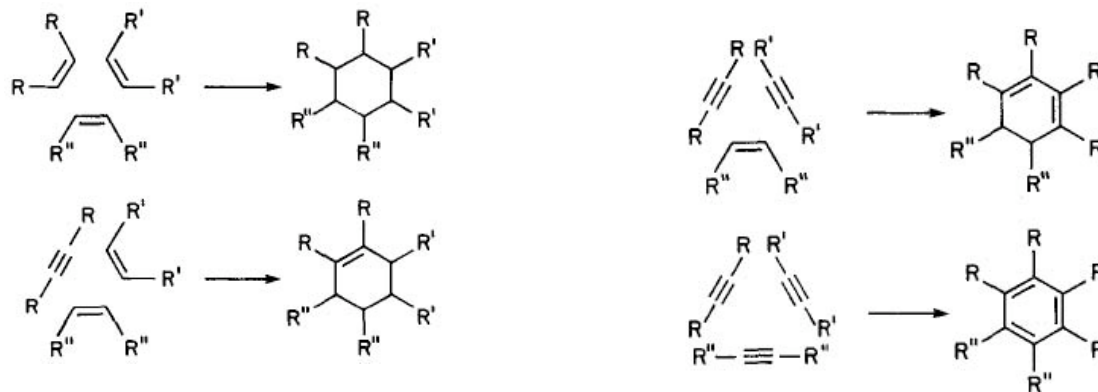


[2+2+2] Cycloadditions

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

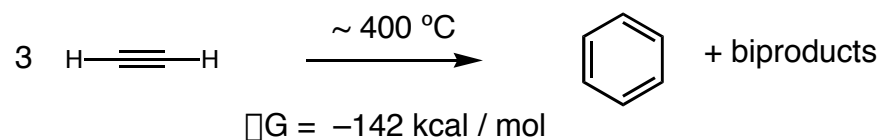
Background Literature

- 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

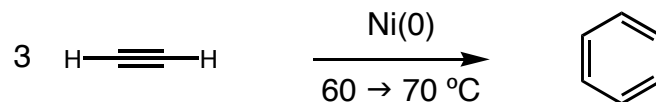
First thermal [2+2+2] cyclotrimerization was reported in 1866 by Berthelot



The reaction is exothermic despite the large loss in entropy

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

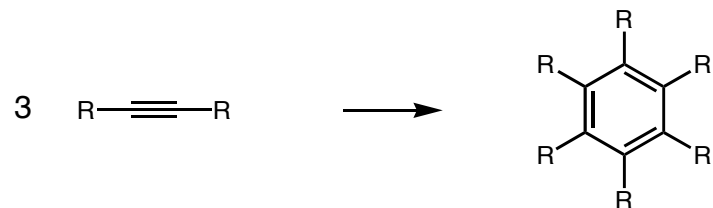
Not a concerted reaction



The reaction occurred at lower temperature and with fewer byproducts

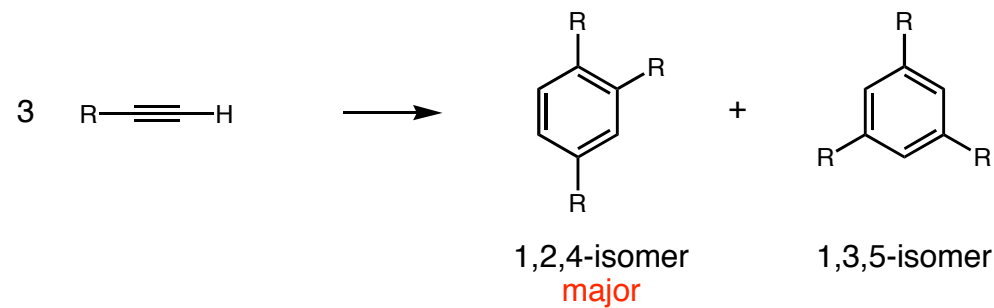
Background

symmetrical alkynes

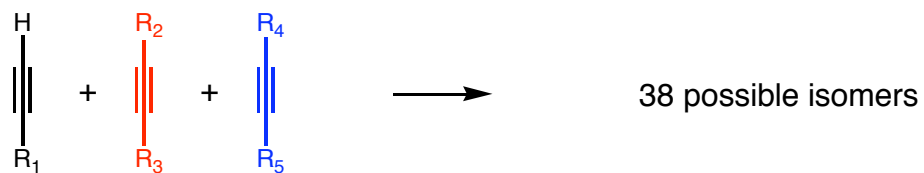


hexa-substituted benzenes

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)

CpRuCl
(Yamamoto)

