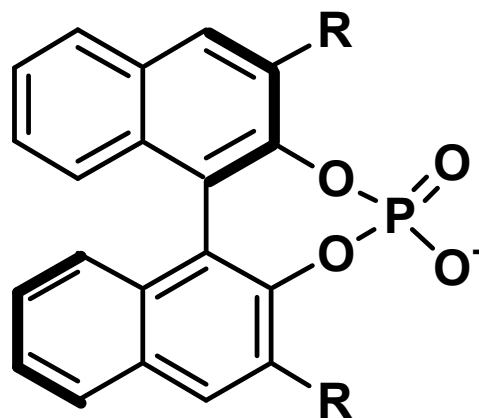
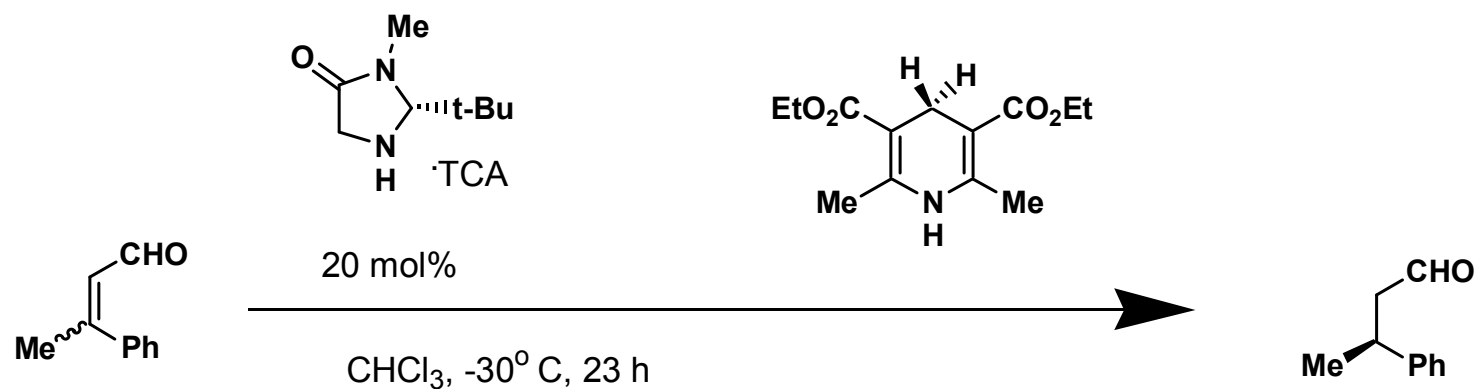


A Powerful Chiral Counterion Strategy for Asymmetric Transition Metal Catalysis



Gregory L. Hamilton, Eun Joo Kang,
Miriam Mba, F. Dean Toste*,
Science, 2007, 317, 496-499

Organocatalytic and Enantioselective Transfer Hydrogenation

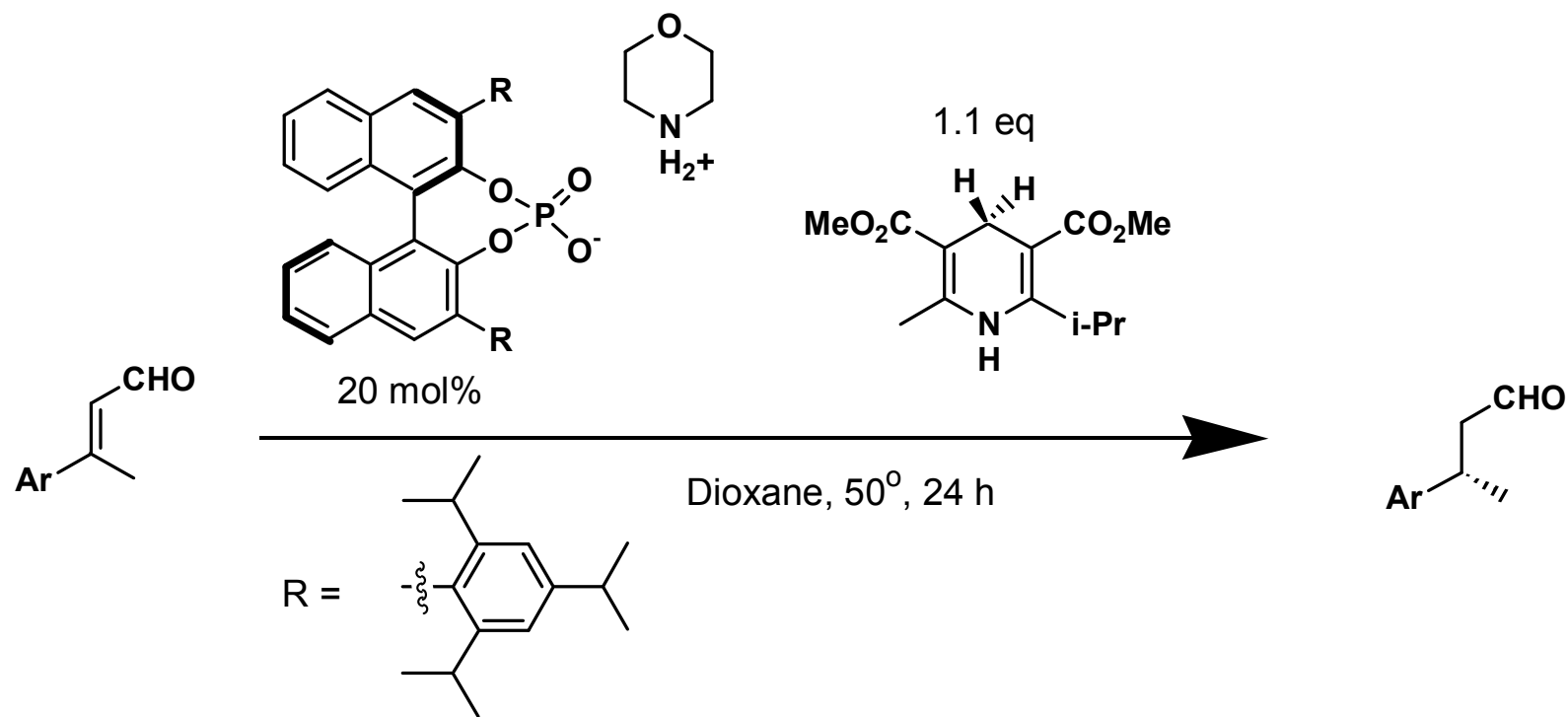


Starting Aldehyde	Yield (%)	ee(%)
E	91	93
Z	90	87
E:Z, 1:1	88	90

G. Lelais, D. W. C. MacMillan, *Aldrichim Acta*, **39**, 79 (2006)

S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **127**, 32 (2005)

