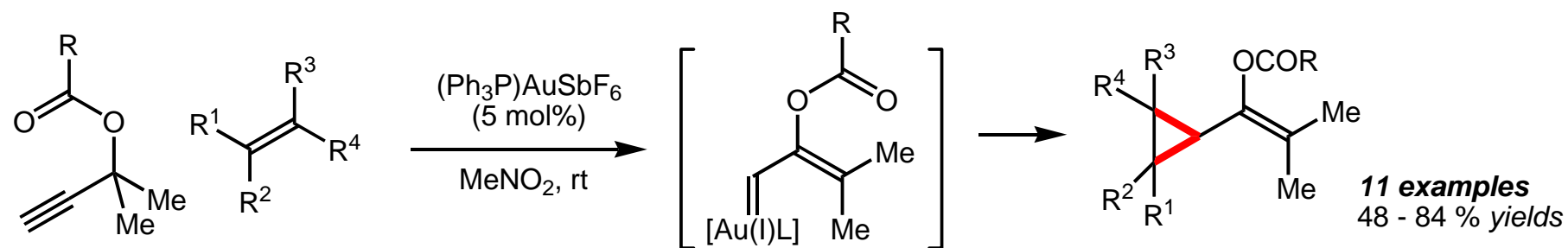
Activation of Alkynes



Gagosz *OL* **2006**, 8, 1957.



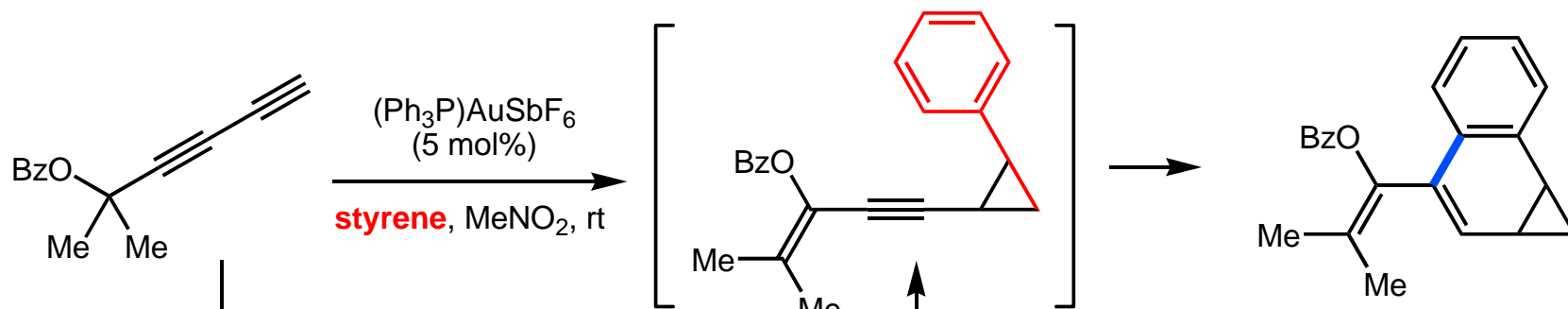
Gagosz *JACS* **2006**, 128, 12614.



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

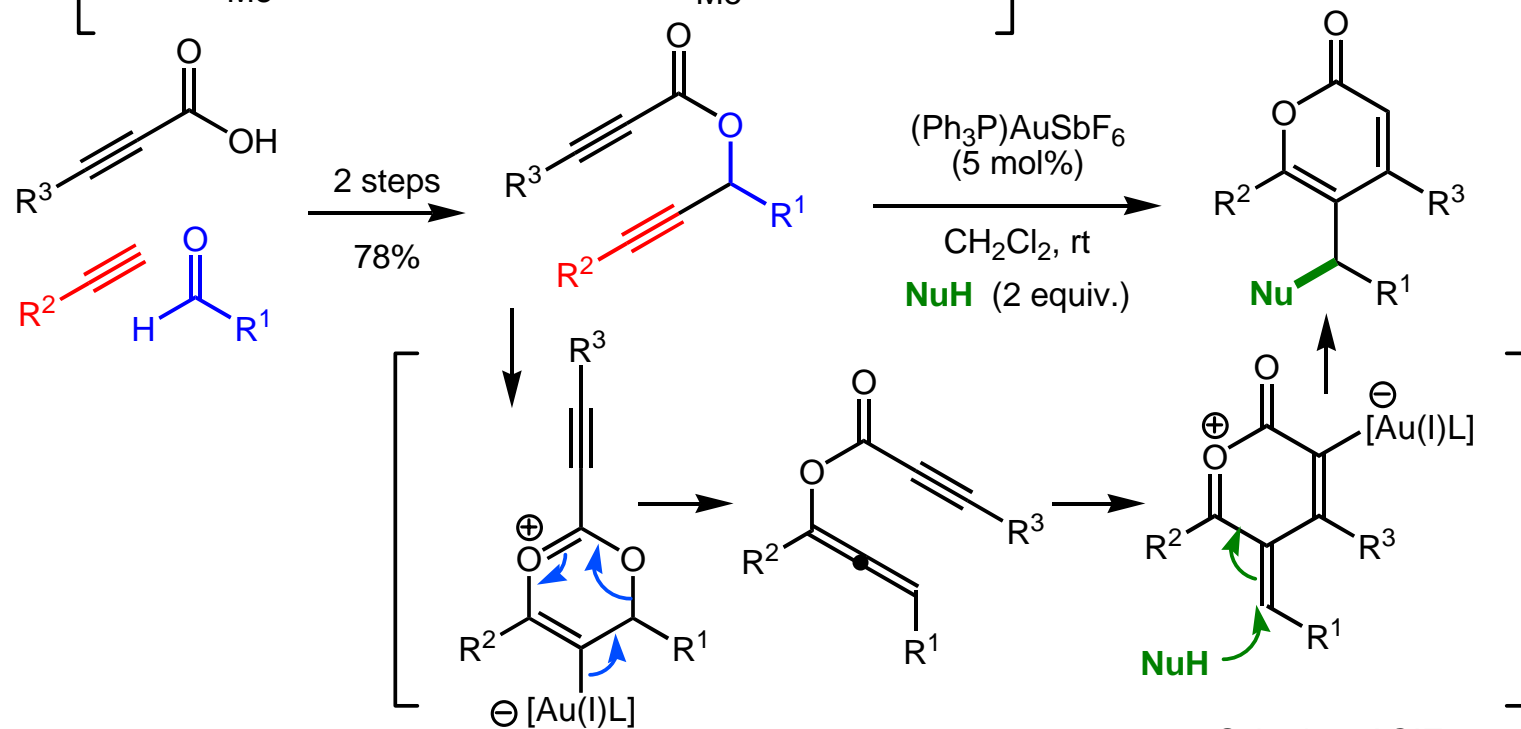
Reactions of Propargylic Esters

Activation of Alkynes



9 examples
54 - 85% yields

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



Schreiber *ACIE* **2007**, 46, 8250.

I. Introduction

II. Activation of Alkynes

III. Activation of Allenes

IV. Activation of Alkenes

Nitrogen Nucleophiles : Hydroamination

Oxygen Nucleophiles : Hydroalkoxylation

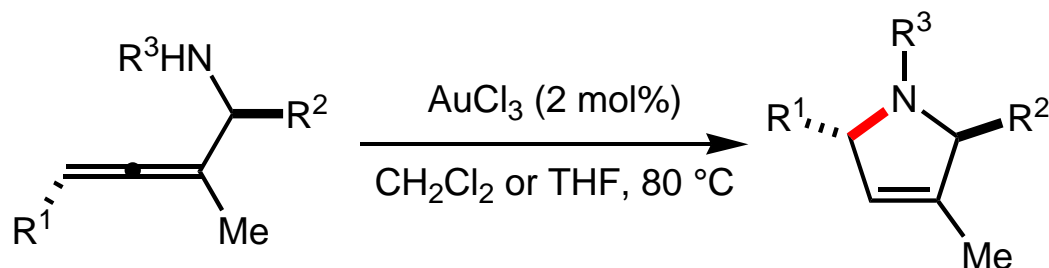
Carbonyl Oxygens

V. Summary

Carbon Nucleophiles : Hydroarylation

Alkenes

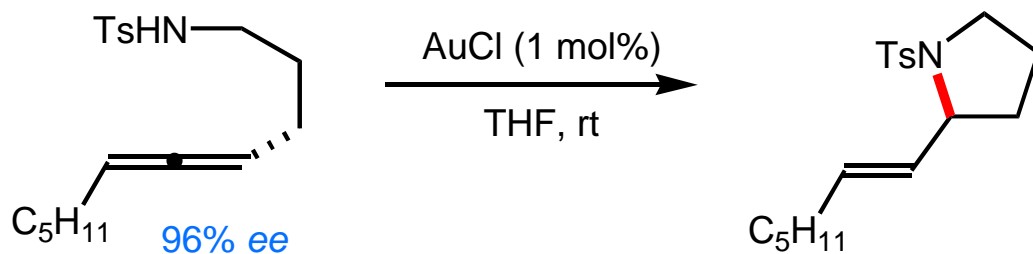
Intramolecular Hydroamination



R^1 = alkyl, aryl
 R^2 = CH_2OR
 R^3 = H, Ms, Ts, Ac, Boc
 69-95% yields

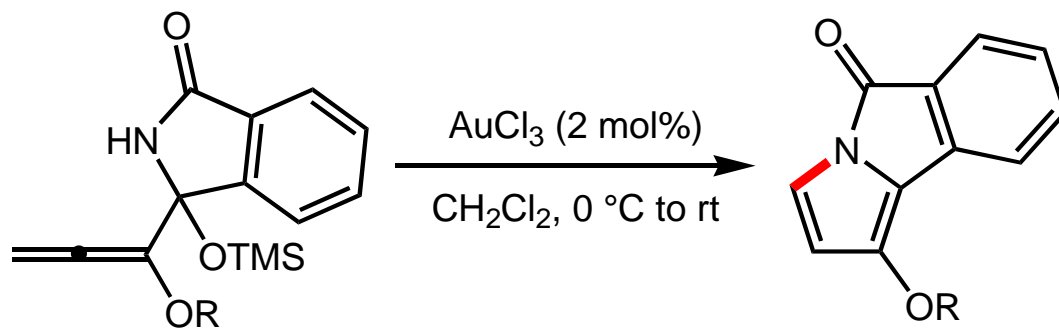
with complete
axis-to-center
chirality transfer

Krause *OL* **2004**, 6, 4121.; *EJOC* **2006**, 4634.



99% yields
 94% ee

Yamamoto *TL* **2006**, 47, 4749.



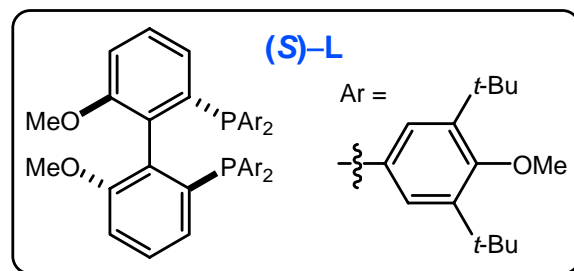
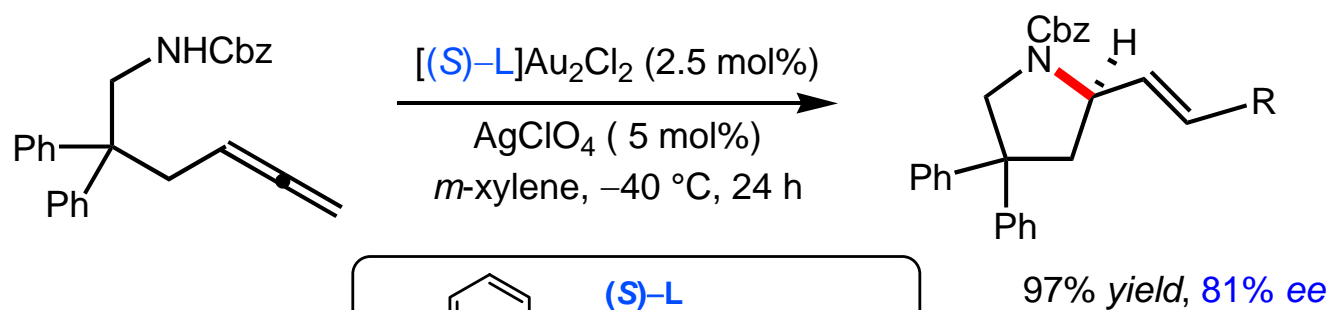
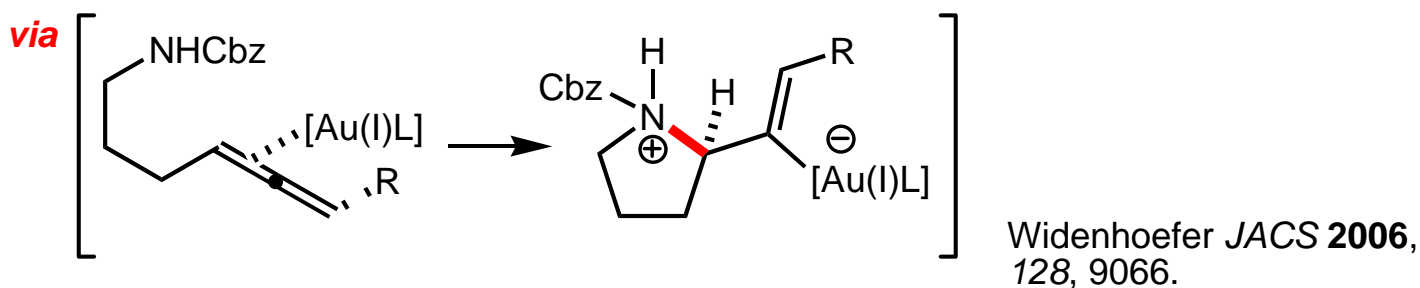
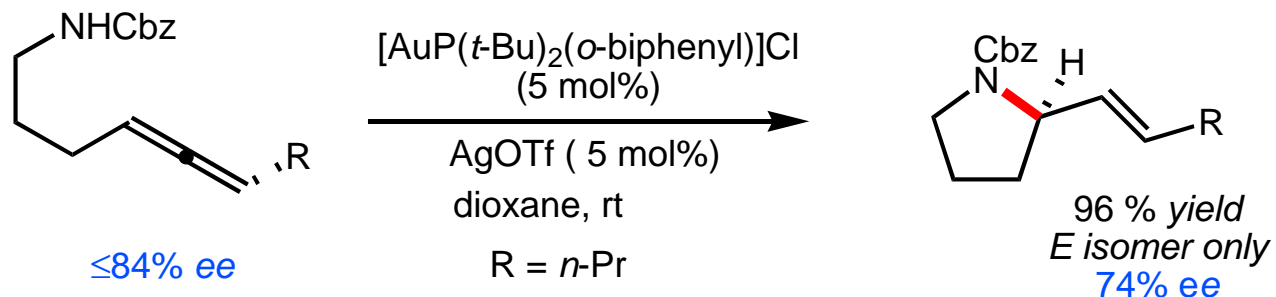
R = Me, Bn,
 $(\text{CH}_2)_2\text{TMS}$

32-40% yields

Reissig *Synthesis* **2006**, 1351.

Intramolecular Enantioselective Hydroamination

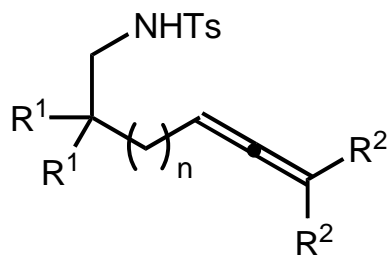
Activation of Allenes



Widenhoefer *OL* 2007, 9, 2887.