Most studied metals are Co, Rh, and Ru

Reaction proceeds by different mechanisms depending on the metal

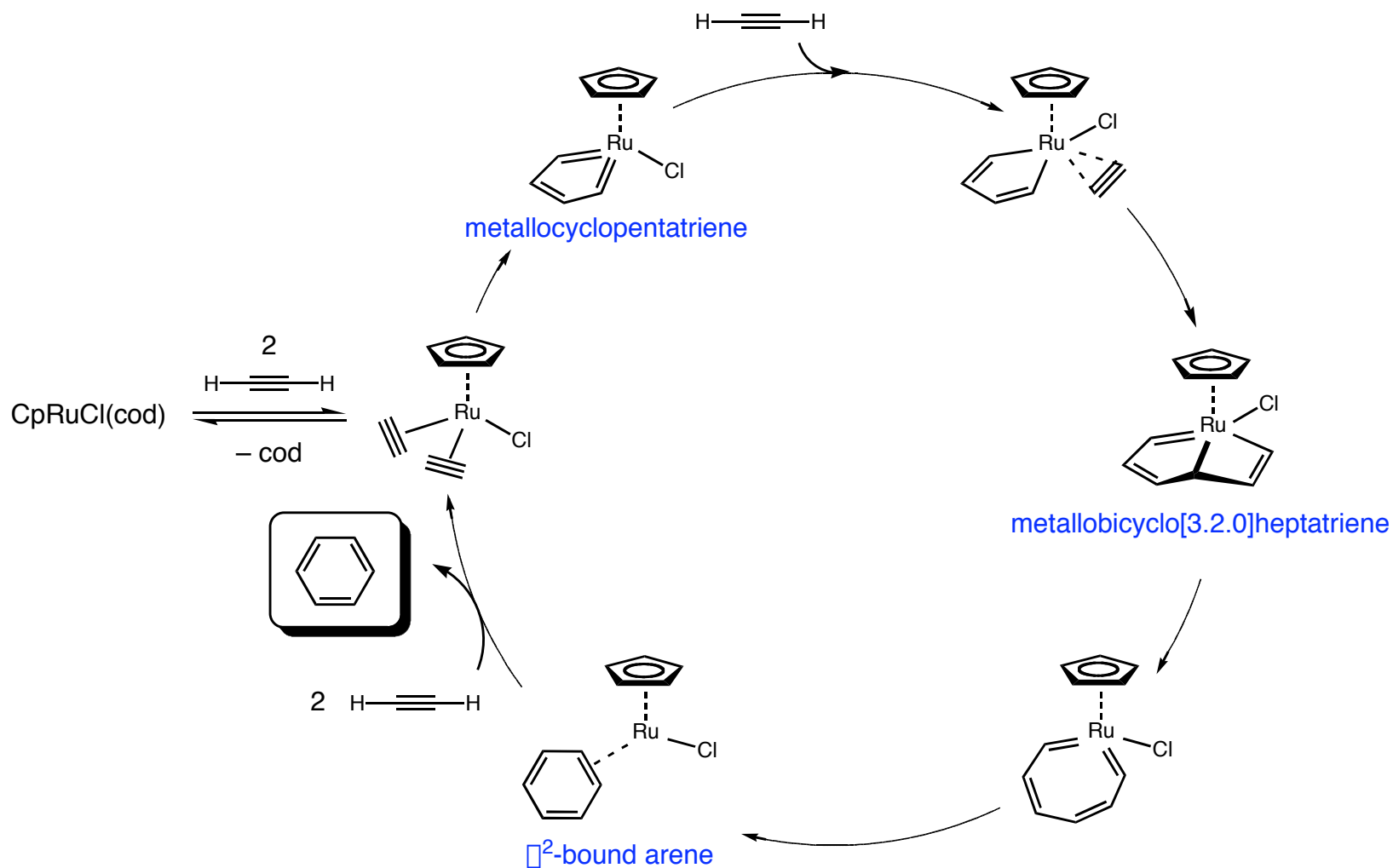
$\text{CpCo}(\text{CO})_2$ requires activation with H_2 before use to aid displacing the CO ligands

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

Rhodium catalyzed reactions are generally limited to tethered substrates

Ruthenium catalysts work only for electron-poor substrates

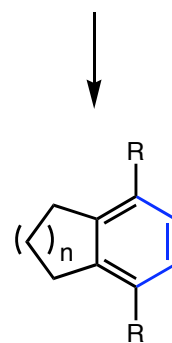
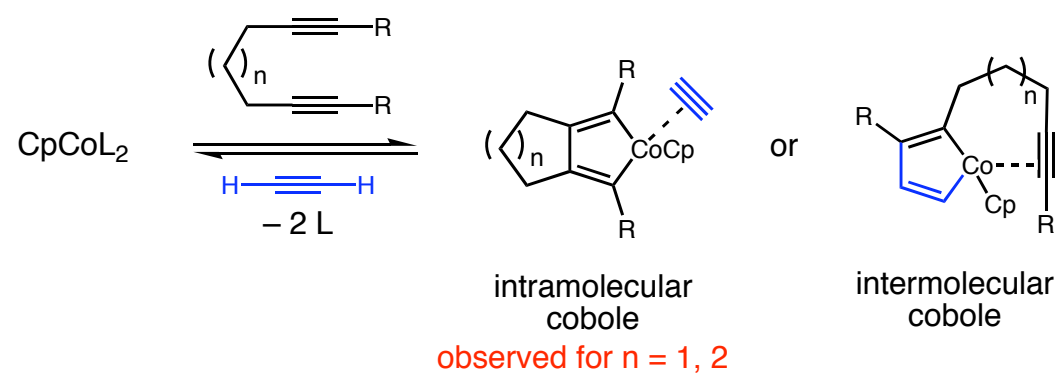
Ruthenium Mechanism



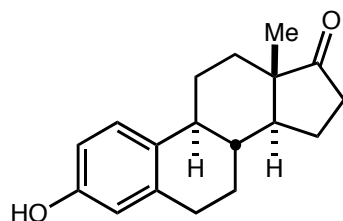
X-ray structure of an Ir[3.2.0] complex
 (Paneque, M. *et. al.* *JACS* **2004**, 126, 1610)

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.

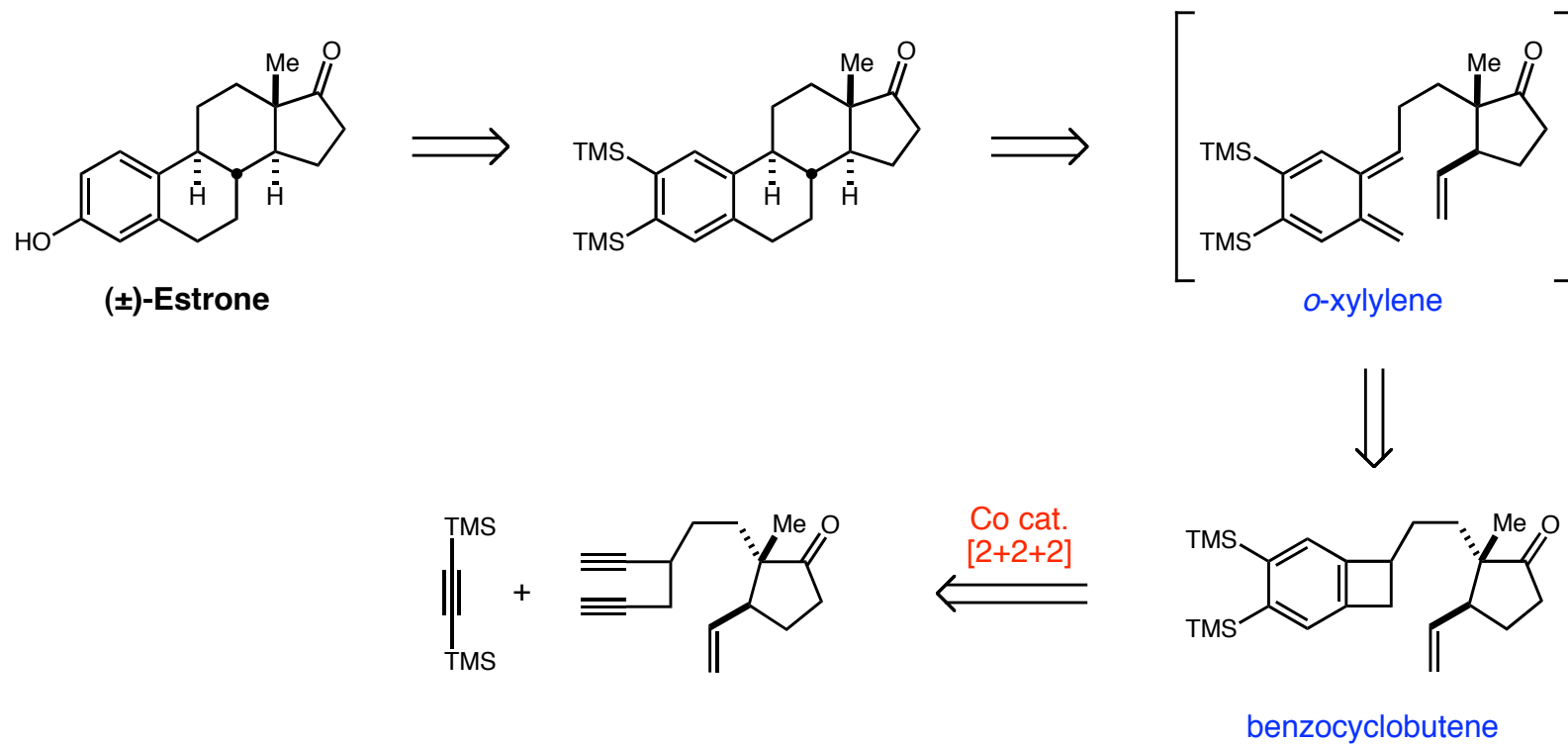
J. Org. Chem. **1982**, *47*, 3447.

