DAE Group Meeting

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

November 2, 2007

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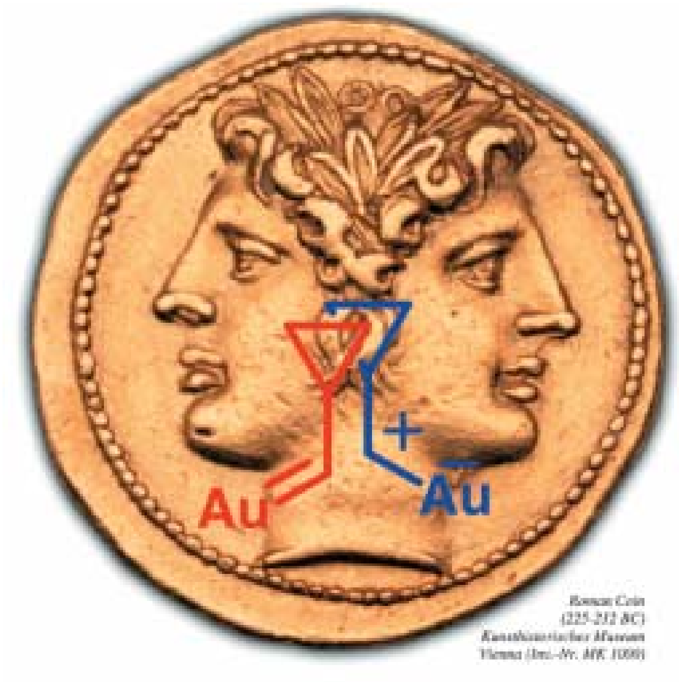

Selected Reviews **:**

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

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II. Activation of Alkynes

π-Acidity of Au

III. Activation of Allenes

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IV. Activation of Alkenes

Advantages of Au catalysts

V. Summary

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 quadropole moment, only a few ^{79}Au NMR spectra in an highly symmetric environment have been reported.

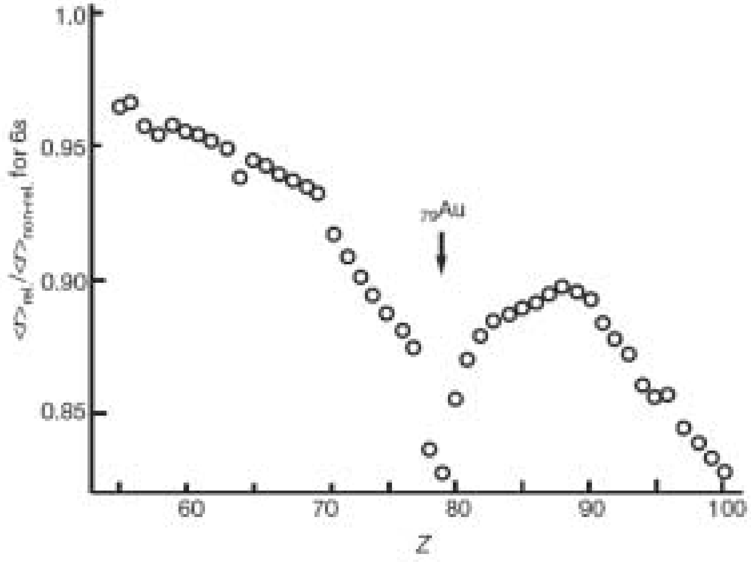
- The **diamagnetic** character of both Au(I) and Au(III) conveniently allows the monitoring of catalysis reactions by NMR.

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

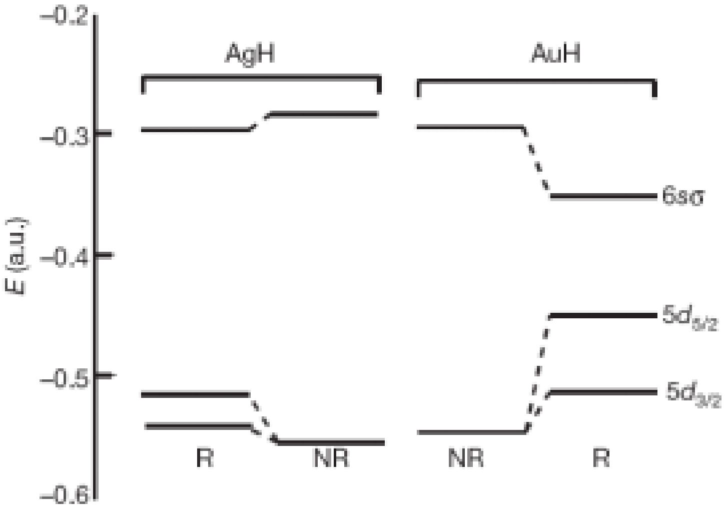
Relativistic Effects

- any phenomenon resulting from the need to consider velocity (*v*) as significant relative to the speed of light (*c*). $m_r = m_o/\sqrt{[1-(v/c)^2]}$ (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 6*s* orbtal
(Pt, Au and Hg are markedly influenced)



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

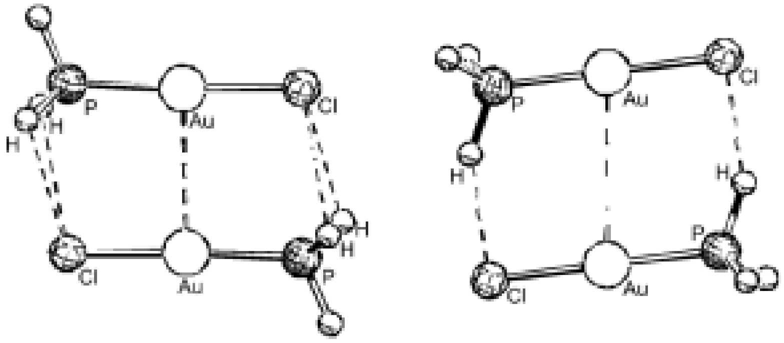
Toste, *Nature* **2007**, *446*, 395-403.
Pyykkö, *ACR* **1979**, *12*, 276-281.

Result of Relativistic Effects

Case Study on Au

- The relativistic contraction of 6*s* orbital results in **greatly strenghthened Au-L**.

- **Aurophilicity** : the tendency of Au-Au interactions, on the order of H-bonding.



- **Redox Stability** : The high held Au 5*d* 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 cosistent 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.

π-Acidity of Au

- Relativistic contraction of valence 6*s* and 6*p* orbitals : **Low-lying LUMO**, thus strong Lewis acidity and **high electronegativity** (2.4, highest among metal)

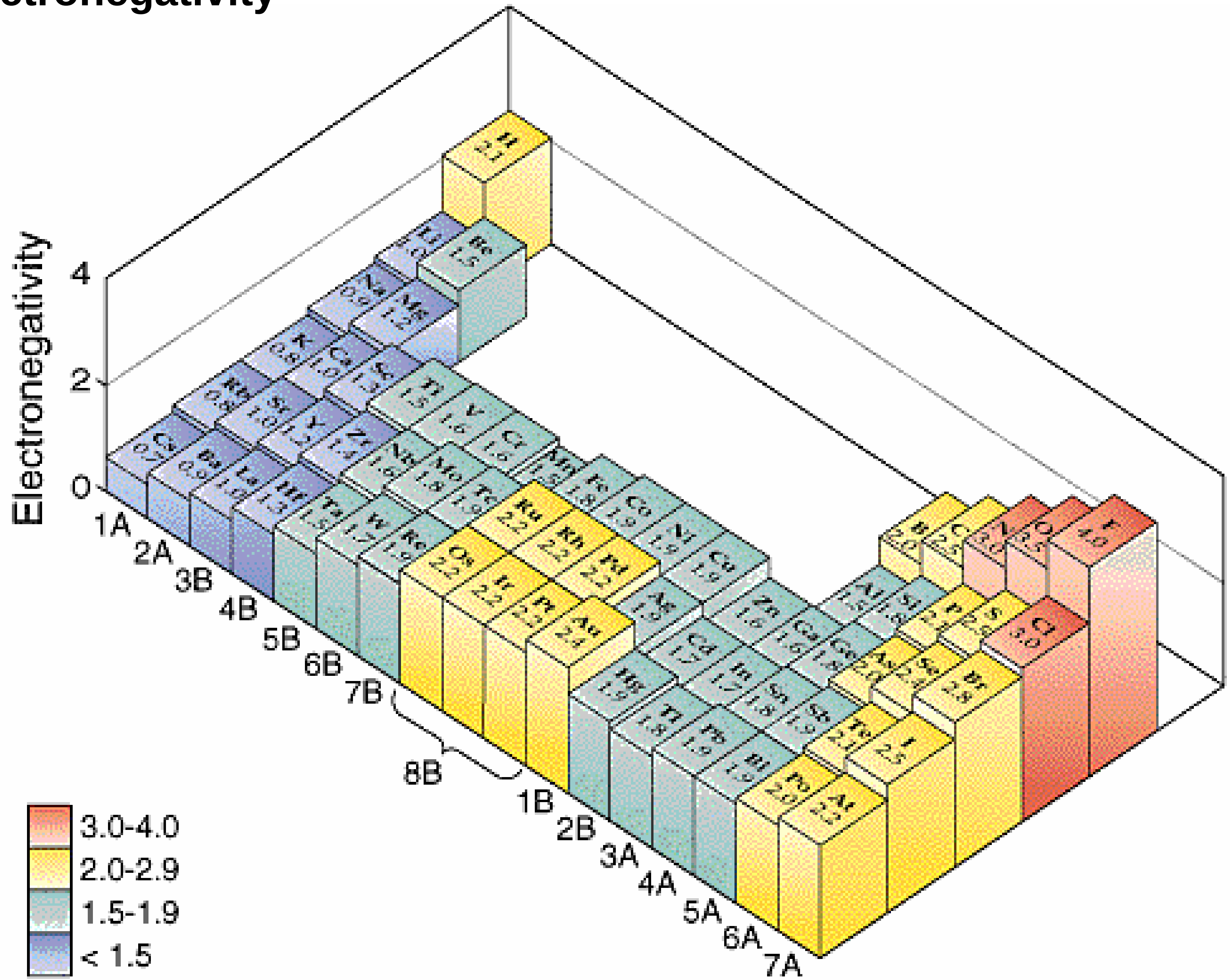
- As a large diffuse cation, Au(I) is **soft Lewis acid**, preferentially activating ‘soft’ Lewis base such as π-system. Compared with Au(I), hard Au(III) exibits a thermodynamic preference for ketone moiety coordination over alkyne coordination by 21.3 kJ/mol while also being capable of catalysing reaction 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.

Electronegativity

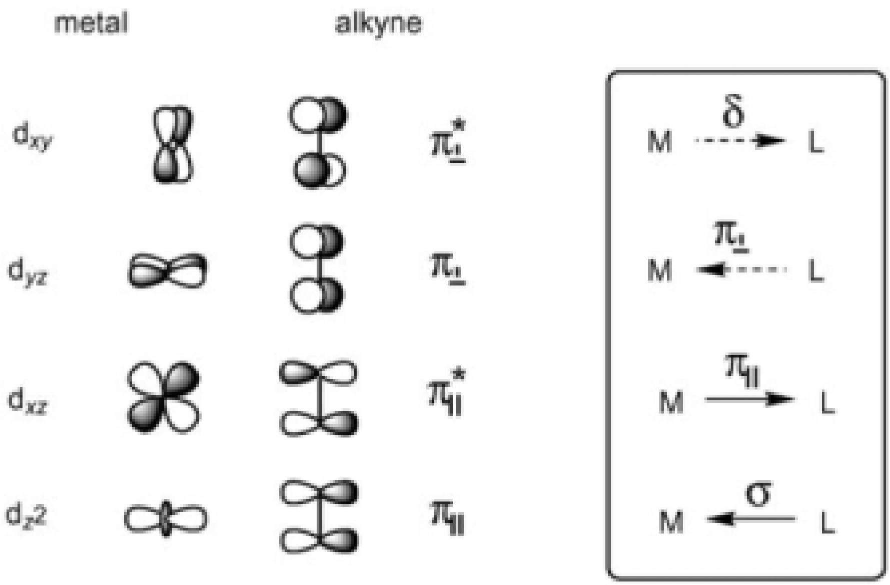
Introduction



FMO Interactions of Au-π 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-π 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.



Contributions

1%

7%

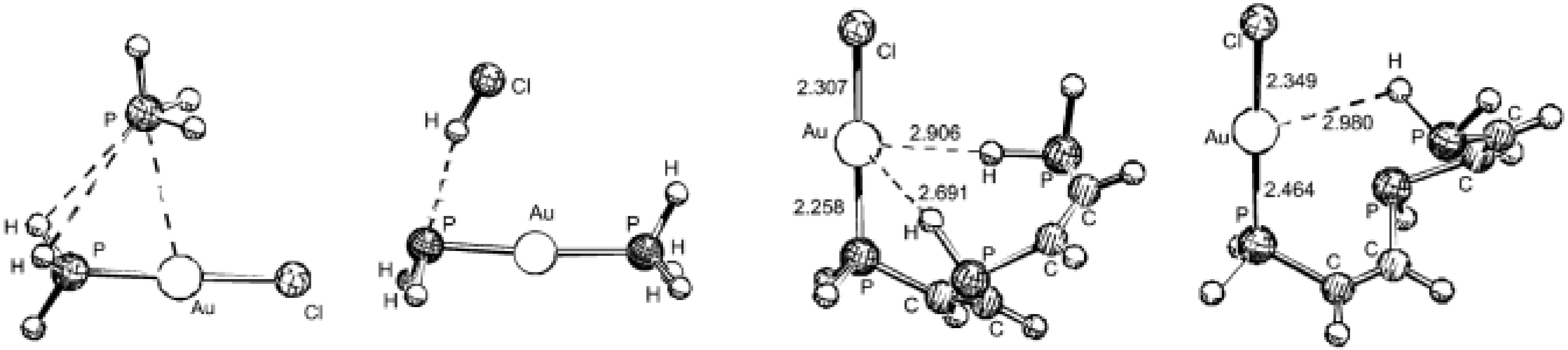
27%

65%

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 $LAuCH_3$ with acid

2) difficulty to chelate bidentate ligands to a single gold atom and thus scarcity of effective chiral catalysis

Fürstner, *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

Nitrogen Nucleophiles : Hydroamination
Schmidt reaction

Oxygen Nucleophiles : Hydration
Hydroalkoxylation
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

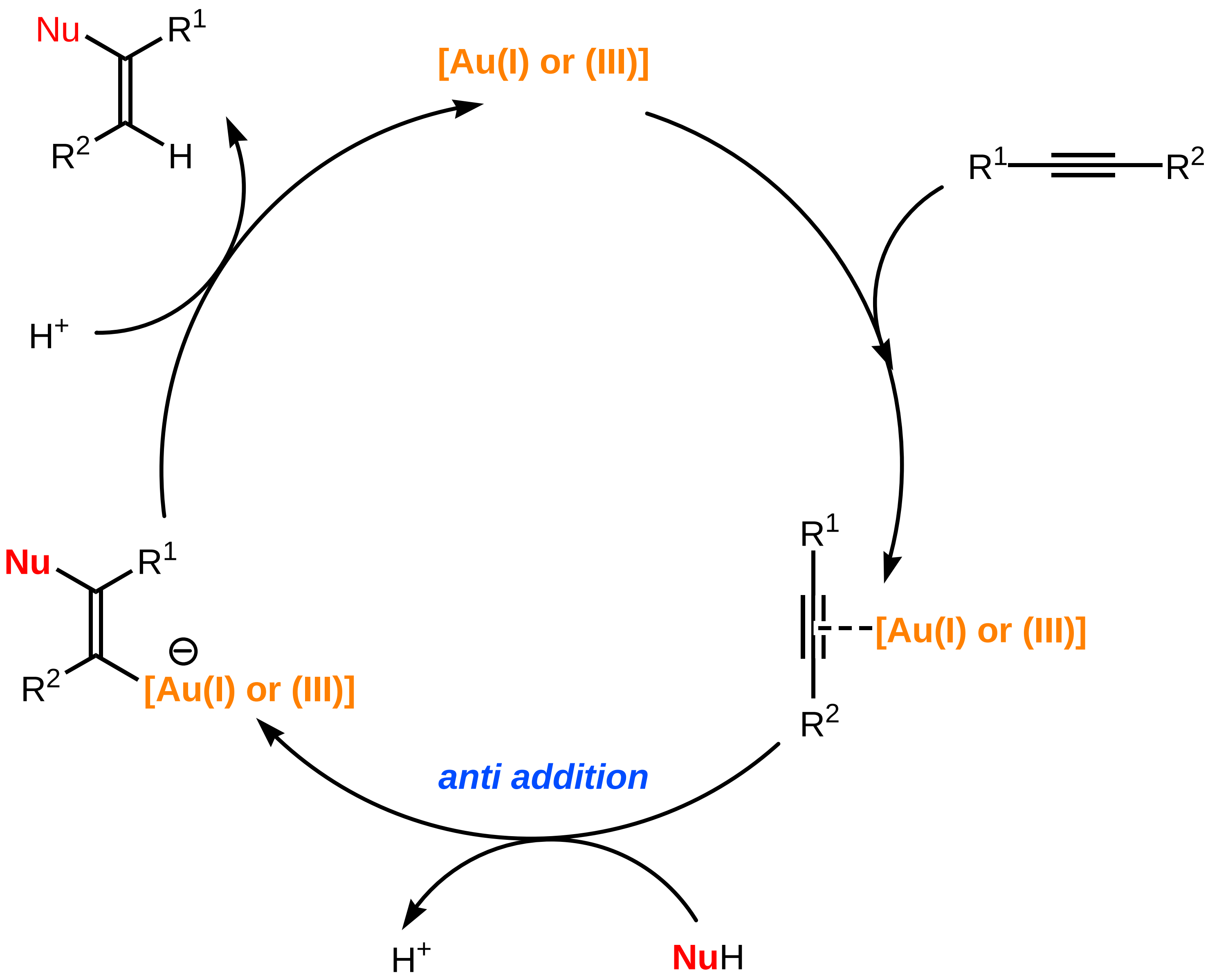
III. Activation of Allenes

IV. Activation of Alkenes

V. Summary

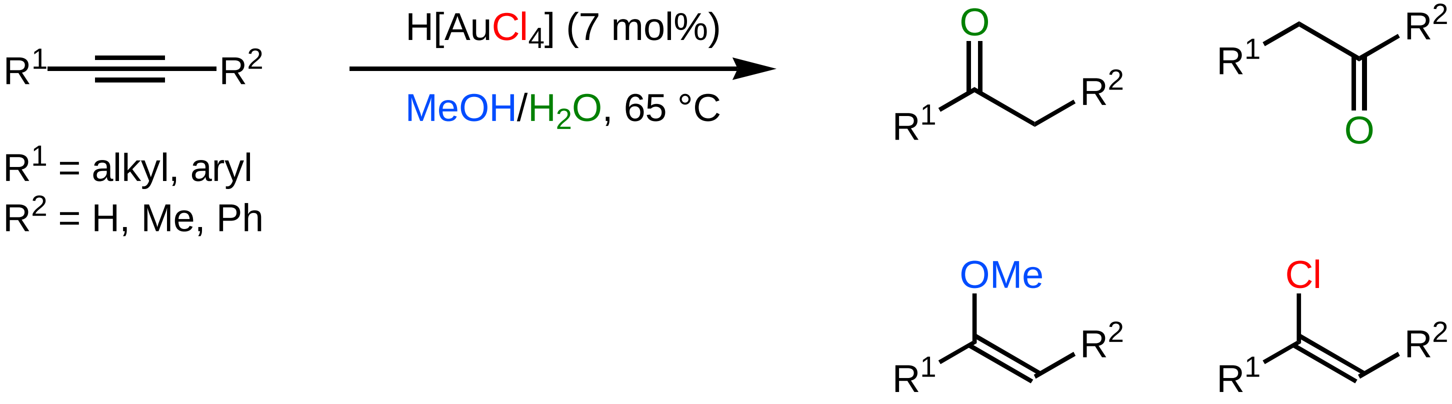
General Mechanism for the Simple Nucleophiles

Activation of Alkynes



Addition of Nucleophile

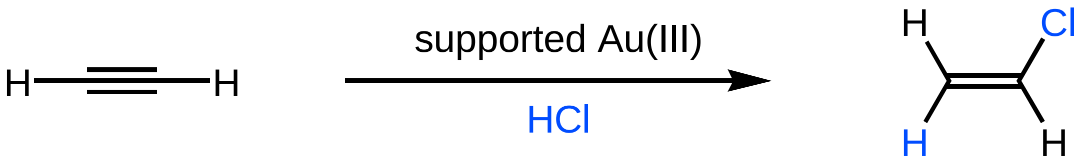
Early Studies



R^1 = alkyl, aryl
R^2 = H, Me, Ph

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

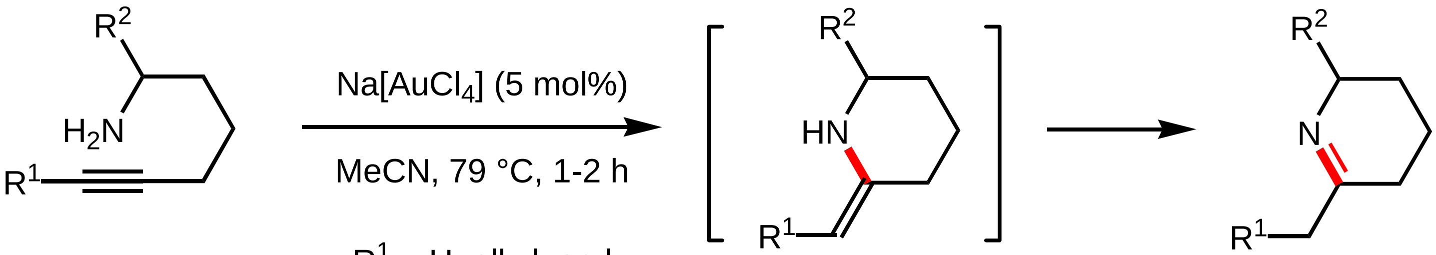
Thomas *JCS PT 1*, **1976**, 1983.



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

Intra- and Intermolecular Hydroamination

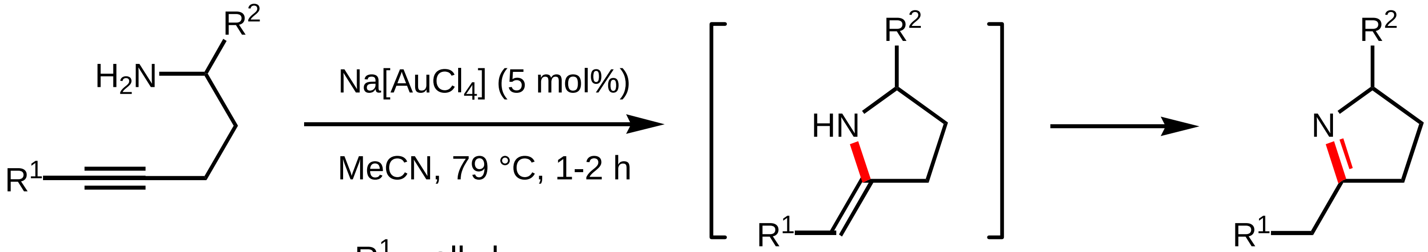
Activation of Alkynes



R^1 = H, alkyl, aryl
R^2 = H, Me, alkyl

7 examples
64-92% *yields*

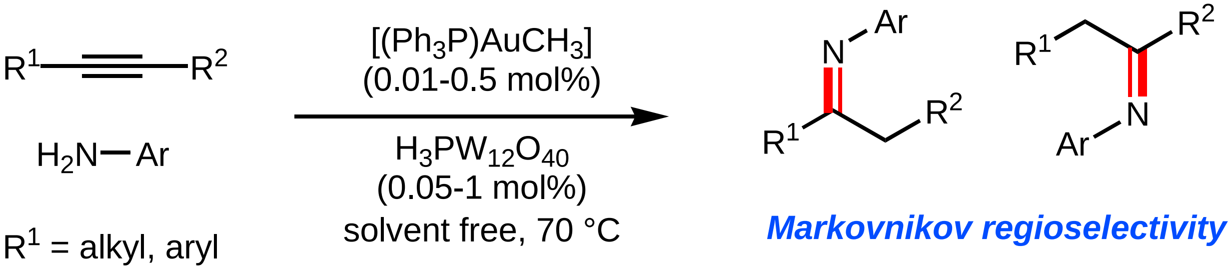
Utimoto *Heterocycles* **1987**, *25*, 297.



R^1 = alkyl
R^2 = H, Me

4 examples
98-100% *yields*

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



28-99% *yields*

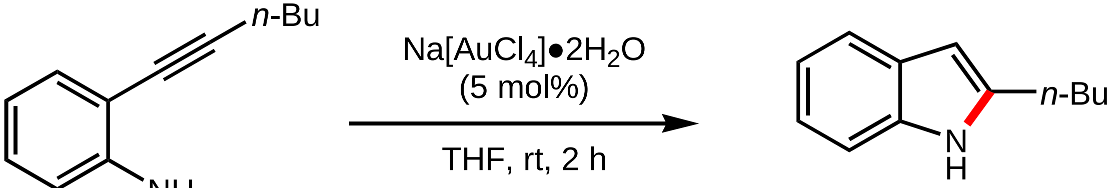
Markovnikov regioselectivity

R^1 = alkyl, aryl
R^2 = H, alkyl

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

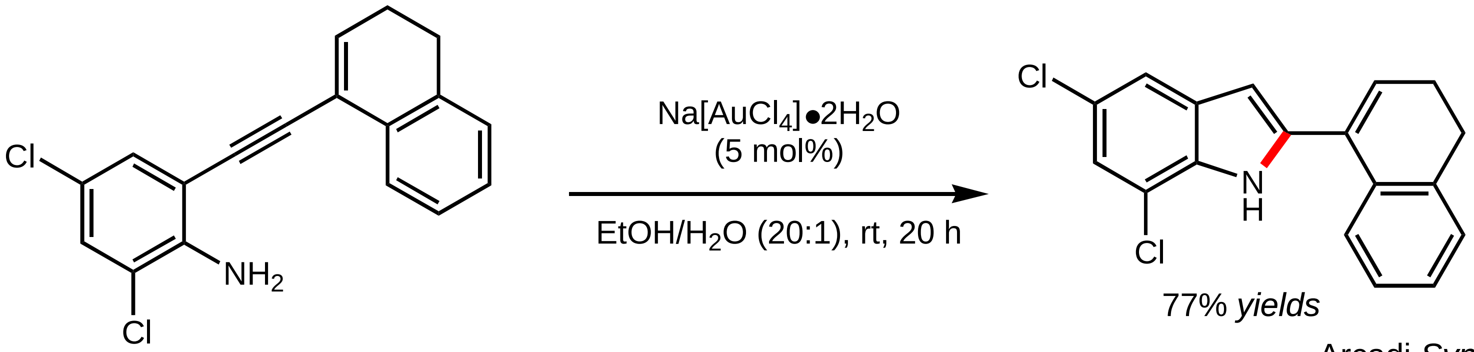
Intramolecular Hydroamination : Indole and Pyrrole

Activation of Alkynes



87% *yields*

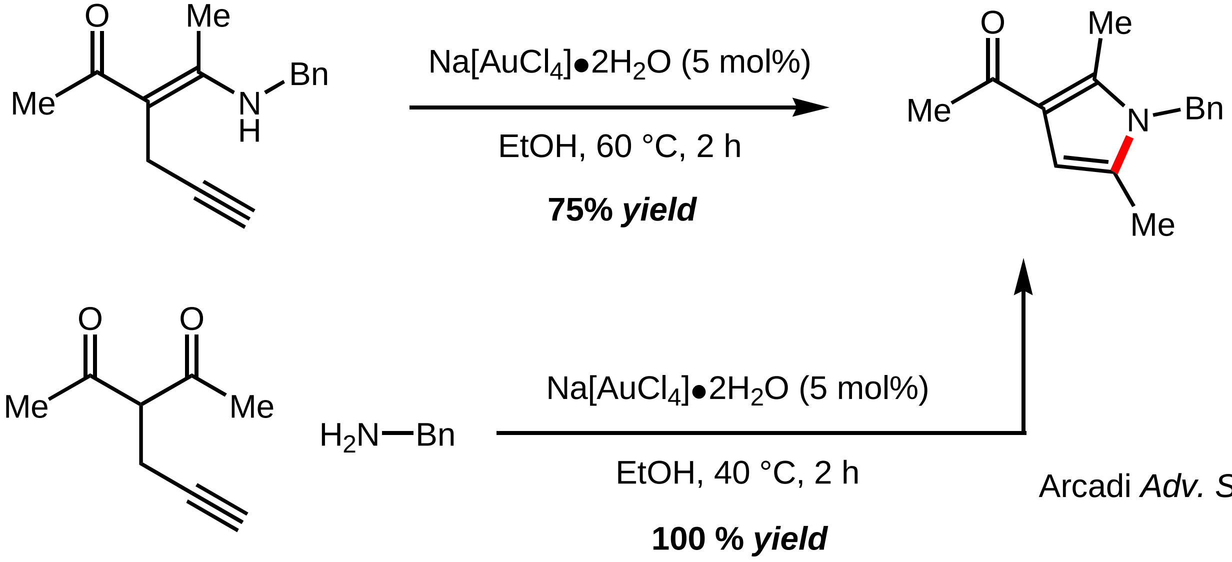
Utimoto *TL* **1988**, *29*, 1799.



77% *yields*

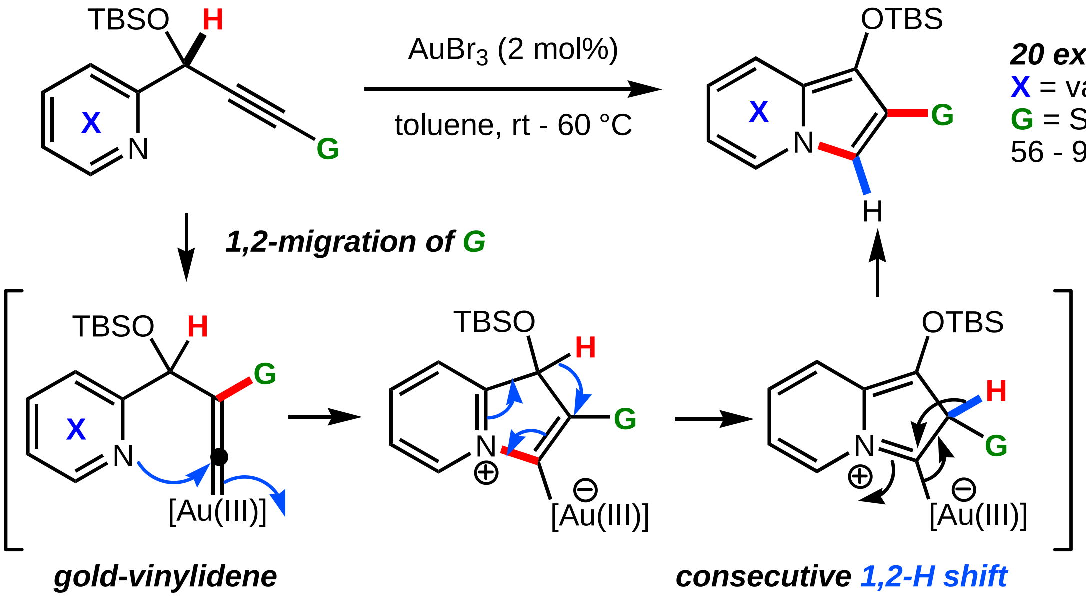
Arcadi *Synthesis* **2004**, 610.

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.

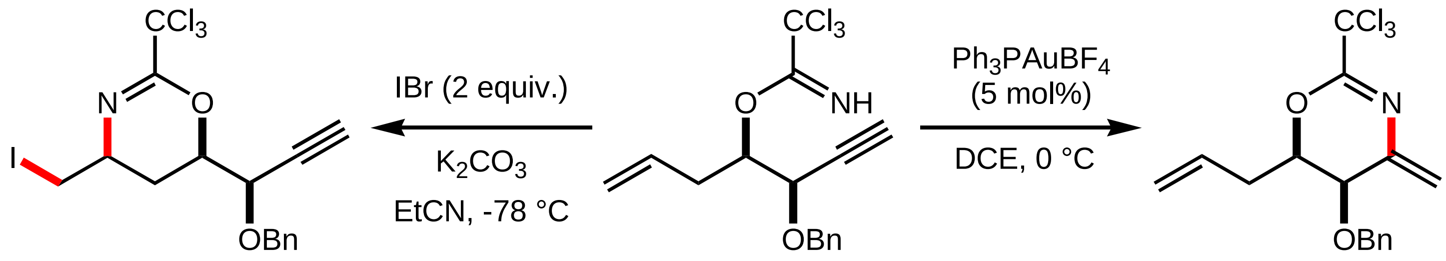
Intramolecular Hydroamination



20 examples
X = various aromatic rings
G = $SiMe_3$, $SnBu_3$, $GeMe_3$
56 - 94% *yields*

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

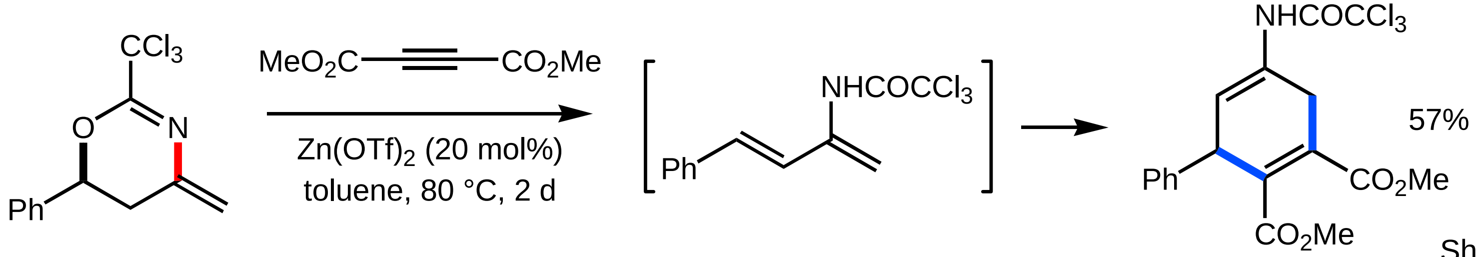
Au(III)-catalyzed three component coupling
of aldehyde, amines and alkynes
to aminoindolizines
Liu *OL* **2007**, *9*, 4323.



62% *yield*

13 other examples
73 - 99% *yields*

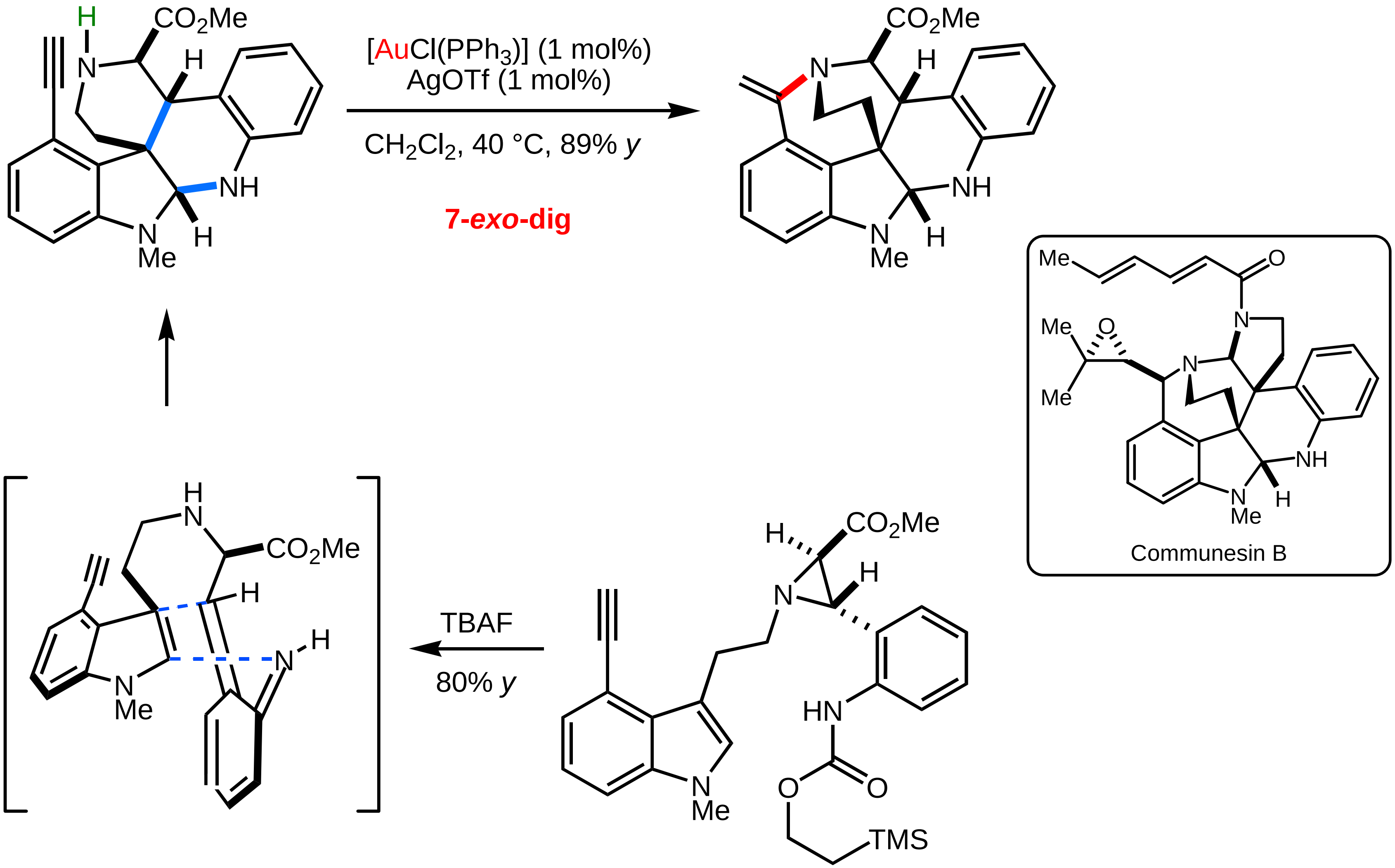
88% *yield*



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

Application of Intramolecular Hydroamination

Communesin (2006)



[AuCl(PPh$_3$)] (1 mol%)
AgOTf (1 mol%)
CH$_2$Cl$_2$, 40 °C, 89% *y*

7-*exo*-dig

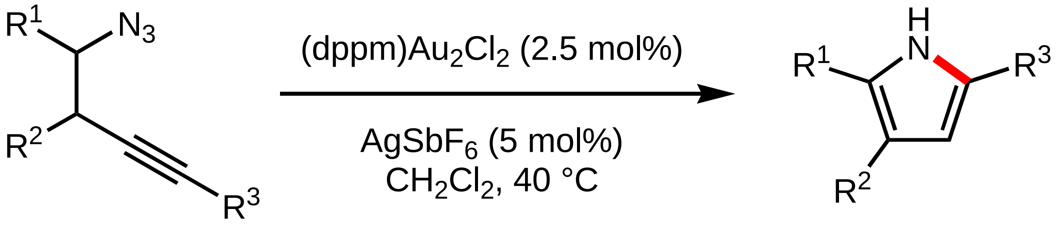
TBAF
80% *y*

Communesin B

Funk *OL* **2006**, *8*, 2995.