Intramolecular Enantioselective Hydroamination

Activation of Allenes

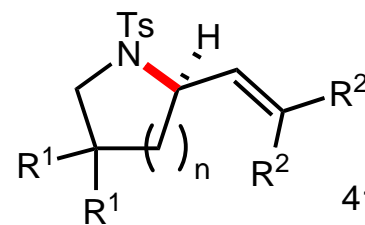
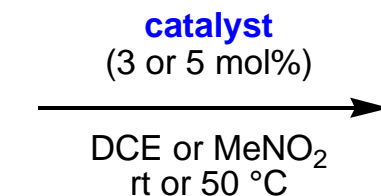


16 examples

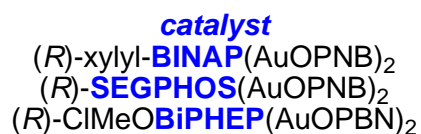
n=1, 2

R¹ = H, alkyl, aryl

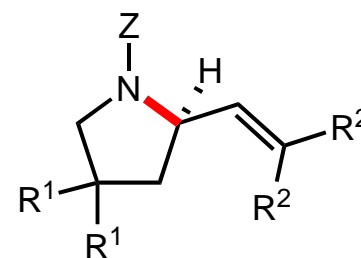
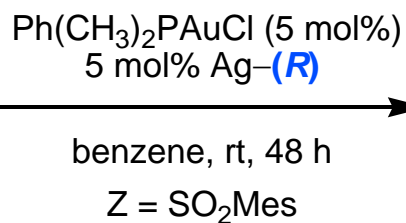
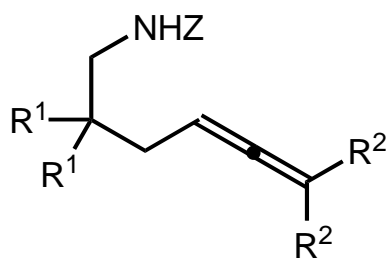
R² = Me, Et, cyclic



41-99% yields
70-99% ee



Toste *JACS* **2007**, 129, 2452.



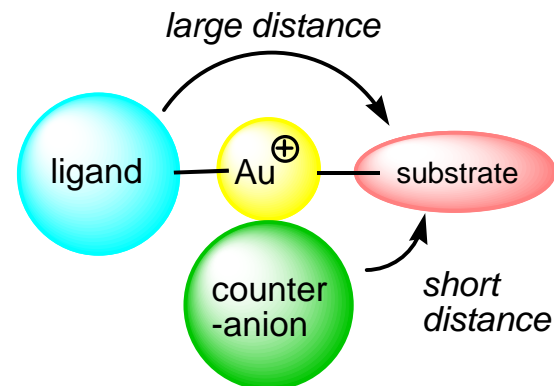
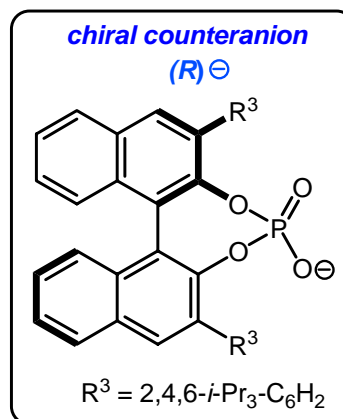
73-97% yields
96-99% ee

5 examples

R¹ = H, Me, -(CH₂)₅-

R² = Me, -(CH₂)₄-, -(CH₂)₅-

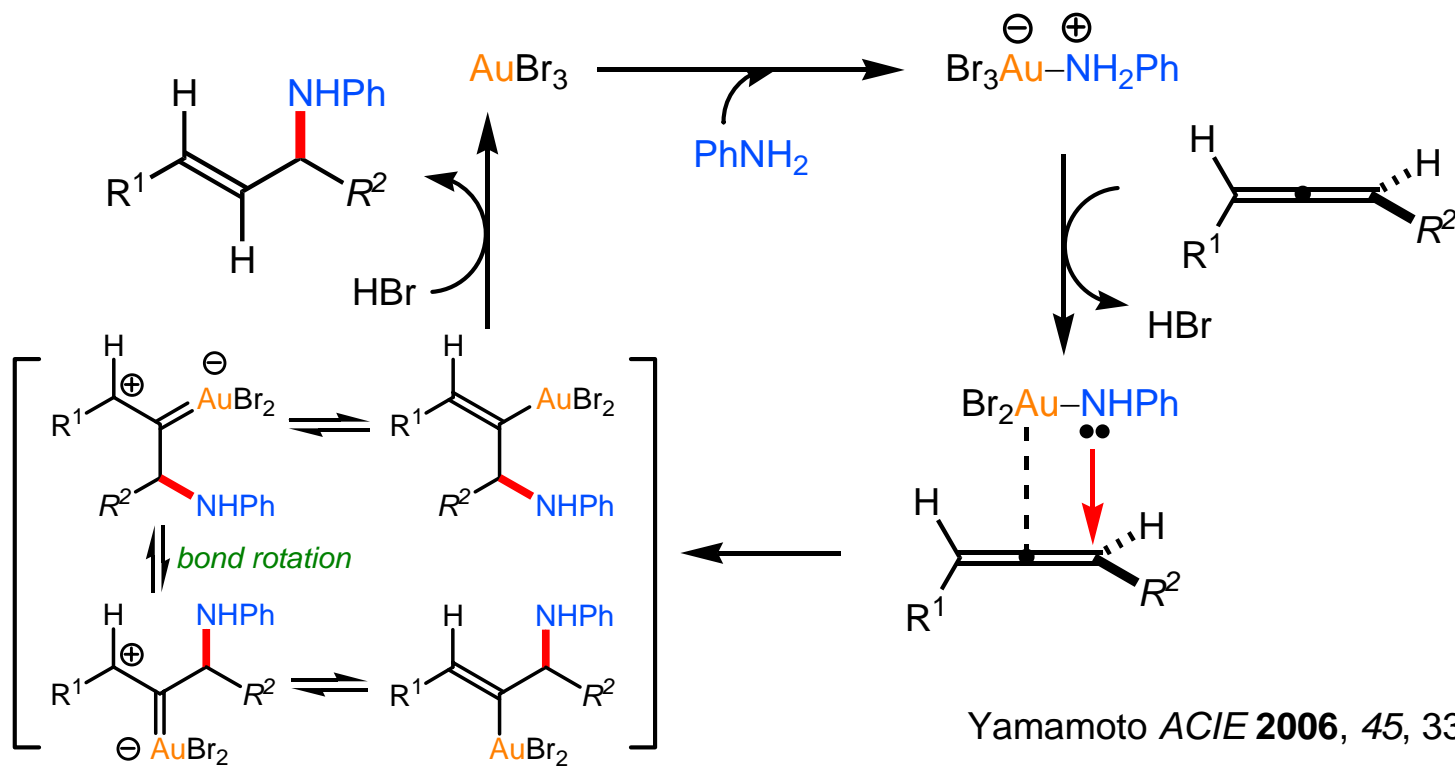
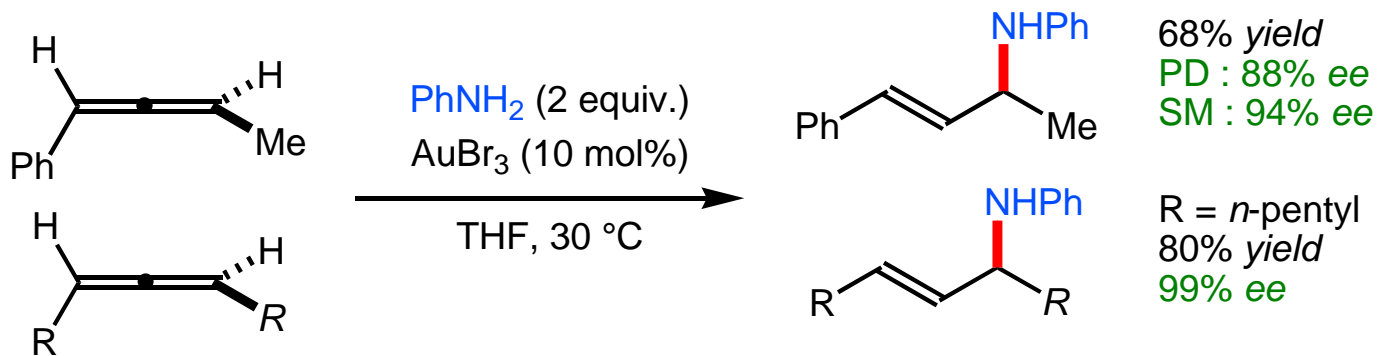
Toeste *Science* **2007**, 317, 496.



Intermolecular Hydroamination

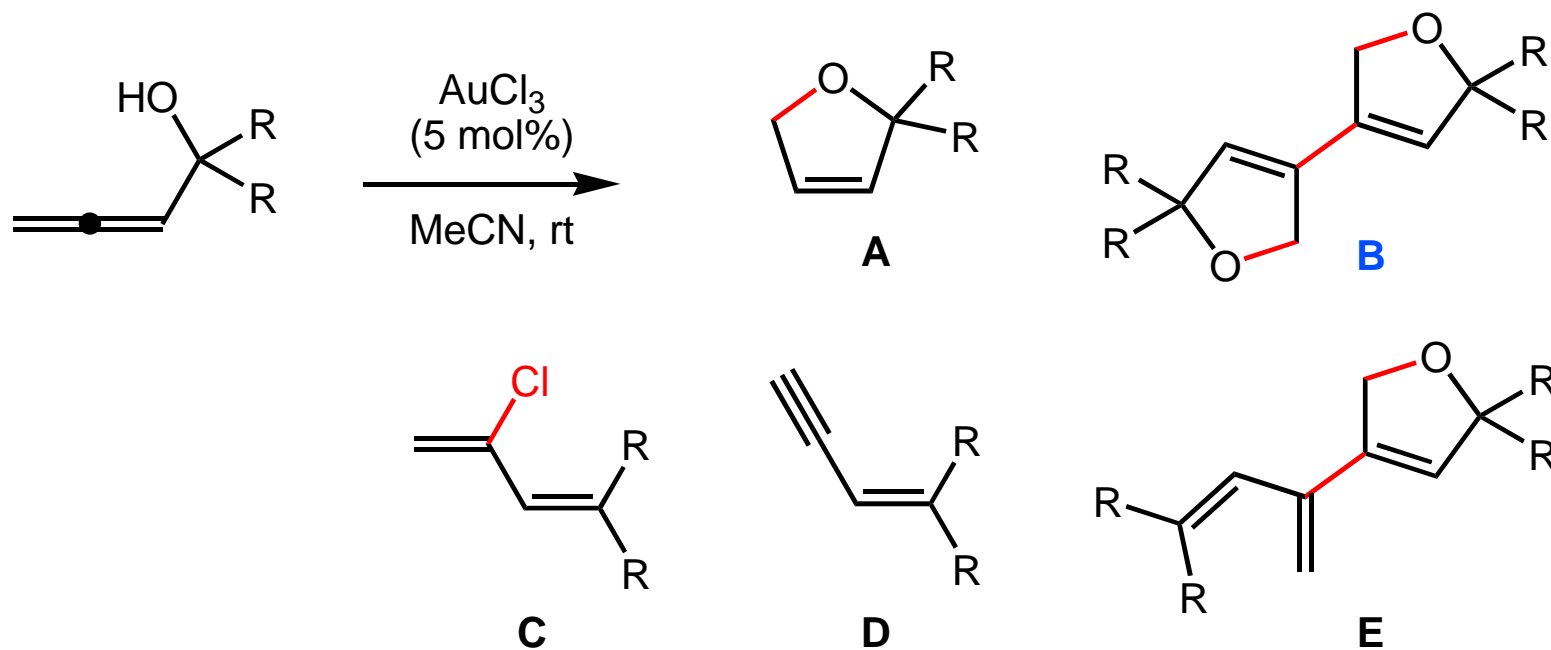
Mechanism of Chiral Transfer

Activation of Allenes



Intramolecular Hydroalkoxylation

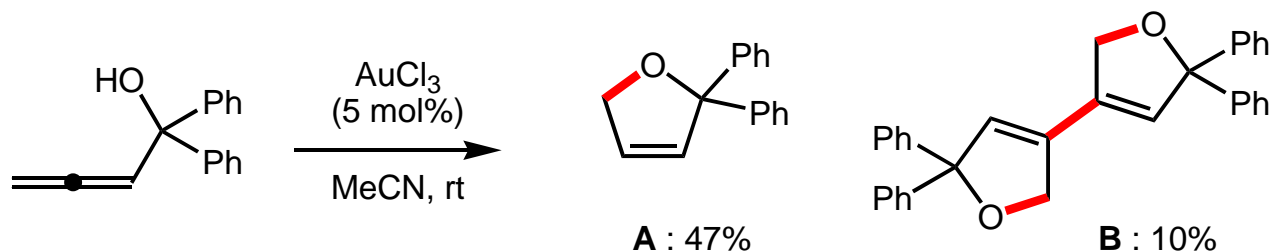
In-situ Reduction of Au(III)



- B** : oxidative coupling
C : $\text{S}_{\text{N}}1$ -like substitution by Cl^-
D : 1,4-elimination
E : dehydrative coupling

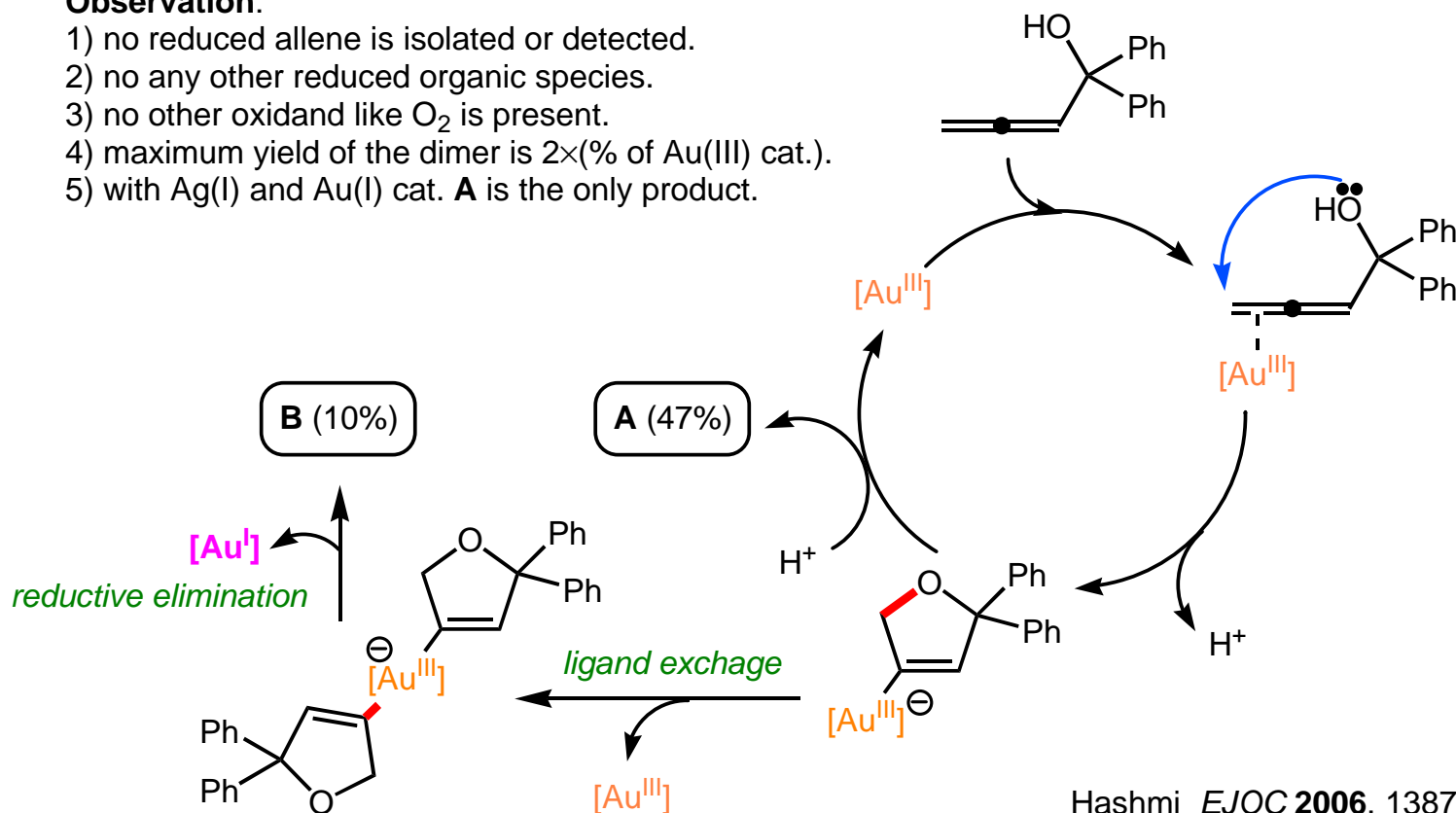
R	A	B	C	D	E
– $(\text{CH}_2)_5$ –	47%	10%	1%	ND	ND
Ph	31%	6%	8%	4%	21%

In-situ Reduction of Au(III) Plausible Mechanism



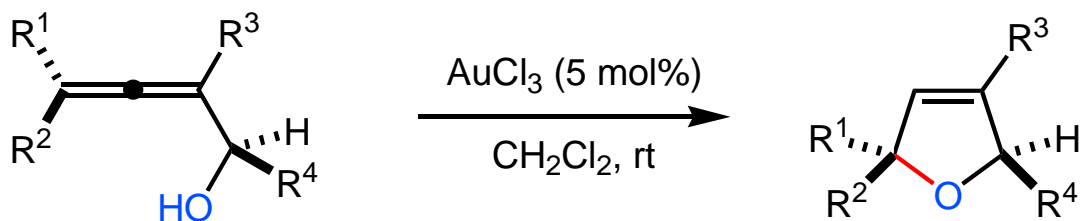
Observation:

- 1) no reduced allene is isolated or detected.
- 2) no any other reduced organic species.
- 3) no other oxidand like O_2 is present.
- 4) maximum yield of the dimer is $2 \times (\% \text{ of Au(III) cat.})$.
- 5) with Ag(I) and Au(I) cat. **A** is the only product.