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

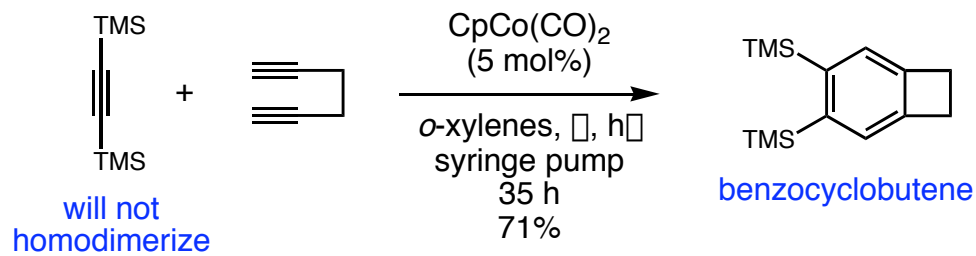
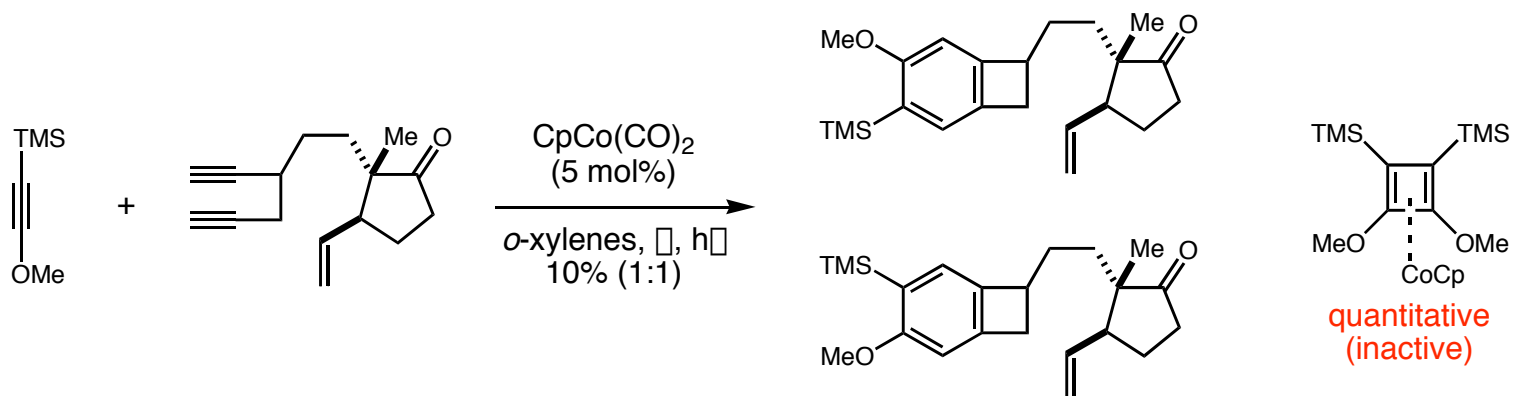
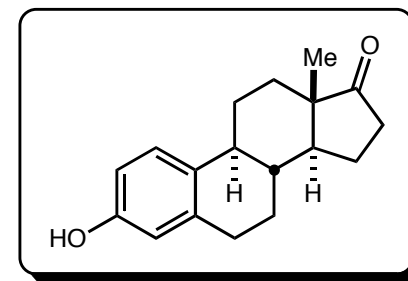
J. Am. Chem. Soc. **1986**, *108*, 856.