Asymmetric Counteranion-Directed Catalysis



Enantioselectivities range from 98:2 to >99:<1

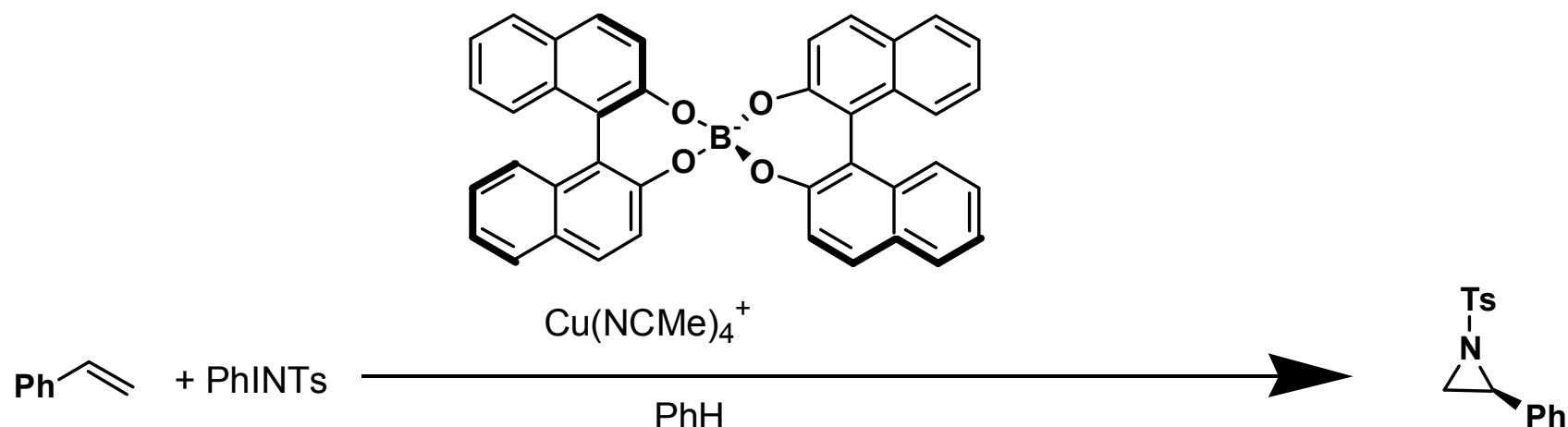
The List group has also used this strategy on non-aromatic and cyclic enones

S. Mayer, B. List, *Angew. Chem. Int. Ed.* **45**, 4193 (2006)

N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **128**, 13368 (2006)

Previous Attempts at Counterion-Directed Organometallic Catalysis

- Arndtsen and coworkers developed an asymmetric aziridination.



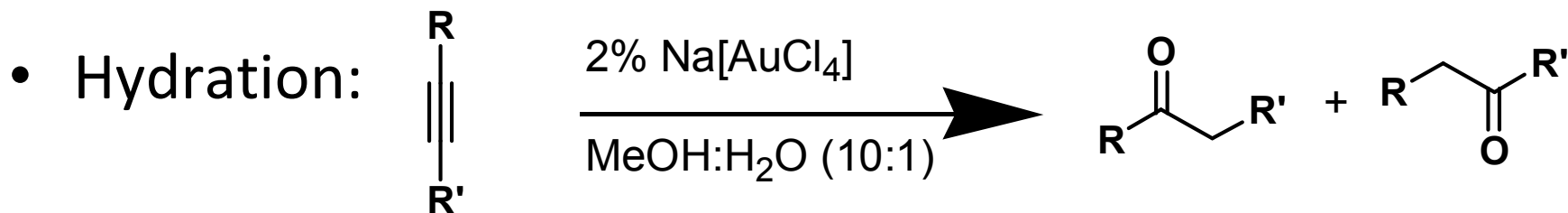
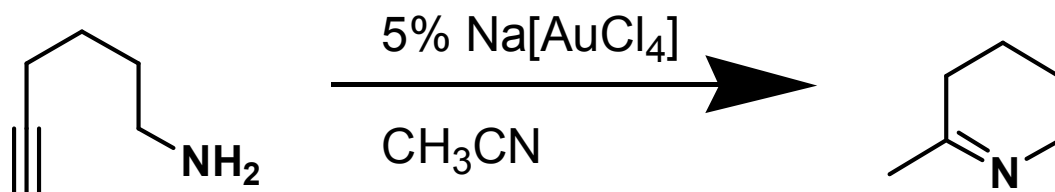
- They also developed a similar cyclopropanation
- The best ee afforded by either reaction was 28%

D. B. Llewellyn, D. Adamson, B. A. Arndtsen, *Org. Lett.*, **2**, 4165 (2000)

D. B. Llewellyn, B. A. Arndtsen, *Tetrahedron Asymmetry*, **16**, 1789 (2005)

Au(I) and Au(III) Catalytic Activation of Alkynes

- Au(I) and (III) act as Lewis Acids and are capable of facilitating the addition of nucleophiles on to alkynes
- Hydroamination:



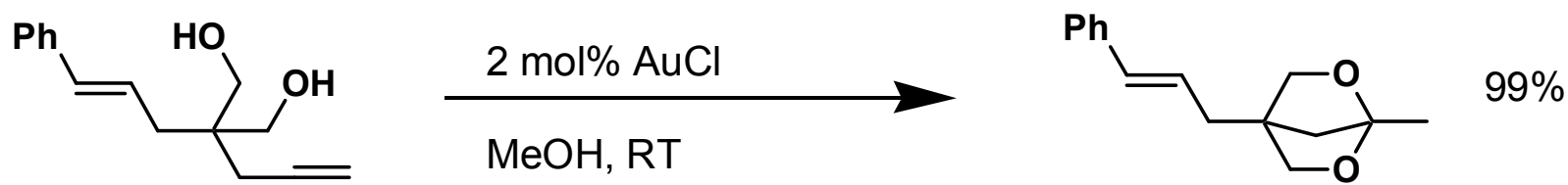
Fukuda, Y., Utimoto, K. & Nozaki, H. *Heterocycles*, **25**, 297–300 (1987)