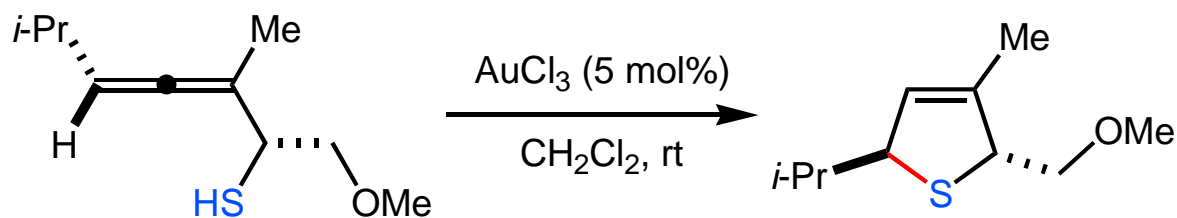


Intramolecular Hydroalkoxylation & Hydrothiolation

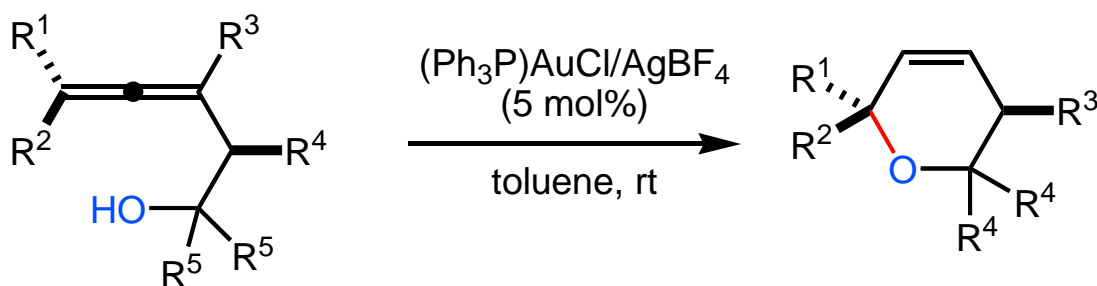
Activation of Allenes



R ¹	R ²	R ³	R ⁴	yield
<i>t</i> -Bu	Me	H	CO ₂ Et	74%
<i>t</i> -Bu	Me	Me	CO ₂ Et	94%
<i>t</i> -Bu	Me	H	CH ₂ OH	24%
H	Me	Me	CH ₂ OTBS	77%



88% yield, >99:1 *dr*



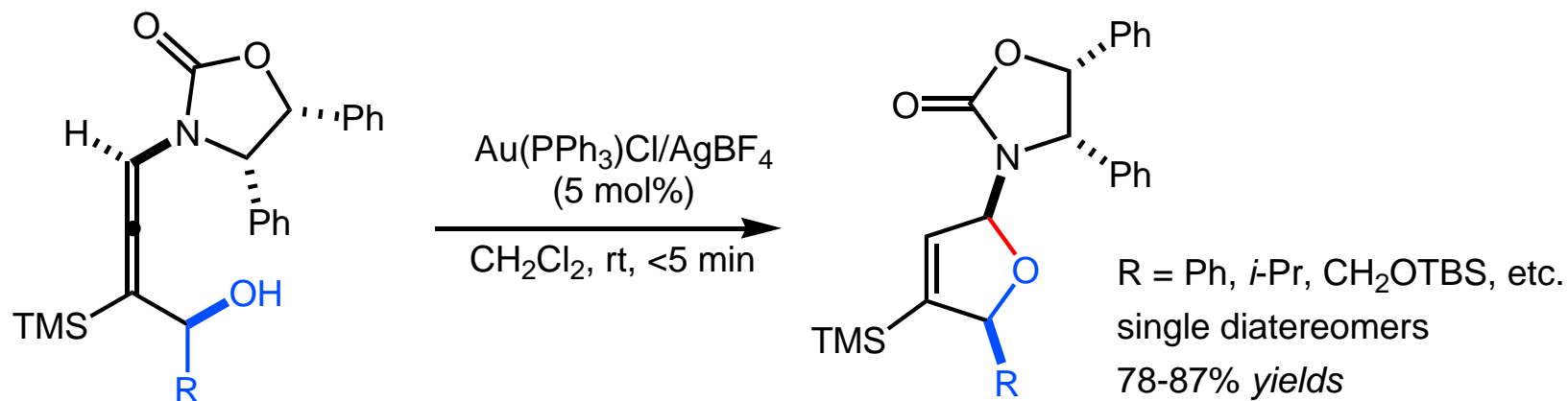
R¹, R² = H, alkyl, aryl
 R³ = H, Me
 R⁴ = H, OAc, CO₂Et
 R⁵ = H, Me

32-84% yield

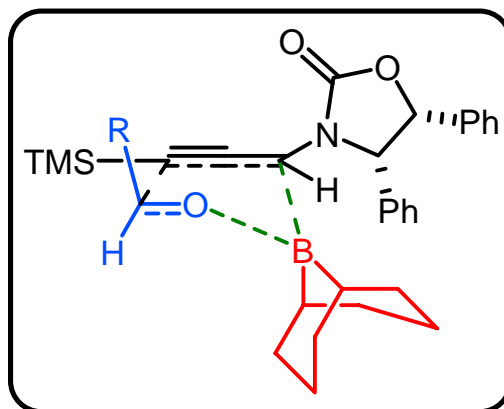
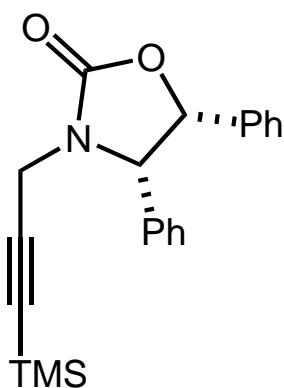
Krause *OL* **2001**, 3, 2537.; *ACIE* **2006**, 45, 1897.; *OL* **2006**, 8, 4485.

Intramolecular Hydroalkoxylation

Activation of Allenes



- 1) *n*BuLi
- 2) *B*-MeO-9-BBN
- 3) BF₃OEt₂
- 4) RCHO

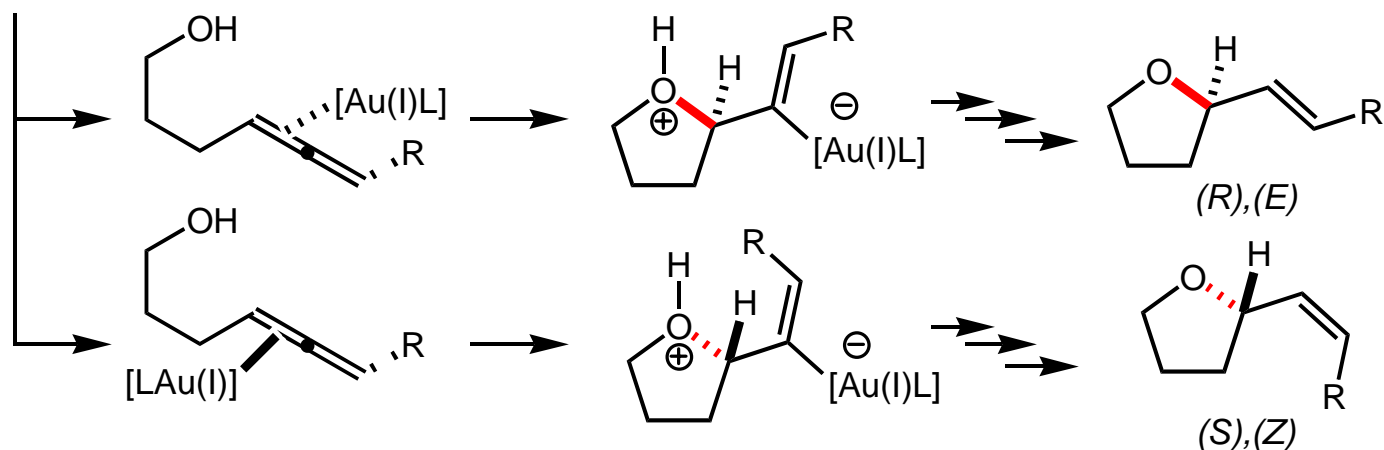
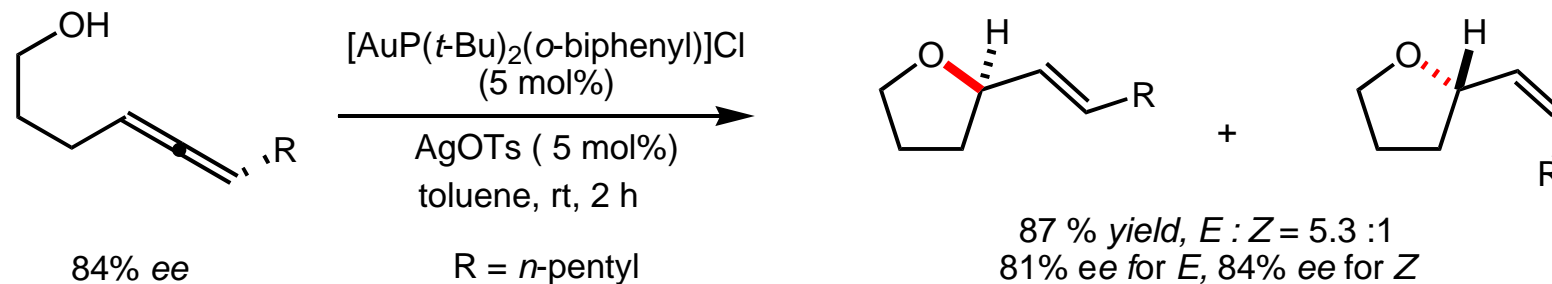
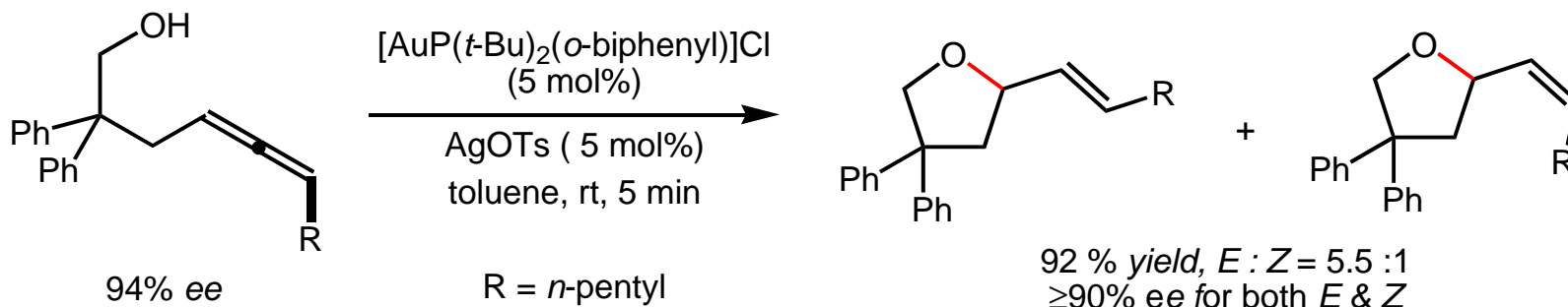


Hegedus *JOC* **2006**, 71, 8658.

Preparation of allenamides :
Hegedus *JOC* **2005**, 70, 8628.

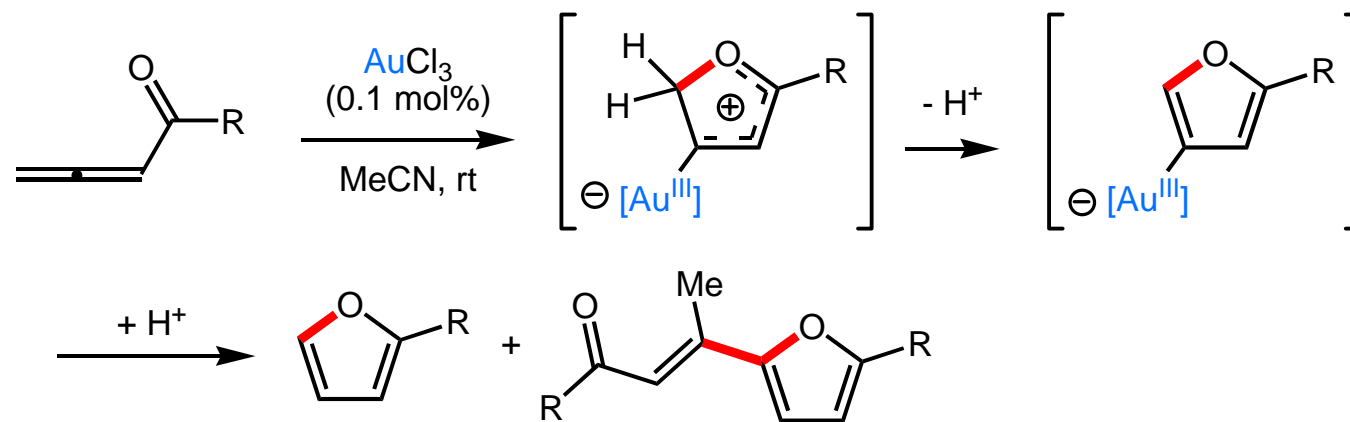
Intramolecular Enantioselective Hydroalkoxylation

Activation of Allenes

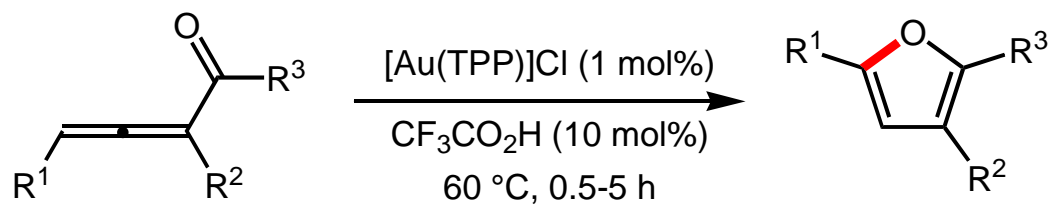


Widenhoefer *JACS* **2006**, 128, 9066.

Ketone Carbonyl as Nucleophiles

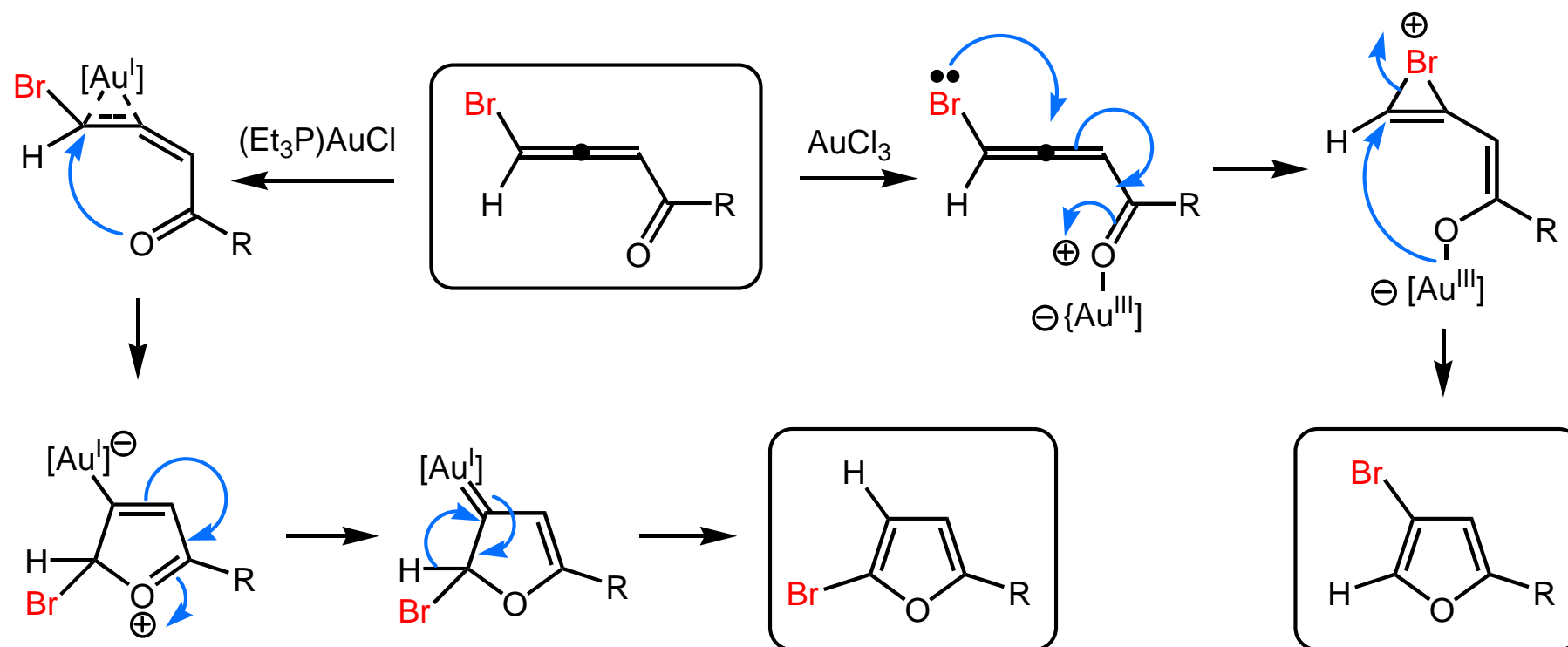


R = 4-(O ₂ N)C ₆ H ₄	88%	4%
R = 3-(MeO)C ₆ H ₄	34%	38%
R = CH ₃	45%	36%

Hashmi *ACIE* **2000**, 39, 2285. $\text{Au}(\text{TPP}) = \text{Au}(\text{III})$ porphyrin $\text{R}^1 \sim \text{R}^3 = \text{H}, \text{alkyl}, \text{aryl}$
73-97% yieldsChe *OL* **2006**, 8, 325.

