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Topic Review

Cycloisomerization Reactions of 1,*n*-Enynes (Pd- and Au-Catalyzed)

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DCB
Universität Bern

5th November 2015

Overview

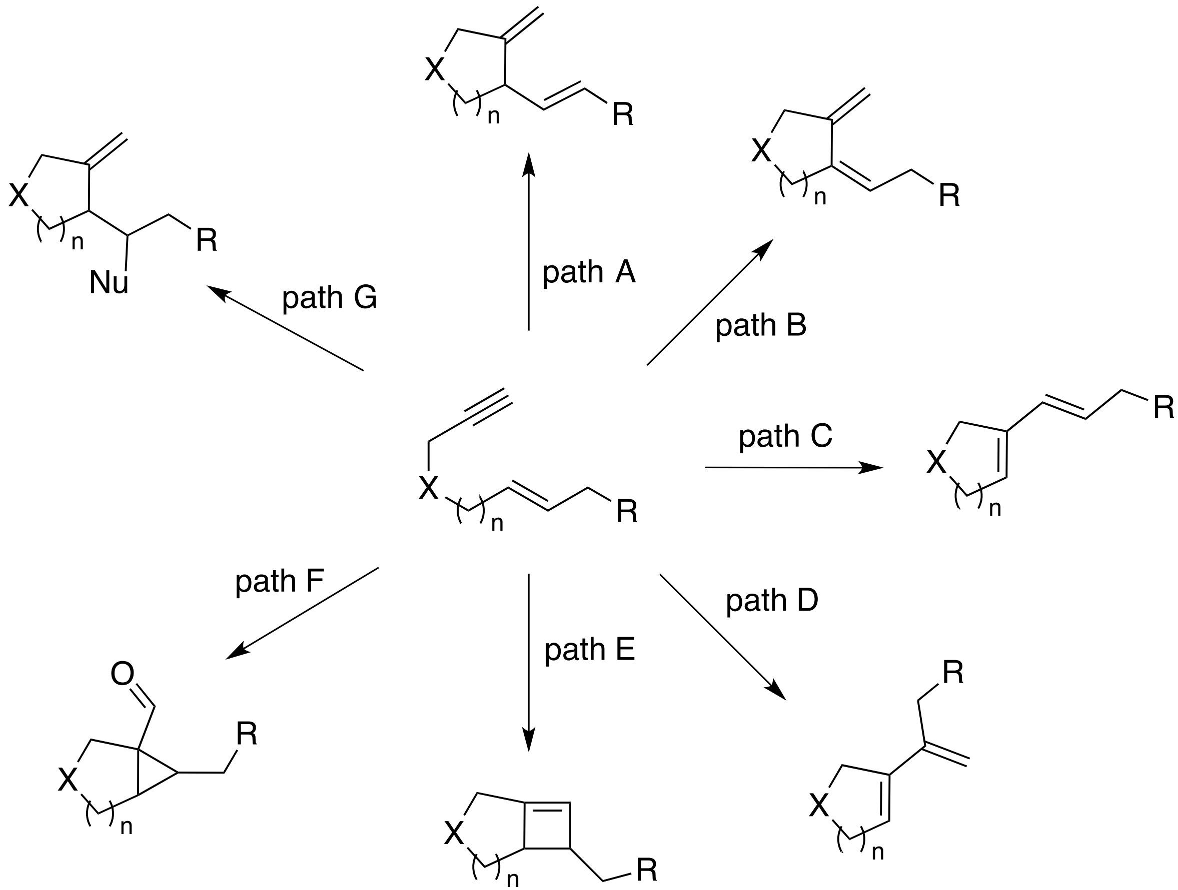
- Enyne C.I.R. Introduction

I. Pd-Catalysis
  - Early Chemistry
  - Mechanism Development
  - Catalysis in Total Synthesis

II. Au-Catalysis
  - Properties of Au(I) (Relativistic)
  - 5-*exo* vs 6-*endo*; Mechanism
  - Catalysis in Total Synthesis

Introduction

Cycloisomerization of Enynes; General Information

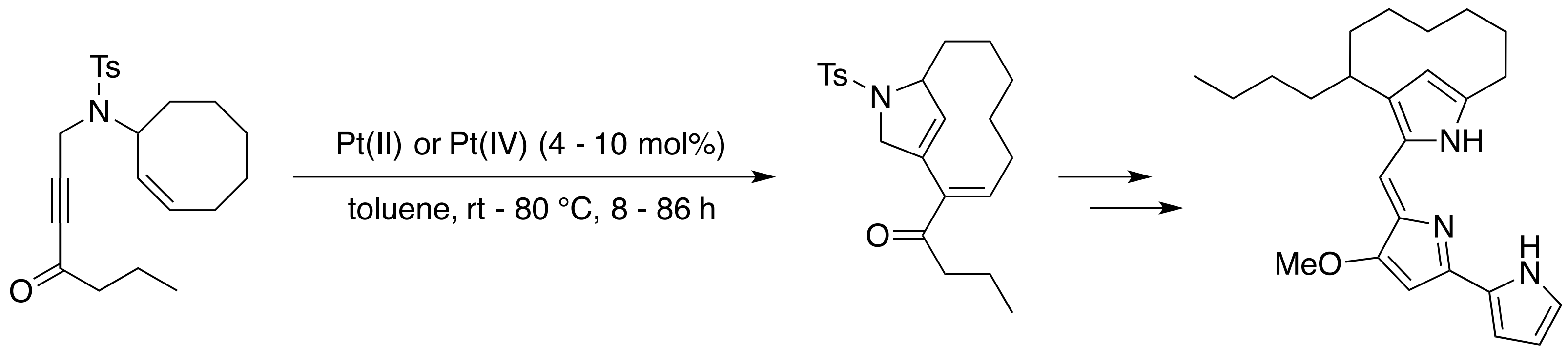


- Atom economical
- Environmentally friendly
- Producing new rings
- High control of:
  - Double bond position
  - Diastereoselectivity
- 1,*n*-Enynes (*n* = 4–8)
- 1,6-Enynes most common

G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1* (2), 215–236

Introduction
Cycloisomerization of Enynes; General Information

- "Enyne-cycloisomerization reactions were the **first noble metal catalyzed processes** to be implemented into a natural product total synthesis"



67 - 95% **Streptorubin B**

- Highly substrate-dependant

A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221
A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120,* 8305-8314

Cycloisomerization
Introduction; Metals

b
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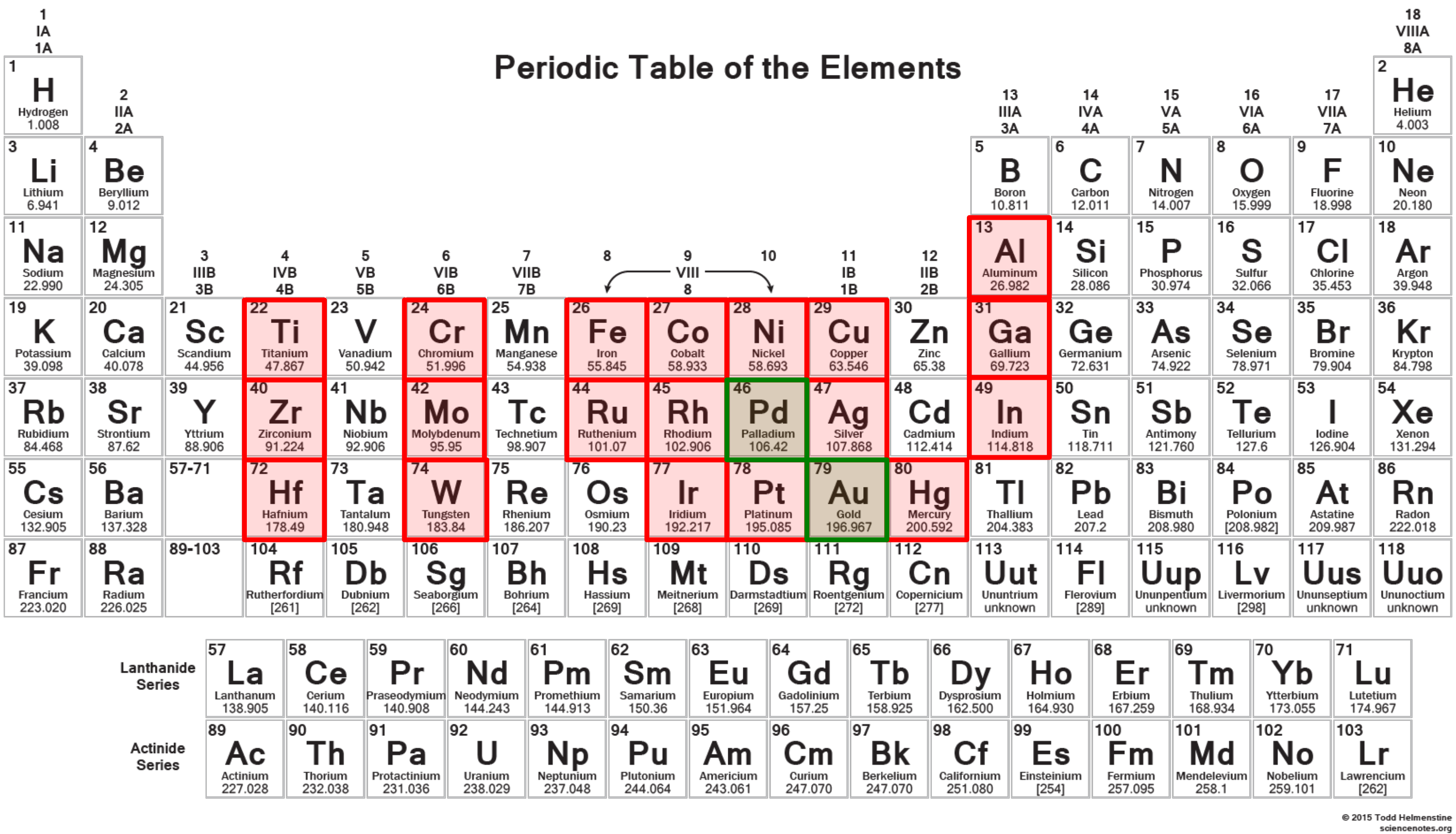
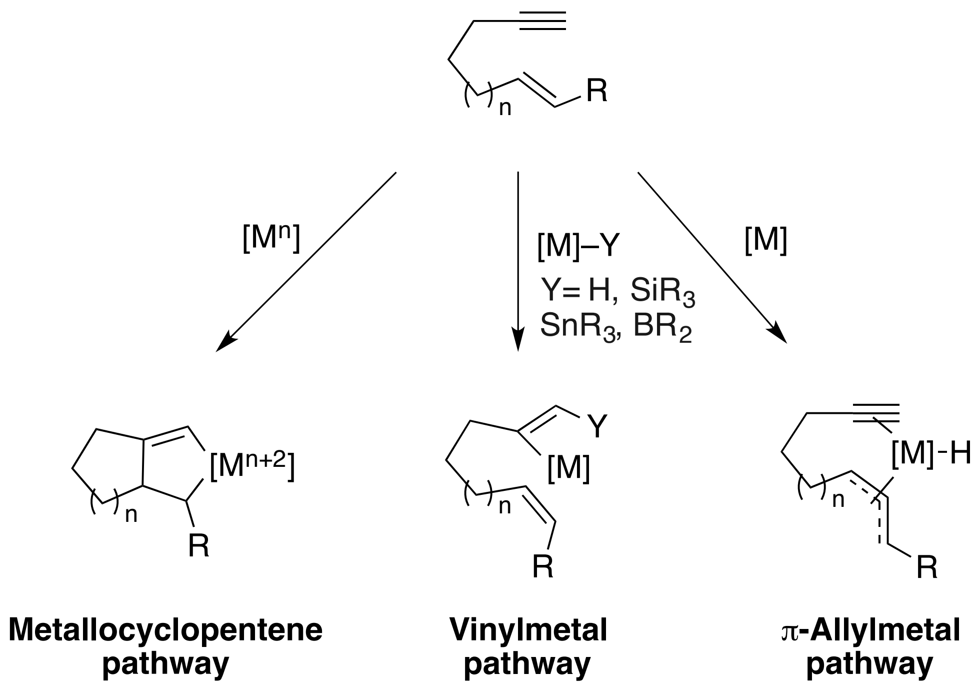
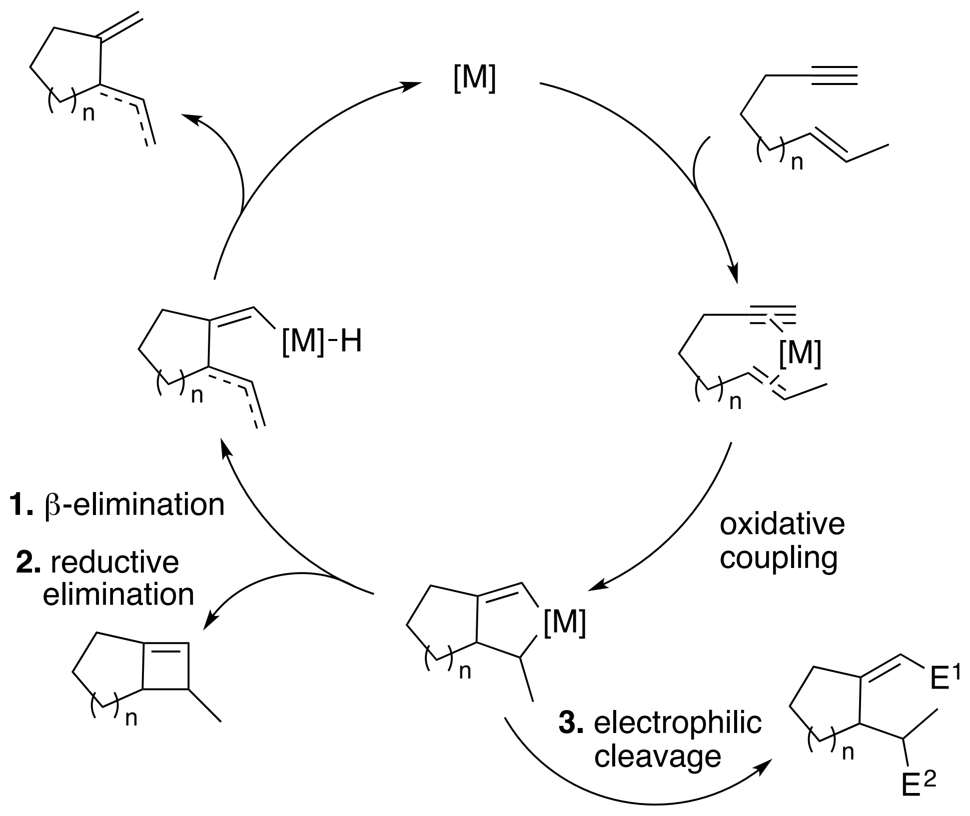


1,*n*-Enyne
Different Pathways (≠Pt, Au)



