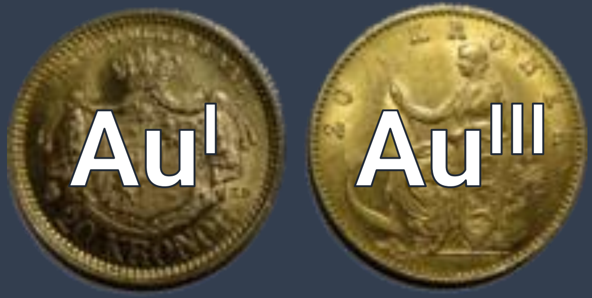
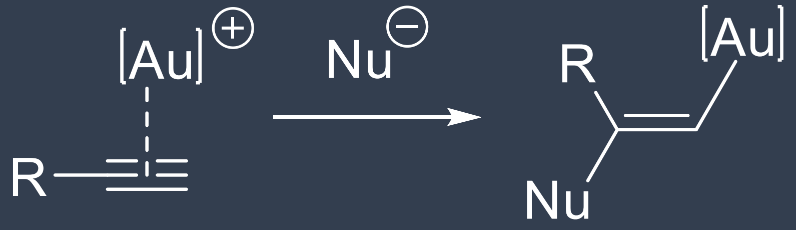
Homogeneous Au(I)/Au(III) Catalysis and Rationalizing Their Reactivity



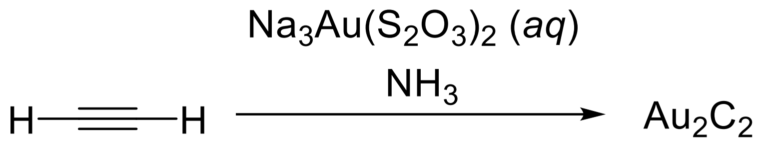
Blake Ocampo

May 24, 2022



The First Published Organogold Compounds

The First Isolated Organogold(I) Compound (1900)



"When thoroughly dried, the carbide of gold is highly explosive, either upon rapid heating, by a blow or even with a camel's hair brush."

The First Isolated Organogold(III) Compound

$$AuBr_3 \xrightarrow[Et_2O\ (0.33\ M)]{EtMgBr\ (2\ eq)} (Et)_2AuBr \xrightarrow{Br_2} EtAuBr_2$$

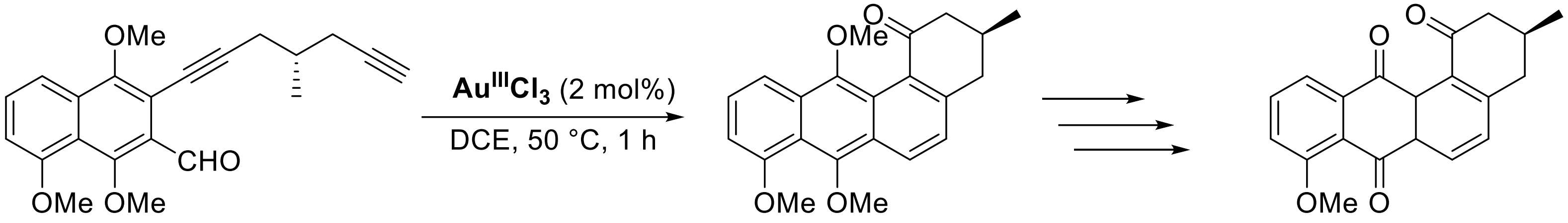
- $(Et)_2AuBr$ forms long, colorless needles, while $EtAuBr_2$ dark ruby-red, doubly-refracting prisms with square ends

Curiously, $(Et)_2AuBr$ was very resistant to β-hydride elimination

Watters *et* al. J. *Am. Chem. Soc.* **1900**, 22, 2, 108-111
Gibson *et al. J. Chem. Soc. Trans* **1907**, 91, 2061-2066

Gold Applications as a Tool for Synthetic Chemistry

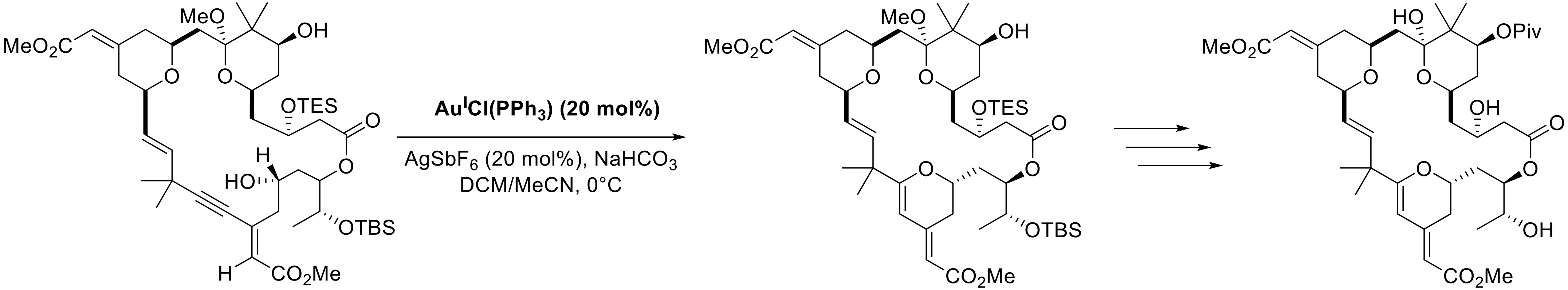
Yamamoto's Synthesis of (+)-rubiginone B2 with Au(III)



84% yield

(+)-rubiginone B2

Trost and Dong's Synthesis of Bryostatin 16 with Au(I)



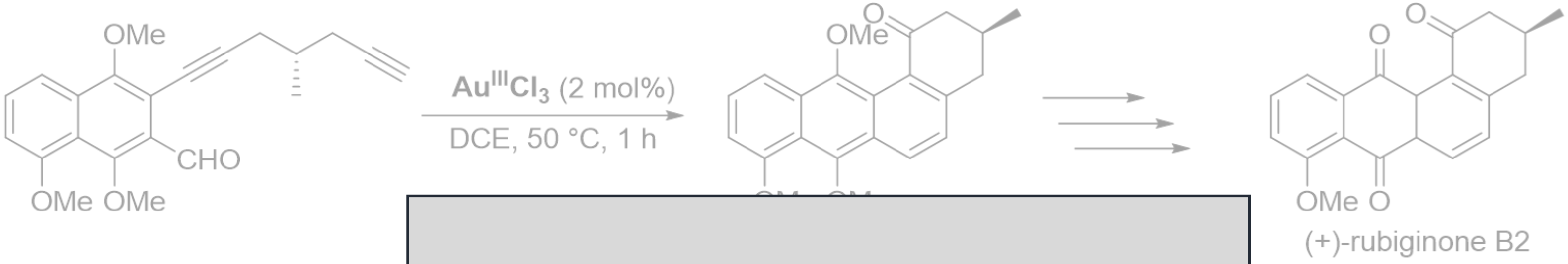
73% yield

Bryostatin 16

Yamomoto *et al.* *J. Org. Chem.* 2005, 70, 8977-8981
Trost *et* al. *Nature* 2008, 456, 485-488

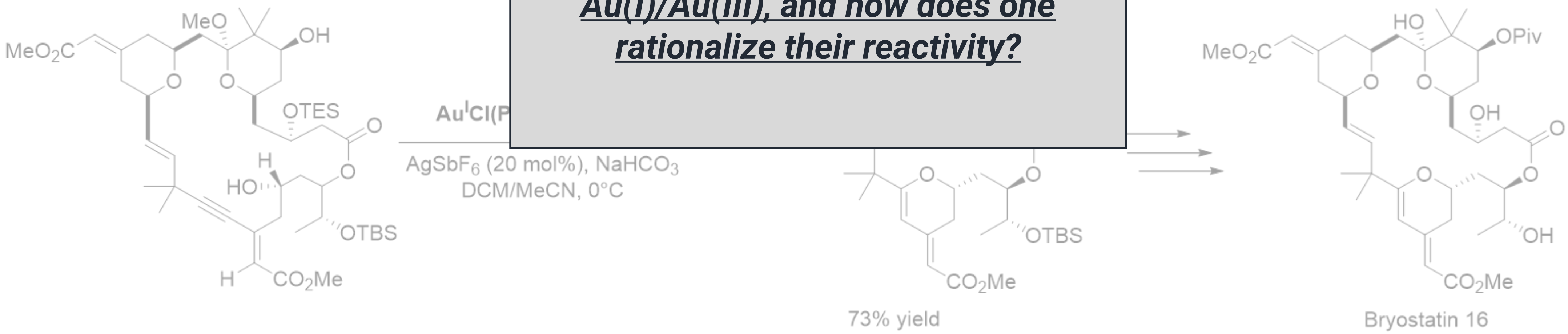
Gold Applications as a Tool for Synthetic Chemistry

Yamamoto's Synthesis of (+)-rubiginone B2 with Au(III)



Trost and Dong's Synthesis of Bryo

What is the difference between Au(I)/Au(III), and how does one rationalize their reactivity?



J. Org. Chem. 2005, 70, 8977-8981
Nature 2008, 456, 485-488

What's So Special About Gold?

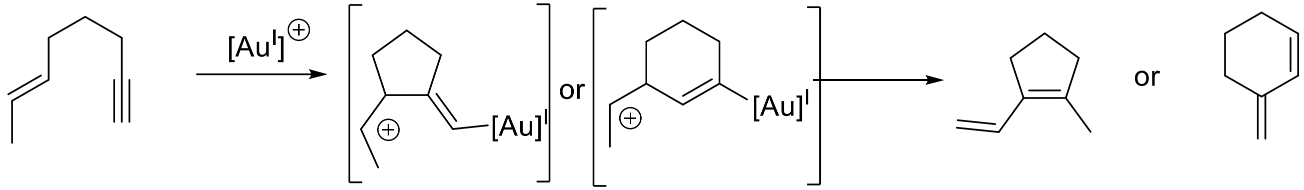
Unusually High Reduction Potential!

Reduction of Metals	Reduction Potential
$Au^{III} + 2\,e^- \rightarrow Au^I$	1.36 V
$Au^{III} + 3\,e^- \rightarrow Au^0$	1.52 V
$Au^I + 1\,e^- \rightarrow Au^0$	1.82 V
$Pd^{II} + 2e^- \rightarrow Pd^0$	0.91 V
$Pt^{II} + 2\,e^- \rightarrow Pt^0$	1.19 V

The Most Electronegative Metal!

26 Fe Iron 1.83	27 Co Cobalt 1.88	28 Ni Nickel 1.91	29 Cu Copper 1.90	30 Zn Zinc 1.65
44 Ru Ruthenium 2.2	45 Rh Rhodium 2.28	46 Pd Palladium 2.20	47 Ag Silver 1.93	48 Cd Cadmium 1.69
76 Os Osmium 2.2	77 Ir Iridium 2.20	78 Pt Platinum 2.28	79 Au Gold 2.54	80 Hg Mercury 2.0

Gold(I) Avoids Changes in Oxidation State



- *β-hydride elimination is disfavored in Gold Catalysis*
- *Au is not oxygen or water sensitive*

Gold is Subject to Relativistic Effects

Bochmann *et* al. Chem. *Rev.* **2021**, 121, 14, 8364-8451
Echavarren *et* al. Chem. *Eur. J.* **2006**, 12, 1677-1693
Corma *et* al. Chem. *Rev.* **2011**, 111, 3, 1657−1712

The Relativistic Effects of Gold

What is a relativistic effect?

Arnold Sommerfeld

Hydrogen Emission Spectrum

The spectral line is split as a result of electron spin and orbital angular momentum!

$$\textit{Fine Structure Constant: } \alpha = \frac{e^2}{(4\pi\epsilon_0)\hbar c} \approx \frac{1}{137}$$

$$\textit{The Bohr Radius: } a_0 = \frac{4\pi\epsilon_0\hbar^2}{m_e e^2}$$

$$mass = \frac{m_0}{\sqrt{\left[1-\left(\frac{v}{c}\right)^2\right]}}$$

$$velocity\ of\ 1s\ e^- = Z \rightarrow \frac{\boldsymbol{v}}{\boldsymbol{c}} = \frac{\boldsymbol{Z}}{\boldsymbol{137}}$$

<u>Variables</u>

- ϵ_0 – vacuum permittivity constant
- m_e – mass of an electron
- m_0 – non-relativistic mass
- v – velocity
- c – speed of light
- Z – number of protons

<u>**The mass of an electron increases when the number of protons increases!**</u>

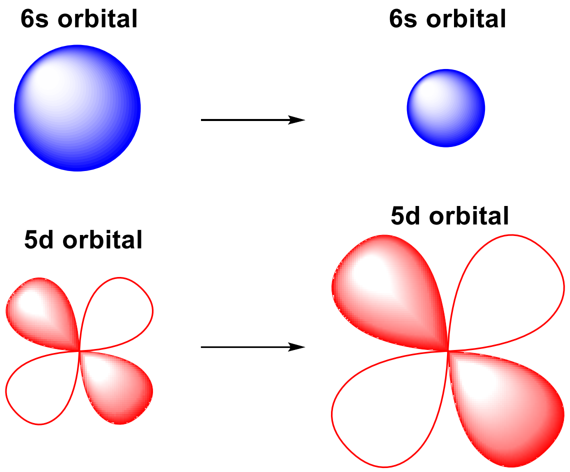
Toste *et al.* *Nature* 2007, 446, 395-403
University of Texas General Chemistry. http://ch301.cm.utexas.edu/atomic/#H-atom/line-spectra.html (accessed May 20, 2022)

Manifestations of Relativistic Effects

Change in relative orbital sizes

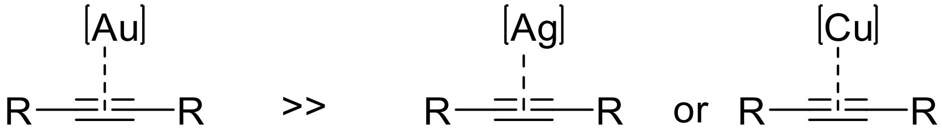
$$a_0 = \frac{4\pi\epsilon_0\hbar^2}{\boxed{m_e}e^2}$$