Fukuda, Y. & Utimoto, K., *J. Org. Chem.*, **56**, 3729–3731 (1991)

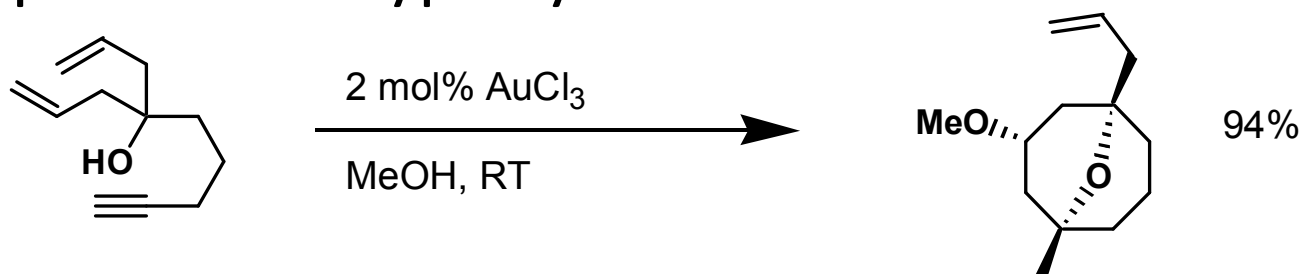
D. J. Gorin, F. D. Toste, *Nature*, **446**, 395 (2007)

Au(I) and Au(III) Catalytic Activation of Alkynes

- Bicyclic ketals can be obtained from alcohols and alkynes:



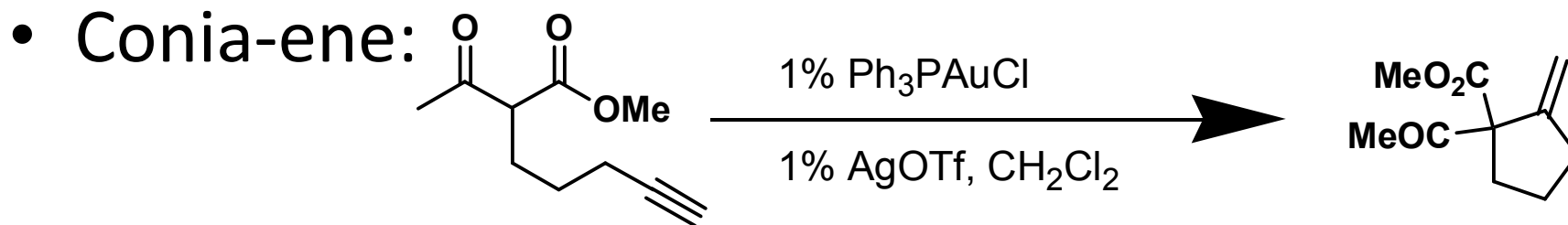
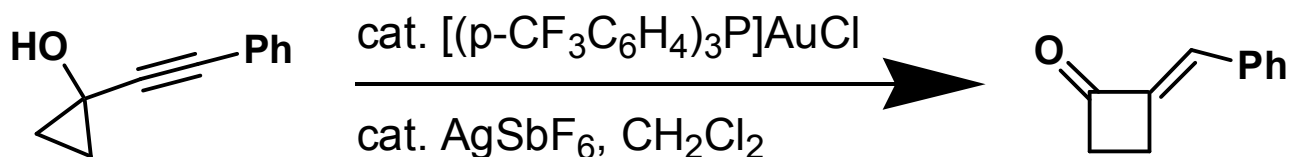
- Cyclization to an enol ether followed by a subsequent Prins-type cyclization:



S. Antoniotti, E. Genin, V. Michelet, J.-P. GenPt, *J. Am. Chem. Soc.*, **127**, 9976 (2005)
J. Barluenga, A. Dieguez, A. Fernandez, F. Rodriguez, F. J. Fananas, *Angew. Chem.*, **118**, 1–4 (2006); *Angew. Chem. Int. Ed.*, **45**, 2091 (2006)
A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.*, **45**, 7896 (2006)

Au(I) and Au(III) Catalytic Activation of Alkynes

- Activated carbon nucleophiles have been explored as well
- Ring expansion:



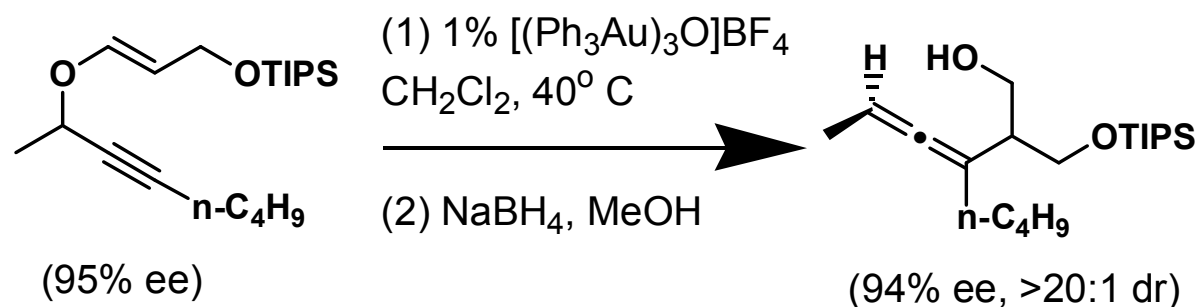
Markham, J. P., Staben, S. T. & Toste, F. D., *J. Am. Chem. Soc.*, **127**, 9708 (2005)

Teles, J. H., Brode, S. & Chabanas, M., *Angew. Chem. Int. Ed.*, **37**, 1415 (1998)

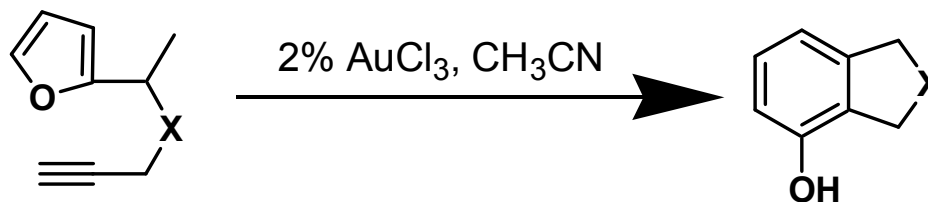
D. I. Gorin, F. D. Toste. *Nature*. **446**. 395 (2007)

