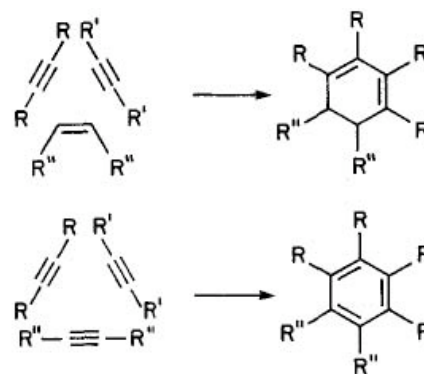
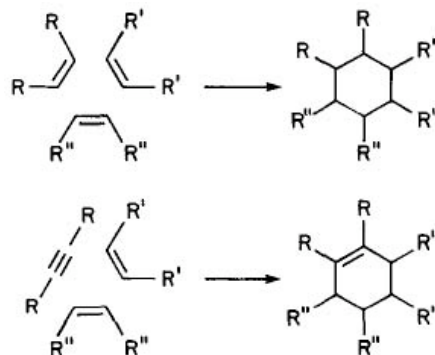


# [2+2+2] Cycloadditions

## Applied to the Synthesis of Natural Products

Dr. Matthew A. Heuft  
Evans Group Seminar  
March 11, 2005



### Overview

- Background
- Catalysts
- Mechanisms
- Natural Product Synthesis
- Asymmetric Reactions

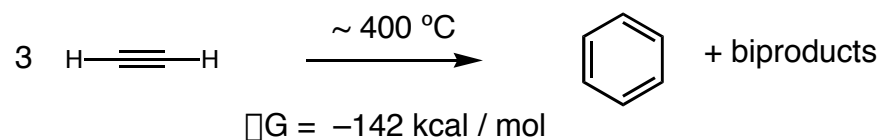
### Background Literature

- Vollhardt, K. P. C. *Acc. Chem. Rev.* **1977**, *10*, 1.  
Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.  
Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.  
Trost, B. M. *Science* **1991**, *254*, 1471.  
Lautens, M. *et. al. Chem. Rev.* **1996**, *96*, 49.  
Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

# Background

Thermal reaction is symmetry allowed

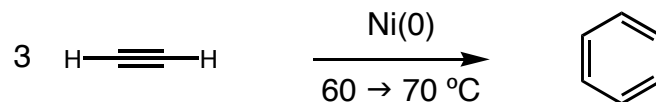
First thermal [2+2+2] cyclotrimerization was reported in 1866 by Berthelot



The reaction is exothermic despite the large loss in entropy

Reppe reported the first metal-catalyzed [2+2+2] cyclotrimerization reaction in 1949

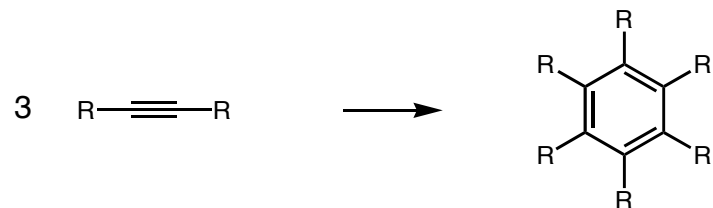
Not a concerted reaction



The reaction occurred at lower temperature and with fewer byproducts

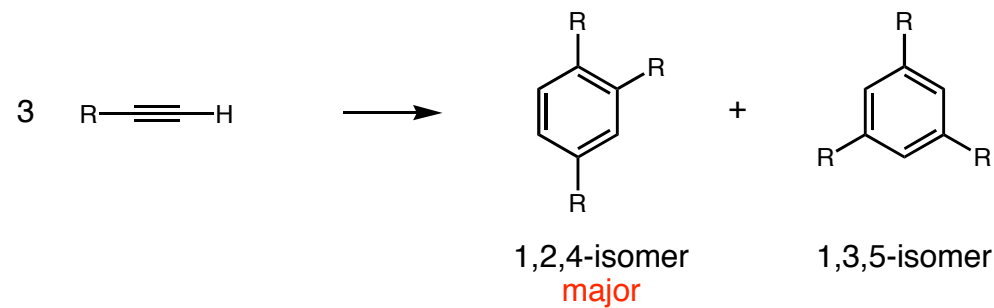
# Background

symmetrical alkynes

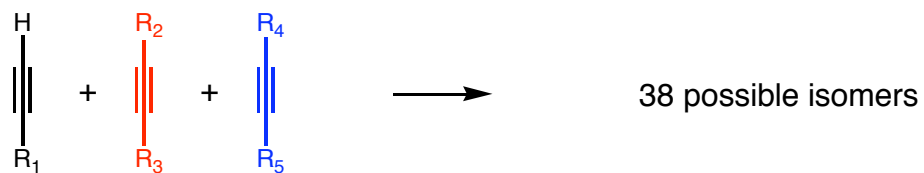


hexa-substituted benzenes

unsymmetrical alkynes



different alkynes



# Catalysts

Metals basic requirements:

- precatalyst must be able to bind two alkynes
- have stable n and n+2 oxidation states

Numerous metals have been used Ni, Co, Rh, Fe, Ir, Zr, Ti, Pd, Ru

$\text{Ni}(\text{cod})_2$   
(Reppe)

$\text{CpCo}(\text{CO})_2$   
(Vollhardt)

$\text{RhCl}(\text{PPh}_3)_3$   
Wilkinson's catalyst  
(Stevenson)

$\text{CpRuCl}$   
(Yamamoto)

Most studied metals are Co, Rh, and Ru

Reaction proceeds by different mechanisms depending on the metal

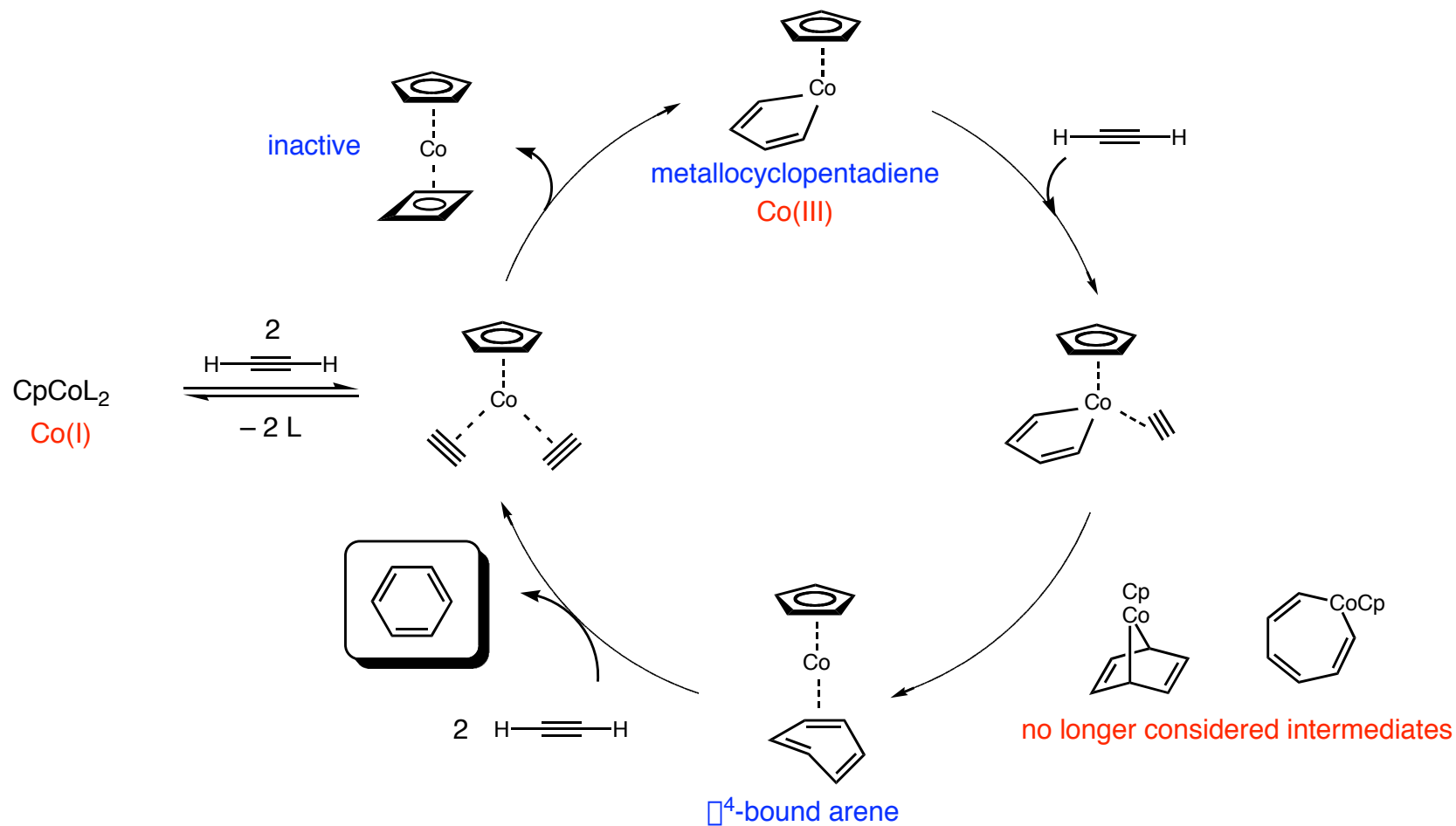
$\text{CpCo}(\text{CO})_2$  requires activation with  $\text{H}_2$  before use to aid displacing the CO ligands

$\text{CpCo}(\text{C}_2\text{H}_4)_2$  is now used

Rhodium catalyzed reactions are generally limited to tethered substrates

Ruthenium catalysts work only for electron-poor substrates

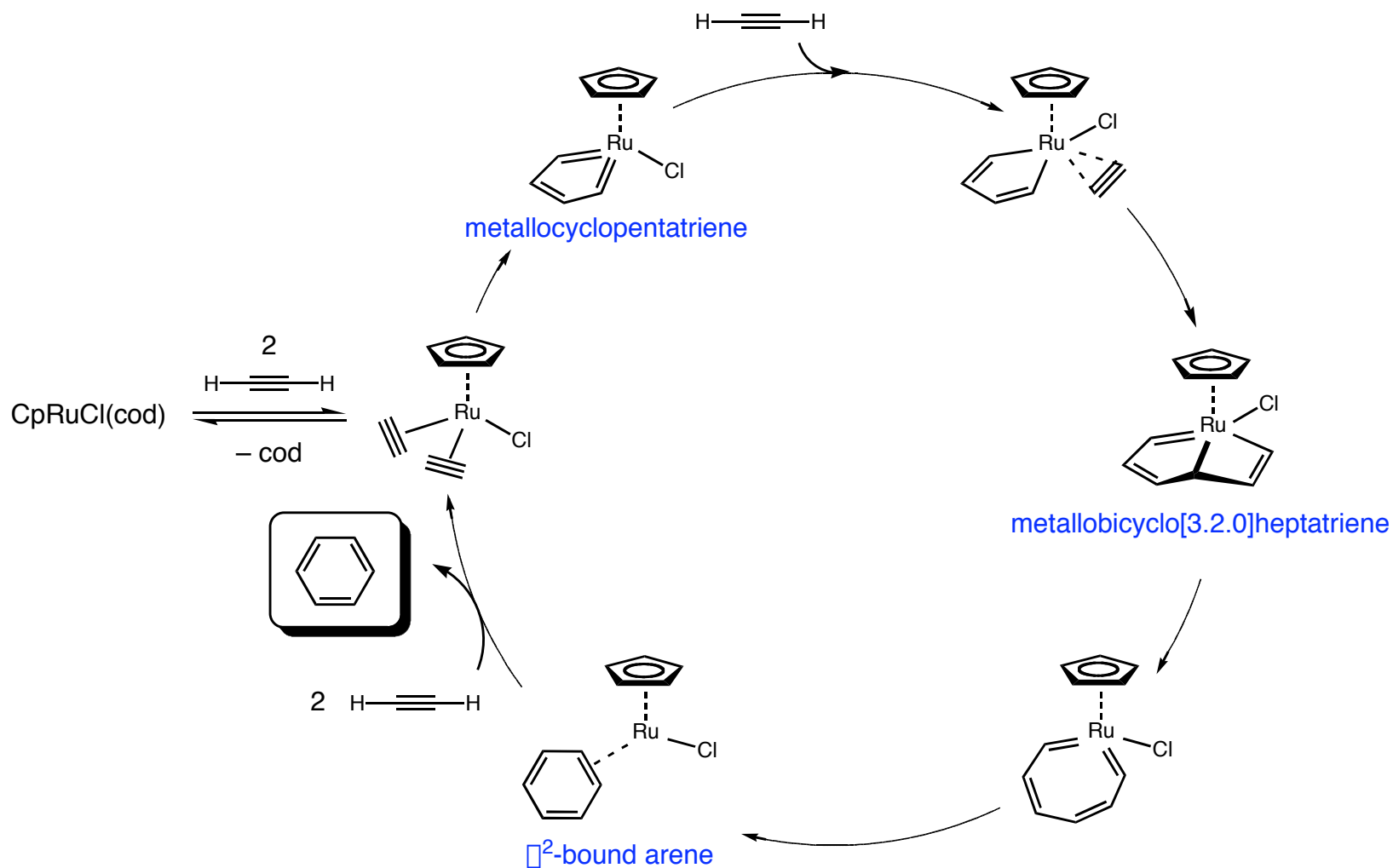
# Cobalt [2+2+2] Mechanism



X-ray structures of cobalt complexes  
(Vollhardt, K. P. C. *JACS* **1998**, *120*, 8247)

Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.  
Albright, T. A. *et. al. J. Am. Chem. Soc.* **1999**, *121*, 6055.

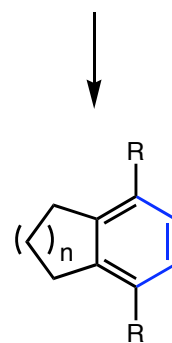
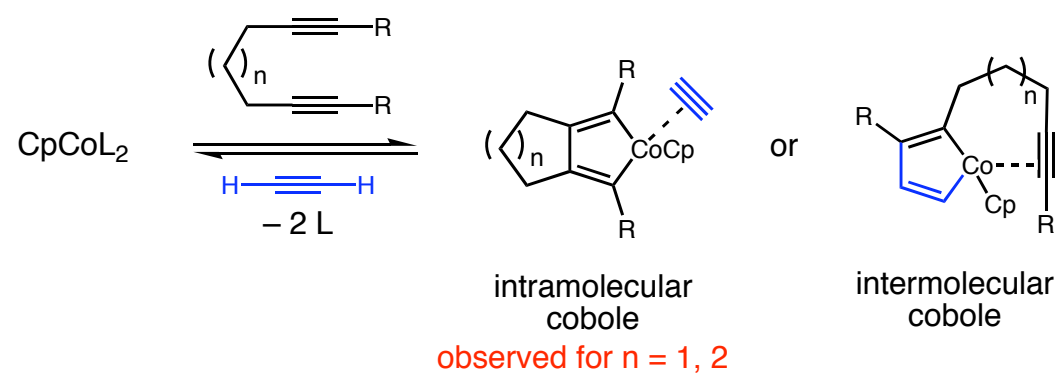
# Ruthenium Mechanism



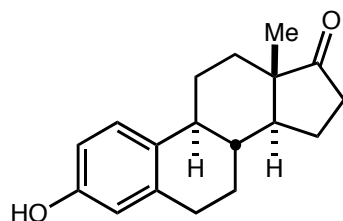
X-ray structure of an Ir[3.2.0] complex  
 (Paneque, M. *et. al.* *JACS* **2004**, 126, 1610)

Kirchner, K. *et. al.* *J. Am. Chem. Soc.* **2003**, 125, 11721.  
 Yamamoto, Y. *et. al.* *J. Am. Chem. Soc.* **2003**, 125, 12143.