Ketone Carbonyl as Nucleophiles

Regiodivergent Synthesis of Halofurans

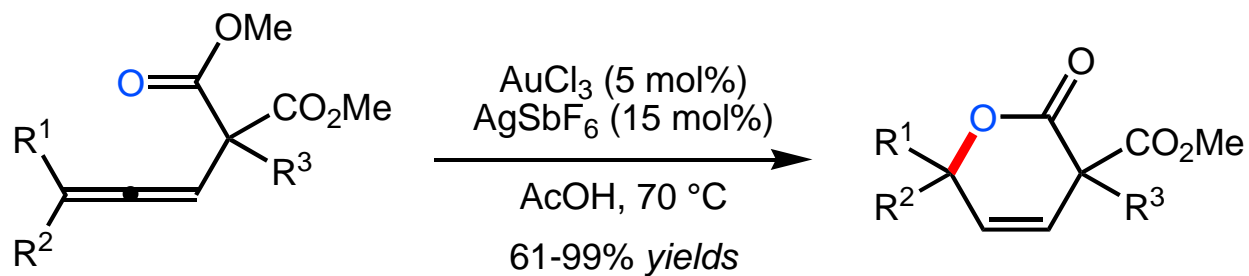
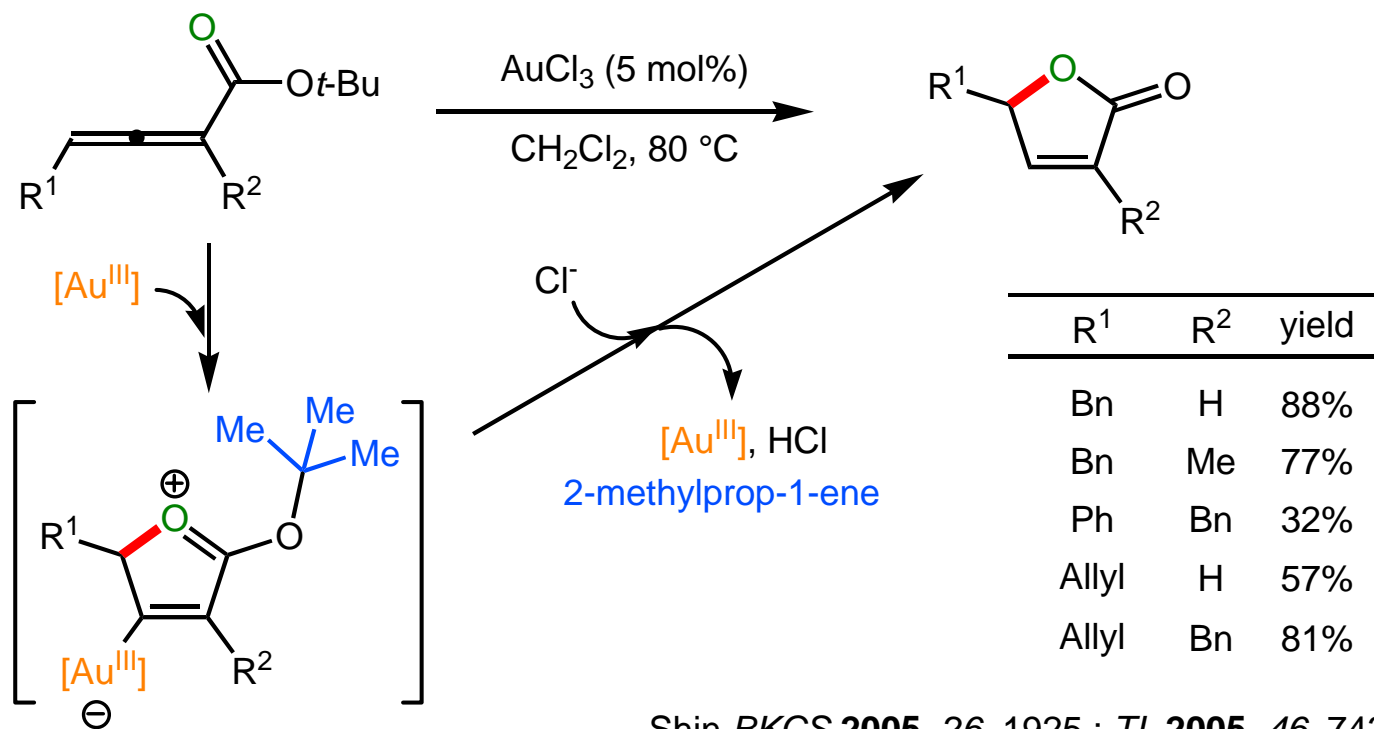


R = C₈H₁₇

AuCl ₃	95%
(Et ₃ P)AuCl	1%

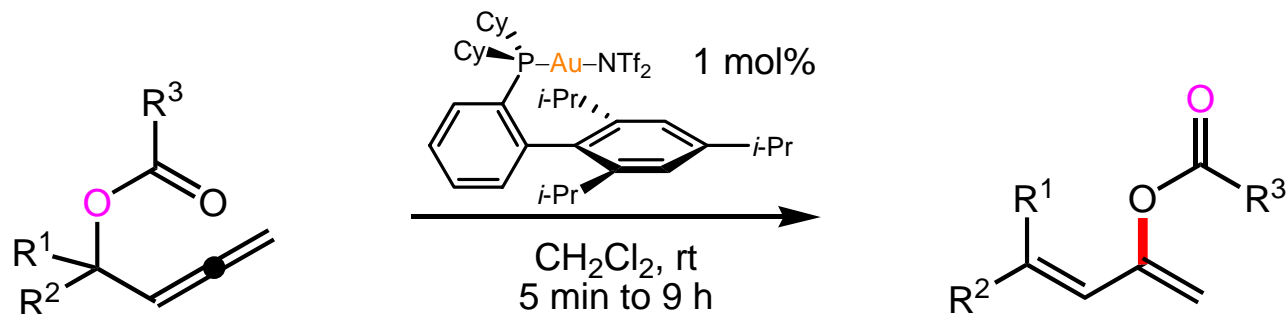
5%
99%

Ester Carbonyl as Nucleophiles

Piera *OL* **2007**, 9, 2235.

Isomerization of Allenyl Carbinol Esters

Activation of Allenes

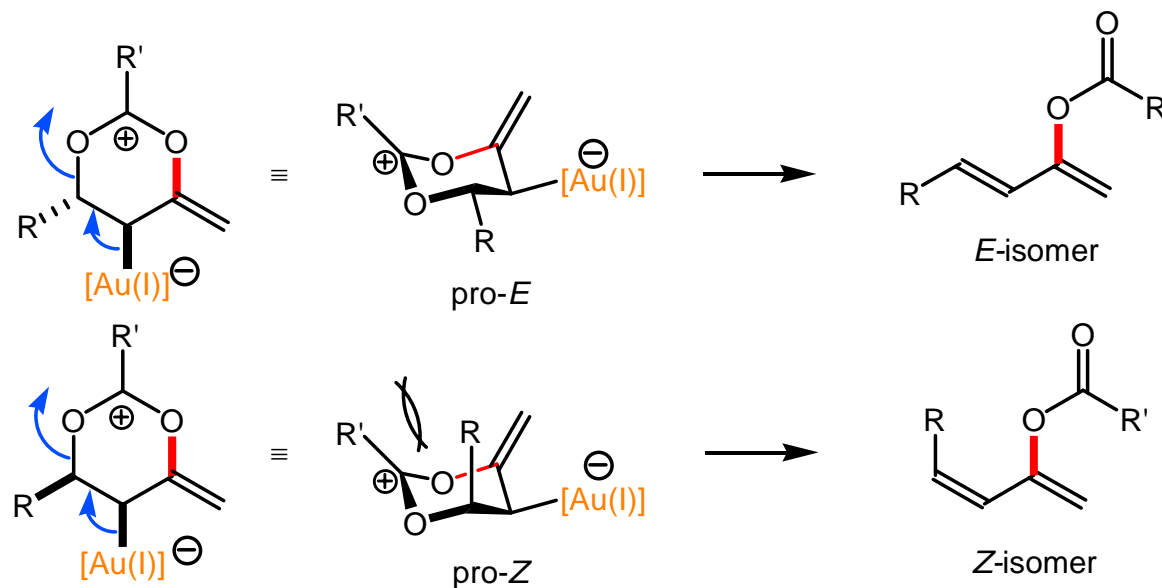


R¹ = H, alkyl
R², R³ = aryl, alkyl

12 examples
53-100% yields

2° carbinol esters → 1:8 to 0:1 (**Z:E**)
3° carbinol esters → 1:1 to 1:2 (**Z:E**)

Source of the *E/Z* Selectivity

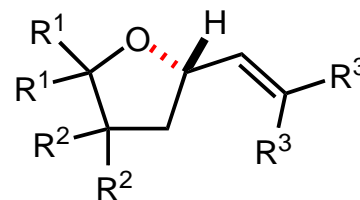
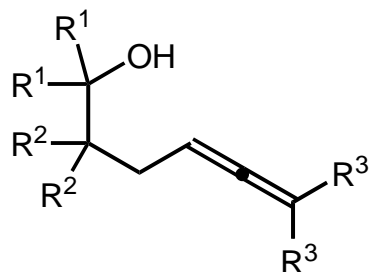
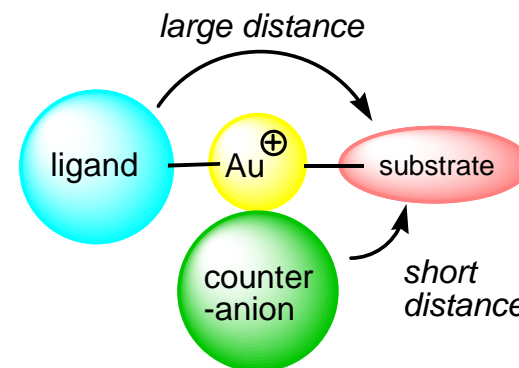
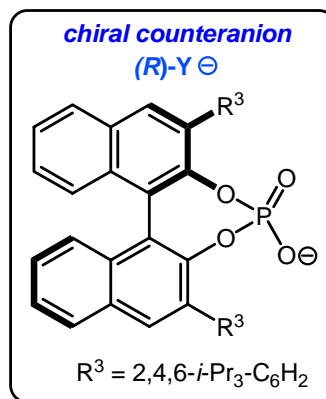


Gagosz *OL* 2007, 9, 985.

Chiral Counteranion Induced Stereoinduction

Activation of Allenes

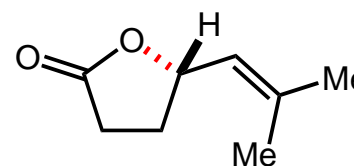
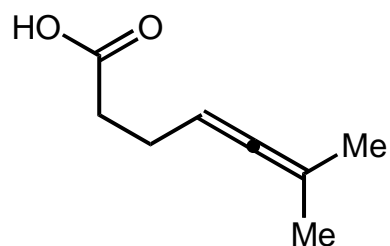
Toeste Science **2007**, 317, 496.



8 examples

$R^1 = \text{H, Me, Ph}$; $R^2 = \text{H, Me}$
 $R^3 = \text{H, Me, Et, } -(\text{CH}_2)_4-$

79-96% yields
90-99% ee



$L = (R)\text{-Z}$, $X = 4\text{-}(\text{NO}_2)\text{-C}_6\text{H}_3\text{-COO}^-$

$L = \text{dppm}$, $X = (R)\text{-Y}$

$L = (R)\text{-Z}$, $X = (R)\text{-Y}$

$L = (S)\text{-Z}$, $X = (R)\text{-Y}$

80% yield, 38% ee

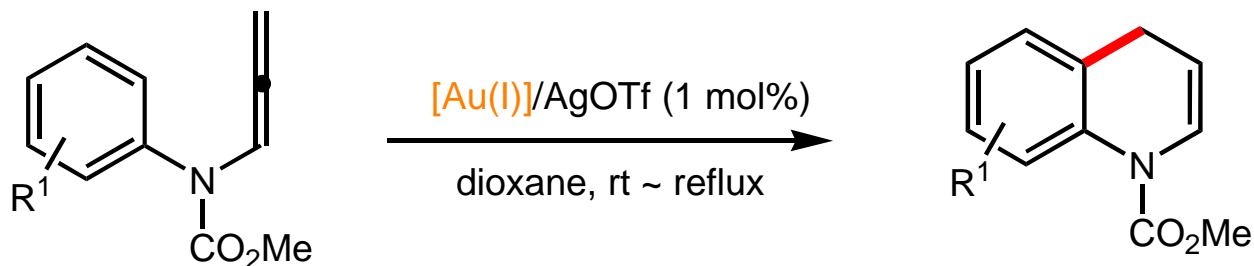
89% yield, 12% ee

91% yield, 3% ee (mismatching pair)