Au(I) and Au(III) Catalytic Activation of Alkynes

- Activated carbon nucleophiles continued
- Propargyl Claisen:



- Cycloaddition/fragmentation:



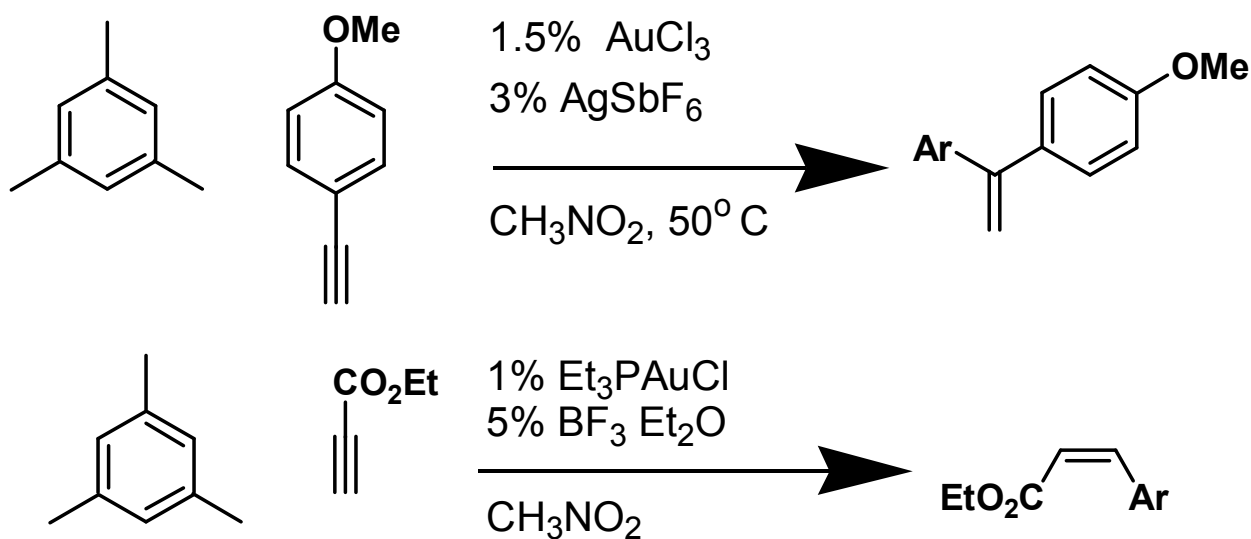
Sherry, B. D. & Toste, F. D., *J. Am. Chem. Soc.*, **126**, 15978–15979 (2004)

Hashmi, A. S. K., Frost, T. M. & Bats, J. W., *J. Am. Chem. Soc.*, **122**, 11553 (2000)

D. J. Gorin, F. D. Toste, *Nature*, **446**, 395 (2007)

Au(I) and Au(III) Catalytic Activation of Alkynes

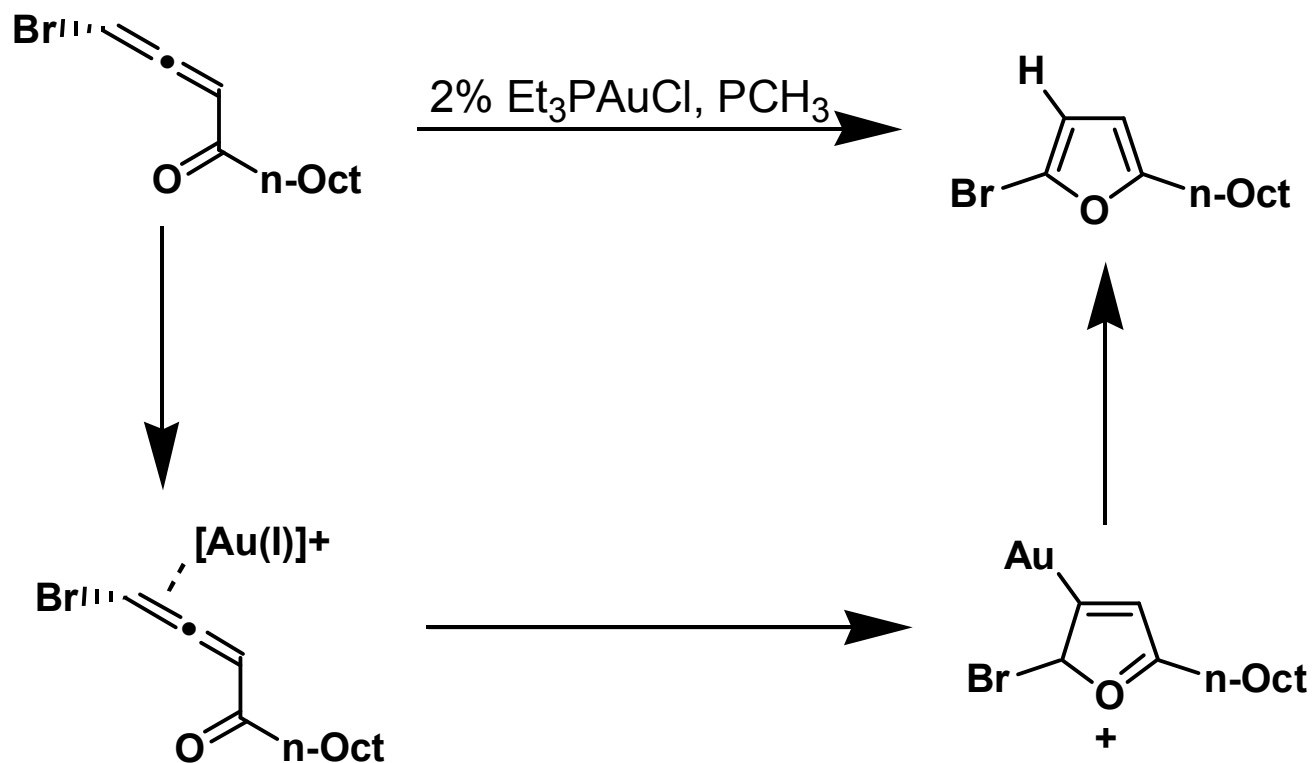
- In the case of hydroarylation, varying reactivity is observed depending on the oxidation state of Au



Reetz, M. T. & Sommer, K., *Eur. J. Org. Chem.*, 2003, 3485–3496 (2003)