Intramolecular Acetylenic Schmidt Reaction

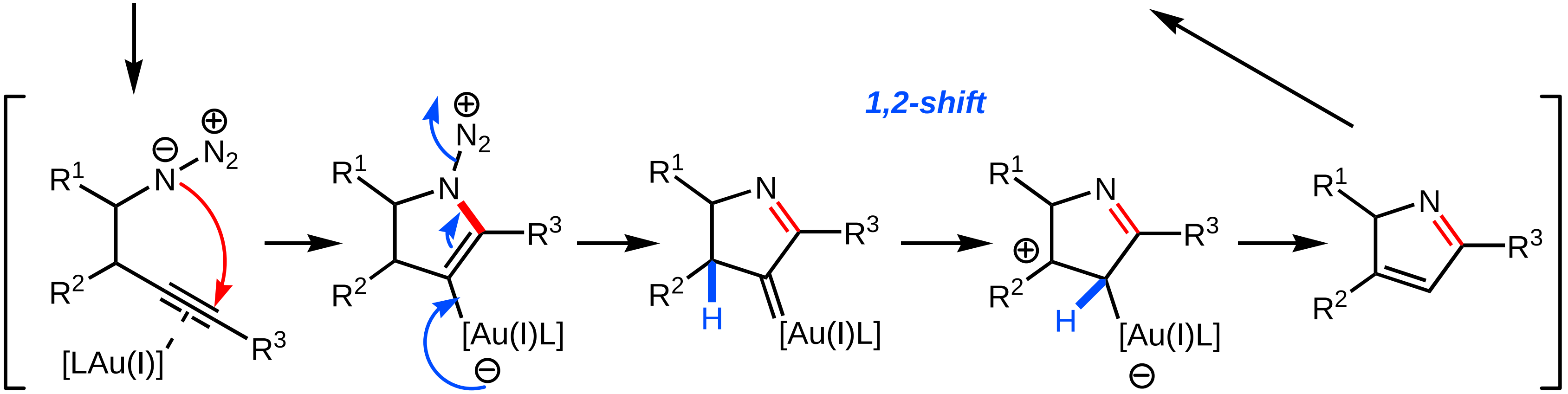
Activation of Alkynes

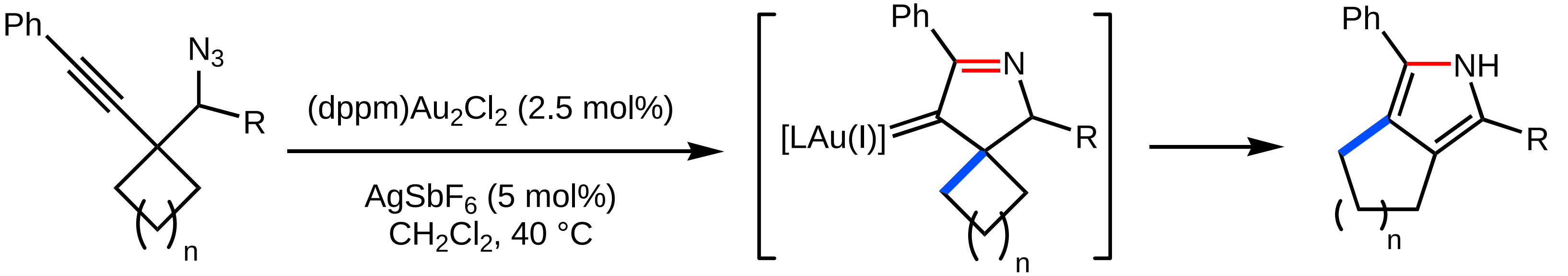


$(dppm)Au_2Cl_2$ (2.5 mol%)

$AgSbF_6$ (5 mol%)
CH_2Cl_2, 40 °C

10 examples
R^1 = H, alkyl, cycle w/R^2
R^3 = alkyl, aryl, furanyl, cyclopropyl
41-93% *yields*





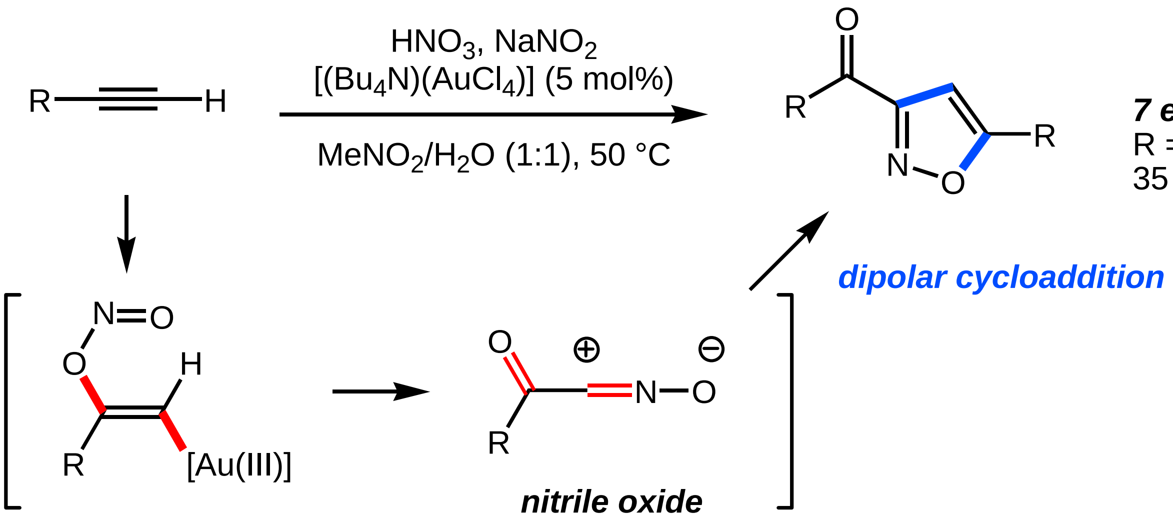
$(dppm)Au_2Cl_2$ (2.5 mol%)

$AgSbF_6$ (5 mol%)
CH_2Cl_2, 40 °C

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

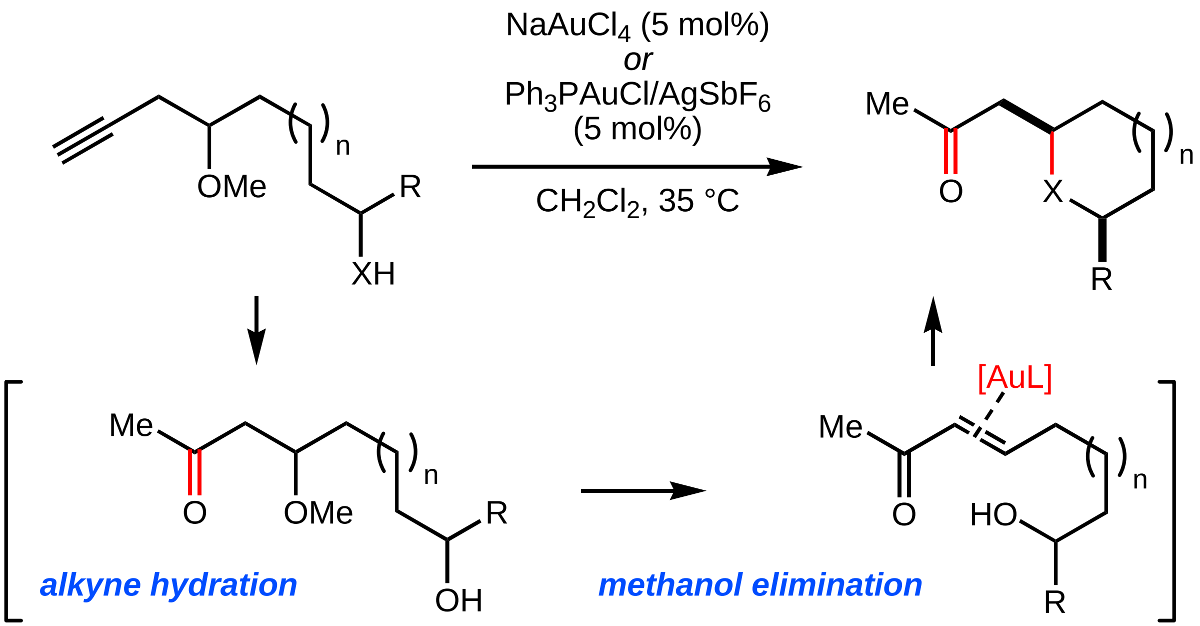
Toste *JACS* **2005**, *127*, 11260.

Nirite and Water Addition onto Alkynes



7 examples
R = Ph, alkyl
35 - 50% *yields*

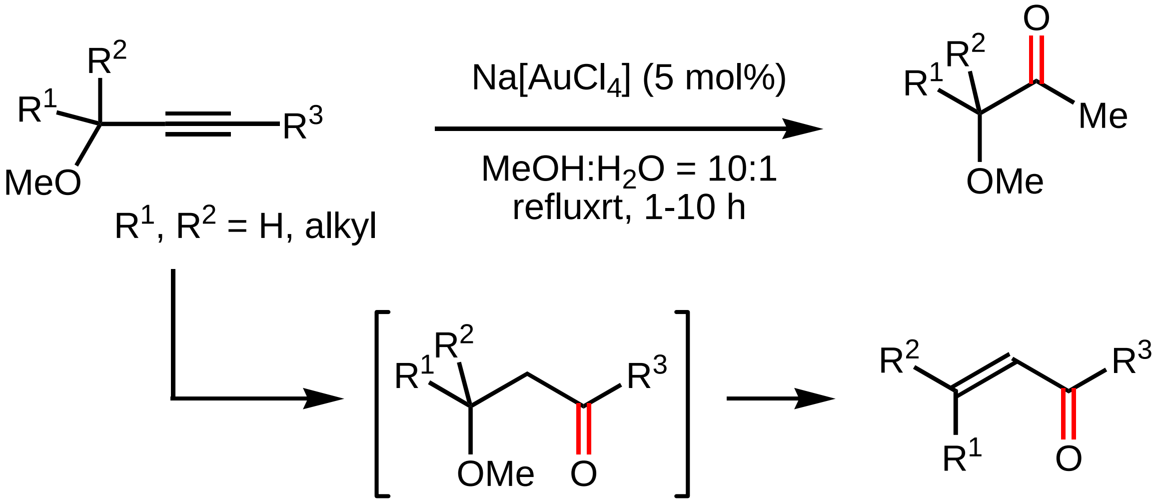
Gasparrini *JACS* **1993**, *115*, 4401.



19 examples
R = alkyl, n= 0, 1, 2
X = O, NNs, NCO_2Me, NCbz, NFmoc
25 - 100% *yields*

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

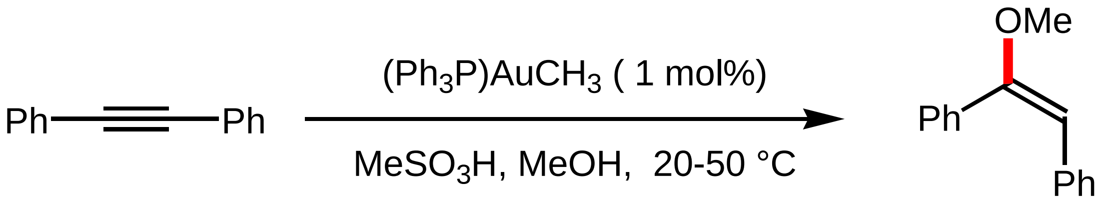
Intermolecular Hydration and Hydroalkoxylation



R^3 = H, 91% *yield*

R^3 = alkyl, aryl
21-91% *yields*

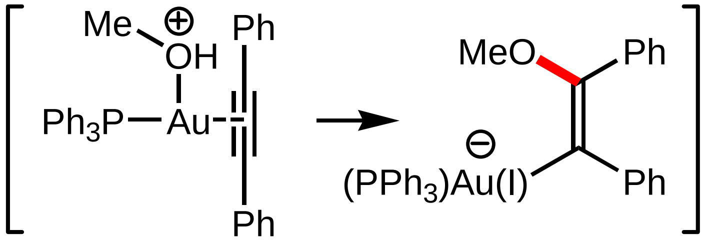
Utimoto *BCS Jp.* **1991**, *64*, 2013.



93% *yield*

initial *Z*:*E* = 8:1
final   *Z*:*E* = 2:1

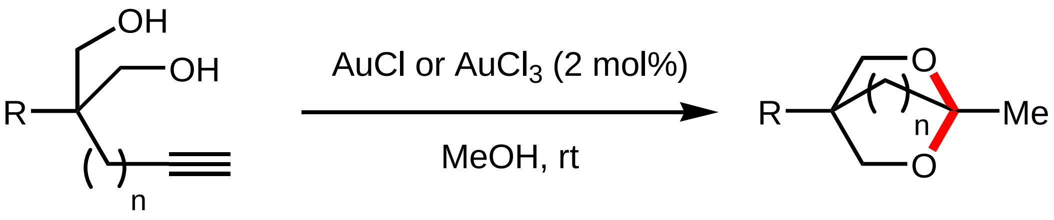
syn **oxyauration** for the C-O bond-forming step



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

Intramolecular Hydroalkoxylation

Activation of Alkynes

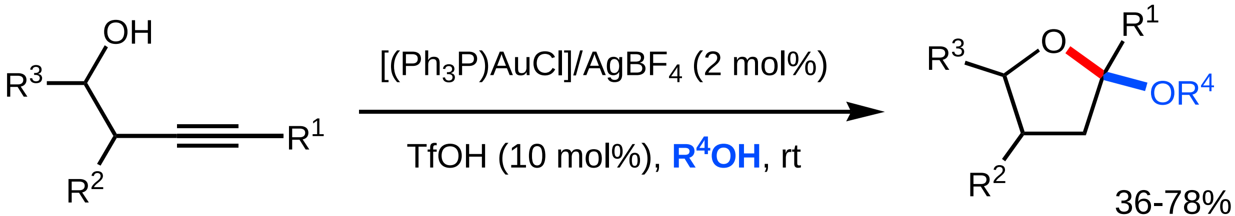


AuCl or $AuCl_3$ (2 mol%)

MeOH, rt

R = alkyl, allyl, aryl
n = 1, 2
77 - 99% *yields*

Genêt *JACS* **2005**, *127*, 9976.



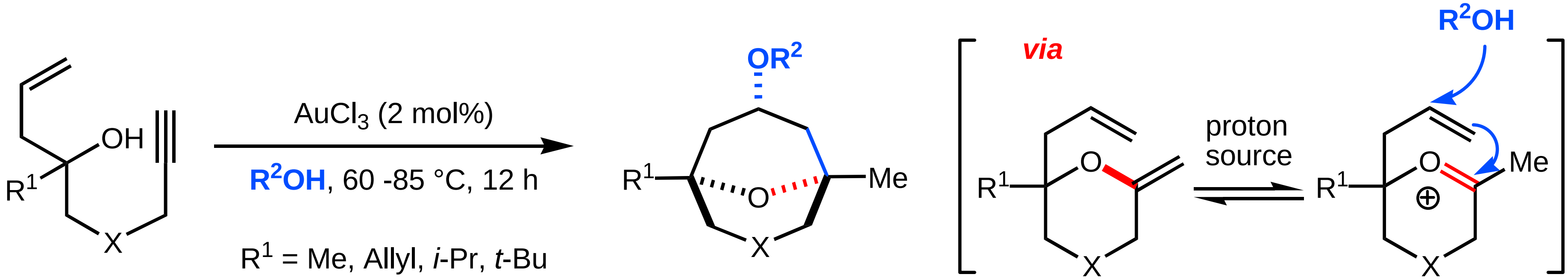
$[(Ph_3P)AuCl]/AgBF_4$ (2 mol%)

TfOH (10 mol%), **R^4OH**, rt

36-78% *yields*

R^1 = H, alkyl, aryl; R^2 = H, aryl
R^3 = H, alkyl, aryl; **R^4** = alkyl

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



$AuCl_3$ (2 mol%)

R^2OH, 60 -85 °C, 12 h

R^1 = Me, Allyl, *i*-Pr, *t*-Bu
X = O, CH_2
R^2 = Me, Et, Pr,

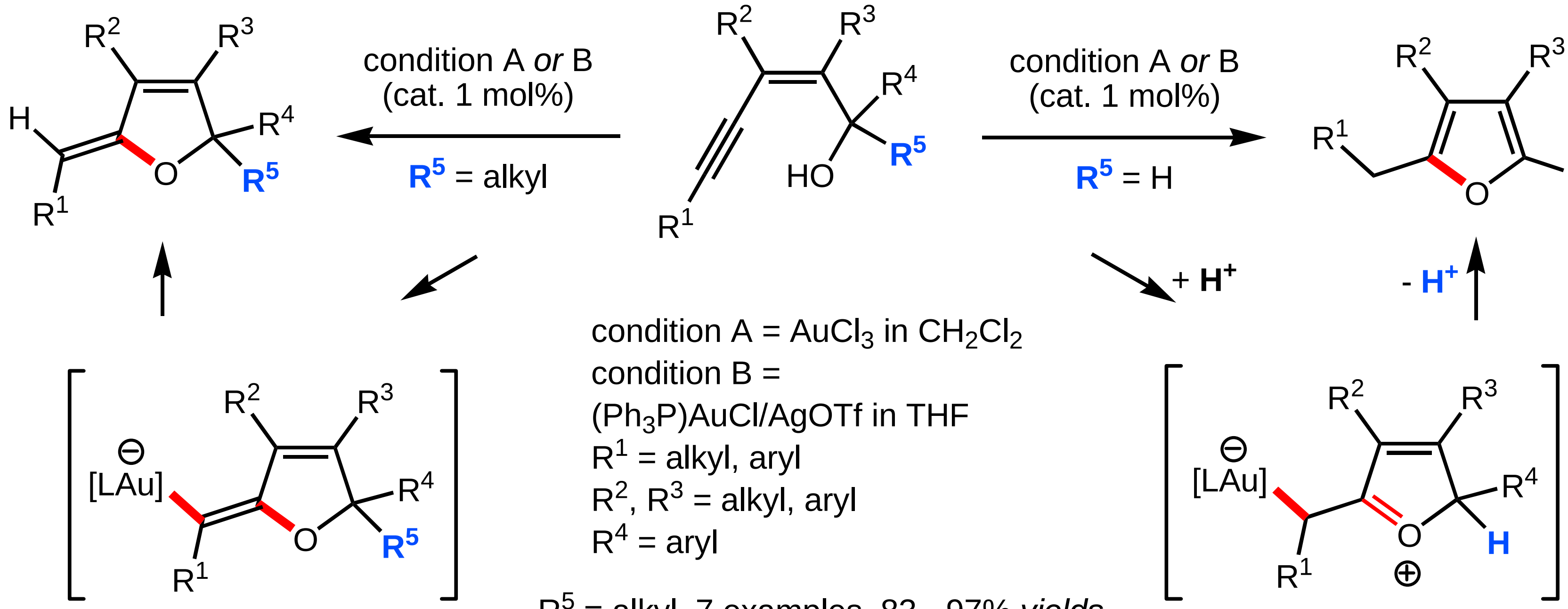
5 examples
88-96% *yields*

Prins-type cyclization

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

Intramolecular Hydroalkoxylation

Activation of Alkynes



condition A *or* B (cat. 1 mol%)

R^5 = alkyl

condition A *or* B (cat. 1 mol%)

R^5 = H

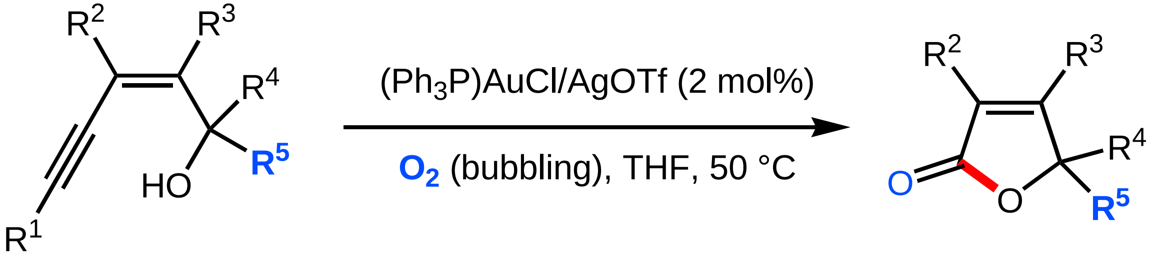
+ **H^+**

- **H^+**

condition A = $AuCl_3$ in CH_2Cl_2
condition B =
$(Ph_3P)AuCl/AgOTf$ in THF
R^1 = alkyl, aryl
R^2, R^3 = alkyl, aryl
R^4 = aryl

R^5 = alkyl, 7 examples, 83 - 97% *yields*
R^5 = H, 8 examples, 12 - 92% *yields*

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



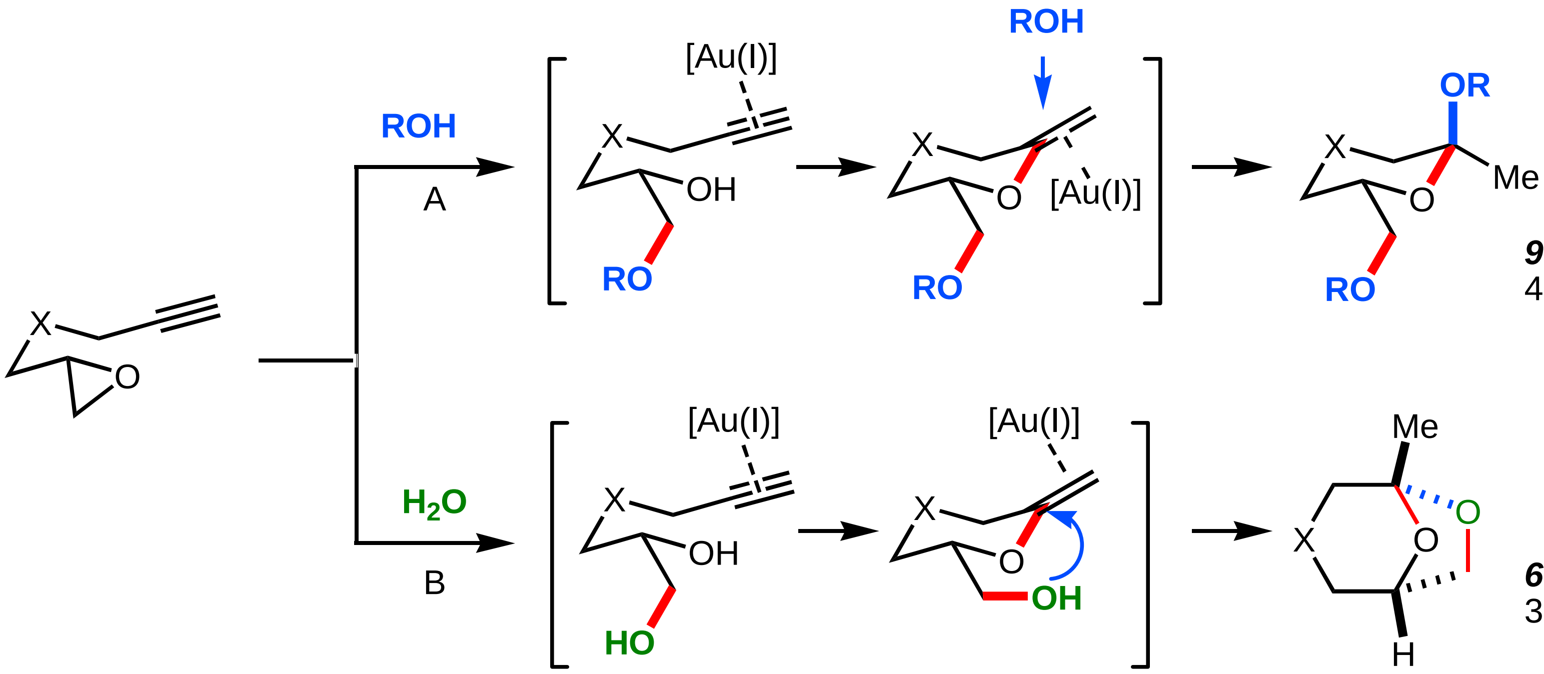
$(Ph_3P)AuCl/AgOTf$ (2 mol%)

O_2 (bubbling), THF, 50 °C

11 examples
R^1 = alkyl, aryl
R^2, R^3 = alkyl, aryl
R^4, R^5 = alkyl, aryl
41 - 97% *yields*

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

Inter and Intramolecular Hydroalkoxylation

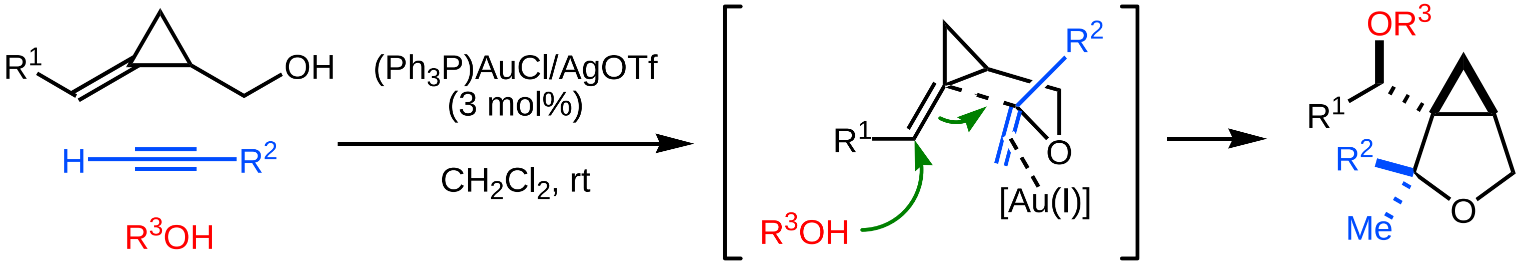


9 examples
44 - 80% *yields*

6 examples
38 - 70% *yields*

condition A : $(Ph_3P)AuCl/AgSbF_6$ (5 mol%), ROH, *p*-TsOH, rt
condition B : $(Ph_3P)AuCl/AgSbF_6$ (5 mol%), H_2O, DCE, rt

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

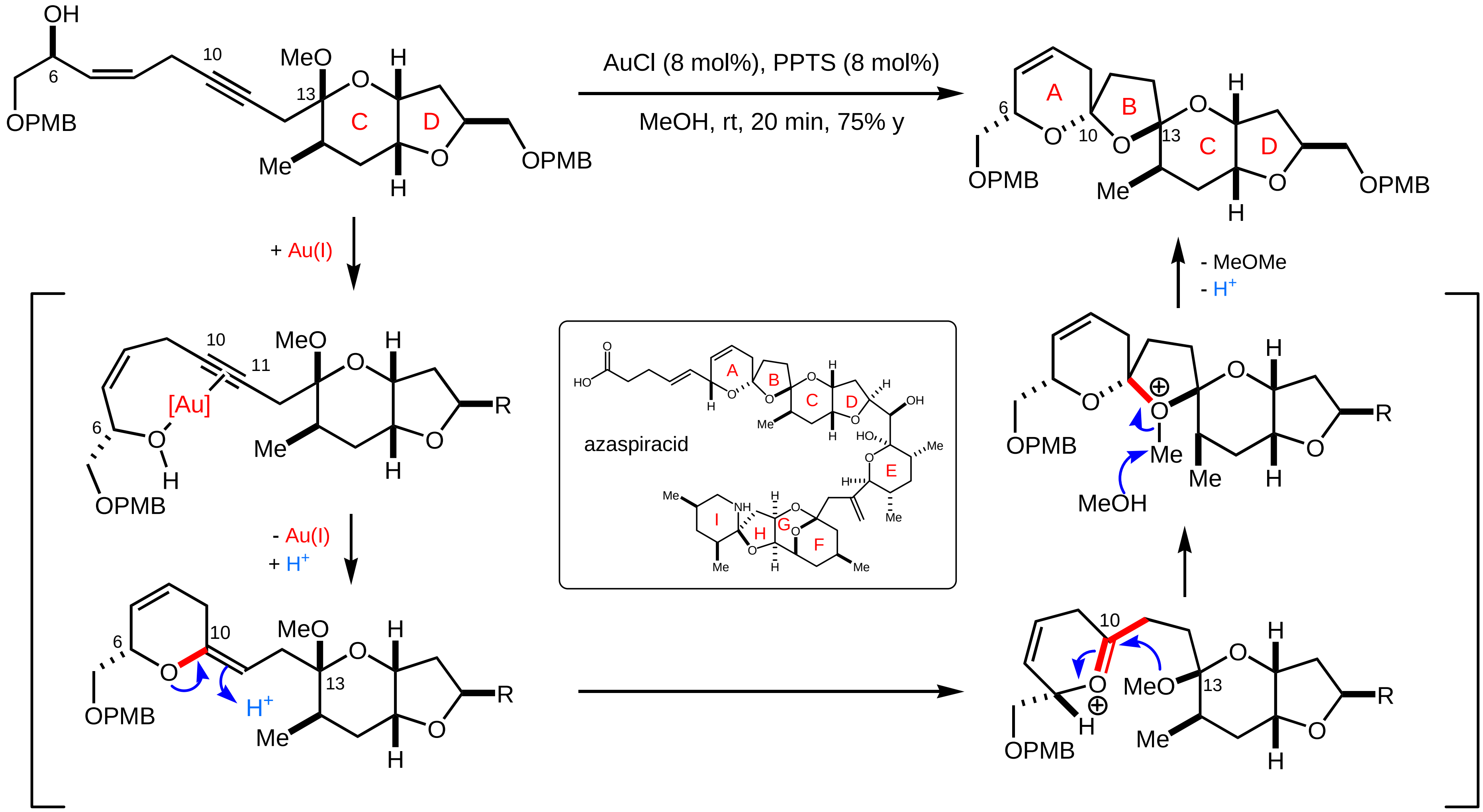


11 examples
R^1, R^2 = aryl
R^3 = alkyl
62 - 93% *yields*

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

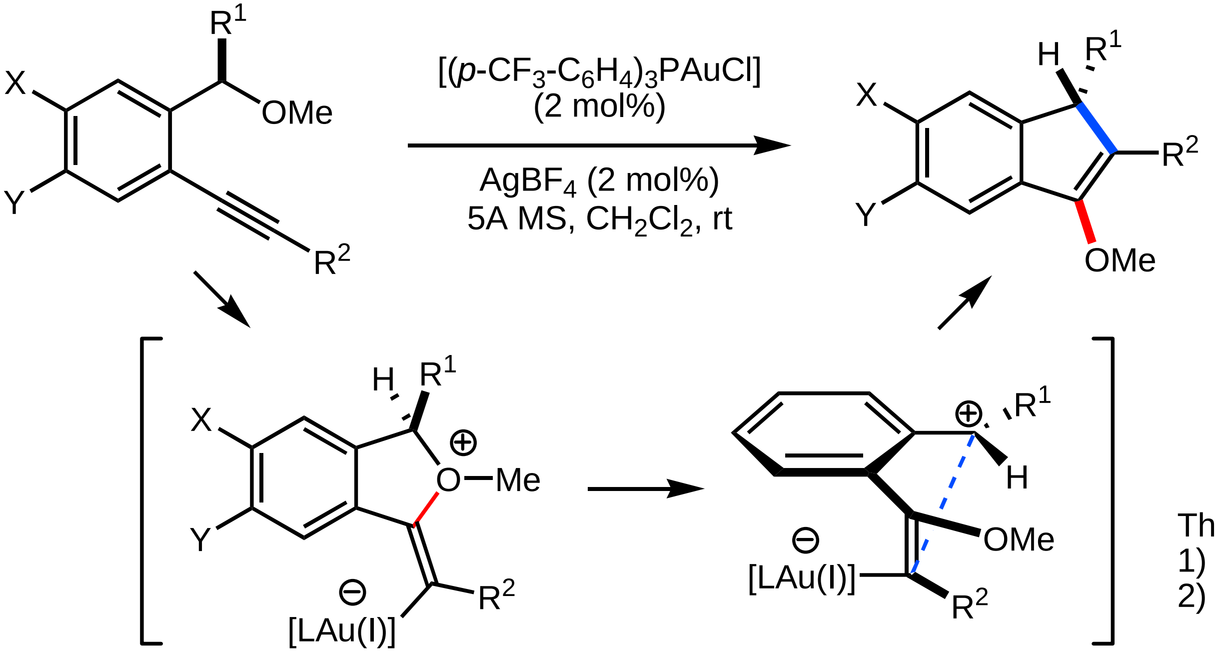
Application of Intramolecular Hydroalkoxylation

Azaspiracid (2007)



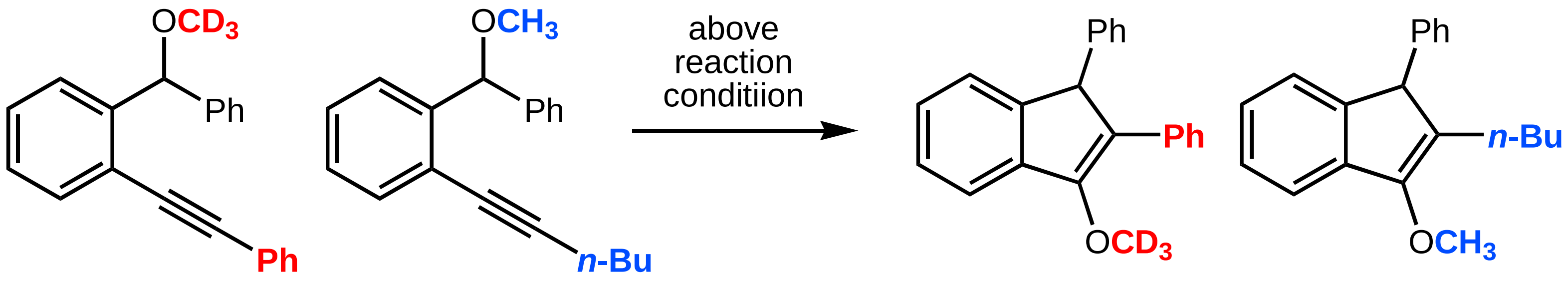
Forsyth *ACIE* **2007**, *46*, 279.

Intramolecular Carboalkoxylation



11 examples
R^1 = vinyl, aryl, cinnamoyl
R^2 = alkyl, aryl, CO$_2$Me
X, Y = H, CF$_3$, OMe
41-99% *yields*

This mechanism is supported by :
1) double label crossover experiment
2) excellent chirality transfer
(99% ee → 95% ee)

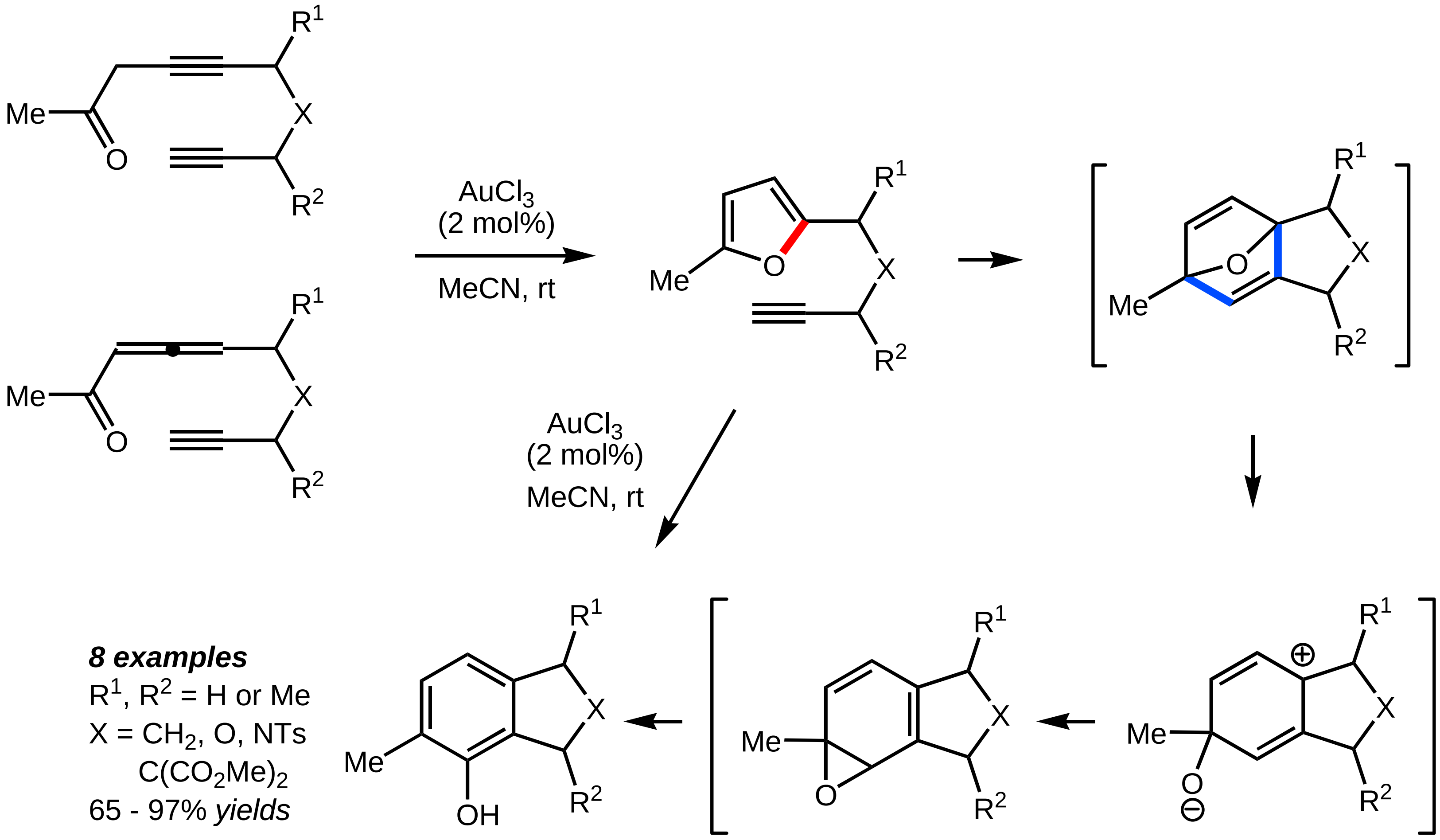


no crossover product observed
consistent with a mechanism involving alkyne activation rather than ionizationof the benzylic ether

Toste *JACS* **2006**, *128*, 12062.