1,*n*-Enyne
Metallacycle; General Mechanism; Different Pathways



Palladium-Catalyzed C.I.R

Barry M. Trost
Stanford

Mark Lautens
Toronto

PhD: Trost

F. Dean Toste
Stanford

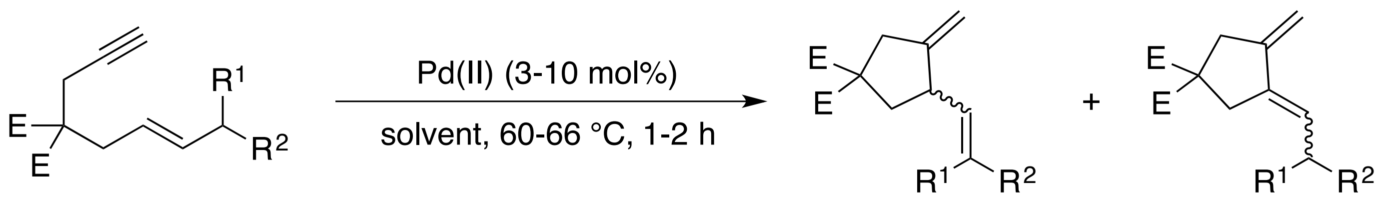
PhD: Trost

Michael J Krische
Texas A&M

PhD: Trost

Palladium-Catalyzed C.I.R.
First Reported Reaction

- "… unanticipated observation that Pd(II) salts catalyze cyclizations *via* an isomerization to lead to related products …"



A **B** **C**

Pd(II): $(Ph_3P)_2Pd(OAc)_2$; $[(o\text{-}CH_3C_6H_4)_3P)]_2Pd(OAc)_2$
solvent: non-polar solvents (max. with benzene)

Conclusions

- Mild conditions
- Pd(0) (*e.g.* $Pd(PPh_3)_3$) does not catalyze the reaction
- Effectiveness of Pd(II) due to Lewis acidity
- Double bond position directed by stereoelectronic effects

B. Trost, M. Lautens, *J. Am. Chem. Soc.* **1985**, *107*, 1781–1783

First Reported Reaction
Mechanism; Palladacycle, β-Elimination

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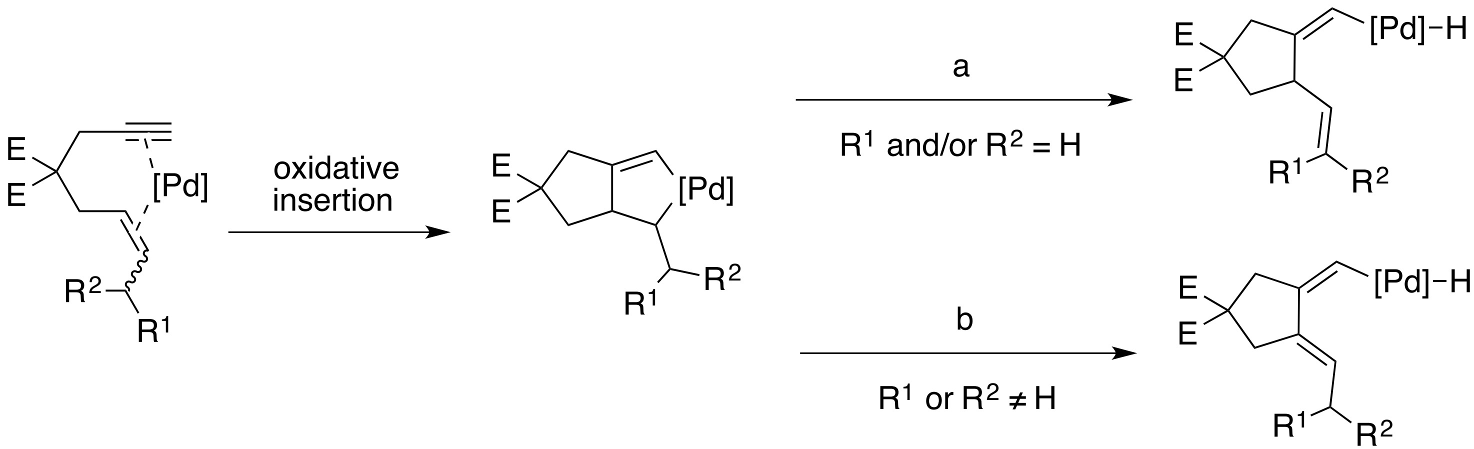
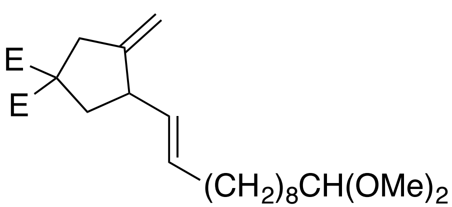
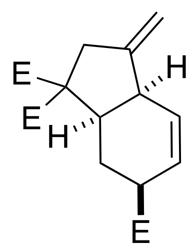


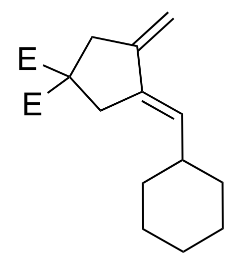
- Examples with allylic carbon mono- or disubstituted



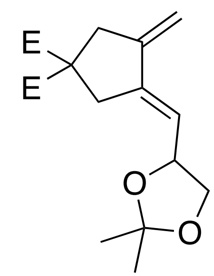
71%



50-85%



64%



71%

Palladium-Catalyzed C.I.R

Trost’s Example; Trapping Intermedaite ([2+2+2])

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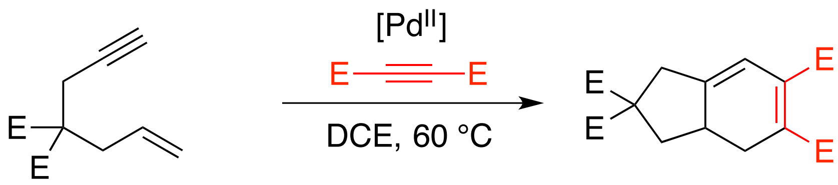
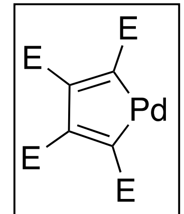
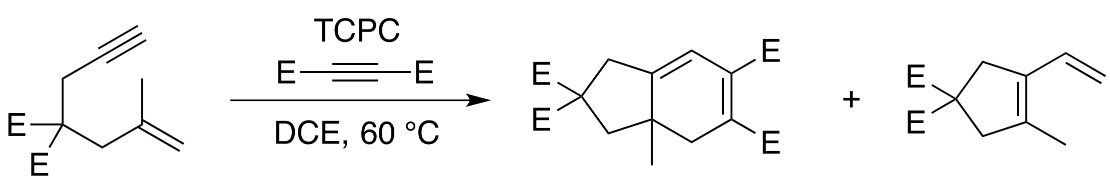


E: CO_2Me



TCPC

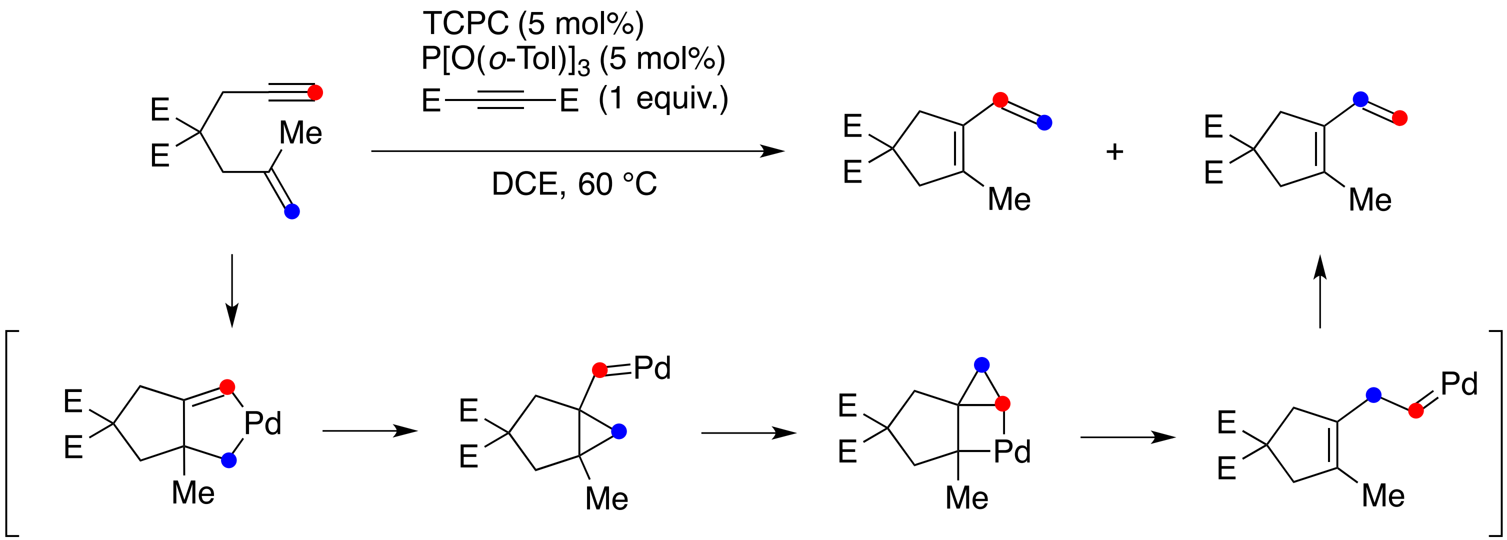
- **$Pd(OAc)_2$** did not work (electron deficient Pd; **H-shift too fast**)
- TCPC furnished product in **82%** yield
- Incorporation of CO unsuccessful; Pd black
- Control Exp. → 1. $E_{reagent}=CO_2Et$; 2. [2+4] **negative**
- Formation of unexpected product (“Metathesis product”)



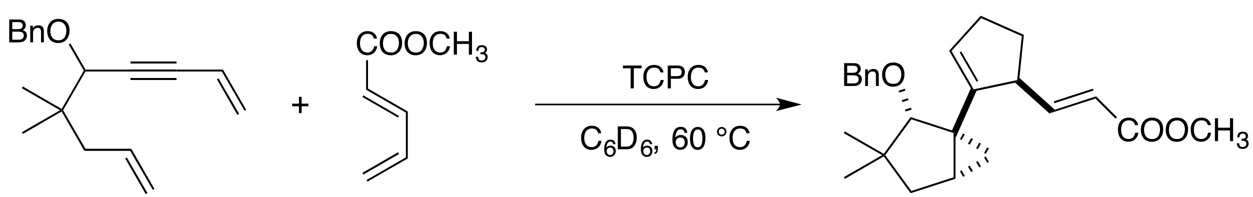
44% **53%**

E: CO_2Me

Palladium-Catalyzed C.I.R
Single vs. Double Cleavage; ^{2}H-, ^{13}C Labelling



- Evidence for a cyclopropyl intermediate



90% (d.r. 5:1)

B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638
B. M. Trost, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* ***1993***, *32* (7), 1085–1087

Palladium-Catalyzed C.I.R
Alkoxy-/Hydroxycyclization

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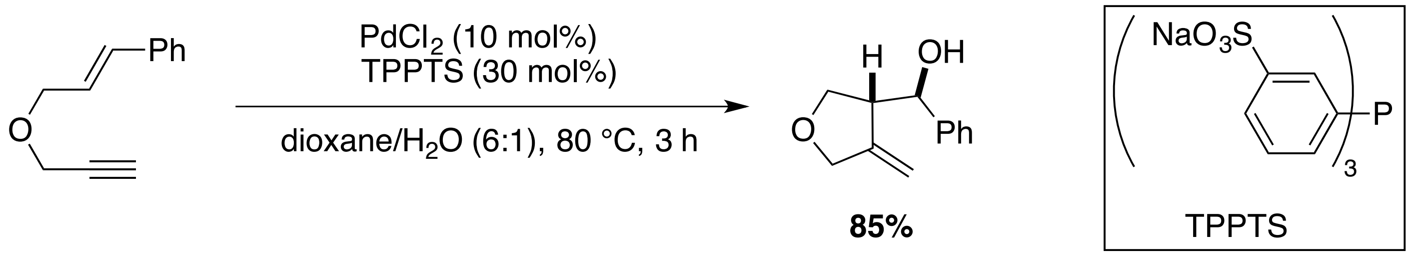
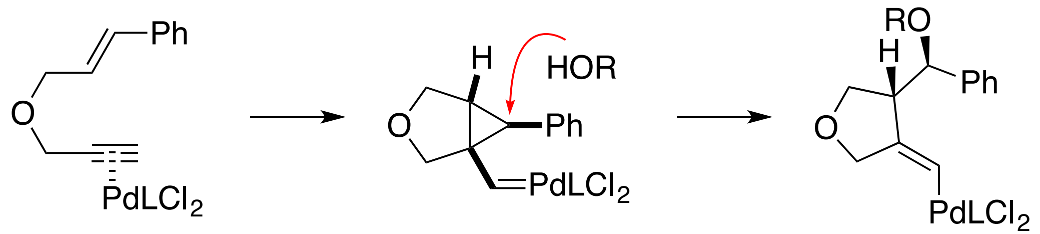
- **Carbohydroxypalladation** of allyl propargyl ethers (diastereoselective)



- Proposed Mechanism (complexation of Pd(II) to alkyne)



- Scope of nucleophiles extended later
  - *N*-nucleophilies, electron-rich aromatics (*e.g.* indoles)

J. C. Galland, M. Savignac, J. P. Genêt, *Tetrahedron Lett.* **1997**, *38*, 8695–8698

Palladium-Catalyzed C.I.R
Asymmetric Reactions; Pd(0) → Pd(II)

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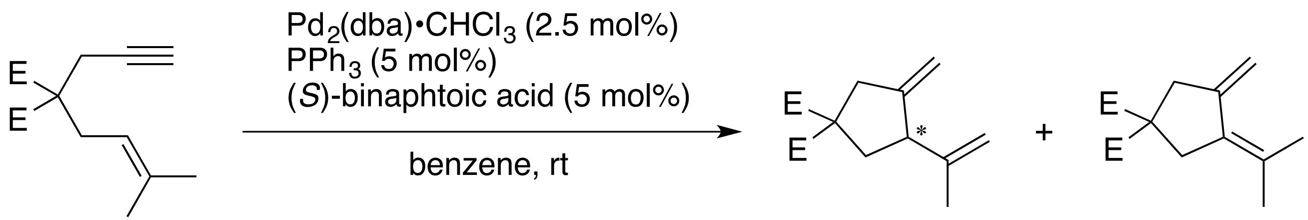
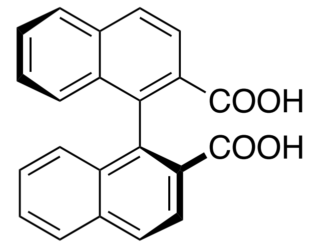
- First example ((*S*)-binaphtoic acid), *in situ* Pd–H

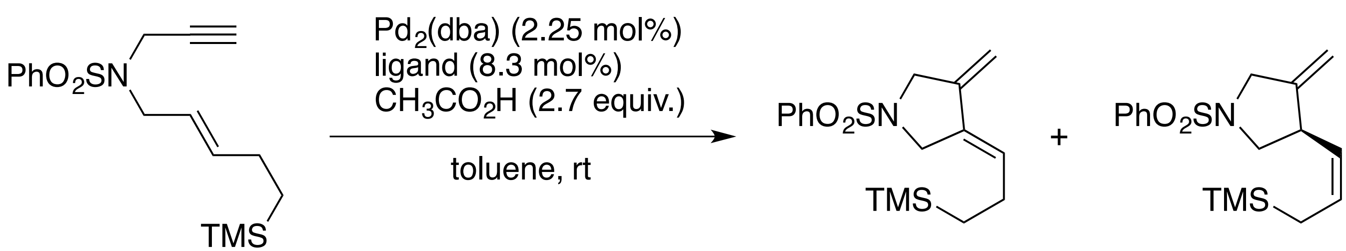


61%, 33% *ee* (3:1)

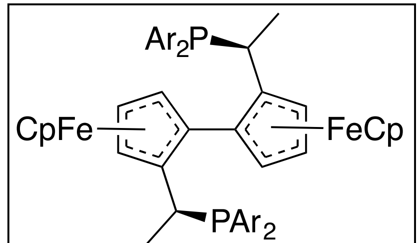


(*S*)-(–)-binaphtoic acid

- Chiral ligand



68%, 95% *ee* (7:2)