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

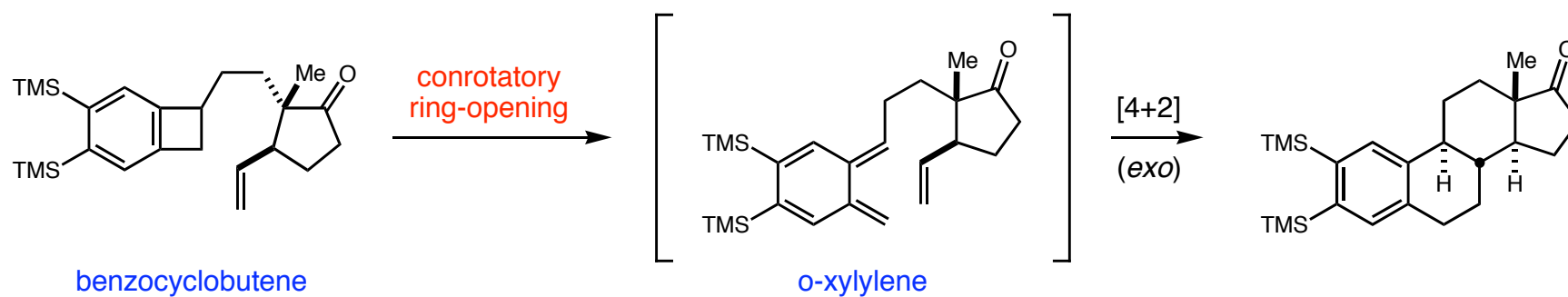
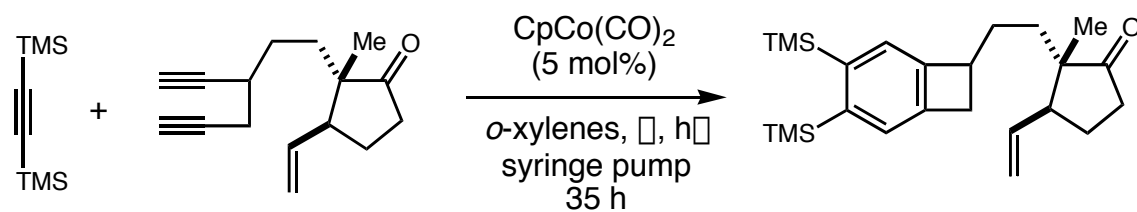
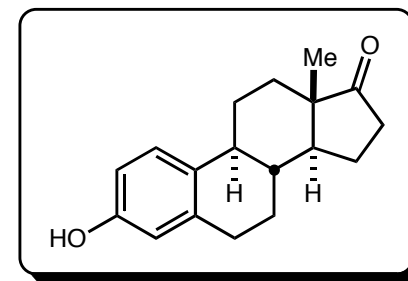
(±)-Estrone
(D → ABCD)



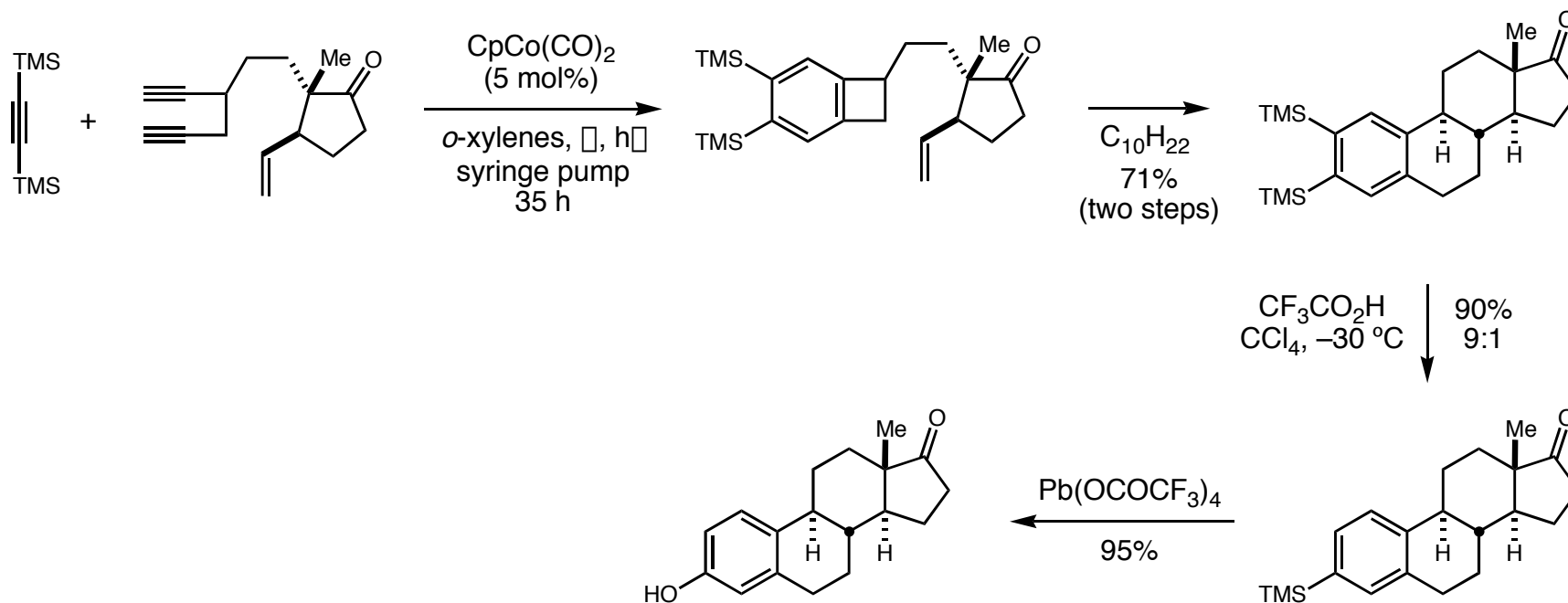
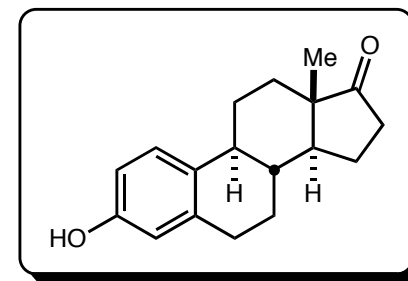
(±)-Estrone