Non-relativistic

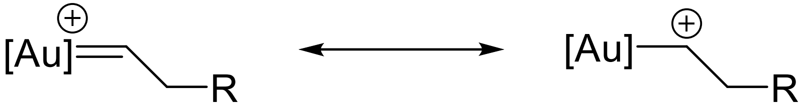


Relativistic

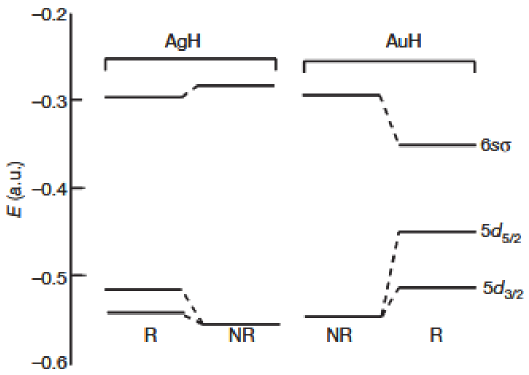
High π-Bond Lewis Acidity



High Potential for Backbonding



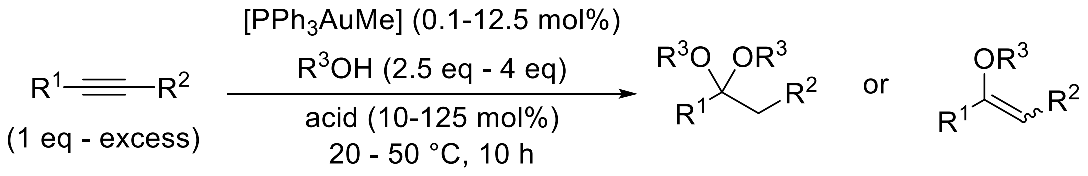
Changes in Band Gap

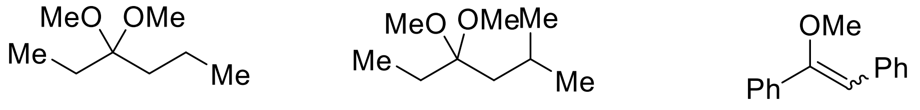


Toste *et al.* *Nature* **2007**, 446, 395-403

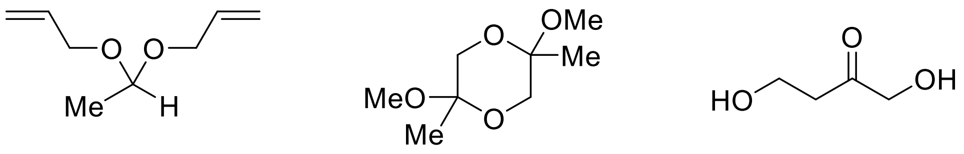
What is the Method of Addition for Au(I)?

Teles Proposes a Cis-Addition Mechanism (1998)



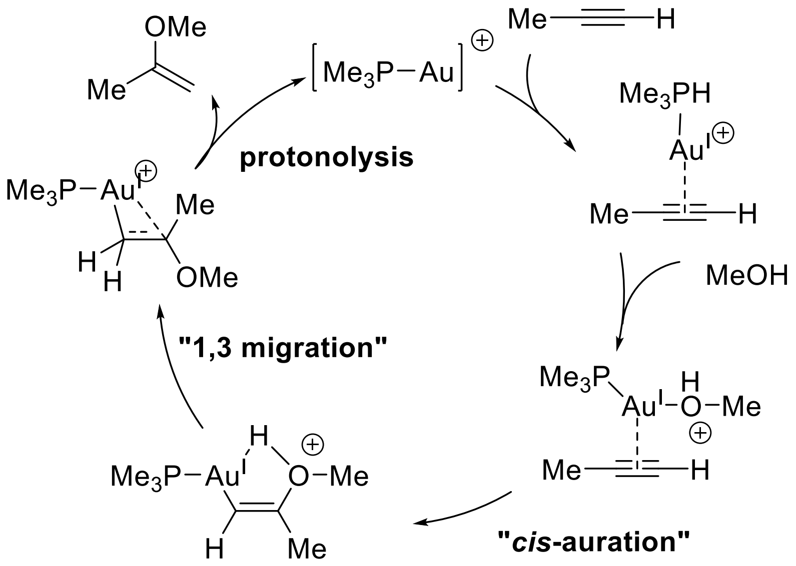


8:1 (*Z*:*E* at low conversion)
2:1 (*Z*:*E* at high conversion)



- Sterics promoted enol ether formation
- Enol ethers form *Z*-isomer selectively

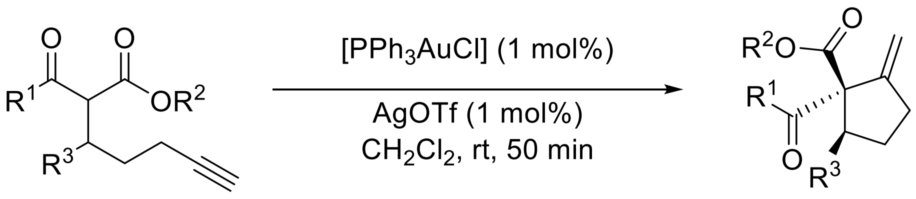
Proposed Catalytic Cycle

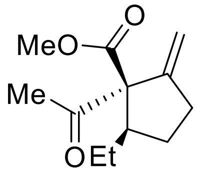


Proposes *cis*-auration due to Z selectivity

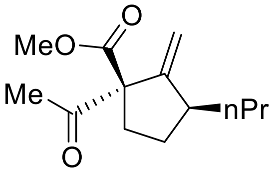
What is the Method of Addition for Au(I)?

Toste Investigates a Gold-Catalyzed Conia-Ene

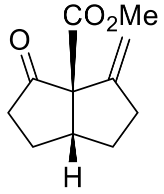




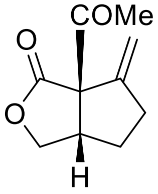
95% yield (17:1 d.r.)



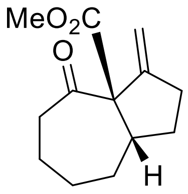
96% yield (2.9:1 d.r.)



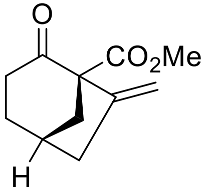
90% yield



80% yield



86% yield

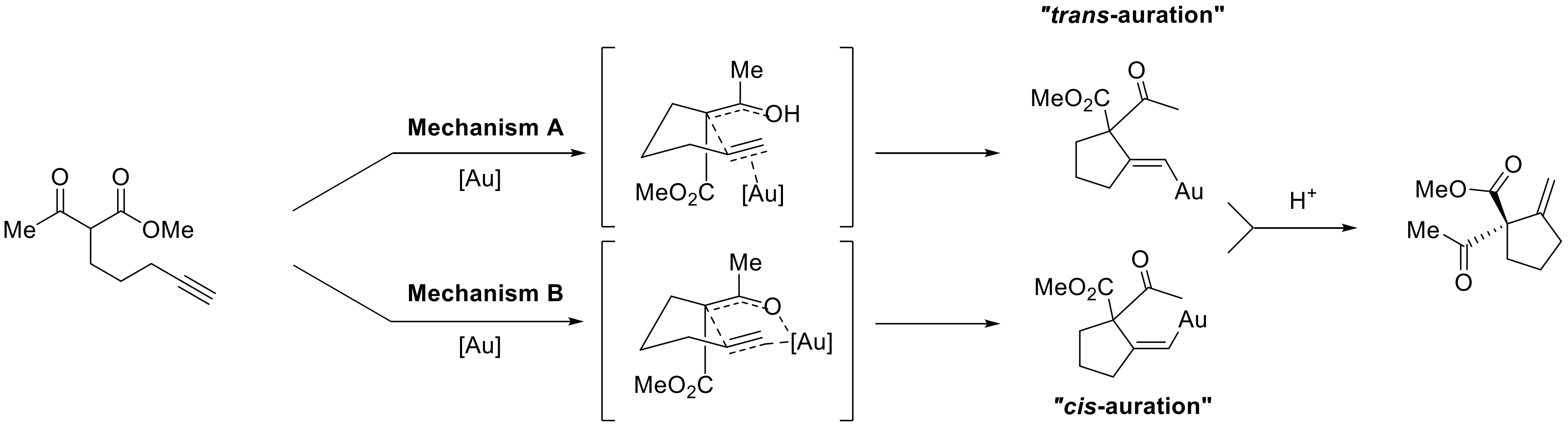


99% yield

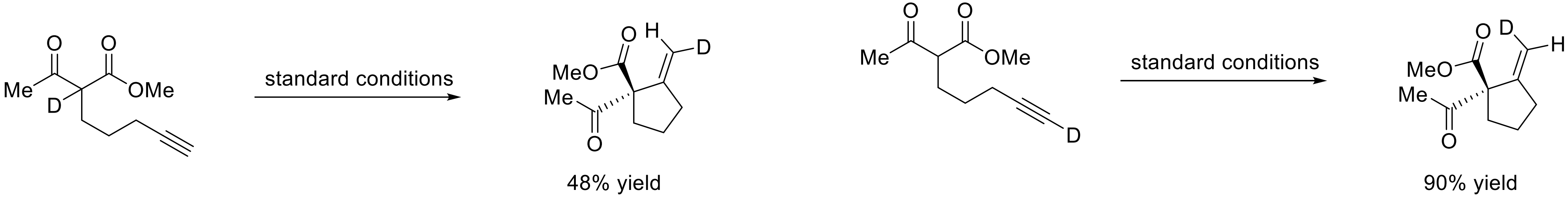
Toste *et al. J. Am. Chem. Soc.* **2004**, 126, 14, 4526−4527

What is the Method of Addition for Au(I)?

Differentiating Two Possible Mechanisms for Addition



Deuterium Labeling Experiments

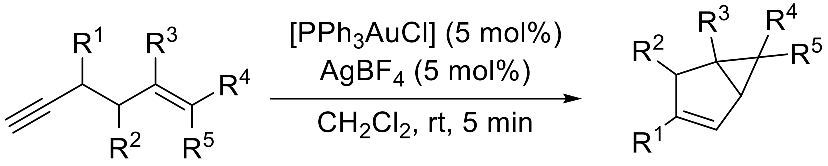


Mechanism A of trans-auration/addition is operative!!

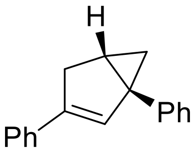
Toste *et al. J. Am. Chem. Soc.* **2004**, 126, 14, 4526–4527

Cycloisomerization of 1,5-Enynes with Au(I)

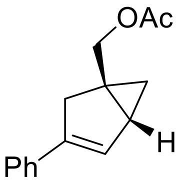
Toste Reports the formation of Bicyclo[3.1.0]hexenes



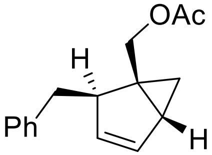
- $PtCl_2$, $PdCl_2$, and $AgBF_4$ gave less than 5% yield
- $AuCl_3$ gave a 50% yield



94% yield

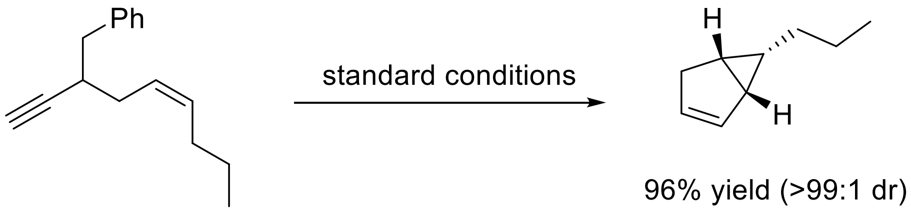


94% yield



82% yield (10:1 dr)

Checking Stereospecificity



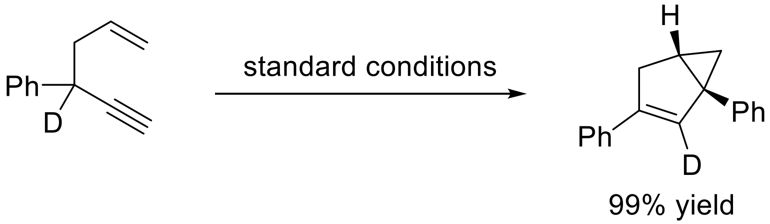
96% yield (>99:1 dr)

98% yield (>99:1 dr)

Toste *et al. J. Am. Chem. Soc.* **2004**, 126, 14, 10858-10859

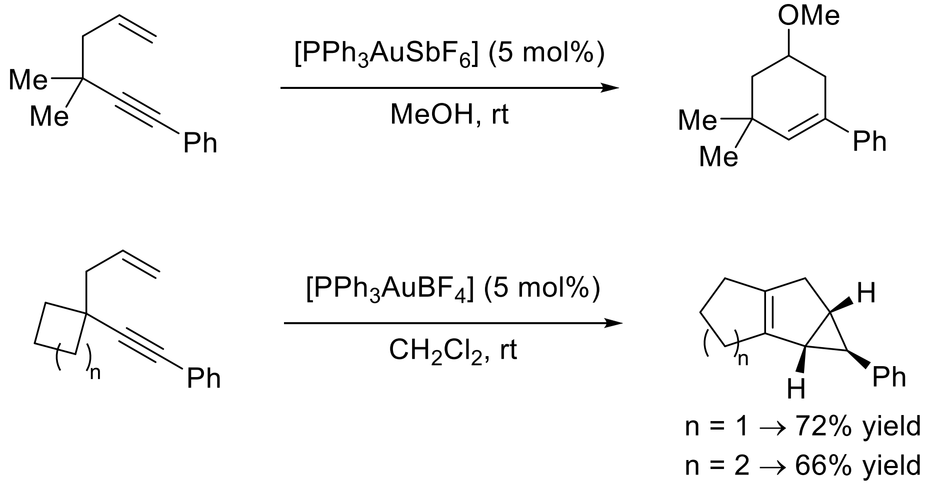
Proposing a Mechanism for Cycloisomerization with Au(I)