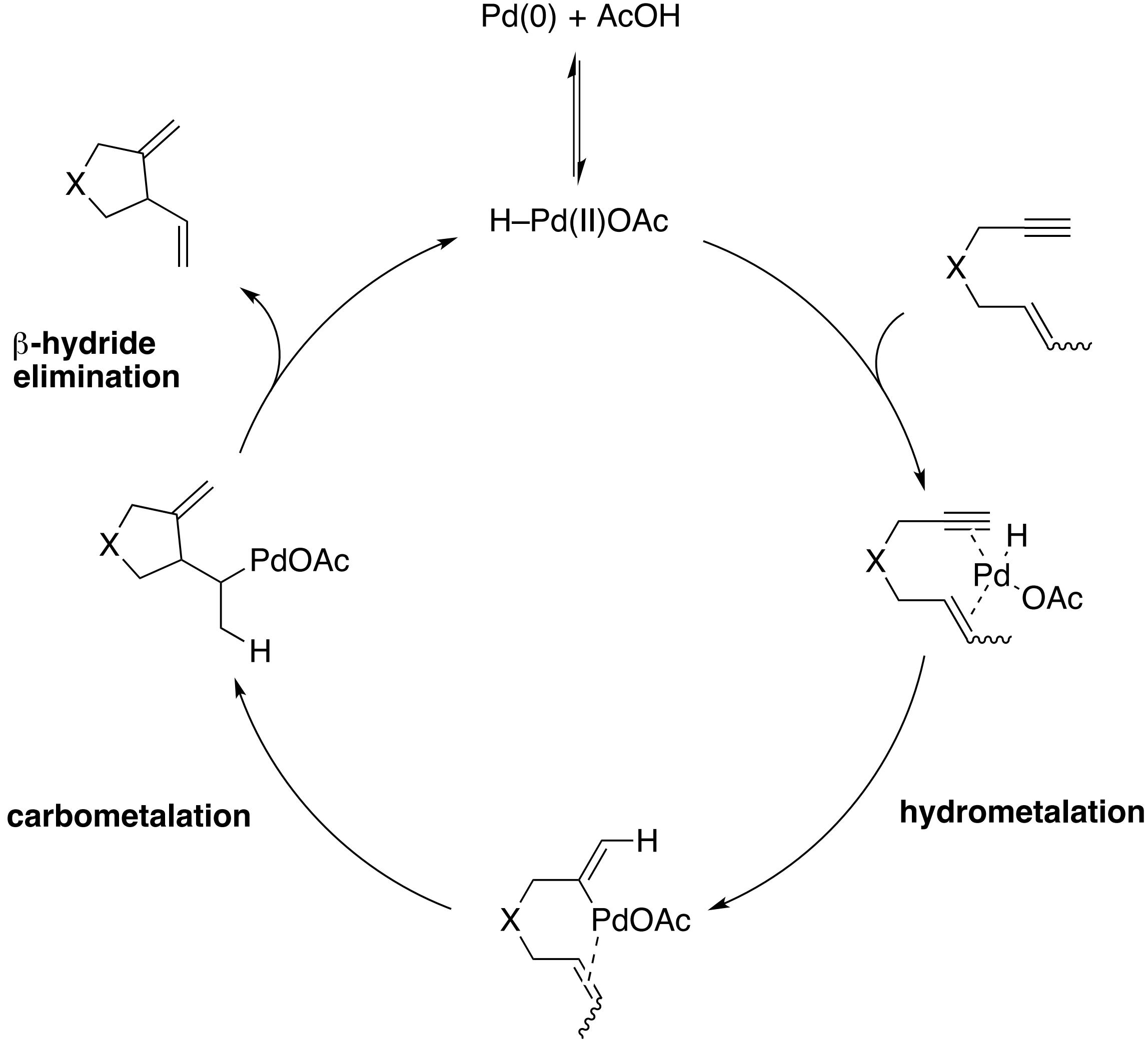


ligand (Ar=*p*-$CF_3C_6H_4$)

B. M. Trost, D. C. Lee, F. Rise, *Tetrahedron Lett.* **1989**, *30*, 651–654
A. Goeke, R. Kuwano, Y. Ito, M. Sawamura, *Angew. Chem. I. Ed.* **1996**, *35*, 662–663

Palladium-Catalyzed C.I.R.

Asymmetric Catalysis; Pd(0) → Pd(II); Vinylmetal PW



I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, *3*, 2899–2919

Palladium-Catalyzed C.I.R
Total Synthesis; Heteroatom-Substituted Alkenes

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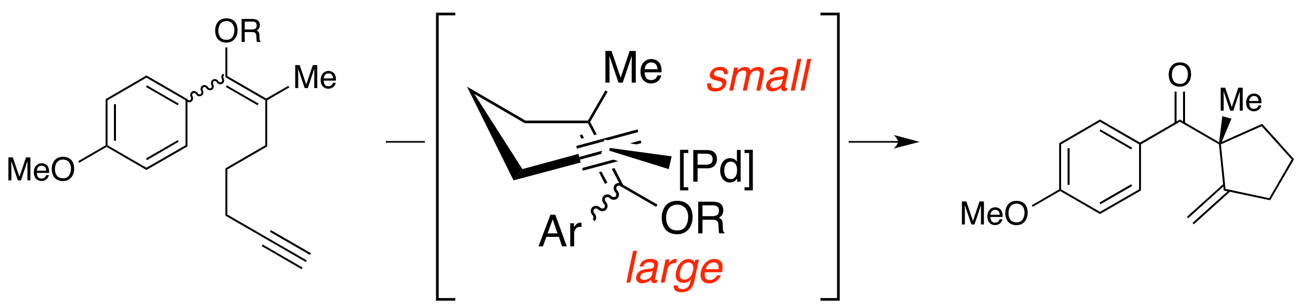
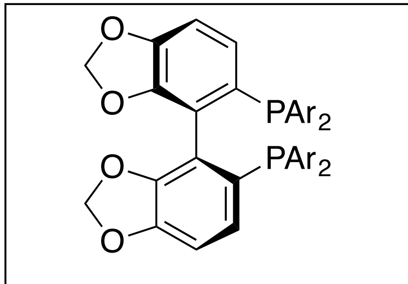
- Enantioselective cycloisomerization of **silyloxy-1,6-enynes**

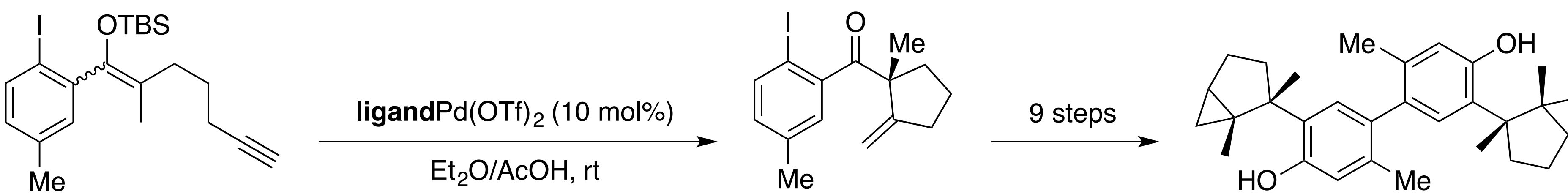


R = TMS; (3:1 *Z*:*E*) 63% ee
R = TBS; (*Z*) 78% ee, **(*E*) 91% ee**



ligand ((*R*)-DTBM-Segphos)
Ar = *p*-OMe-*m*,*m*'-*t*-BuPh

- Total synthesis of (–)-laurebiphenyl



formed *in situ*
E:*Z* = 1:4

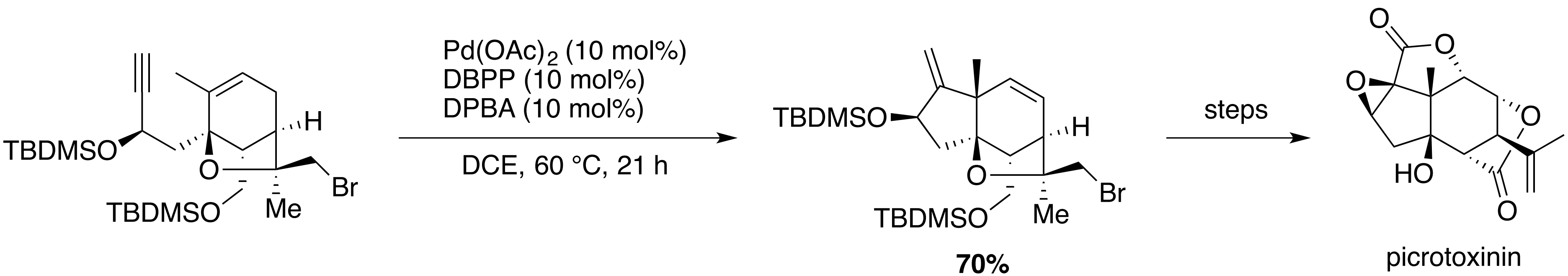
96% (95% ee)
91% recov. cat.

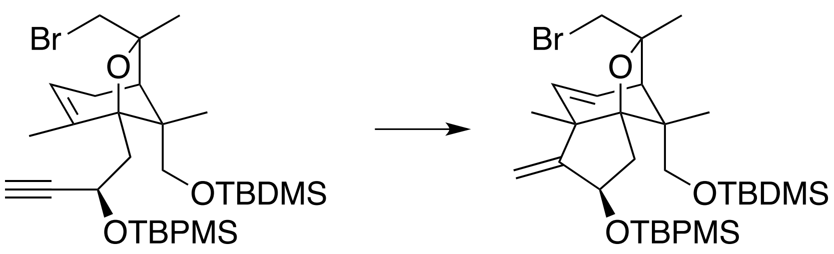
(–)-laurebiphenyl

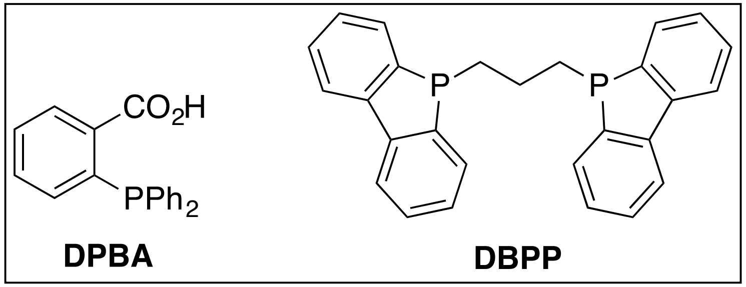
B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc*. **2007**, *129*, 2764–2765

Palladium-Catalyzed C.I.R
Total Synthesis; Substrate Controlled

- Preparation of C.I.R. precursor from (*R*)-carvone in 6 steps







M. J. Krische, B. M. Trost, *J. Am. Chem. Soc.* **1996**, *118*, 233-234

Gold Catalyzed C.I.R.
“The Ultimate Catalyst for Enyne C.I.R.”

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Antonio M. Echavarren
ICR Catalonia

Alois Fürstner
Max-Planck

F. Dean Toste
Stanford

Pekka Pyykkö
Helsinki

Metals as π-Acids
Activation of Enynes; η-Complexation

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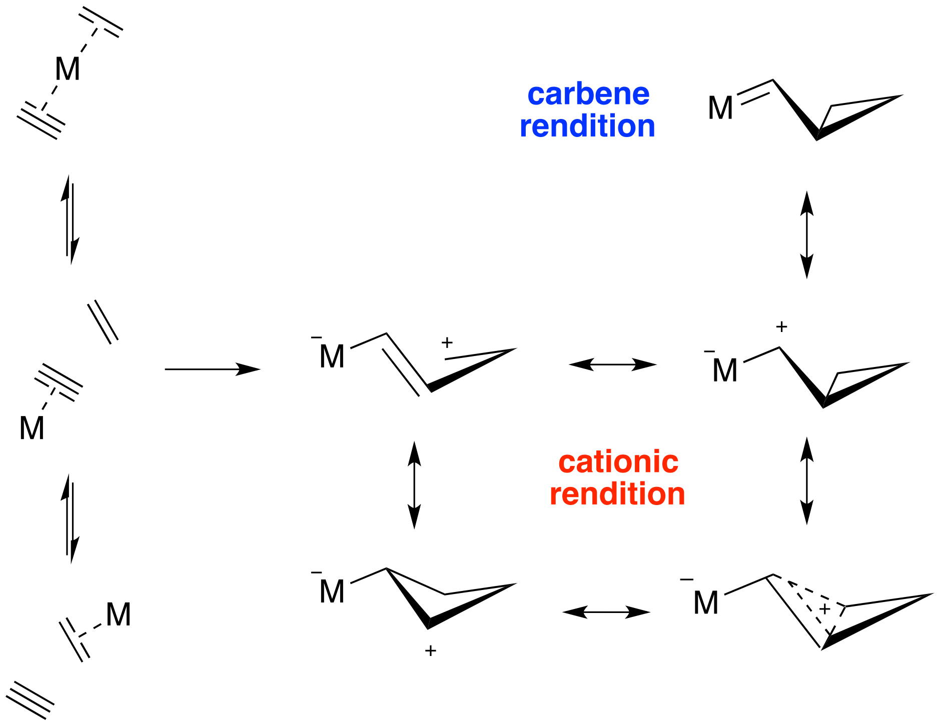
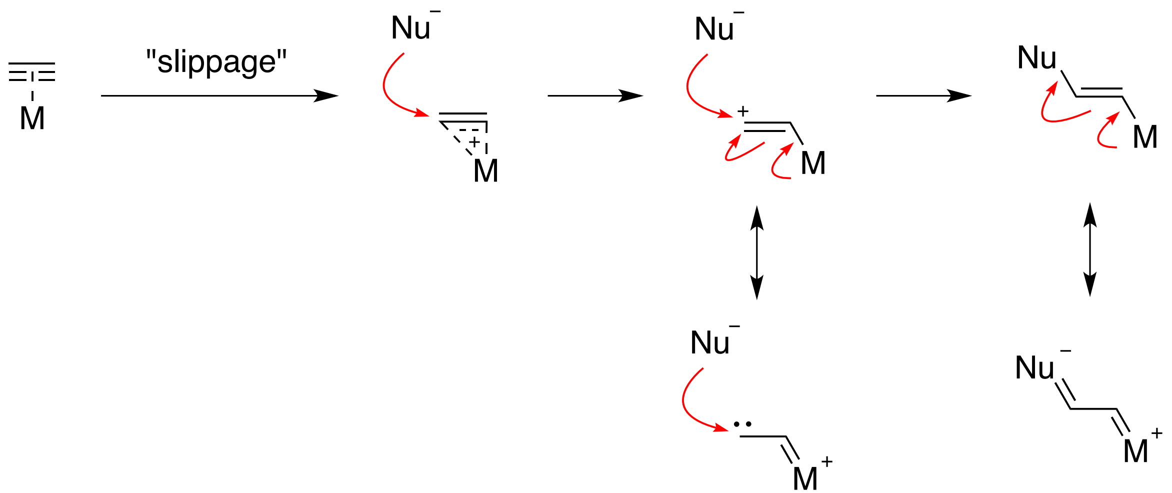
- Formation of a non-classical carbocation (after "**slippage**" and attack of the alkene