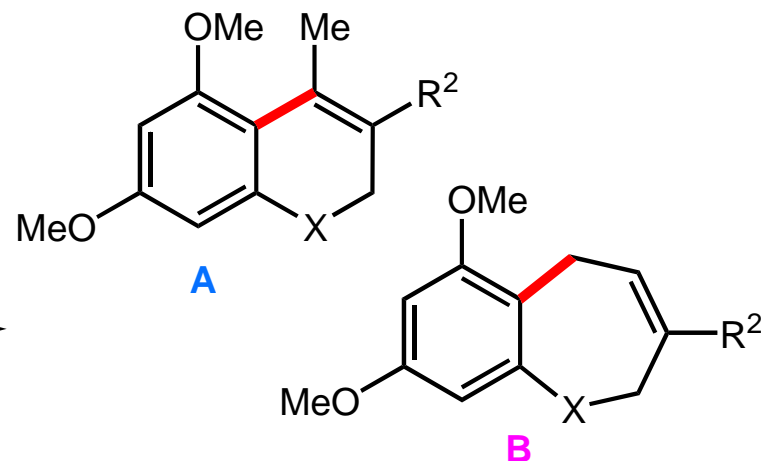
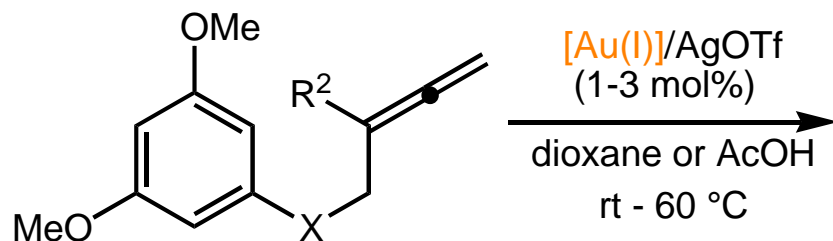
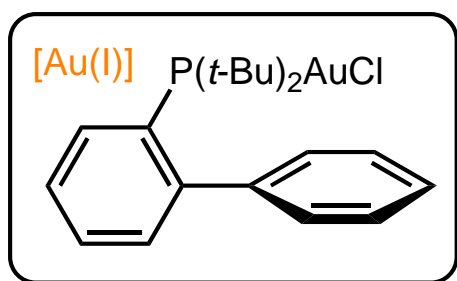
88% yield, 82% ee (matching pair)

e⁻-Rich Benzene Ring as Nucleophiles

Activation of Allenes



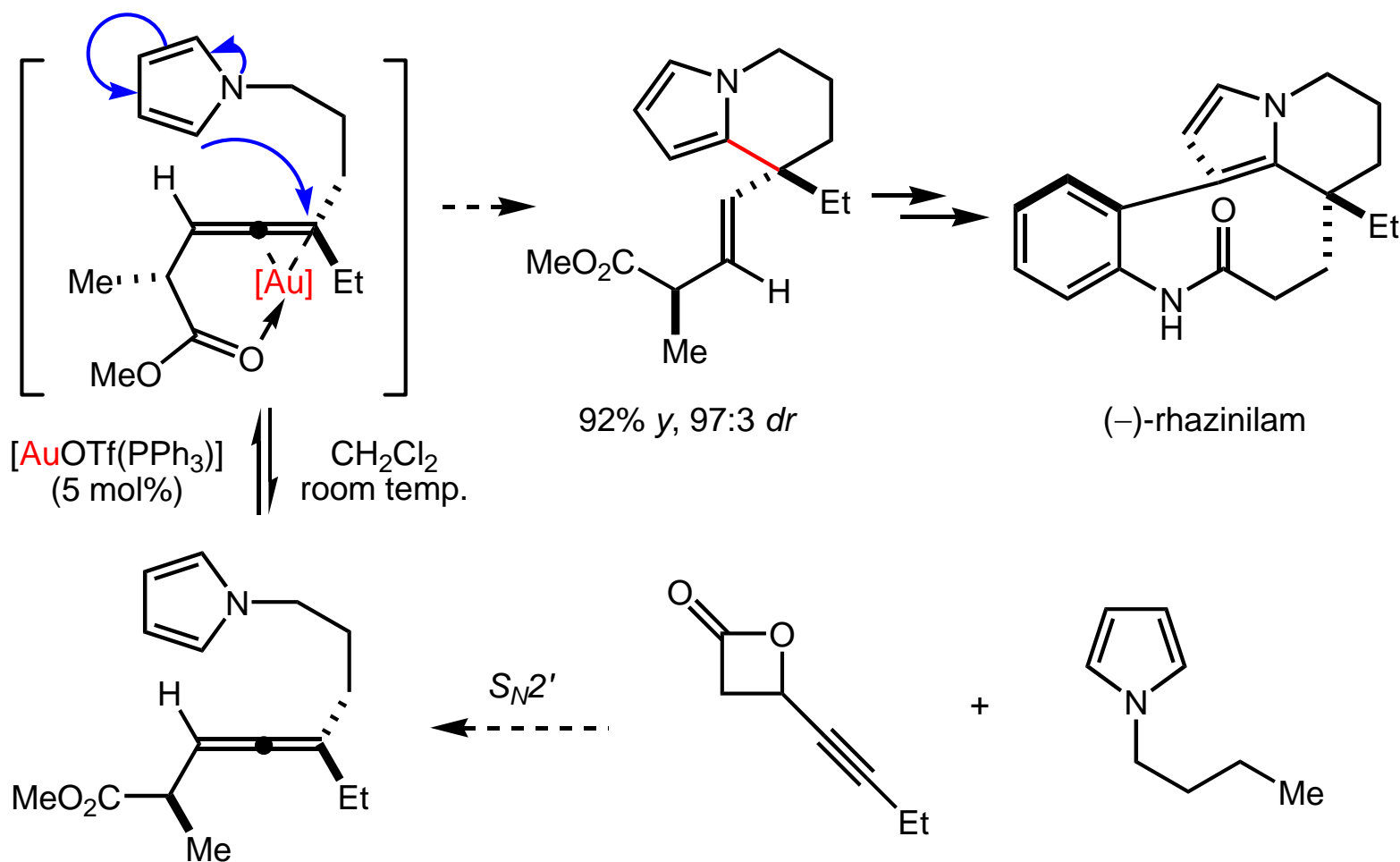
R¹ = 3-OMe (90%), 3,5-di-OMe (92%)
3-Me (72%), 3,5-di-Me (88%), H (40%)



X = N-CO₂Me, R² = H (A 85%)
X = N-CO₂Me, R² = Me (A 75%)
X = O, R² = H (A 98%)
X = O, R² = Me (A 48%, B 52%)

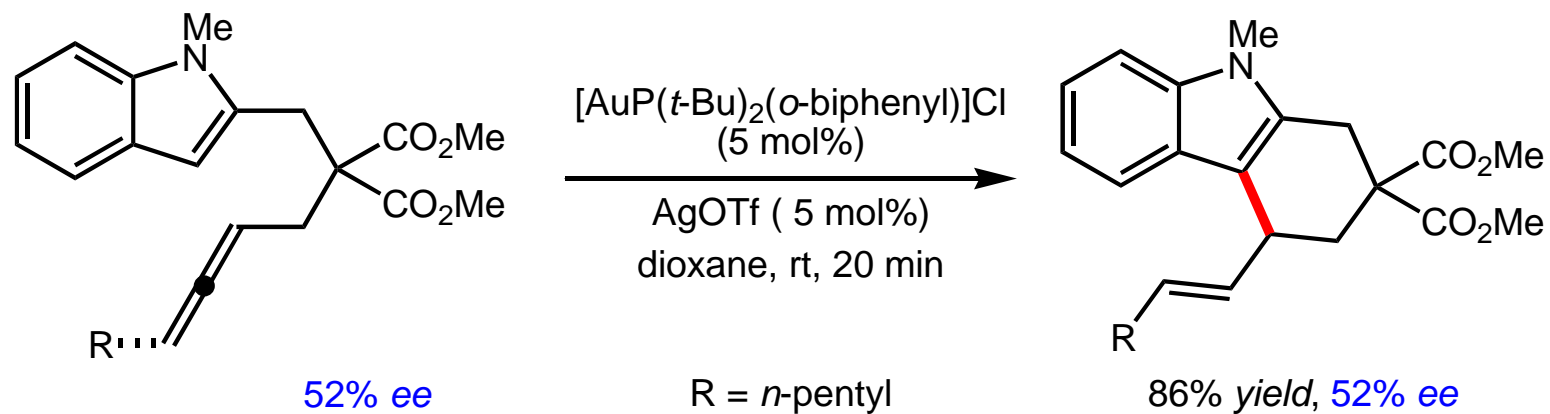
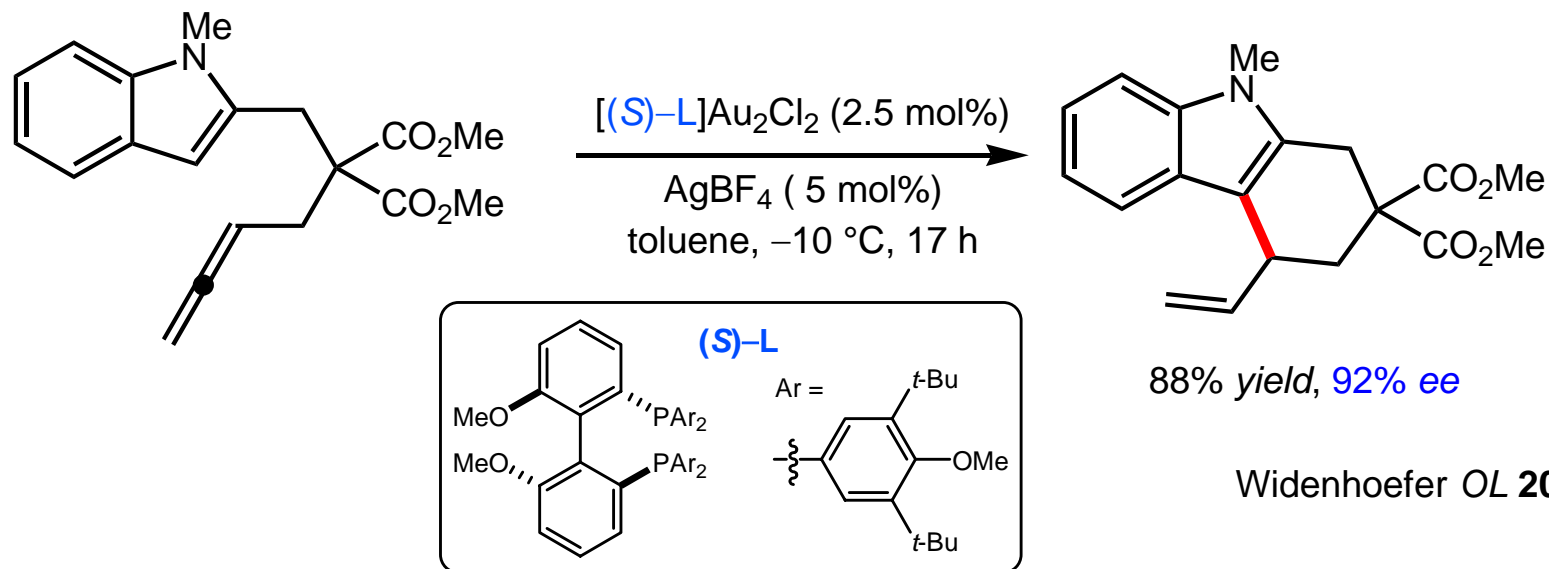
Fujii OL, 2007, 9, ASAP.

Pyrrole Rings as Nucleophiles

(-)-Rhazinilam (2006)

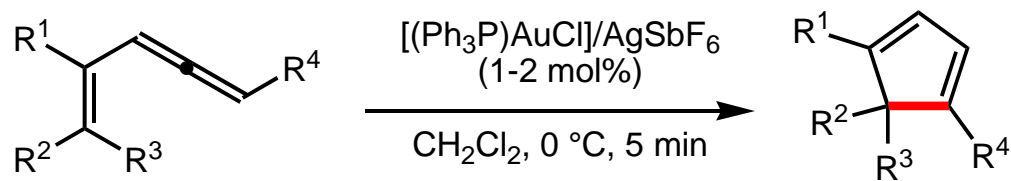
Nelson JACS 2006, 128, 10352.

Indole Rings as Nucleophiles

Widenhoefer *JACS* **2006**, 128, 9066.Widenhoefer *OL* **2007**, 9, 1935.

Alkenes as Nucleophiles : *Metalla-Nazarov*

Activation of Allenes



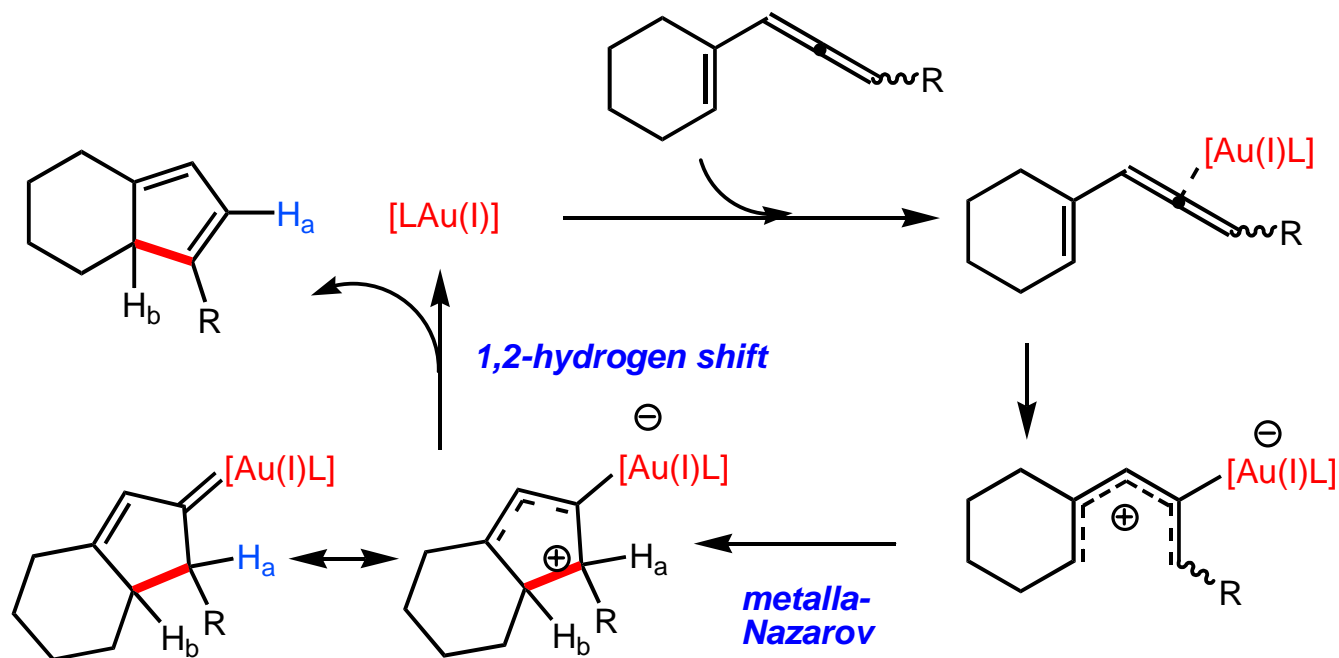
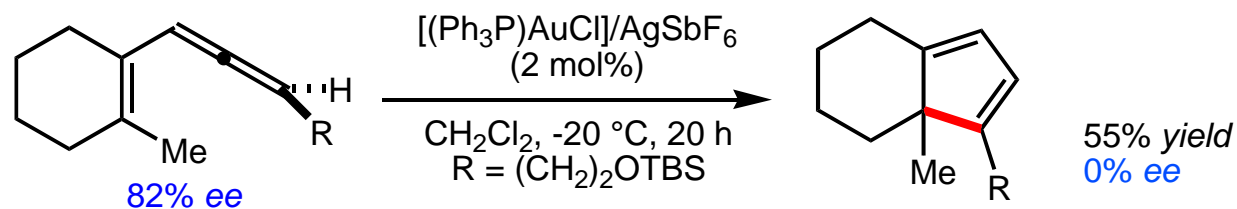
9 examples