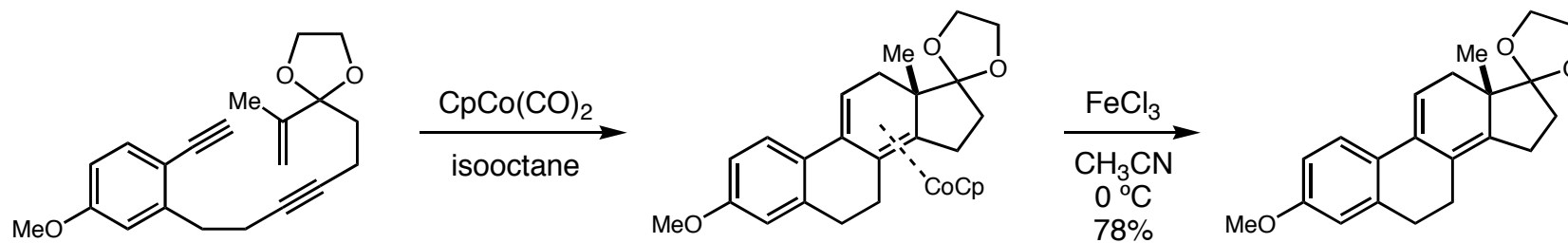
(±)-Estrone



(±)-Estrone

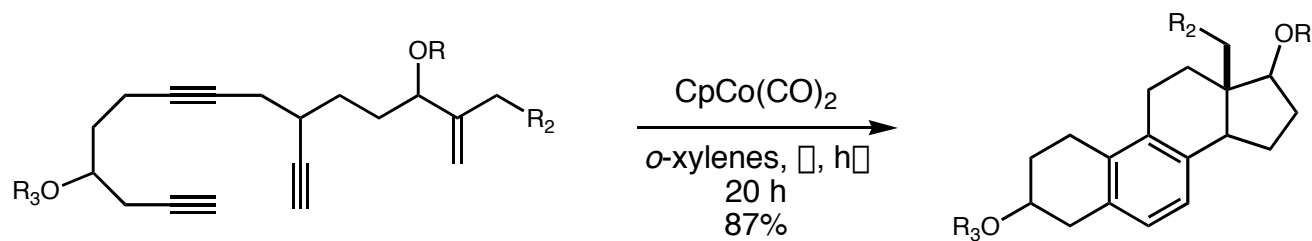


(±)-Estrone (A → ABCD)



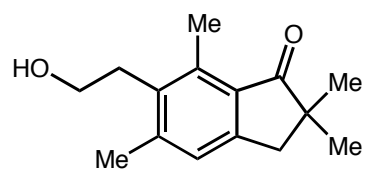
Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1982**, *47*, 3447.
Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1984**, *49*, 1574.

Aromatic B-ring Steroid

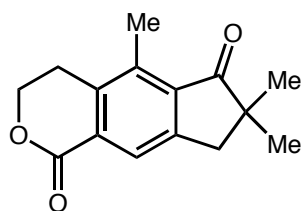


Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1986**, *108*, 856.

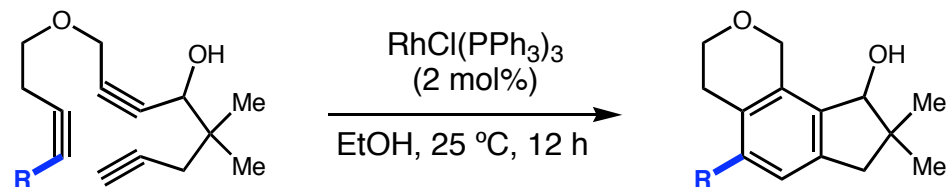
Illudalanes



Pterosin

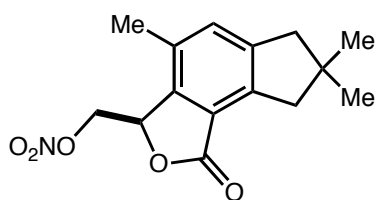


Calomelanolactone

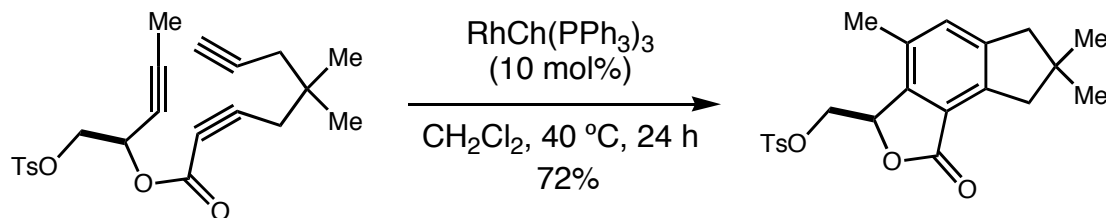


R = Me 82% (pterosin)
R = CH₂OH 86% (calomelanolactone)