Metals as π-Acids
Alkyne Interaction; Slippage $\eta^2 \rightarrow \eta^1$

- Fundamental processes in the noble metal activation of an alkyne



Au-Catalyzed C.I.-Reactions
Properties of Gold; Relativistic effects

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- Au(I) **linear, bicoordinate** geometry
- Au(I) species are **not particular nucleophilic** (compared to corr. Cu complexes)
- Au(I) species avoid oxidative addition
- **Reductive elimination** of $LR_3Au(III)$ disvafored as well
- Au(I) and Au(III) do **not readily cycle** between oxidation states
- Au(I) species generally **tolerant of oxygen**

- Au: $[Xe]4f^{14}5d^{10}6s^1$
- **Relativistic contraction** of 6s-orbital
    - Large first ionization potential (**9.22 eV**)
    - greatly **strenghtened Au-L bonds**
    - "**Aurophilicity**": tendency of Au-Au interactions stabilizing on the order of H-bond

D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403
A. Simonneau, *Gold-Catalyzed Cycloisomerization Reactions Through Activation of Alkynes*, Springer, Cham, **2014**

Au-Catalyzed C.I.-Reactions
Properties of Cationic Au(I) Species

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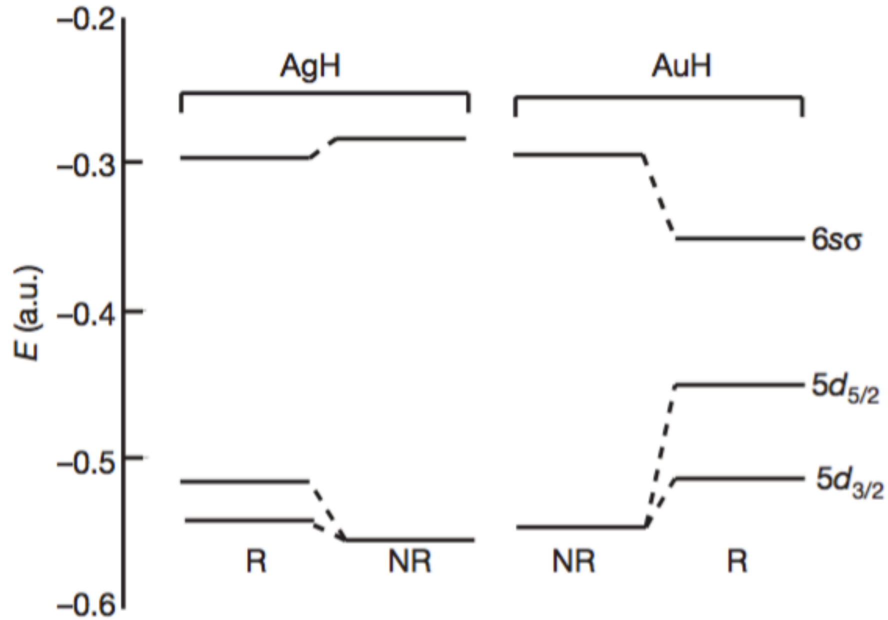
- **Superior Lewis** acids compared with other group 11 metals (Cu, Ag)
- Relatively low-lying LUMO
- For ligands: Au–P bond much **more covalent** than Ag–P bond
- **LAu(I)+** large, diffuse → charge is shared with P
  - **Orbital interaction** rather than charge interaction
- **"Soft" Lewis acid** for soft electrophiles (*e.g.* alkenes, alkynes)



E_h (atom units): [hartree] = 27.211 eV
ΔE = 2.7 eV

D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403
P. Pyykko, J. P. Desclaux, *Acc. Chem. Res.*, **1979**, *12* (8), 276–281

Au-Catalyzed C.I.-Reactions
Alkyne Interaction

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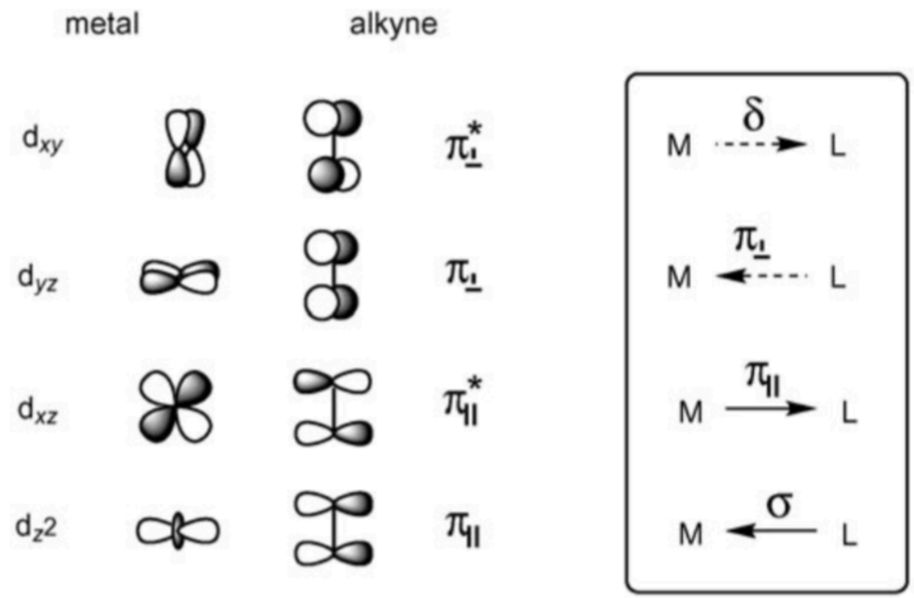
- Au(I)–ethene vs. Au(I)–ethyne ($\Delta E_{stabilization}$ ~ 10 kcal mol^{-1})
- Apparently favoured complexation to alkenes
  - Discrimination by the nucleophile
  - LUMO/HOMO (alkyne) < LUMO/HOMO (alkene) (~ 0.5 eV)
  - → Au(I)-alkyne lower LUMO



M. S. Nechaev, V. M. Rayon, G. Frenking, *J. Phys. Chem. A*, **2004**, *108* (15), 3134–3142
A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449

Au-Catalyzed C.I.R; 1,6-enynes
Mechanism; *5-exo* vs. *6-endo*

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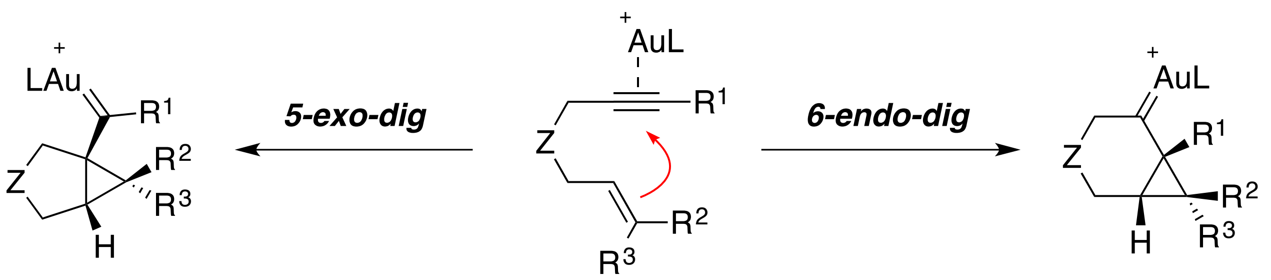
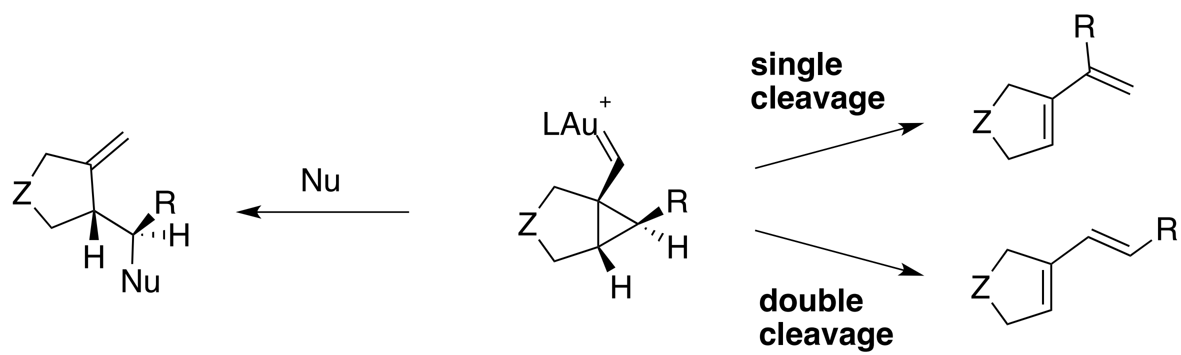
- $[Au(PR_3)]^+$ isolobal to H^+ → cannot coordinate both unsaturated moieties

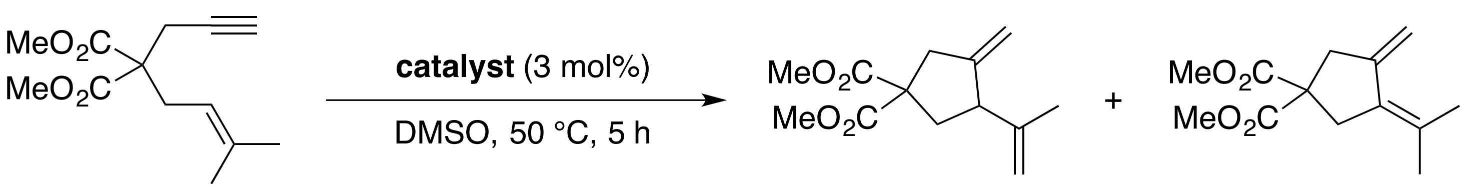


- Alder-Ene does not compete
- Further reactions (*5-exo-dig*)

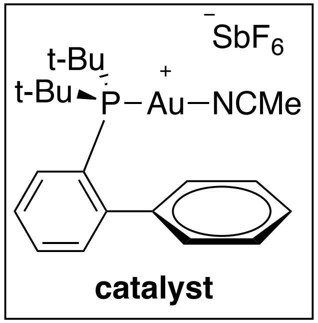


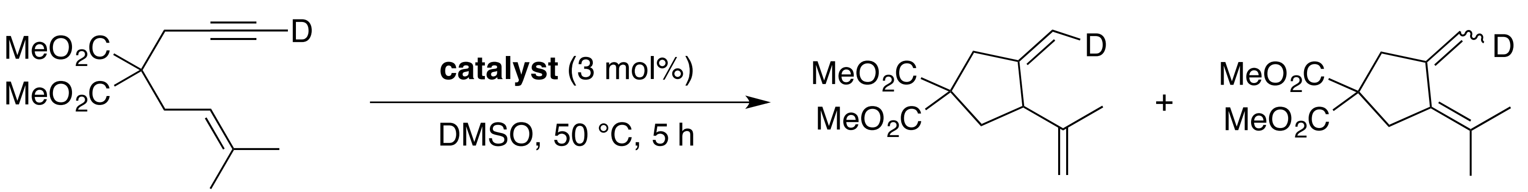
Au-Catalyzed C.I.R.; 1,6-enynes
Trost's substrate; Effect of Nucleophilie/Substitution

- **Alder-Ene** product found occasionaly (DMSO = Nu)

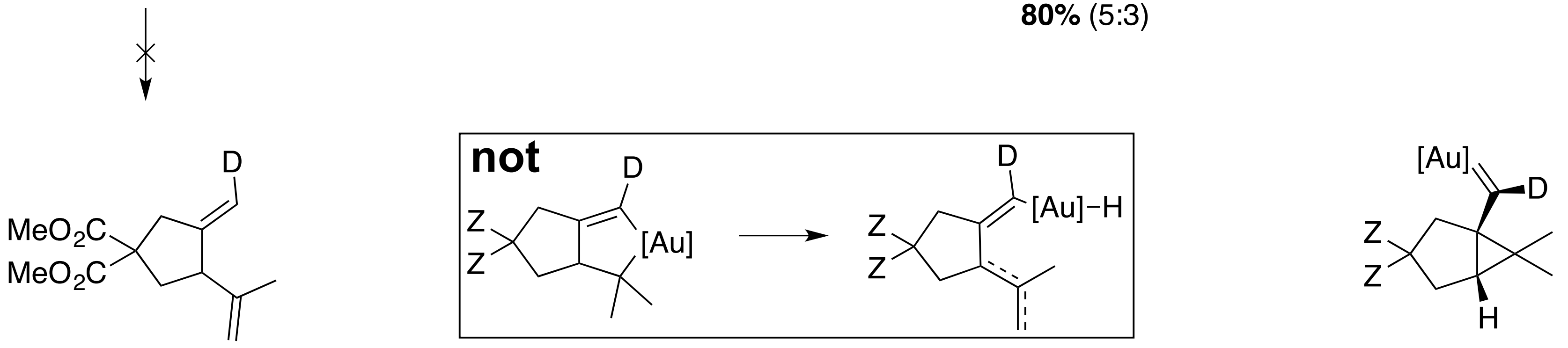


67% (2:1)



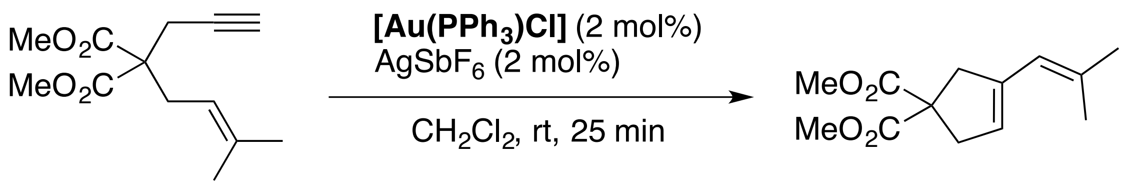


80% (5:3)



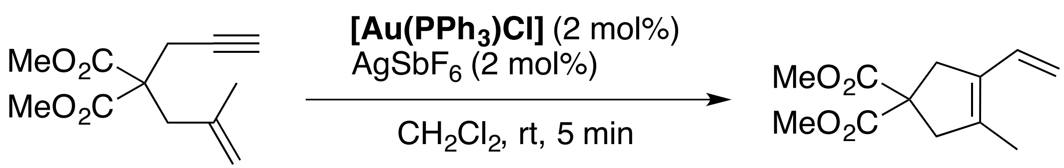
Au-Catalyzed C.I.R.; 1,6-enynes
Trost's substrate; Effect of Nucleophilie/Substitution