# Intramolecular Diynes



# (±)-Estrone



(±)-Estrone

Steroid Skeleton

Aromatic A ring Steroids (D → ABCD)

[Total Synthesis of \*d\*-Estrone](#)

Aromatic A ring Steroids (A → ABCD)

Aromatic A ring Steroids (A → ABCD)

Aromatic B ring Steroids (acyclic precursor)

*J. Am. Chem. Soc.* **1977**, *99*, 5483.

*J. Am. Chem. Soc.* **1979**, *101*, 215.

*J. Am. Chem. Soc.* **1980**, *102*, 5253.

*J. Org. Chem.* **1982**, *47*, 3447.

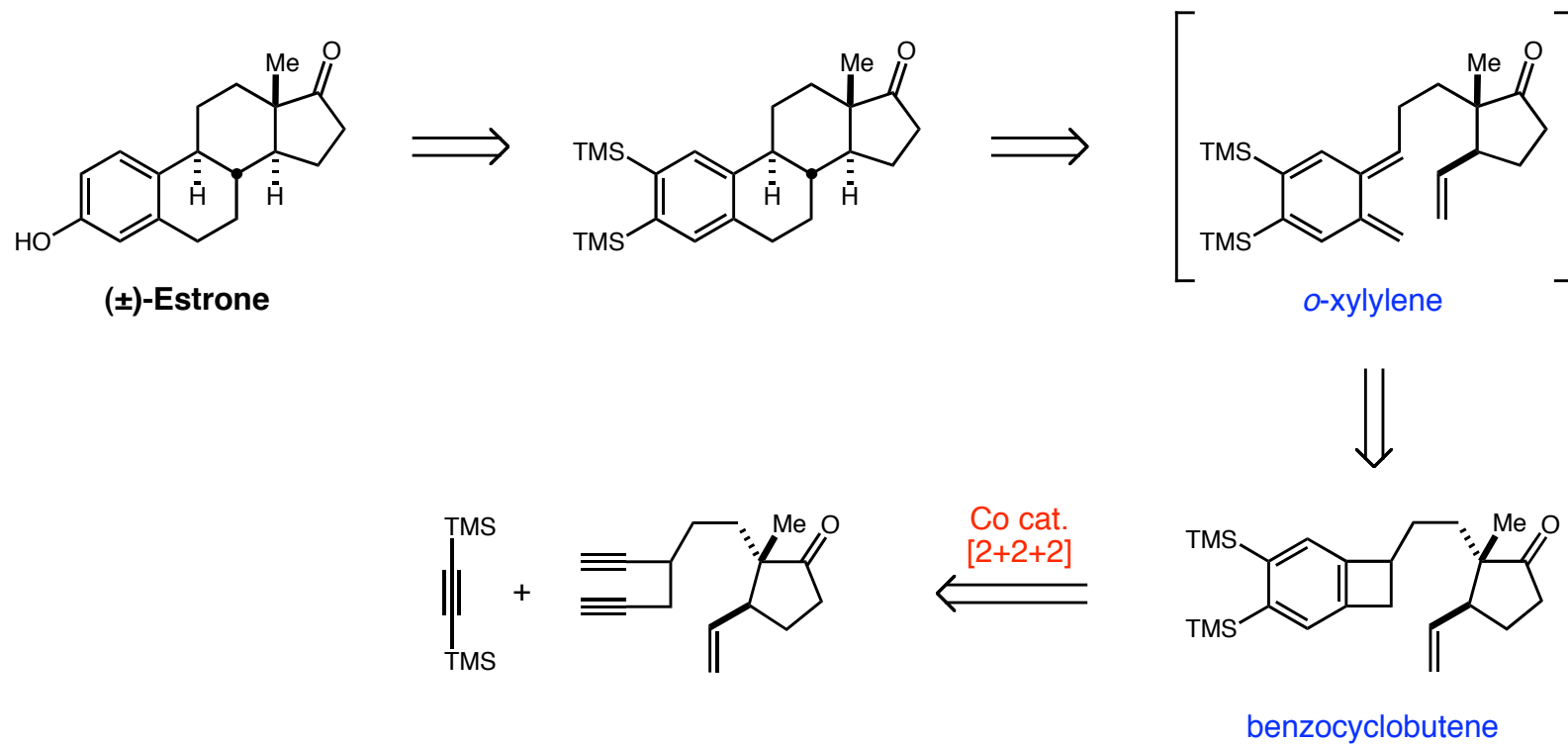
*J. Org. Chem.* **1984**, *49*, 1574.

*J. Am. Chem. Soc.* **1986**, *108*, 856.

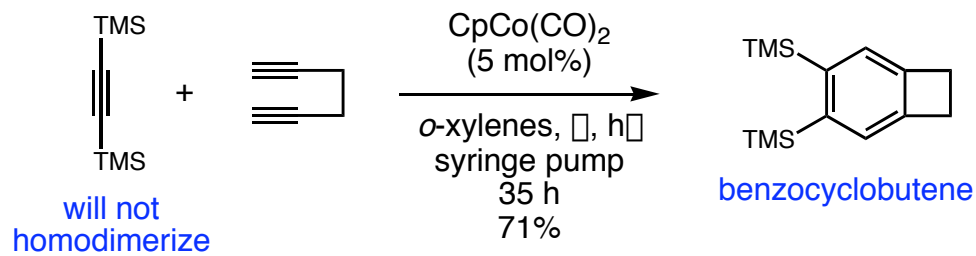
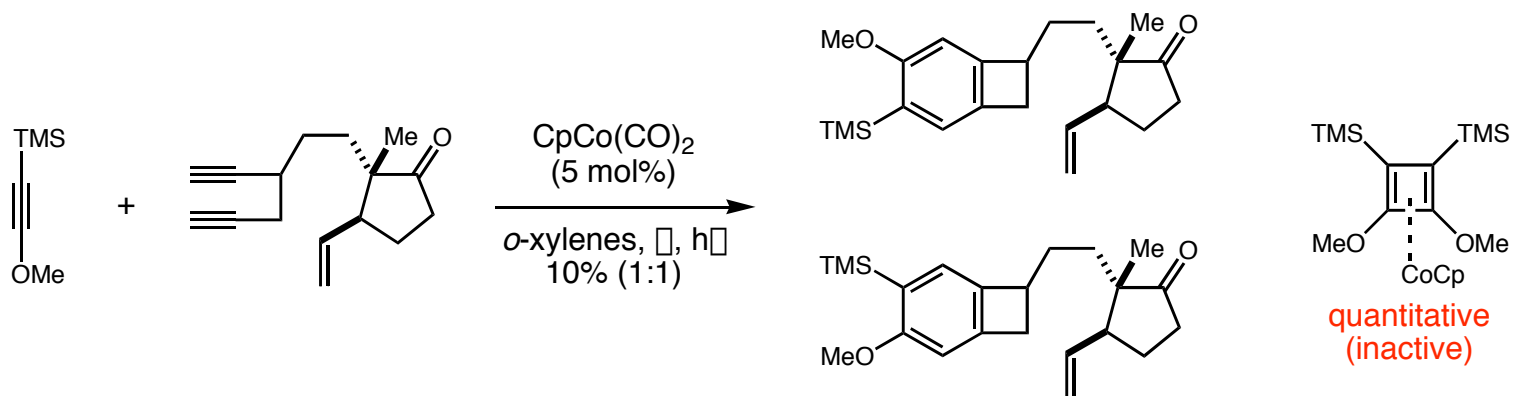
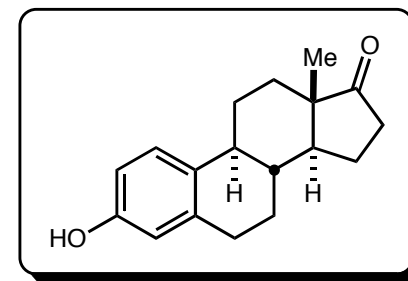
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, Ch. 10, 1996.



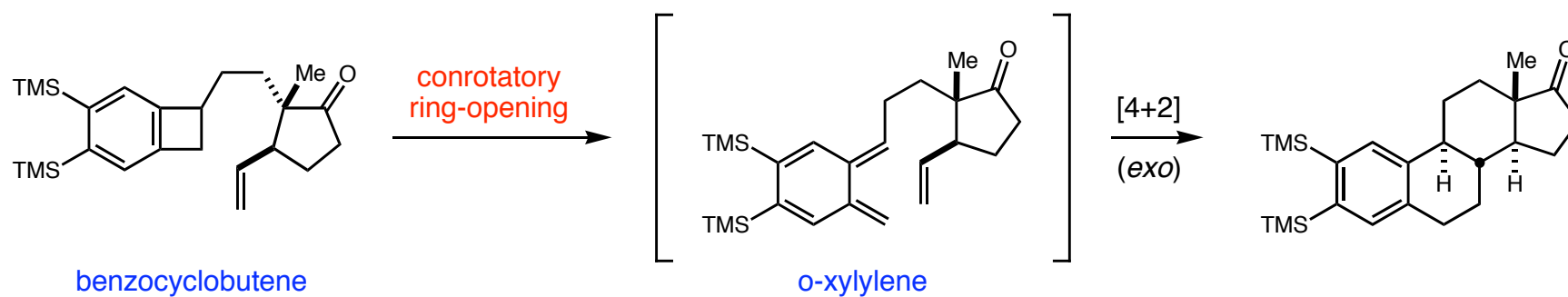
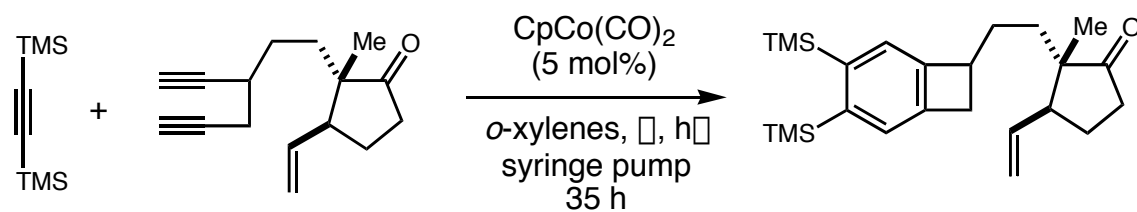
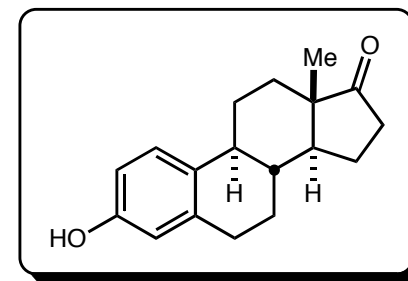
(±)-Estrone  
(D → ABCD)



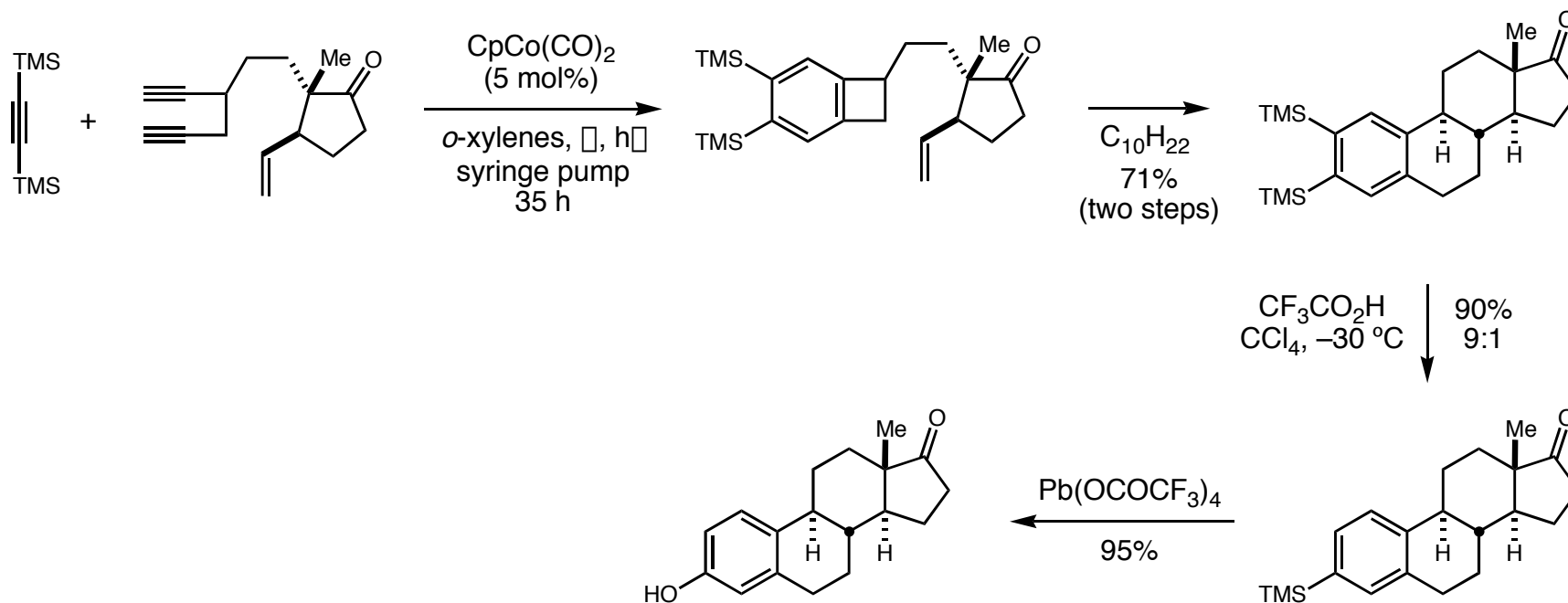
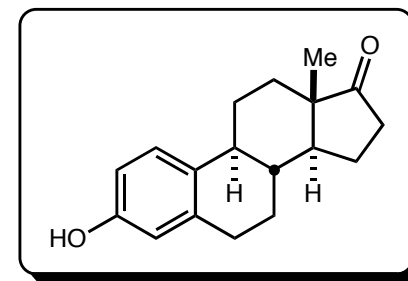
# (±)-Estrone