Carbonyl Oxygen as Nucleophile

Cycloaddition/Fragmentation Domino Reaction



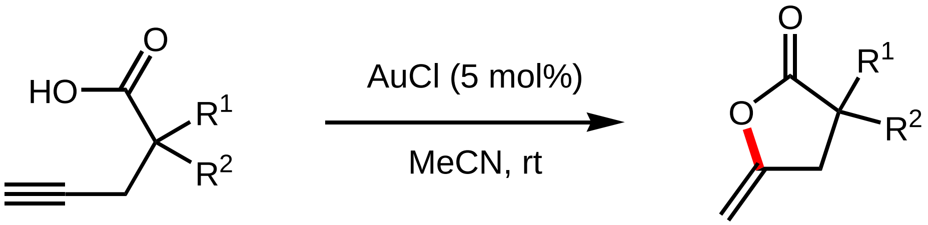
8 examples
R^1, R^2 = H or Me
X = CH_2, O, NTs
$C(CO_2Me)_2$
65 - 97% *yields*

Hashmi *JACS* **2000**, *122*, 11553.

related follow-up study : Hashimi *ACIE*, **2004**, *43,* 6545.

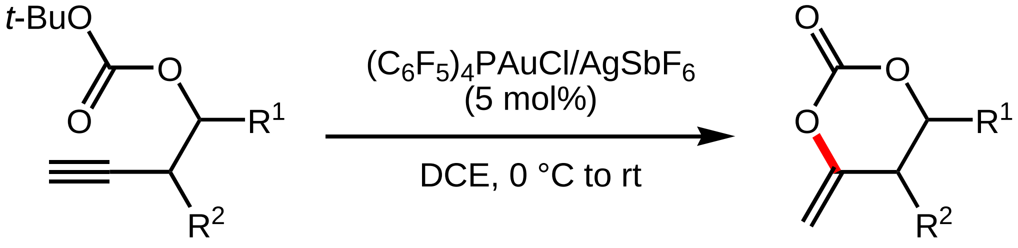
Carbonyl Oxygen as Nucleophile

Activation of Alkynes



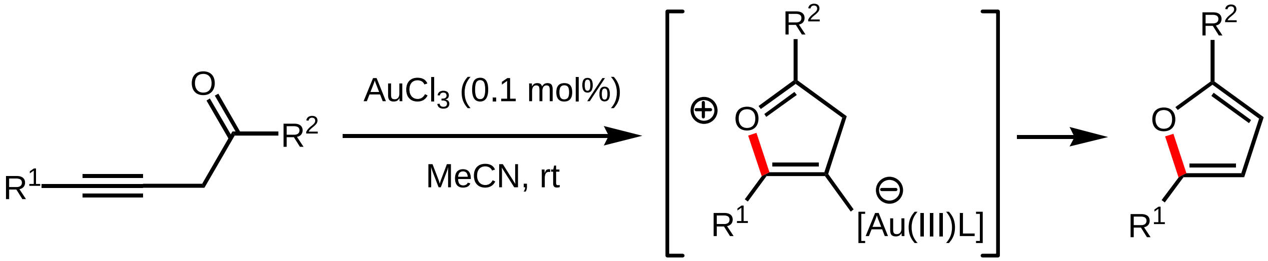
R^1 = CO_2R, CH_2OBn, Ph
R^2 = alkyl, allyl, benzyl,
propargyl, Cl, vinyl, aryl
72 - 98% *yields*

Genêt *JACS* **2006**, *128*, 3112.



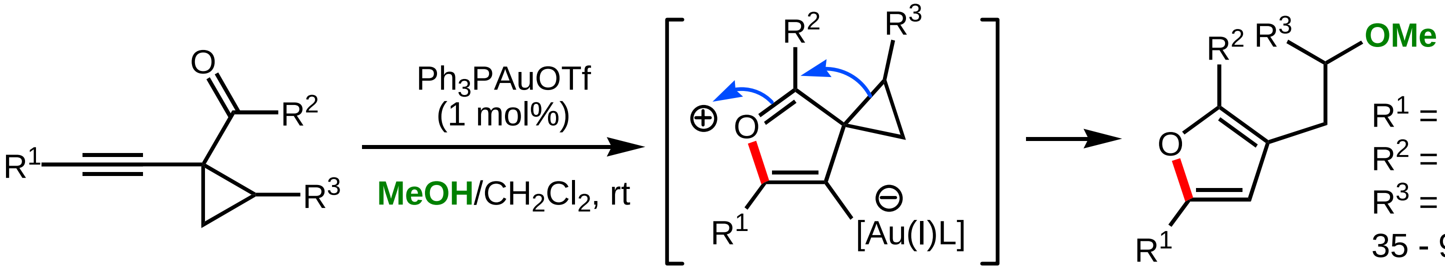
R^1 = alkyl, aryl
R^2 = H, alkyl
58 - 80% *yields*

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



R^1, R^2 = alkyl
quantitative

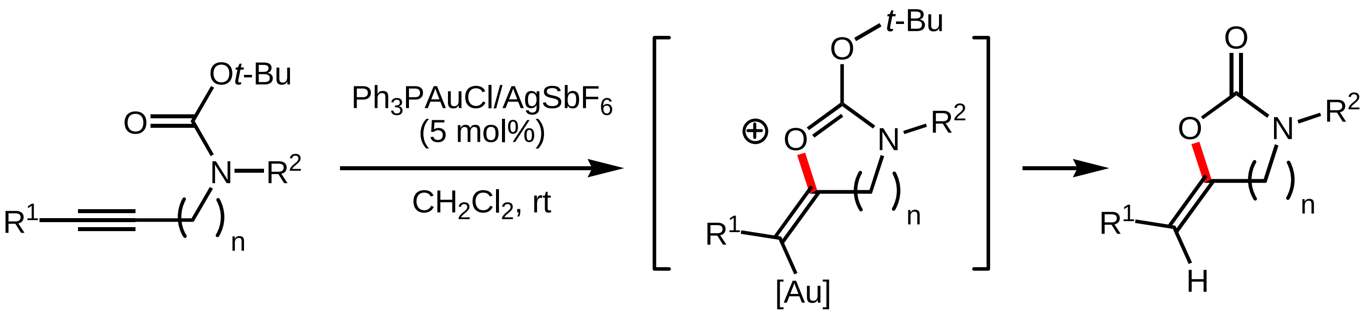
Hashmi *ACIE* **2000**, *39*, 2285.



R^1 = H, alkyl vinyl, aryl, TMS
R^2 = alkyl, alkyl
R^3 = alkyl, aryl, alkyloxy
35 - 96% *yields*

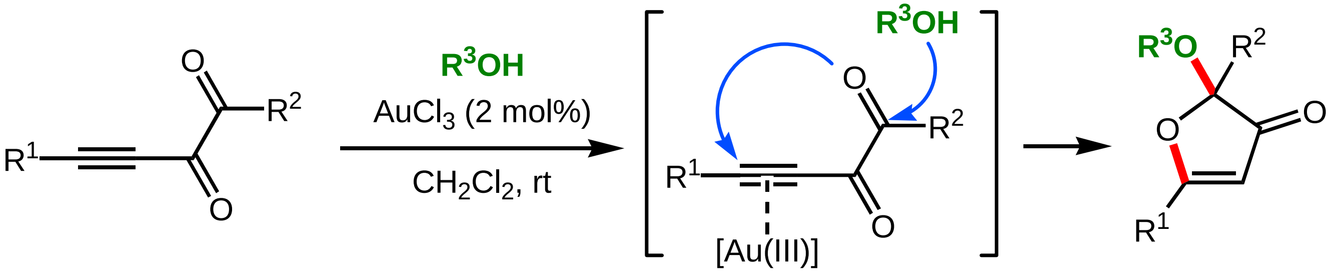
Schmalz *ACIE* **2006**, *45*, 6704.

Carbonyl Oxygen as Nucleophile



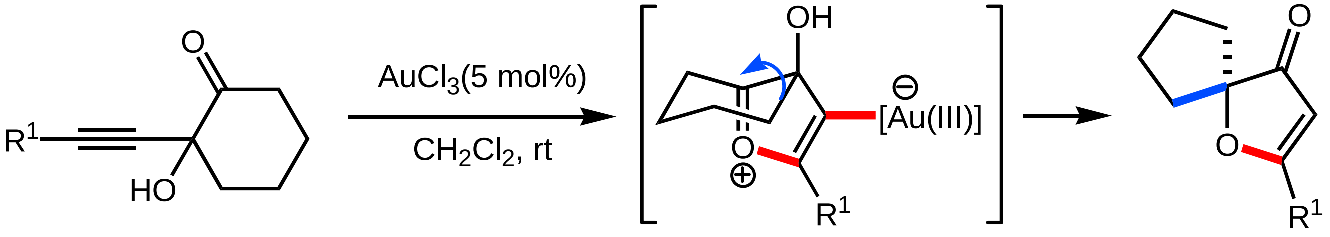
18 examples n = 1, 2
R^1 = H, Me, Ph, CO$_2$Et
R^2 = H, alkyl, aryl
69 - 95% *yields*

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



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

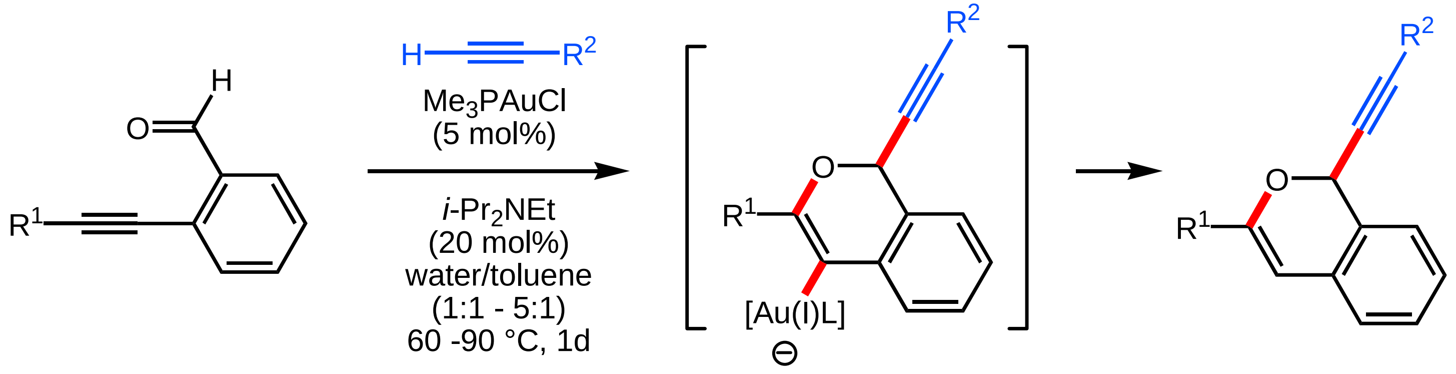
Liu *OL* **2006**, *8*, 3445.



3 examples
R^1 = aryl, alkyl
11 - 81% *yields*

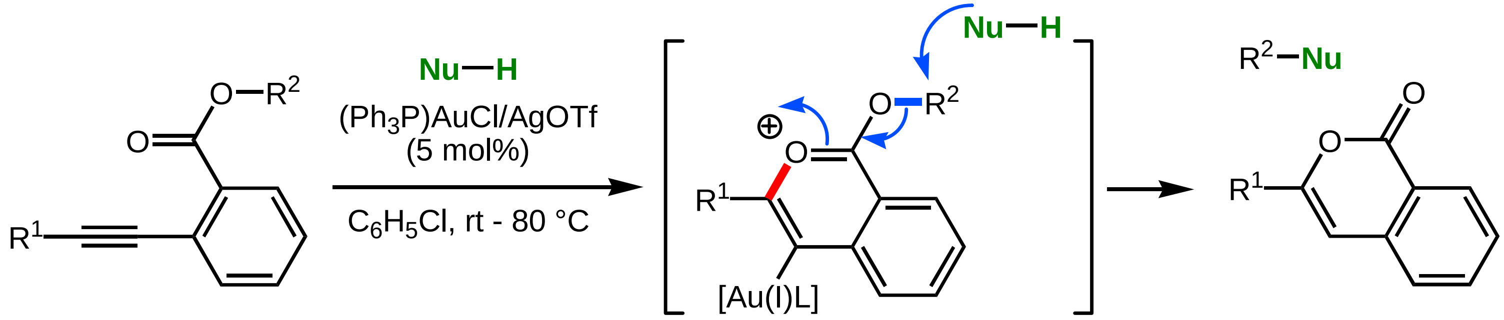
Kirsch *ACIE* **2006**, *45*, 5878.

Carbonyl Oxygen as Nucleophile



15 examples
R^1 = aryl, alkyl
R^2 = aryl, alkyl
16 - 89% *yields*

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



as an efficient alkylating agent

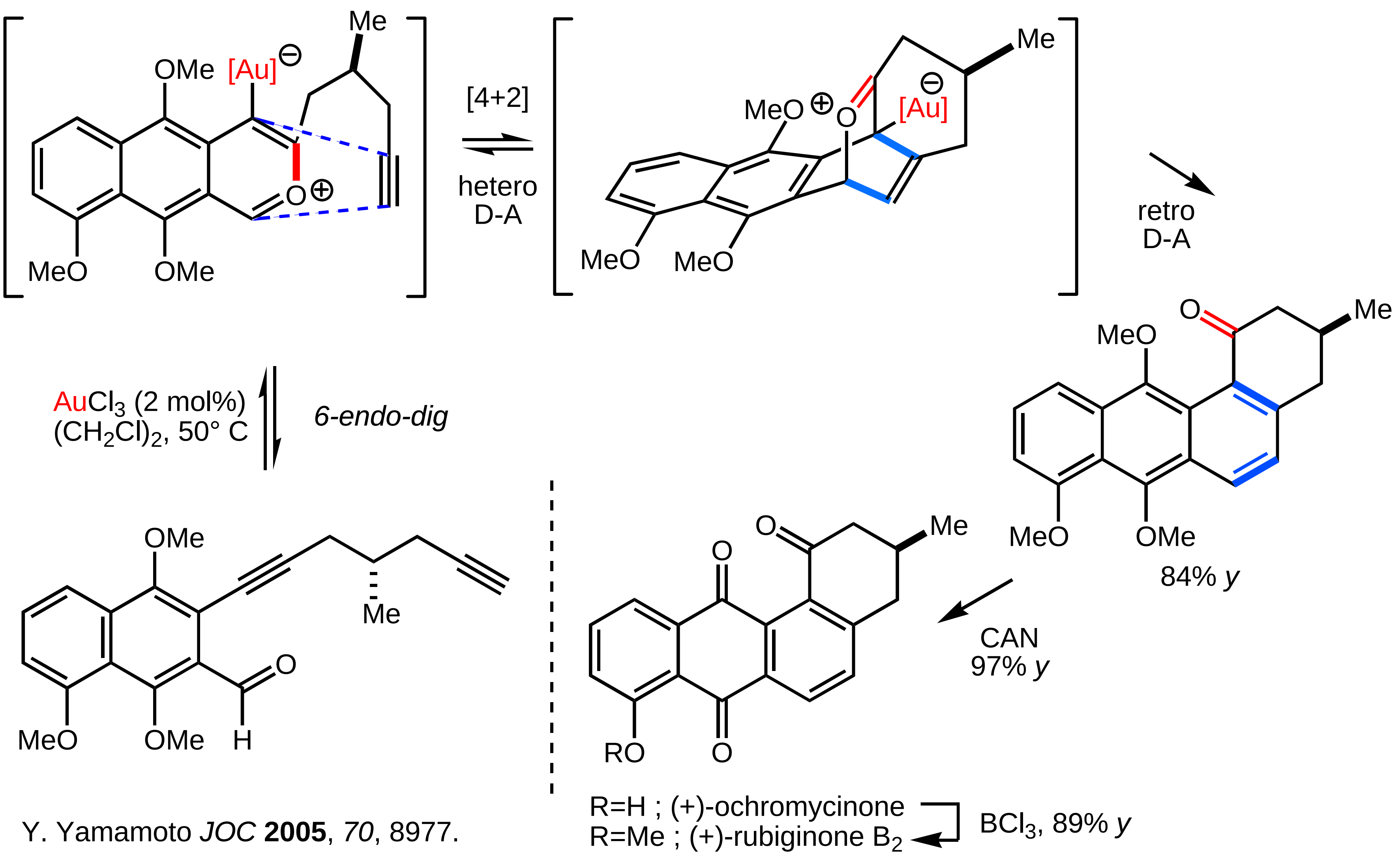
Nu-H = alkyl alcohols, 8 examples, 50 - 92% yields
Nu-H = 2-alkyl furan, 3 examples, 61 - 80% *yields*

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

Carbonyl Oxygen as Nucleophile

(+)-Rubiginone B_2 (2005)

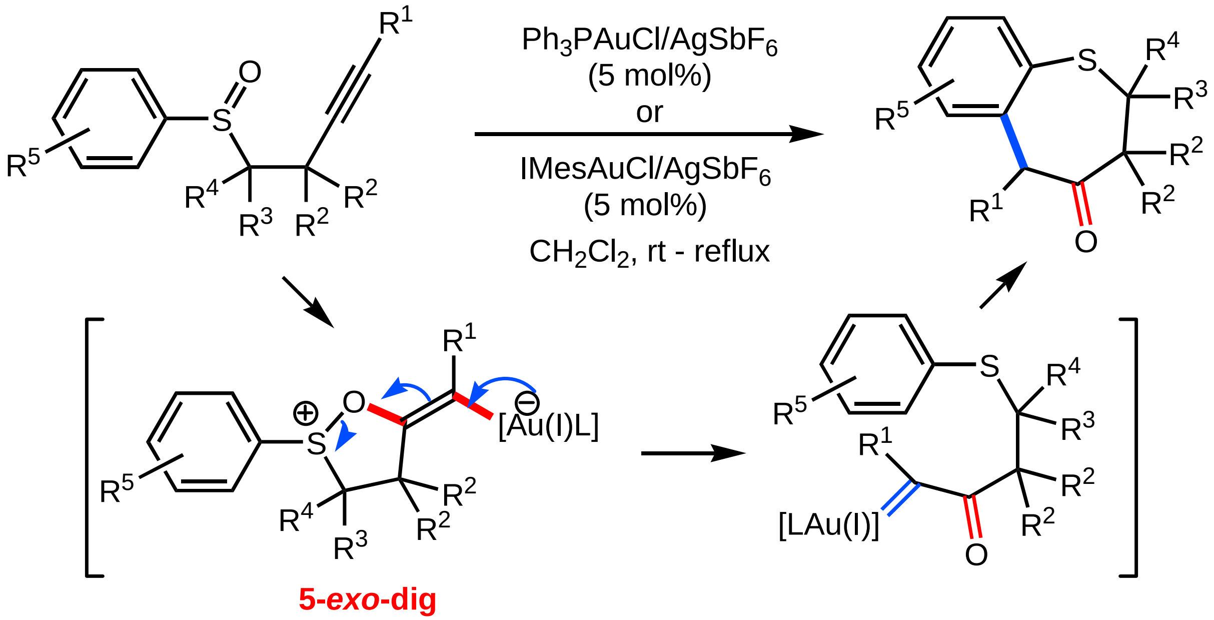
Activation of Alkynes



Y. Yamamoto *JOC* **2005**, *70*, 8977.

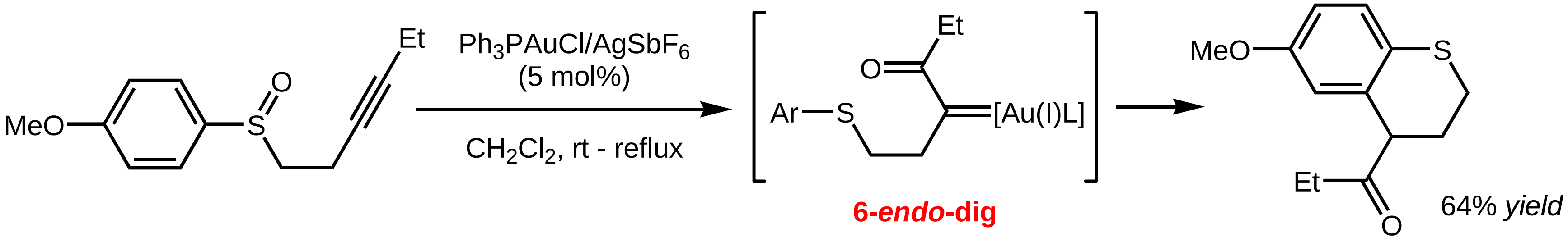
Similar application : **Heliophenanthrone**, Dyker *JOC* **2005**, *70*, 6093.
Similar study : **[3+2] dipolar cycloaddition**, Oh *OL*, **2005**, *7*, 5289.

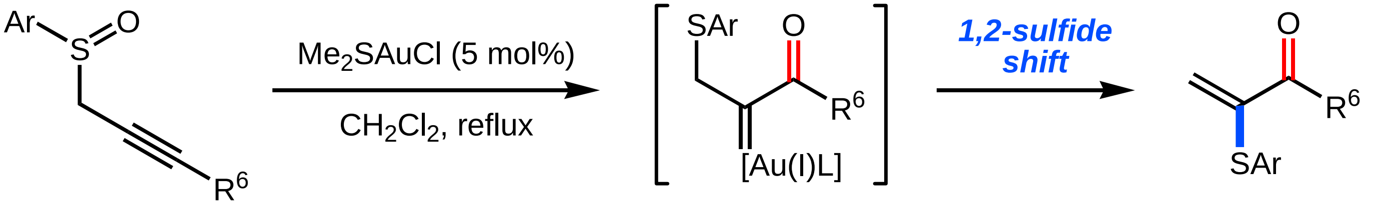
Rearrangement of Alkynyl Sulfoxides



7 Examples
R^1 = H, aryl, CO$_2$Et
R^2 = H, *n*-Bu
R^3 = H, cycle w/ R^4
R^4 = H, Ph
R^5 = H, NO$_2$, OMe, Cl

63 - 94% *yields*

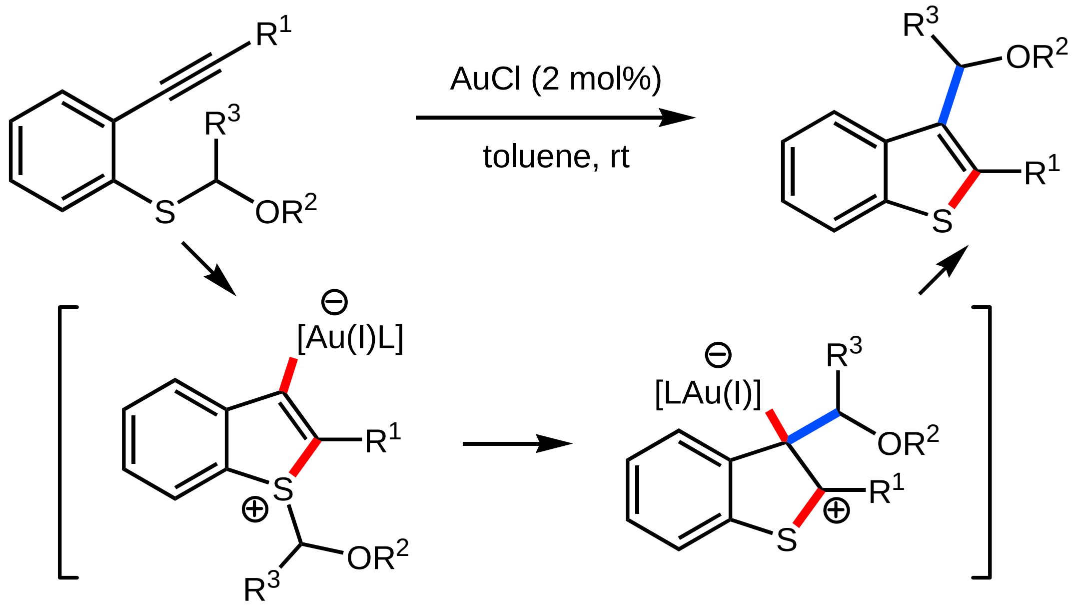




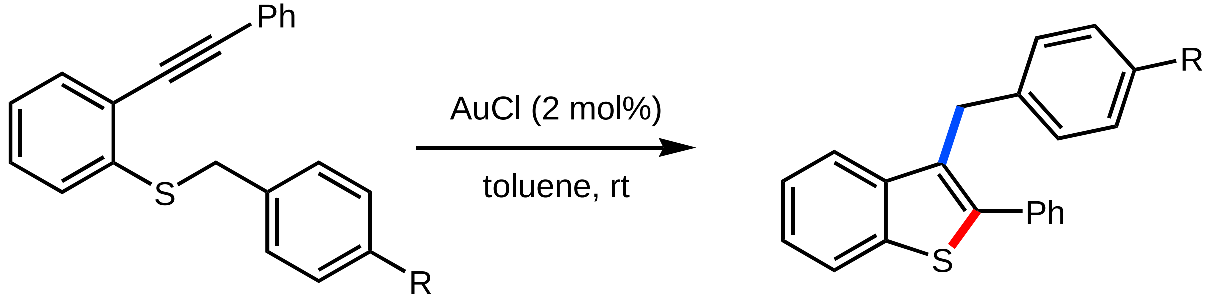
R^6 = H, alkyl, ary
51-91% *yields*l

Toste *JACS* **2007**, *129*, 4160.
Similar chemistry : Zhang *ACIE* **2007**, *46*, 5156.

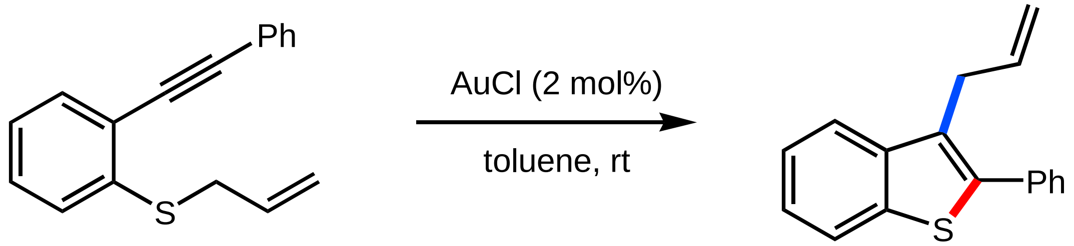
Intermolecular Carbothiolation



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



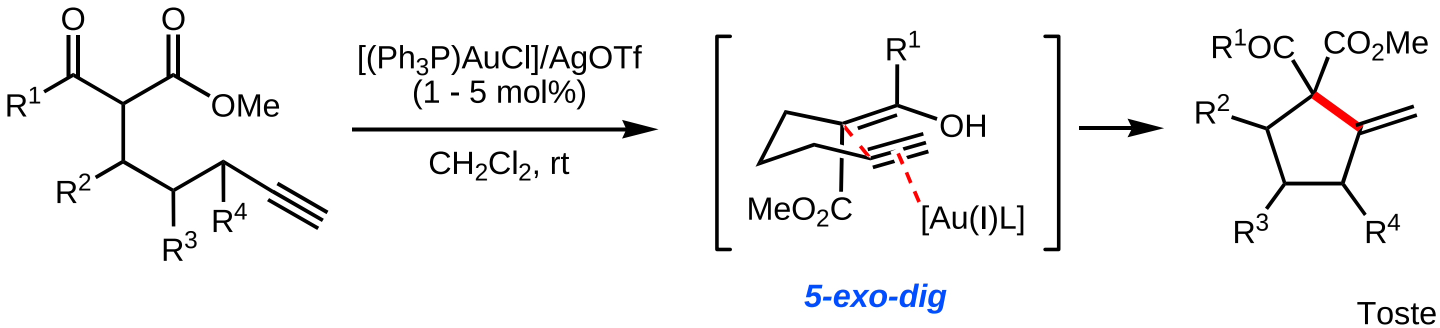
93% *yield*

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

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

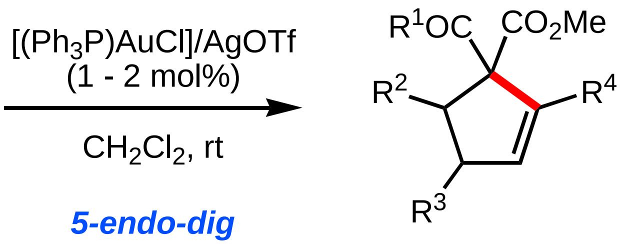
Enolates and Enol Ethers as Nucleophiles

Activation of Alkynes



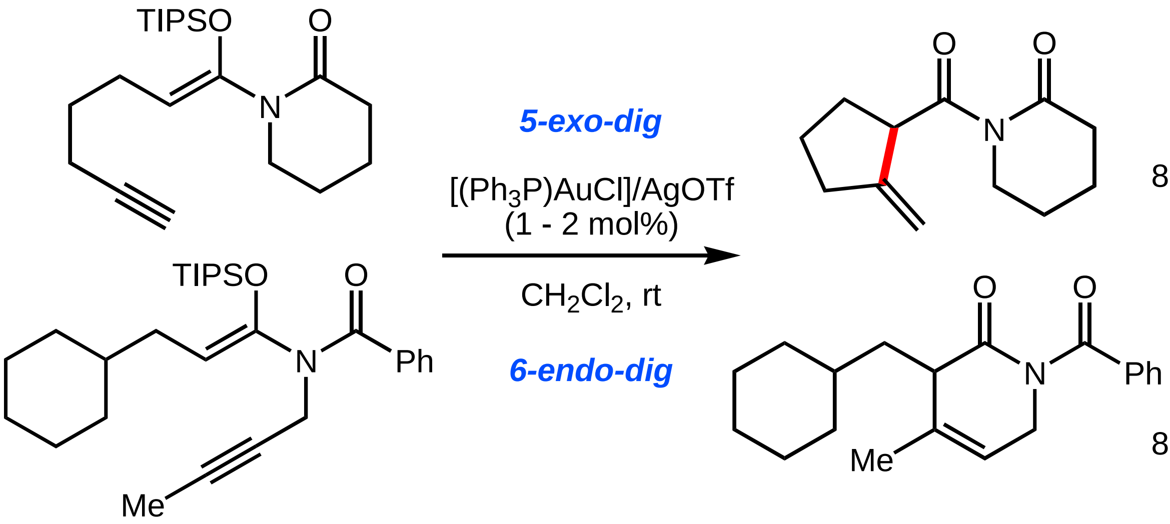
15 examples
R^1 = alkyl, cyclic w/ R^2
R^3, R^4 = H, alkyl
79 - 99% *yields*

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



12 examples
R^1 = alkyl, aryl, cyclic w/ R^2 or R^3
R^3, R^4 = H, alkyl
74 - 99% *yields*

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



82% *yield*

12 other examples
32 - 82% *yields*

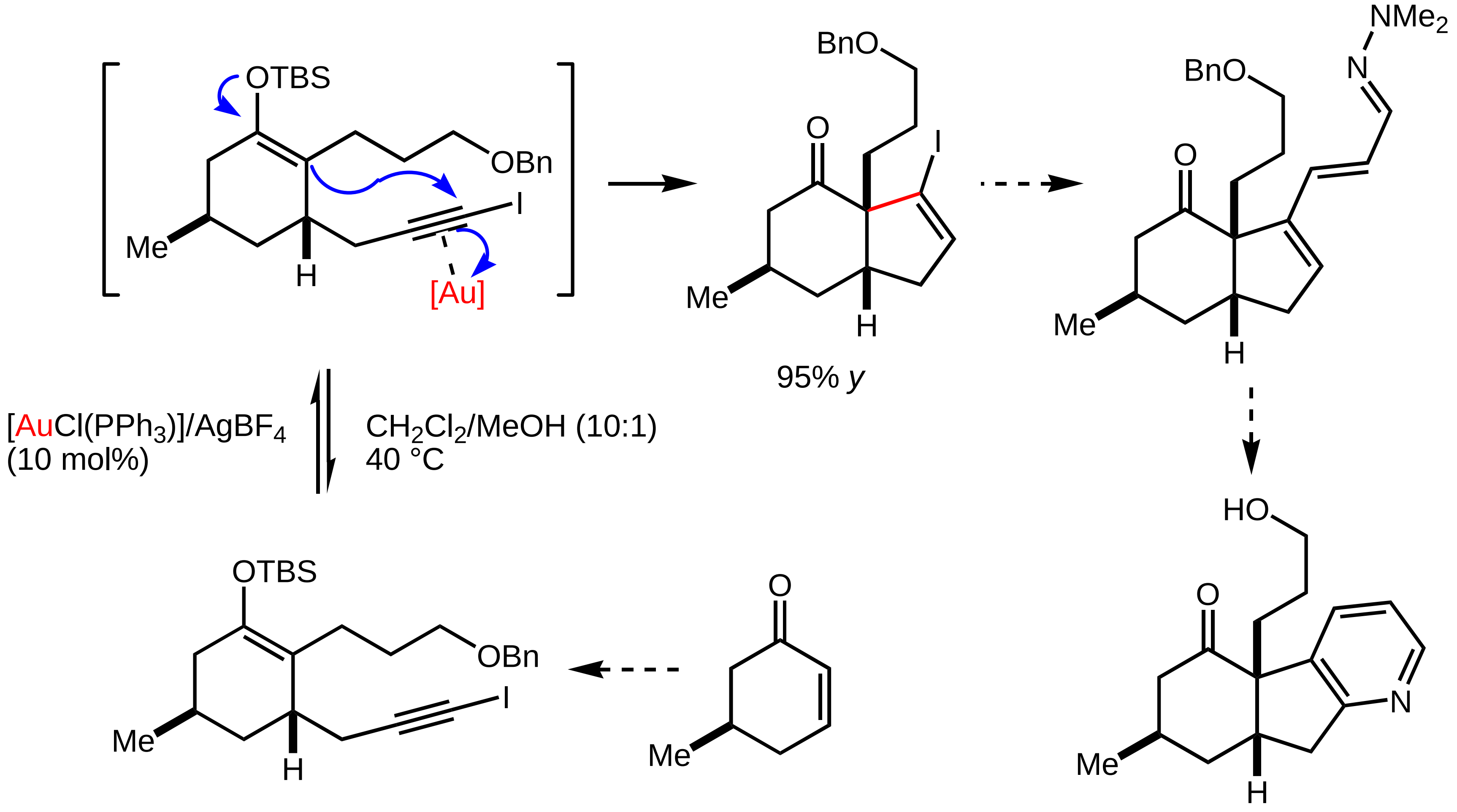
80% *yield*

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

(+)-Lycopladine A (2006)



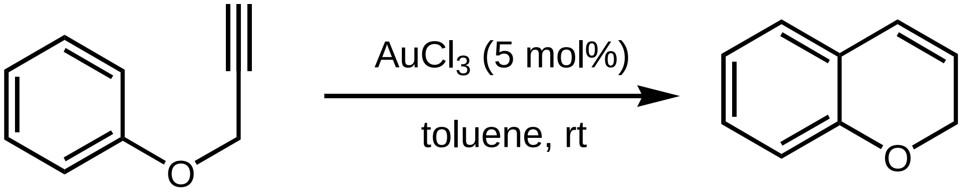
[AuCl(PPh$_3$)]/AgBF$_4$
(10 mol%)

CH$_2$Cl$_2$/MeOH (10:1)
40 °C

Toste *ACIE* **2006**, *45*, 5991.

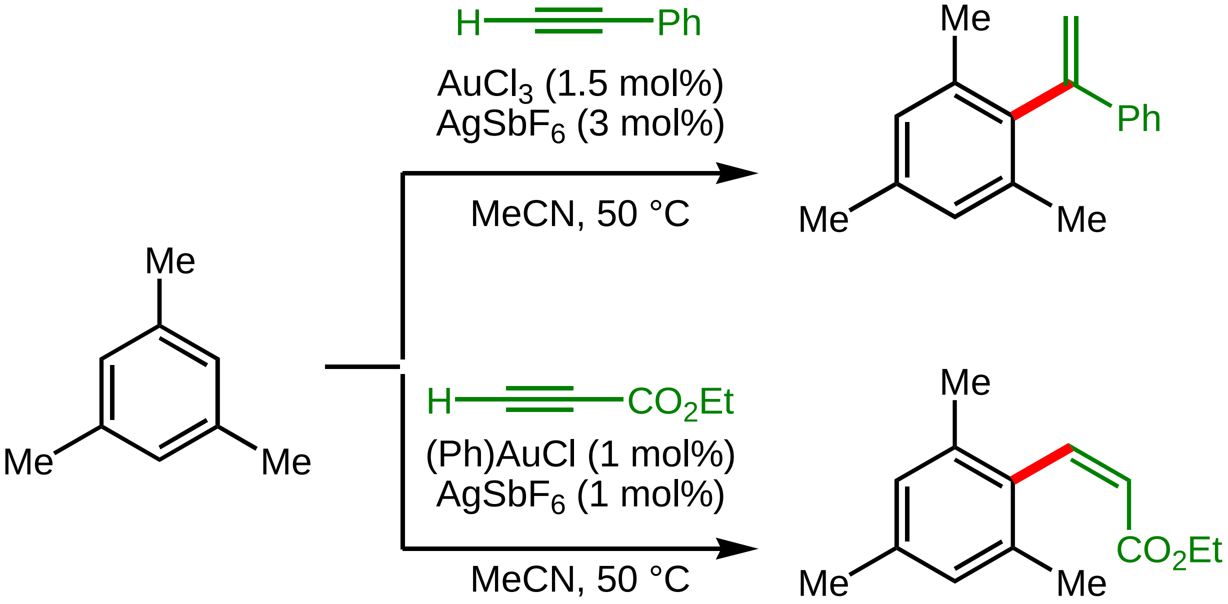
(+)-lycopladine A

Hydroarylation – Early Studies



only 6% (82% recovered SM)
32% with PtCl$_4$

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

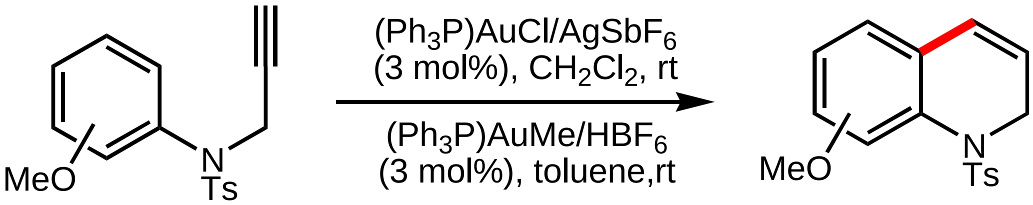


16 examples
9 - 100% *yields*

8 examples
0 - 98% *yields*

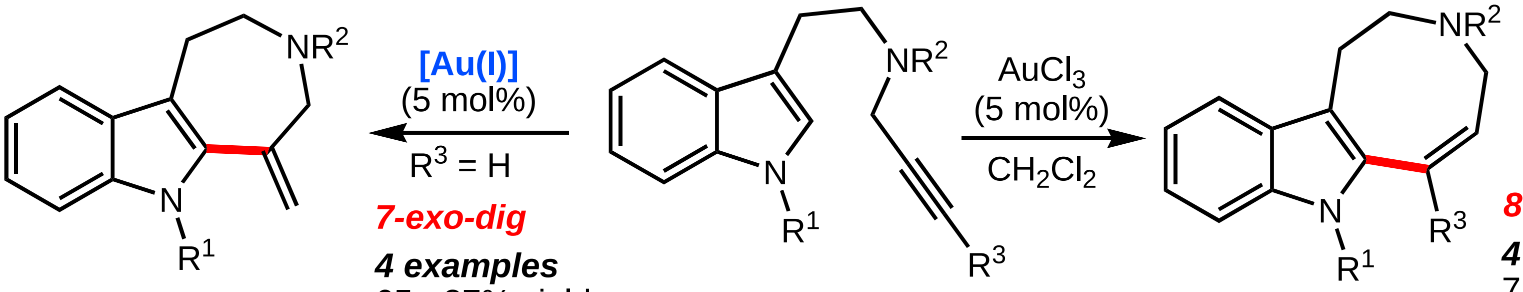
Reetz *EJOC* **2003**, *3485*.