$R^1 = \text{Me, 6-member-ring w/ } R^2$

$R^2 = \text{H, CH}_2\text{OBn, CH}_2\text{OTHP}$

$R^3 = \text{H, Me; } R^4 = \text{alkyl, Ph}$

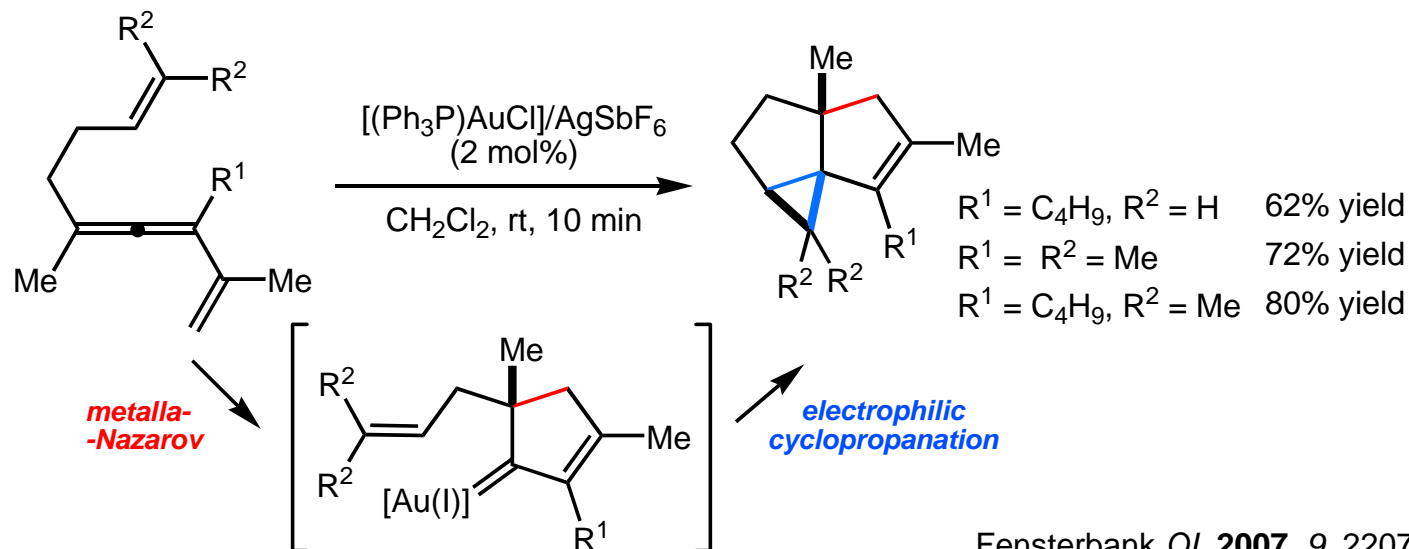
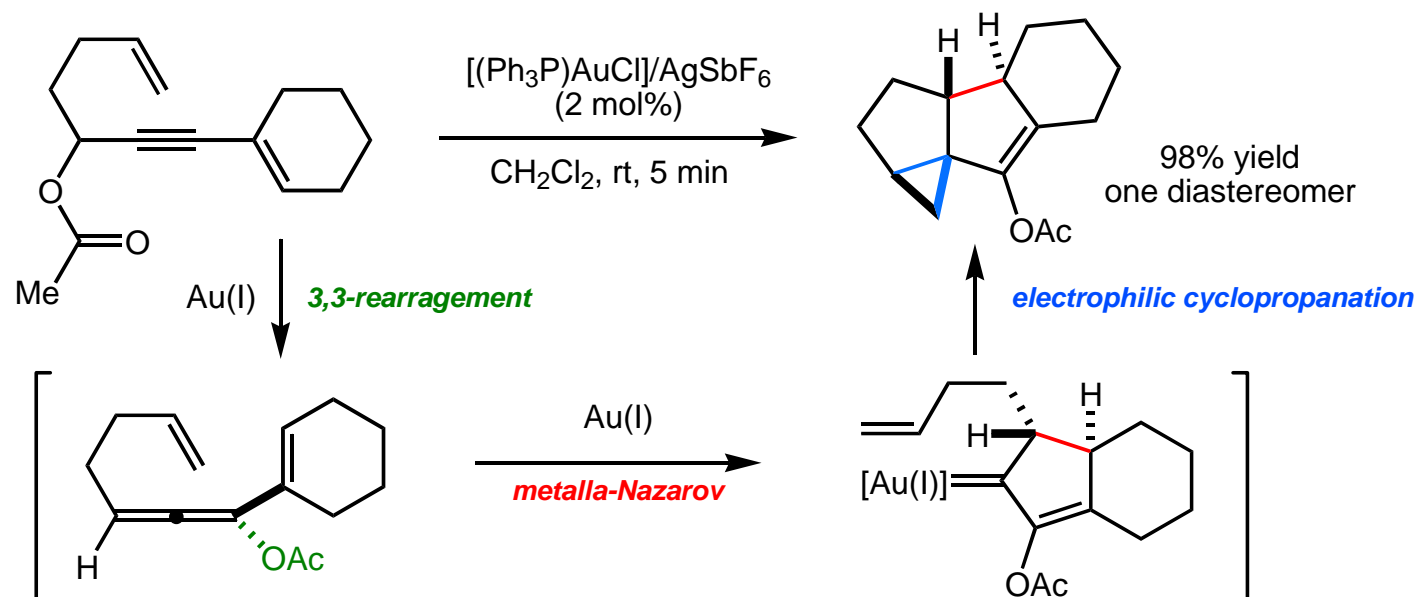
39-98% yields



Toste *ACIE* **2007**, *46*, 912.

Alkenes as Nucleophiles : *Metalla-Nazarov*

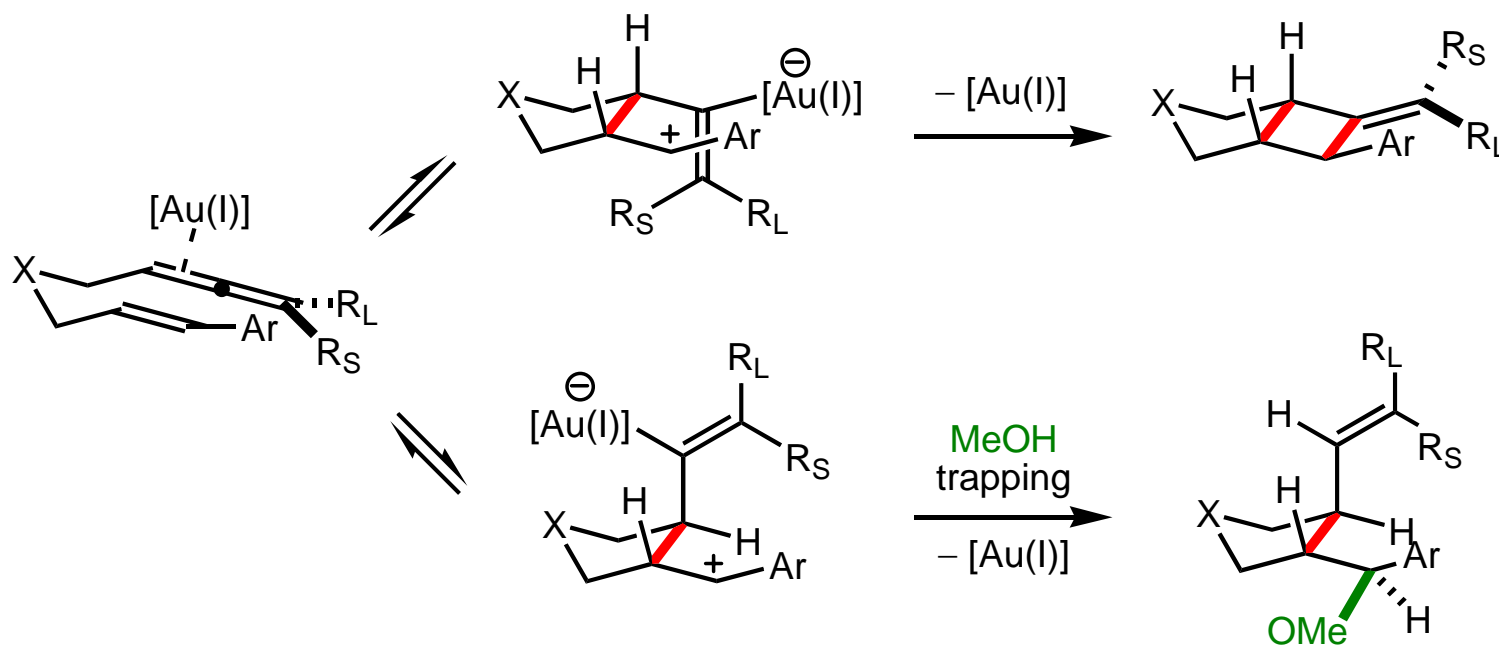
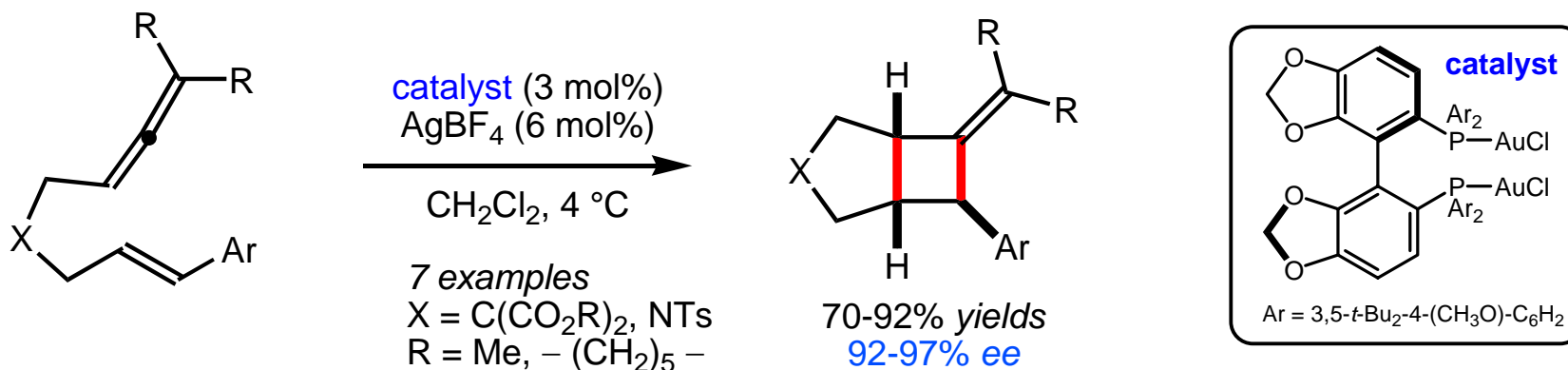
Activation of Allenes



Fensterbank *OL* 2007, 9, 2207.

Alkenes as Nucleophiles

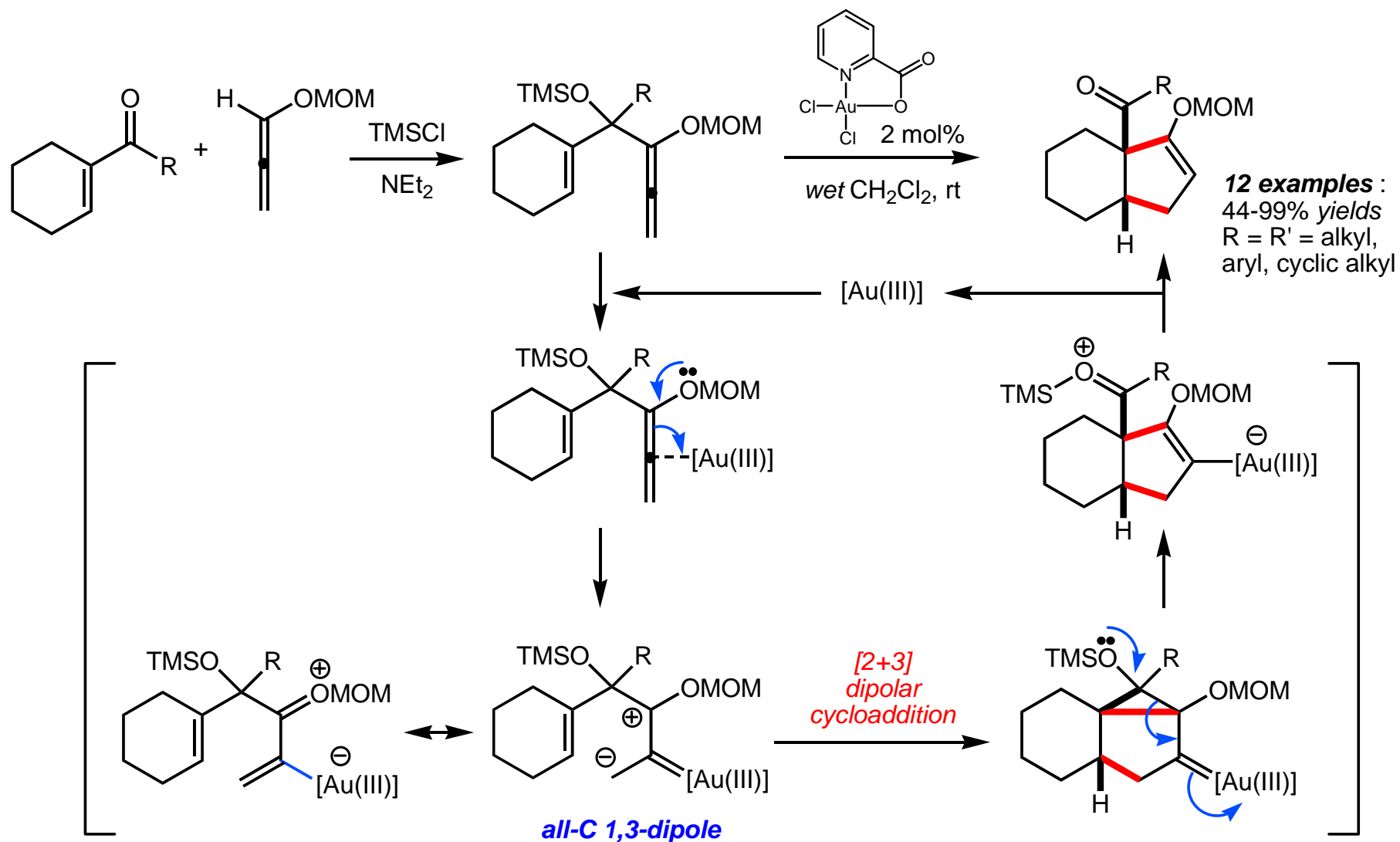
Activation of Allenes



Toste *JACS* **2007**, 129, 12402.

Au(III)-Induced All-Carbon 1,3-Dipoles

Activation of Allenes



Zhang *JACS* **2007**, 129, 6398.

I. Introduction

II. Activation of Alkynes

III. Activation of Allenes

IV. Activation of Alkenes

V. Summary

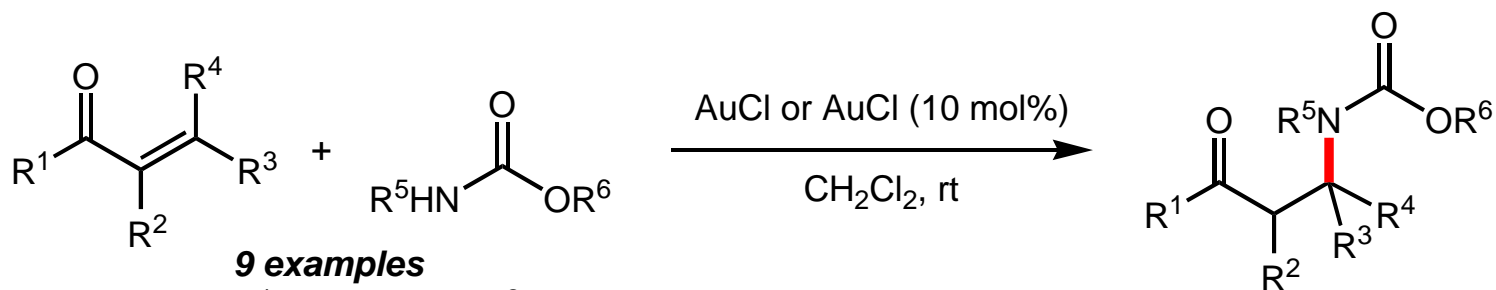
Nitrogen Nucleophiles : Hydroamination
Nitrene Transfer

Oxygen Nucleophiles : Hydroalkoxylation

Carbon Nucleophiles : Enolates

Intramolecular Hydroamination

Activation of Alkenes



9 examples

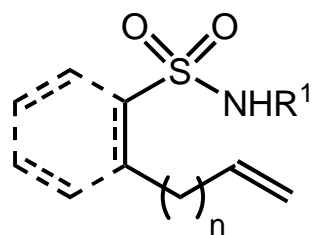
$\text{R}^1 = \text{alkyl, aryl}; \text{R}^2 = \text{H, alkyl};$

$\text{R}^3, \text{R}^4 = \text{H, alkyl}$

$\text{R}^5 = \text{H, alkyl}; \text{R}^6 = \text{alkyl, Bn}$

51-100% yields

Kobayashi *OL*, **2002**, *4*, 1319.