Deuterium Labeling Experiment

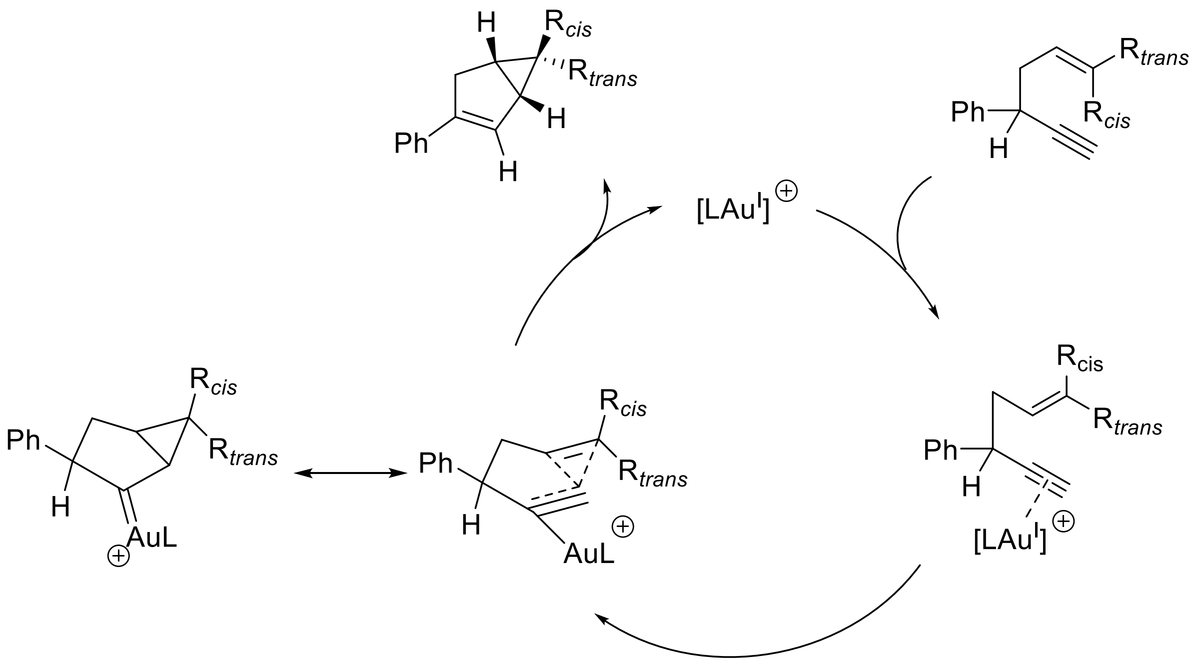


1,2-hydride shift is occurring!

Further Mechanistic Experiments



Proposed Catalytic Cycle

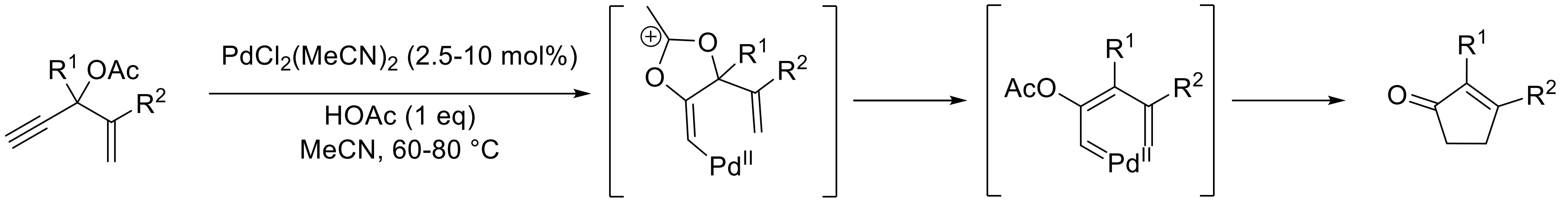


- Strong evidence for cationic intermediate
- Alkyl shifts can occur in the absence of a nucleophile

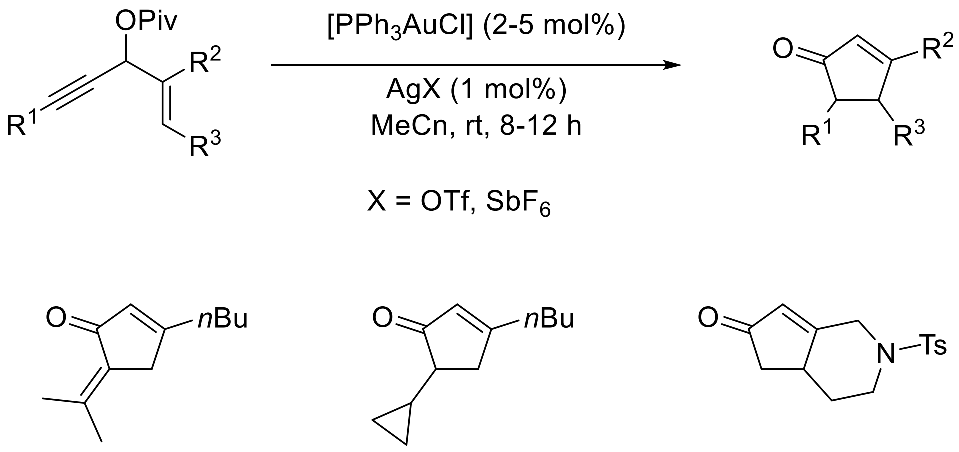
Toste *et al. J. Am. Chem. Soc.* **2004**, 126, 14, 10858-10859

Another Cycloisomerization with Au(I)

Rautenstrauch Rearrangement with Palladium



Toste Utilizes Gold(I) to Catalyze the Rearrangement

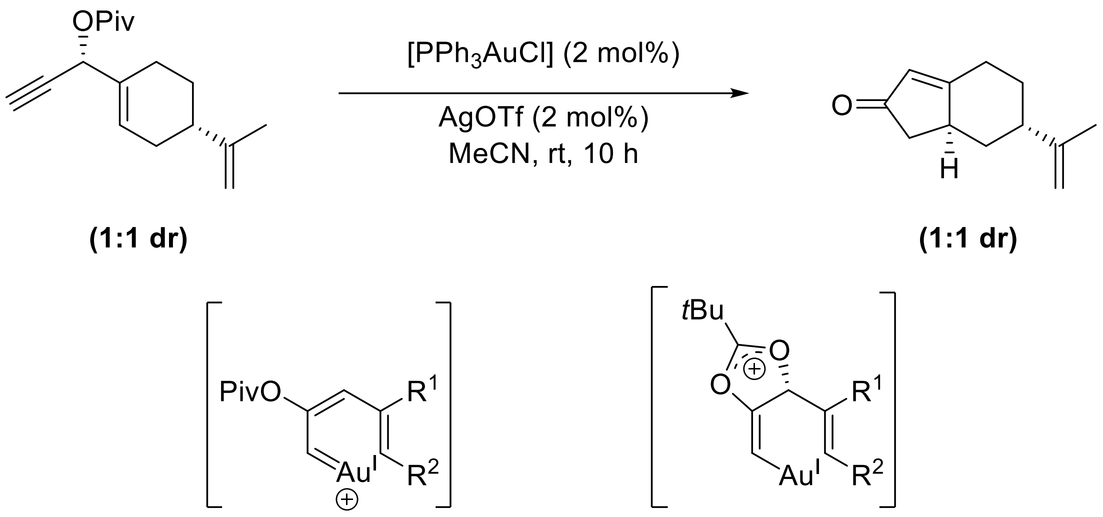


81% yield

85% yield

45% yield

Mechanistically Probing the Cycloisomerization

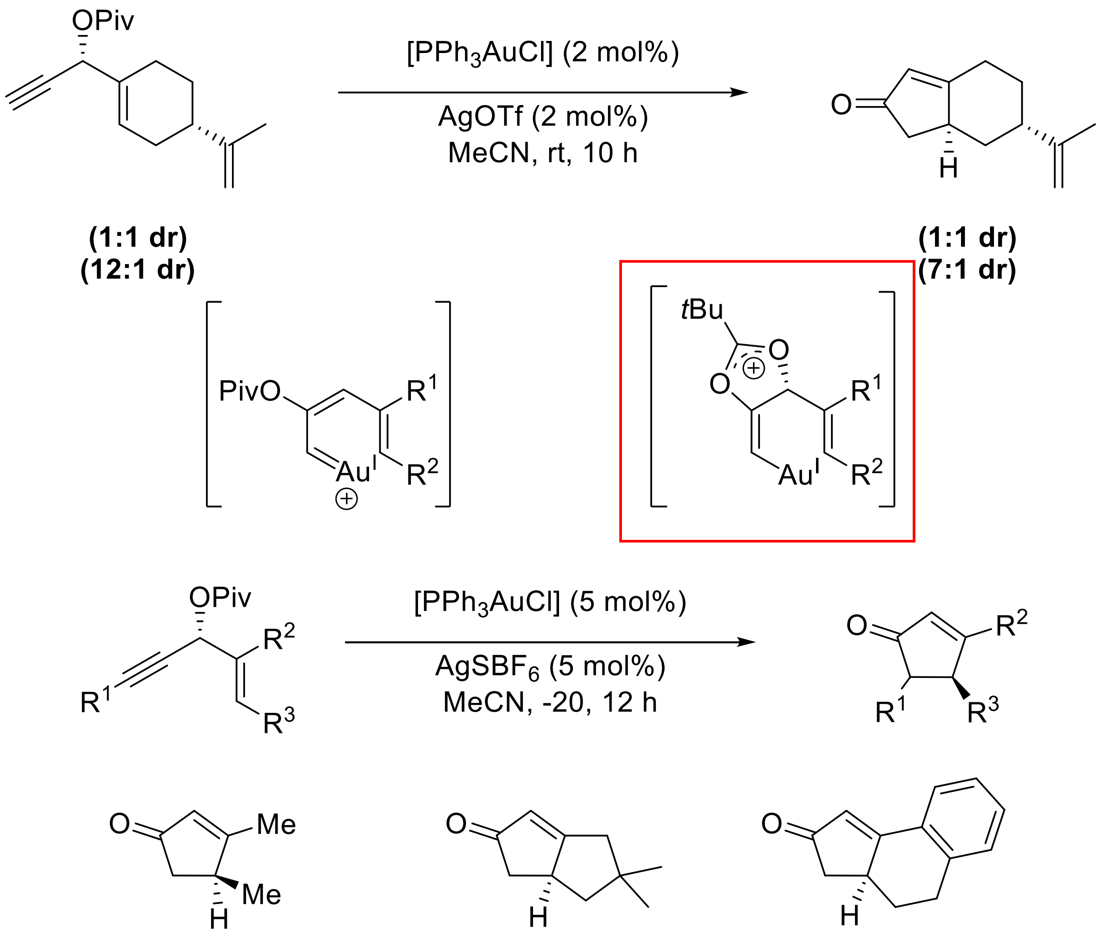


Carbene or cation?

Toste *et al.* *J. Am. Chem. Soc.* **2005**, 127, 5802-5803

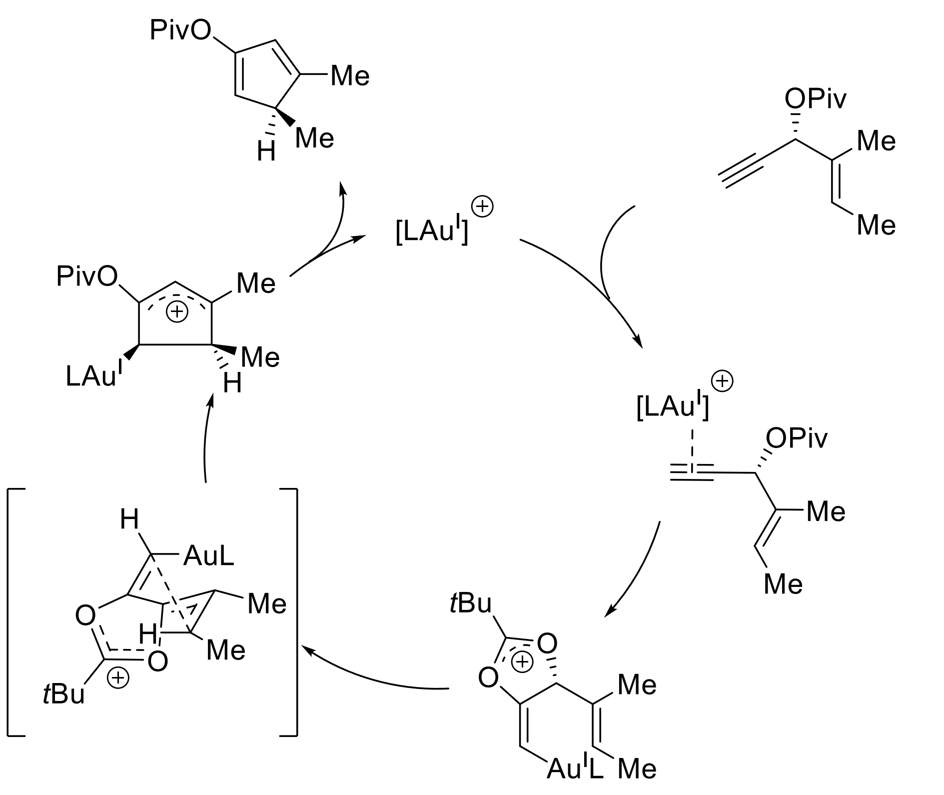
Cycloisomerization with Au(I) Biased Towards a Cation

Mechanistically Probing the Cycloisomerization



84% yield (4.5:1 e.r.) 80% yield (3.3:1 e.r.) 88% yield (>19:1 e.r.)