Intramolecular Hydroarylation



72 - 92% *yields*

Echavarren *CEJ* **2005**, *11*, 3155.



7-exo-dig

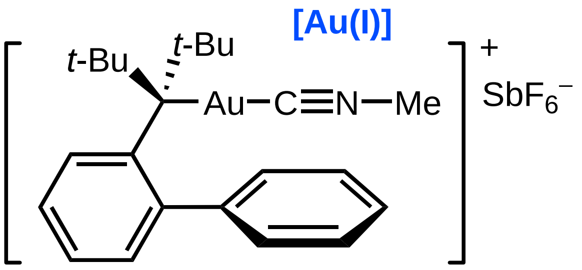
4 examples

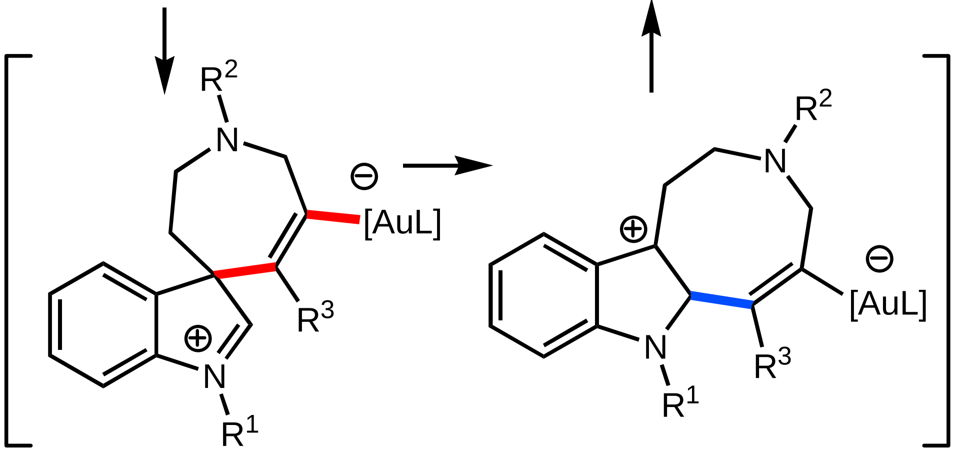
65 - 87% yields

8-endo-dig

4 examples

71 - 87% yields

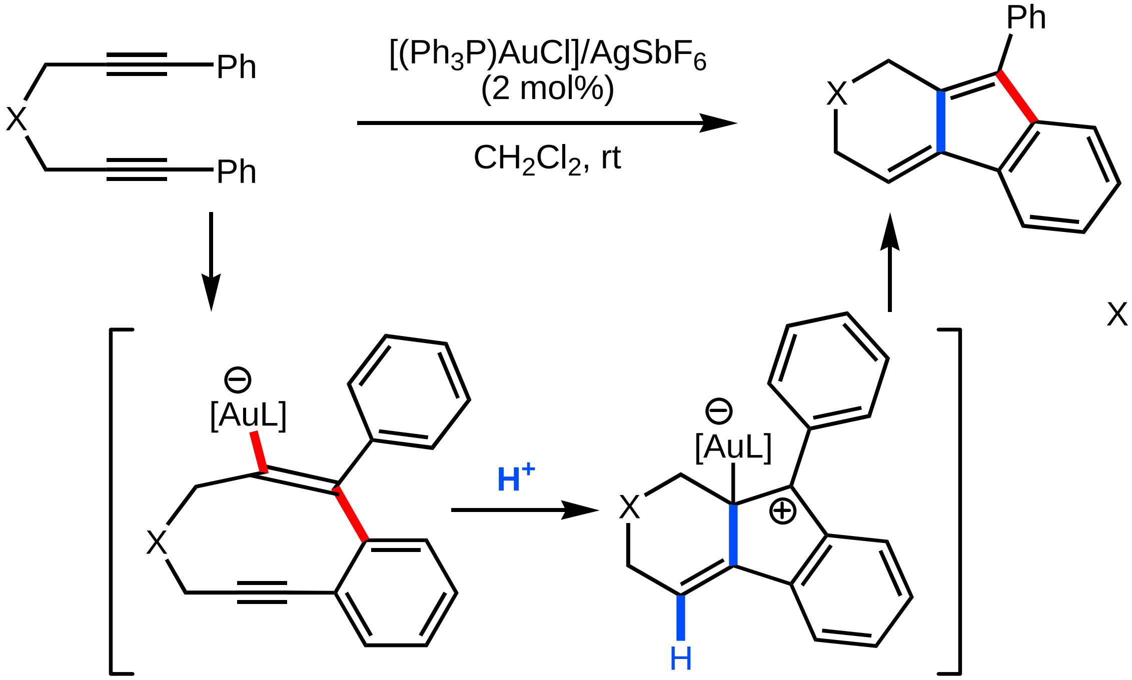




Echavarren *ACIE* **2006**, *45*, 1105.

[3+2] Cycloaddition / aza-Claisen Rearrangement

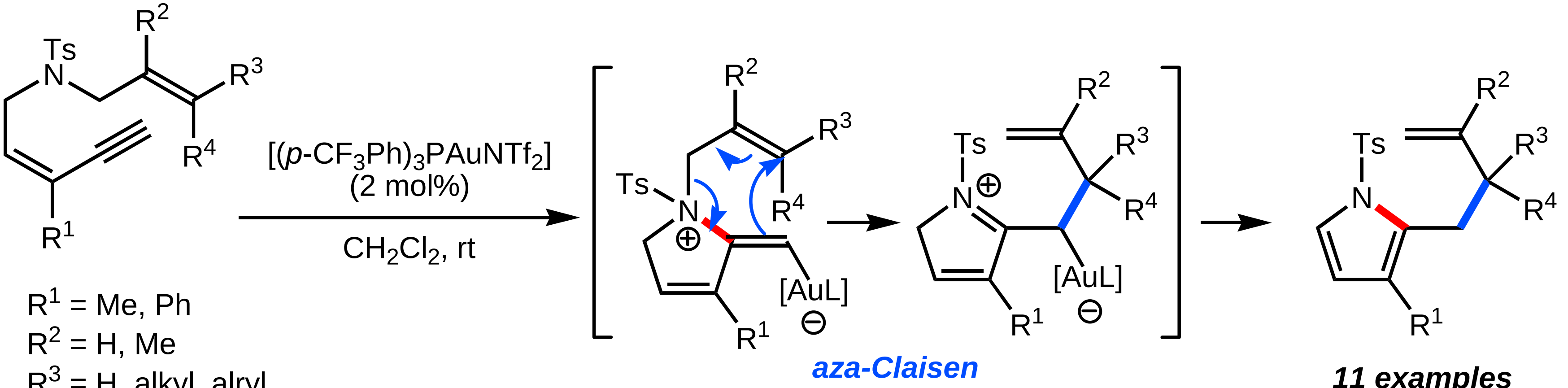
Activation of Alkynes



12 examples
60 - 90% *yields*

X = NTs, $C(CO_2Me)_2$, CH_2
$C(SO_2Ph)_2$
$C(COMe)(CO_2Me)$
$C(COPh)(CO_2Et)$

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

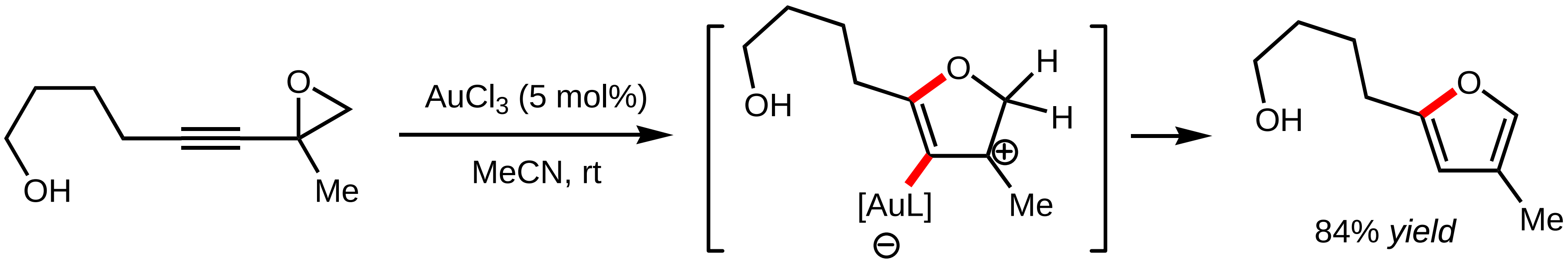


R^1 = Me, Ph
R^2 = H, Me
R^3 = H, alkyl, alryl
R^4 = H, Me

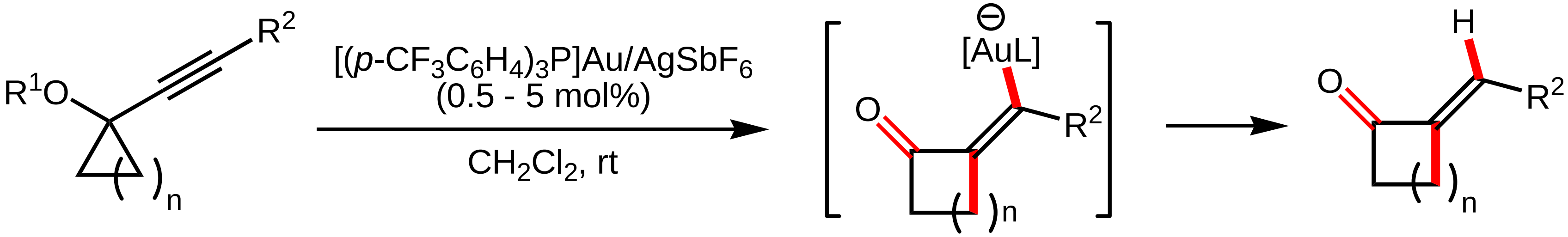
11 examples
72 - 97% *yields*

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

Ring Enlargement Reactions



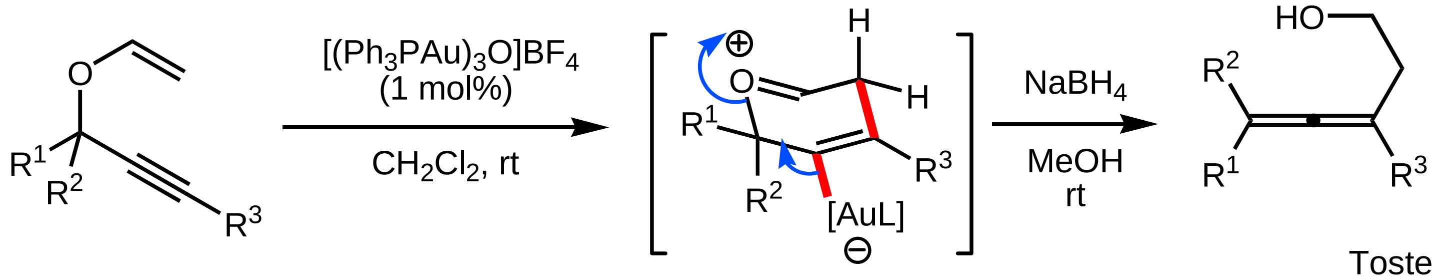
Hashmi *Adv. Synth. Catal.* **2004**, *346*, 432.



16 examples
R^1 = H, TBS, TMS
R^2 = H, alkyl, aryl, I
61 - 98% *yields*

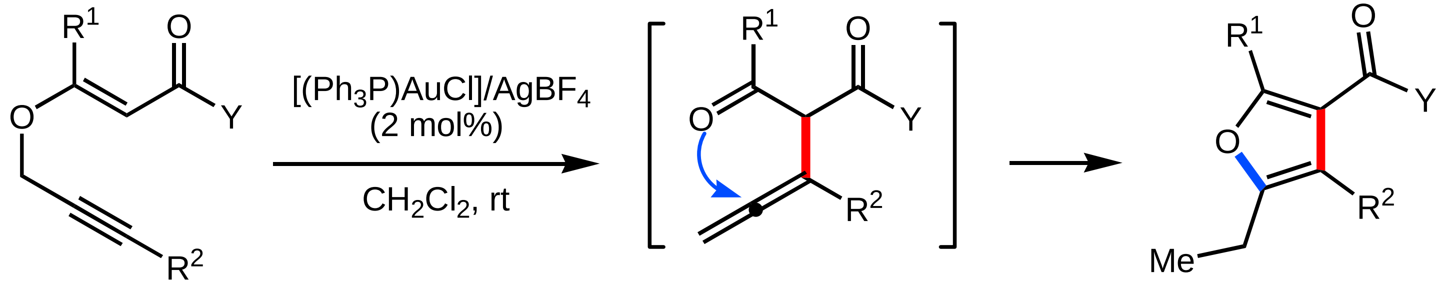
Toste *JACS* **2005**, *127,* 9708.

Propargyl Vinyl Ethers



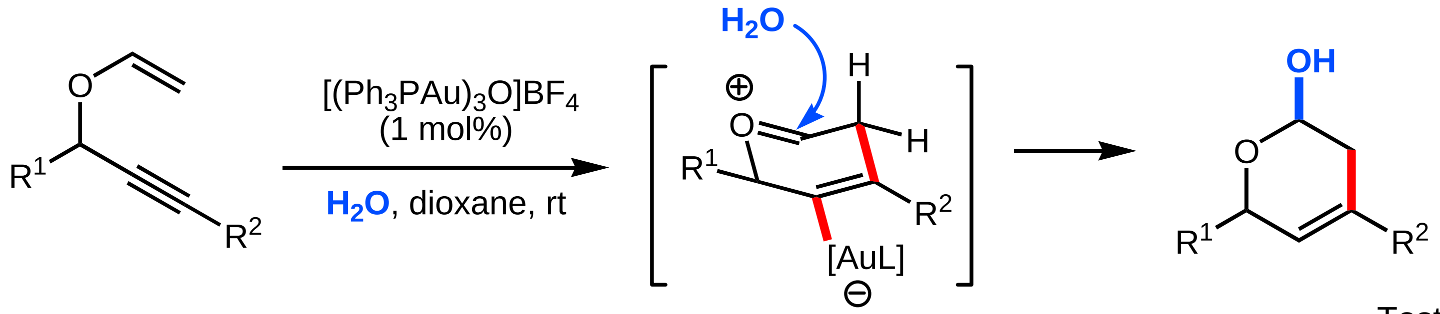
13 examples
R^1, R^3 = alkyl, aryl
R^2 = H, Me
61 - 96% *yields*

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



17 examples
R^1, R^2 = H, alkyl, aryl
Y = OMe, OEt, Ph
45 - 97% *yields*

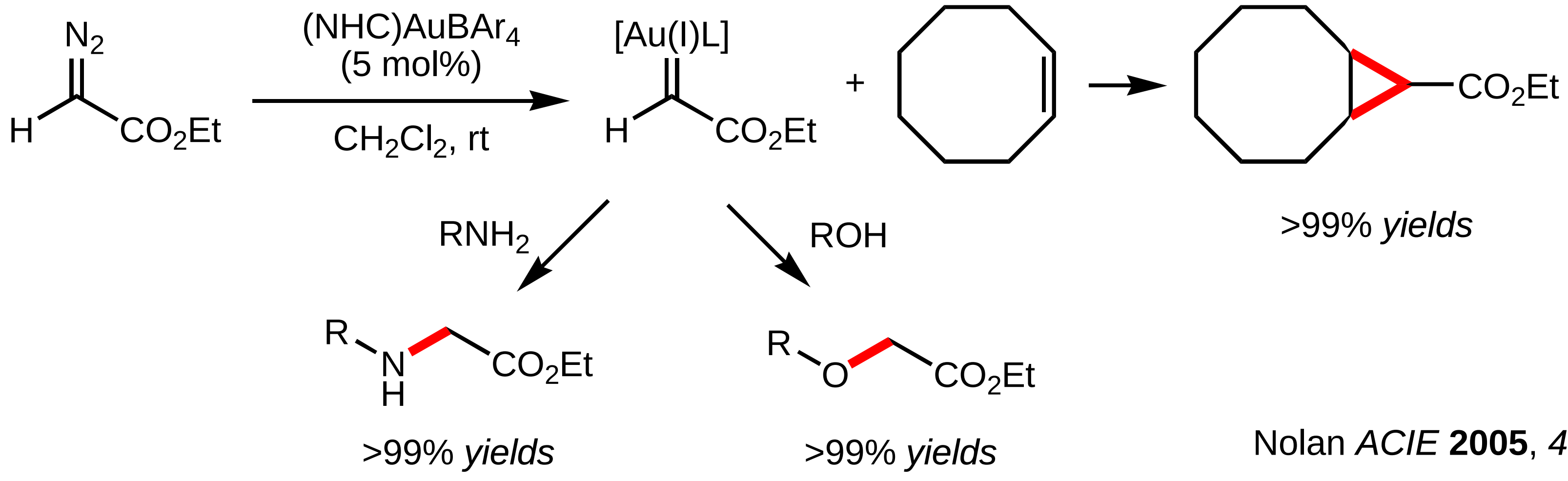
KirschOL **2005**, *7*, 3925.



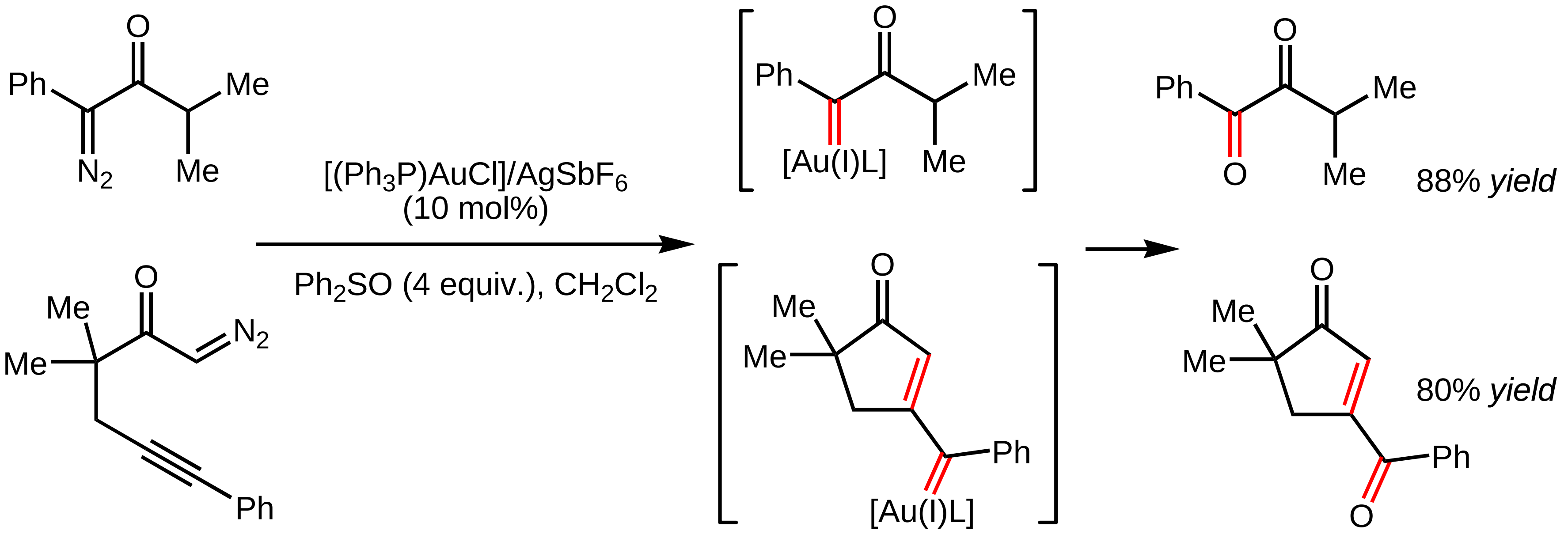
10 examples
R^1, R^2 = alkyl
60 - 95% *yields*

Toste *JACS* **2006**, *128, 8132*.

Gold Carbenoid

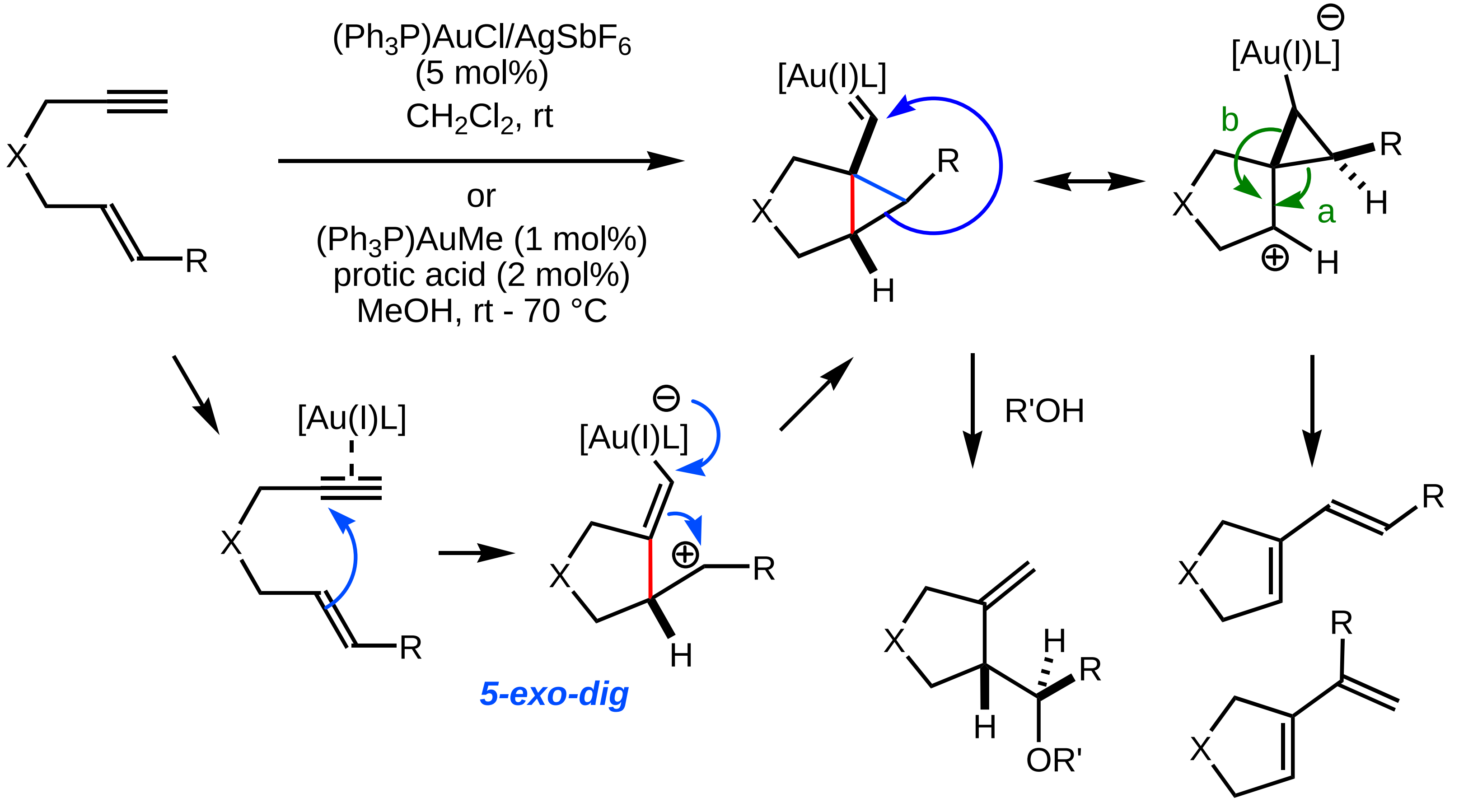


Nolan *ACIE* **2005**, *44*, 5284.



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

1, 6-Enyne Cylizations


$(Ph_3P)AuCl/AgSbF_6$
(5 mol%)
CH_2Cl_2, rt

or

$(Ph_3P)AuMe$ (1 mol%)
protic acid (2 mol%)
MeOH, rt - 70 °C

R'OH

5-exo-dig

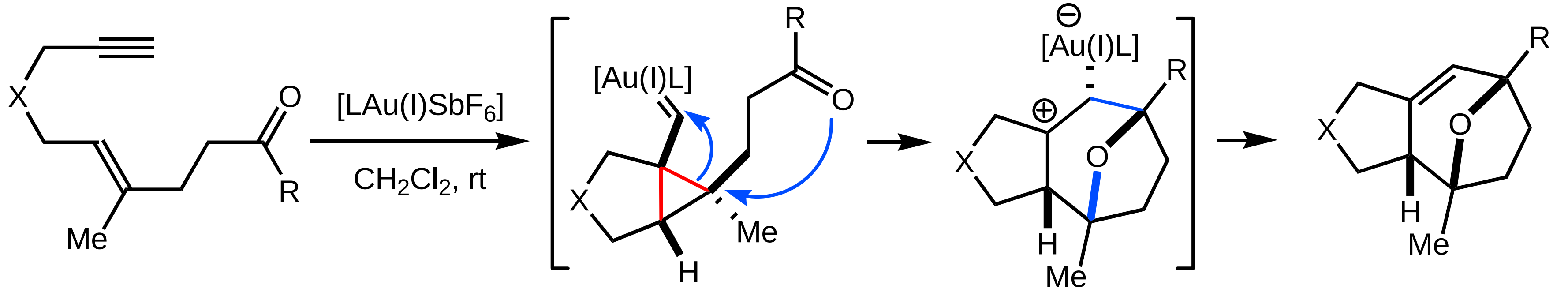
48 - 100% yields

47 - 100% *yields*

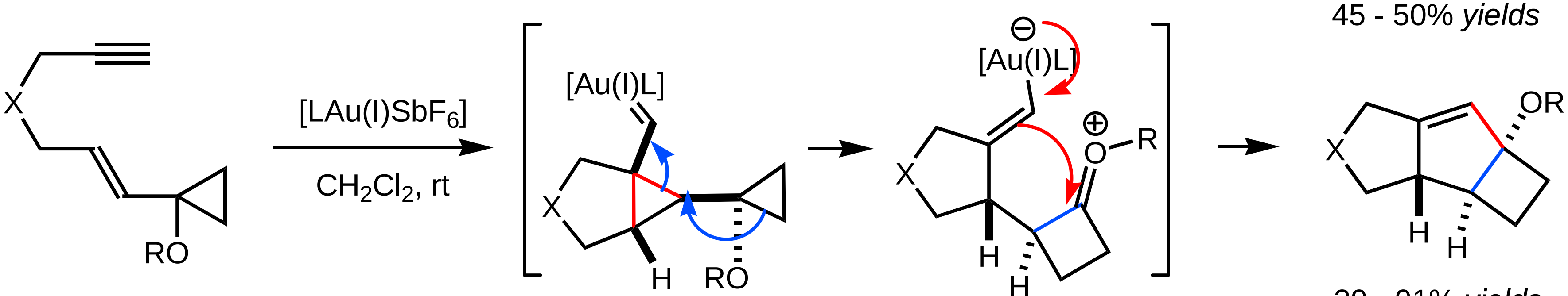
Echavarren *ACIE* **2004**, *43*, 2402.
OM **2005**, *24*, 1293.
CEJ **2006**, *12*, 1677.

1,6-Enyne Cyclizations

Activation of Alkynes

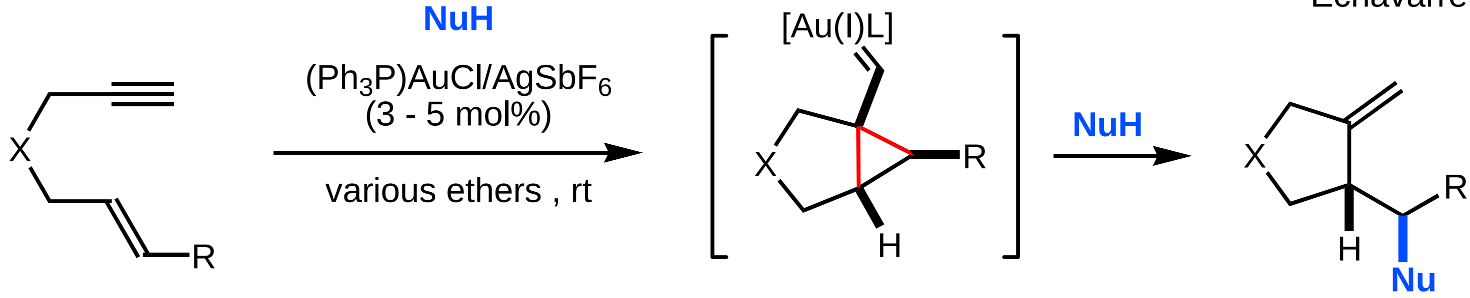


45 - 50% *yields*



39 - 91% *yields*

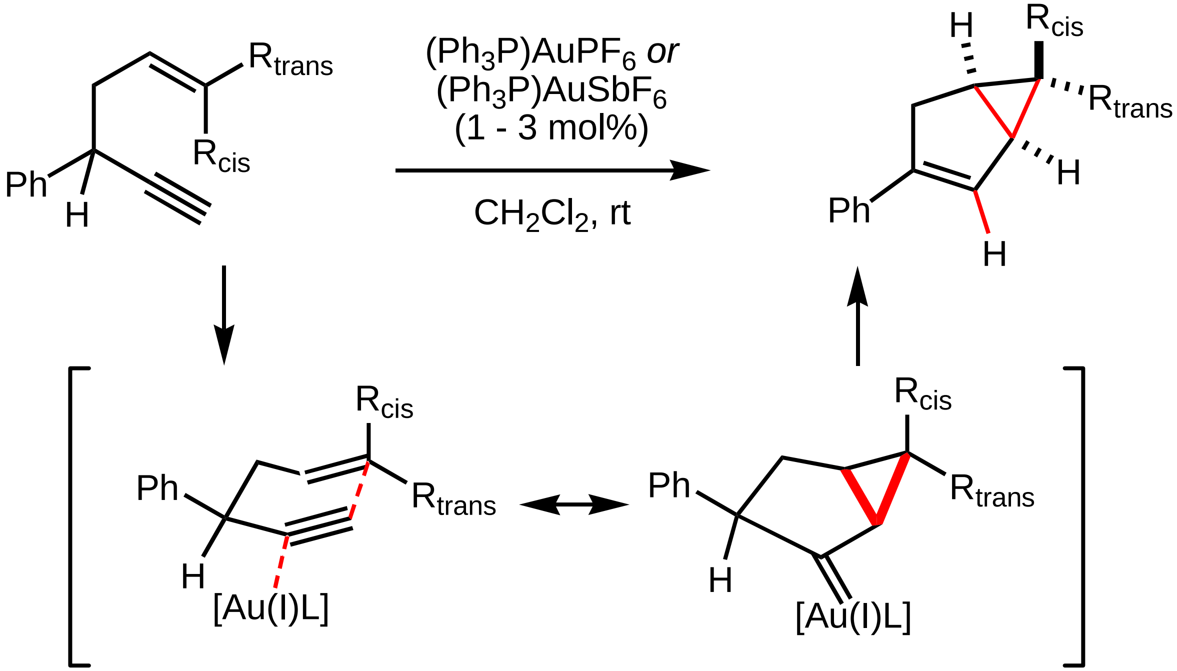
Echavarren *ACIE* **2006**, *45*, 5452.



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

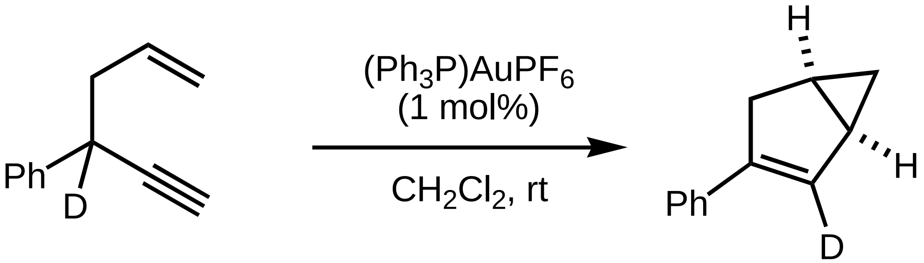
Genêt *ACIE* **2006**, *45*, 7427.
OL **2007**, *9*, 4049.

Cycloisomerization of 1,5-Enyne

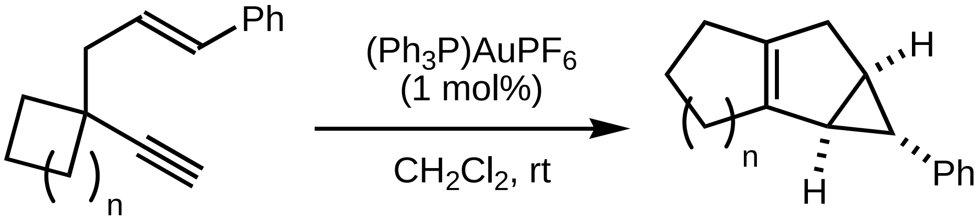


10 examples, 61 - 99% *yields*

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

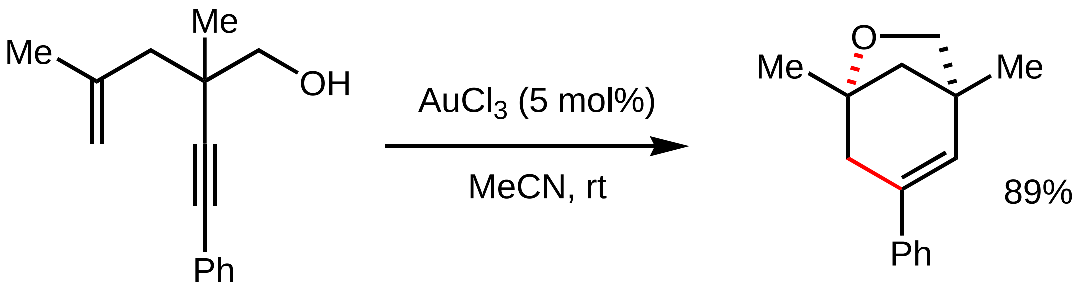


Ring-Enlargement
by the 1,2-C Shift



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

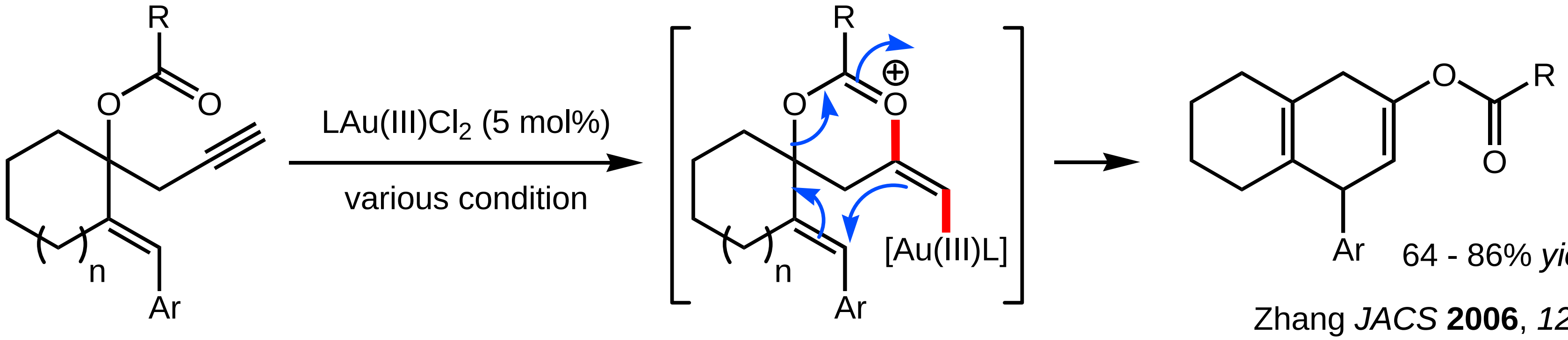
More 1,5-Enyne Cyclizations



89% *yield*

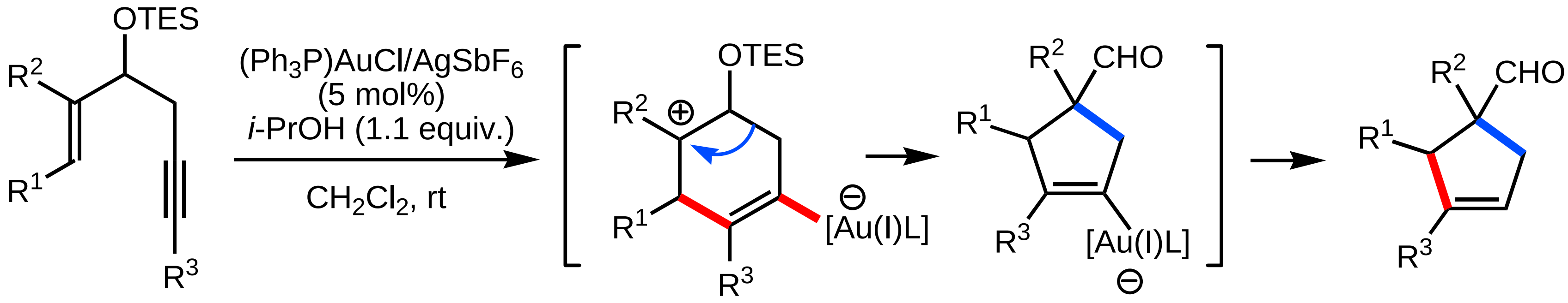
7 examples
82 - 96% *yields*

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



64 - 86% *yields*

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

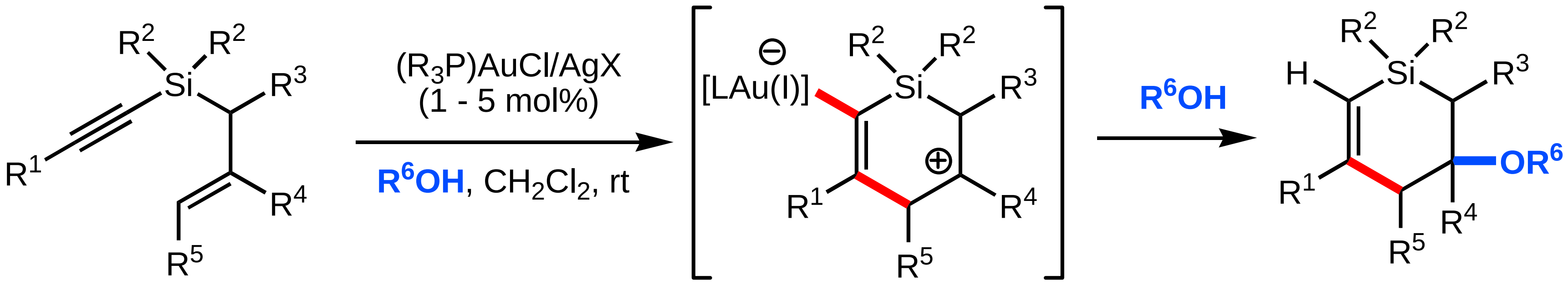


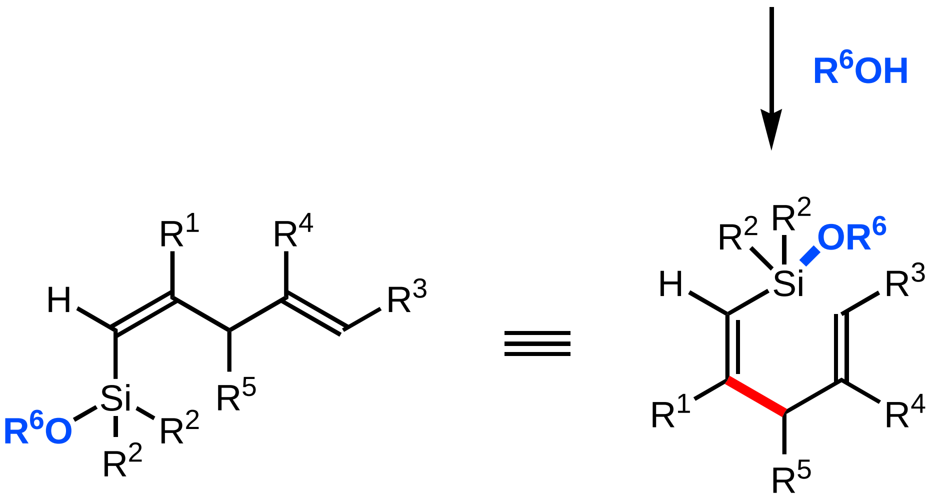
12 examples, 28 - 83% *yields*

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

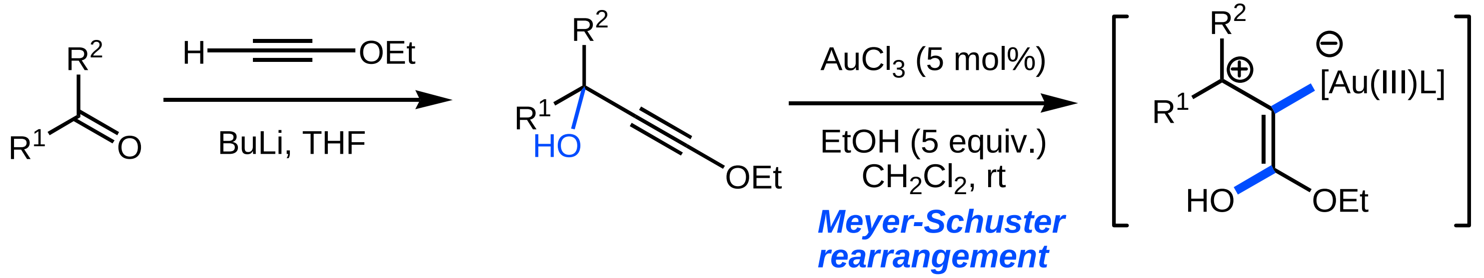


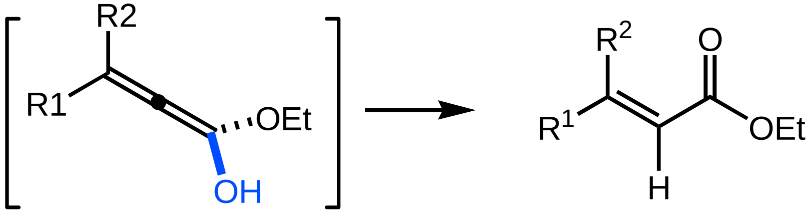


with (t-Bu$_3$P)AuCl/AgBF$_4$ (5 mol%) catalyst vinyl silanes products were favored when R^6 = Ph and silacycle products were favored when R^6 = alkyl .
21 examples, 46 - 99% *yields*
Toste *JACS* **2006**, *128*, 11364.

with (Ph$_3$P)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.