D. J. Gorin, F. D. Toste, *Nature*, **446**, 395 (2007)

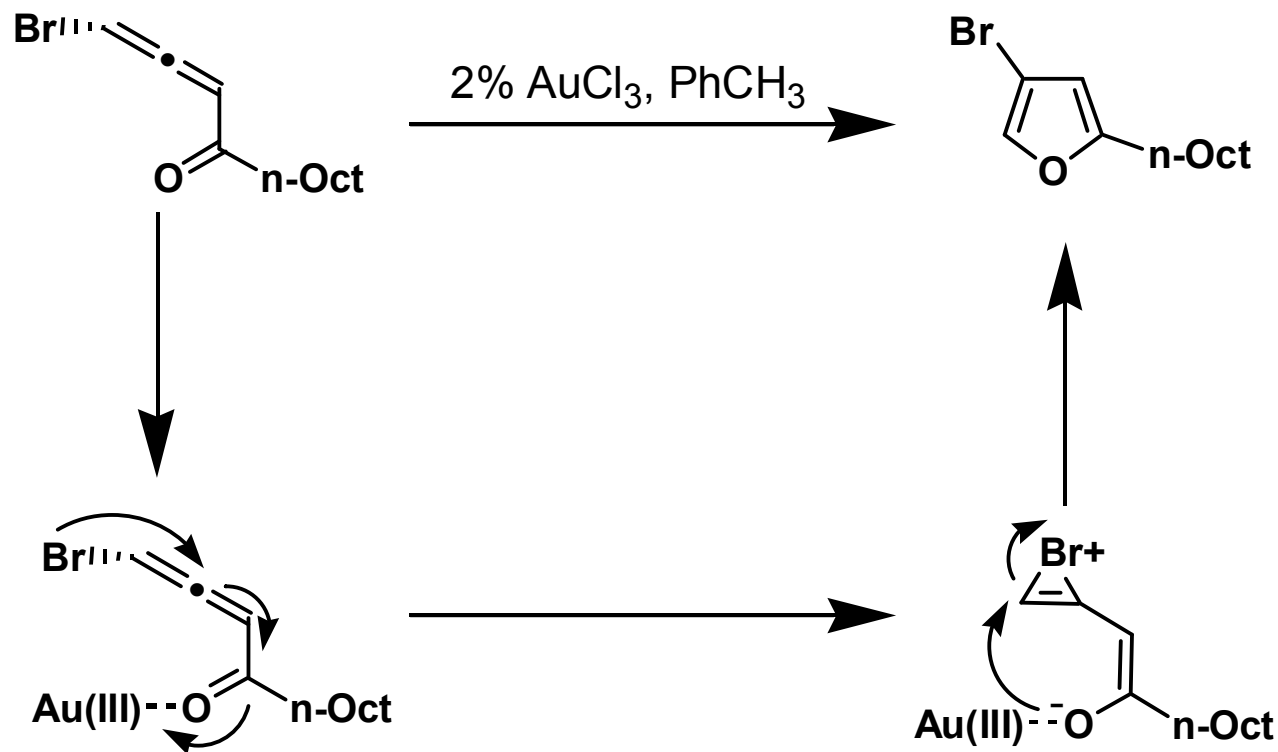
Oxidation State Determines the Product



Sromek, A. W., Rubina, M. & Gevorgyan, *J. Am. Chem. Soc.*, **127**, 10500 (2005)

D. J. Gorin, F. D. Toste, *Nature*, **446**, 395 (2007)

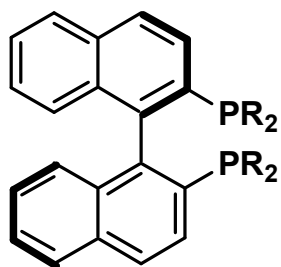
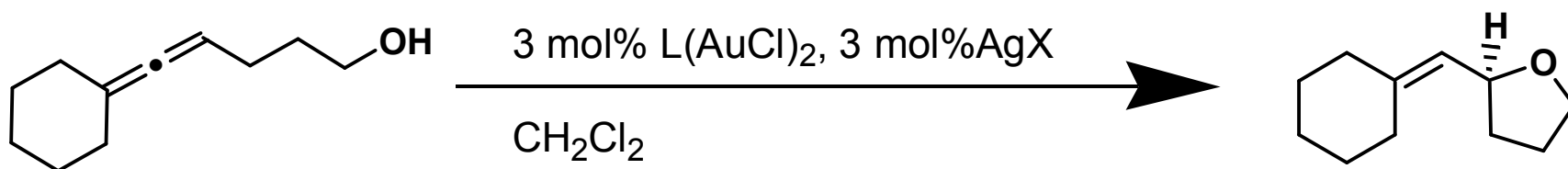
Oxidation State Determines the Product



Sromek, A. W., Rubina, M. & Gevorgyan, *J. Am. Chem. Soc.*, **127**, 10500 (2005)

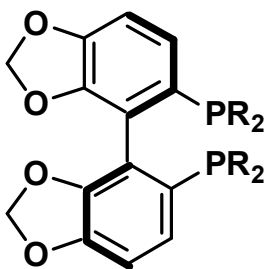
D. J. Gorin, F. D. Toste, *Nature*, **446**, 395 (2007)