Proposed Catalytic Cycle

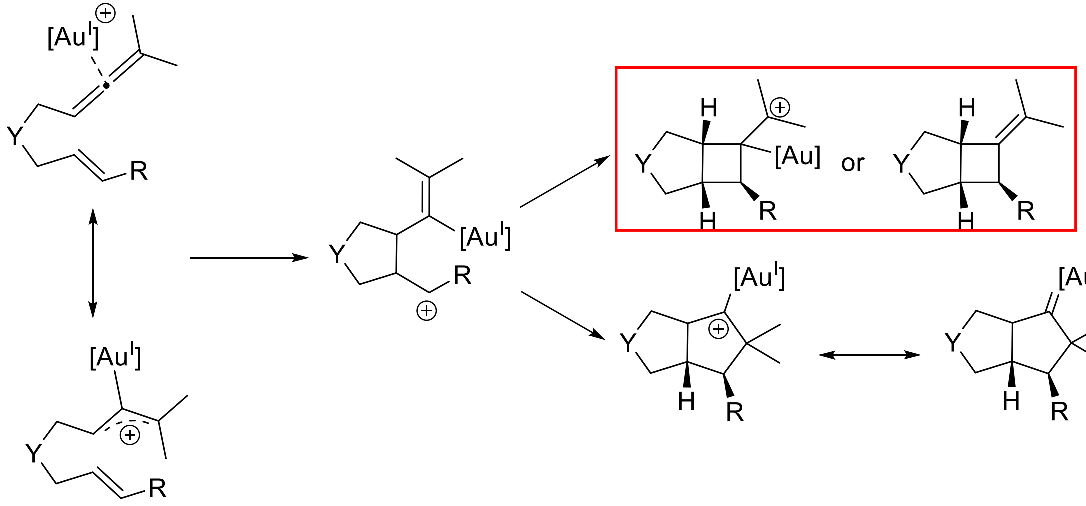


There is transfer of chirality in this transformation!

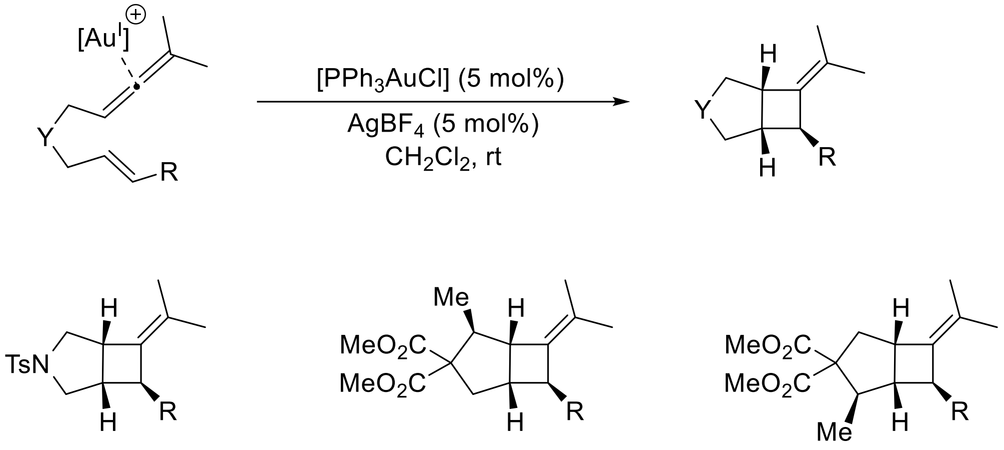
Toste et al. *J. Am. Chem. Soc.* **2005**, 127, 5802-5803

Cycloisomerizations with Allenes Using Au(I)

Toste's Hypothesis for promoting a [2+2]-Cycloaddition



Substrate Scope

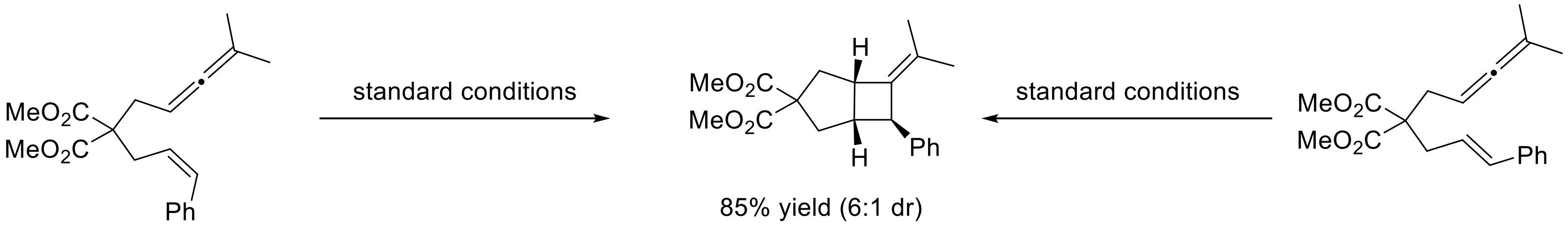


82% yield

84% yield (>19:1 dr)

85% yield (6:1 dr)

Illustrating Stereoconvergence of Alkene

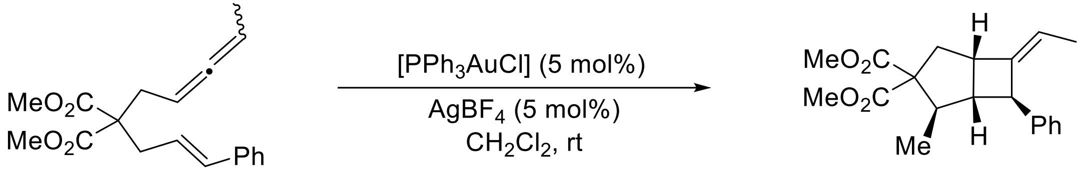


85% yield (6:1 dr)

Toste *et al.* *J. Am. Chem. Soc.* **2007**, 129, 12402-12403

Cycloisomerizations with Allenes Using Au(I)

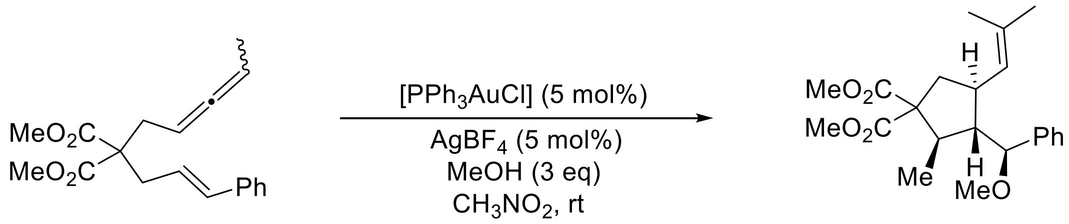
Stereoconvergence of Allene



85% yield (6:1 dr)

Reactants converge to same product!

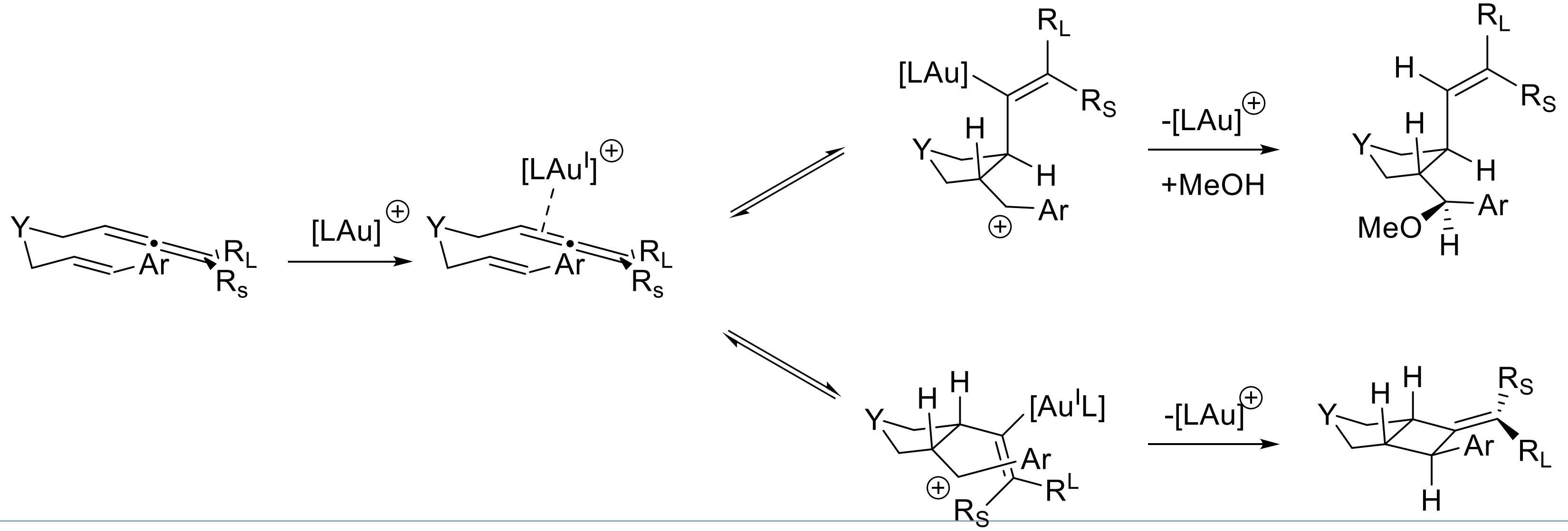
Reactivity in The Presence of Another Nucleophile



81% yield

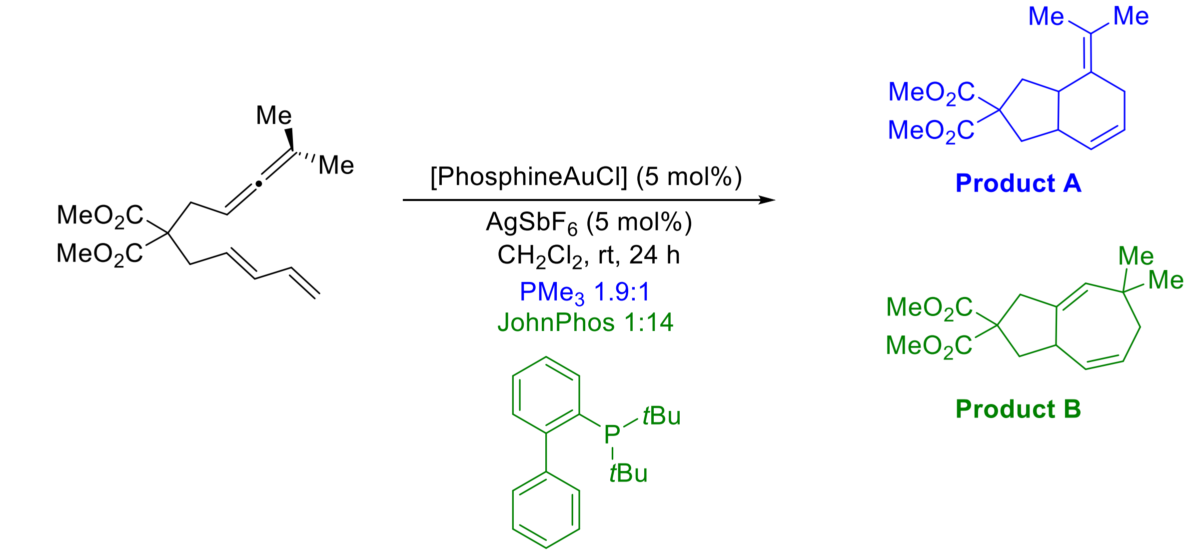
Stereoinversion Implies Reversibility!

Final Proposed Mechanism



Toste *et al. J. Am. Chem. Soc.* **2007**, 129, 12402-12403

Group Problem 1: Understanding Divergent Reactivity in Au(I)

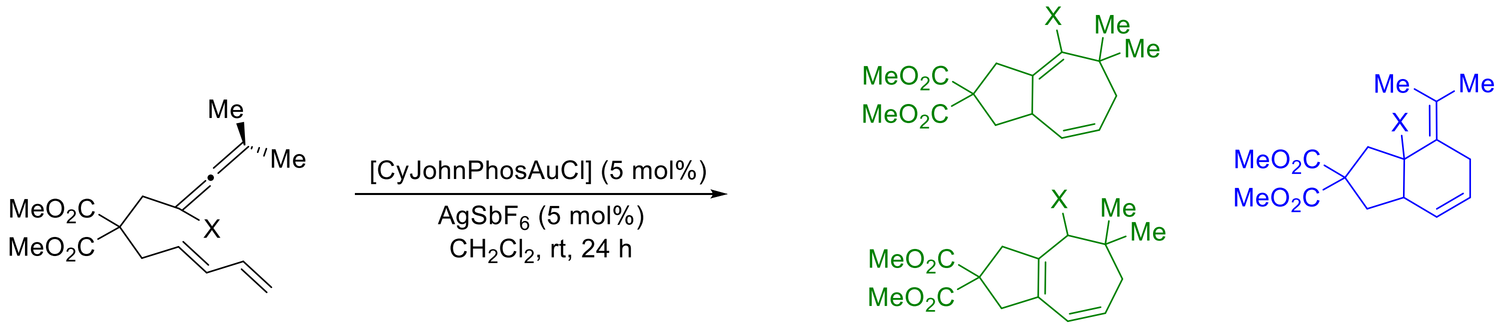


Propose a Mechanism to form Products A and B!

Hint 1: Both products involve a [4+3] cycloaddition

Hint 2: Both are from the same intermediate!