- Absence of nucleophile



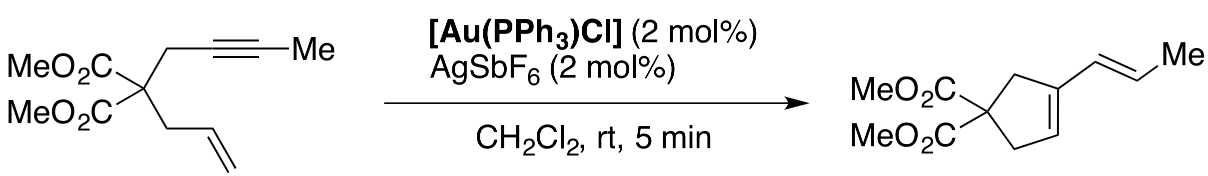
91%

- Alkene substituent



76%

- Alkyne substituent

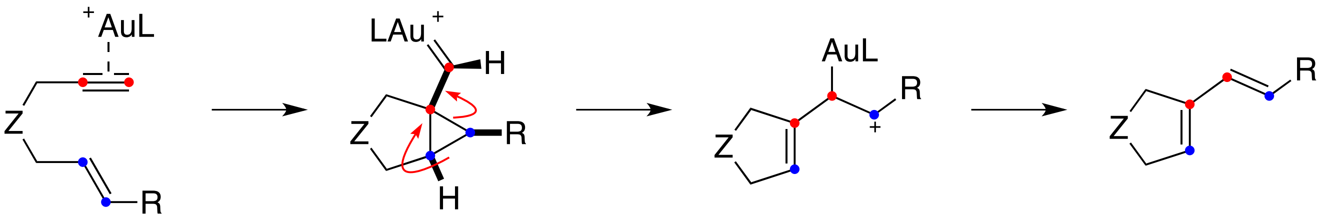


95%

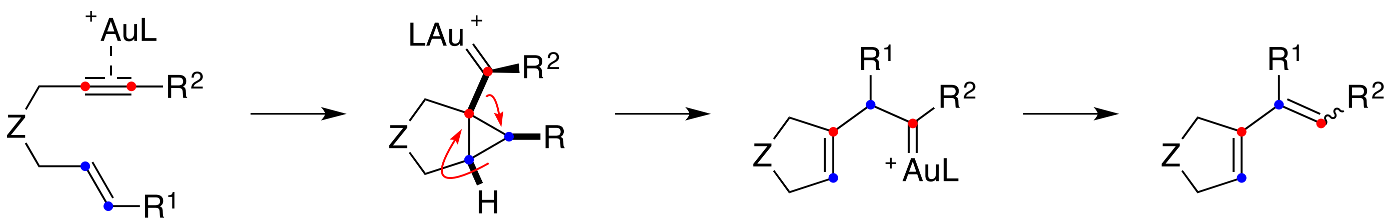
C. Nieto-Oberhuber *et al.*, *Chem. Eur. J.* **2006**, *12*, 1677–1693
C. Nieto-Oberhuber *et al.*, *Angew. Chem. I. Ed.* **2004**, *43*, 2402–2406

Au-Catalyzed C.I.R.; 1,6-enynes
Single- and Double Cleavage

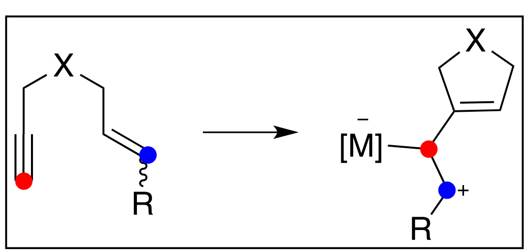
single cleavage

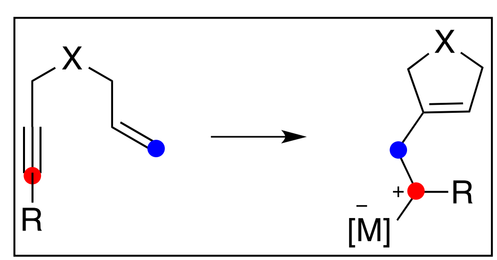


double celavage



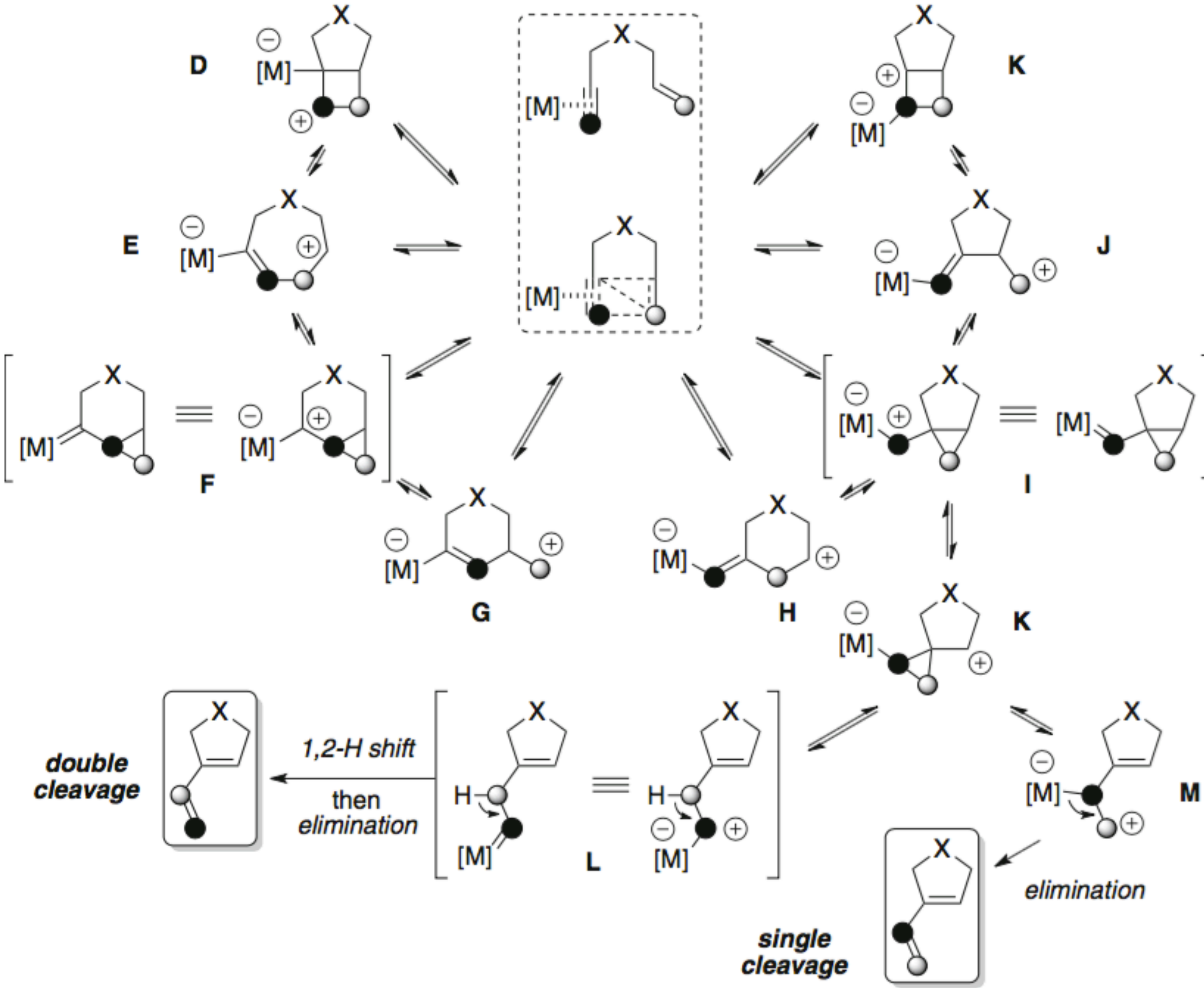
- Effect of substituents (Stabilization of carbocation)





E. Jimenez-Nunez, A. M. Echavarren, *Chem. Rev*. **2008**, *108*, 3326–3350
S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics*, **2001**, *20* (17), 3704–3709

Au-Catalyzed C.I.R: 1,6-enynes
Single *vs* Double Cleavage; Mechansim

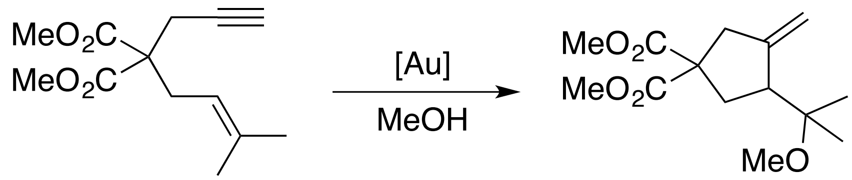


S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics*, **2001**, *20* (17), 3704–3709

Au-Catalyzed C.I.R.; 1,6-enynes
5-*exo* Pathway; Alkoxycyclization

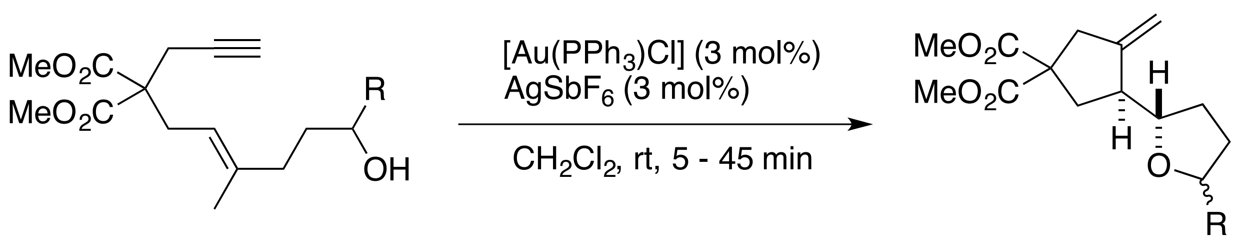
b UNIVERSITÄT BERN

- **Intermolecular** alkoxycyclization of enynes



[Au(PPh_3)Me] (1 mol%), TFA (2 mol%), rt — 82%
[Au(PPh_3)(NTf_2)] (0.1-1 mol%), rt — 77-94%

- **Intramolecular** alkoxycyclization of enynes



60-85% (1:1)

R = H; Me; *t*Bu; $CH=CH_2$; Ph; $C(OH)Me_2$

V. Michelet, P. Y. Toullec, J.-P. Genet, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315
C. Nieto-Oberhuber *et al.*, *Chem. Eur. J.* **2006**, *12*, 1677–1693

Au-Catalyzed C.I.R.; 1,6-enynes
5-*exo* Pathway; Ketocylization

b
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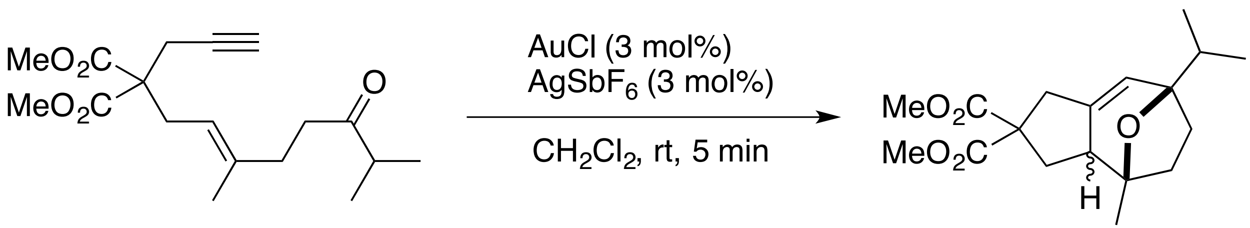
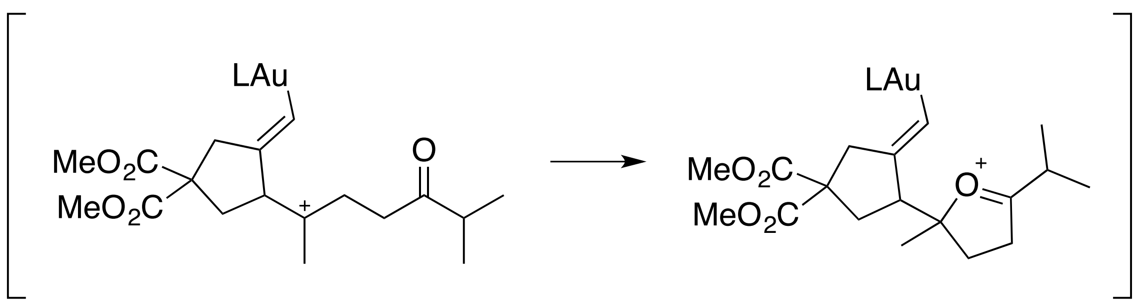
BERN

- **Intermolecular** ketocyclization of enynes



84%



- Reaction works as well with **epoxides**
- Many different catalysts work

Au-Catalyzed C.I.R: 1,6-enynes
Cyclopropanation; Conformation of *c*Pr-Carbenoid

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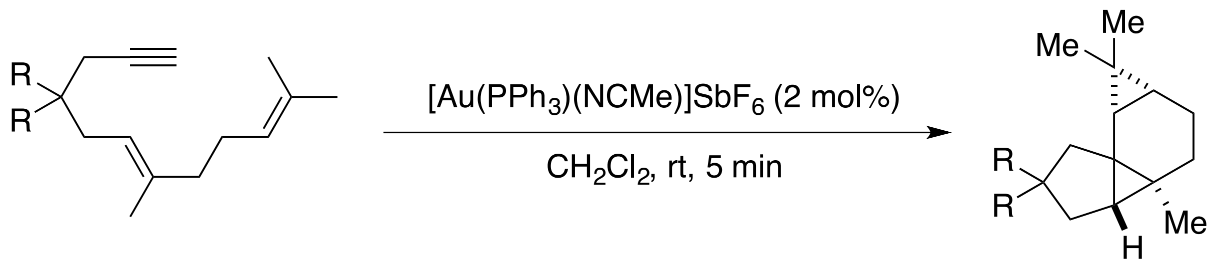
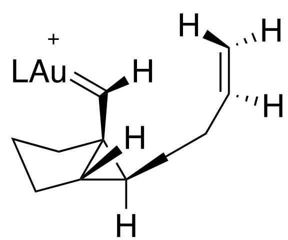
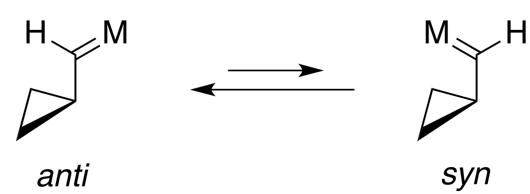
- Trapping of the intermediate carbene



R = CO_2Me (**98%**)
R = SO_2Ph (**quant.**)
R = CH_2OAc (**96%**)

- Cyclopropanes have wrong relative stereochemistry (unnatural)

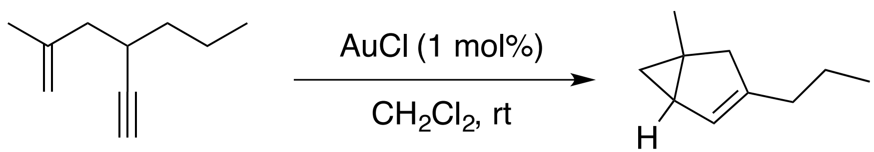




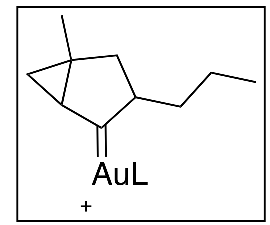
Au-Catalyzed C.I.R: 1,5-enynes
Cyclopropanation; Cyclohexadienes

b UNIVERSITÄT BERN

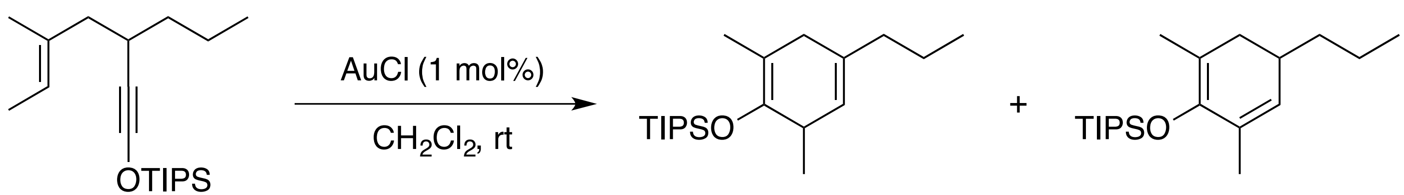
- Preparation of **bicyclo[3.1.0]hexenes**