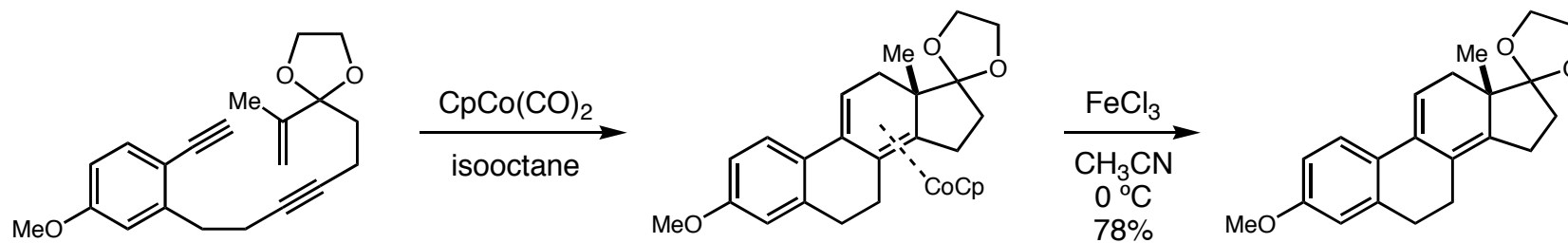
# (±)-Estrone



# (±)-Estrone

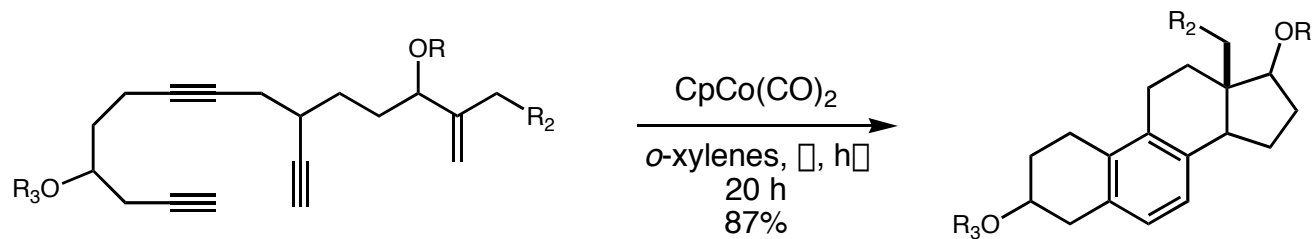


## (±)-Estrone (A → ABCD)



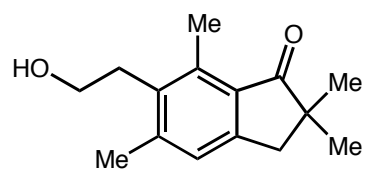
Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1982**, *47*, 3447.  
Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1984**, *49*, 1574.

## Aromatic B-ring Steroid

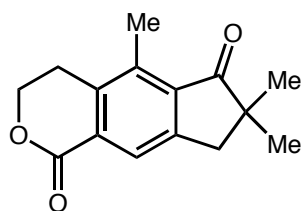


Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1986**, *108*, 856.

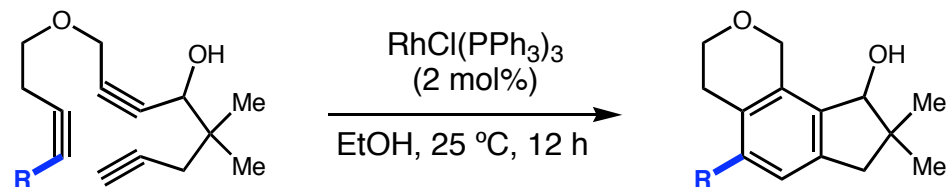
# Illudalanes



**Pterosin**

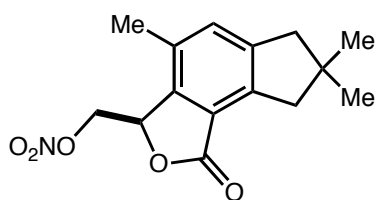


**Calomelanolactone**

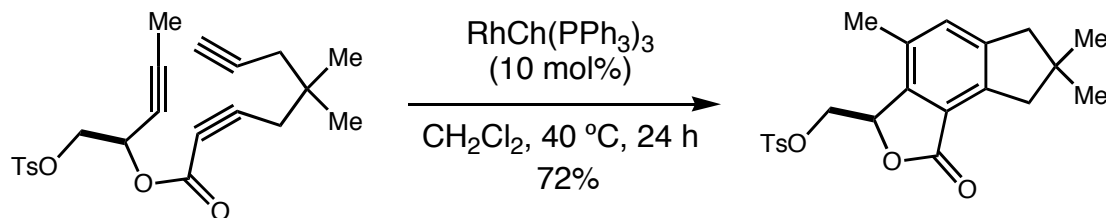


R = Me 82% (pterosin)  
R = CH<sub>2</sub>OH 86% (calomelanolactone)

Stevenson, P. J. *et. al. Tetrahedron* **1989**, 45, 6239.

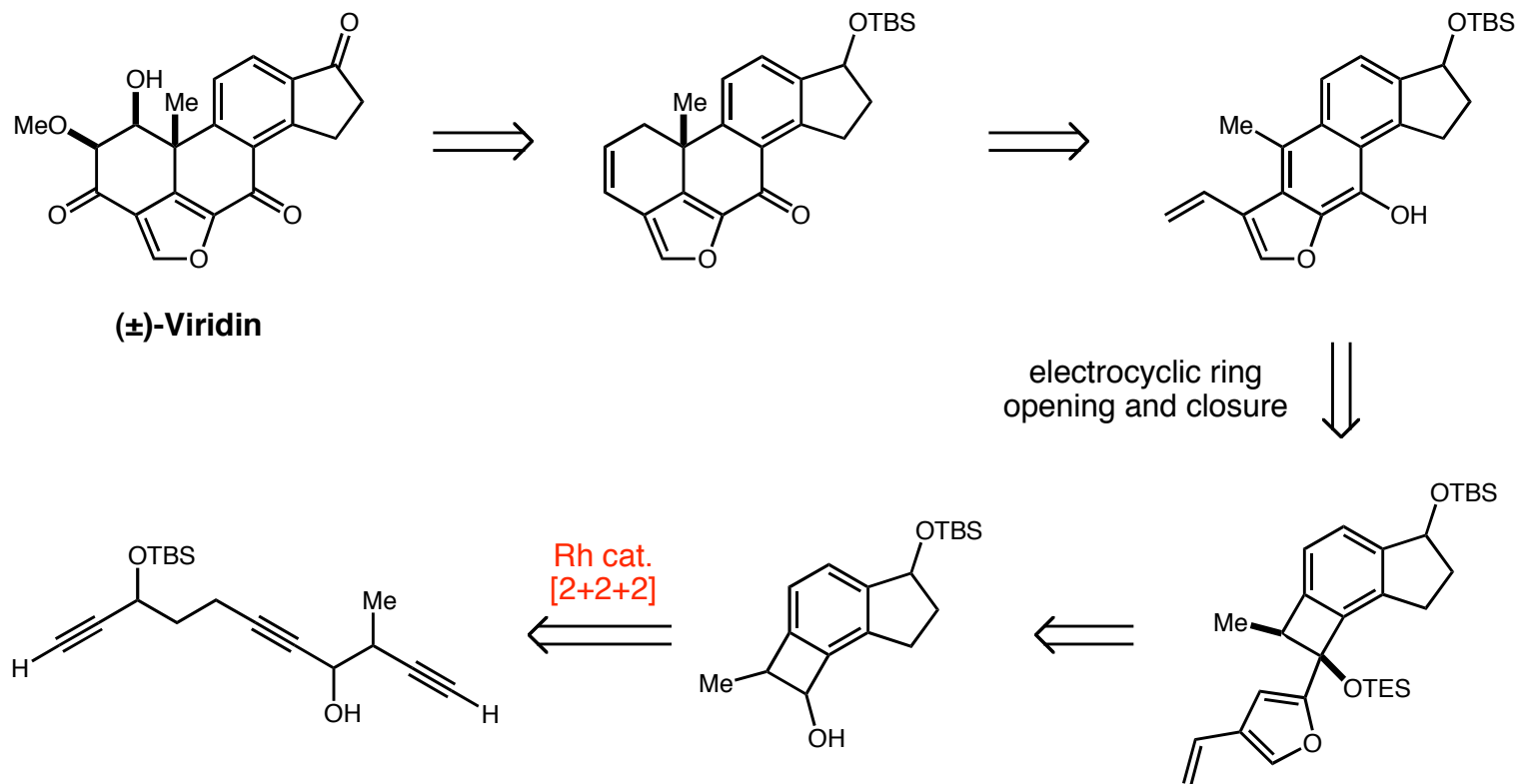


**Alcyopterosin E**

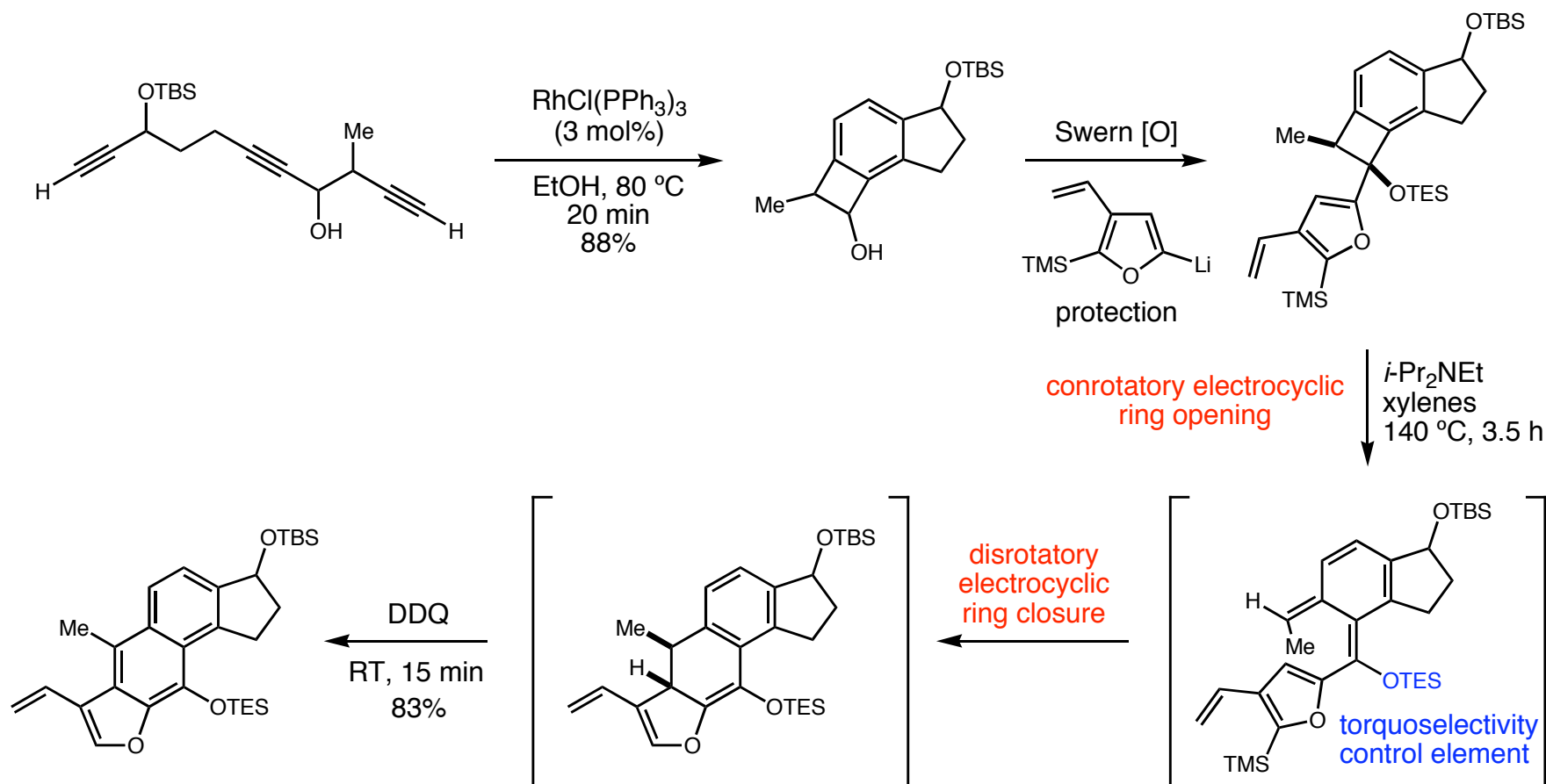
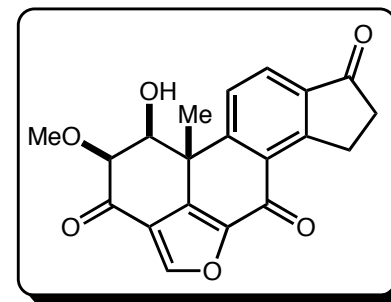


Witulski, B. *et. al. Chem. Commun.* **2002**, 2985.

# (±)-Viridin



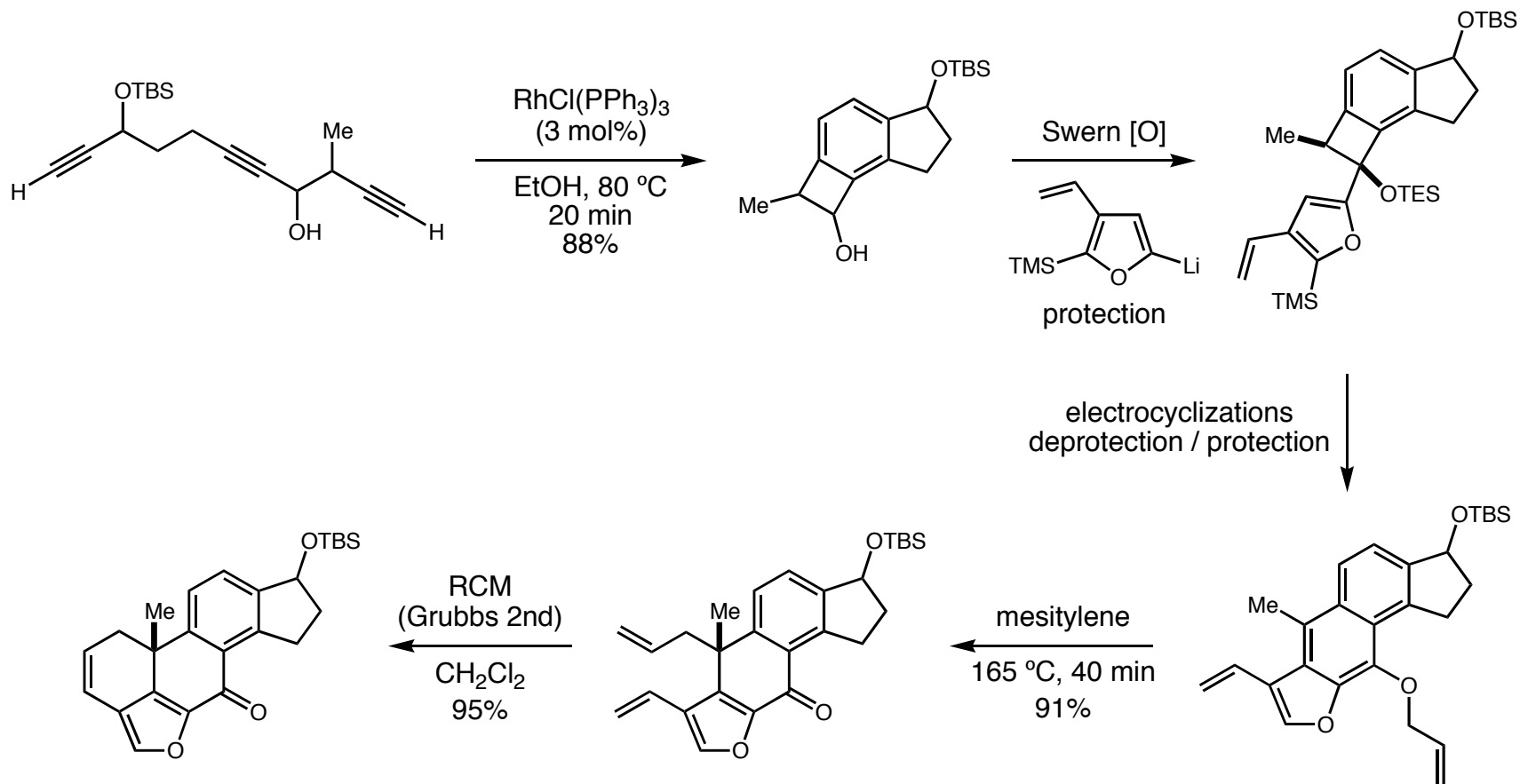
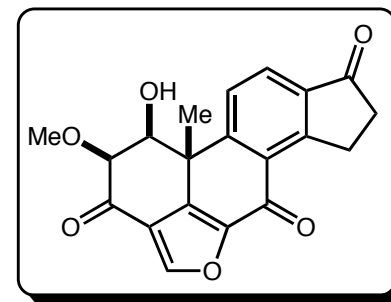
# (±)-Viridin



Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, 43, 1998.