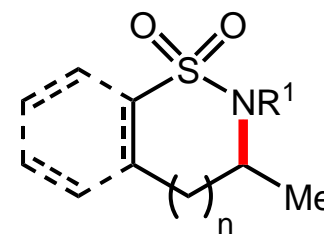
13 examples

$\text{R}^1 = \text{H, Et, } t\text{-Bu, Ts}$

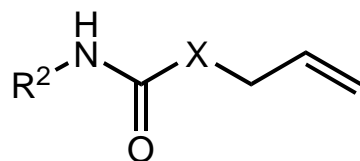
$[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgOTf (5 mol\%)}$
toluene, 60-100 °C, 12-48 h

or

DCE, microwave, 30 min



88-100% yields



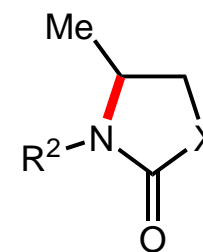
5 examples $\text{X} = \text{C, O}$

$\text{R}^2 = \text{Ph, } p\text{-Cl-C}_6\text{H}_4, \text{PhCO, Ts}$

$[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgOTf (20-100 mol\%)}$
toluene, 60-100 °C, 24-30 h

or

DCE, microwave, 30 min

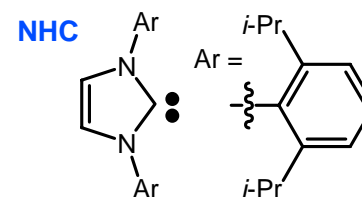
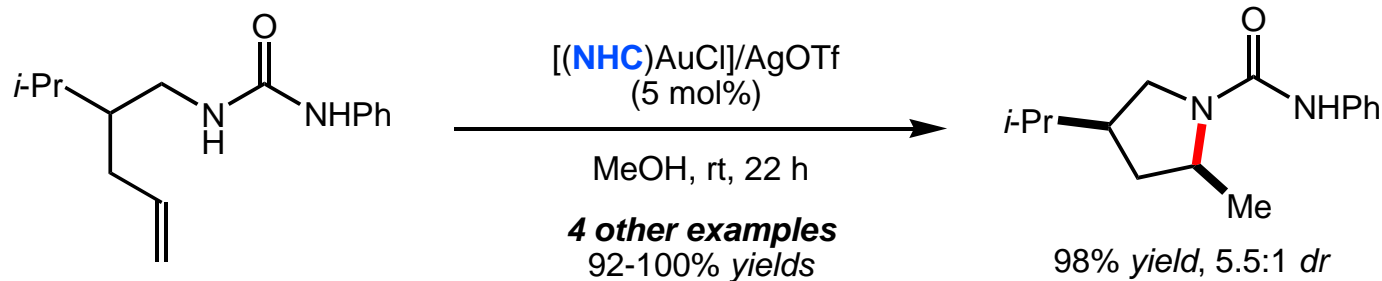


0-90% yields

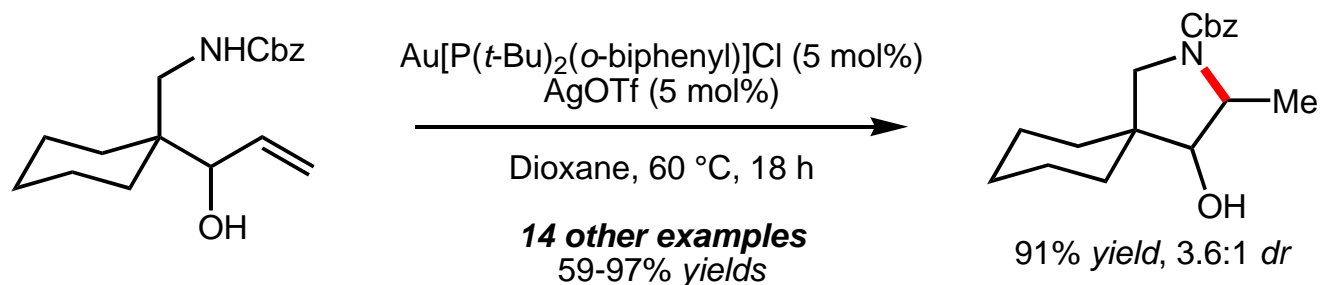
Che *OL*, **2006**, *8*, 2707.

Intramolecular Hydroamination

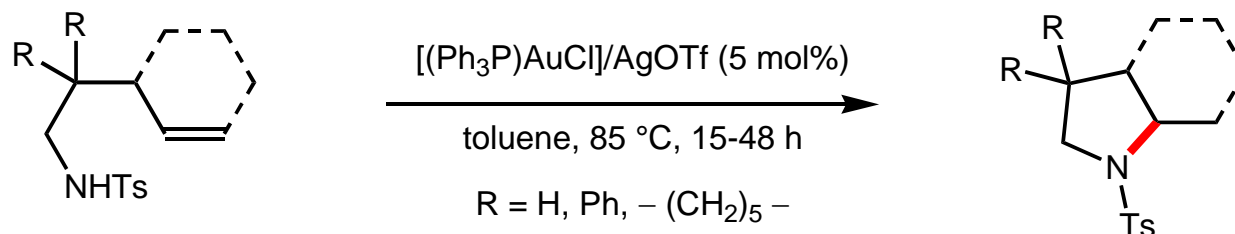
Activation of Alkenes



Widenhoefer *OL* **2002**, 8, 5303.



Widenhoefer *ACIE* **2006**, 45, 1747.

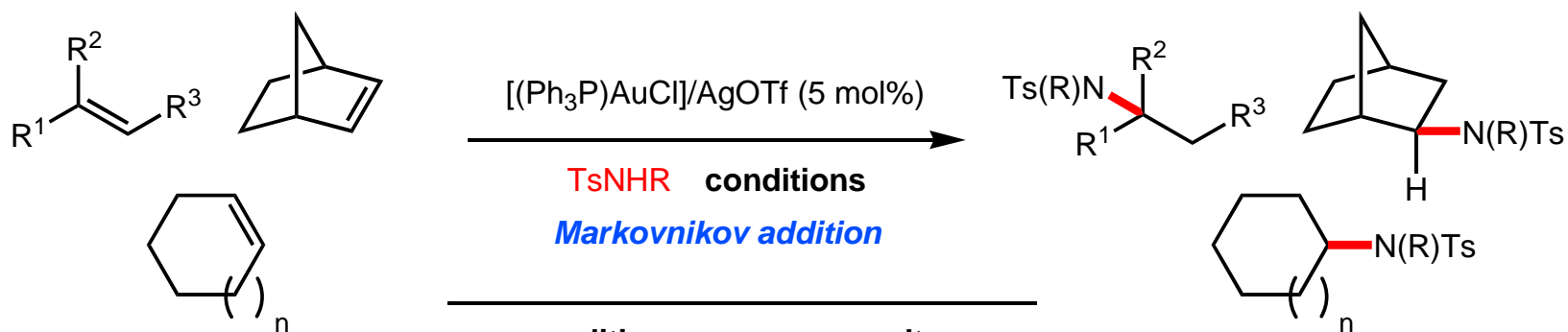


4 examples
91-99% yields

He *JACS* **2006**, 128, 1798.

Intermolecular Hydroamination

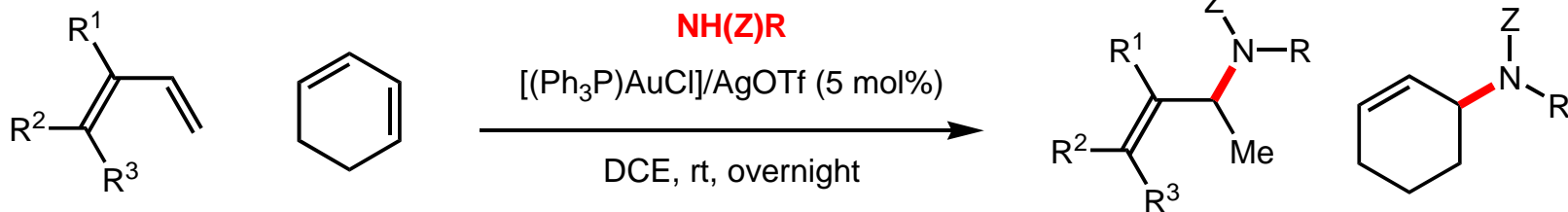
Activation of Alkenes



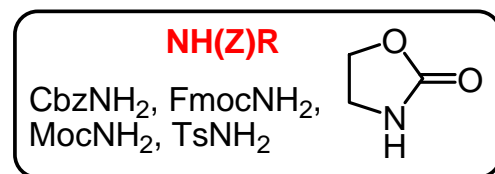
$\text{R}^1 = \text{R}^2 = \text{R}^3 =$
 H, alkyl, aryl

conditions	results
DCE, microwave 40-60 min	6 examples 50-97% yields
toluene, 85 °C 14-48 h	13 examples 44-95% yields

Che *OL*, **2006**, 8, 2707.
 He *JACS*, **2006**, 128, 1798.



$\text{R}^1 = \text{R}^2 =$
 $\text{R}^3 = \text{H or Me}$

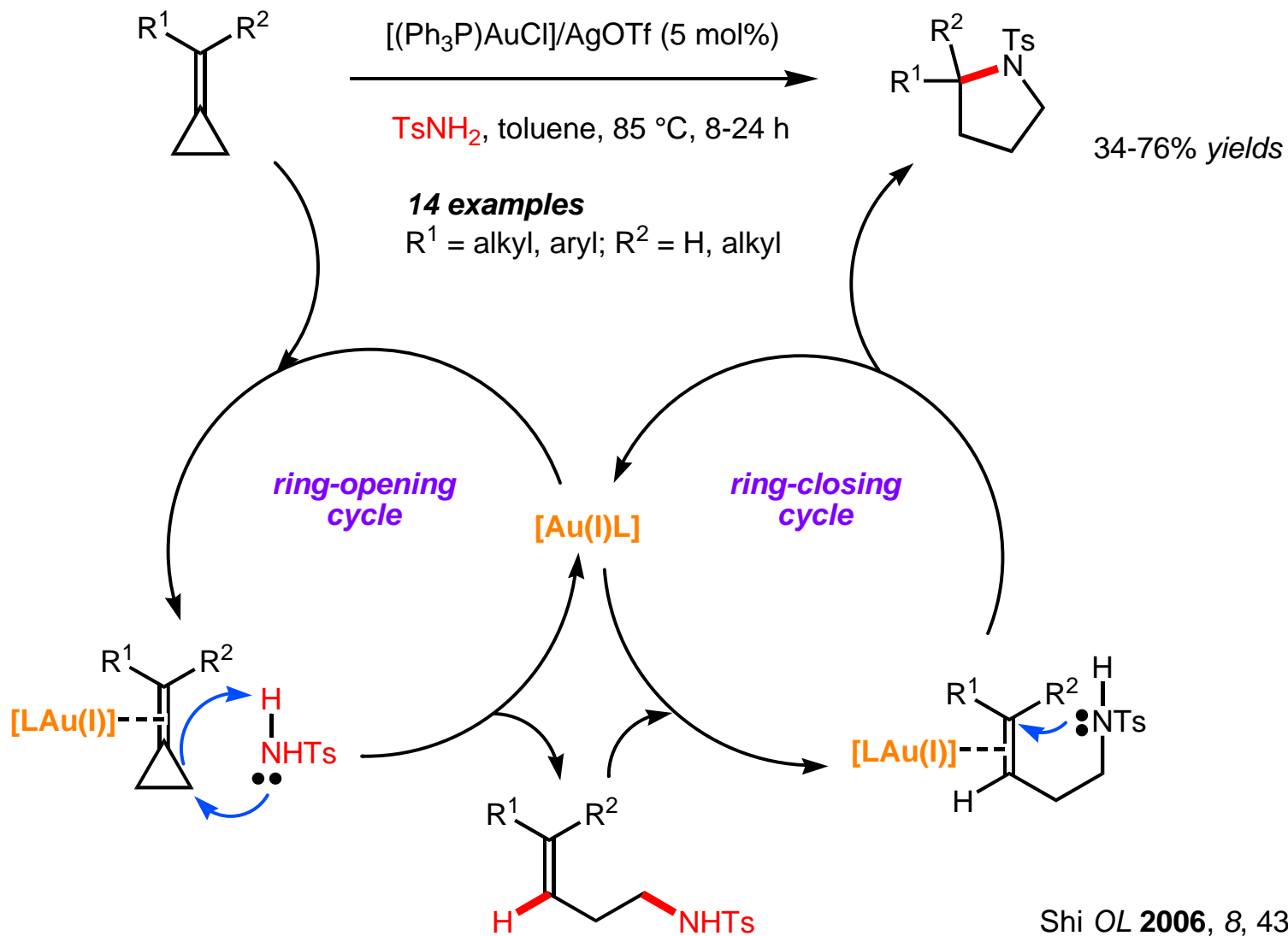


33-87% yields

He *ACIE*, **2006**, 45, 1744.

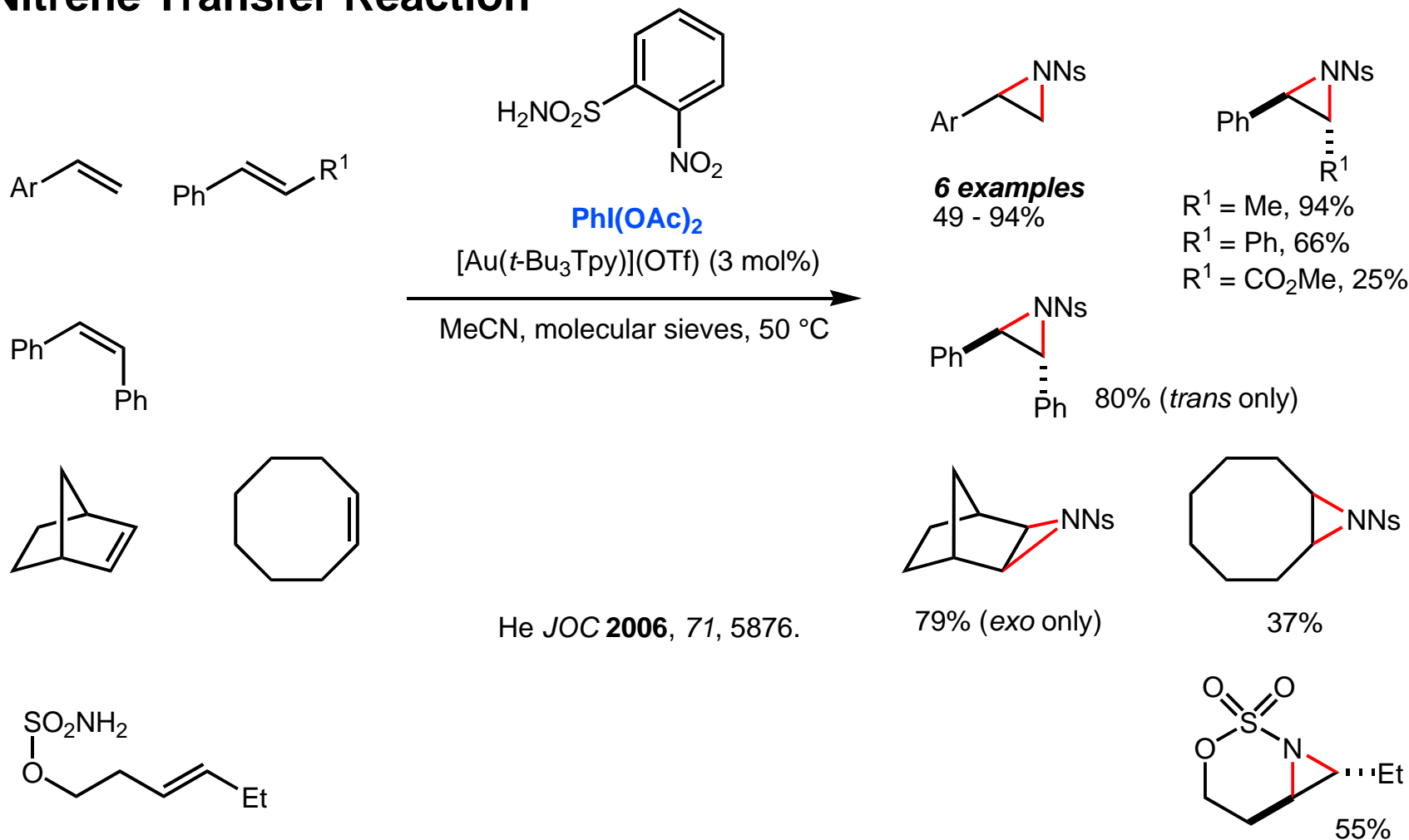
Domino Ring-Opening Ring-Closing Hydroamination

Activation of Alkenes



Nitrene Transfer Reaction

Activation of Alkenes



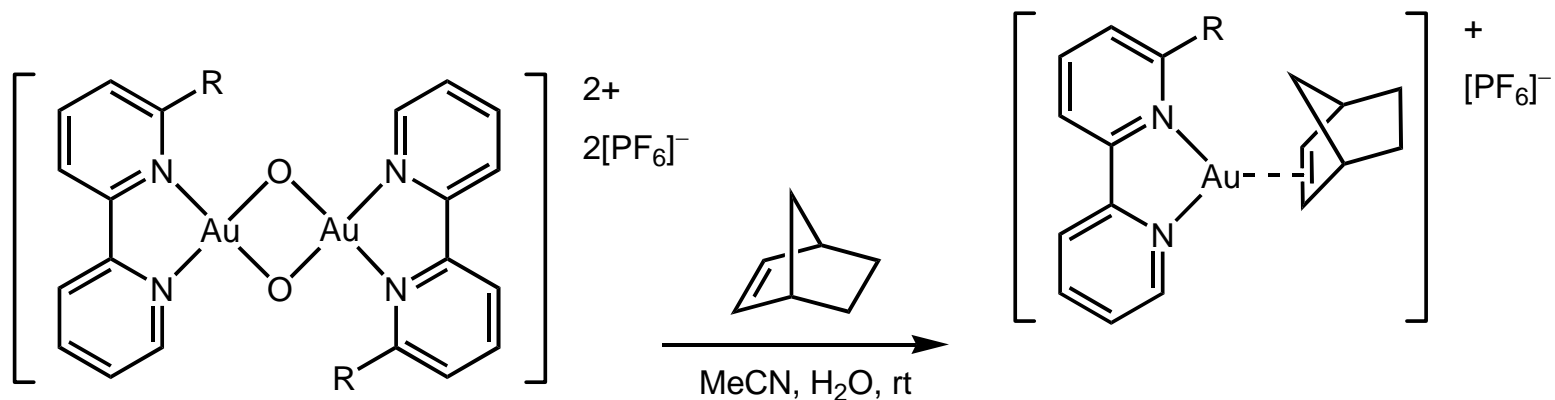
Au(III)-Au(I) Redox Mechanism

"all commonly used Au(I) Lewis acid did not show catalytic activity, which seems to argue strongly against the Lewis acid mechanism."