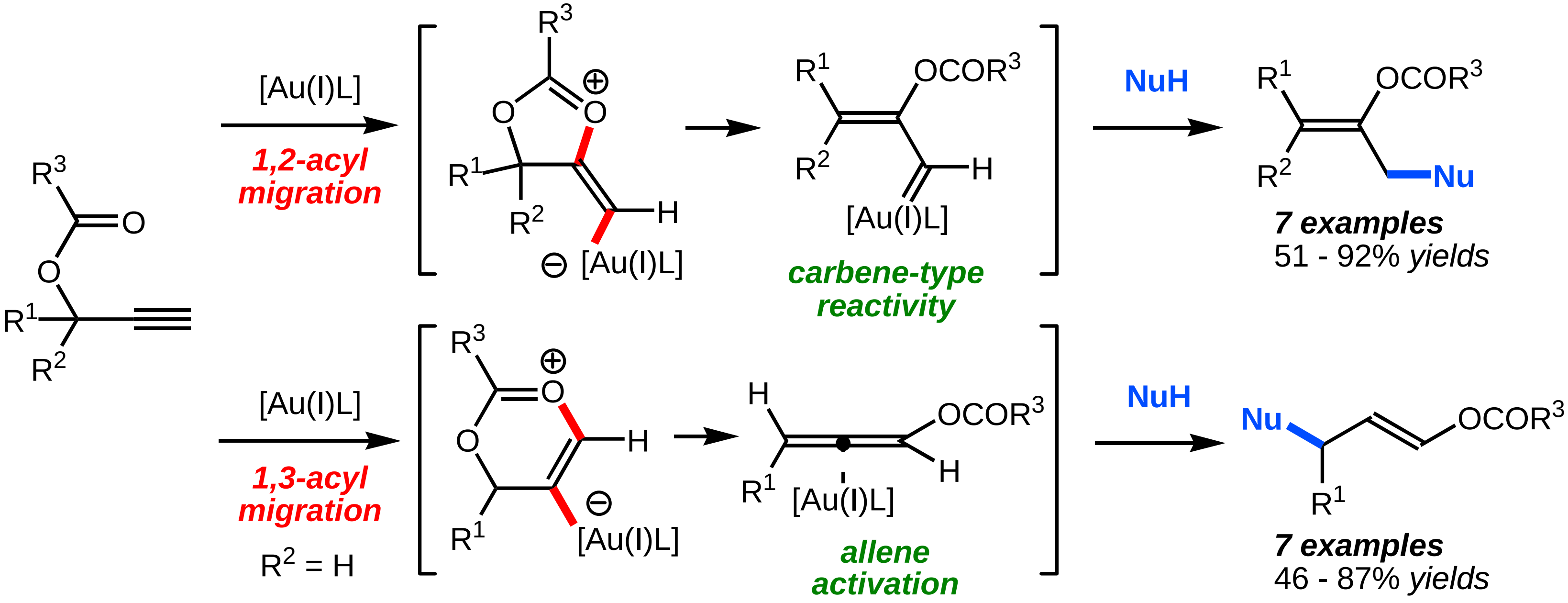
Migration of Propargyl Functional Groups





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

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



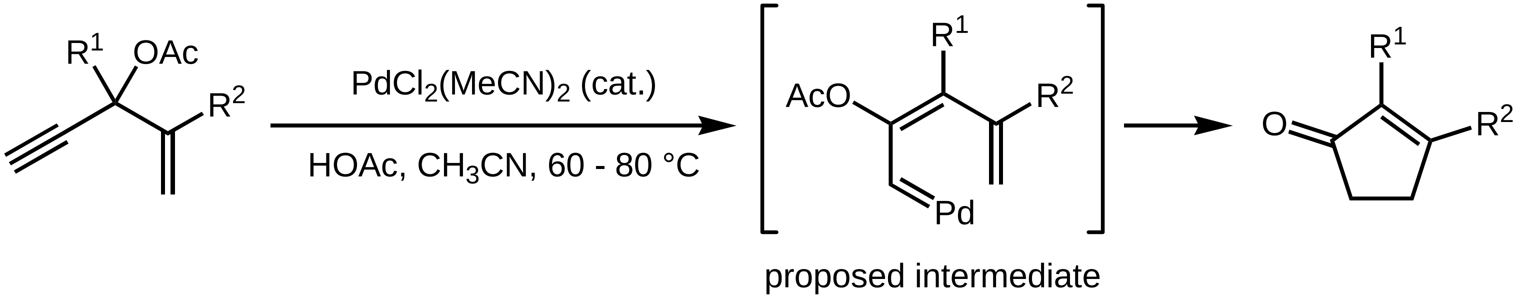
7 examples
51 - 92% *yields*

7 examples
46 - 87% *yields*

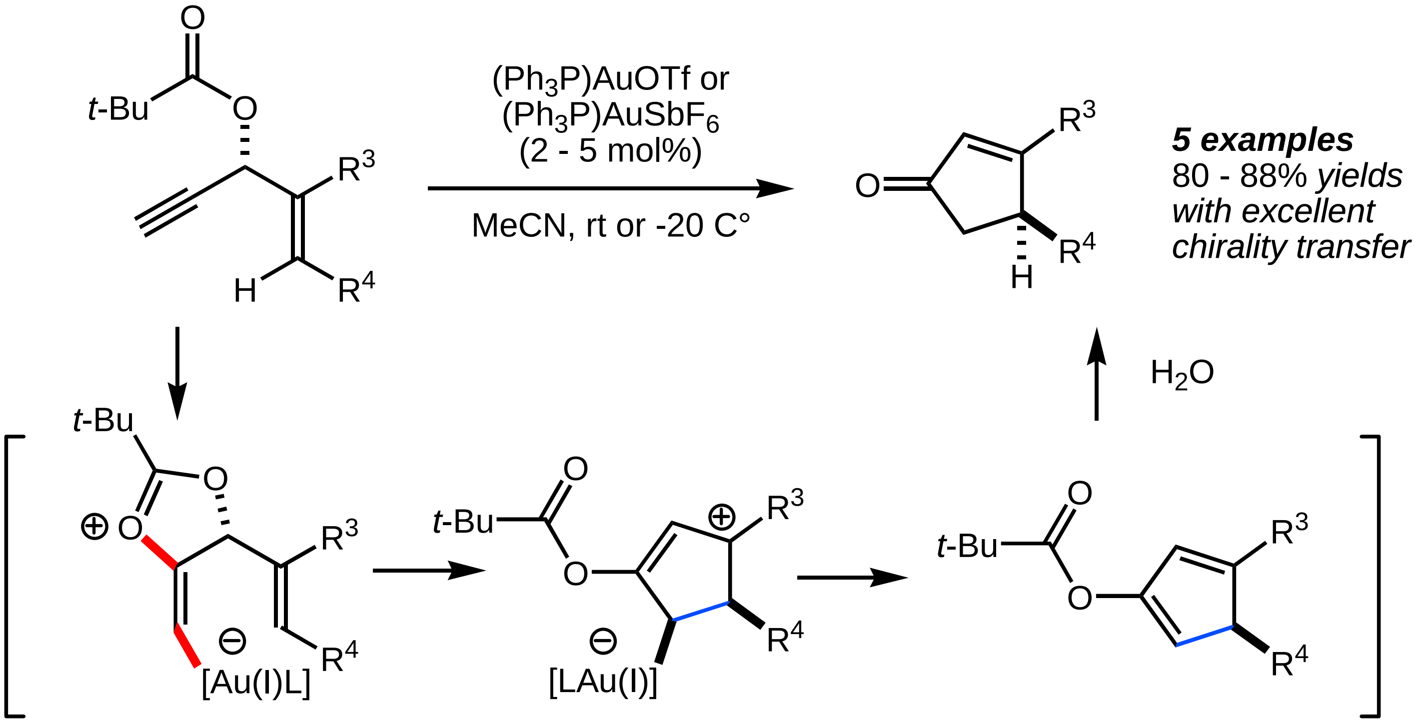
results depending on the ligands on catalysts and subsrates

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

Reactions of Propargylic Esters
Rautenstrauch Reaction



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

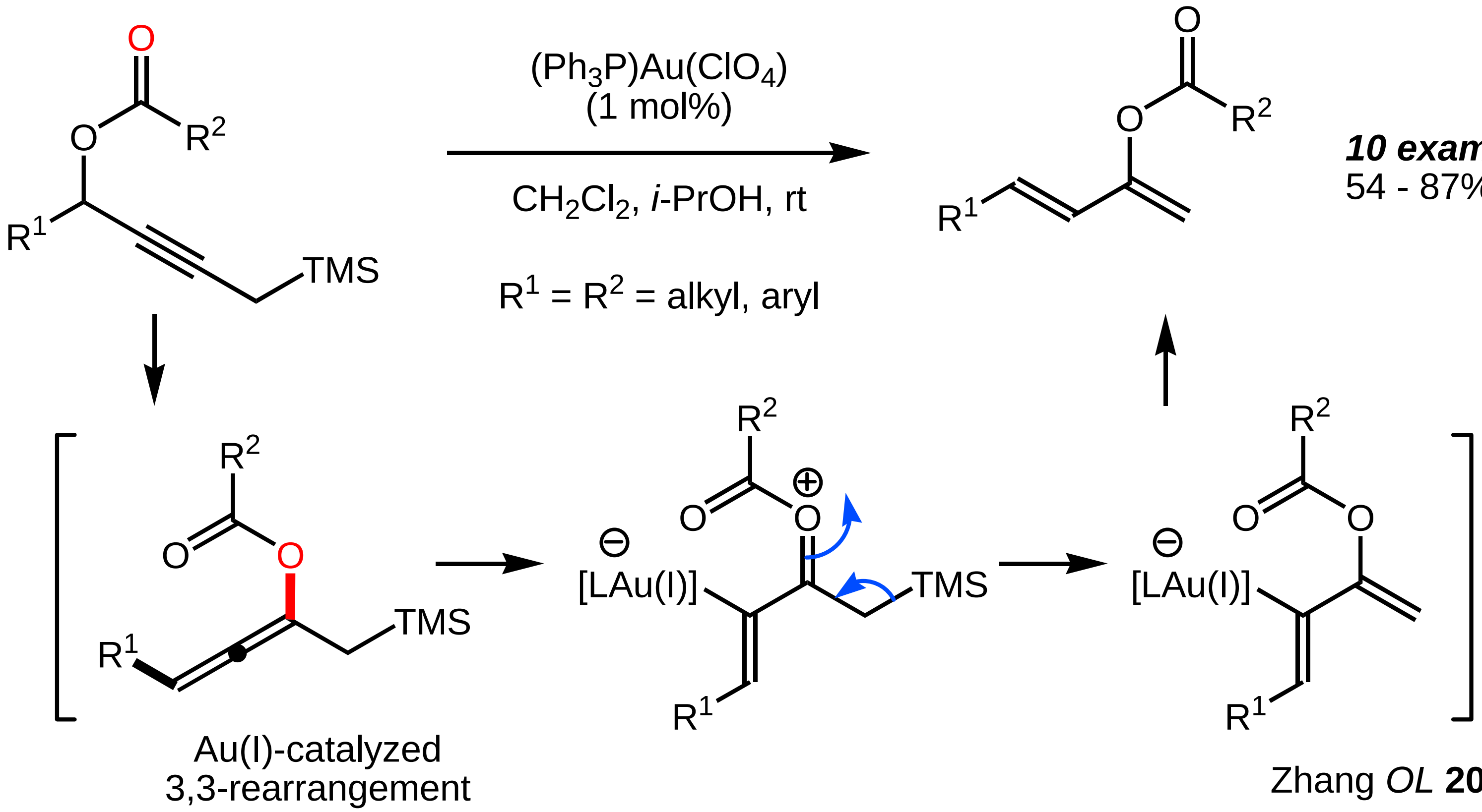


5 examples
80 - 88% *yields*
with excellent
chirality transfer

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



$(Ph_3P)Au(ClO_4)$
(1 mol%)

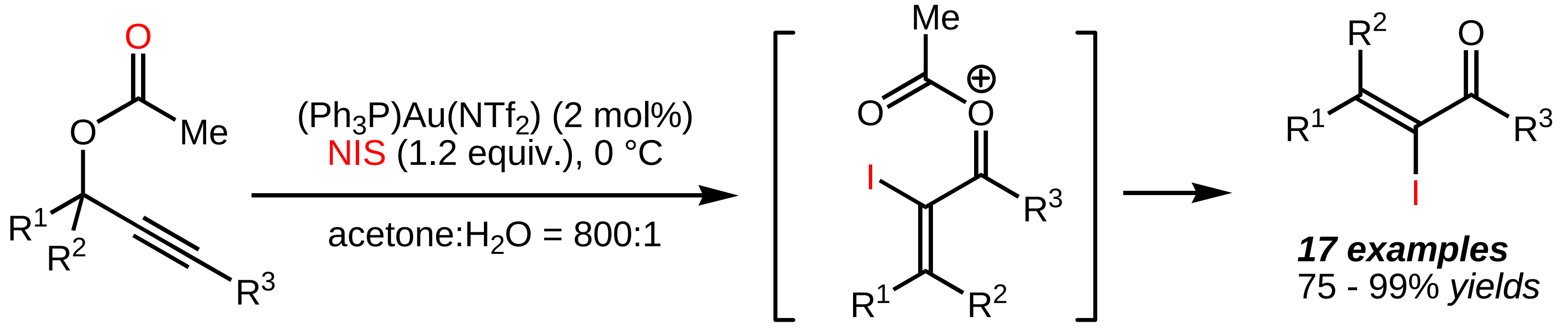
CH_2Cl_2, *i*-PrOH, rt

$R^1 = R^2$ = alkyl, aryl

10 examples
54 - 87% *yields*

Au(I)-catalyzed
3,3-rearrangement

Zhang *OL* **2006**, *8*, 4585.



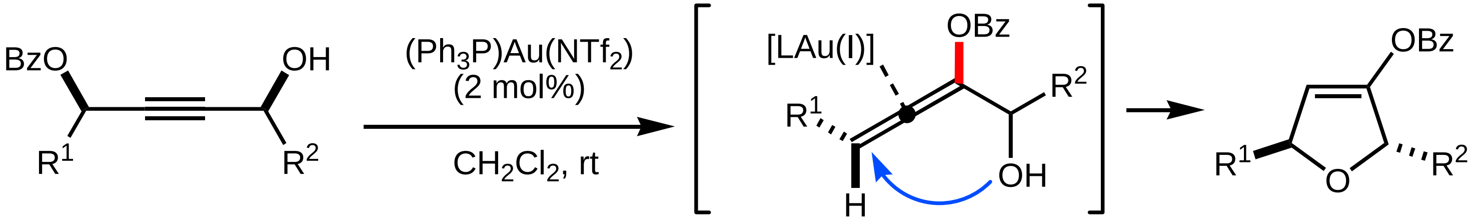
$(Ph_3P)Au(NTf_2)$ (2 mol%)
NIS (1.2 equiv.), 0 °C

acetone:H_2O = 800:1

17 examples
75 - 99% *yields*

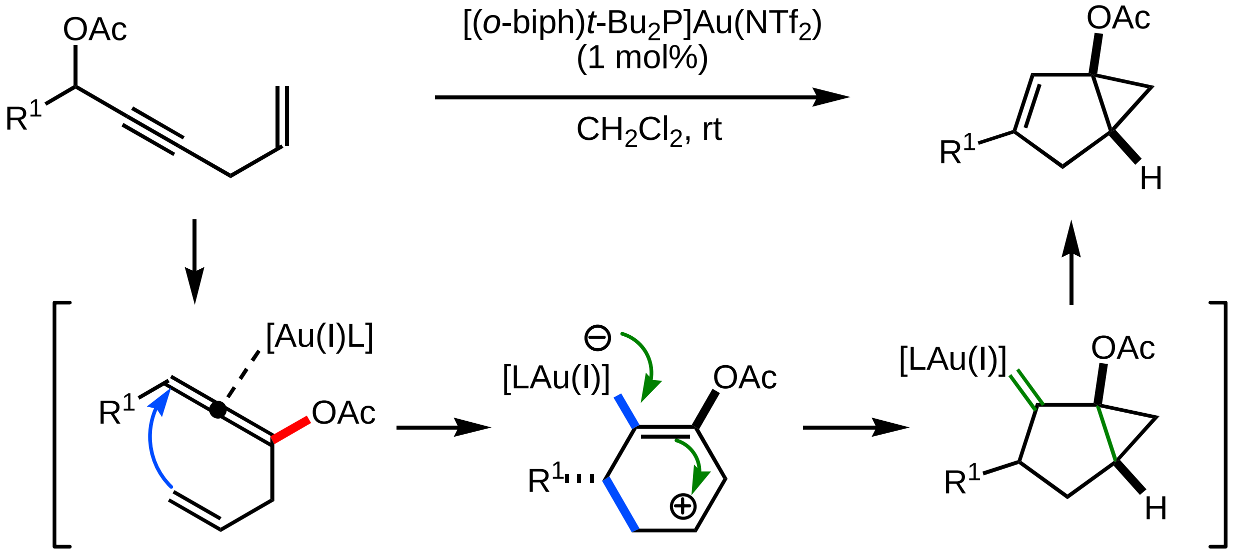
Zhang *OL* **2007**, *9*, 2147.

Reactions of Propargylic Esters



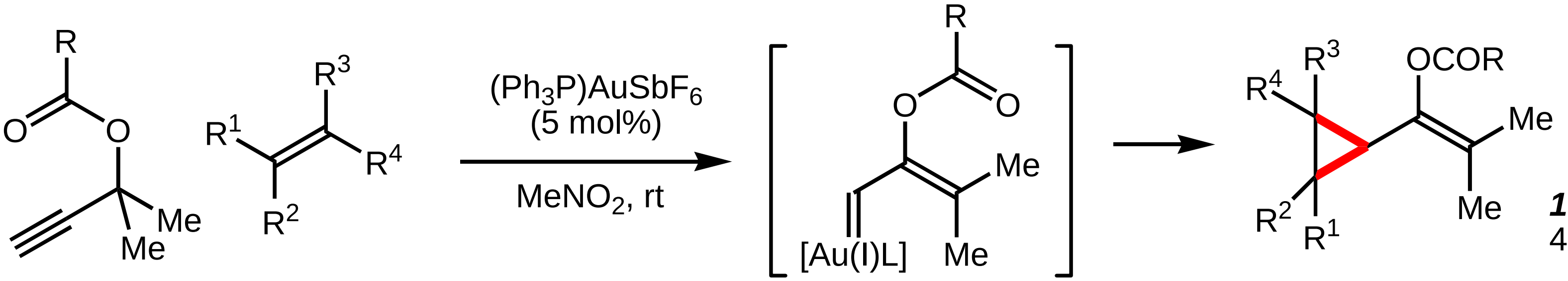
15 examples
69 - 99 % *yields*
with excellent
chirality tranfer

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



9 examples
38 - 99 % *yields*

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

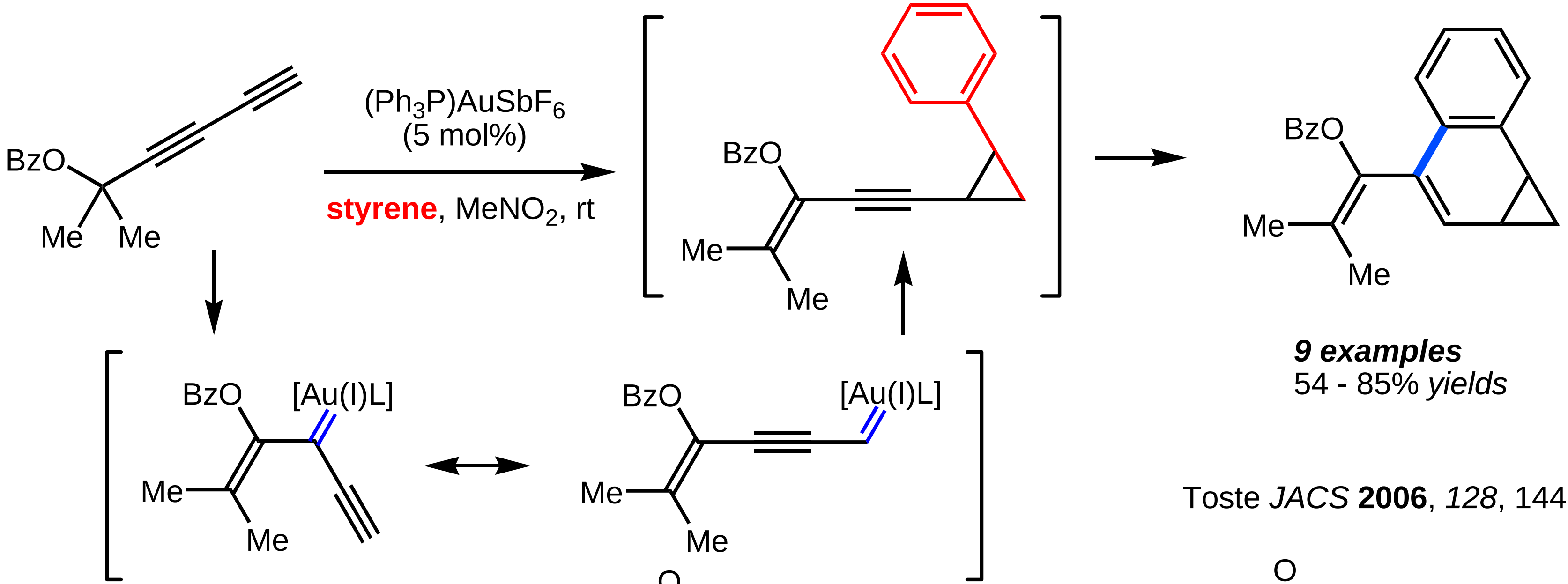


11 examples
48 - 84 % *yields*

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

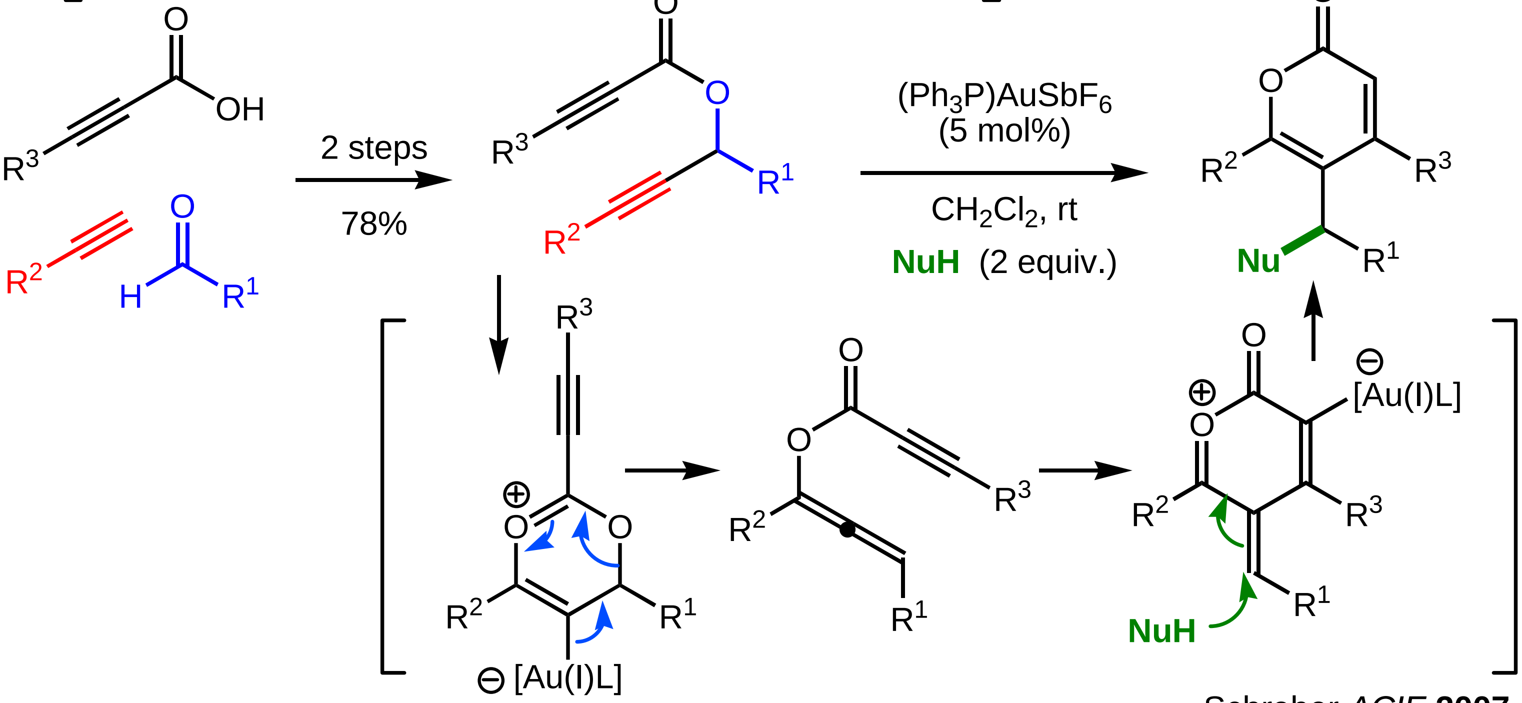
Reactions of Propargylic Esters

Activation of Alkynes



9 examples
54 - 85% *yields*

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



Schreber *ACIE* **2007**, *46*, 8250.

I. Introduction

II. Activation of Alkynes

III. Activation of Allenes

Nitrogen Nucleophiles : Hydroamination

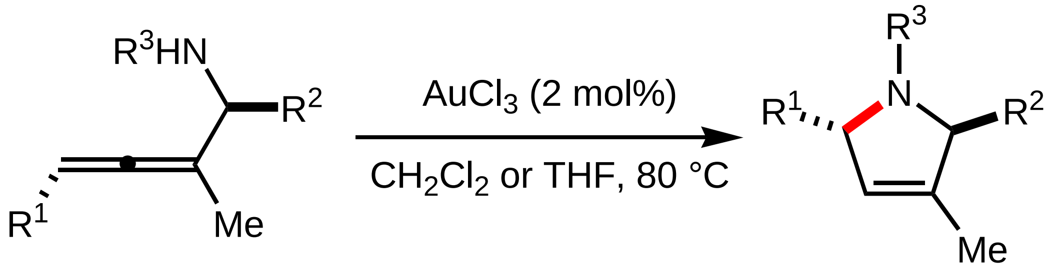
Oxygen Nucleophiles : Hydroalkoxylation
Carbonyl Oxygens

Carbon Nucleophiles : Hydroarylation
Alkenes

IV. Activation of Alkenes

V. Summary

Intramolecular Hydroamination

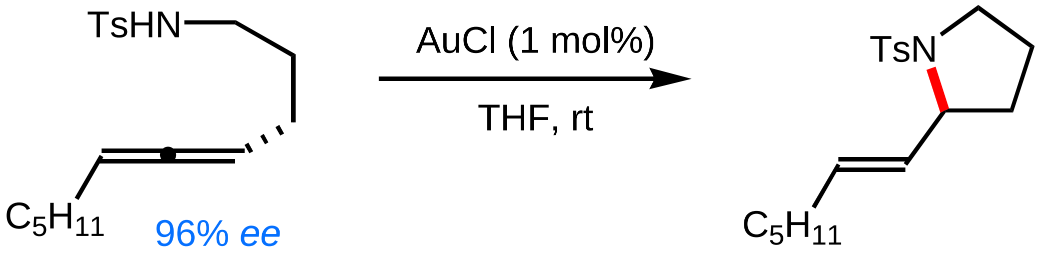


R^1 = alkyl, aryl
R^2 = CH$_2$OR
R^3 = H, Ms, Ts, Ac, Boc

69-95% *yields*

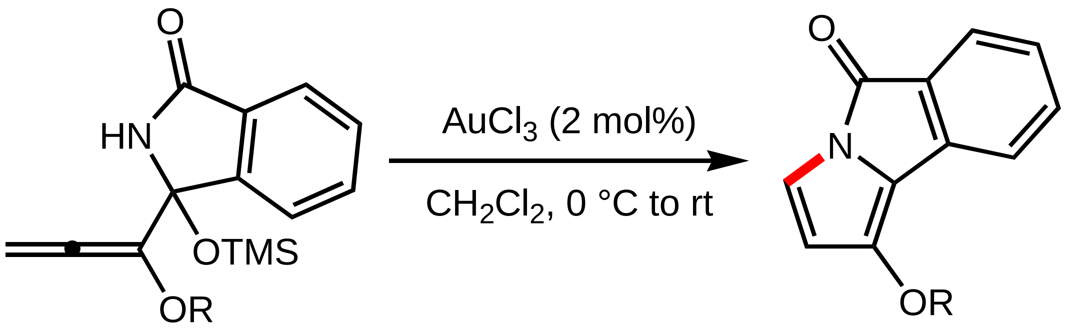
with complete
axis-to-center chirality transfer

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



99% *yields*
94% *ee*

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



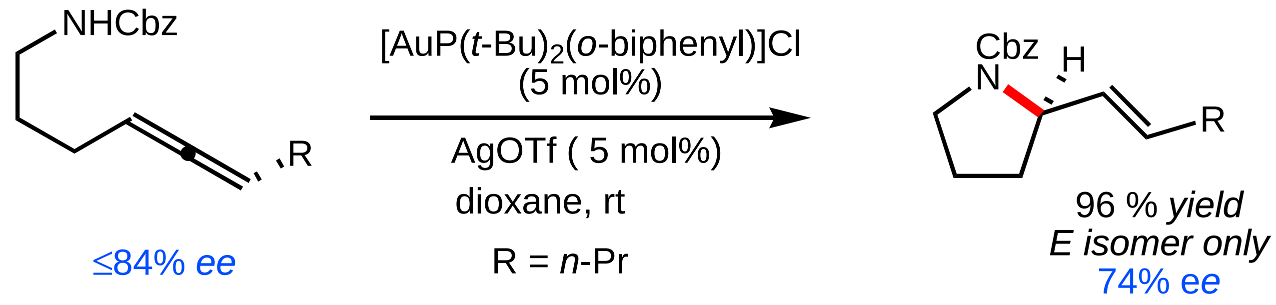
R = Me, Bn,
(CH$_2$)$_2$TMS

32-40% *yields*

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

Intramolecular Enantioselective Hydroamination

Activation of Allenes



$[AuP(t\text{-}Bu)_2(o\text{-biphenyl})]Cl$ (5 mol%)

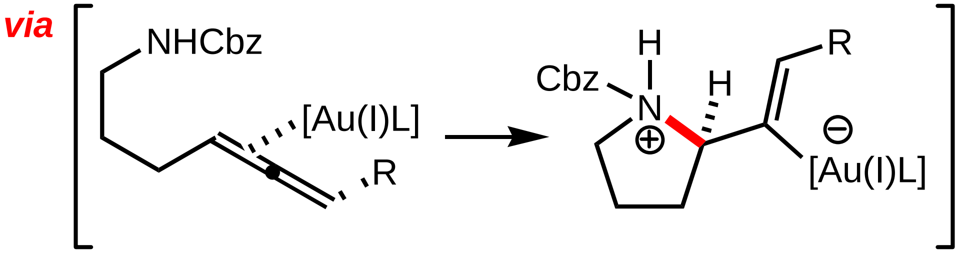
AgOTf (5 mol%)

dioxane, rt

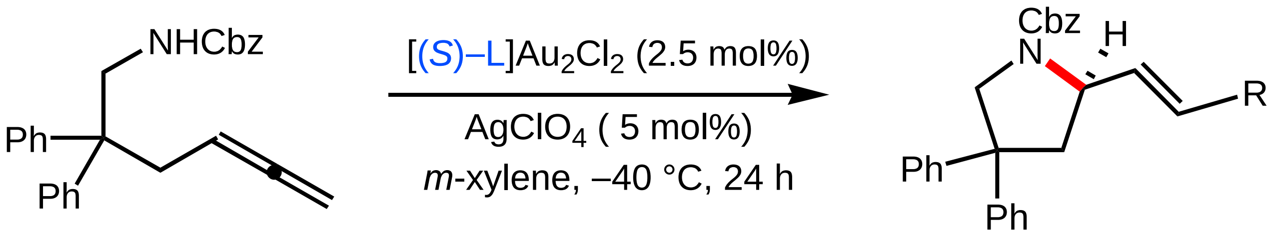
R = *n*-Pr

≤84% *ee*

96 % *yield*
E isomer only
74% ee



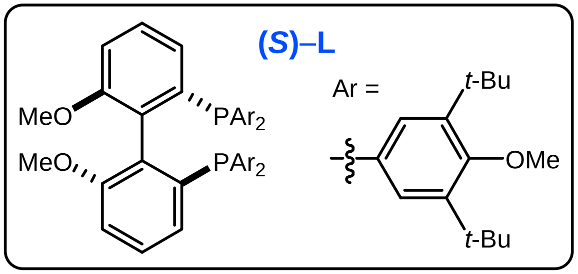
Widenhoefer *JACS* **2006**, *128*, 9066.



[(*S*)–L]Au_2Cl_2 (2.5 mol%)

$AgClO_4$ (5 mol%)

m-xylene, –40 °C, 24 h

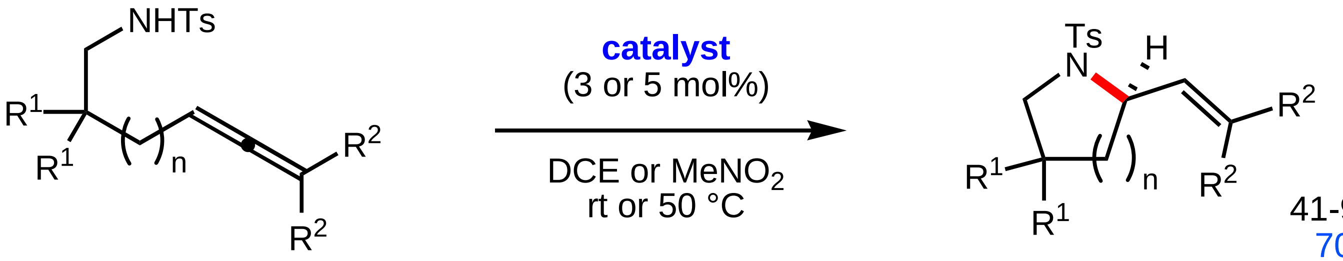


97% *yield*, 81% *ee*

Widenhoefer *OL* **2007**, *9*, 2887.