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

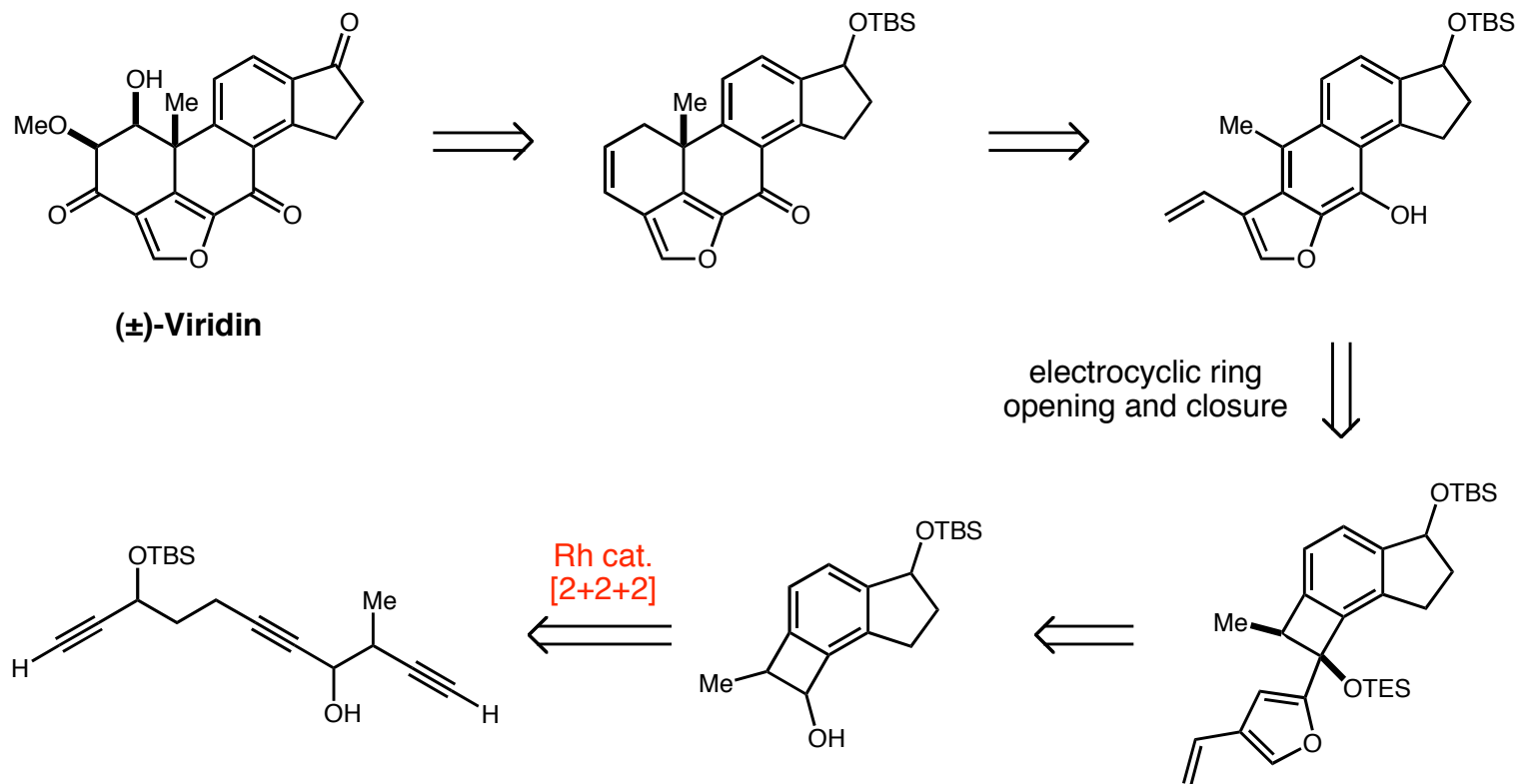


Alcyopterosin E

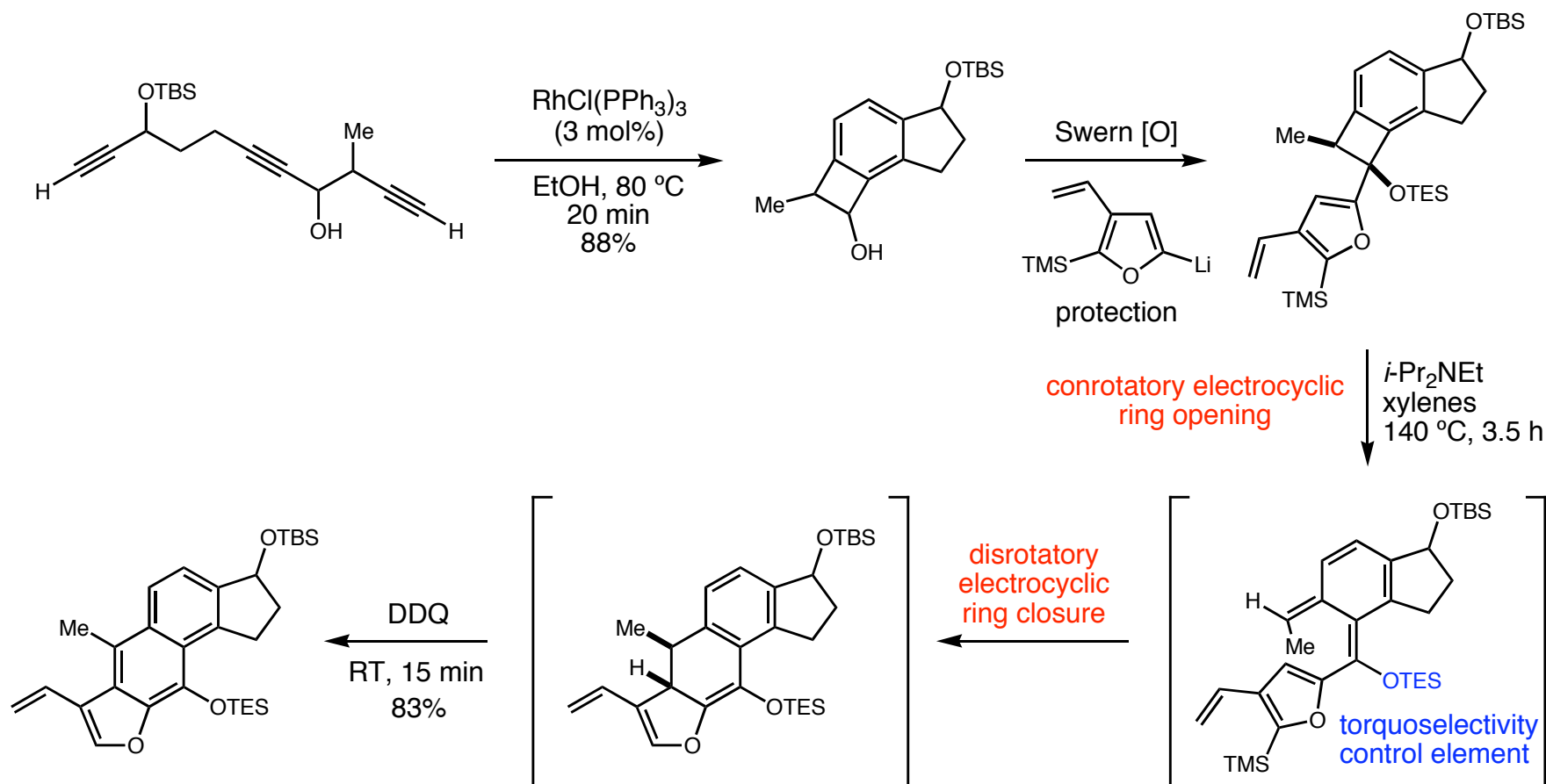
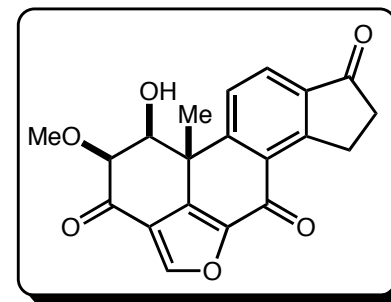


Witulski, B. *et. al. Chem. Commun.* **2002**, 2985.