Chiral Ligands vs. Chiral Counterions



3, R = Ph

4, R = 3,5-(CH₃)₂-C₆H₃



5, R = 3,5-t-Bu₂-4-(CH₃O)-C₆H₂

L = **3**, X = BF₄⁻

L = **4**, X = BF₄⁻

L = **5**, X = BF₄⁻

L = **4**, X = 4-(NO₂)-C₆H₃-CO₂⁻

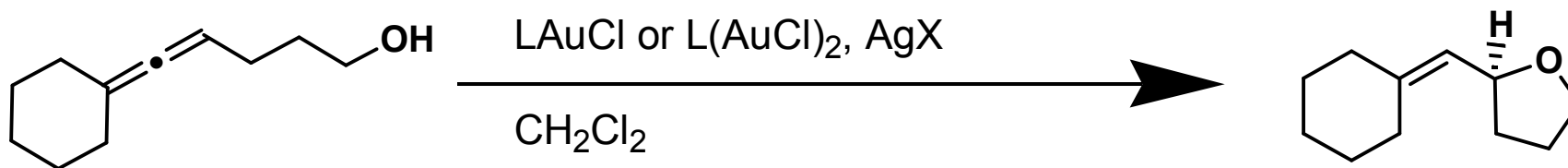
52% yield, 6% ee

68% yield, 0% ee

79% yield, 2% ee

89% yield, 8% ee

Chiral Ligands vs. Chiral Counterions

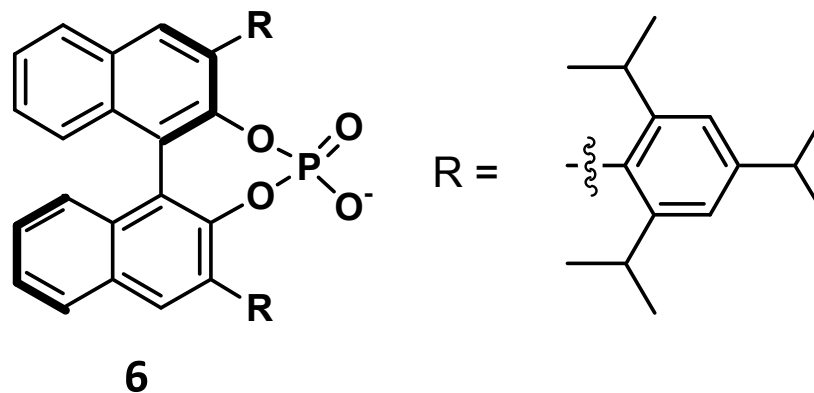


$\text{L} = \text{Ph}_3\text{P}$ (5 mol%), $\text{X} = (\text{R})\text{-6}$ (5 mol%)

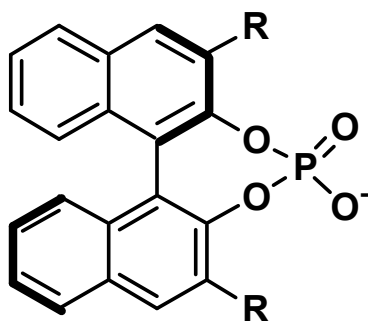
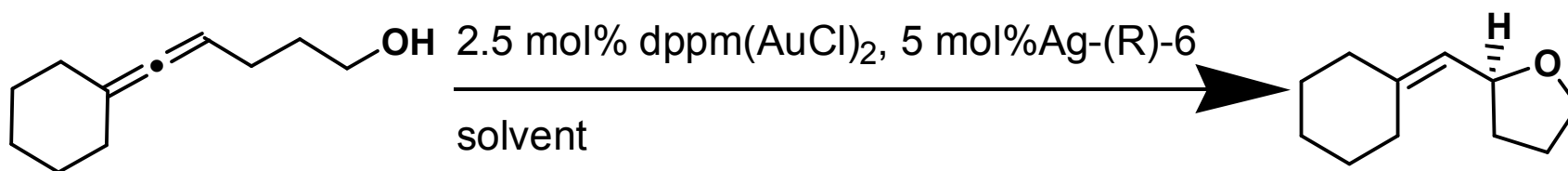
89% yield, 48% ee

$\text{L} = \text{dppm}$ (2.5 mol%), $\text{X} = (\text{R})\text{-6}$ (5 mol%)

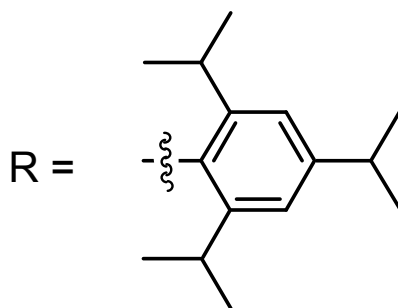
76% yield, 65% ee



Solvent Effects

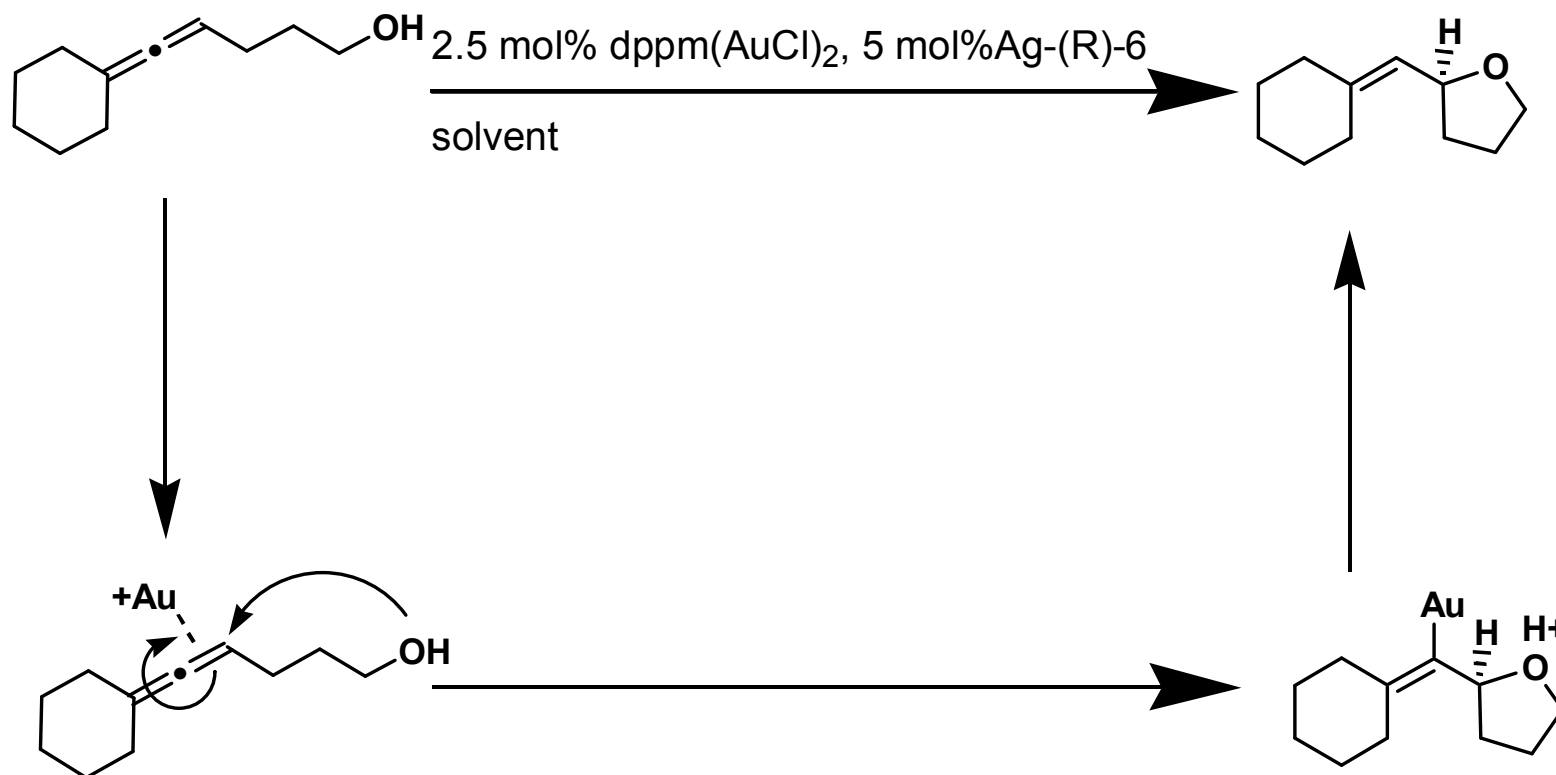
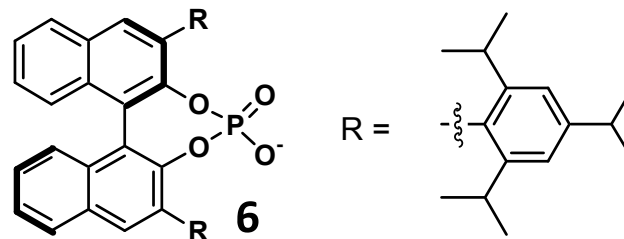