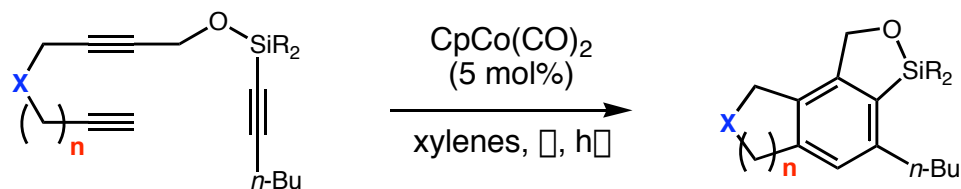
# (±)-Viridin



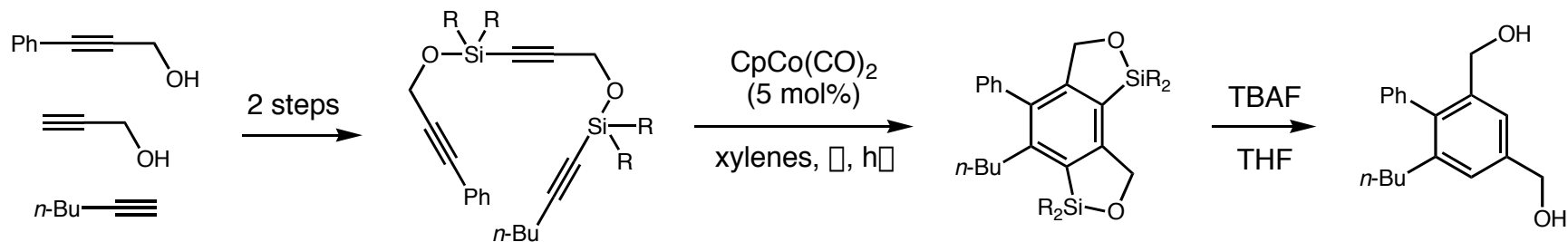
13 more steps to elaborate  
the A ring, deprotect, and oxidize

Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, 43, 1998.

# Tethered Alkynes

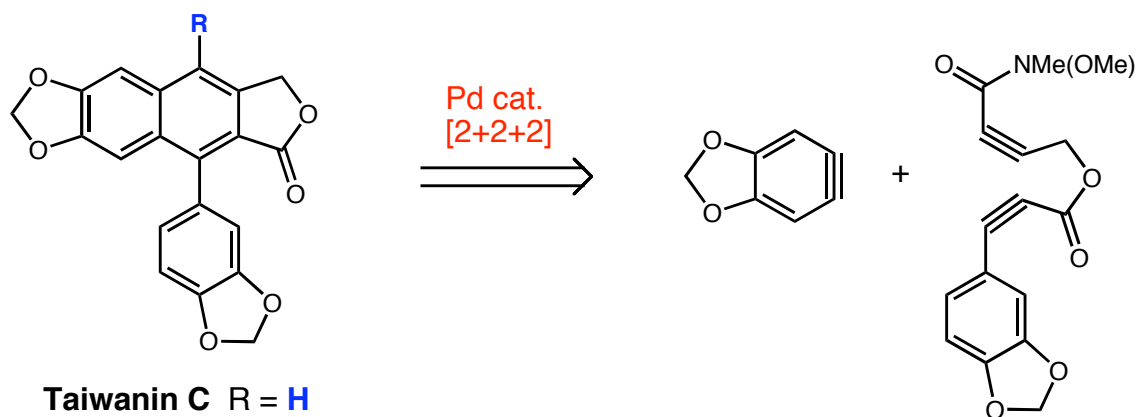


| X               | n | Yield (%) |
|-----------------|---|-----------|
| CH <sub>2</sub> | 1 | 77        |
| CH <sub>2</sub> | 2 | 78        |
| CH <sub>2</sub> | 3 | 73        |
| O               | 1 | 67        |
| NCbz            | 1 | 73        |

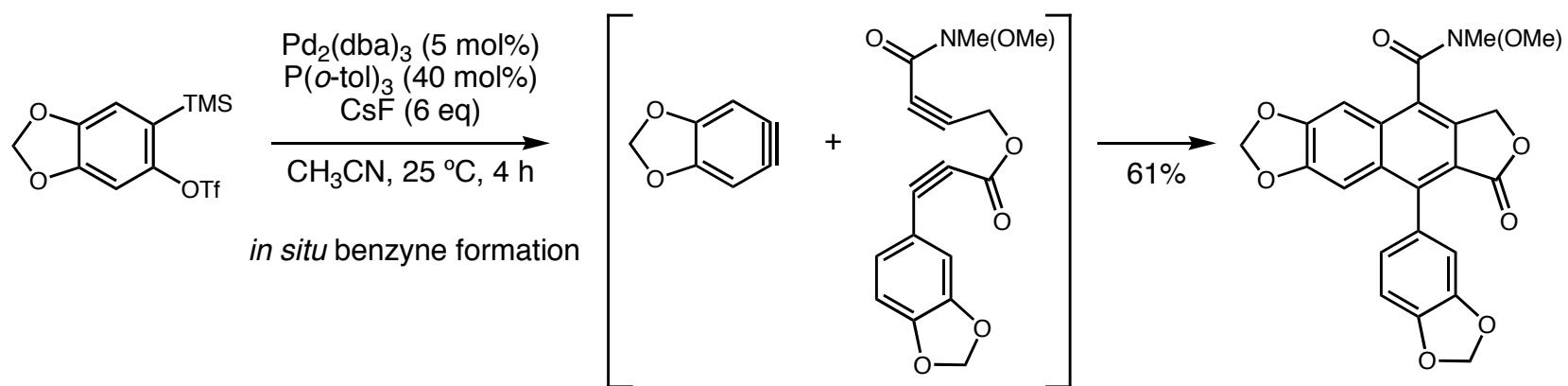


Silicon-tethered alkynes (illustrated): Malacria, M. *et al. Org. Lett.* **2004**, 6, 1519.  
 Boron-tethered alkynes: Yamamoto, Y. *et al. J. Am. Chem. Soc.* **2004**, 126, 3712.

# Taiwanins C and E

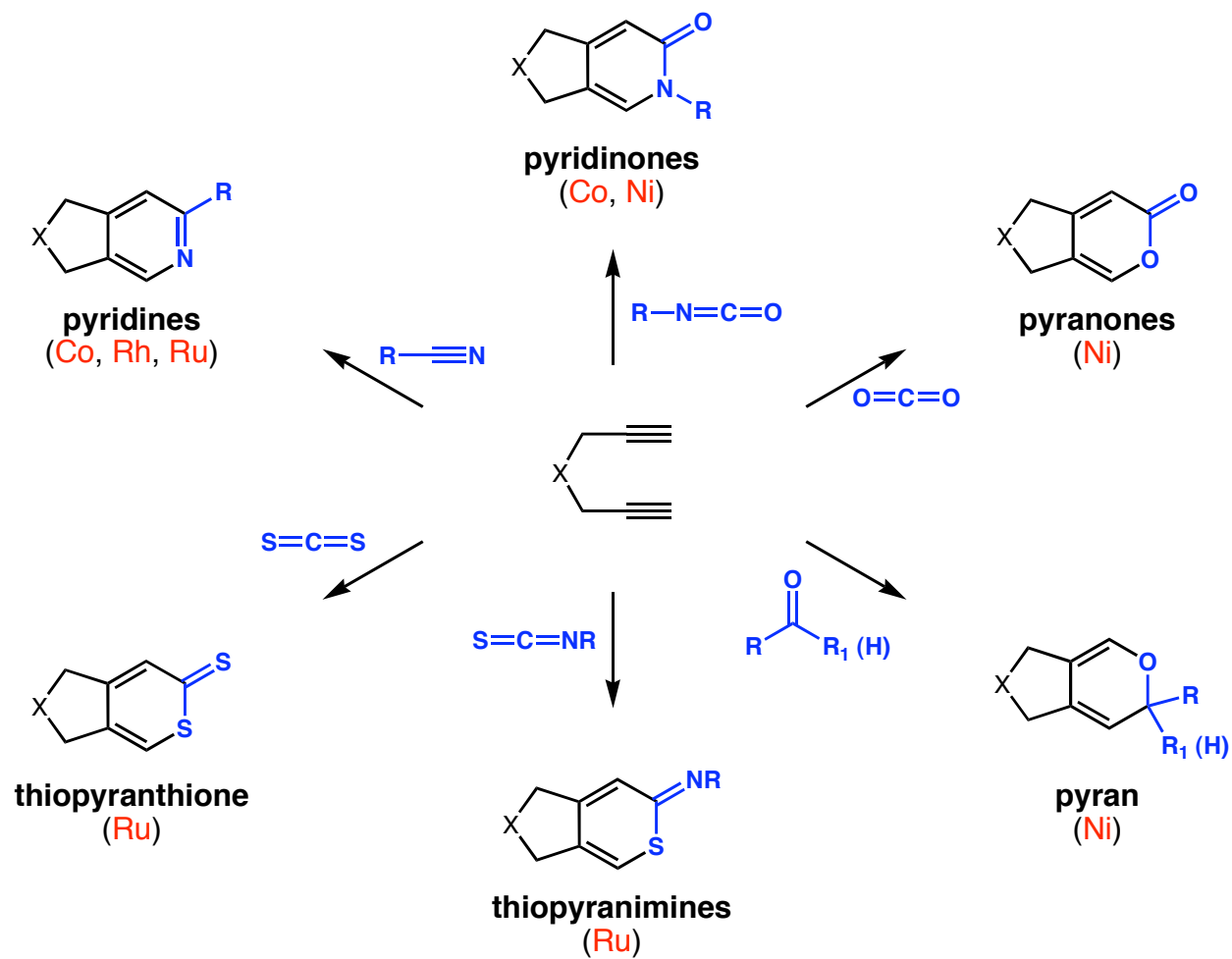


Taiwanin C R = H  
Taiwanin E R = OH



(R could not be an alcohol, aldehyde, or ester)

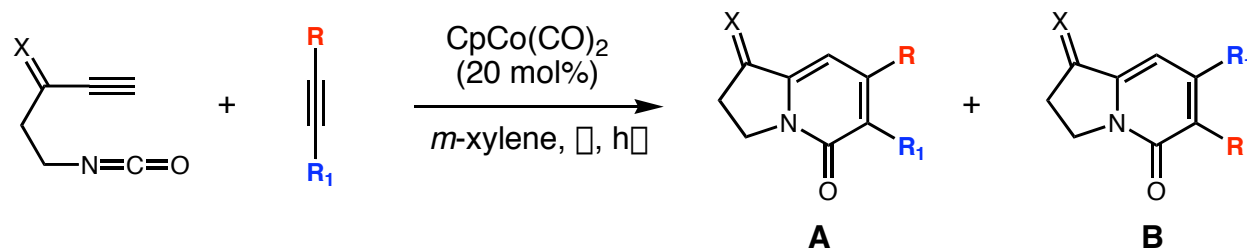
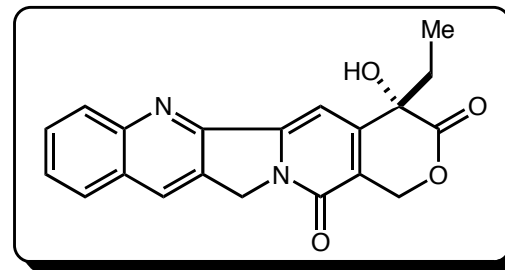
# Heterocycle Synthesis



Lautens, M. *et al. Chem. Rev.* **1996**, 96, 49.  
Yamamoto, Y. *et al. J. Am. Chem. Soc.* **2005**, 127, 605.