(±)-Viridin

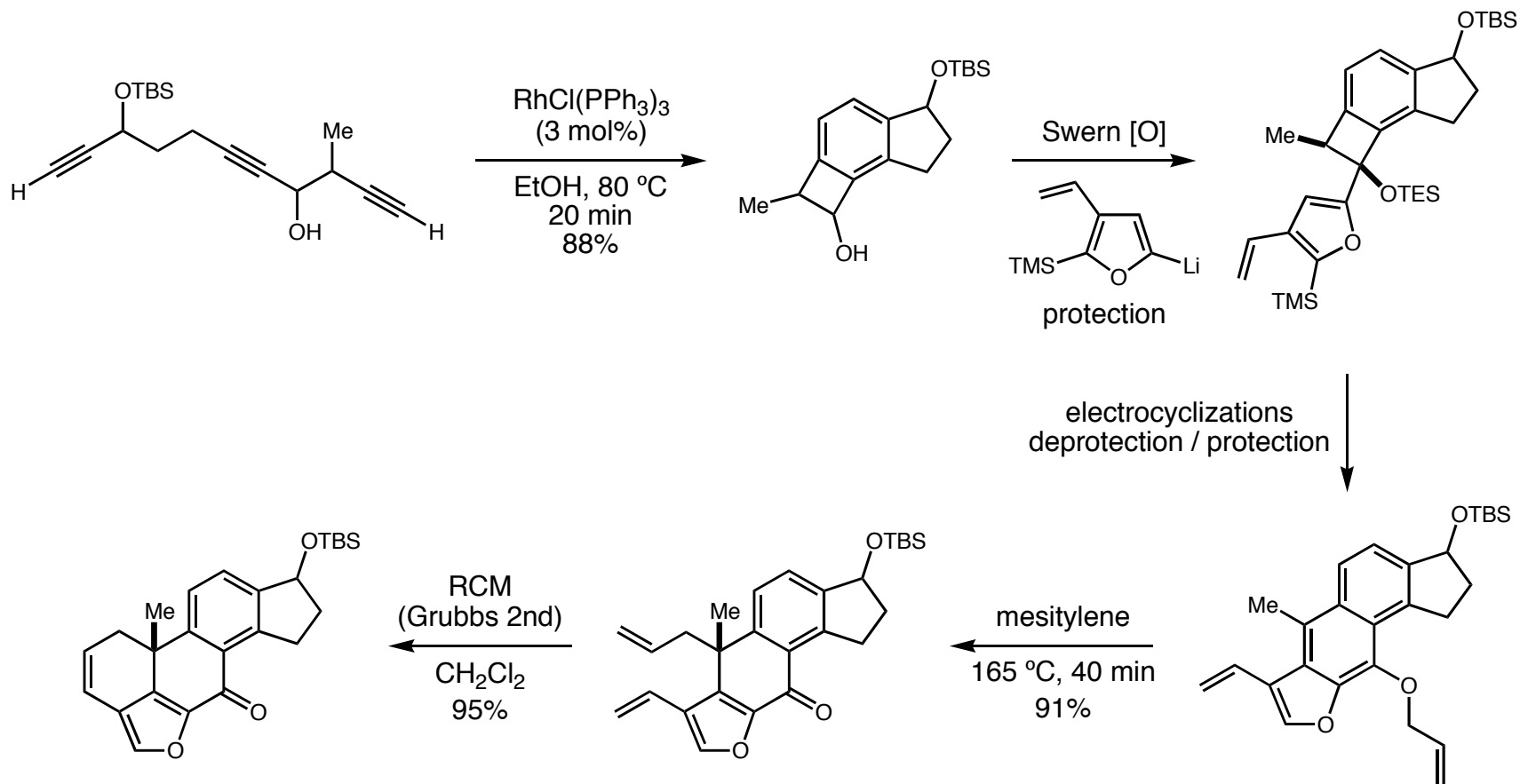
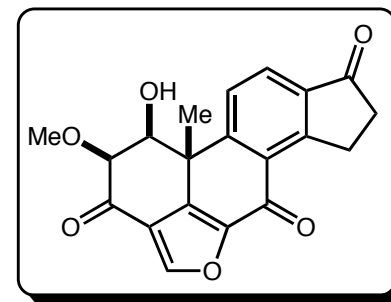


(±)-Viridin



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

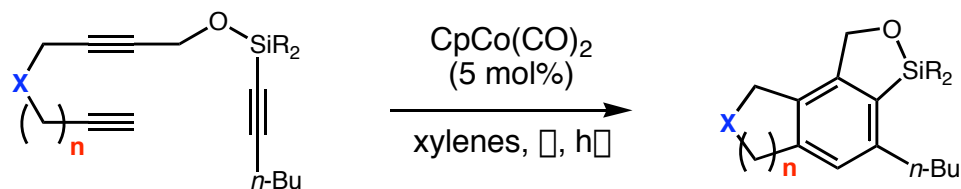
(±)-Viridin



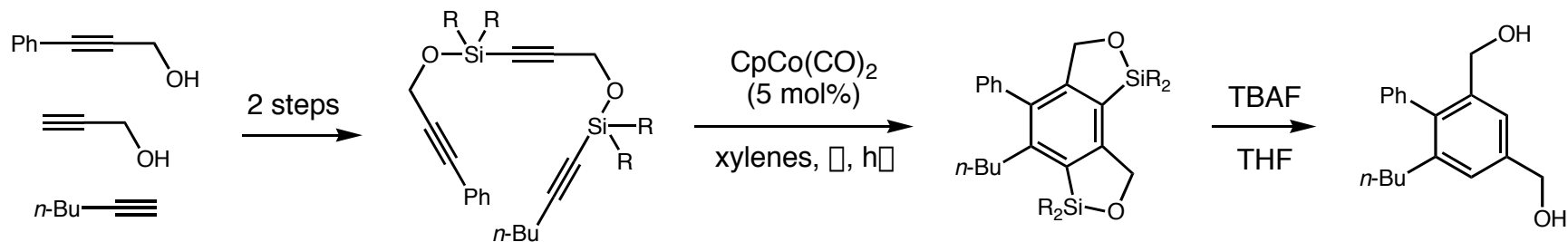
13 more steps to elaborate the A ring, deprotect, and oxidize