74%



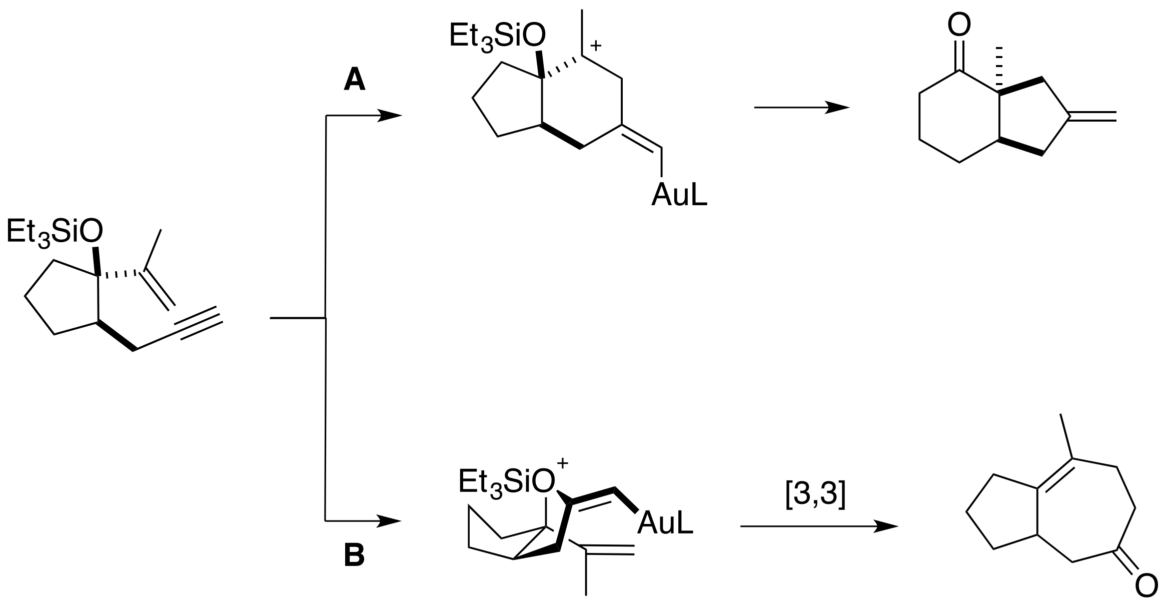
- Preparation of **cyclohexadienes** (from silyloxylalkynes)



99% (3:1)

Au-Catalyzed C.I.R: 1,6-enynes
Effect of Ligand (Electron-Density)

- Electron rich (**A**) vs electron poor (**B**)



A:[(t-Bu)$_2$P(o-biphenyl)]AuCl (10 mol%), AgSbF$_6$ (5 mol%)
i-PrOH, CH$_2$Cl$_2$, **88% (19:1)**
B: (C$_6$F$_5$)$_3$AuCl (10 mol%), AgSbF$_6$ (5 mol%)
i-PrOH, CH$_2$Cl$_2$, **83% (1:8)**

B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605–2607

Au-Catalyzed C.I.R: 1,6-enynes
Ring Expansion; Heteroatom Assisted 1,2-shift

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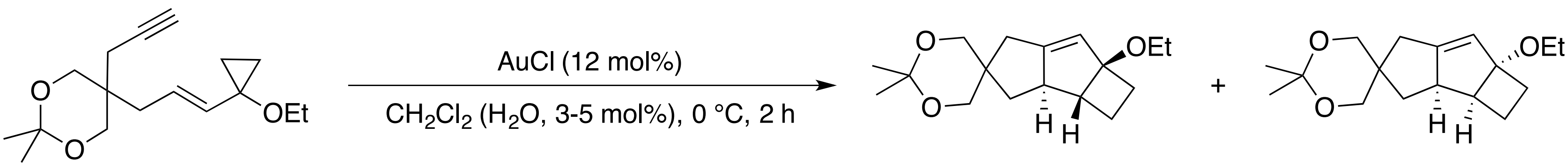
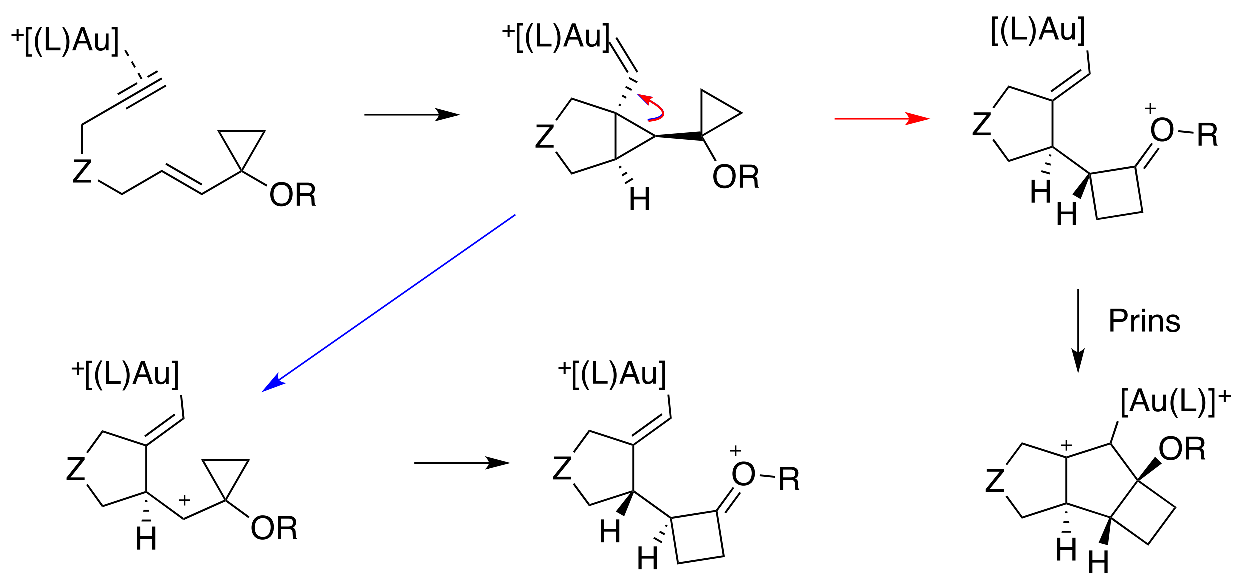
- Starting from cyclopropyl enynes



91% (12:1)



E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455.

Au-Catalyzed C.I.R: 1,6-enynes
Total Synthesis; Heteroatom-Substituted Alkenes

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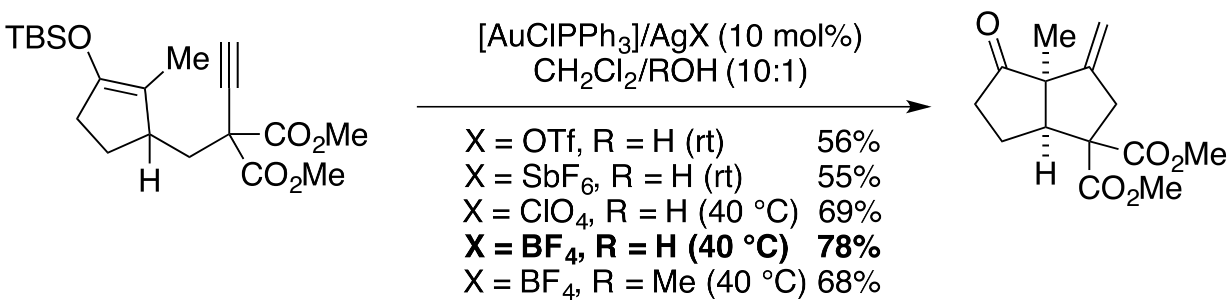
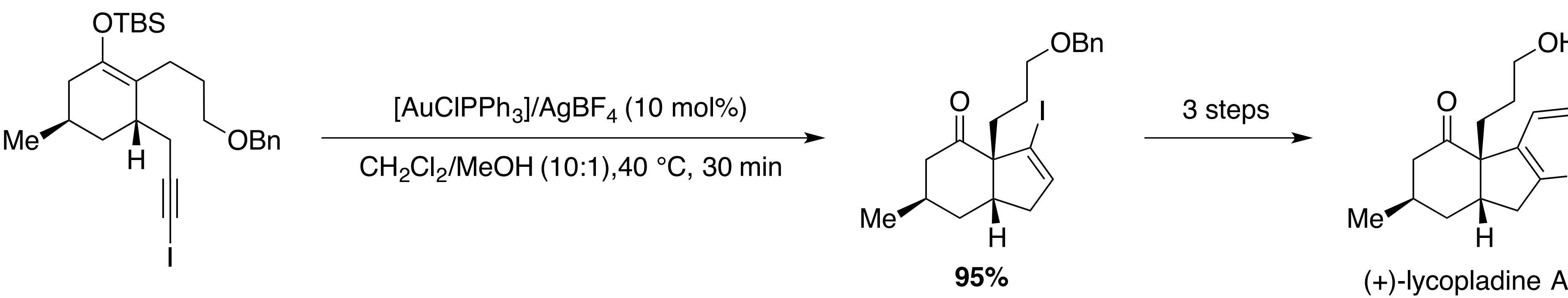
- Formation of an all-carbon 4° stereogenic center



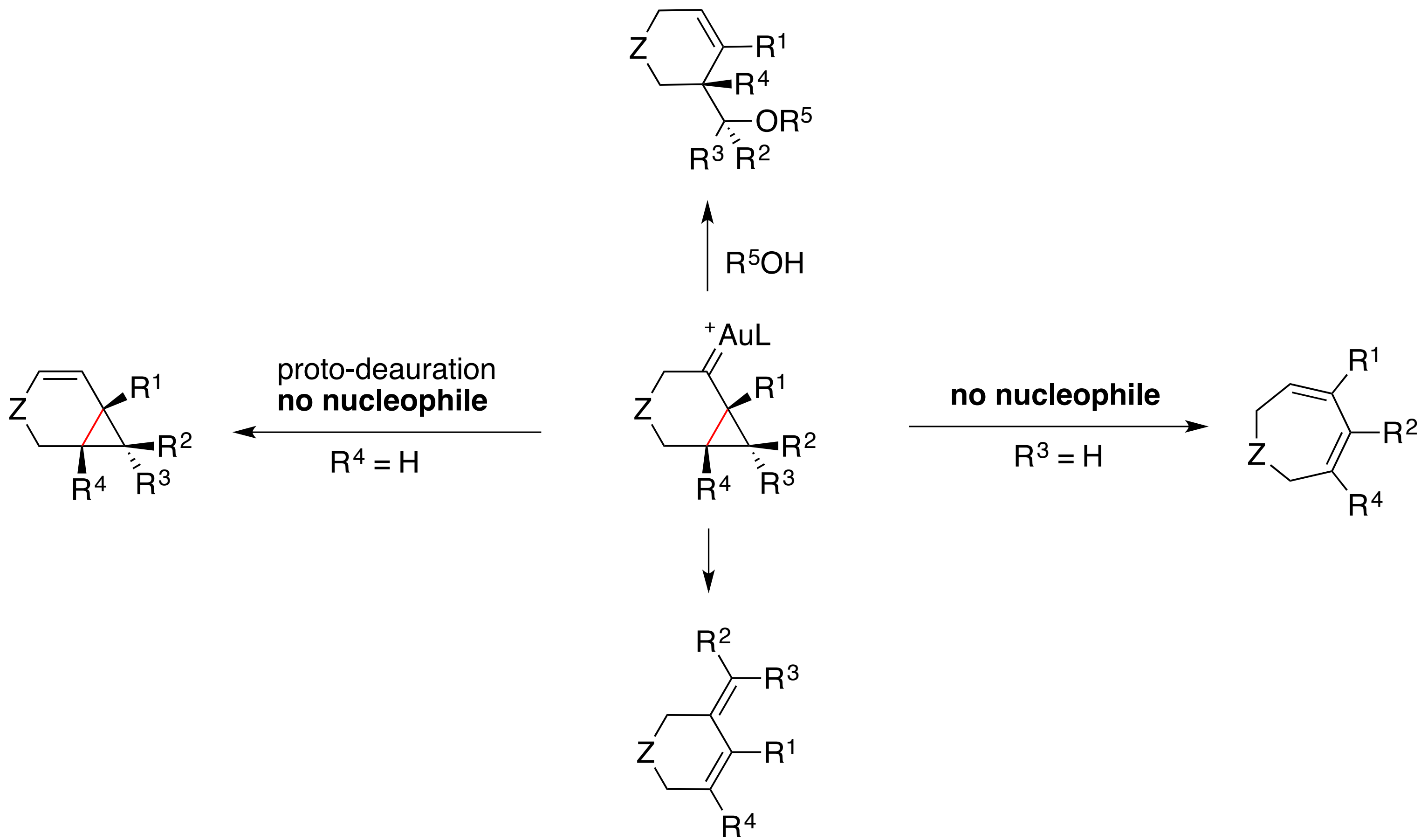
- Application to the synthesis of (+)-lycopladine A



S. T. Staben *et al.*, *Angew. Chem. Int. Ed.* **2006**, *45*, 5991–5994

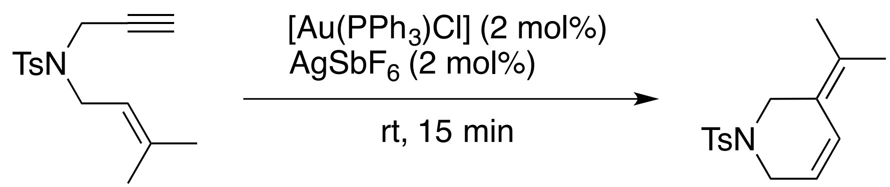
Au-Catalyzed C.I. Reactions
6-*endo* Pathway

- *6-endo-dig* cyclization (**TRENDS**)



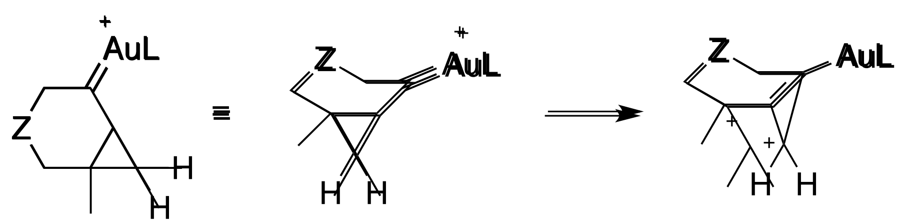
Au-Catalyzed C.I. Reactions
6-*endo* Pathway; Influence of Nucleophile + Tether

- In absence of a nucleophile and Z = O, NTs (*6-endo-dig*)



96%

- Initially proposed mechanism / **Revised Mechanism**



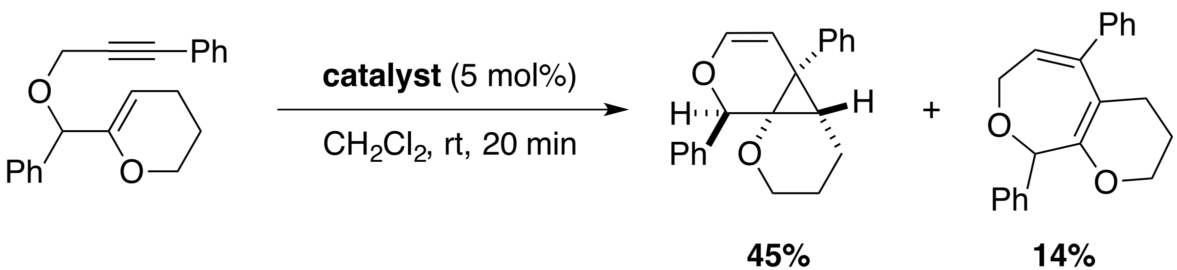
- Mechanism can't explain formation of **A**

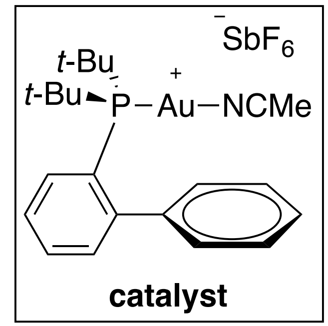
A **B**

93% (1:2.4)