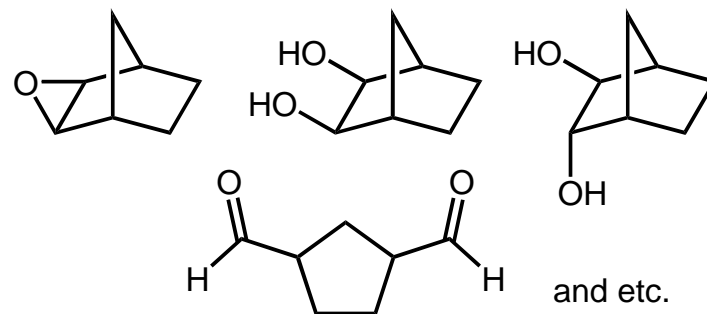
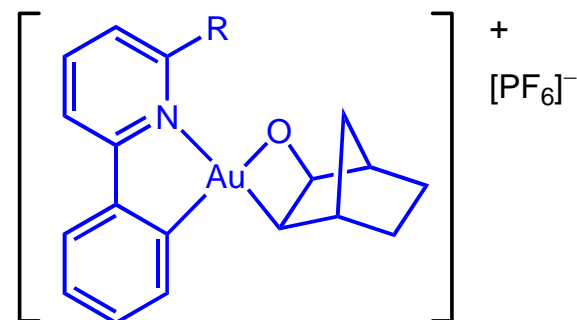
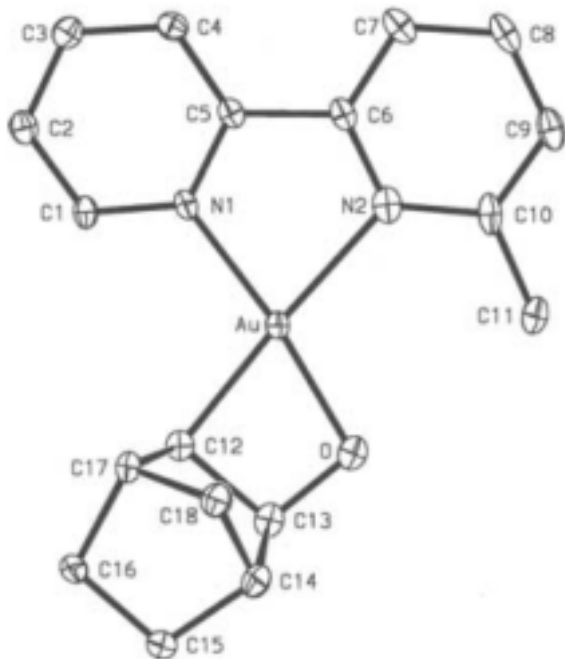
homocoupling of phenylboronic acid catalyzed by gold supported on nanocrystalline cerium oxide
 Corma *ACIE* **2005**, 44, 2242.

Au(III)-Oxo complexes with Cyclic Alkenes

Activation of Alkenes



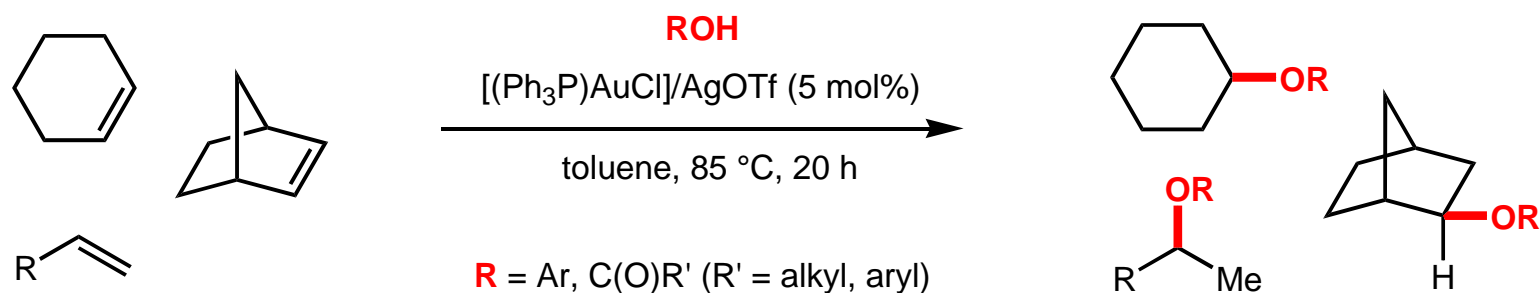
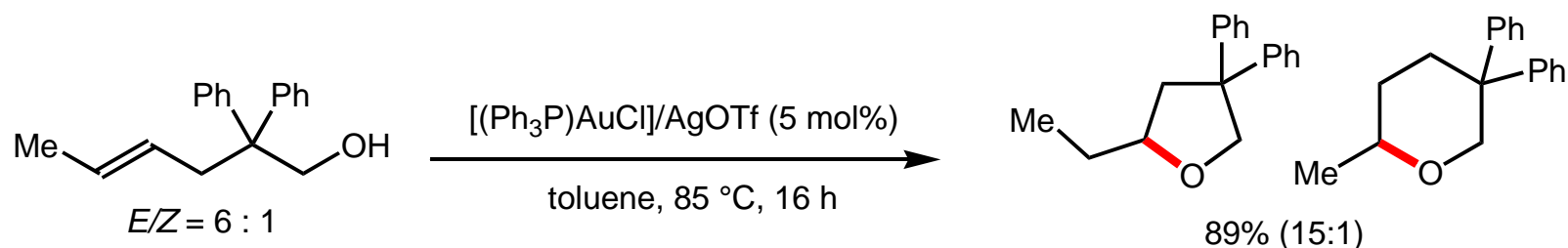
R = Me, *i*-Pr, neopentyl
2,6-(H₃C)C₆H₃



Cinellu *ACIE* **2005**, *44*, 6892.

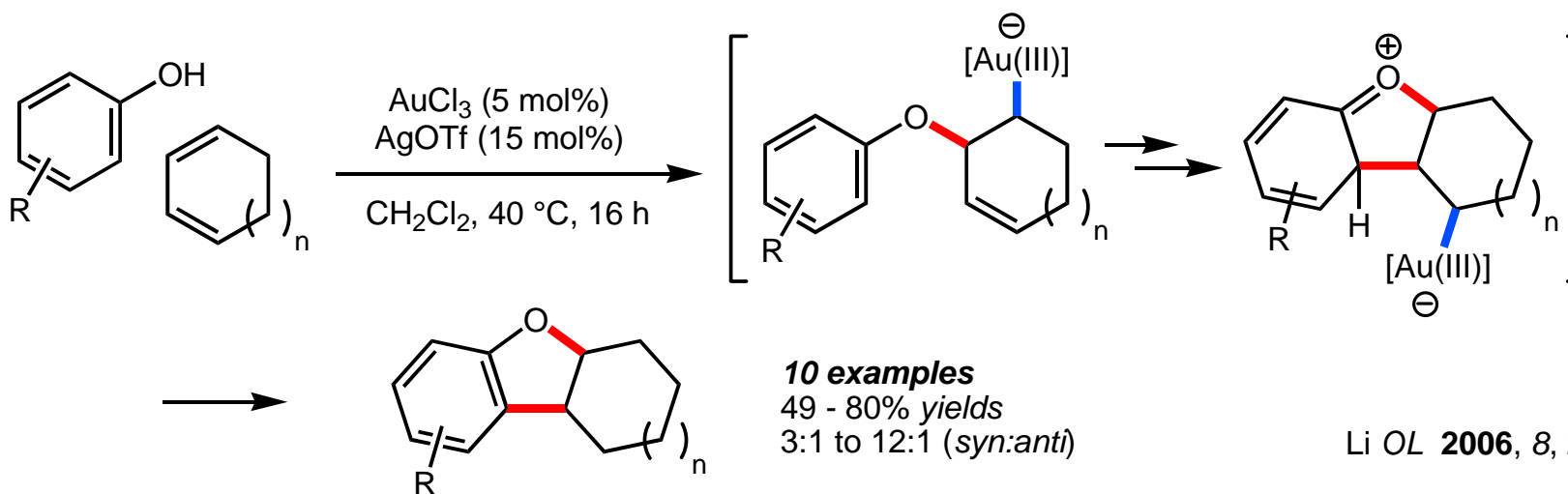
Intra- and intermolecular Hydroalkoxylation

Activation of Alkenes



16 examples
58 - >95% yields

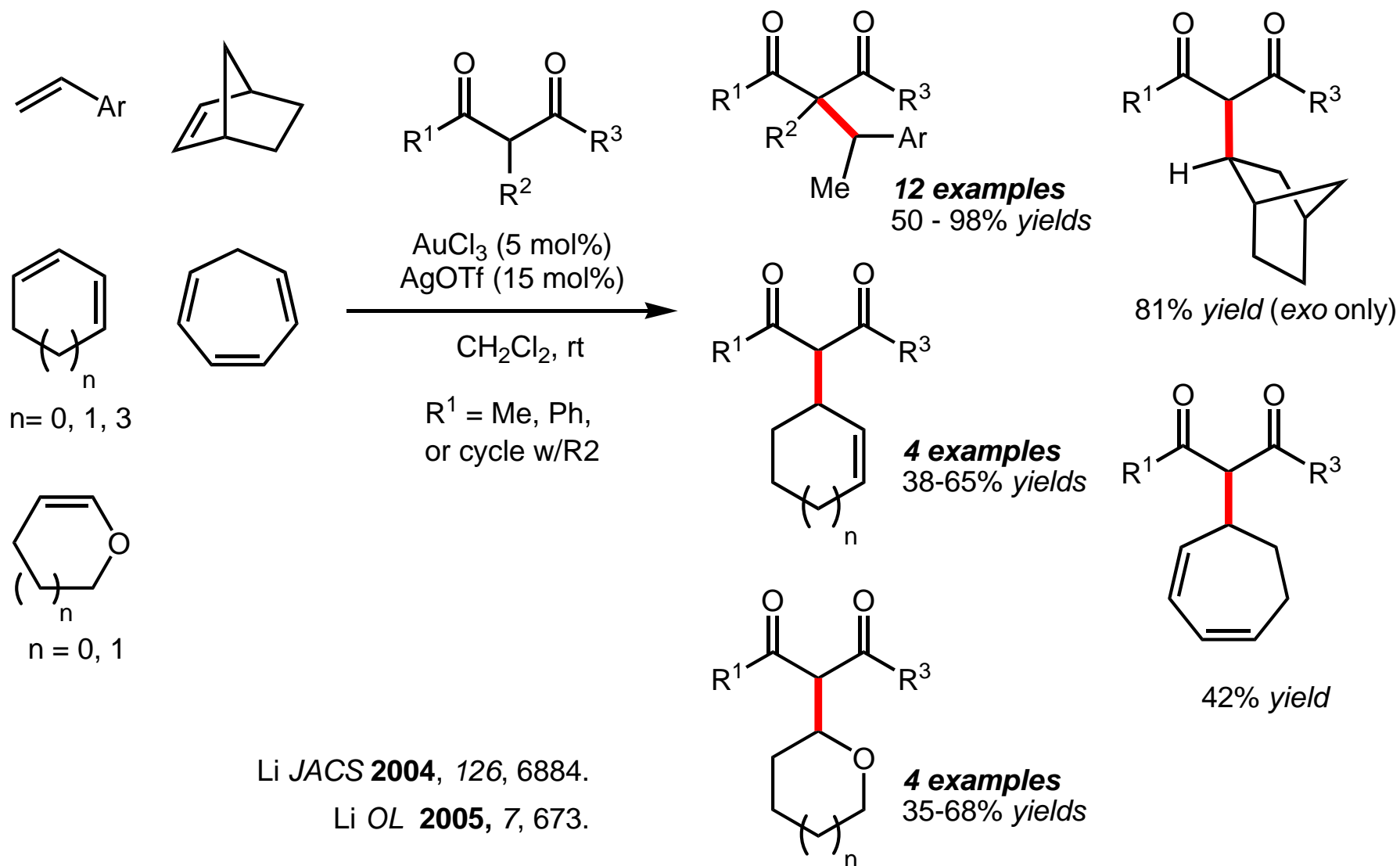
He *JACS* **2005**, 127, 6966.



Li *OL* **2006**, 8, 2397.

Enolates as Nucleophiles

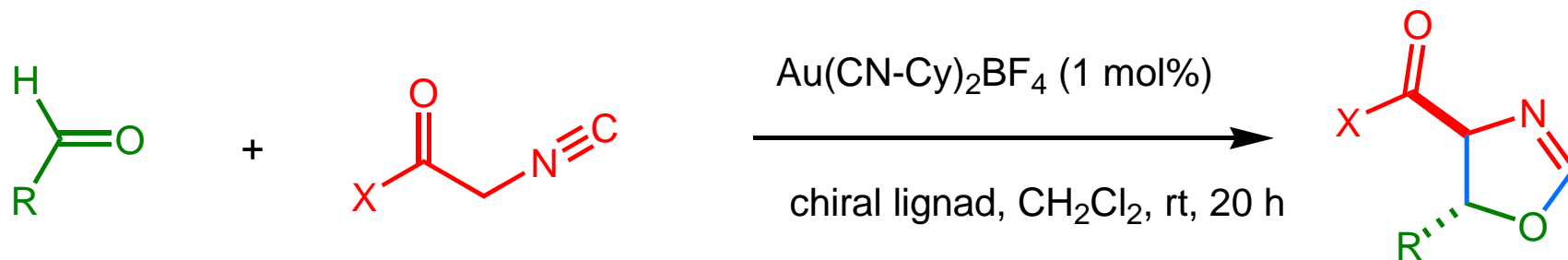
Activation of Alkenes



Li JACS 2004, 126, 6884.

Li OL 2005, 7, 673.

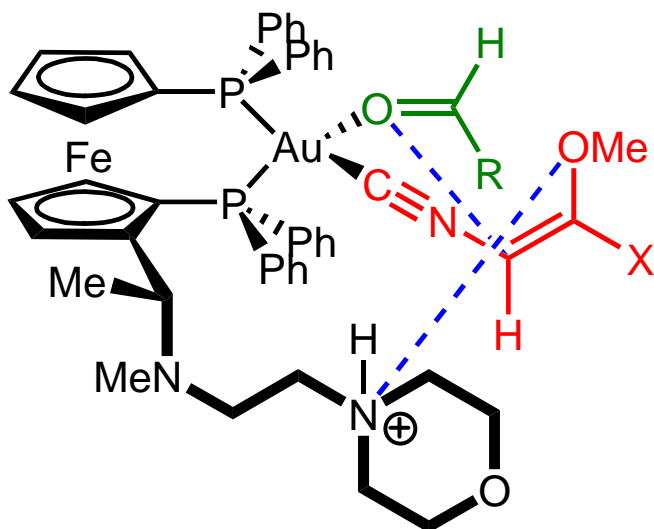
Catalytic Asymmetric Aldol Reaction



R = Ph, Me, *i*-Pr, *c*-Hex, *t*-Bu,
 MeCH=CMe-, *n*-PrCH=CH-

X=OMe , 82-100 % yields
 81/19 to 100/0 (*trans/cis*)
 81-97% ee

X = N(OMe)Me, 82-90% yields
 95/5 to 98/2 (*trans/cis*)
 93-99% ee



Ito & Hayashi *JACS* **1986**, *108*, 6405.
 Ito *JOC* **1995**, *60*, 1727.
 Togni & Pastor *JOC* **1990**, *55*, 1649.
 Review : Ito *CR* **1992**, *92*, 857.

Summary

- 1) Strong π -**acidity** of Au(I) and Au(III) species is originated from the **relativistic contraction** of valence *s* and *p* orbitals.
- 2) Au(I) predominantly adopts a **linear, bicoordinate** geometry.
- 3) Alkynes have been the most extensively studied substrates. Various Nucleophiles and interesting substrates such as enynes and propargyl esters were investigated.
- 4) Allenes and Alkenes also have shown the reactivities originated from the strong π -**acidity** of Au(I) and Au(III) species.
- 5) Alkyne activation were adopted as a useful tool in many target-oriented natural product syntheses.
- 6) Recently, Toste and coworkers reported excellent stereoinduction induced from chiral counteranion with the allene substrates.