Intramolecular Enantioselective Hydroamination

Activation of Allenes



catalyst
(3 or 5 mol%)

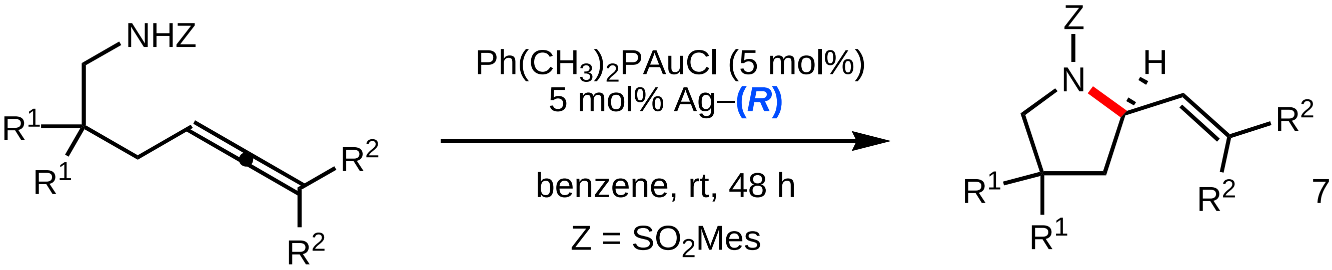
DCE or $MeNO_2$
rt or 50 °C

41-99% *yields*
70-99% ee

16 examples
n=1, 2
R^1 = H, alkyl, aryl
R^2 = Me, Et, cyclic

catalyst
(*R*)-xylyl-**BINAP**$(AuOPNB)_2$
(*R*)-**SEGPHOS**$(AuOPNB)_2$
(*R*)-ClMeO**BiPHEP**$(AuOPBN)_2$

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



$Ph(CH_3)_2PAuCl$ (5 mol%)
5 mol% Ag–**(*R*)**

benzene, rt, 48 h

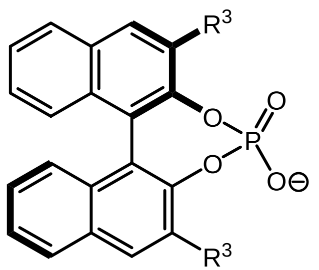
Z = SO_2Mes

73-97% *yields*
96-99% *ee*

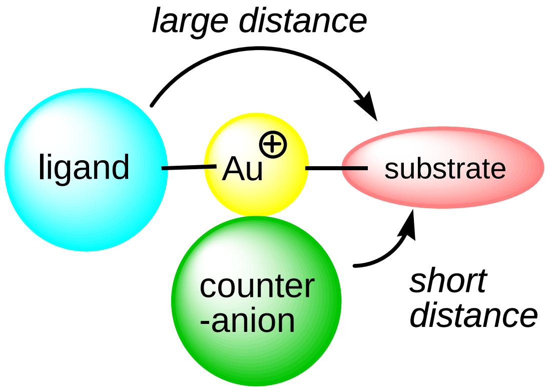
5 examples
R^1 = H, Me, – $(CH_2)_5$ –
R^2 = Me, – $(CH_2)_4$ –, – $(CH_2)_5$ –

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

chiral counteranion
(R) ⊖



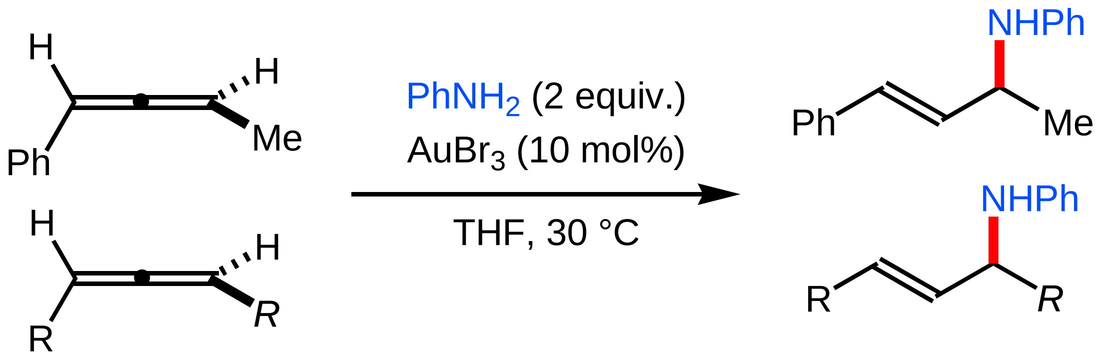
R^3 = 2,4,6-*i*-Pr_3-C_6H_2



Activation of Allenes

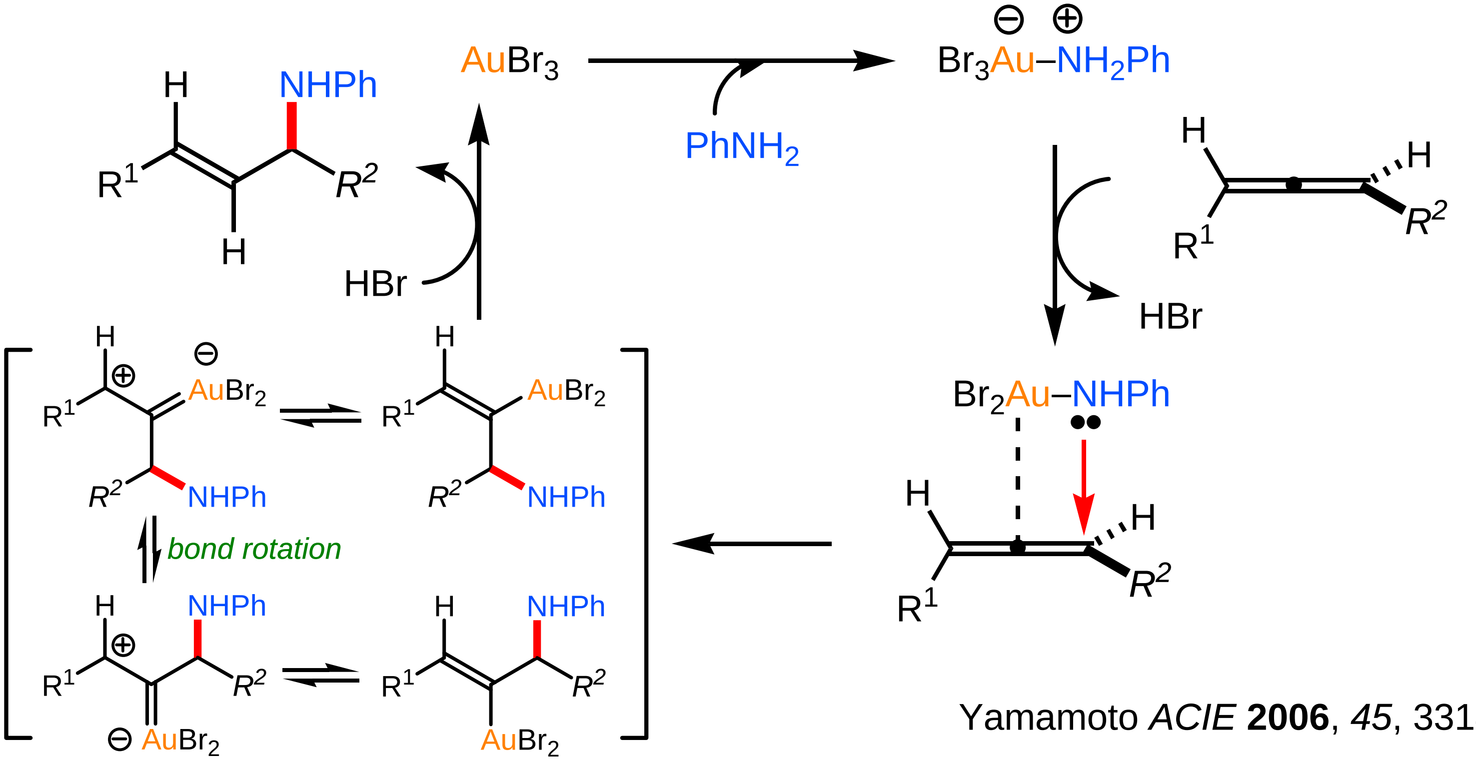
Intermolecular Hydroamination

Mechanism of Chiral Transfer



68% *yield*
PD : 88% *ee*
SM : 94% *ee*

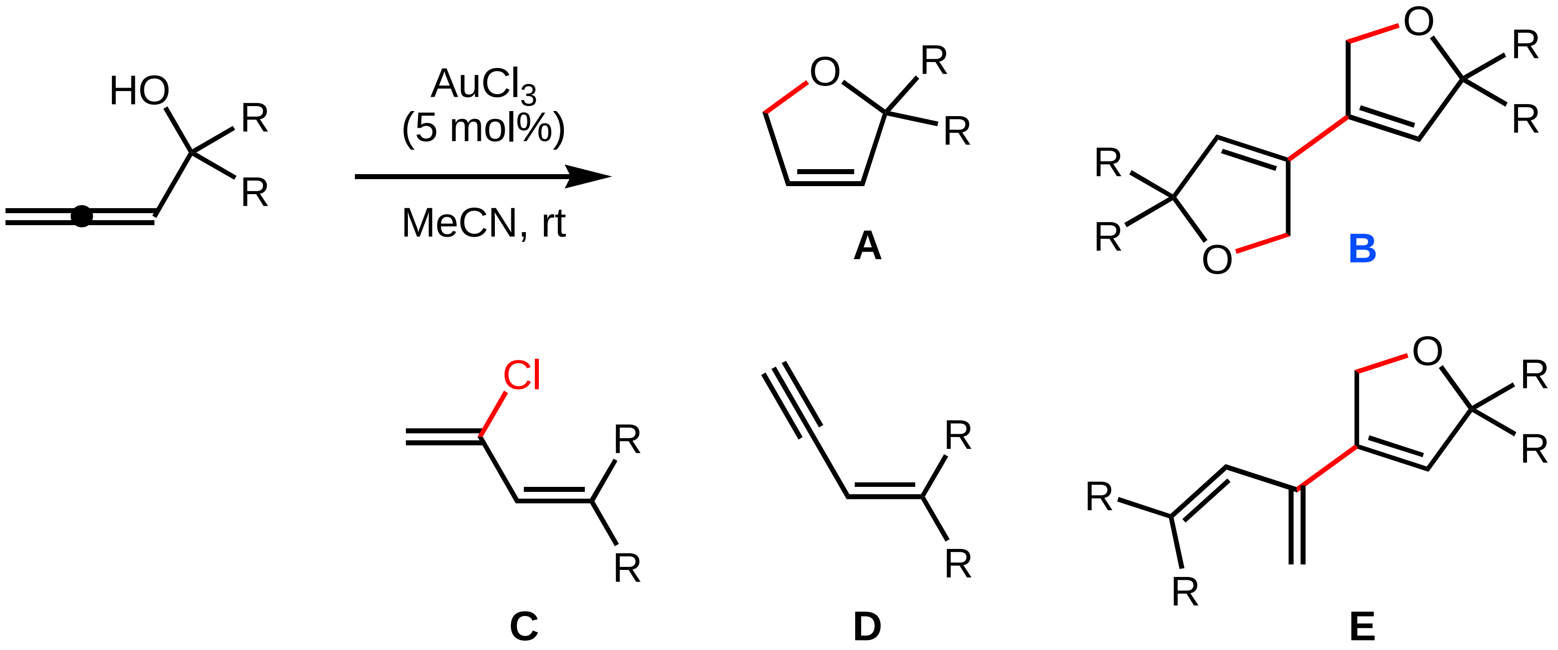
R = *n*-pentyl
80% *yield*
99% *ee*



Yamamoto *ACIE* **2006**, *45*, 3314.

Intramolecular Hydroalkoxylation

In-situ Reduction of Au(III)

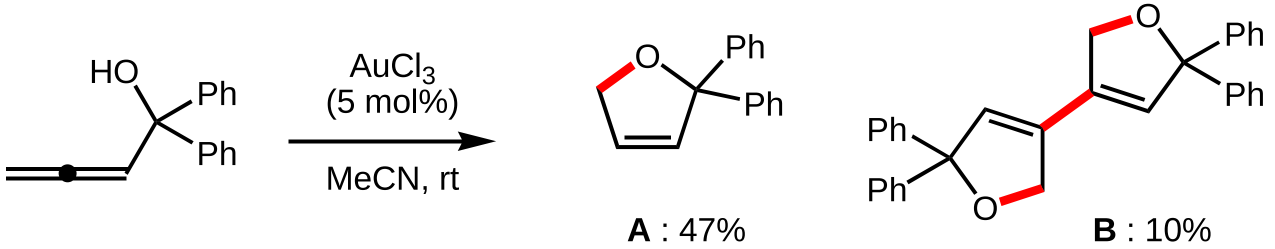


B : oxidative coupling
C : S_N'-like substitution by Cl^-
D : 1,4-elimination
E : dehydrative coupling

R	A	B	C	D	E
$-(CH_2)_5-$	47%	10%	1%	ND	ND
Ph	31%	6%	8%	4%	21%

Hashmi *EJOC* **2006**, 1387.

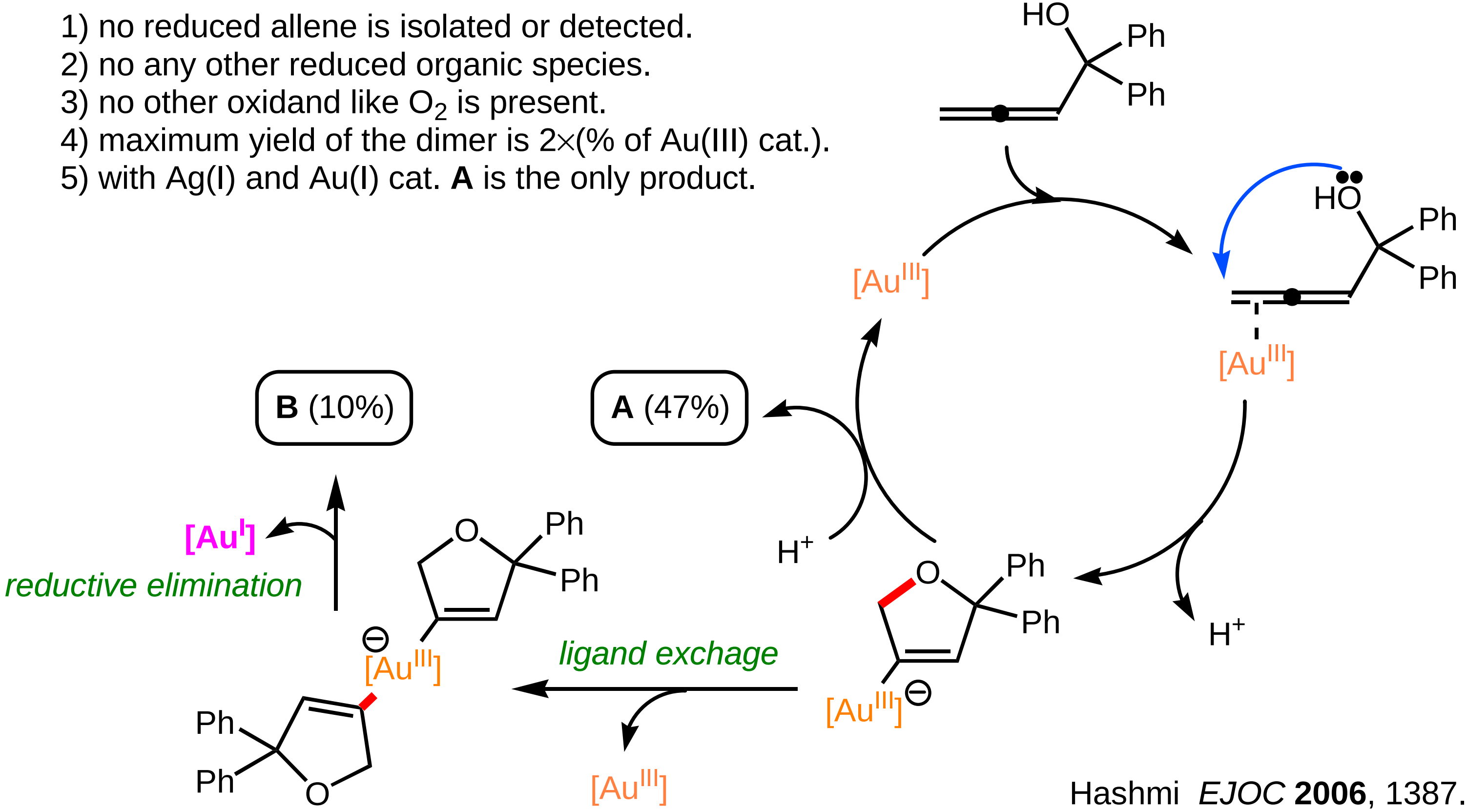
In-situ Reduction of Au(III)
Plausible Mechanism



A : 47%

B : 10%

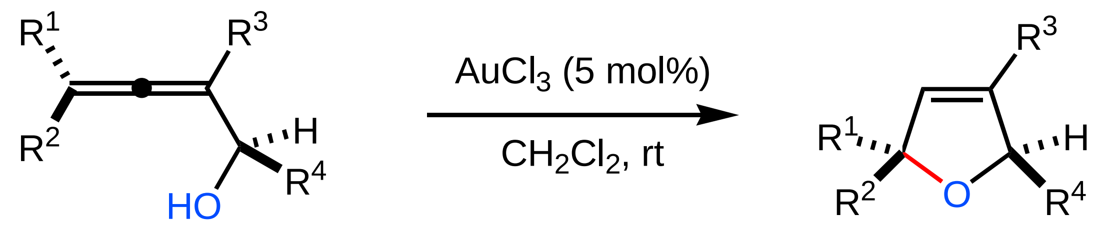
Observation:
1) no reduced allene is isolated or detected.
2) no any other reduced organic species.
3) no other oxidand like O_2 is present.
4) maximum yield of the dimer is 2×(% of Au(III) cat.).
5) with Ag(I) and Au(I) cat. **A** is the only product.



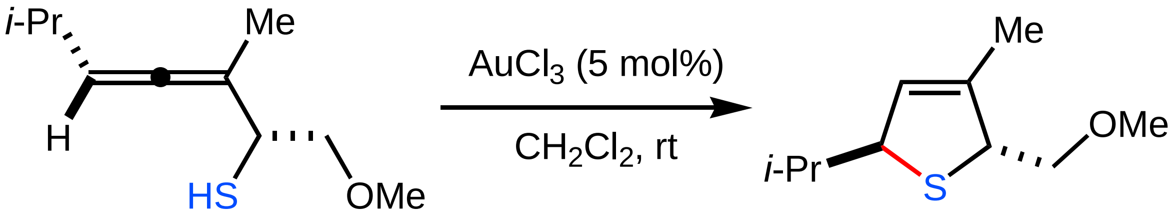
Hashmi *EJOC* **2006**, 1387.

Intramolecular Hydroalkoxylation & Hydrothiolation

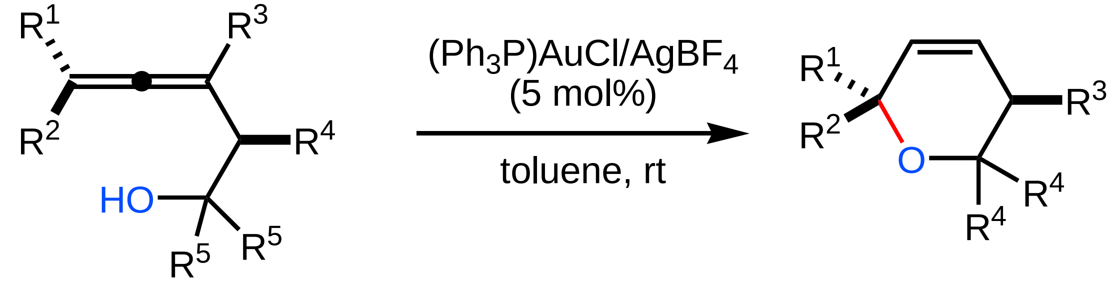
Activation of Allenes



R^1	R^2	R^3	R^4	yield
t-Bu	Me	H	CO_2Et	74%
t-Bu	Me	Me	CO_2Et	94%
t-Bu	Me	H	CH_2OH	24%
H	Me	Me	CH_2OTBS	77%



88% *yield*, >99:1 *dr*

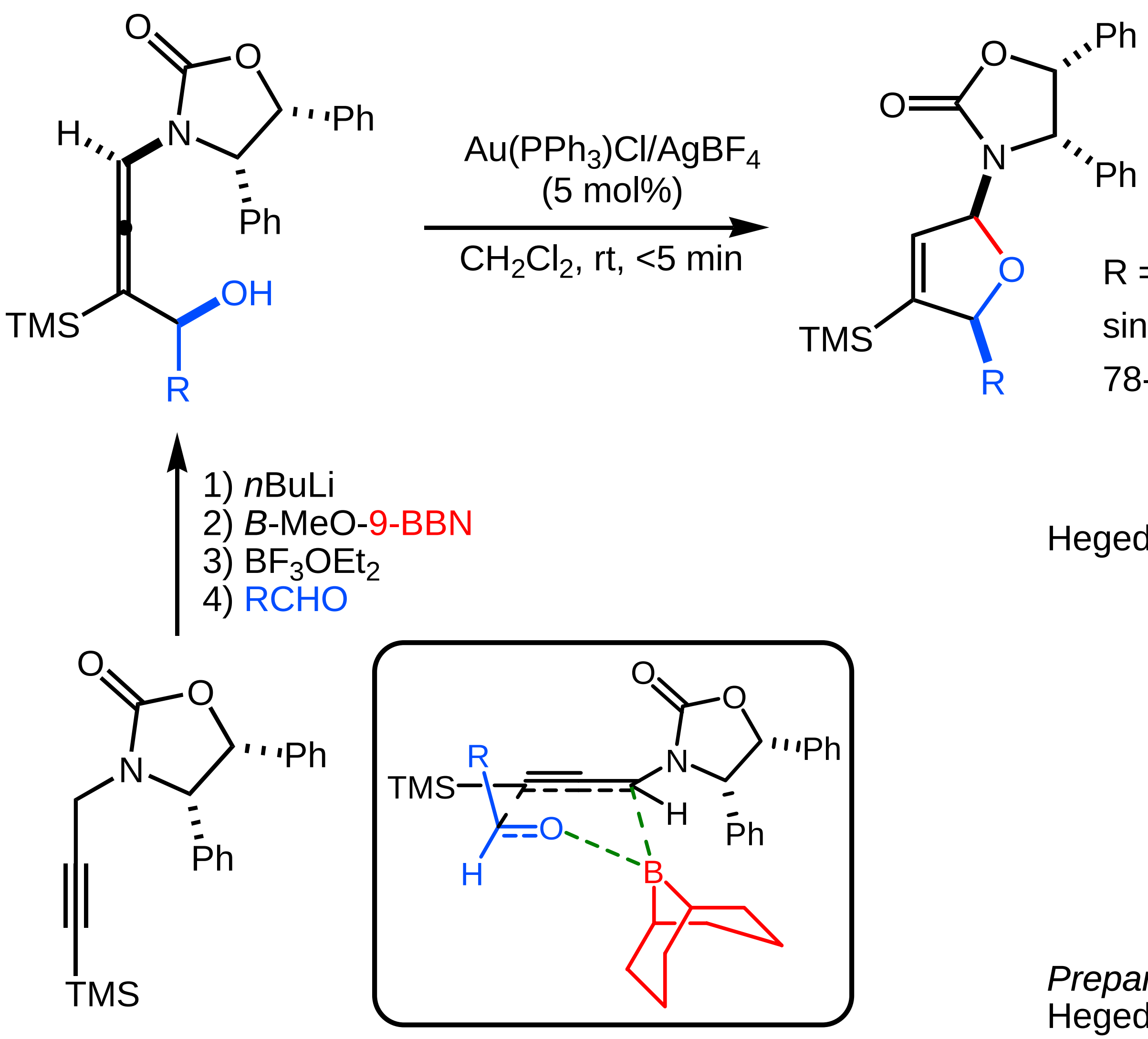


R^1, R^2 = H, alkyl, aryl
R^3 = H, Me
R^4 = H, OAc, CO_2Et
R^5 = H, Me

32-84% yield

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

Intramolecular Hydroalkoxylation



Au(PPh$_3$)Cl/AgBF$_4$
(5 mol%)
CH$_2$Cl$_2$, rt, <5 min

1) *n*BuLi
2) *B*-MeO-9-BBN
3) BF$_3$OEt$_2$
4) RCHO

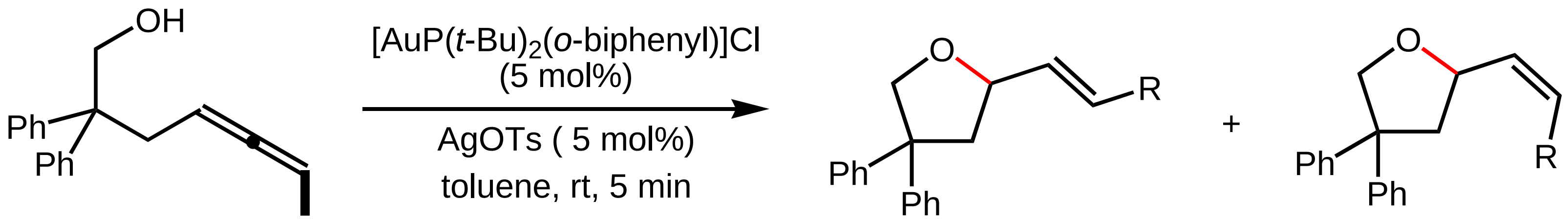
R = Ph, *i*-Pr, CH$_2$OTBS, etc.
single diatereomers
78-87% *yields*

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

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

Intramolecular Enantioselective Hydroalkoxylation

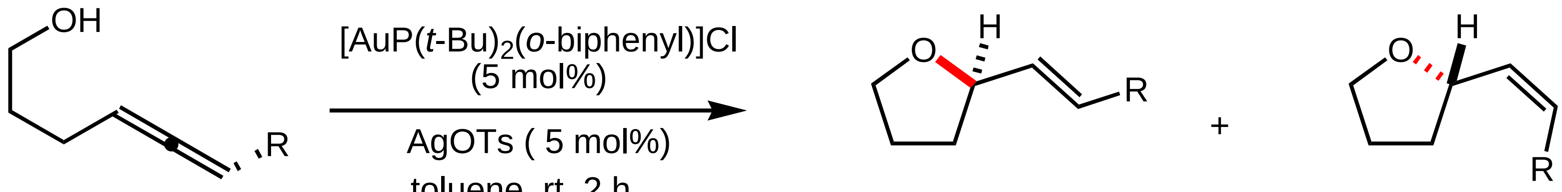
Activation of Allenes



94% *ee*

R = *n*-pentyl

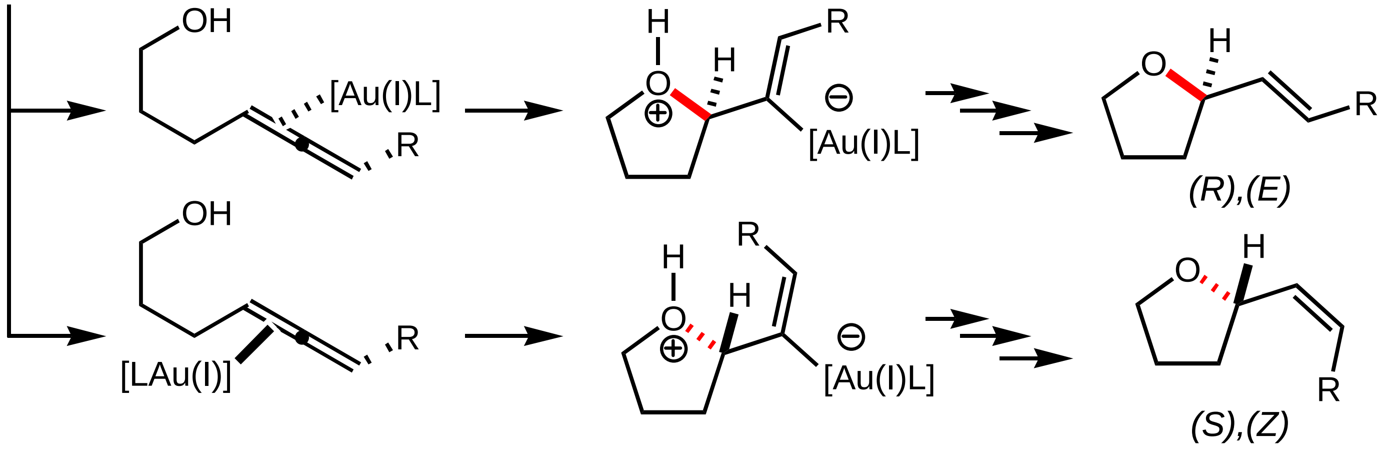
92 % *yield, E : Z* = 5.5 :1
≥90% *ee* for both *E* & *Z*



84% *ee*

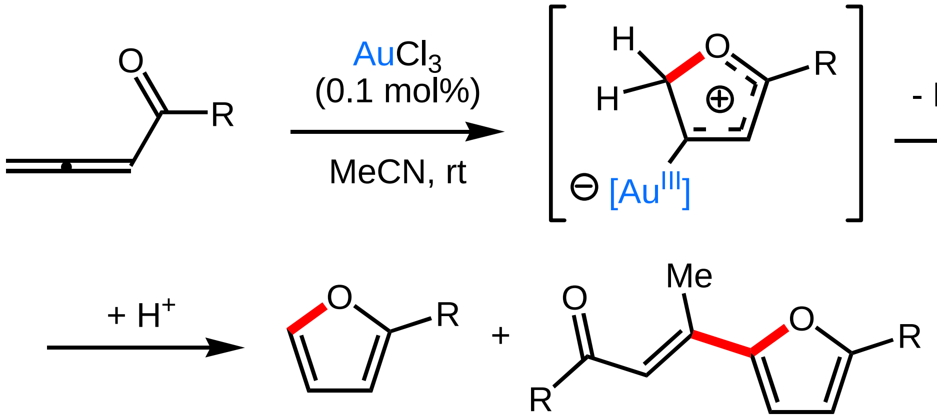
R = *n*-pentyl

87 % *yield, E : Z* = 5.3 :1
81% *ee* for *E*, 84% *ee* for *Z*



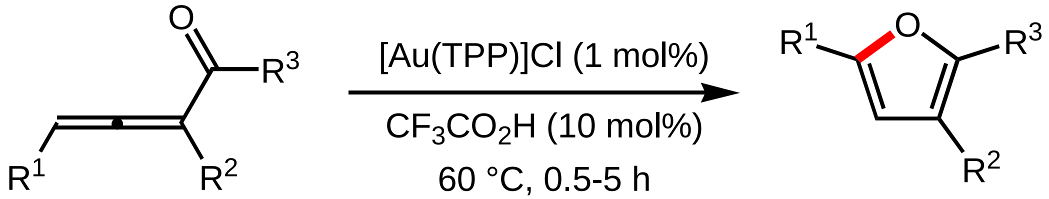
Widenhoefer *JACS* **2006**, *128*, 9066.

Ketone Carbonyl as Nucleophiles



R = 4-$(O_2N)C_6H_4$	88%	4%
R = 3-$(MeO)C_6H_4$	34%	38%
R = CH_3	45%	36%

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



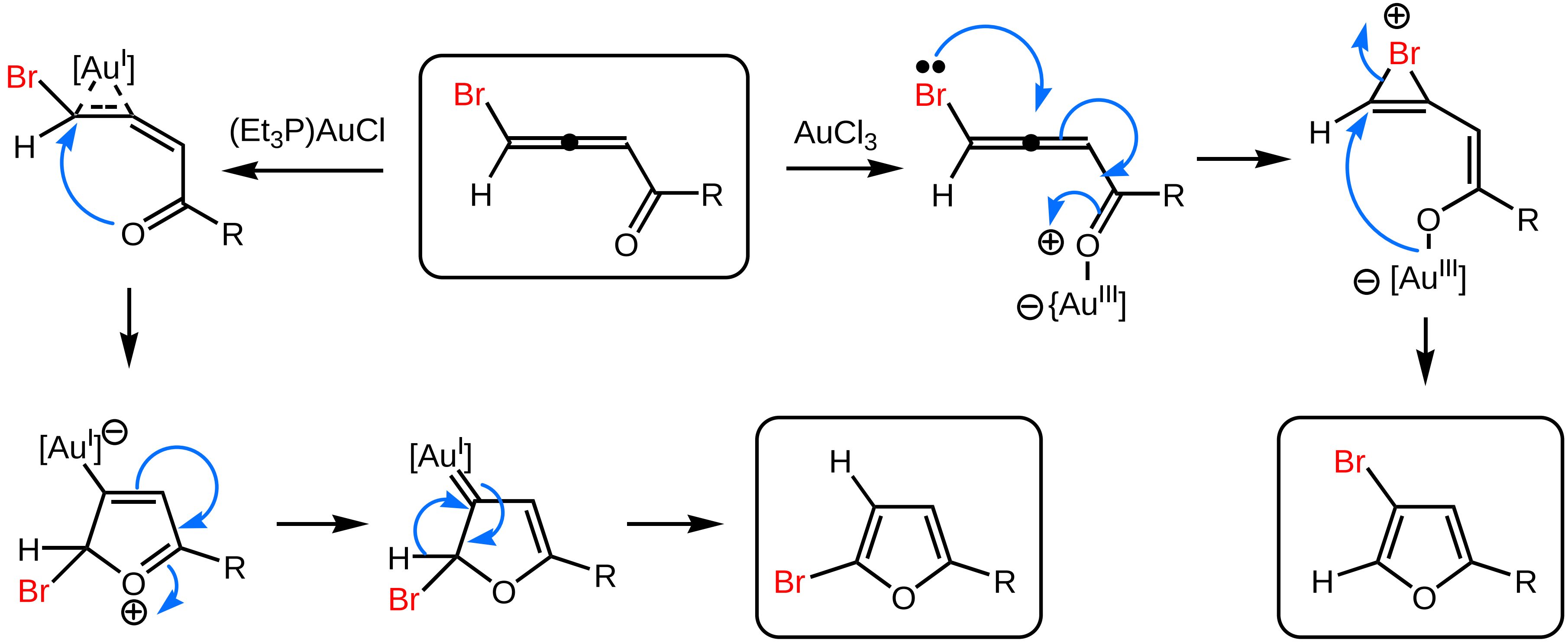
R^1 ~ R^3 = H, alkyl, aryl
73-97% *yields*

Au(TPP) = Au(III) porphyrin

Che *OL* **2006**, *8*, 325.

Ketone Carbonyl as Nucleophiles

Regiodivergent Synthesis of Halofurans

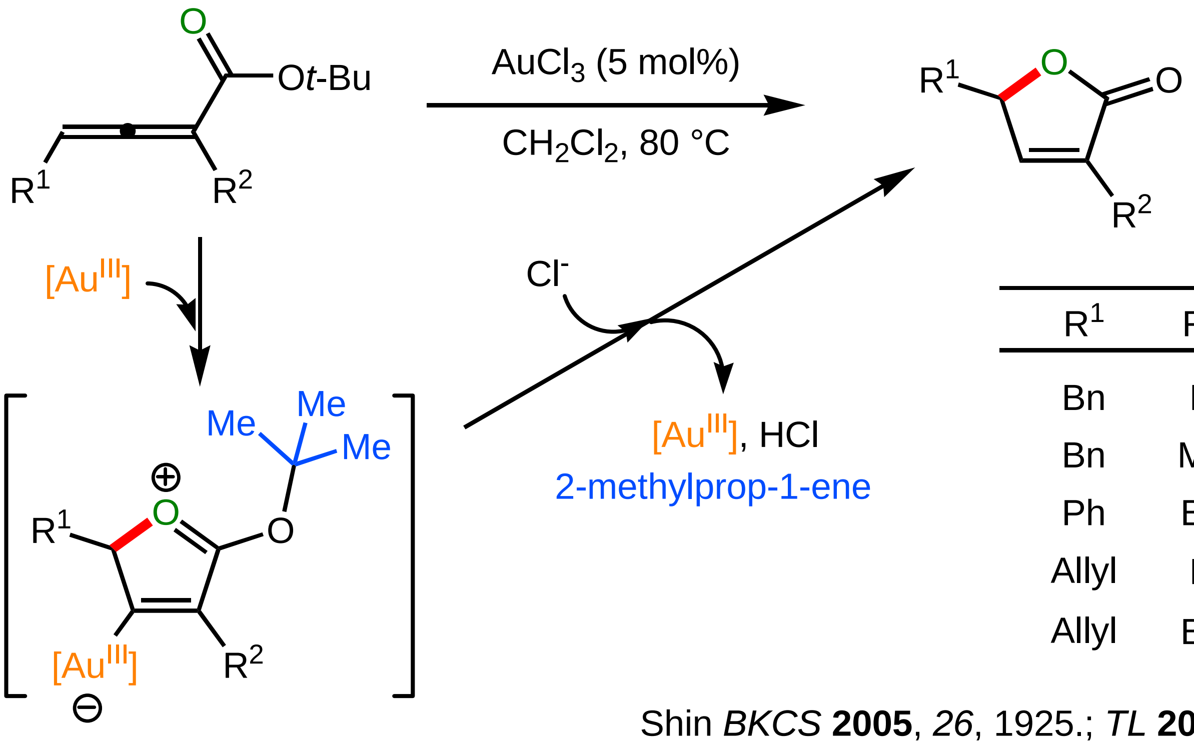


R = C_8H_{17}

$AuCl_3$	95%	5%
$(Et_3P)AuCl$	1%	99%

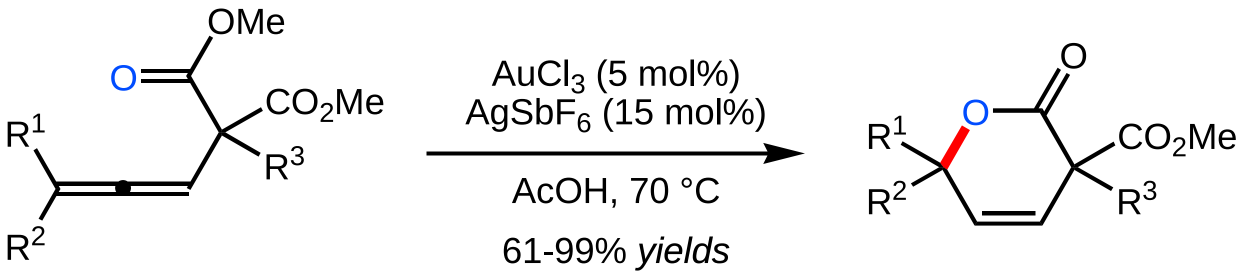
Gevorgyan *JACS* **2005**, *127*, 10500.

Ester Carbonyl as Nucleophiles



R^1	R^2	yield
Bn	H	88%
Bn	Me	77%
Ph	Bn	32%
Allyl	H	57%
Allyl	Bn	81%

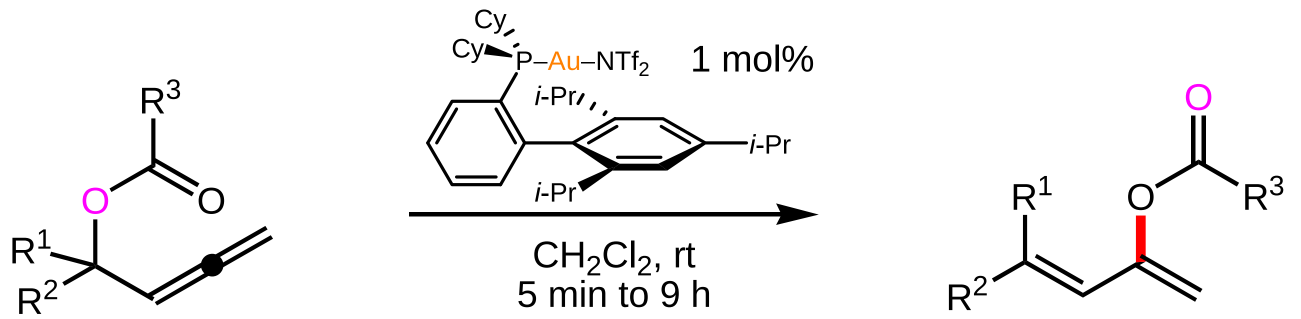
Shin *BKCS* **2005**, *26*, 1925.; *TL* **2005**, *46*, 7431.