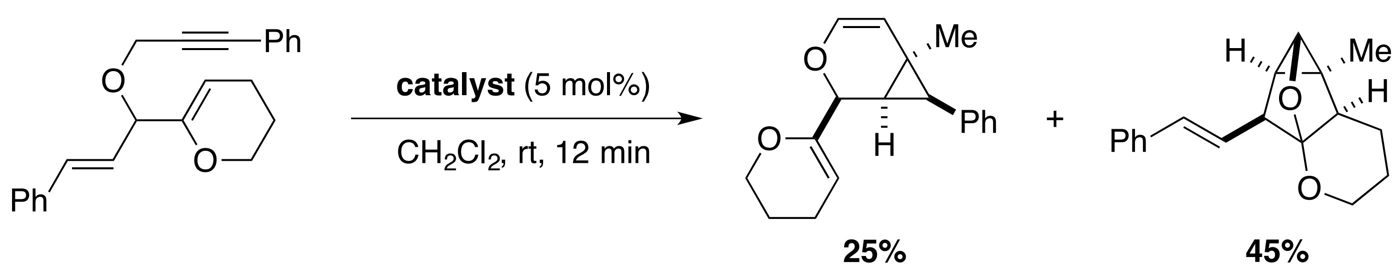
Au-Catalyzed C.I.R: 1,6-enynes
6-*endo* Pathway; Cyclopropanation

- Cyclopropanation of allylic ether





- Modification of the substrate



C. Ferrer, M. Raducan, C. Nevado, C. K. Claviere, A. M. Echavarren, *Tetrahedron* **2007**, *63*, 6306–6316

Au-Catalyzed C.I.R: 1,6-enynes
6-*endo* Pathway; Macrocycles; Polycyclization

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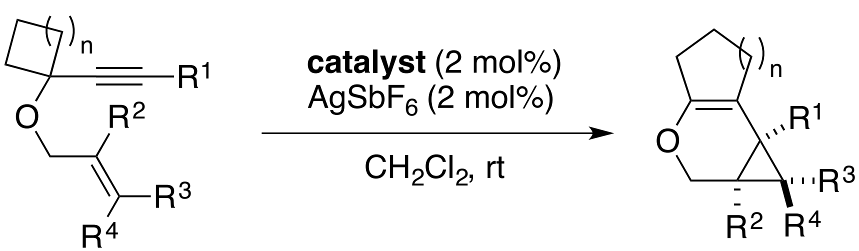
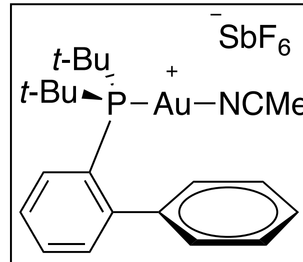
- Route to macrocycles (1,2-alkyl shift)

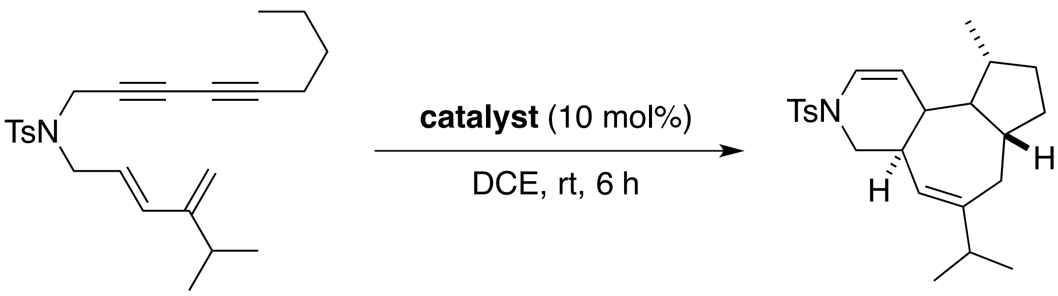


15-98%

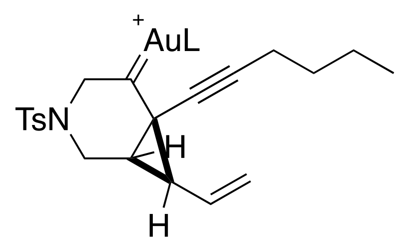


catalyst

- Tandem Cyclopropanation/Cope Rearrangement/C–H activation



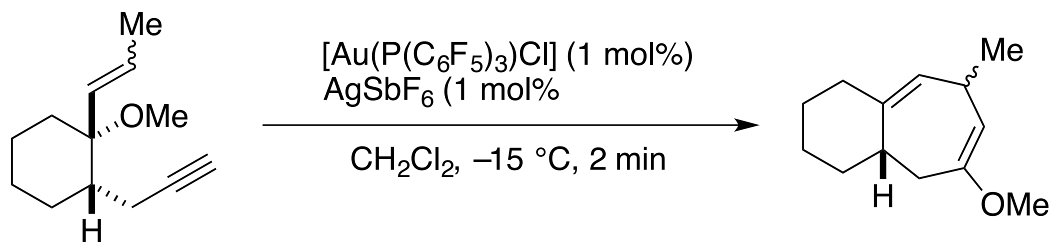
94% (10:1)



A. Simonneau *et al.*, *Chem. Cat. Chem* **2012**, *5*, 1096–1099
P.-J. Cai, Y. Wang, C.-H. Liu, Z.-X. Yu, *Org. Lett.* **2014**, *16*, 5898–5901

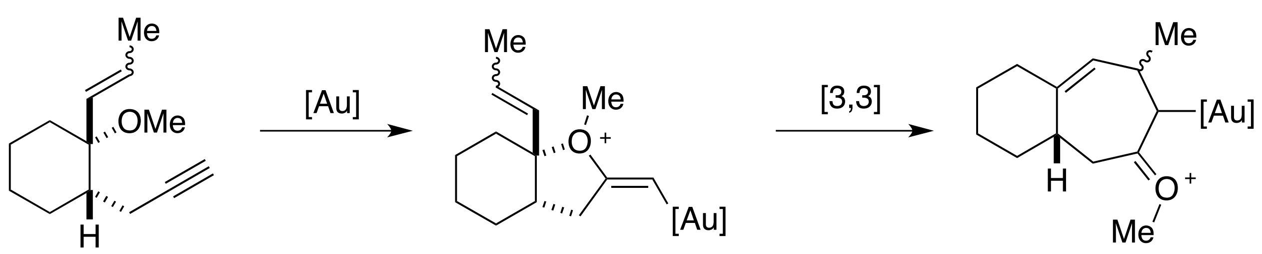
Au-Catalyzed C.I.R: 1,6-enynes
Selected Examples; Alkoxycyclization, [3,3]

- Generation of 1,4-Cycloheptadienes



81% (after hydrolysis)

- Formation via [3,3]-sigmatropic rearrangement



H. J. Bae *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 2263–2266

Au-Catalyzed C.I.R: 1,6-enynes
Total Synthesis

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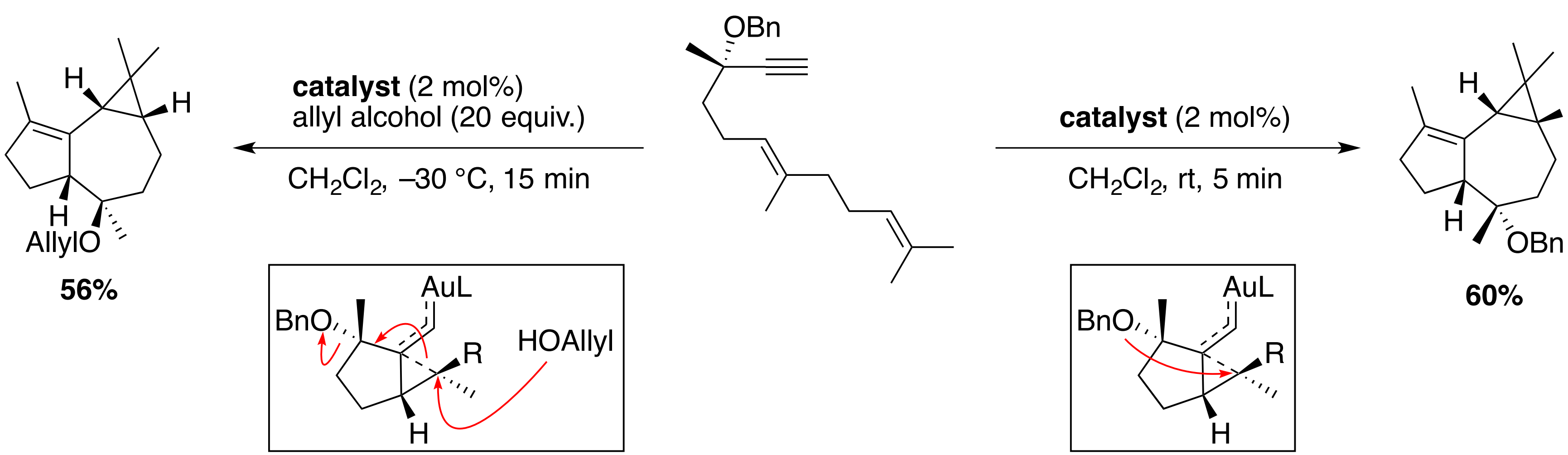
- Towards **ventricosene**, 1,2-alkyl shift

ventricosene

- Towards Aromadendrane sesquiterpenes (artificial cyclase)



S. G. Sethofer, S. T. Staben, O. Y. Hung, F. D. Toste, *Org. Lett.* **2008**, *10*, 4315–4318
J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2014**, *53*, 5896–4899

Conclusion

- Not covered in this Topic Review
  - Most metals
  - Pauson-Khand
  - Conia-Ene
  - Dienes
  - Allenynes
  - [2+2+2]

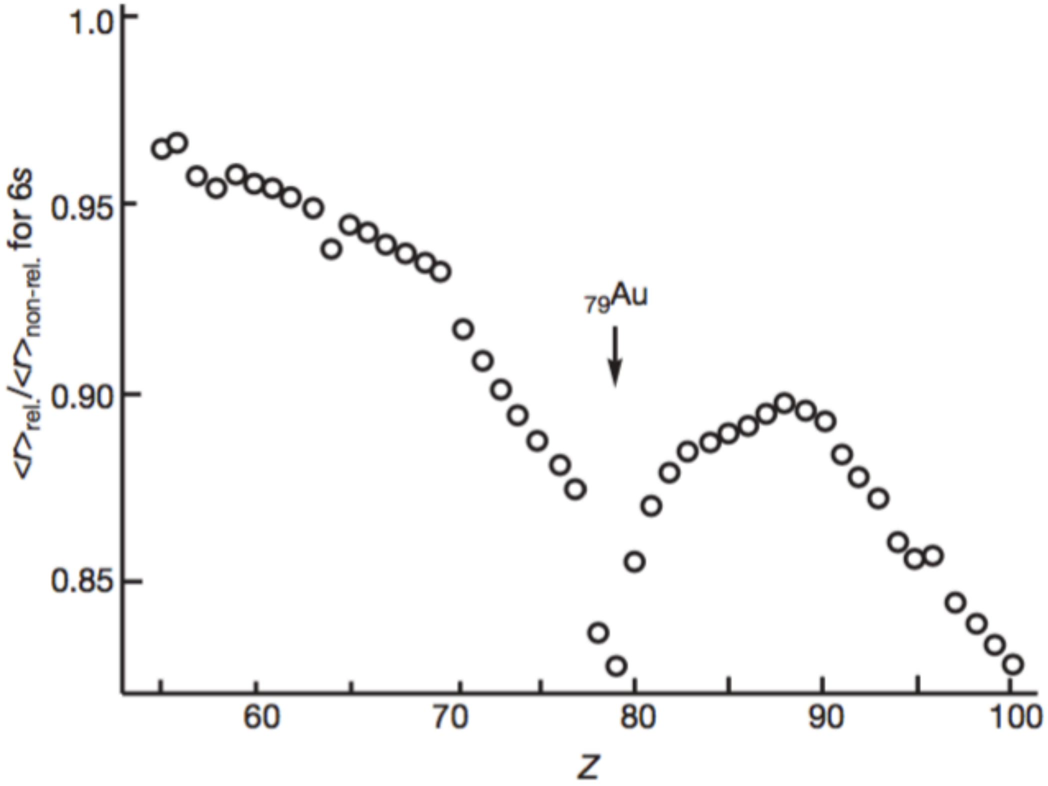
Thank you for your attention!

Backup
Isolobality

Table 1 Isolobality of H^+, R^+, and LAu^+ units at oxygen, nitrogen and carbon centres

H^+	R^+	LAu^+
H_2O	R_2O	$(LAu)_2O$
H_3O^+	R_3O^+	$(LAu)_3O^+$
H_4O^{2+}	R_4O^{2+}	$(LAu)_4O^{2+}$
H_3N	R_3N	$(LAu)_3N$
H_4N^+	R_4N^+	$(LAu)_4N^+$
H_5N^{2+}	R_5N^{2+}	$(LAu)_5N^{2+}$
H_4C	R_4C	$(LAu)_4C$
H_5C^+	R_5C^+	$(LAu)_5C^+$
H_6C^{2+}	R_6C^{2+}	$(LAu)_6C^{2+}$

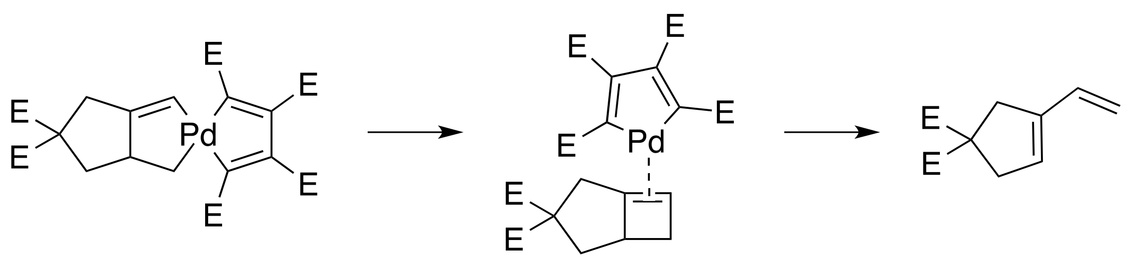
Backup
Orbital Contraction



- Orbital contraction
- Colour of Gold

Backup
Proposed Mechanism for unexpected Product (Trost)

- Reductive Elimination (Metathesis Product)