Kinetic Isotope Effect Experiment



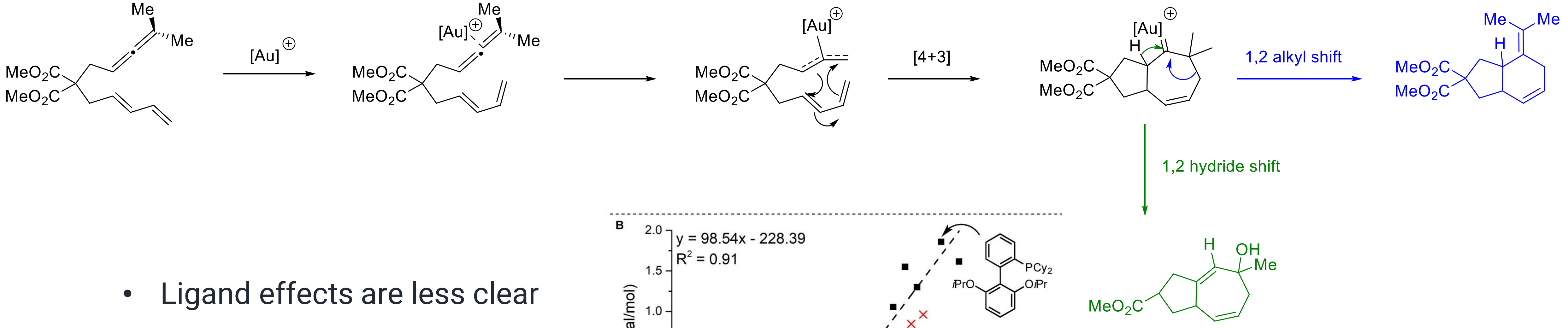
$\boxed{k_H/k_D = 1.43}$

X = H	6.2	:	1
X = D	4.4	: :	1

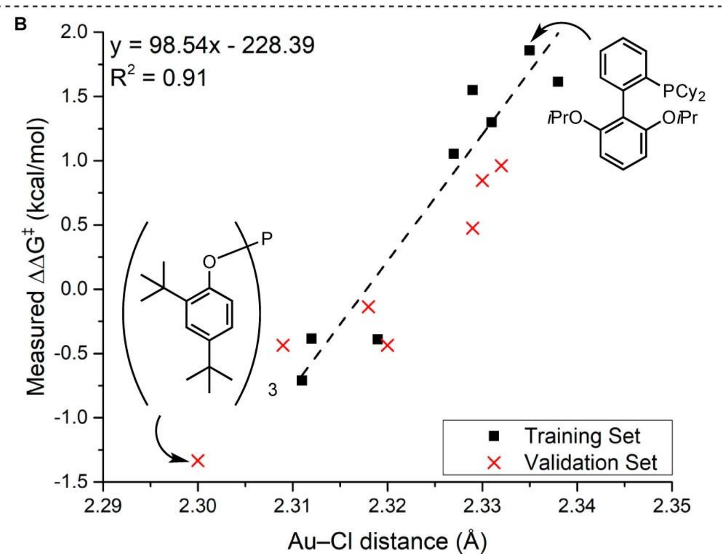
Toste *et al. ACS Catal.*. 2017, 7, 3973-3978

Group Problem 1: Answer

Proposed [4+3] Mechanism Based on Computation and Experimental Evidence



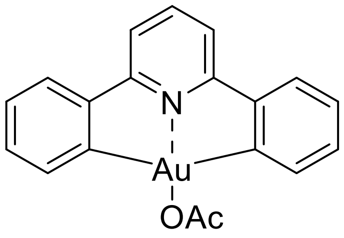
- Ligand effects are less clear
- Relating $\Delta\Delta G^{\neq}$ to Au-Cl distance performed better than other steric descriptors



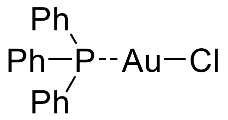
Toste *et al.* *ACS Catal.*. 2017, 7, 3973-3978
Toste *et al.* *Org. Lett.* 2009, 11, 21, 4798–4801

What's The Difference with Au(III)?

Difference In Coordination Sphere



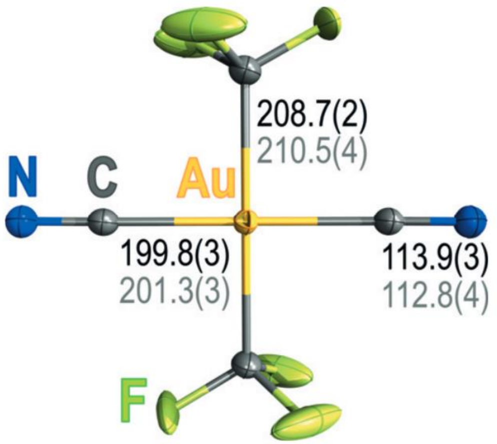
Vs.



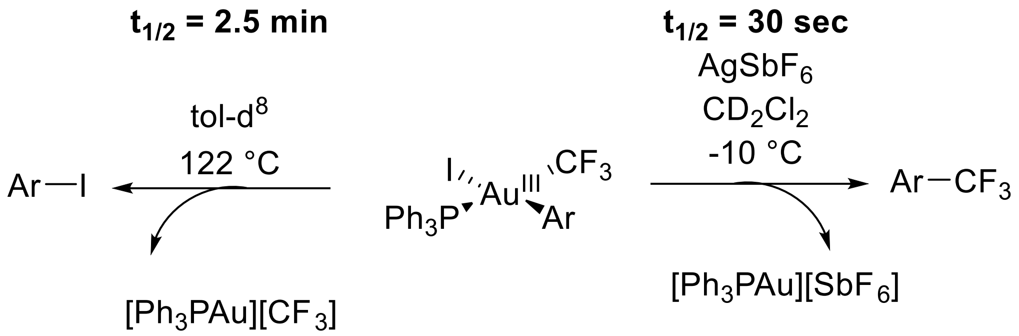
Gold(III) adopts a square planar geometry

Gold(I) adopts a linear geometry

Gold(III) is More Comparable to Ag(III)



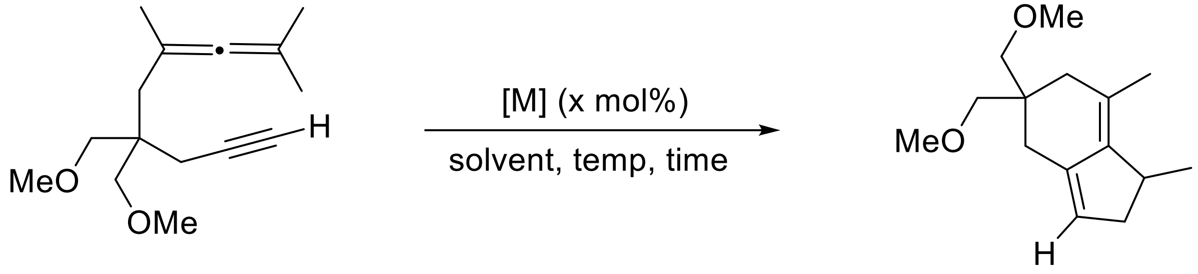
Gold(III) is Highly Prone To Reductive Elimination



Menjón *et al. Angew.Chem.Int.Ed.* **2018**, 57, 6517 –6521
Toste *et al. J. Am. Chem. Soc.* **2015**, 137, 7921-7928

Au(III) as a Usable Intermediate

Gold(III) Reactivity Is Not Always Different

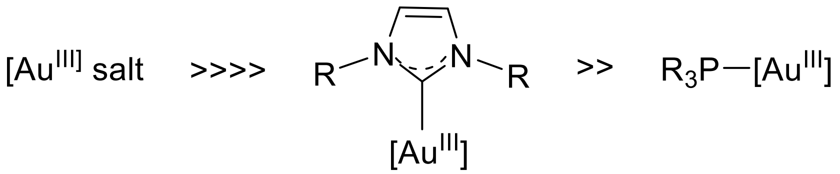


$Pt^{II}Cl_2$ (5 mol%), toluene, rt, 24h **(80% yield)**

$Au^{III}Cl_3$ (1 mol%), CH_2Cl_2, 0 °C, 0.5 h **(80% yield)**

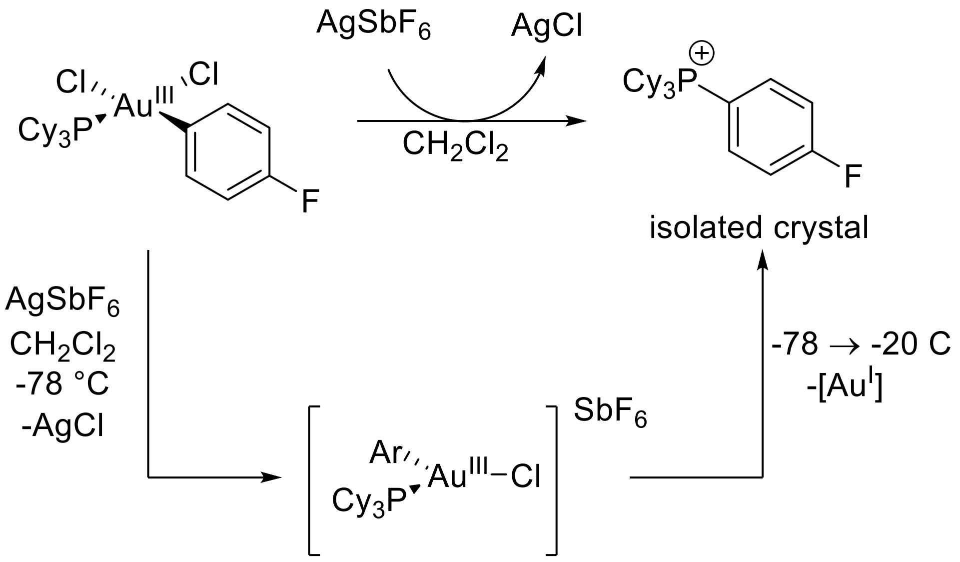
$Au^{I}Cl$ (1 mol%), CH_2Cl_2, 0 °C, 0.5 h **(79% yield)**

Prevalence in the Synthetic Chemistry



- Creating Stable Au(III) complexes was non-trivial for a long time
- Au(III) is a “harder” Lewis Acid

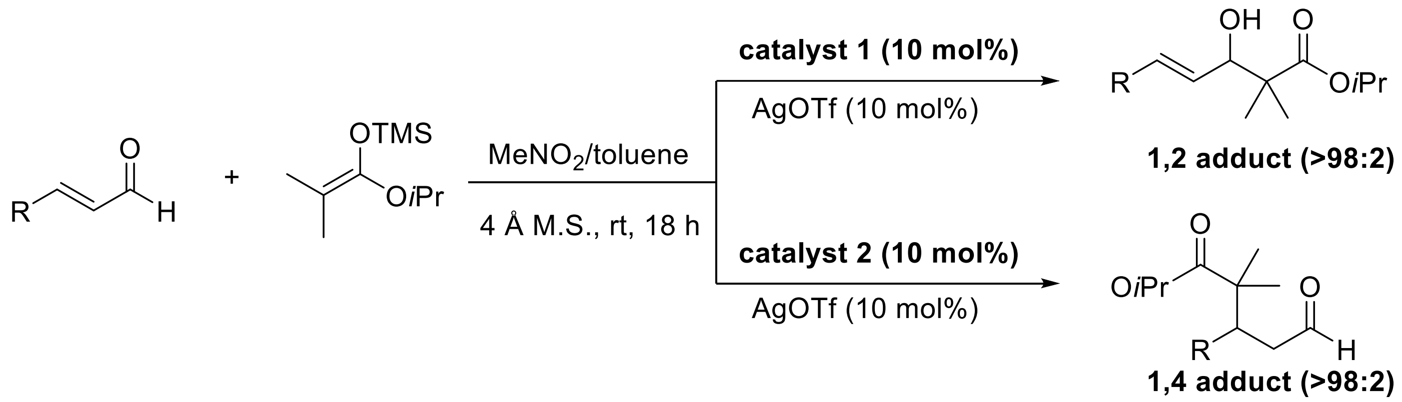
Toste Demonstrates the Issue with Phosphines

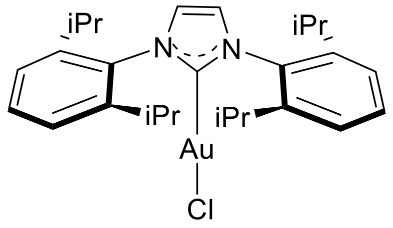


Malacria *et al.* *Angew. Chem. Int. Ed.* **2006**, 45,7596–7599
Toste *et al.* *J. Am. Chem. Soc.* **2016**, 138, 587-593

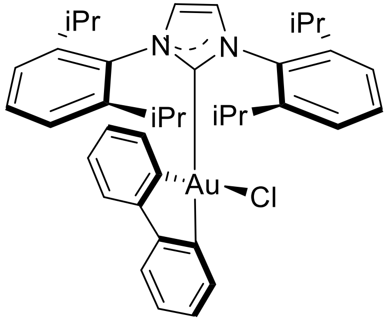
Divergence in Reactivity Between Au(III) and Au(I)

Toste Demonstrates 1,4 selectivity with a High-Valent Gold Species



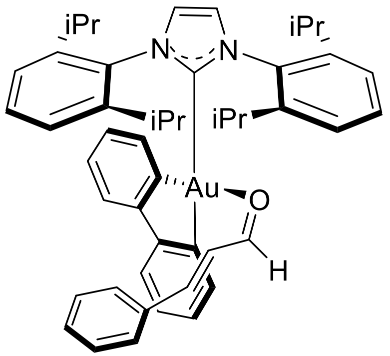


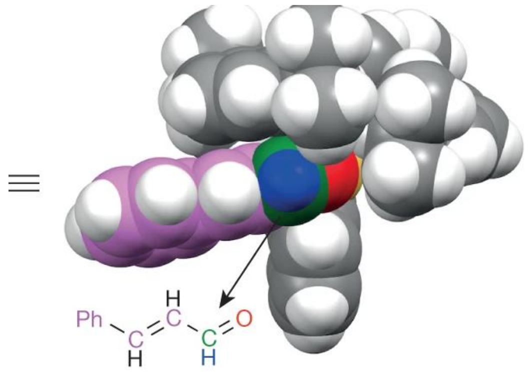
catalyst 1



catalyst 2

Coordination of Au(III)