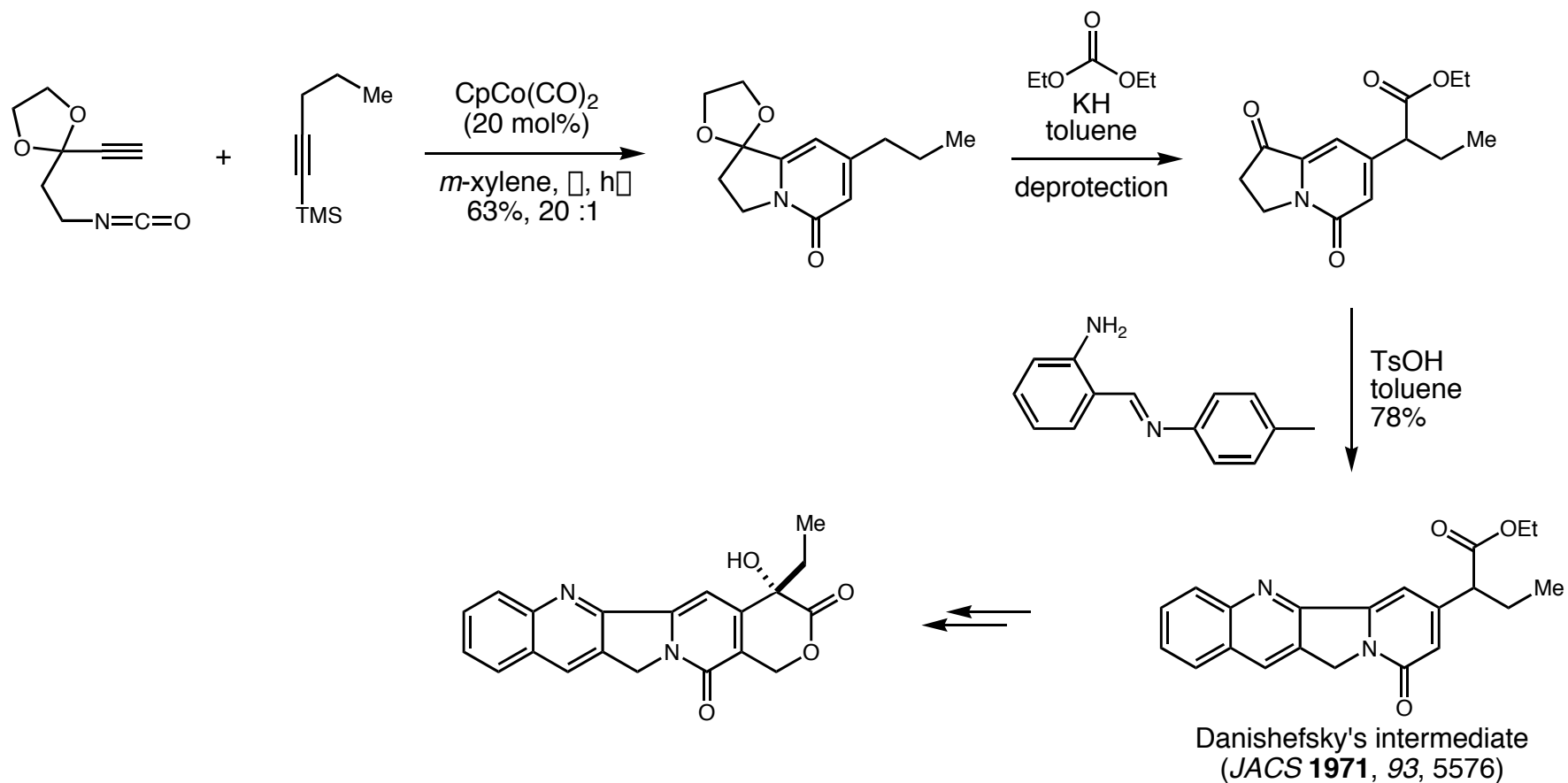
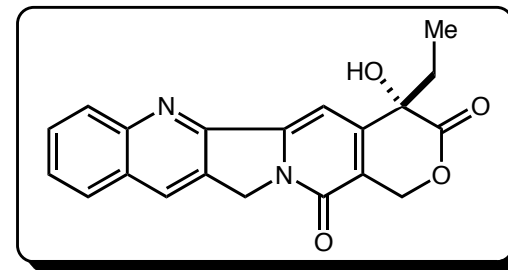
# (±)-Camptothecin



| X                                  | R               | R <sub>1</sub>         | Yield (%) | A : B    |
|------------------------------------|-----------------|------------------------|-----------|----------|
| H <sub>2</sub>                     | TMS             | TMS                    | 72        | –        |
| H <sub>2</sub>                     | <i>n</i> -Pr    | TMS                    | 73        | 12 : 1   |
| H <sub>2</sub>                     |                 | TMS                    | 76        | > 40 : 1 |
| OCH <sub>2</sub> CH <sub>2</sub> O | TMS             | TMS                    | 68        | –        |
| OCH <sub>2</sub> CH <sub>2</sub> O | <i>n</i> -Pr    | TMS                    | 63        | 20 : 1   |
| OCH <sub>2</sub> CH <sub>2</sub> O | <i>n</i> -Pr    | CH <sub>2</sub> OTBDPS | 38        | 1 : 1    |
| OCH <sub>2</sub> CH <sub>2</sub> O | CH <sub>3</sub> | CO <sub>2</sub> Et     | 21        | 1 : 1    |

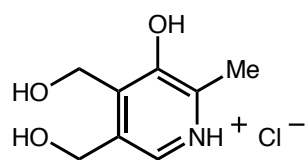
Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1983**, *105*, 6991.  
 Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1984**, *49*, 4786.

# (±)-Camptothecin

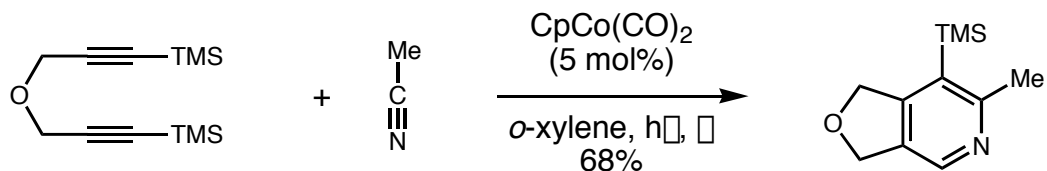


Vollhardt, K. P. C. et al. *J. Am. Chem. Soc.* **1983**, *105*, 6991.  
Vollhardt, K. P. C. et al. *J. Org. Chem.* **1984**, *49*, 4786.

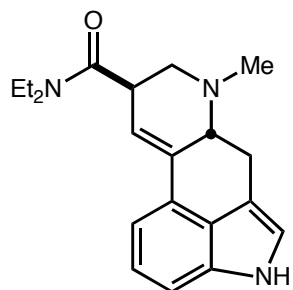
# Alkaloids



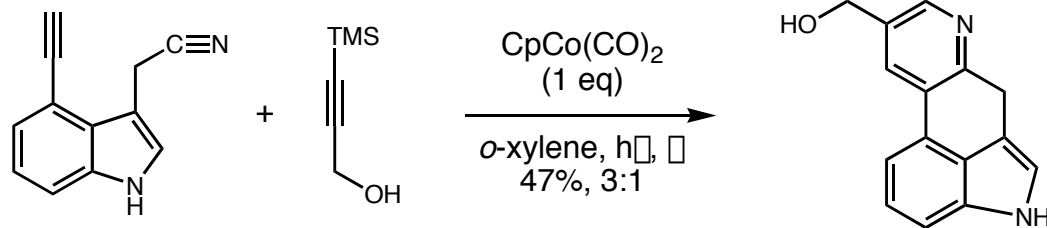
**Vitamin B<sub>6</sub>**



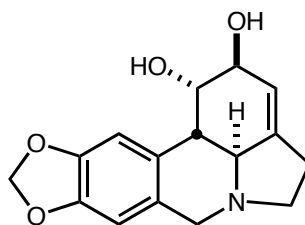
Vollhardt, K. P. C. *et. al. Tetrahedron* **1985**, 41, 5796.



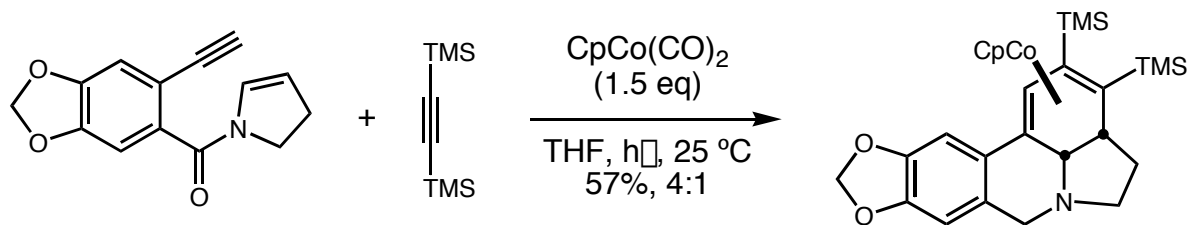
**(±)-Lysergic acid diethylamide**



Vollhardt, K. P. C. *et. al. Syn. Lett.* **1994**, 487.



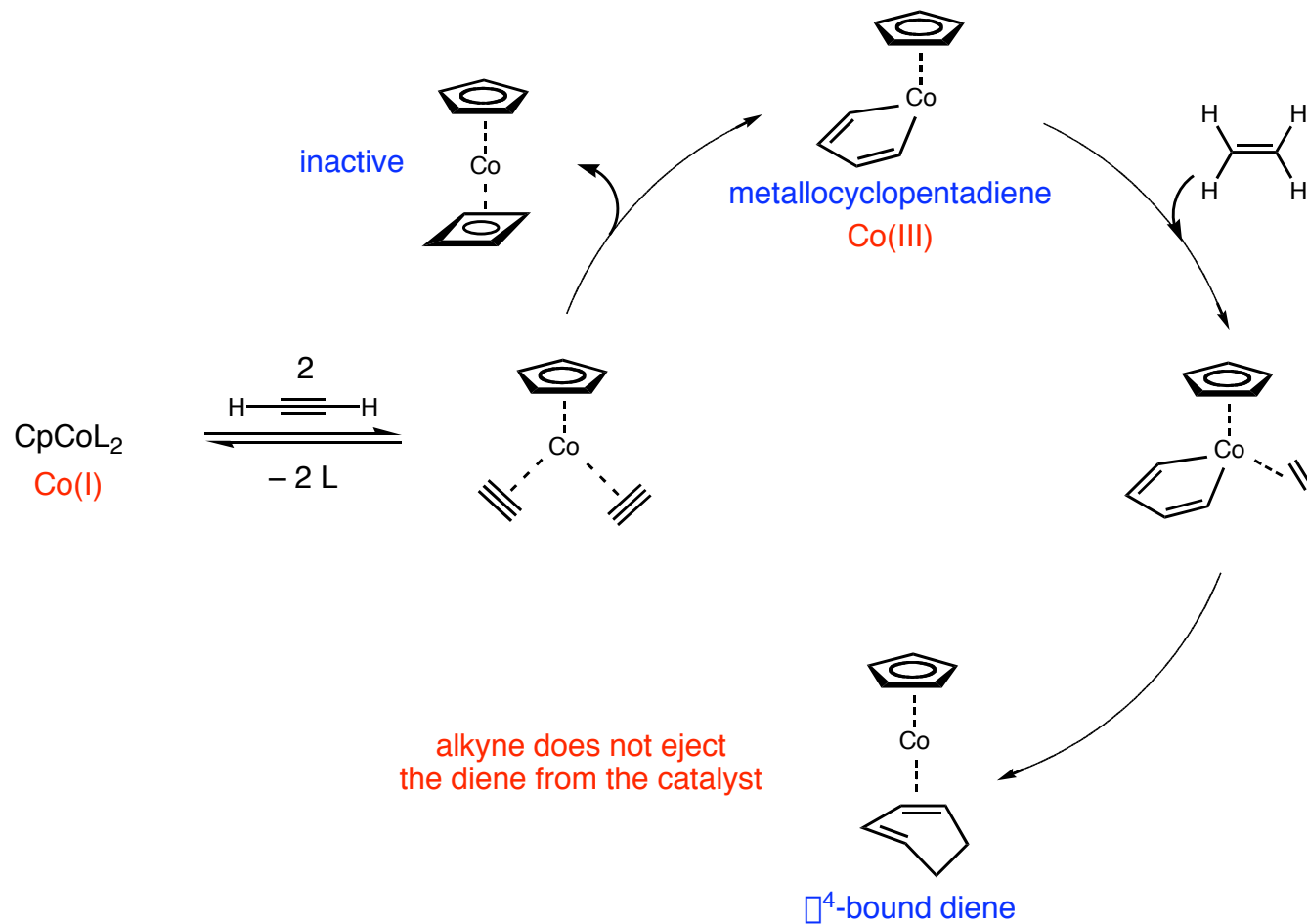
**Lycorane**



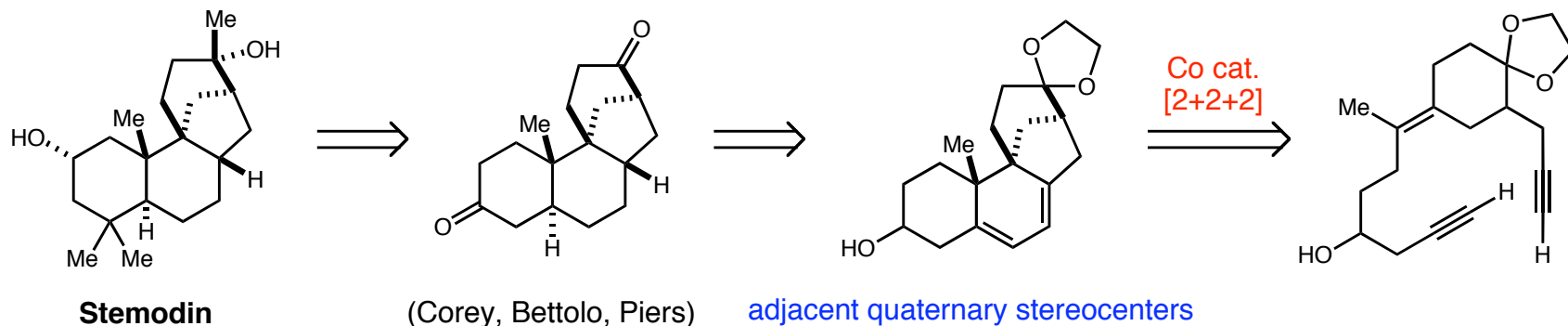
Vollhardt, K. P. C. *et. al. Synthesis* **1994**, 579.