6



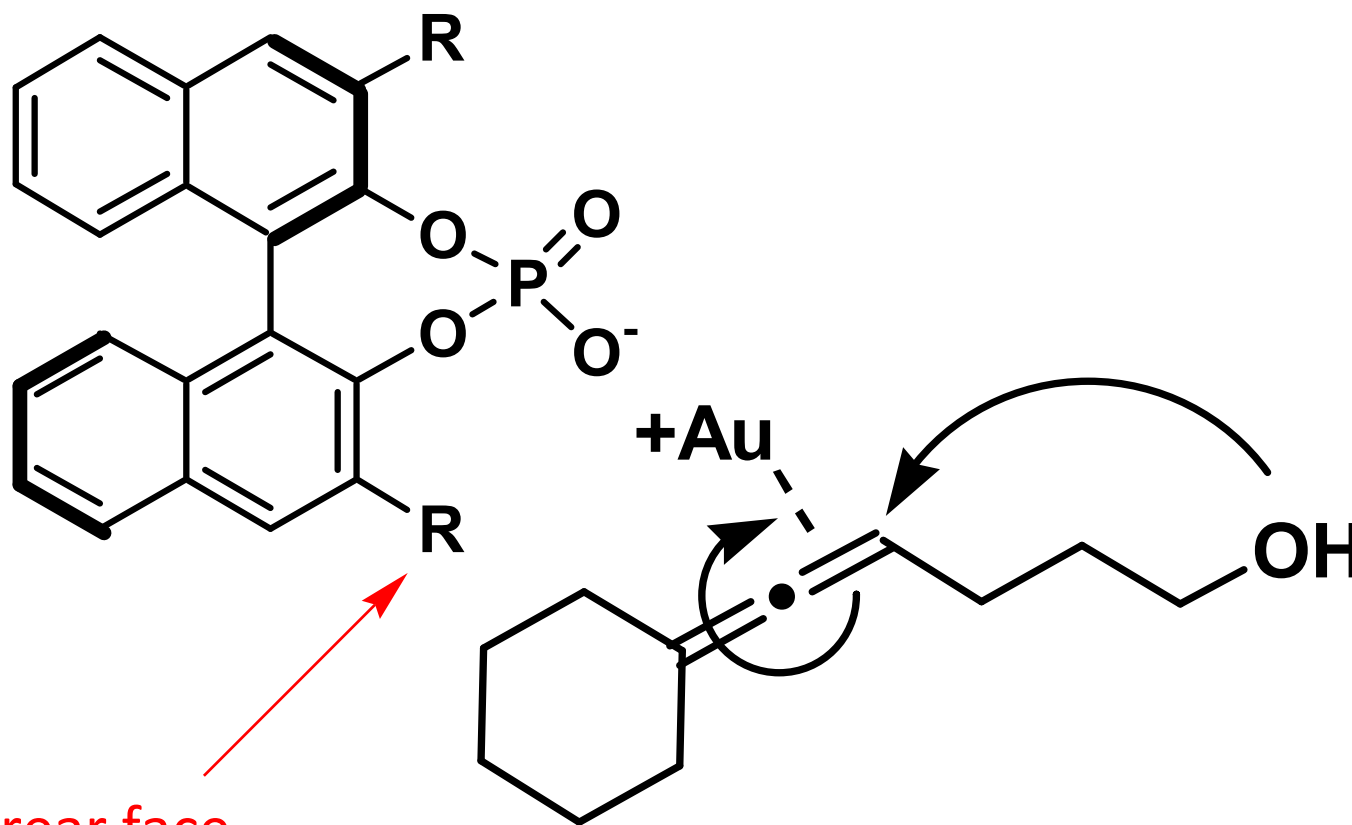
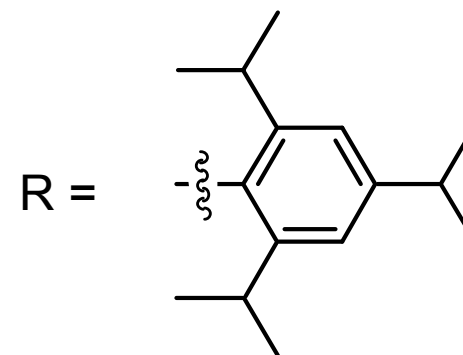
CH ₃ NO ₂	60% yield, 18% ee
acetone	71% yield, 37% ee
THF	83% yield, 76% ee
benzene	90% yield, 97% ee