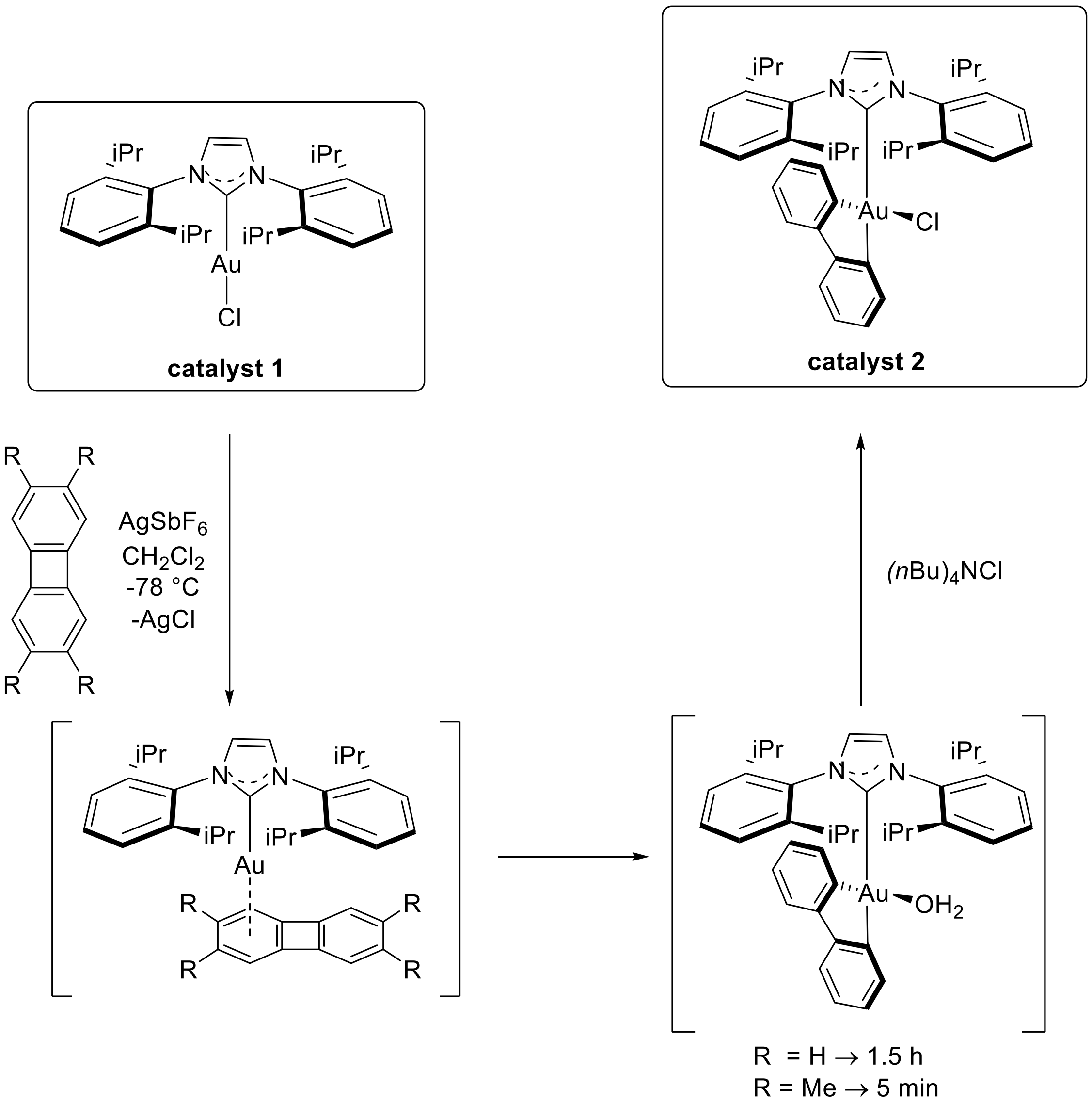




- This structure is not only stable, but also catalytically active!
- Au(III) is oxophilic
- Steric bulk around the coordination site is driving selectivity

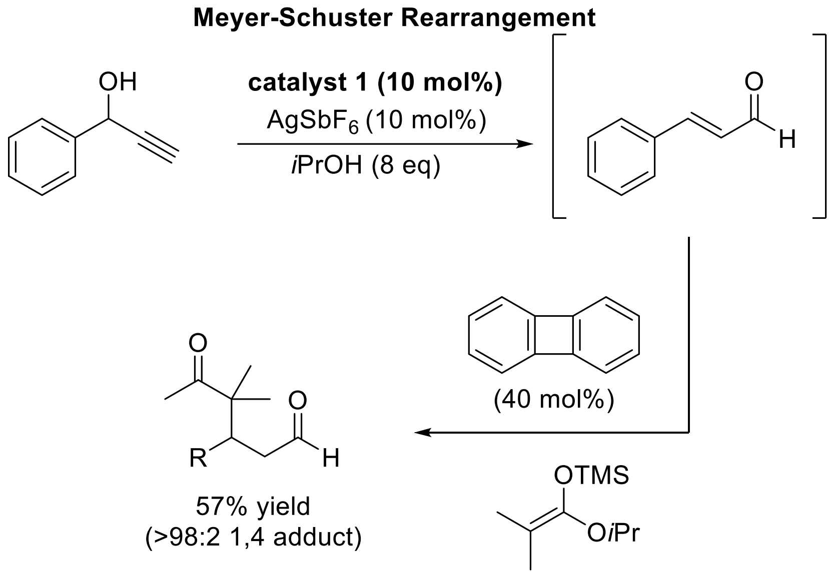
Toste *et al.* *Nature* **2015**, 517, 449-454

Understanding the Catalysts



- Au(I) can oxidatively insert into biphenylene due to strain release (BDE = 65.4 kcal/mol)
- Utilizing AgOTf results in an increase reaction time for oxidative addition

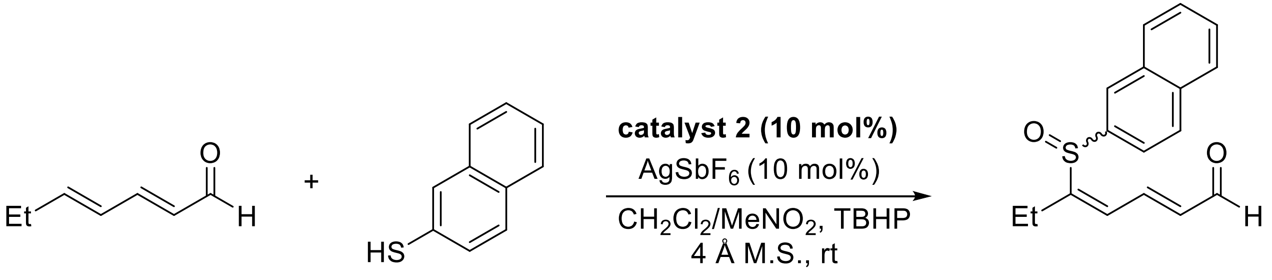
Generating Catalyst 2 In Situ



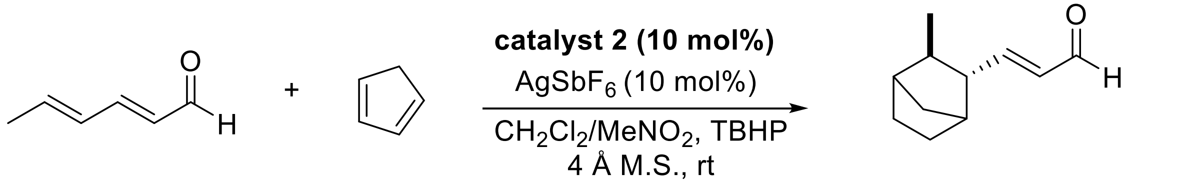
Toste *et al.* *Nature* **2015**, 517, 449-454

Further Demonstrating Reactivity

Applications to Dienes

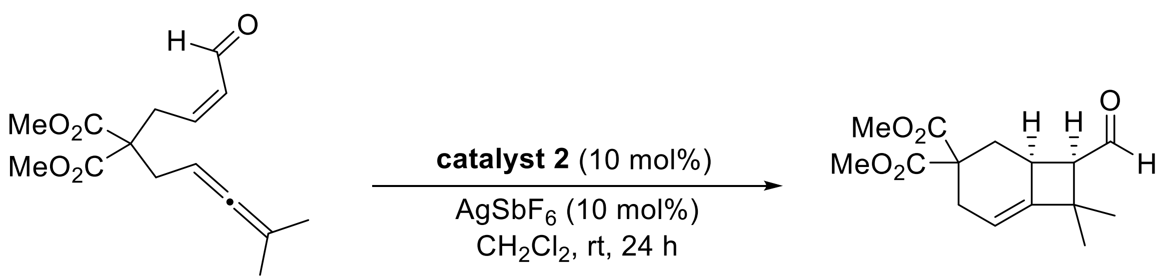


64% yield
(>98:2 δ-selectivity)



85% yield
(>98:2 δ,γ-/α,β-selectivity)
(88:12 *endo*:*exo*)

Lewis-Acid Catalyzed [2+2] Cycloaddtion



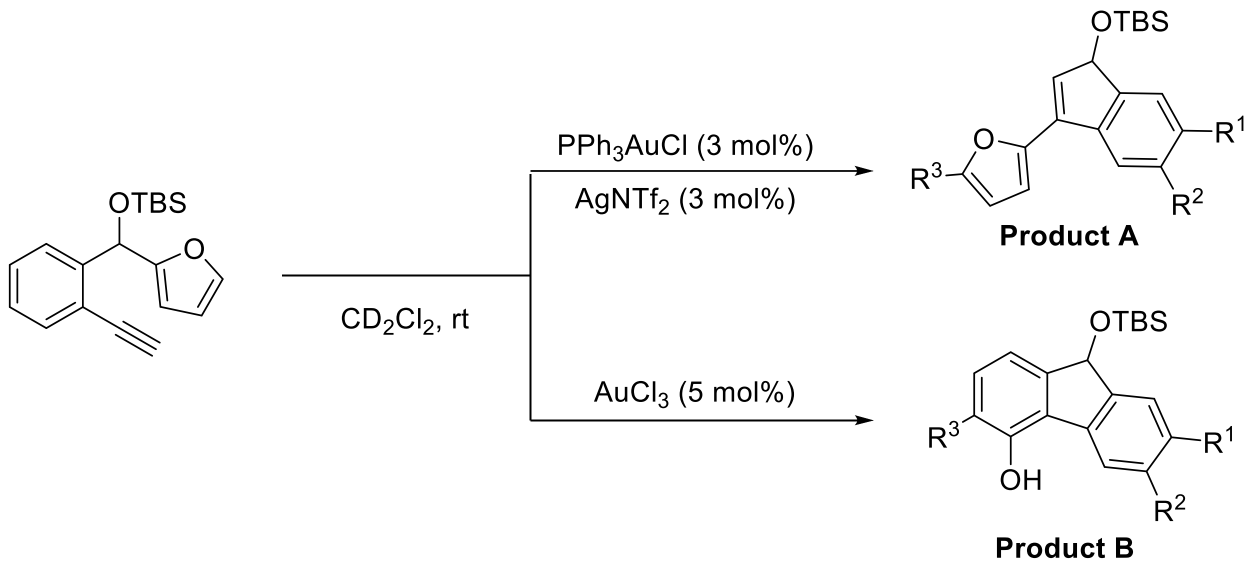
70% yield
cis:*trans*

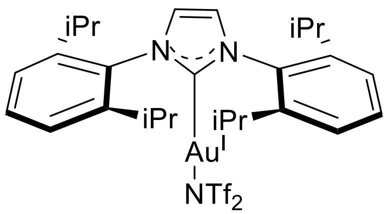
- The first time a Lewis-acid has ever been used for this transformation!
- Catalyst 1, $MeAlCl_2$, $h\nu$, nor proline-derivatives could affect this transformation

Toste *et al.* *Nature* **2015**, 517, 449-454

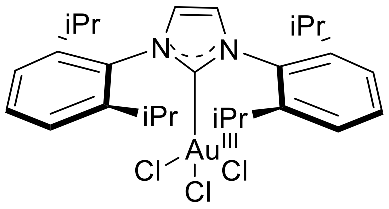
Divergent Regioselectivity of Au(III) and Au(I)

Cyclization of Furan-Yne Systems



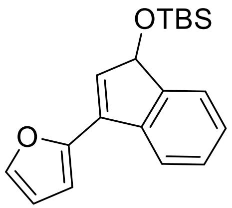


*Selective for **Product A***

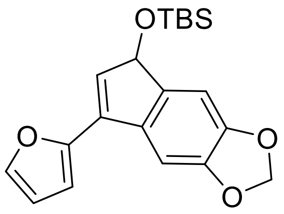


*Selective for **Product B***

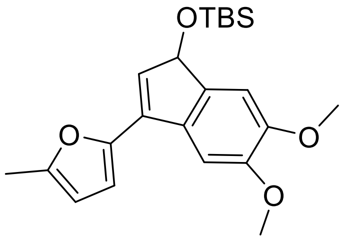
Product A (Au^{I} substrates)



70% yield

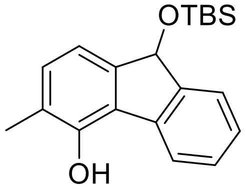


99% yield

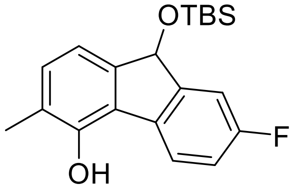


"complex mixture"

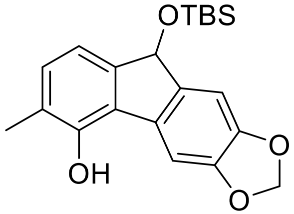
Product B (Au^{III} substrates)