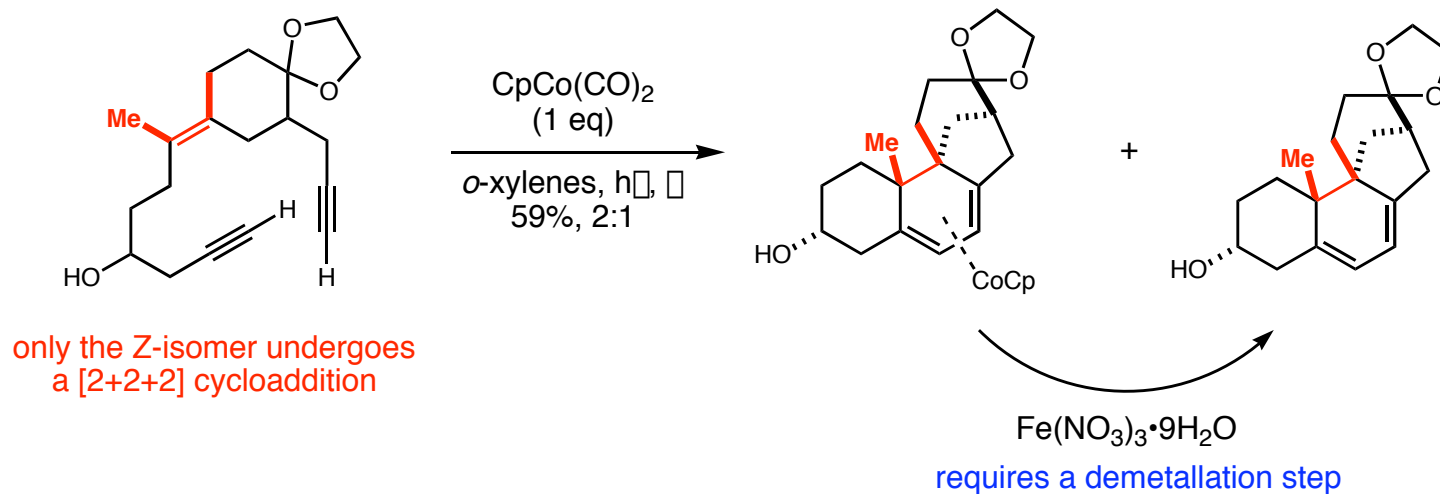
# Cobalt Eneidyne [2+2+2] Mechanism



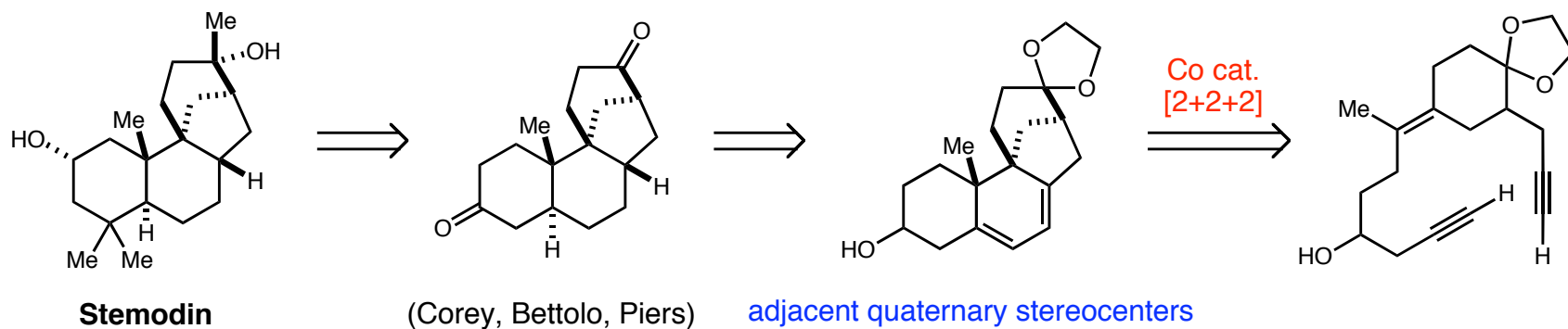
# Enediyne [2+2+2] Cyclizations



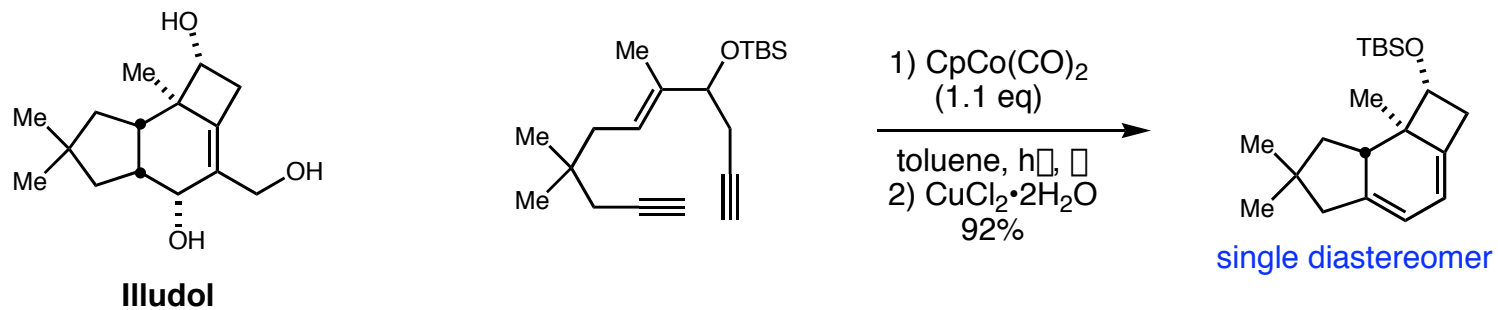
Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1991**, 113, 4006.



# Enediyne [2+2+2] Cyclizations

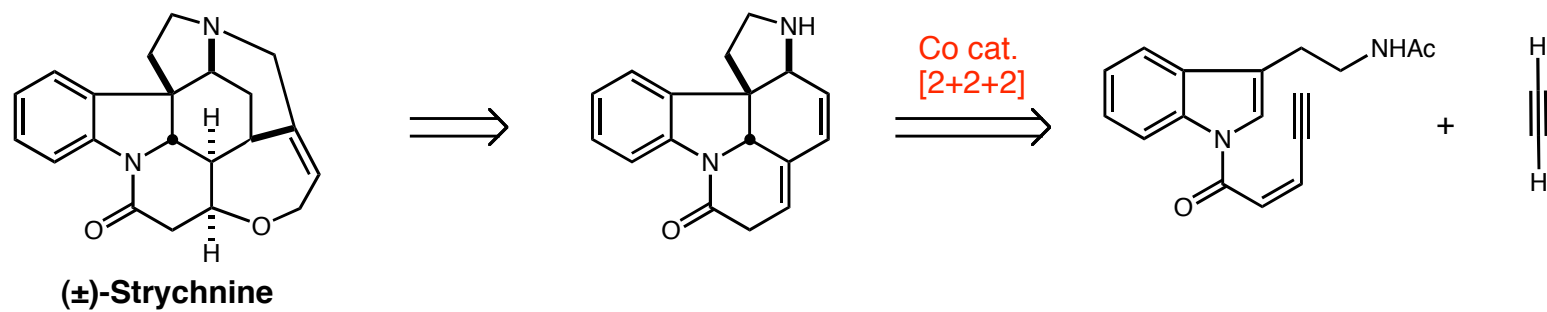


Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1991**, *113*, 4006.



Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1991**, *113*, 381.

# (±)-Strychnine



## Isolation and Structure Determination

Isolated in 1818 from beans of *Strychnos ignatii*

Structure proposed by Robinson and Leuchs (1946) and Woodward (1948)

X-ray structure Robinson (1951)

24 atoms, seven rings, six stereocenters

## Total Synthesis

First Synthesis: Woodward (*J. Am. Chem. Soc.* **1954**, 76, 4749.)

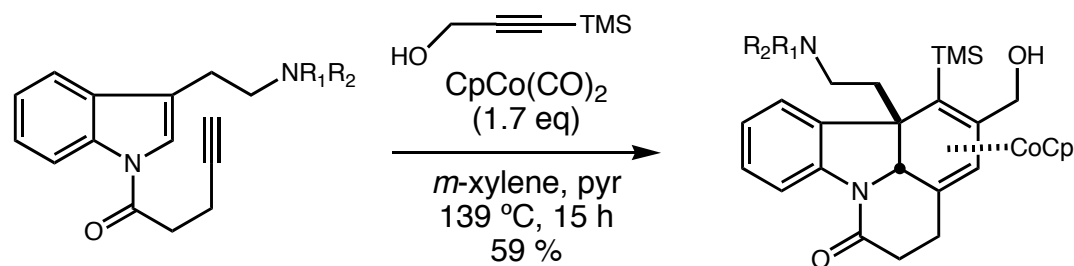
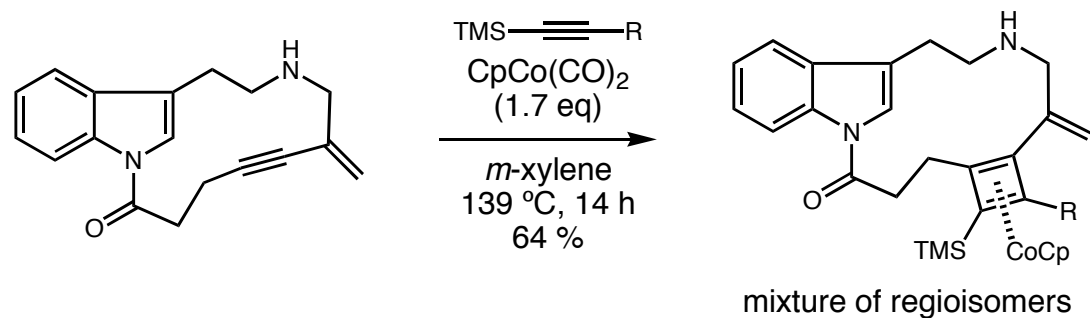
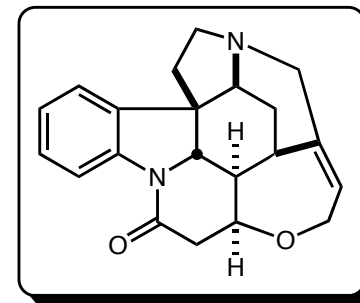
Racemic syntheses: Magnus (1992), Stork (1992), Kuehne (1993), Rawal (1994), Martin (1996)

Enantioselective syntheses: Overman (1995), Kuehne (1998), Bosch (2000), Bodwell (2003)

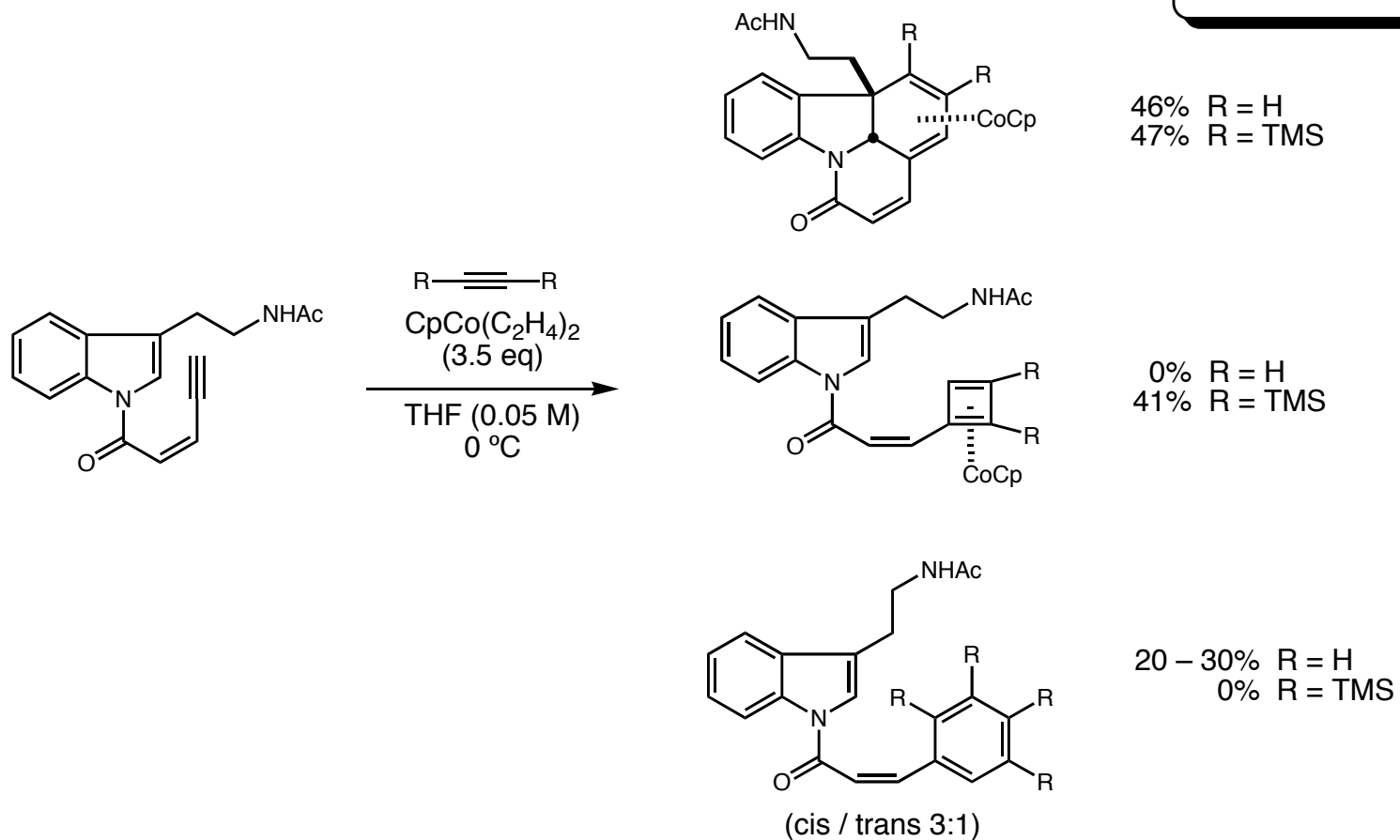
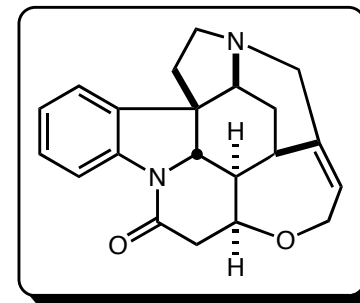
Vollhardt, K. P. C. *et. al. Org. Lett.* **2000**, 2, 2479.

Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **2001**, 123, 9324.

# (±)-Strychnine

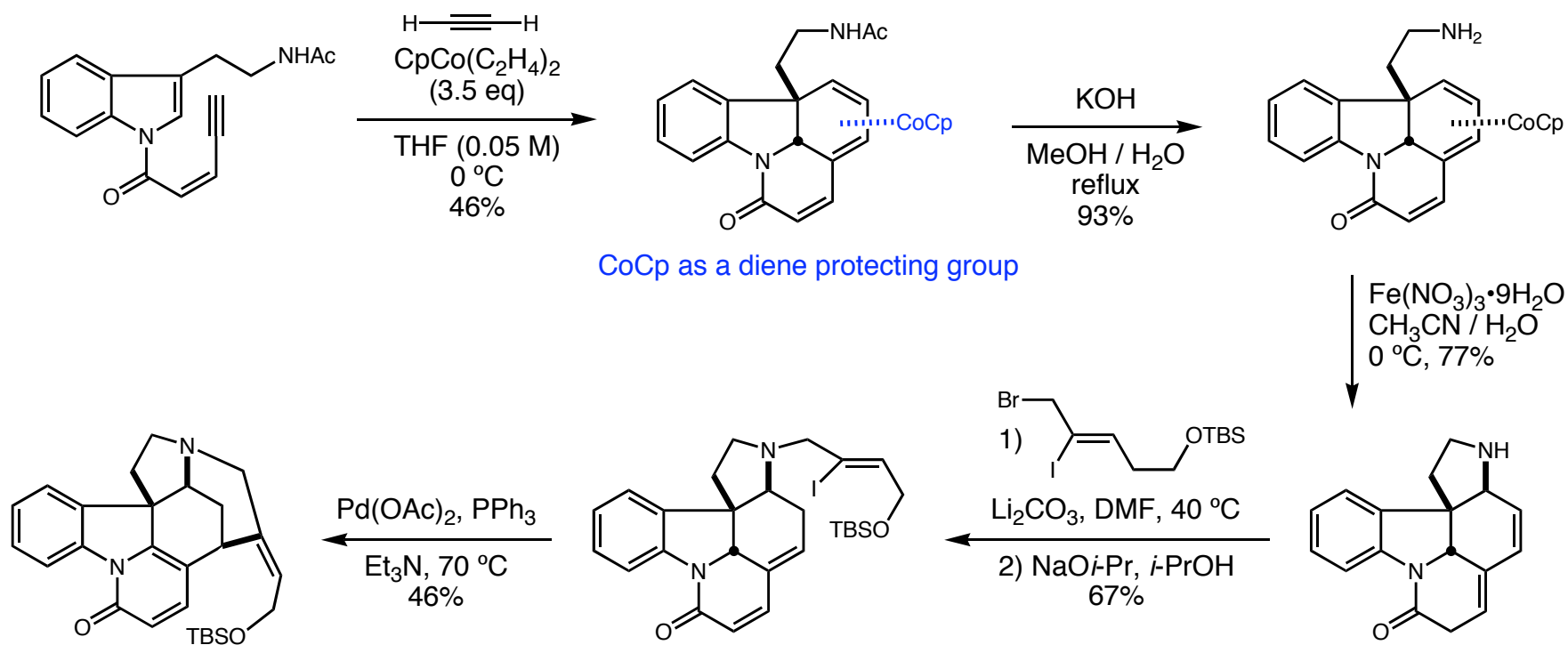
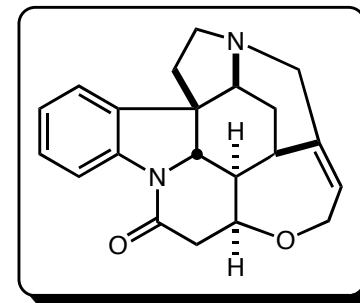