Mechanistic Insight



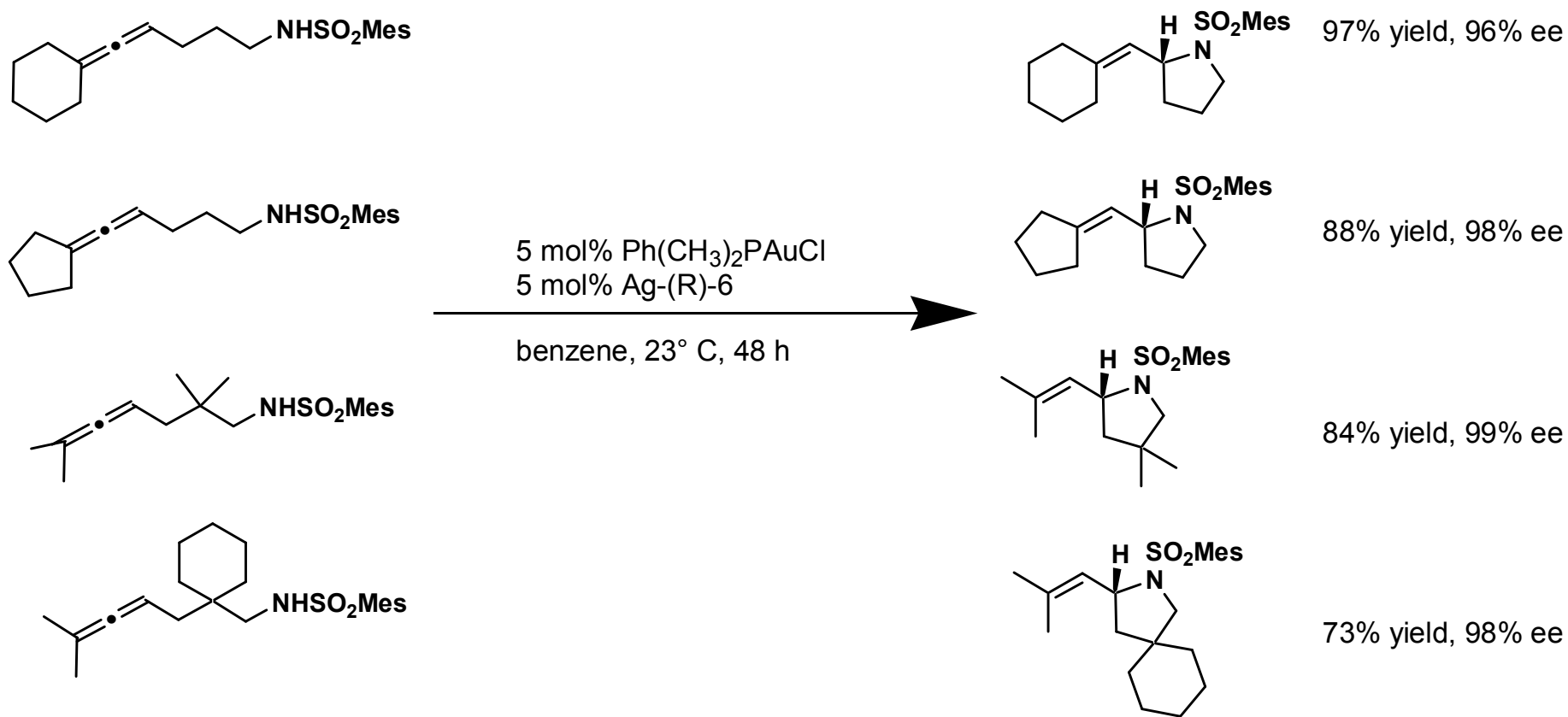
G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste*, **Science**, 2007, 317, 496-499

Possible Transition State



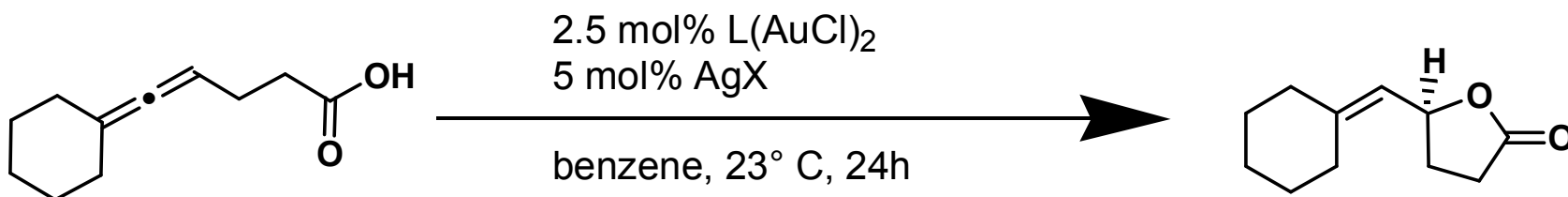
Blocks rear face

Counterion-Mediated Hydroamination



G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste*, **Science**, 2007, 317, 496-499

Hydrocarboxylation Using a Chiral Ligand and Counterion



L = (R)-**3**, X = 4-(NO₂)-C₆H₃-COO⁻

L = dppm, X = (R)-**6**

L = (R)-**3**, X = (R)-**6**

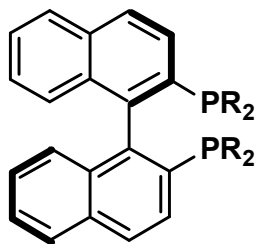
L = (S)-**3**, X = (R)-**6**

80% yield, 38% ee (R)

89% yield, 12% ee (S)

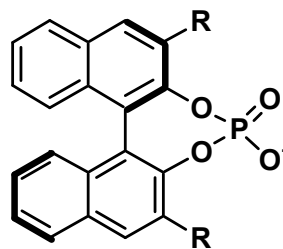
91% yield, 3% ee (R)

88% yield, 82% ee (S)



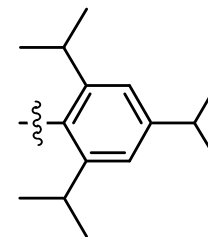
3, R = Ph

4, R = 3,5-(CH₃)₂-C₆H₃



6

R =



Summary

- Chiral counterions are particularly effective for Au due to the 180° ligand-Au-substrate angle
- The combination of chiral ligands and chiral counterions leads to “matched” and “mismatched” enantioselectivity
- This concept is tolerant of changes in the oxidation state of the transition metal

Summary

- This approach is not limited to gold
- This concept only requires that ion pairing be maintained in the transition state of the enantiodetermining step
- Reactions catalyzed by Pd, Ru, Rh and Ir could be possible targets of this strategy
- The combination of chiral ligands and chiral counterions has the potential to be an extremely powerful tool