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

Isomerization of Allenyl Carbinol Esters

Activation of Allenes

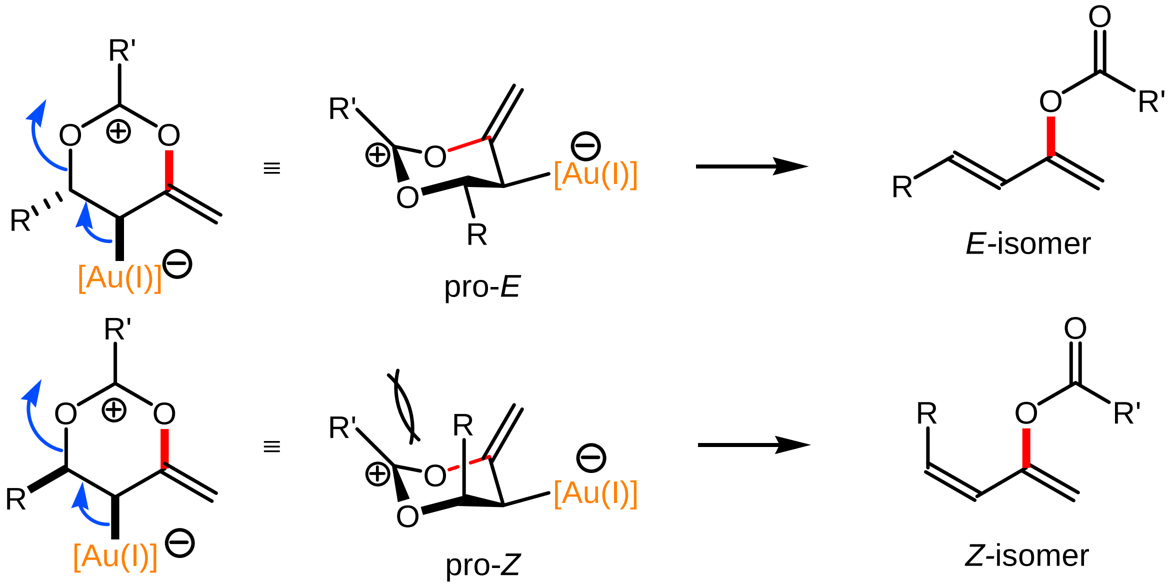


R^1= H , alkyl
R^2, R^3 = aryl, alkyl

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***)

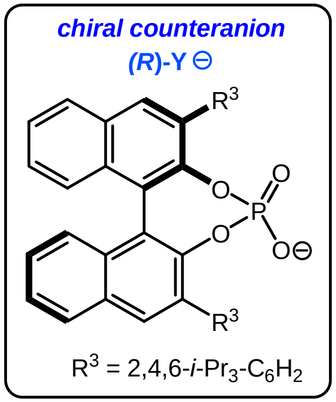
Source of the *E*/*Z* Selectivity



Gagosz *OL* **2007**, *9*, 985.

Chiral Counteranion Induced Stereoinduction

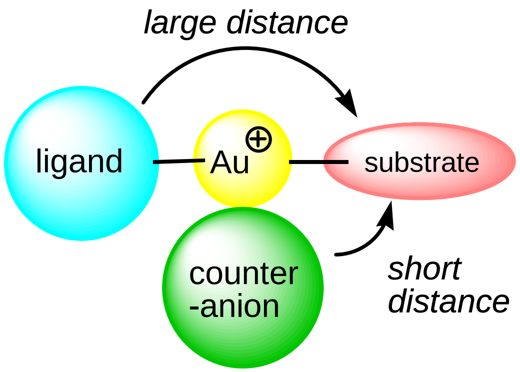
Toeste *Science* **2007**, *317*, 496.

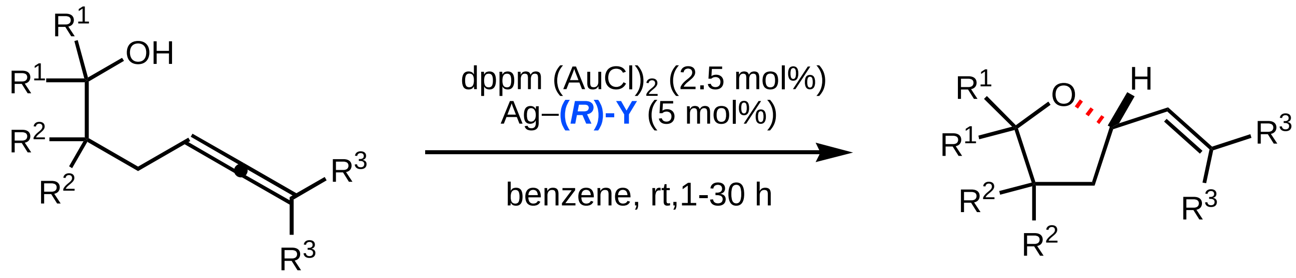


chiral counteranion

***(R)*-Y ⊖**

R^3 = 2,4,6-*i*-Pr_3-C_6H_2





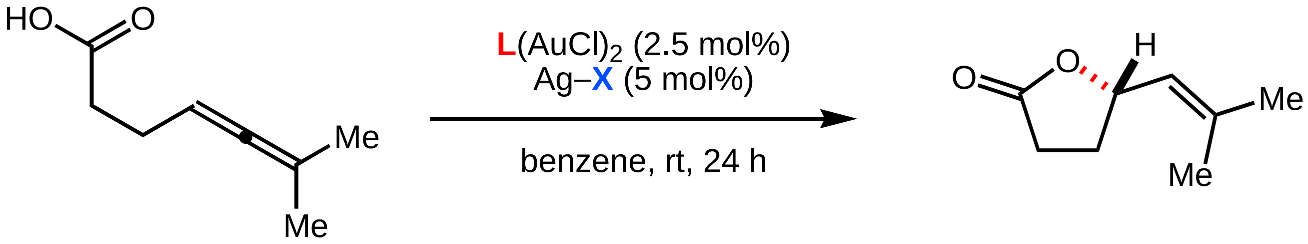
8 examples

R^1 = H, Me, Ph ; R^2 = H, Me

R^3 =H, Me, Et, $-(CH_2)_4-$

79-96% *yields*

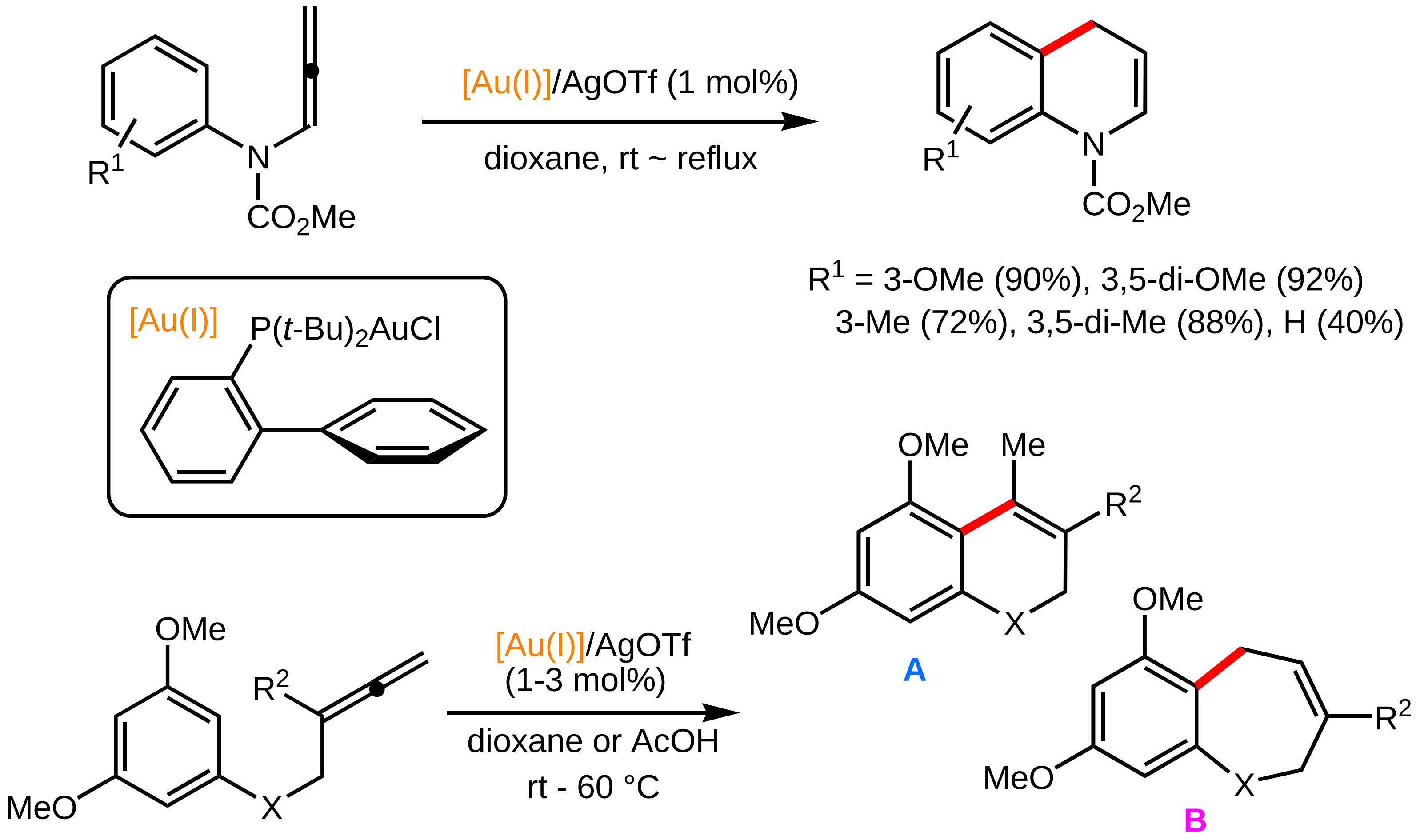
90-99% *ee*



L = (*R*)-Z, X = 4-(NO_2)-C_6H_3-COO^-	80% *yield*, 38% *ee*	
L = dppm, X = (*R*)-Y	89% *yield*, 12% *ee*	
L = (*R*)-Z, X = (*R*)-Y	91% *yield*, 3% *ee*	(mismatching pair)
L = (*S*)-Z, X = (*R*)-Y	88% *yield*, 82% *ee*	(*matching pair*)

e⁻-Rich Benzene Ring as Nucleophiles

Activation of Allenes



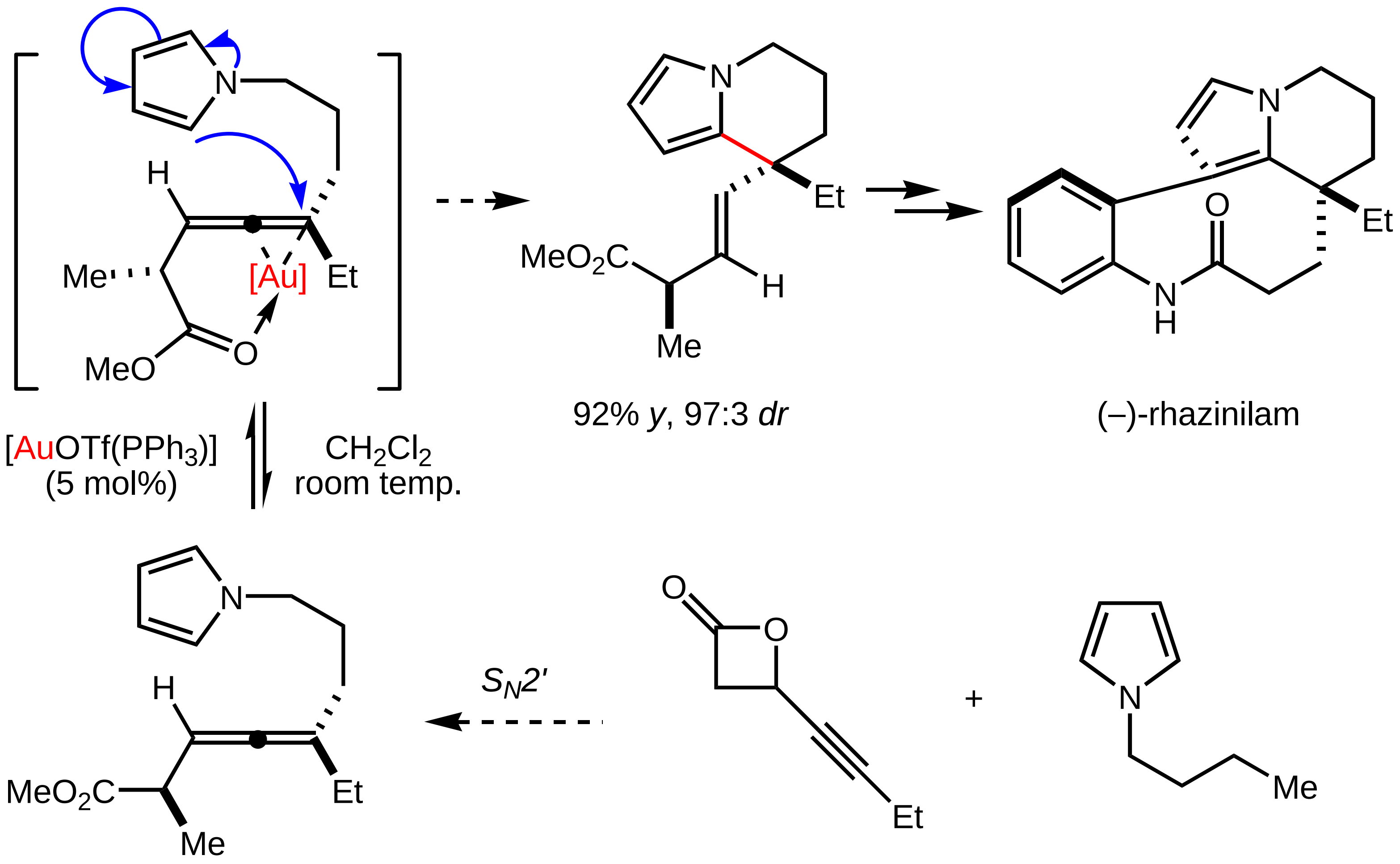
R^1 = 3-OMe (90%), 3,5-di-OMe (92%)
3-Me (72%), 3,5-di-Me (88%), H (40%)

X = N-CO_2Me, R^2 = H (**A** 85%)
X = N-CO_2Me, R^2 = Me (**A** 75%)
X = O, R^2 = H (**A** 98%)
X = O, R^2 = Me (**A** 48%, **B** 52%)

Fujii OL, **2007**, *9*, ASAP.

Pyrrole Rings as Nucleophiles

(−)-Rhazinilam (2006)



[AuOTf(PPh$_3$)]
(5 mol%)

CH$_2$Cl$_2$
room temp.

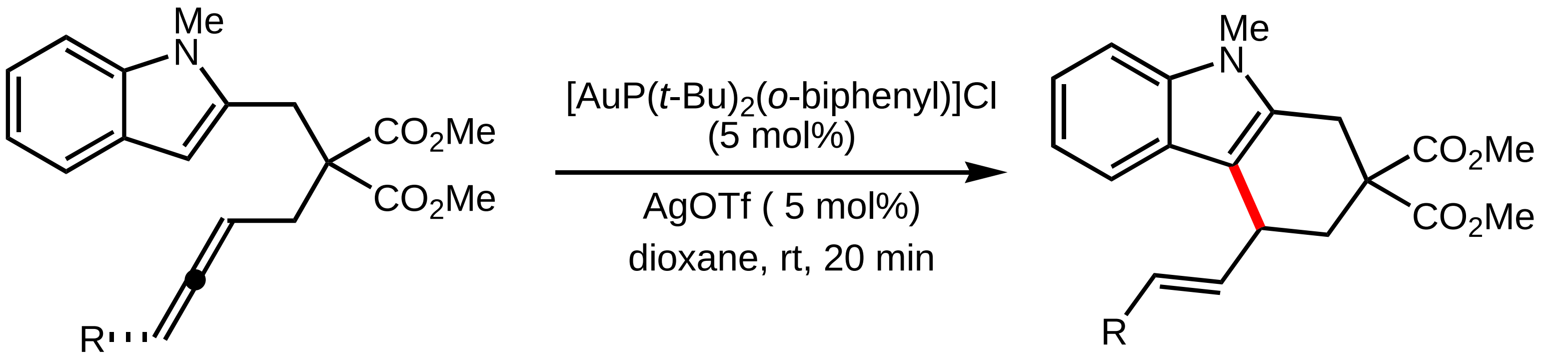
92% *y*, 97:3 *dr*

(–)-rhazinilam

S$_N$2′

Nelson *JACS* **2006**, *128*, 10352.

Indole Rings as Nucleophiles



[AuP(*t*-Bu)$_2$(*o*-biphenyl)]Cl (5 mol%)

AgOTf (5 mol%)

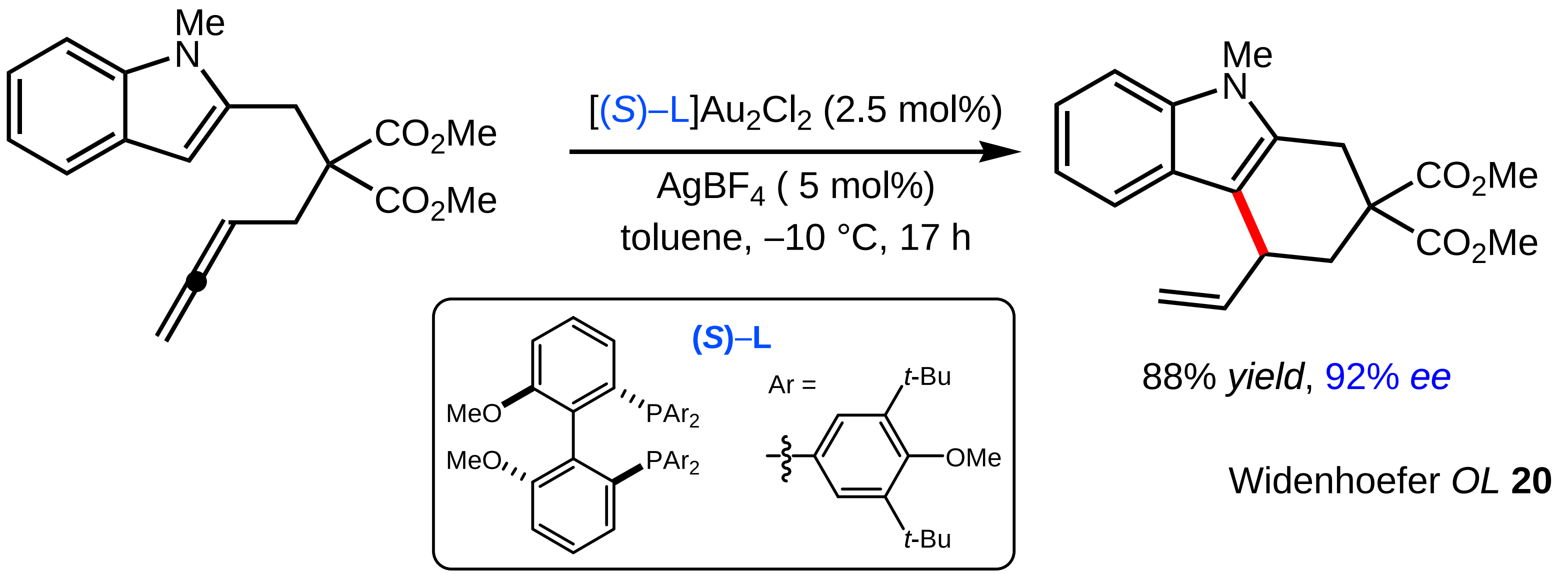
dioxane, rt, 20 min

52% *ee*

R = *n*-pentyl

86% *yield*, 52% *ee*

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



[(*S*)–L]Au$_2$Cl$_2$ (2.5 mol%)

AgBF$_4$ (5 mol%)

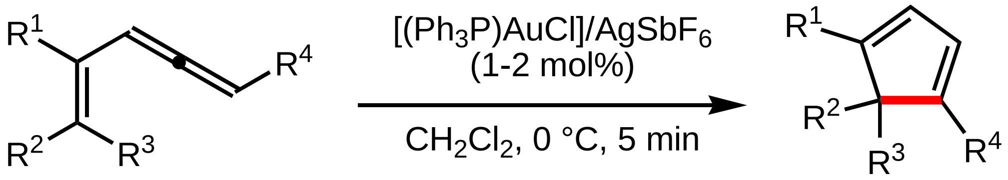
toluene, –10 °C, 17 h

88% *yield*, 92% *ee*

Widenhoefer *OL* **2007**, *9*, 1935.

Alkenes as Nucleophiles : *Metalla-Nazarov*

Activation of Allenes



$[(Ph_3P)AuCl]/AgSbF_6$ (1-2 mol%)

CH_2Cl_2, 0 °C, 5 min

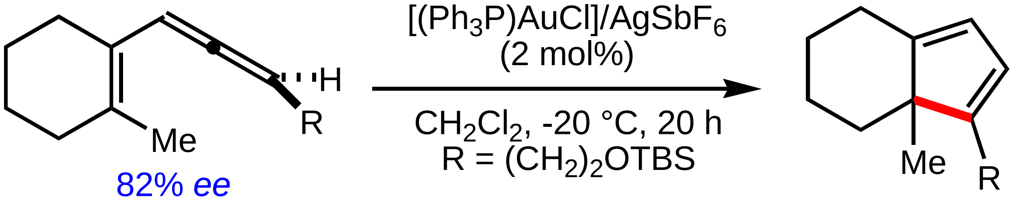
9 examples

R^1 = Me, 6-member-ring w/ R^2

R^2 = H, CH_2OBn, CH_2OTHP

R^3 = H, Me; R^4 = alkyl, Ph

39-98% *yields*



82% *ee*

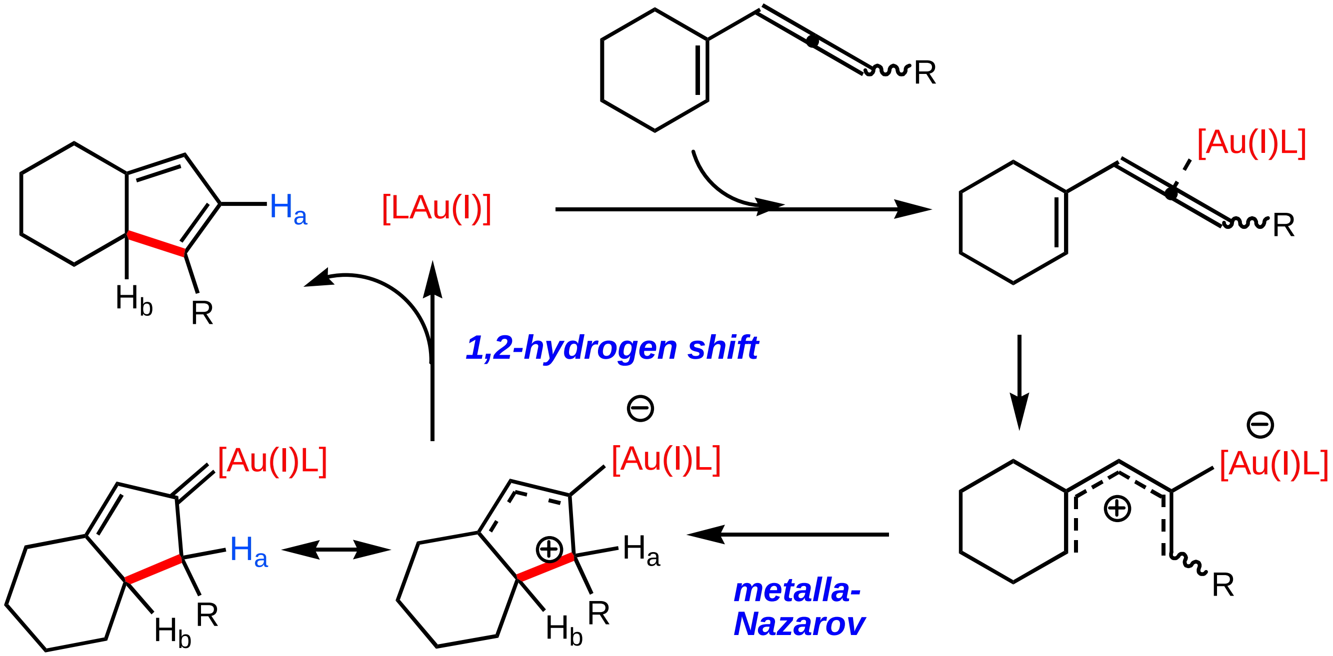
$[(Ph_3P)AuCl]/AgSbF_6$ (2 mol%)

CH_2Cl_2, -20 °C, 20 h

R = $(CH_2)_2OTBS$

55% *yield*

0% *ee*



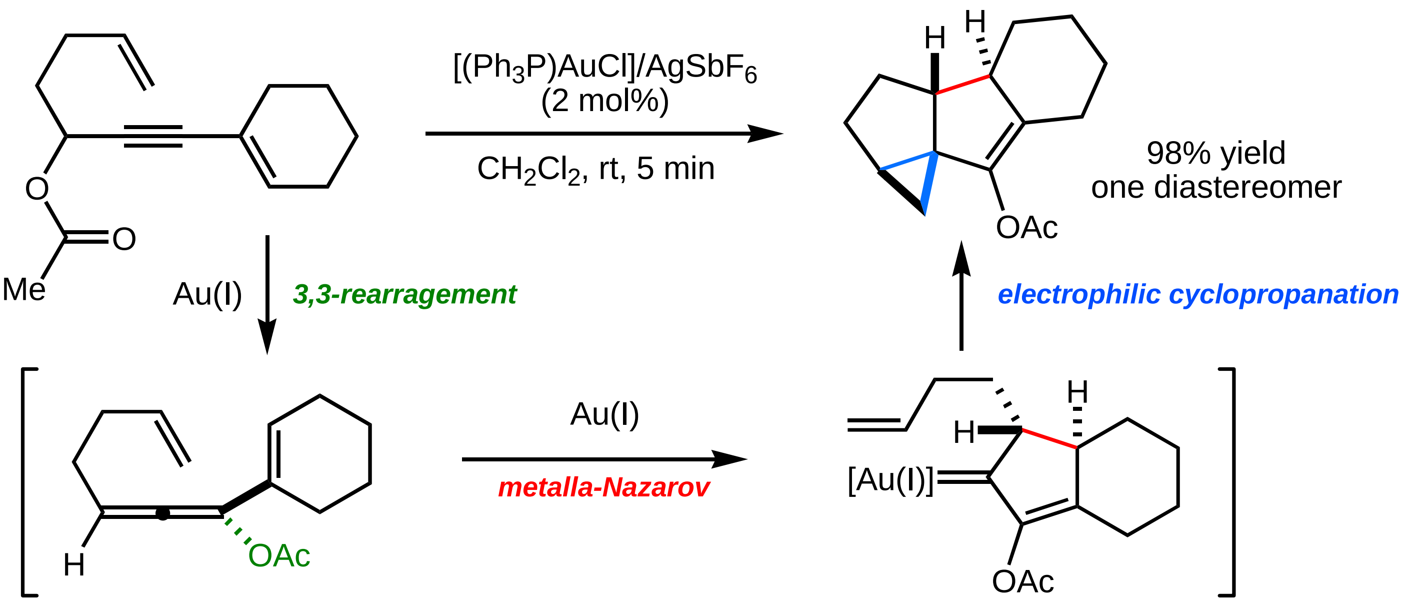
1,2-hydrogen shift

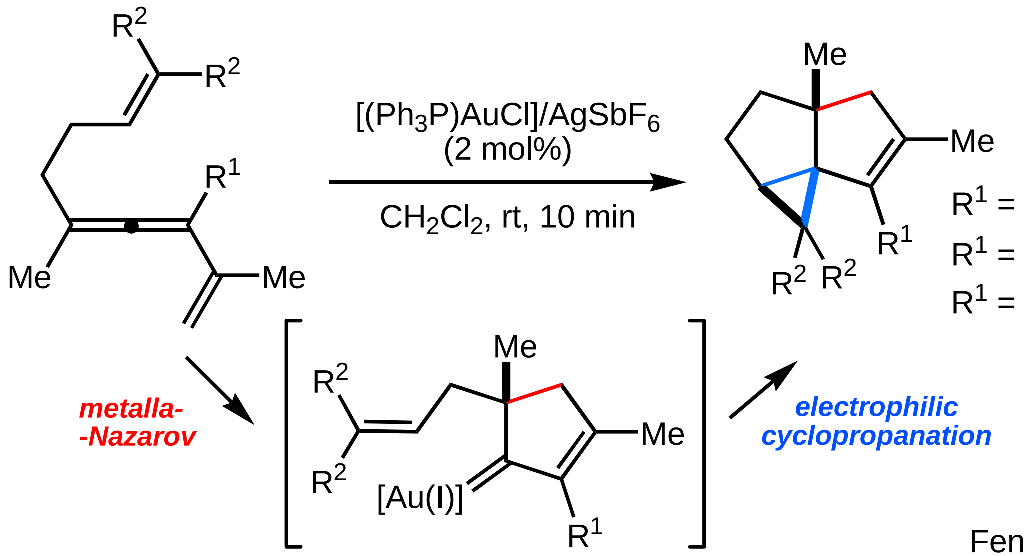
metalla-Nazarov

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

Alkenes as Nucleophiles : *Metalla-Nazarov*

Activation of Allenes



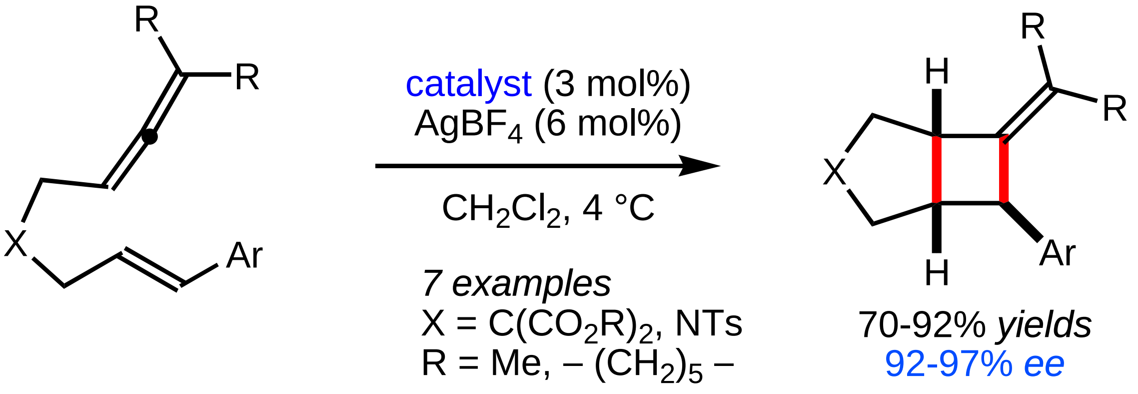


R^1 = C$_4$H$_9$, R^2 = H	62% yield
R^1 = R^2 = Me	72% yield
R^1 = C$_4$H$_9$, R^2 = Me	80% yield

Fensterbank *OL* **2007**, *9*, 2207.

Alkenes as Nucleophiles

Activation of Allenes

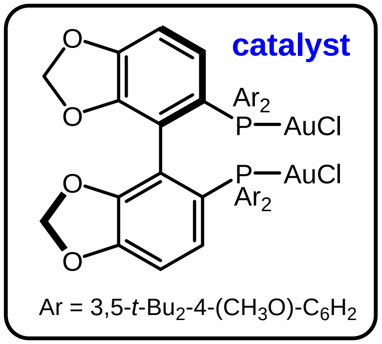


catalyst (3 mol%)
$AgBF_4$ (6 mol%)

CH_2Cl_2, 4 °C

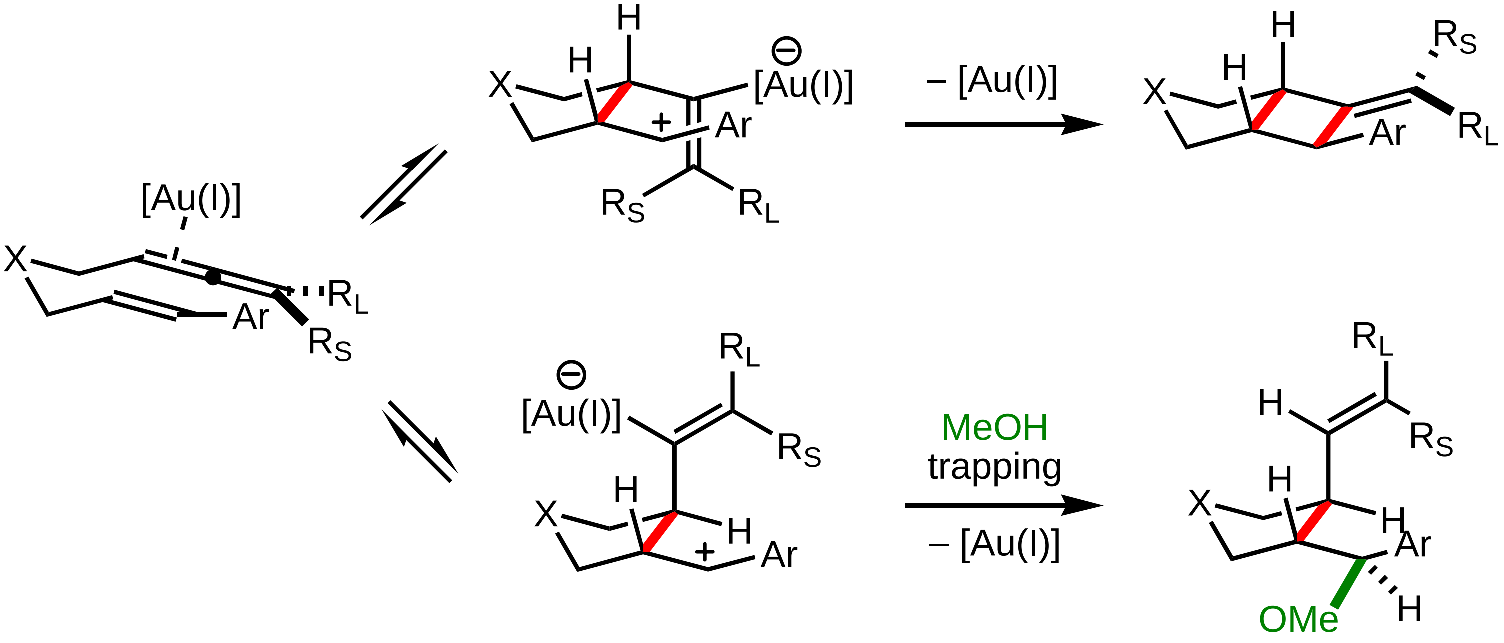
7 examples
X = $C(CO_2R)_2$, NTs
R = Me, – $(CH_2)_5$ –

70-92% *yields*
92-97% *ee*



catalyst

Ar = 3,5-*t*-Bu_2-4-(CH_3O)-C_6H_2



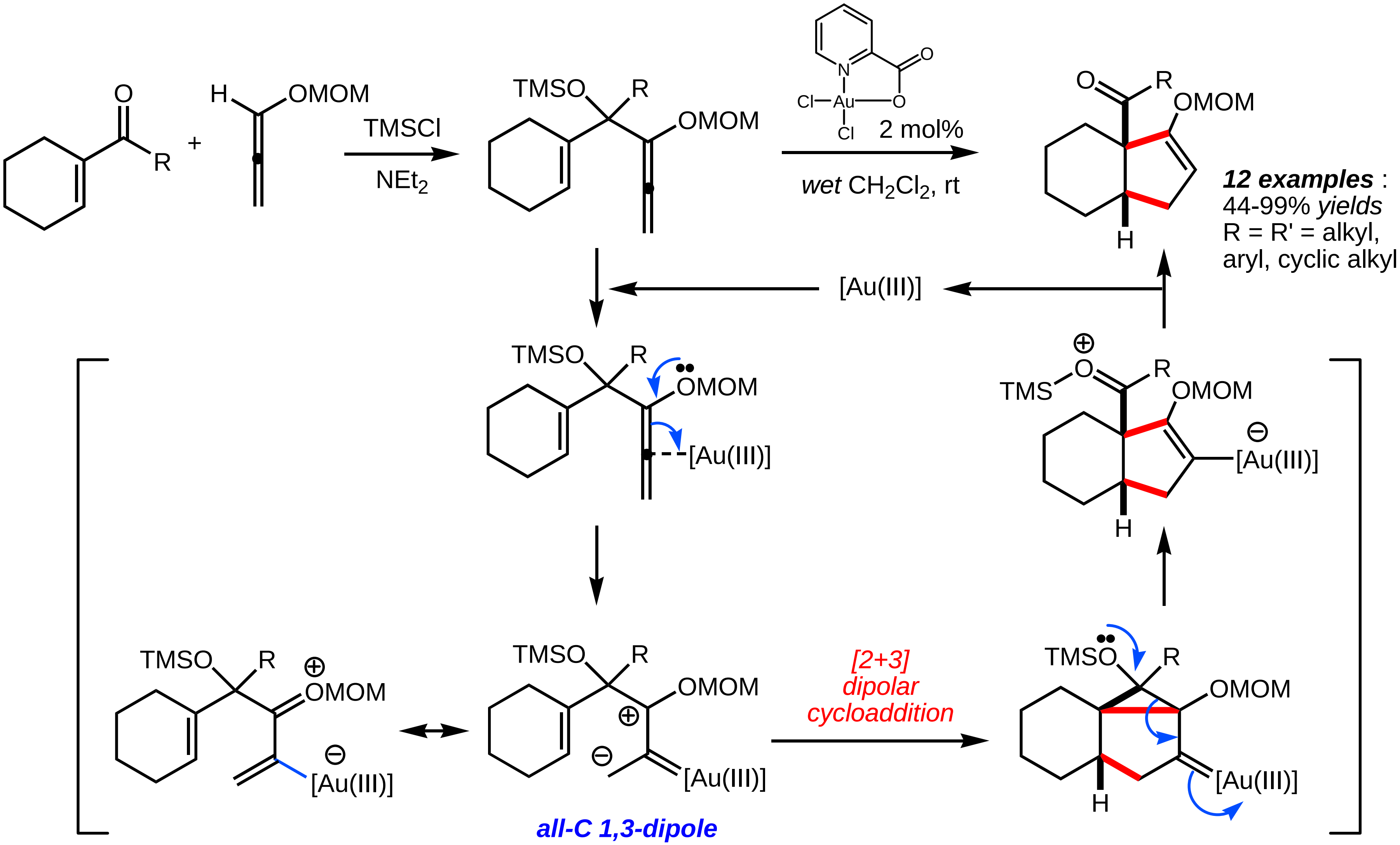
– [Au(I)]