# (±)-Strychnine



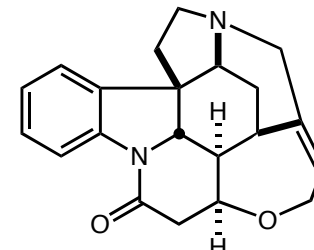
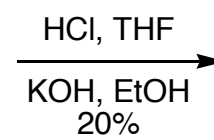
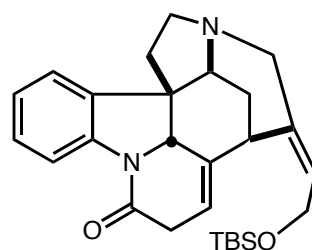
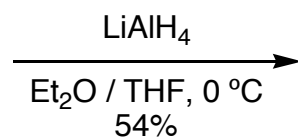
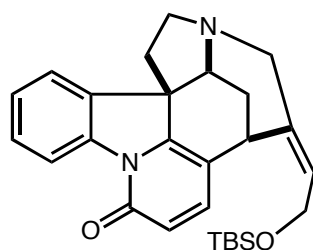
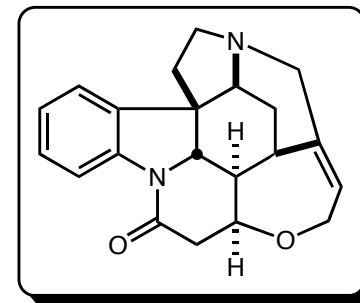
Vollhardt, K. P. C. *et. al. Org. Lett.* **2000**, 2, 2479.  
 Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **2001**, 123, 9324.

# (±)-Strychnine



Vollhardt, K. P. C. *et al. Org. Lett.* **2000**, 2, 2479.  
Vollhardt, K. P. C. *et al. J. Am. Chem. Soc.* **2001**, 123, 9324.

# (±)-Strychnine

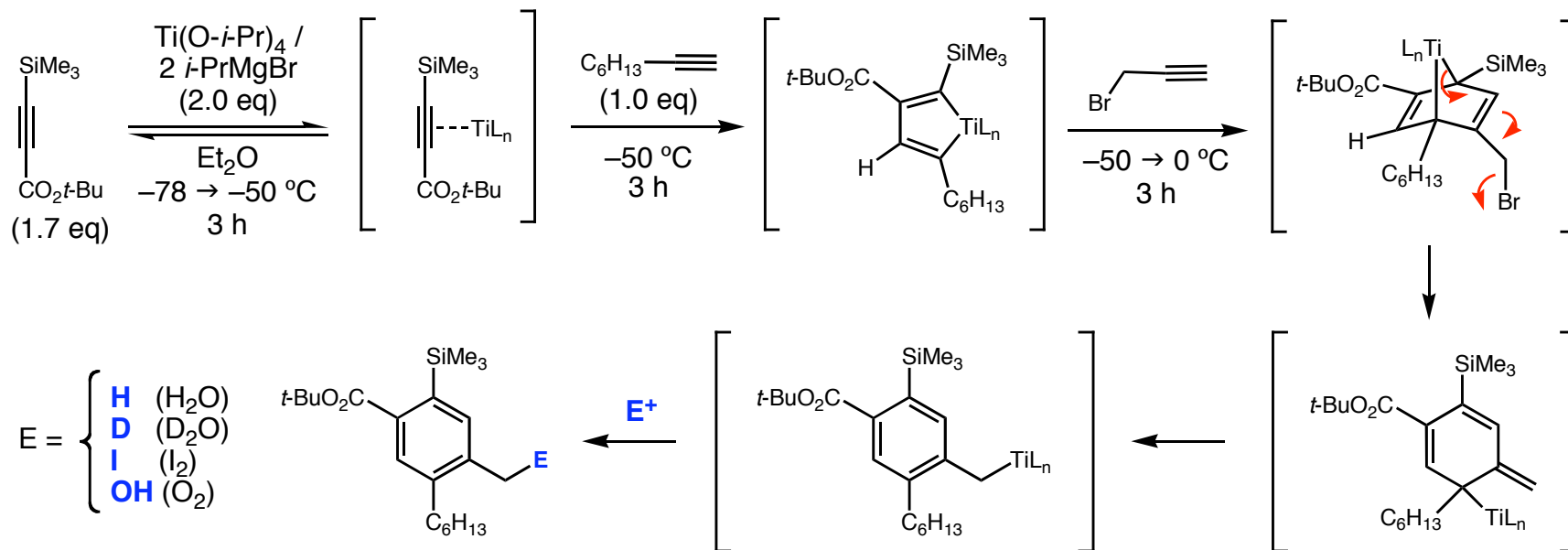
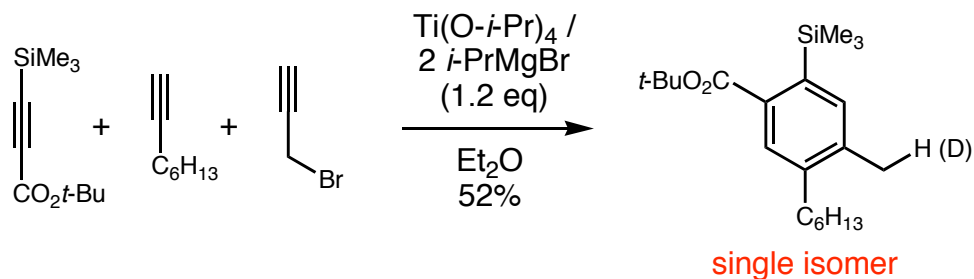


14 linear steps

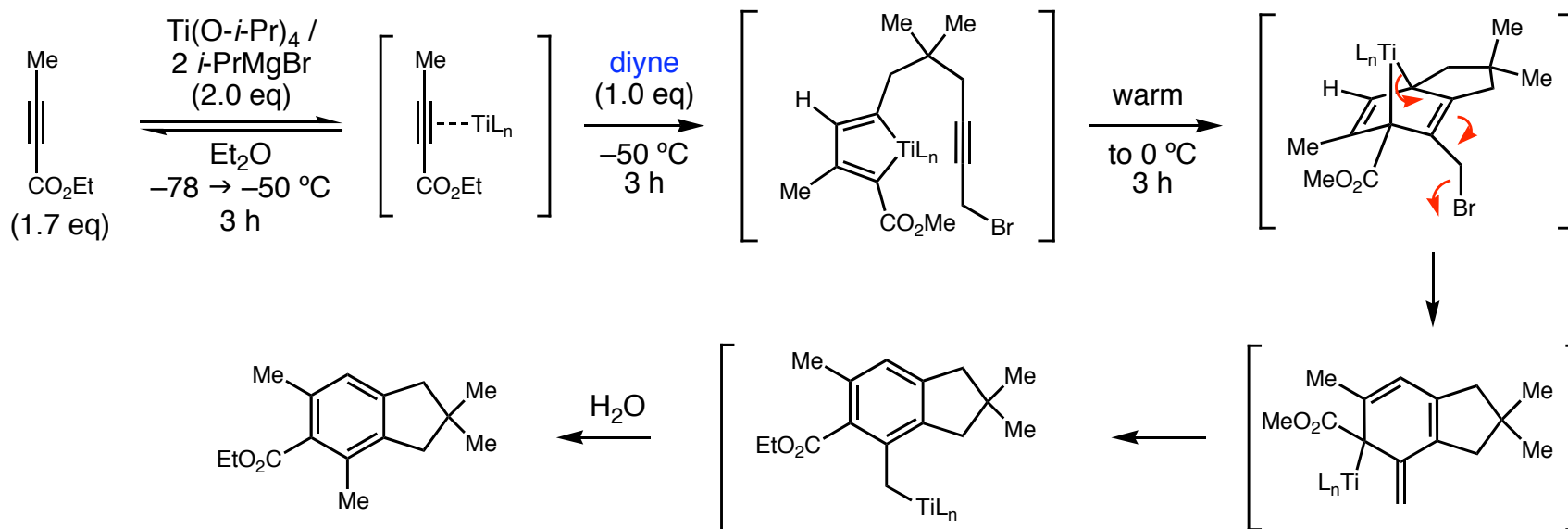
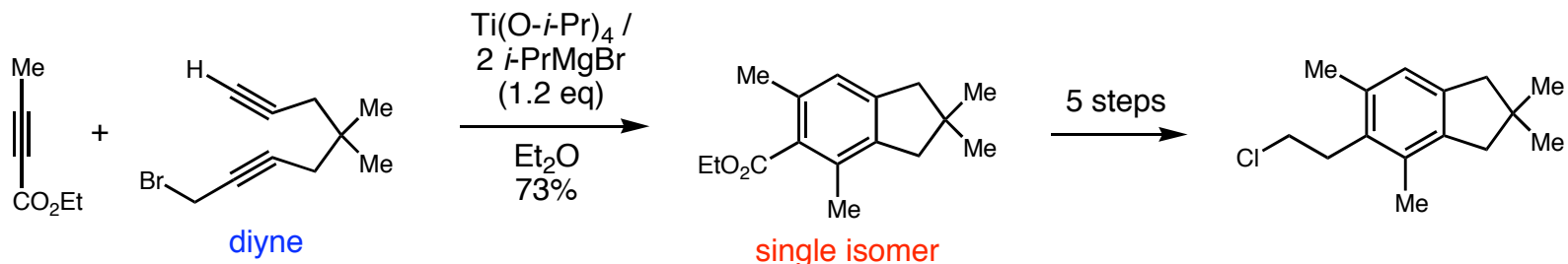
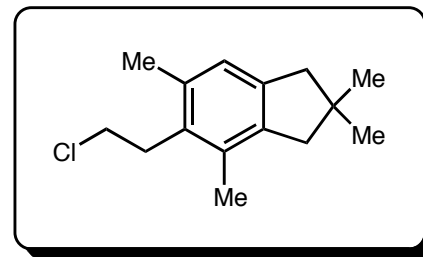
Vollhardt, K. P. C. *et. al. Org. Lett.* **2000**, 2, 2479.  
Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **2001**, 123, 9324.



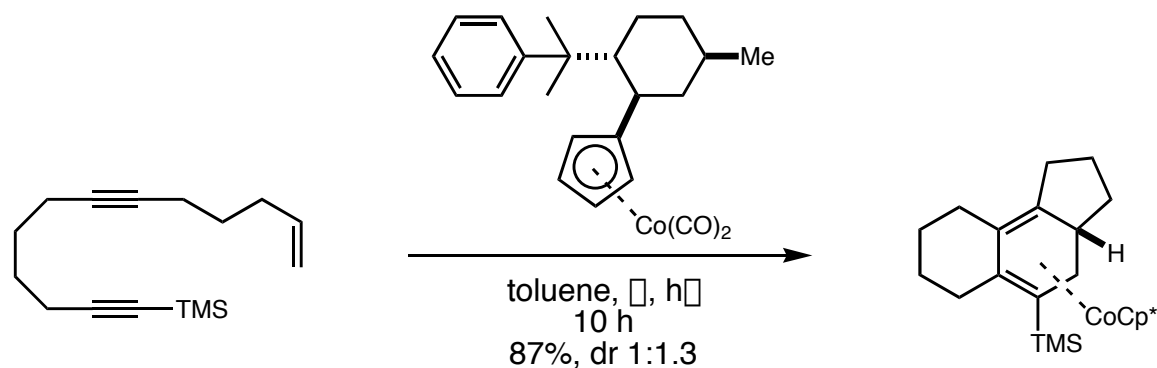
# [2+2+2] Cycloaddition of Three Unsymmetrical Alkynes



# Alcyopterosin A

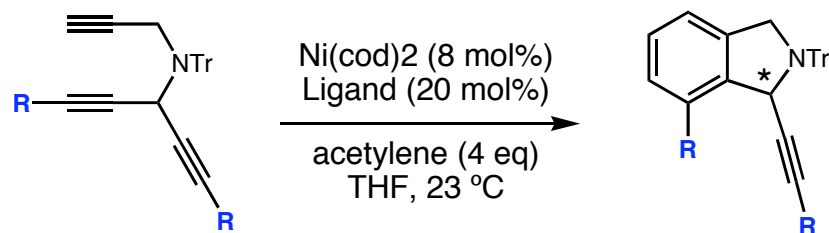


# Enantioselective [2+2+2] Cyclotrimerizations

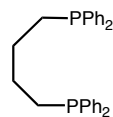


this was the only [2+2+2] cycloaddition reported in the paper

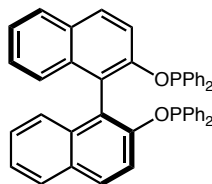
# Enantioselective [2+2+2] Cyclotrimerizations