60% yield



30% yield

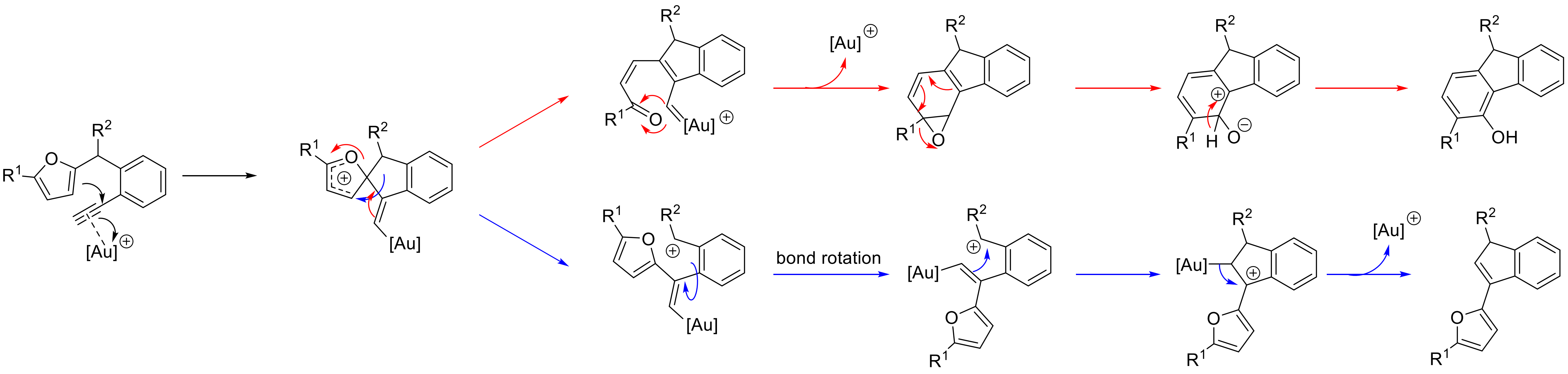


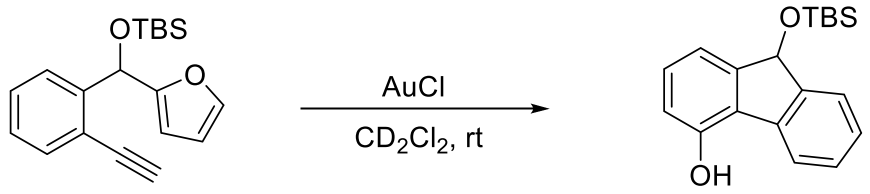
30% yield

Hashmi *et al. Chem. Eur. J.* **2013**, 19, 382-389

Divergent Regioselectivity of Au(III) and Au(I)

Proposed Mechanistic Pathways





Only Product

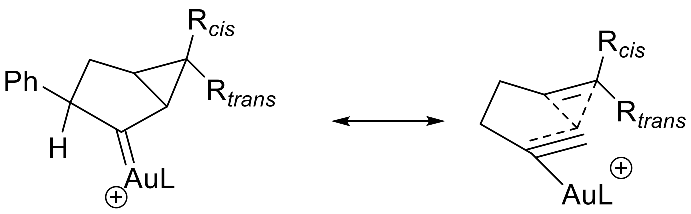
- “Charge Donating Ability for Au(III) is greater since it is not technically cationic”
- “AuCl working could indicate catalyst disproportionation”

Conclusion: *It’s still unclear!*

Hashmi *et al. Chem. Eur. J.* **2013**, 19, 382-389

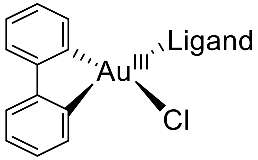
The First Highly Enantioselective Transformation by Au(III)

A Reminder of Au(I) Cycloisomerization



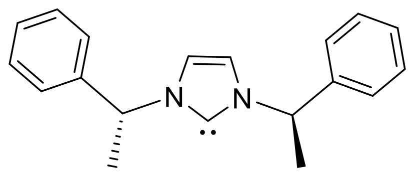
Significant Transfer of Chirality

Hypothesis



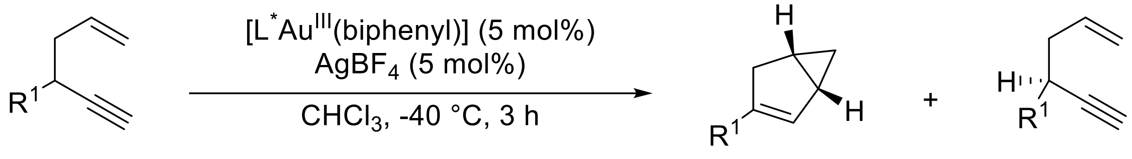
Ligand--Au^{I}–Cl

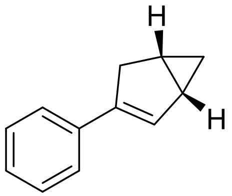
Ligand is Much Closer to Active Site



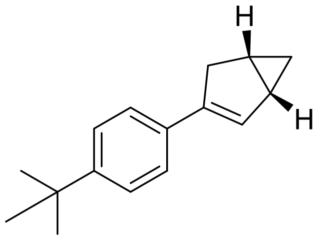
L*

Enantioconvergent Cycloisomerization

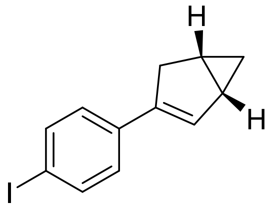




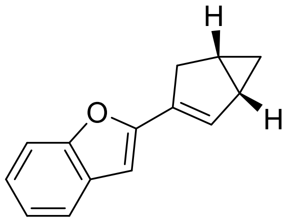
44% conversion
(5.5:1 er)



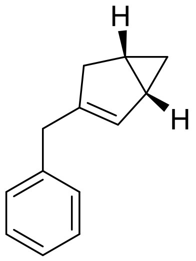
28% conversion
(7.3:1 er)



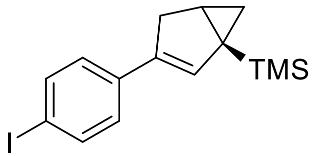
40% conversion
(7.3:1 er)



35% conversion
(2:1 er)



64% conversion
(er = nd)

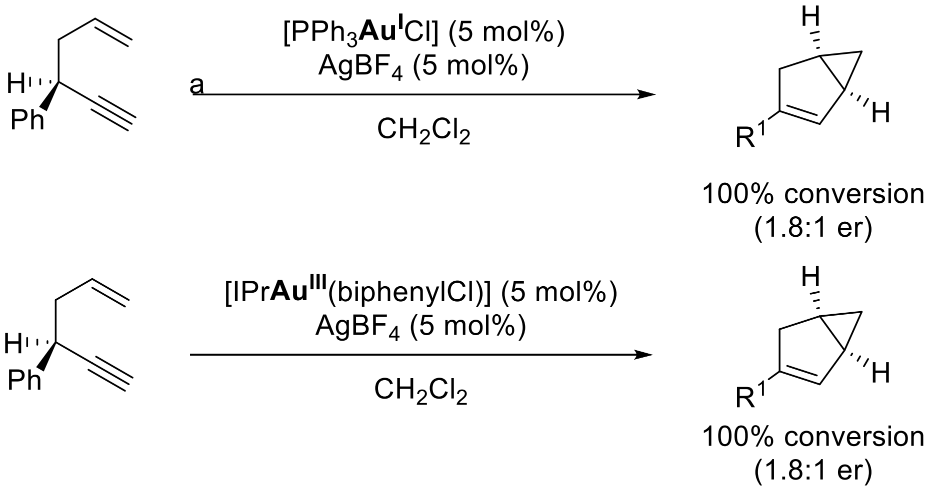


0% conversion

Toste *et al.* *J. Am. Chem. Soc.* **2017**, 139, 11016-11019

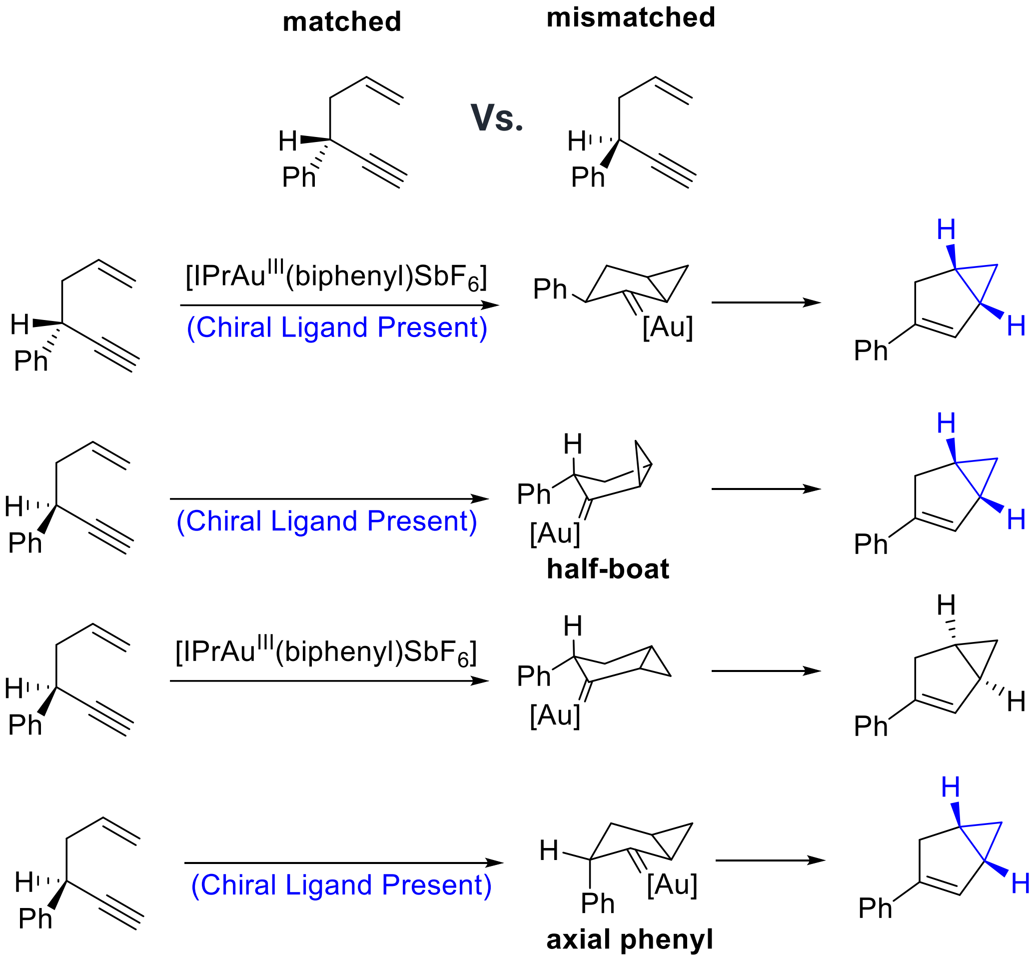
The First Highly Enantioselective Transformation by Au(III)

Testing Chirality Transfer with Achiral Ligands



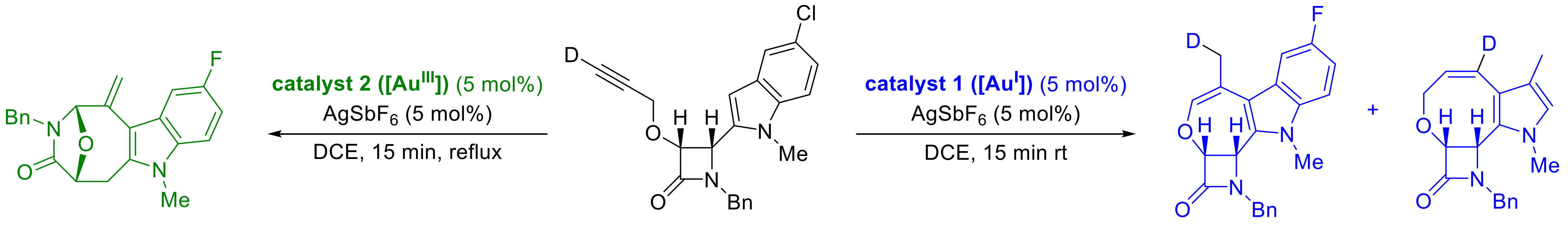
- Suggests the reaction does proceed with some chirality transfer
- Au(I) is unable to do this chemistry, most likely due to coordination sphere

Transition States to Explain Enantioconvergence

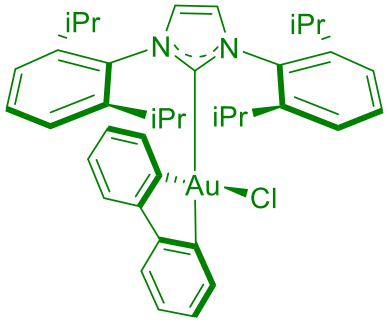


J. Am. Chem. Soc. 2017, 139, 11016-11019

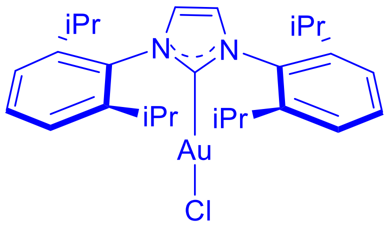
Group Problem 2: Regiodivergent reactivity of Au(I) and Au(III)