MeOH
trapping
– [Au(I)]

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

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

Activation of Allenes



12 examples :
44-99% *yields*
R = R' = alkyl,
aryl, cyclic alkyl

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

I. Introduction

II. Activation of Alkynes

III. Activation of Allenes

IV. Activation of Alkenes

Nitrogen Nucleophiles : Hydroamination
Nitrene Transfer

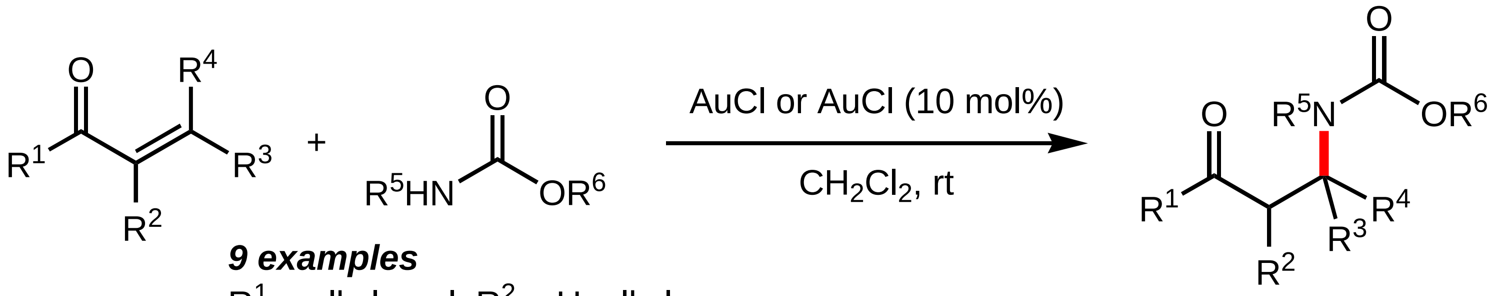
Oxygen Nucleophiles : Hydroalkoxylation

Carbon Nucleophiles : Enolates

V. Summary

Intramolecular Hydroamination

Activation of Alkenes



AuCl or AuCl (10 mol%)

CH_2Cl_2, rt

9 examples

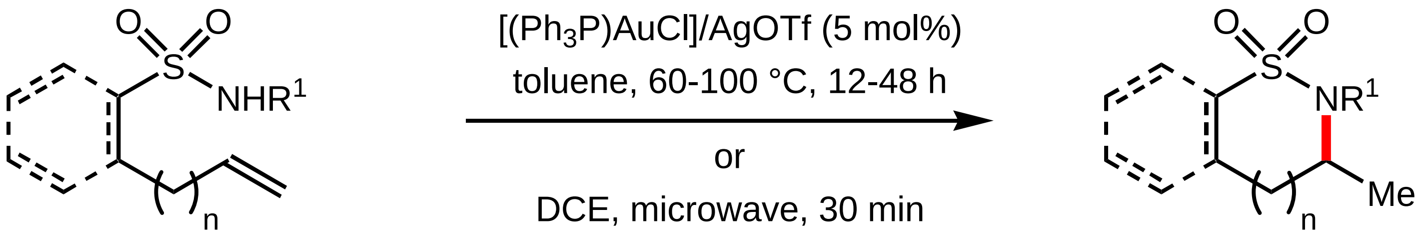
R^1 = alkyl, aryl; R^2 = H, alkyl;

R^3, R^4 = H, alkyl

R^5 = H, alkyl; R^6 = alkyl, Bn

51-100% *yields*

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



[(Ph_3P)AuCl]/AgOTf (5 mol%)

toluene, 60-100 °C, 12-48 h

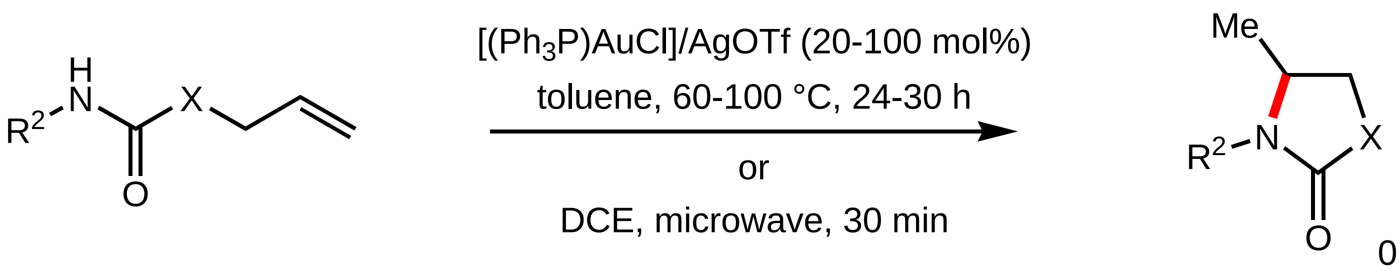
or

DCE, microwave, 30 min

13 examples

R^1 = H, Et, *t*-Bu, Ts

88-100% *yields*



[(Ph_3P)AuCl]/AgOTf (20-100 mol%)

toluene, 60-100 °C, 24-30 h

or

DCE, microwave, 30 min

0-90% *yields*

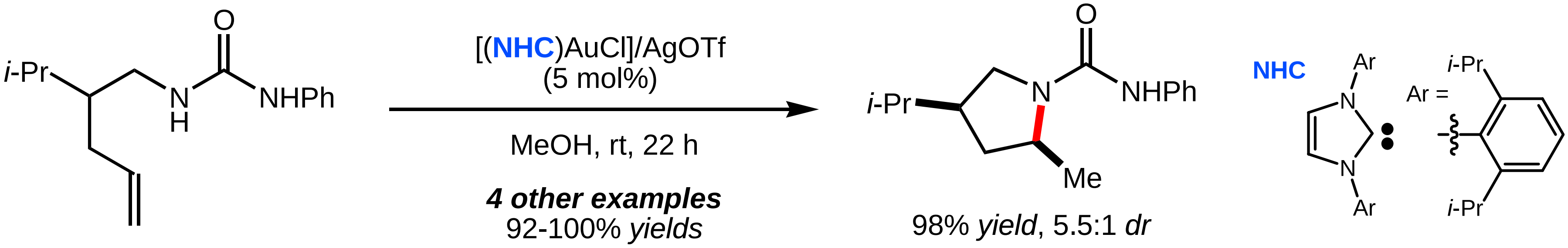
5 examples   X = C, O

R^2 = Ph, *p*-Cl-C_6H_4 ,PhCO, Ts

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

Intramolecular Hydroamination

Activation of Alkenes



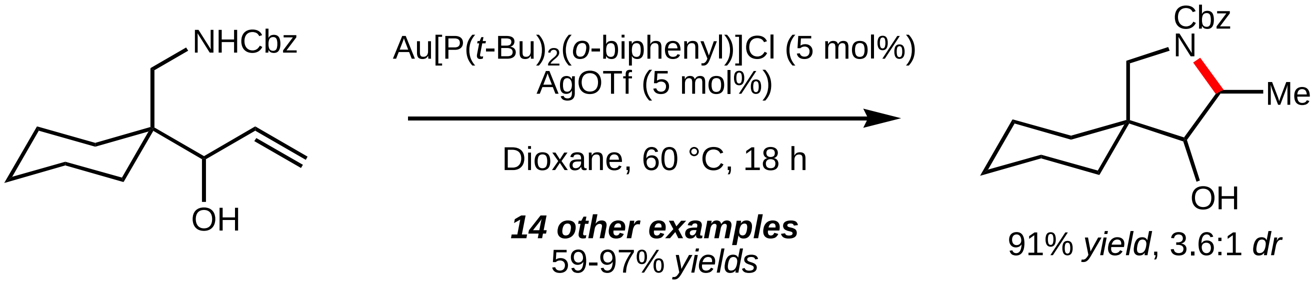
[(**NHC**)AuCl]/AgOTf (5 mol%)

MeOH, rt, 22 h

4 other examples
92-100% *yields*

98% *yield*, 5.5:1 *dr*

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



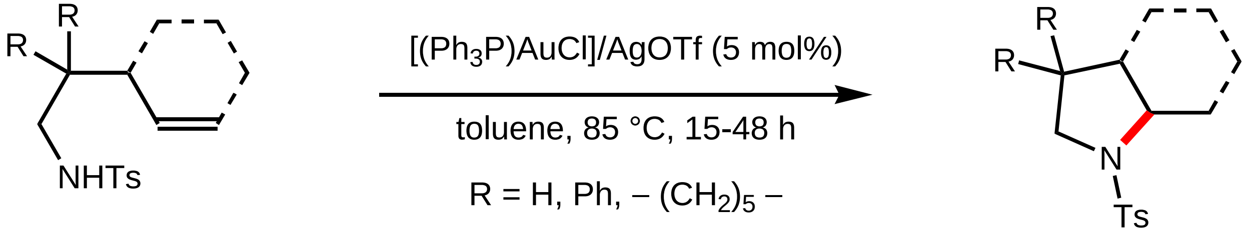
Au[P(t-Bu)$_2$(o-biphenyl)]Cl (5 mol%)
AgOTf (5 mol%)

Dioxane, 60 °C, 18 h

14 other examples
59-97% *yields*

91% *yield*, 3.6:1 *dr*

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



[(Ph$_3$P)AuCl]/AgOTf (5 mol%)

toluene, 85 °C, 15-48 h

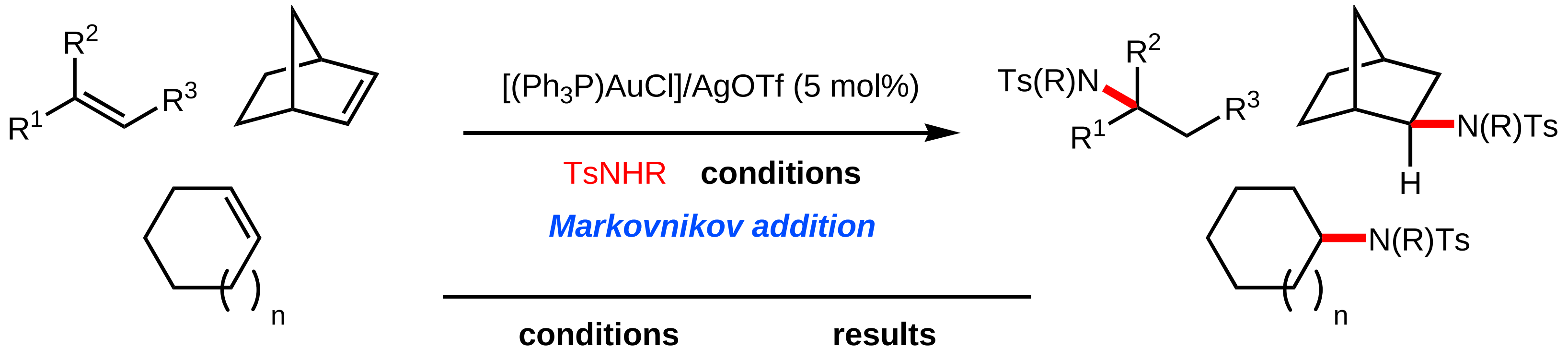
R = H, Ph, – (CH$_2$)$_5$ –

4 examples
91-99% *yields*

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

Intermolecular Hydroamination

Activation of Alkenes



[(Ph$_3$P)AuCl]/AgOTf (5 mol%)

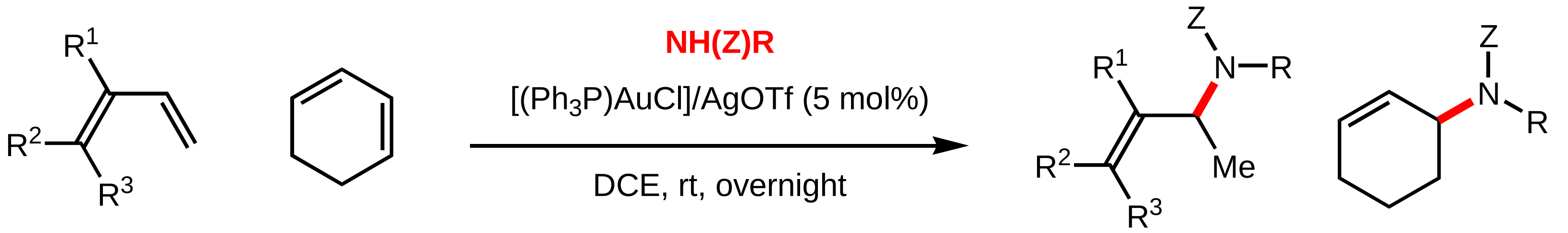
TsNHR **conditions**

Markovnikov addition

R^1 = R^2 = 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.



NH(Z)R

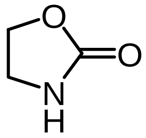
[(Ph$_3$P)AuCl]/AgOTf (5 mol%)

DCE, rt, overnight

R^1 = R^2 =
R^3 = H *or* Me

NH(Z)R

CbzNH$_2$, FmocNH$_2$,
MocNH$_2$, TsNH$_2$

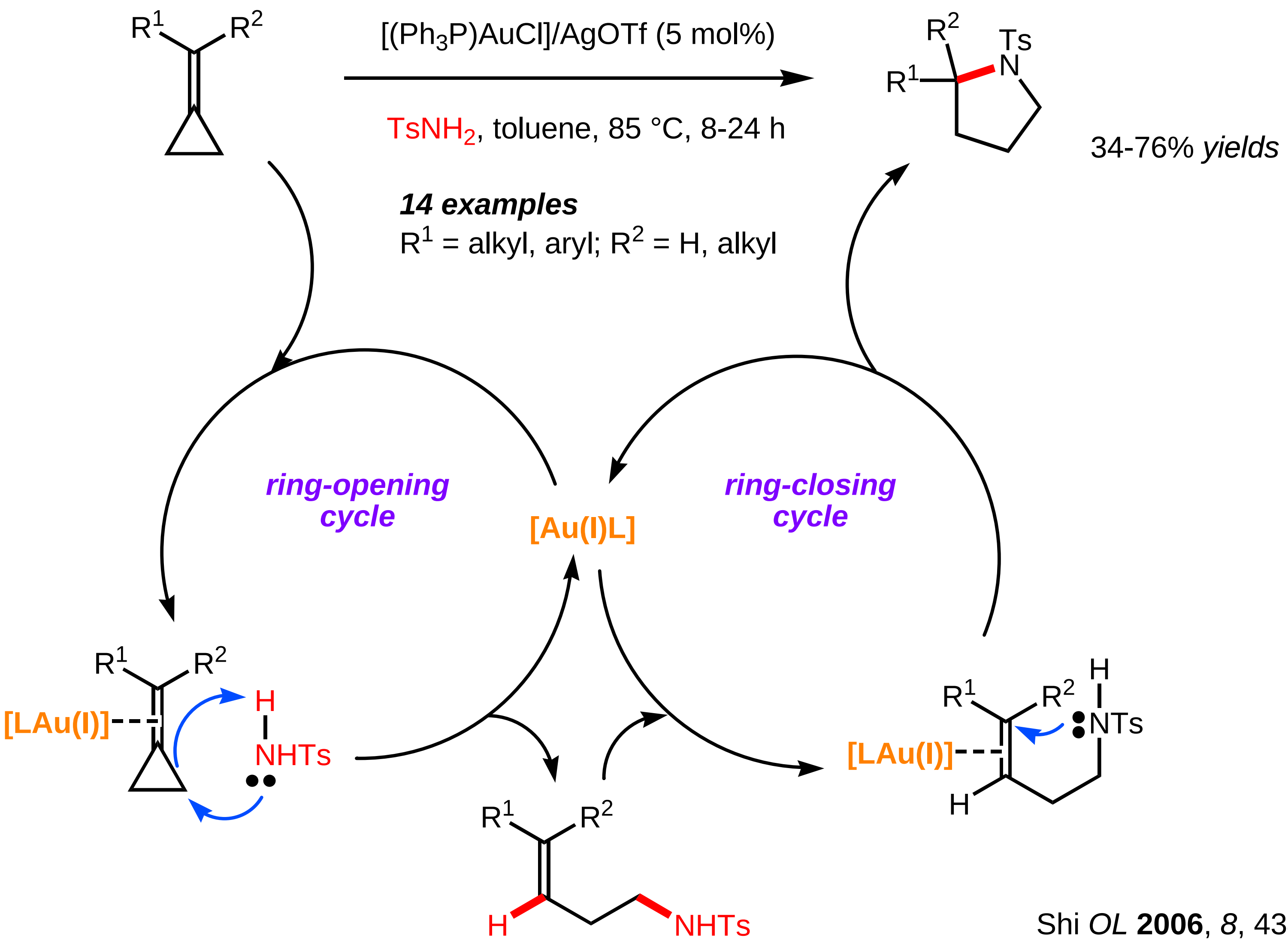


33-87% *yields*

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

Domino Ring-Opening Ring-Closing Hydroamination

Activation of Alkenes



[(Ph$_3$P)AuCl]/AgOTf (5 mol%)

TsNH$_2$, toluene, 85 °C, 8-24 h

34-76% *yields*

14 examples

R^1 = alkyl, aryl; R^2 = H, alkyl

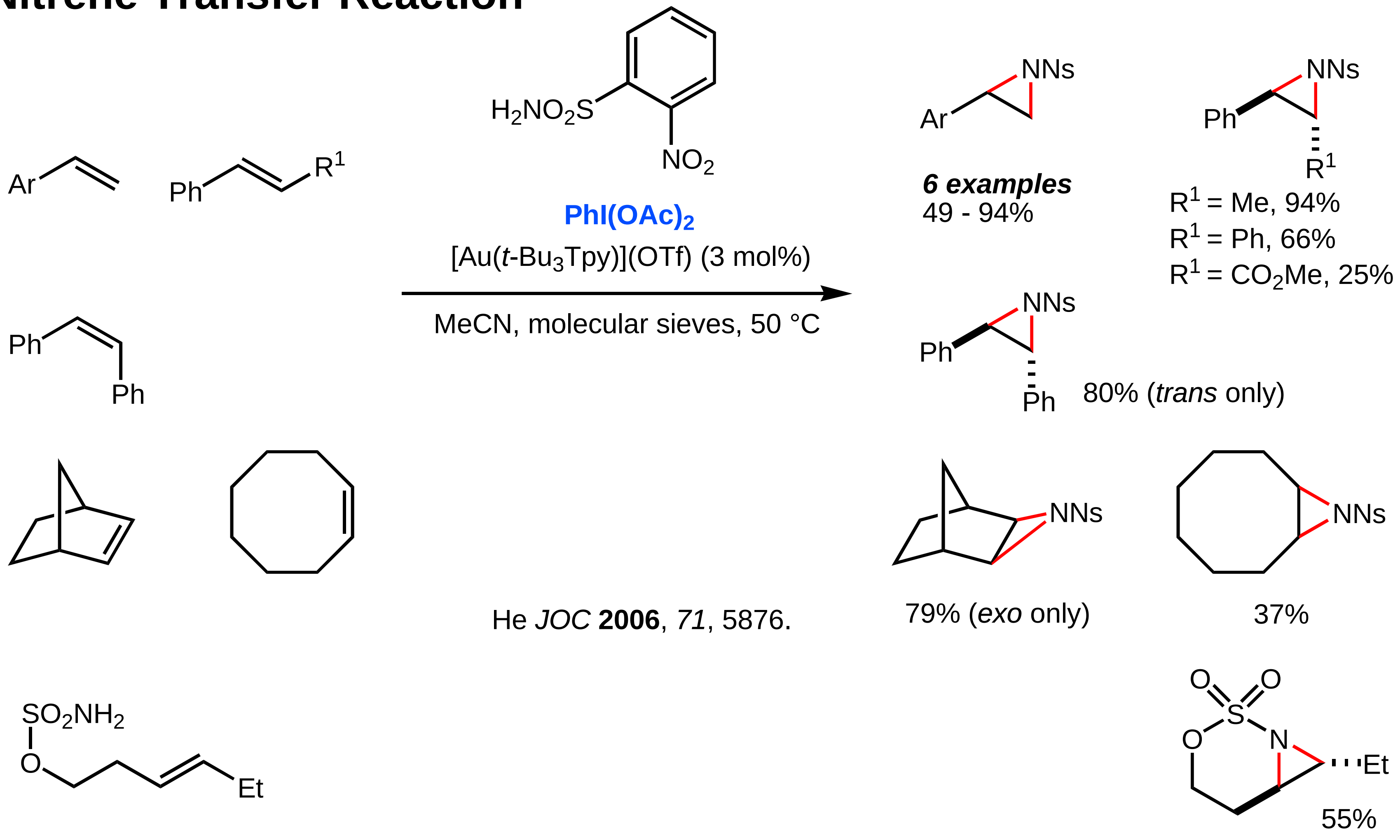
ring-opening cycle

[Au(I)L]

ring-closing cycle

Shi *OL* **2006**, *8*, 4340.

Nitrene Transfer Reaction



PhI(OAc)$_2$

[Au(*t*-Bu$_3$Tpy)](OTf) (3 mol%)

MeCN, molecular sieves, 50 °C

6 examples
49 - 94%

R^1 = Me, 94%
R^1 = Ph, 66%
R^1 = CO$_2$Me, 25%

80% (*trans* only)

79% (*exo* only)

37%

55%

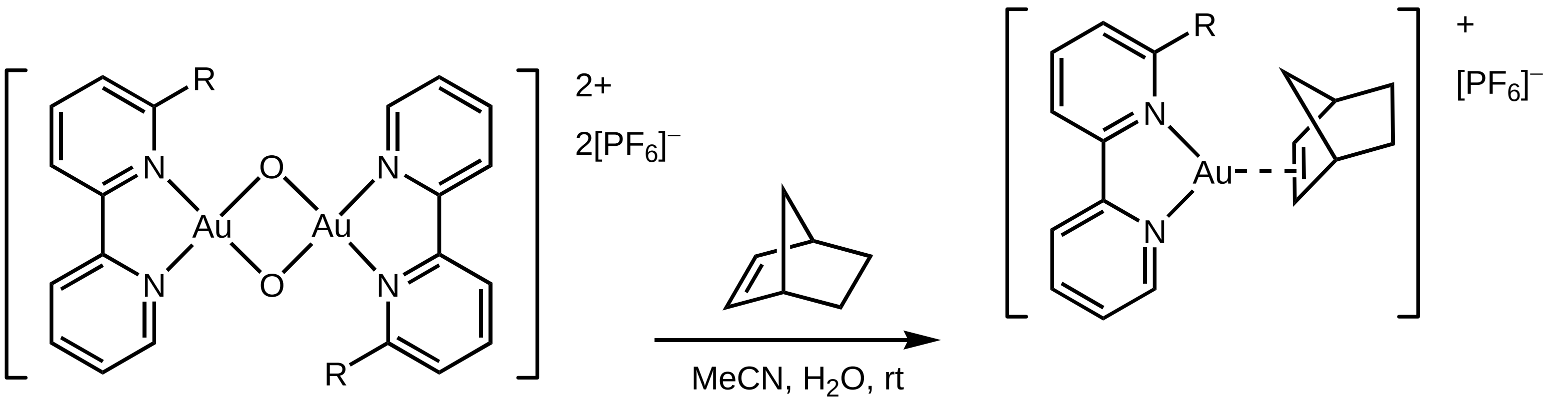
He *JOC* **2006**, *71*, 5876.

Au(III)-Au(I) Redox Mechanism

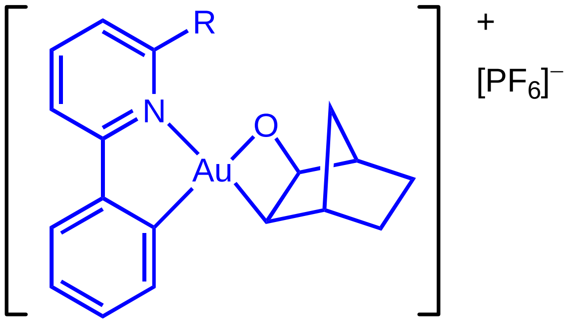
"*all commonly used Au(I) Lewis acid did not show catalytic activity, which seems to argue strongly against the Lewis acid mechanism.*"

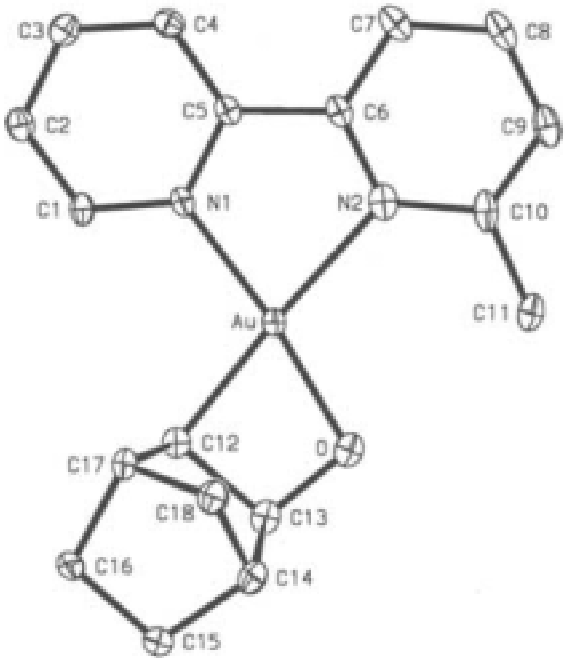
homocoupling of phenylboronic acid catalyzed
by gold supported on nanocrystalline cerium oxide
Corma *ACIE* **2005**, *44*, 2242.

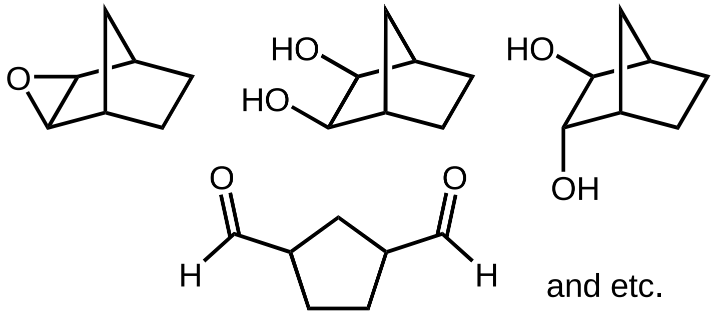
Au(III)-Oxo comples with Cyclic Alkenes



R = Me, *i*-Pr, neopentyl
2,6-(H_3C)C_6H_3



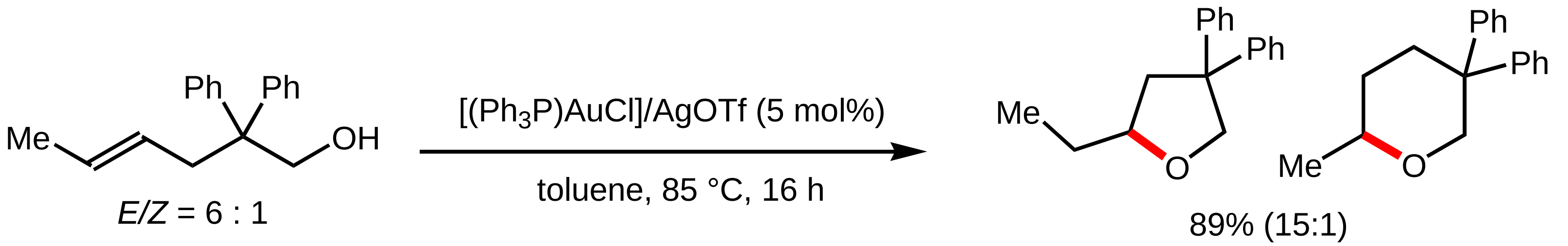




and etc.

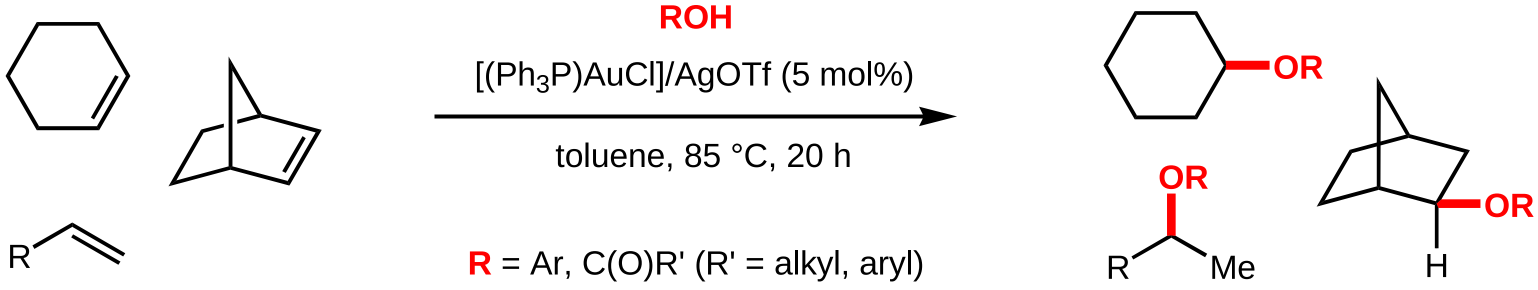
Cinellu *ACIE* **2005**, *44*, 6892.

Intra- and intermolecular Hydroalkoxylation



E/Z = 6 : 1

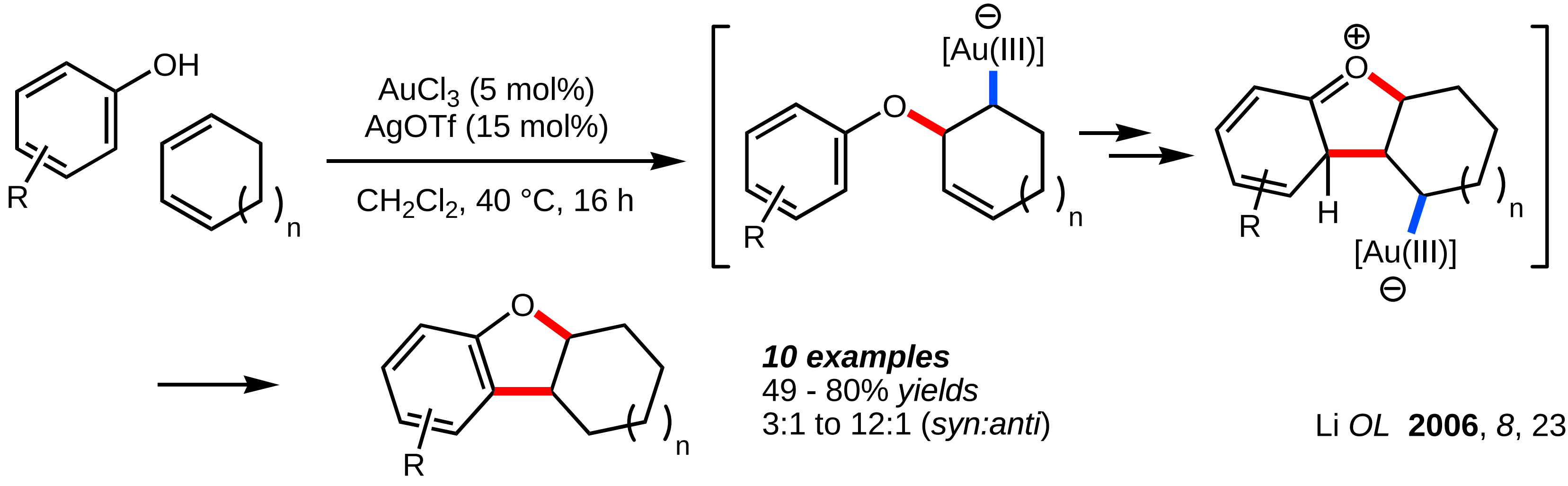
89% (15:1)



R = Ar, C(O)R' (R' = alkyl, aryl)

16 examples
58 - >95% *yields*

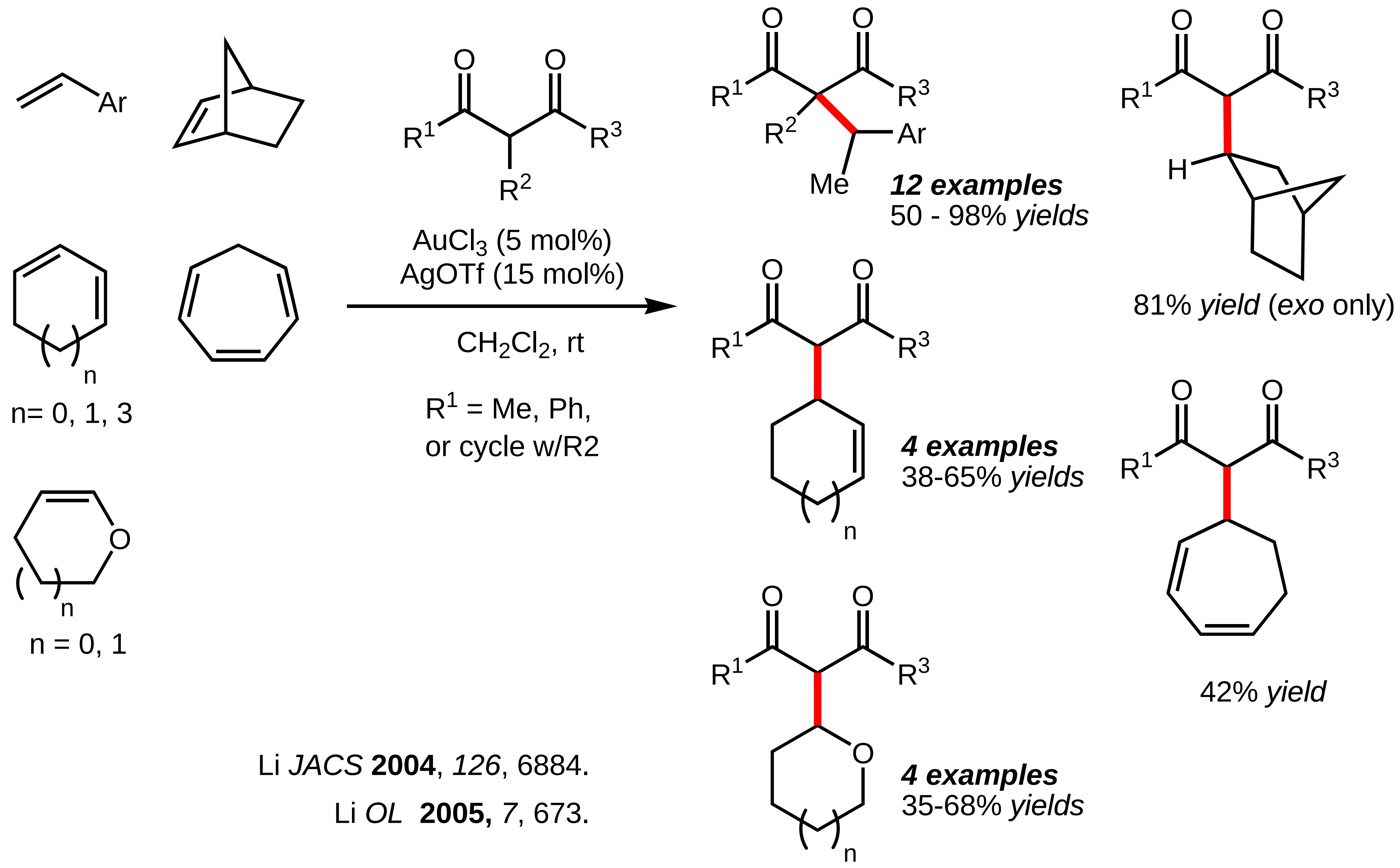
He *JACS* **2005**, *127*, 6966.



10 examples
49 - 80% *yields*
3:1 to 12:1 (*syn:anti*)

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

Enolates as Nucleophiles



AuCl$_3$ (5 mol%)
AgOTf (15 mol%)

CH$_2$Cl$_2$, rt

R^1 = Me, Ph,
or cycle w/R2

12 examples
50 - 98% *yields*

81% *yield* (*exo* only)

4 examples
38-65% *yields*

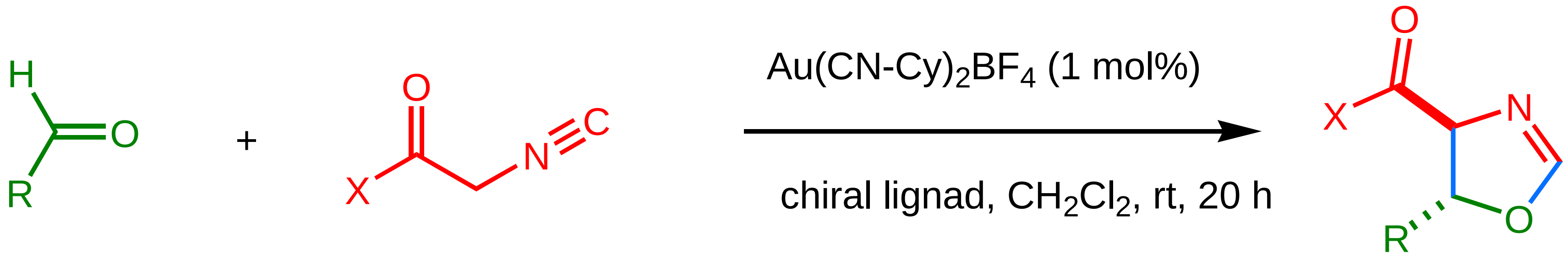
42% *yield*

4 examples
35-68% *yields*

Li *JACS* **2004**, *126*, 6884.

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

Catalytic Asymmetric Aldol Reaction



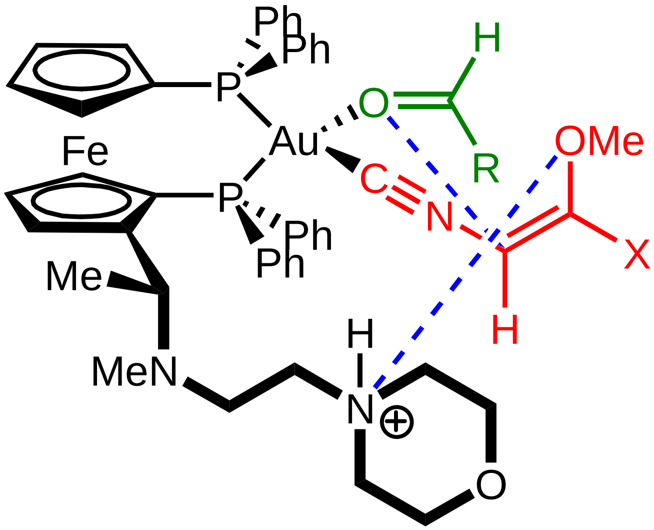
Au(CN-Cy)$_2$BF$_4$ (1 mol%)

chiral lignad, CH$_2$Cl$_2$, rt, 20 h

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 **– aciditiy** 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 – aciditiy 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.