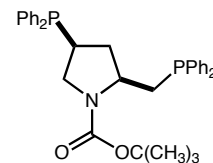
| Ligand     | R   | Time (h) | Yield (%) | ee (%) |
|------------|-----|----------|-----------|--------|
| dppb       | H   | 1.5      | 74        | –      |
|            | TMS | 5        | 83        | –      |
| (S)-BINAPO | H   | 16       | 66        | 12     |
|            | TMS | 115      | 52        | 18     |
| (S,S)-BPPM | H   | 2        | 82        | 45     |
|            | TMS | 18       | 92        | 60     |



dppb



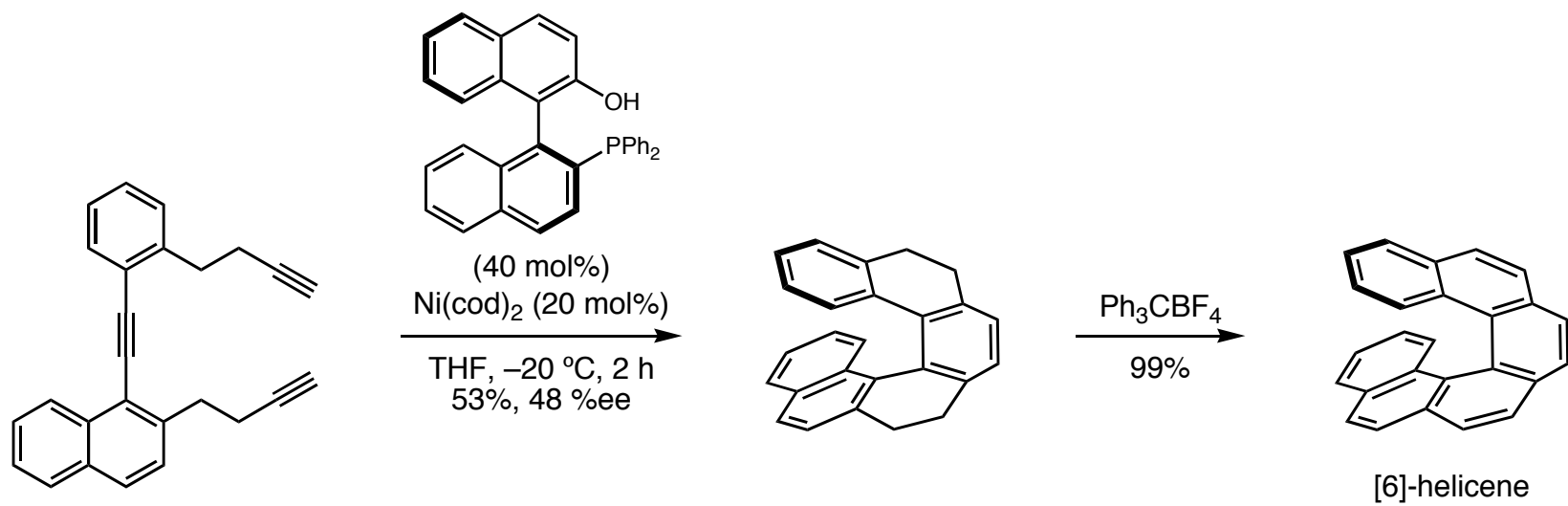
(S)-BINAPO



(S,S)-BPPM

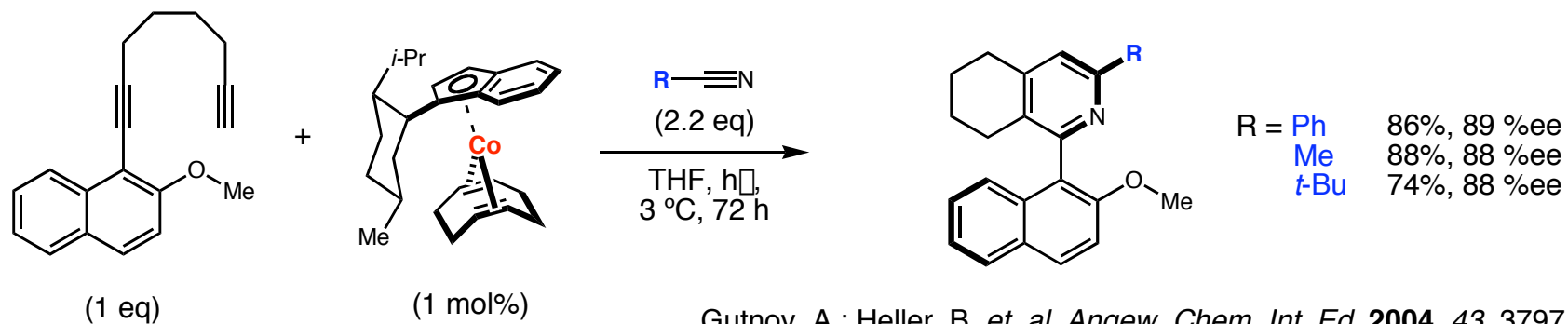
Mori, M. *et. al. J. Org. Chem.* **1994**, *59*, 6133.

# Helicene

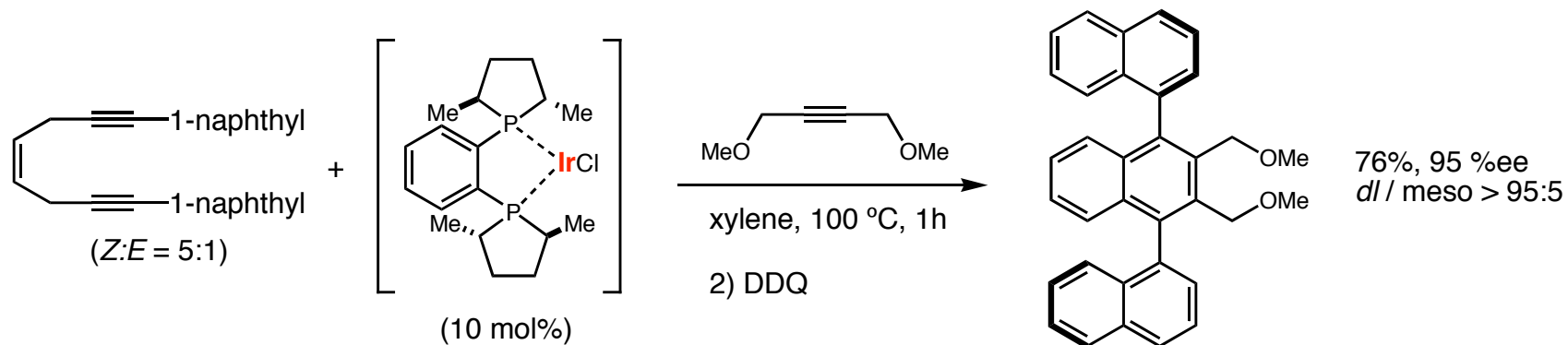


Stará, I. G. *et. al. Tetrahedron Lett.* **1999**, 40, 1993.  
Stará, I. G. *et. al. J. Org. Chem.* **2003**, 68, 5193.

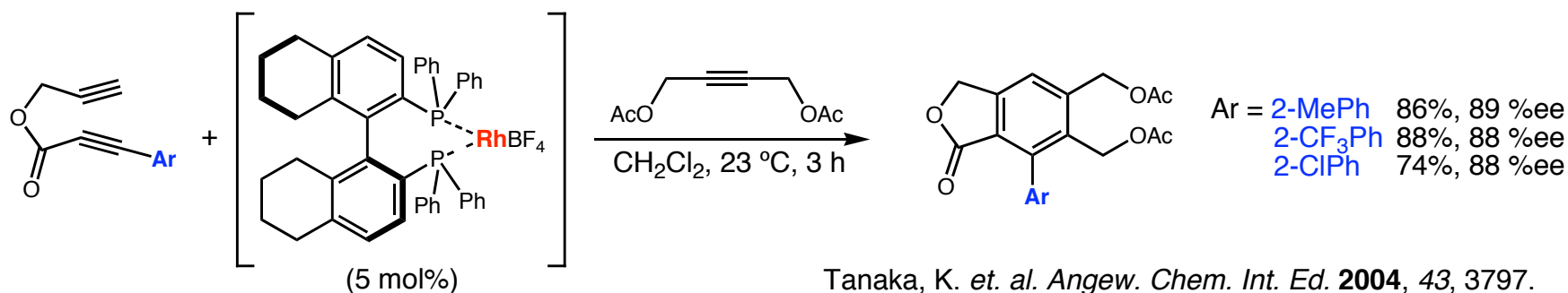
# Enantioselective Biphenyl Synthesis



Gutnov, A.; Heller, B. *et. al. Angew. Chem. Int. Ed.* **2004**, 43, 3797.

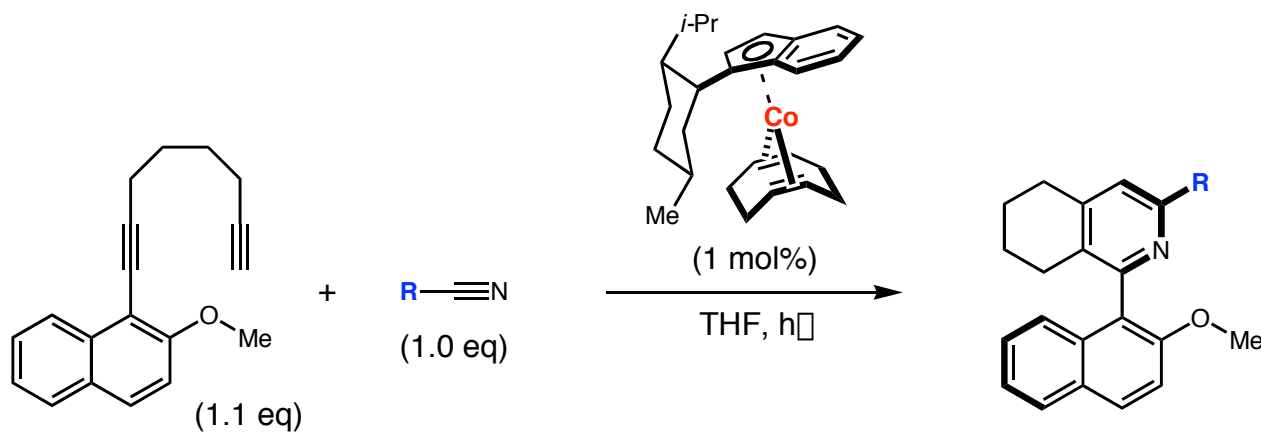


Shibata, T. *et. al. J. Am. Chem. Soc.* **2004**, 126, 8383.



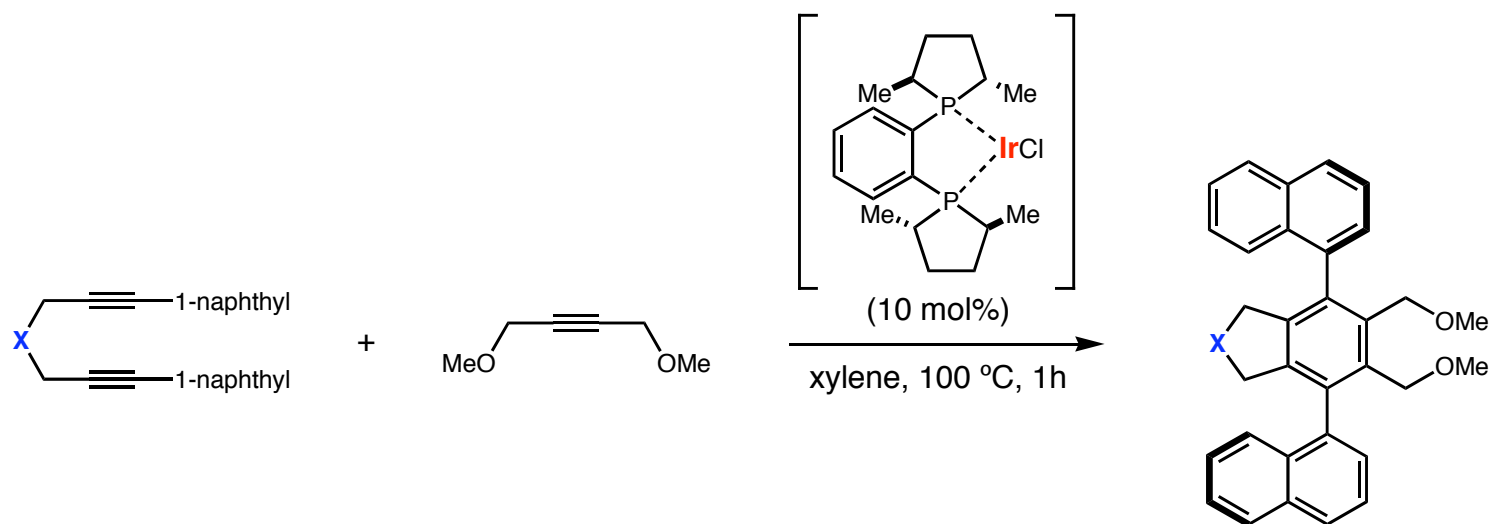
Tanaka, K. *et. al. Angew. Chem. Int. Ed.* **2004**, 43, 3797.

# Enantioselective Biphenyl Synthesis



| R            | Temp (°C) | Time (h) | Yield (%) | ee (%) |
|--------------|-----------|----------|-----------|--------|
| Ph           | 20        | 24       | 79        | 82     |
| Ph           | 3         | 24       | 86        | 89     |
| Ph           | -20       | 72       | 86        | 93     |
| Me           | 3         | 24       | 88        | 88     |
| <i>t</i> -Bu | 3         | 24       | 74        | 88     |

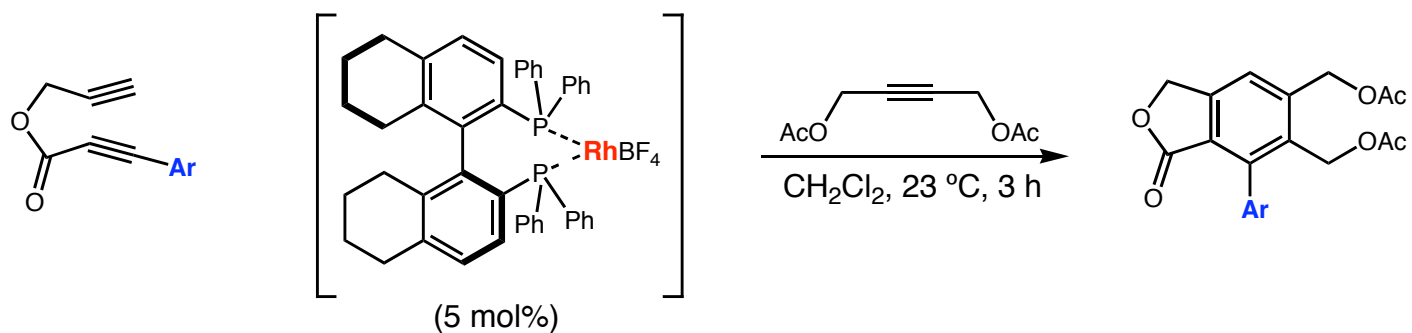
# Enantioselective Biphenyl Synthesis



| X                     | Yield (%) | ee (%) |
|-----------------------|-----------|--------|
| O                     | 76        | 99.5   |
| NTs                   | 92        | 99.4   |
| C(CO <sub>2</sub> Et) | 77        | >99.8  |
| CH <sub>2</sub>       | 96        | >99.8  |



# Enantioselective Biphenyl Synthesis



| Ar  | Yield (%) | ee (%) |
|---|-----------|--------|
| <b>2-MeC<sub>6</sub>H<sub>4</sub></b>             | 67        | >99    |
| <b>1-naphthyl</b>                                 | 57        | 94     |
| <b>2-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub></b> | 73        | >99    |
| <b>2-ClC<sub>6</sub>H<sub>4</sub></b>             | 45        | >86    |

# Conclusions

- Cobalt catalysts work well for most alkyne, enediyne, heterocycle [2+2+2] cycloadditions
- Rhodium catalysts require tethered substrates
- Ruthenium catalysts are used for electron-poor substrates and operate by a different mechanism
- Excellent regioselectivities are obtained for intramolecular reactions with catalytic amount of material
- High levels of chemo- and regioselectivity are obtained with stoichiometric amounts of metal reagents
- Asymmetric [2+2+2] cyclotrimerizations are just beginning to be explored and will be useful for preparing compounds with helical, axial, and planar chirality