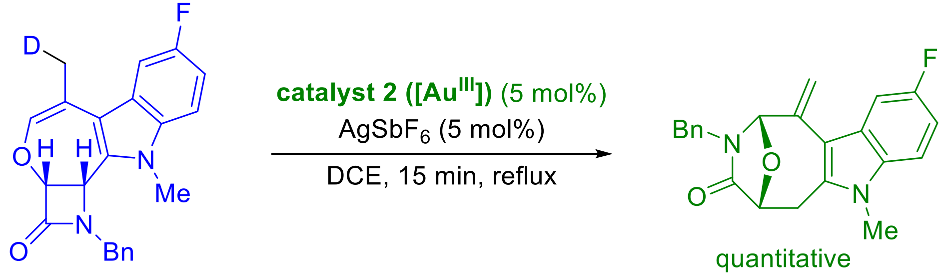
Product A **Product B** **Product C**



catalyst 2



catalyst 1



Product B **Product A**

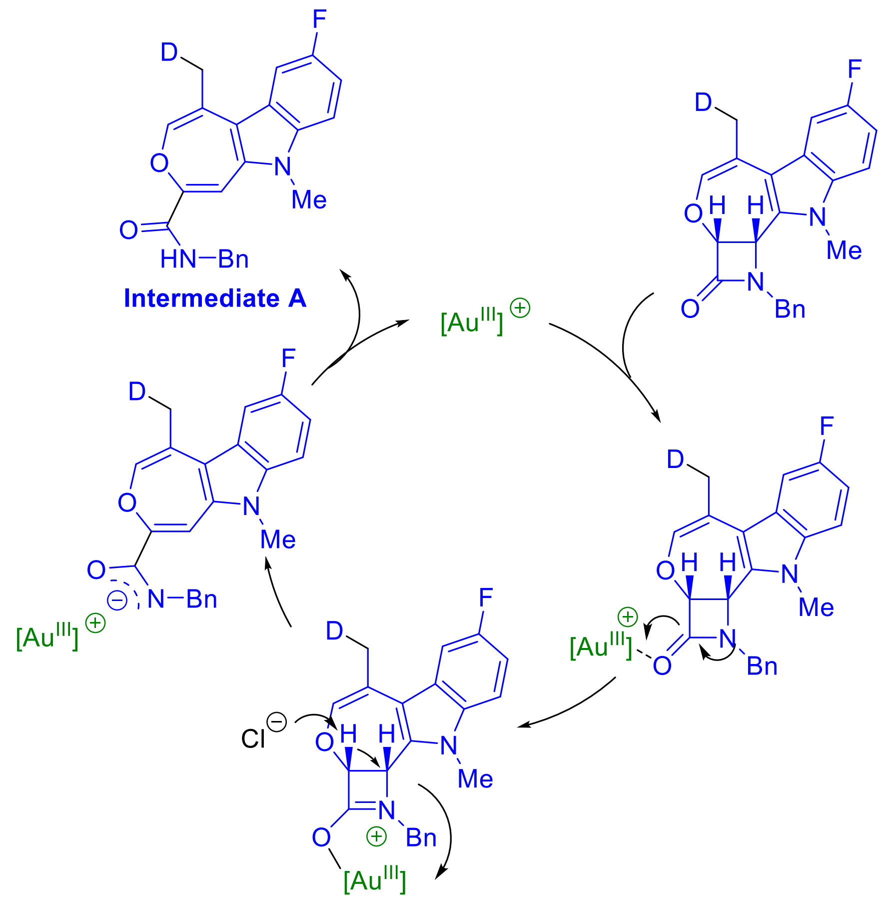
Propose a mechanism to access product A!
*Assume **Product B** is the starting reagent.*

<u>Hint 1: Au(III) is acting a hard Lewis acid to catalyze ring opening</u>

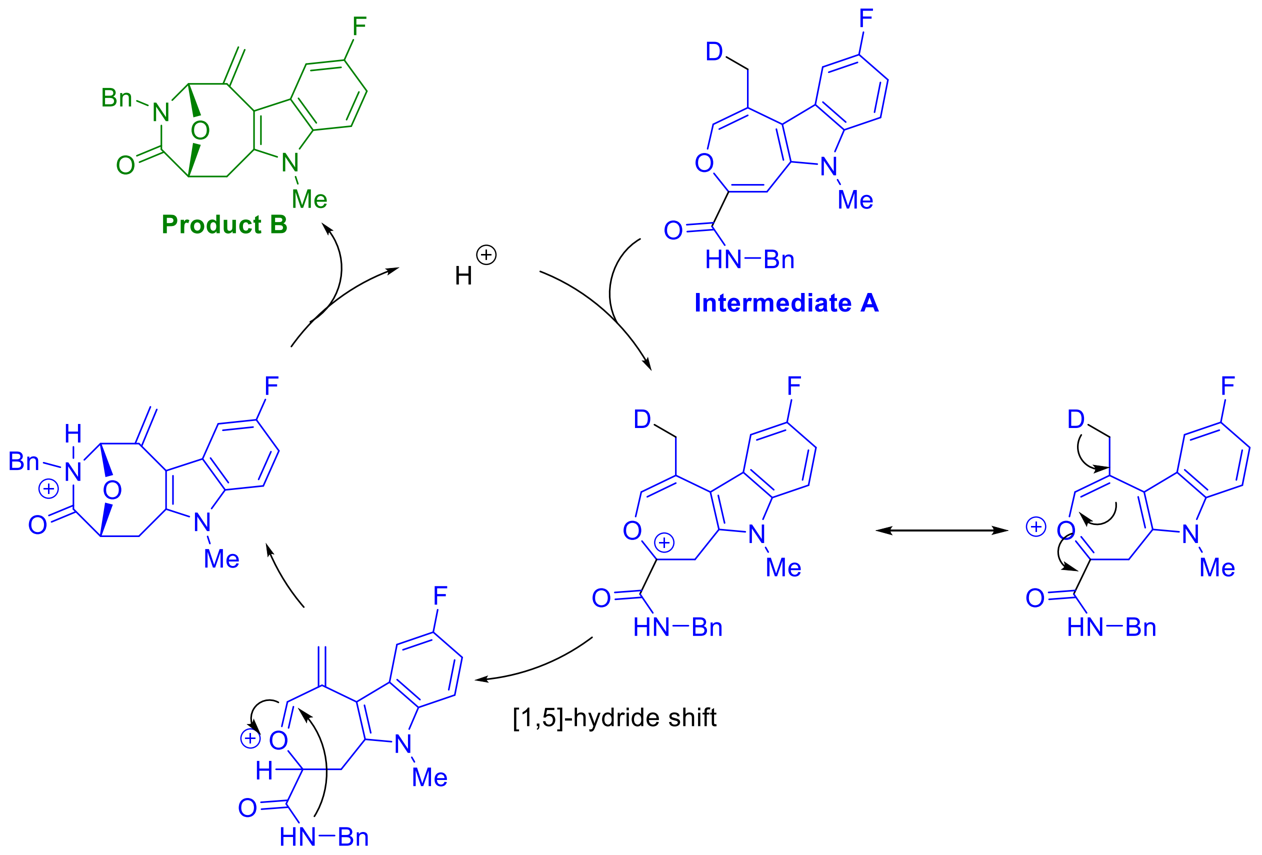
Alcaide *et al.* *Chem. Eur. J.* 2017, 23, 3012-3015

Group Problem 2: Answer

Hint 2: Intermediate A is created after Au(III) cycle



Formation of Product B



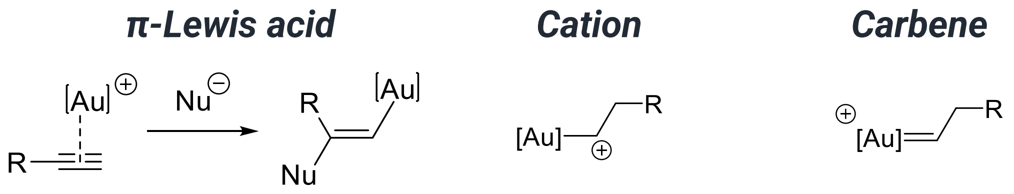
Computationally Investigated

Alcaide *et al.* *Chem. Eur. J.* 2017, 23, 3012-3015

A Summary of Reactivity and Thoughts

Gold (I) as a Catalyst

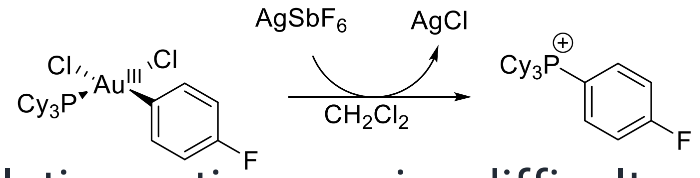
- Reactivity falls into 3 overlapping categories:



- “Softer” Lewis acid, often carbophilic and adaptable with phosphine ligands
- Very well-studied and understood, with clear trends in reactivity
- Linear geometry predominates Gold (I), making complexes more sensitive to ligand electronic effects than steric

Gold (III) as a Catalyst

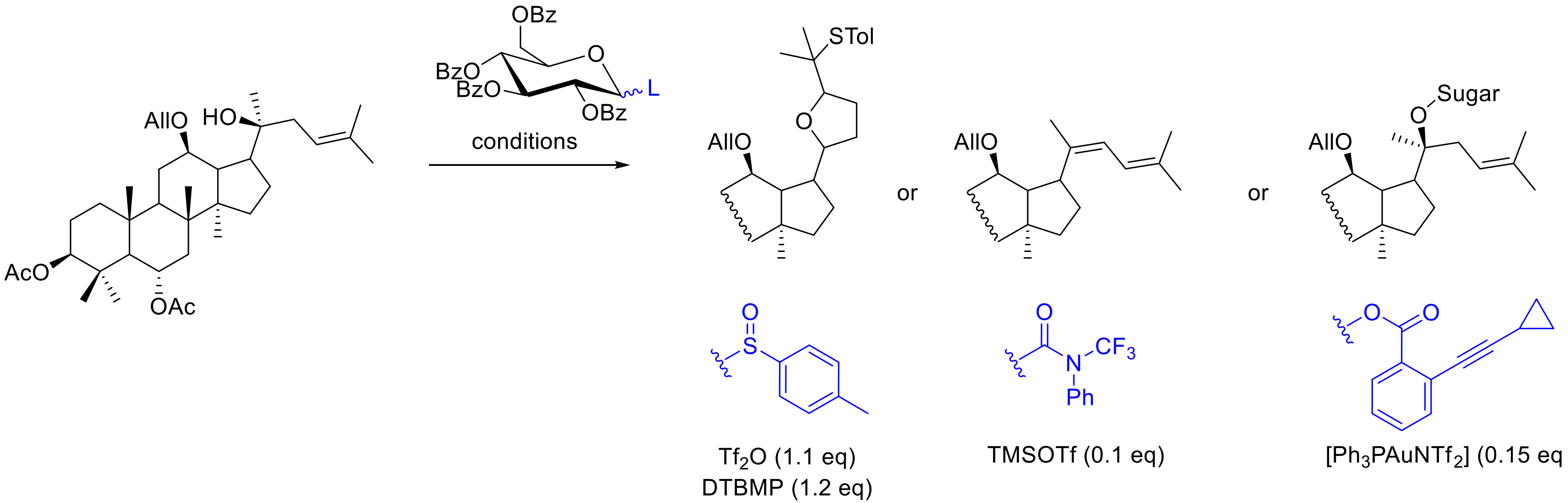
- Reactivity mimics Gold(I) in being π-philic
- Easily reduced, leading to unusual mechanisms not seen with other metals



- Isolating active species difficult, resulting in much more speculative mechanisms
- “Harder” Lewis acid, can be both oxophilic and carbophilic, adaptable with NHCs
- Reactivity can be different than that of Au(I)

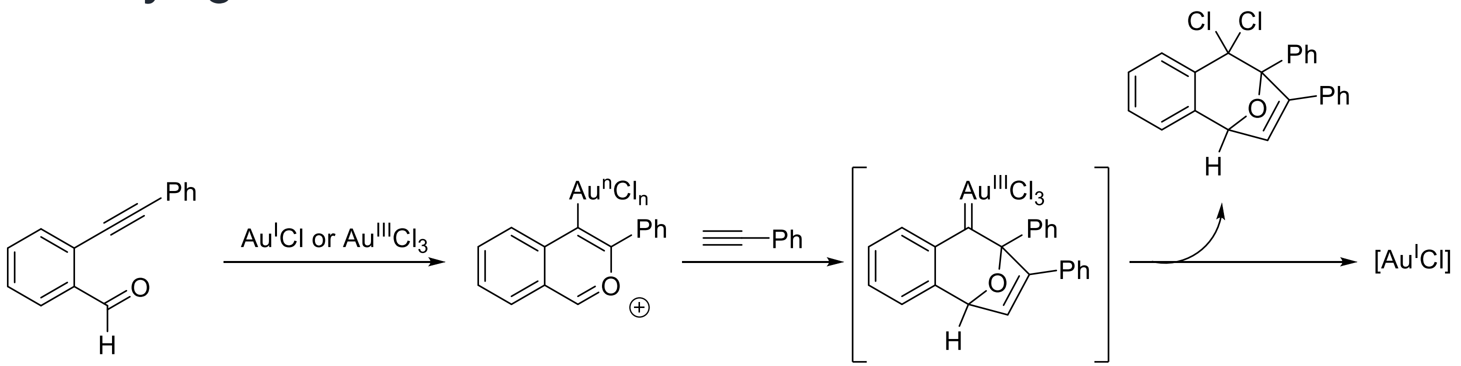
Outlook and Future Directions

Glycoside Formation



- Mild Conditions
- Highly Selective
- Prevents Side Reactivity

Identifying Reactive Intermediates



- There is some evidence that Au(III) salts may react by accessing Au(I)

Biao Yu. *Acc. Chem. Res*. **2018**, 51, 507−516
Zhang *et al. ACS Catal.* **2020**, 10, 12, 6682-6690

Reviews of Interest

A. Corrna, A. Leyva-Pérez, and Maria J. Sabater

Gold-Catalyzed Carbon-Heteroatom Bond-Forming Reactions

Chem Rev. **2011**, 111, 3, 1657-1712

Luca Rocchigiani and Manfred Bochmann

Recent Advances in Gold(III) Chemistry: Structure, Bonding, Reactivity, and Role in Homogeneous Catalysis

Chem. Rev. **2021**, 121, 14, 8364-8451

Zhitong Zheng, Xu Ma, Xinpeng Cheng, Ke Zhao, Kaylaa Gutman, Tianyou Li, and Liming Zhang

Homogeneous Gold-Catalyzed Oxidation Reactions

Chem. Rev. **2021**, 121, 14, 8979-9038

David J. Gorin & F. Dean Toste

Relativistic effects in homogeneous gold catalysis

Nature. **2007**, 446, 395-403