Backup
Mechansim; Silyloxylalkynes, 1,5-enynes

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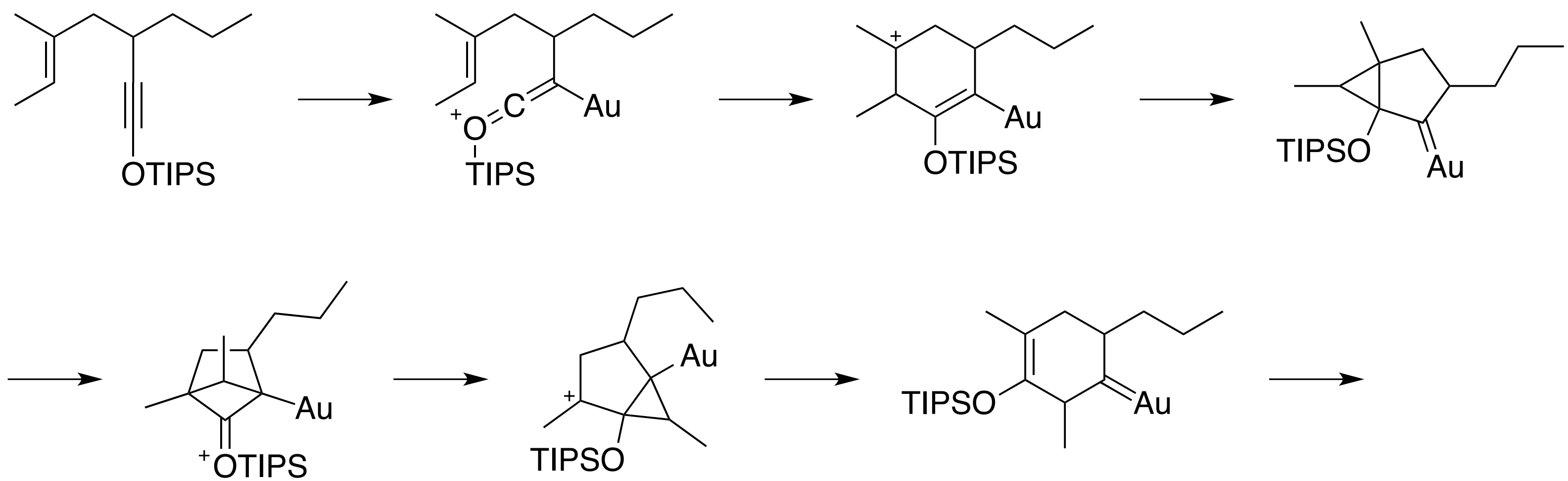
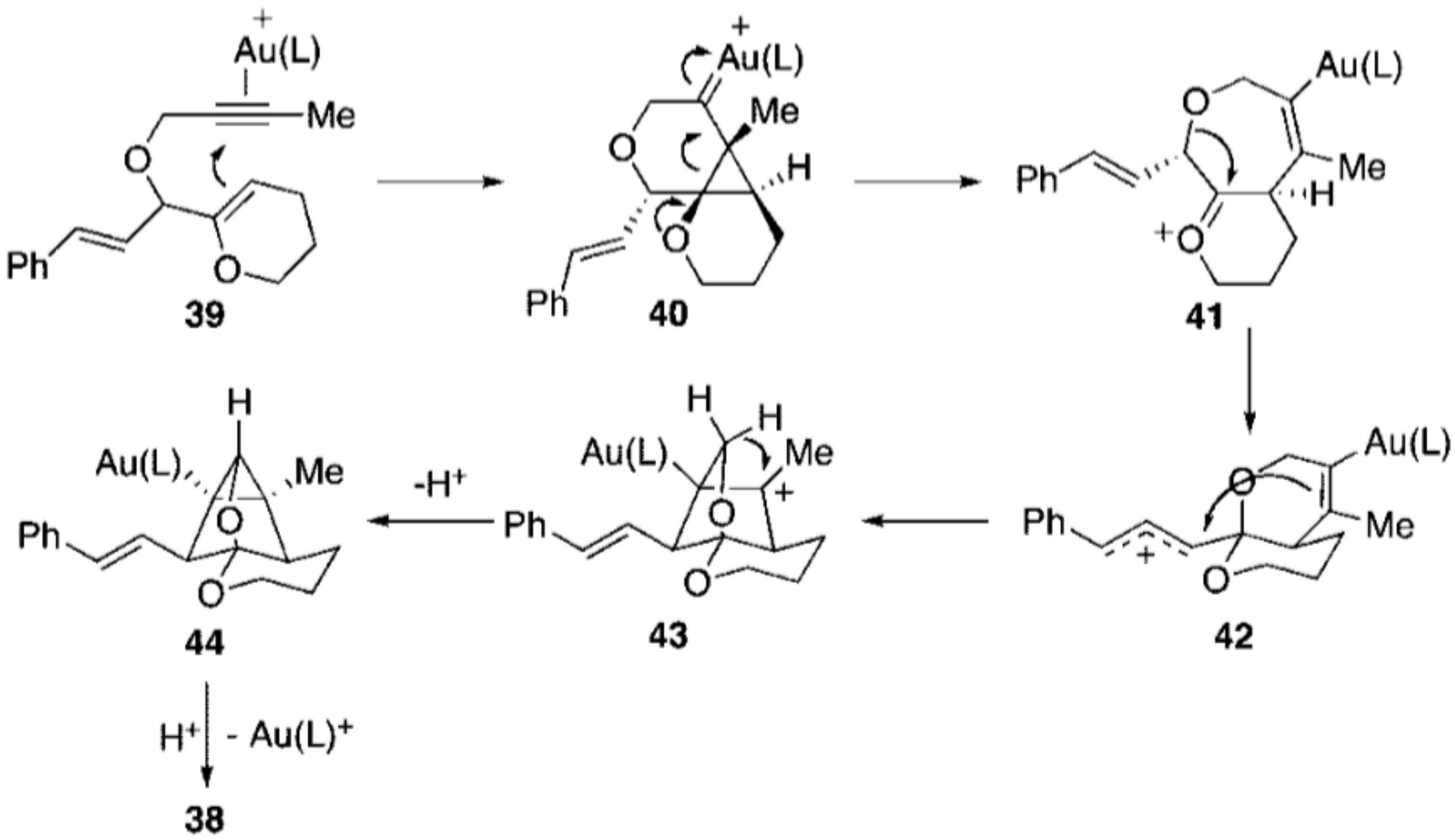


J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710

Backup
Mechansim; 6-endo, allylic ether

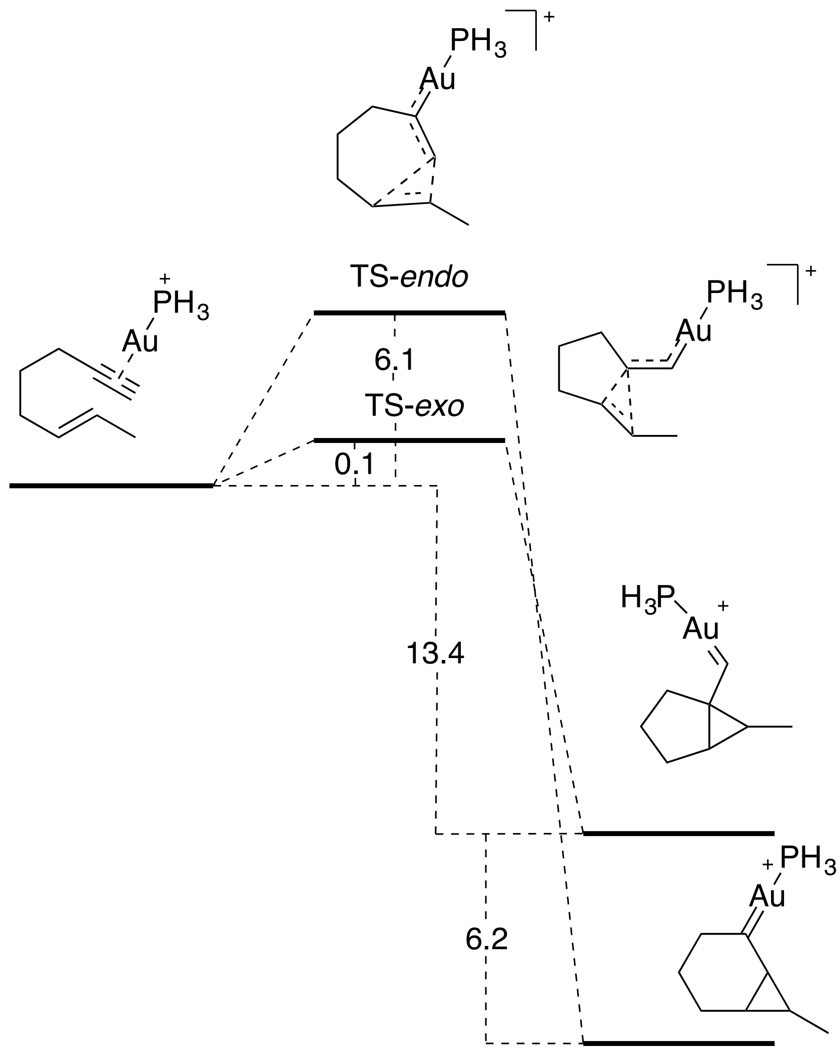


J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710

Backup

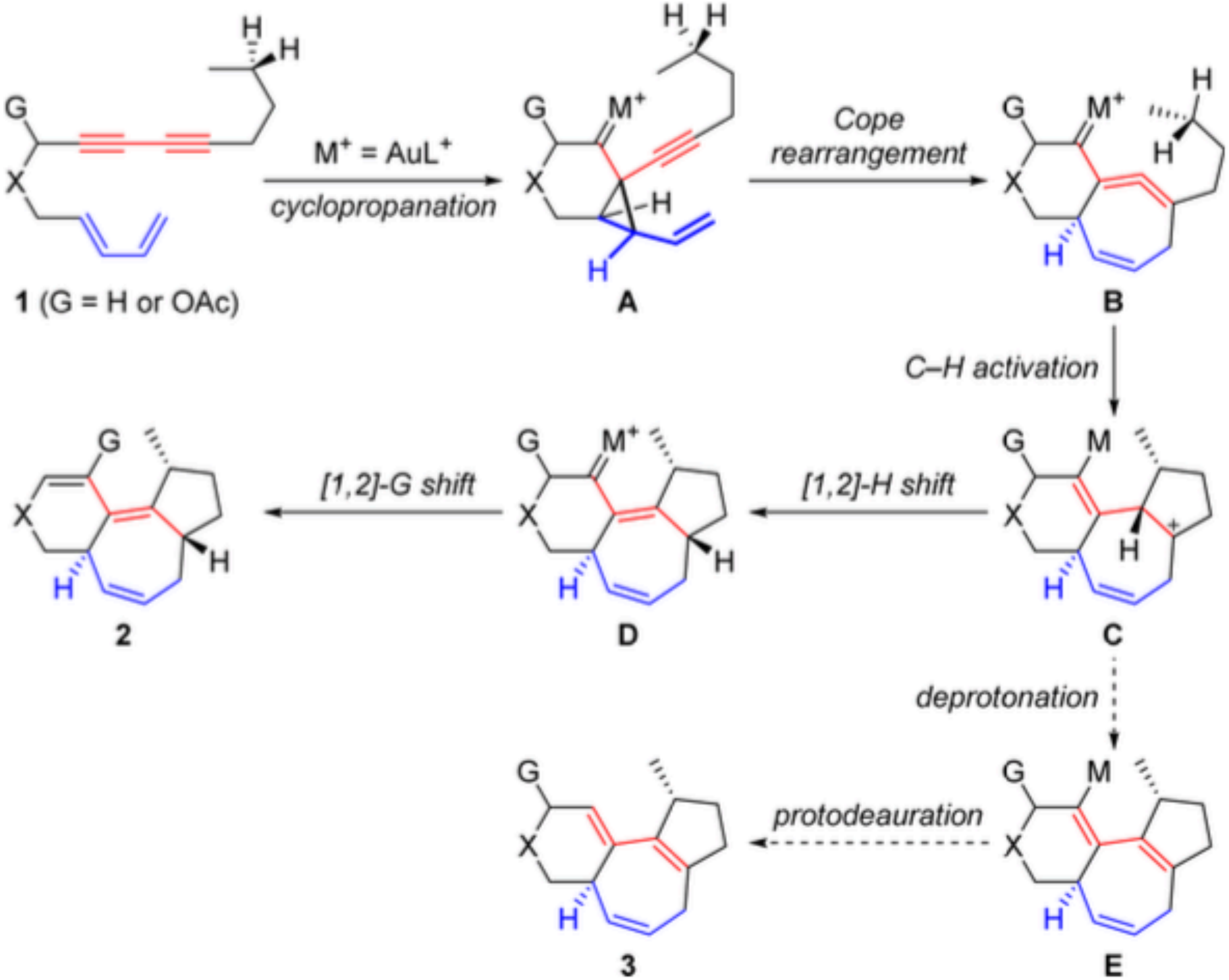
endo- vs *exo*-Cyclization; DFT calculations

- Very reactive propyne-metal complex (compared to Pd(II), Pt(II), and Au(III))
- Highly polarized (η^1-alkyne)gold complex
- 5-exo-dig cyclization favoured
- Comparison to Pt(II): E_a(*exo*) = 10.3, E_a(*endo*) = 11.2 kcal mol^{-1}



C. Nieto-Oberhuber *et. al.*, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406

Backup
6-endo Pathway; Tandem



P-.J. Cai, Y. Wang, C.-H. Liu, Z.-X. Yu, *Org. Lett.* **2014**, *16*, 5898–5901

Backup
Au(I) Catalysts & Precursors

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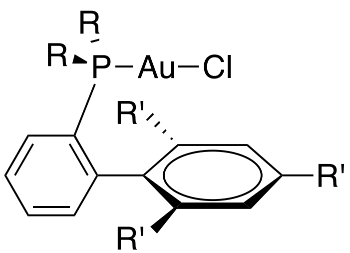
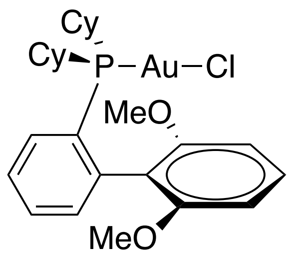
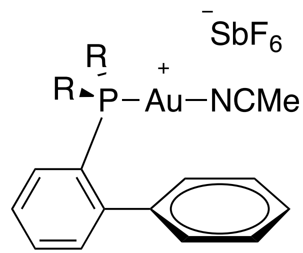
- **A-D** very active with Ag(I) salt
- **E**, **F**, **I** → [Au^+] (stable crystalline solids)



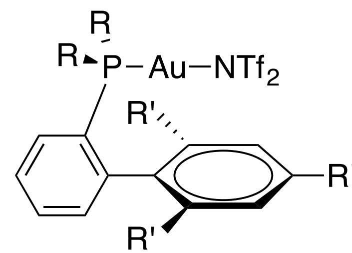
A: R = Cy, R' = H
B: R = *t*-Bu, R' = H
C: R = Cy, R = *i*-Pr



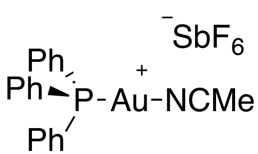
D



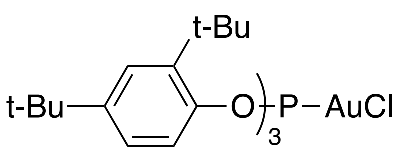
E: R = *t*-Bu
F: R = Cy



G: R = *t*-Bu, R' = H
H: R = Cy, R' = *i*-Pr



I



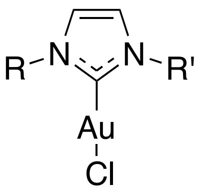
J

- **G+H** weakly coordinating $^{-}NTf_2$ (cleaner reactions in absence of Ag(I))
- **J** highly electrophilic catalyst

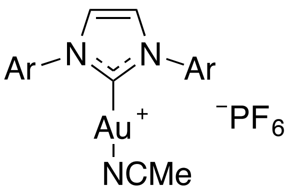
E. Jimenez-Nunez, A. M. Echavarren, *Chem. Rev*. **2008**, *108*, 3326–3350

Backup
Au(I) Catalysts & Precatalysts

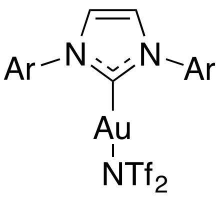
- **K-N** strongly donating NHC
- **O** moderate stability at rt



K: R = R' = 2,4,6-$Me_3C_6H_2$
L: R = Mes, R' = Me
M: R = R' = Me
N: R = R' = 2,6-*i*-$Pr_2C_6H_3$



O: Ar = 2,6-*i*-$Pr_2C_6H_3$



P: Ar = Mes
Q: Ar = 2,6-*i*-$Pr_2C_6H_3$