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

Tethered Alkynes

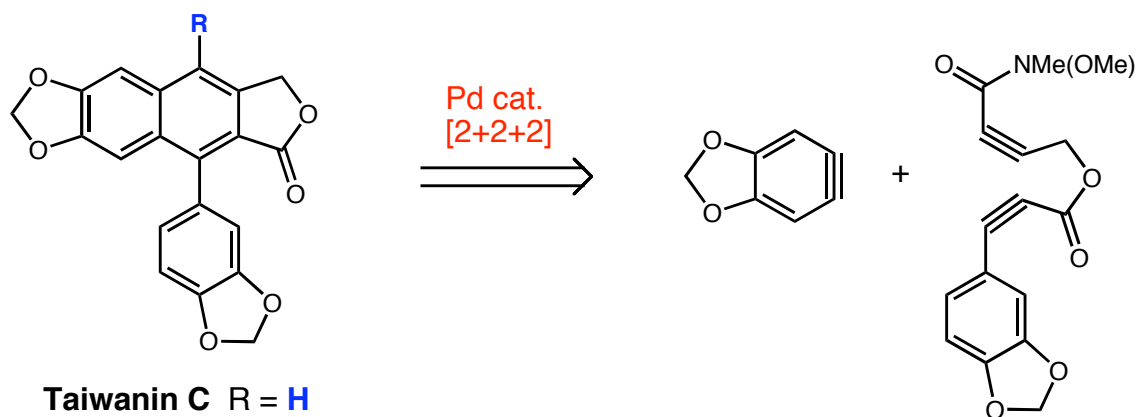


X	n	Yield (%)
CH ₂	1	77
CH ₂	2	78
CH ₂	3	73
O	1	67
NCbz	1	73

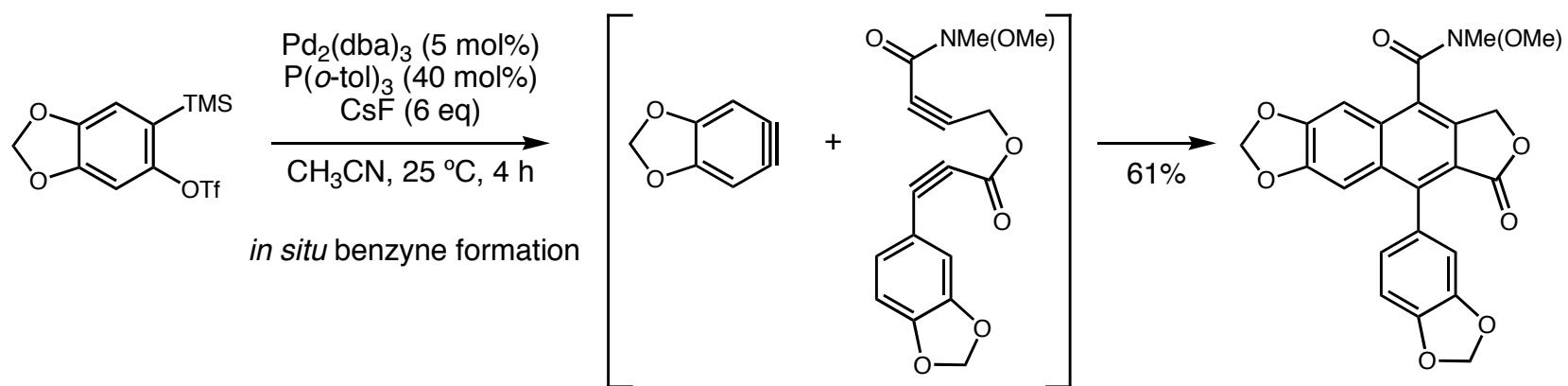


Silicon-tethered alkynes (illustrated): Malacria, M. *et al. Org. Lett.* **2004**, 6, 1519.
 Boron-tethered alkynes: Yamamoto, Y. *et al. J. Am. Chem. Soc.* **2004**, 126, 3712.

Taiwanins C and E

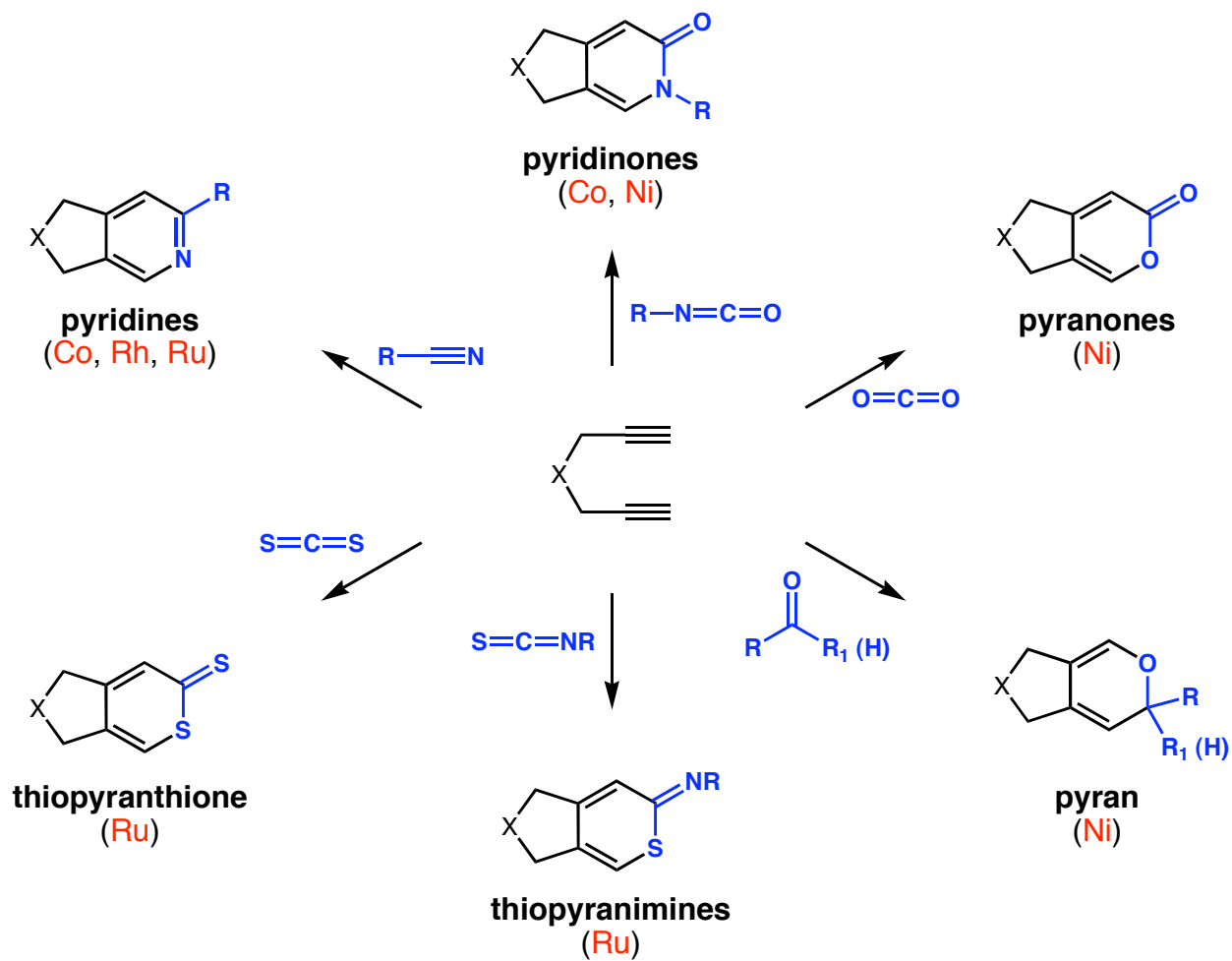


Taiwanin C R = H
Taiwanin E R = OH



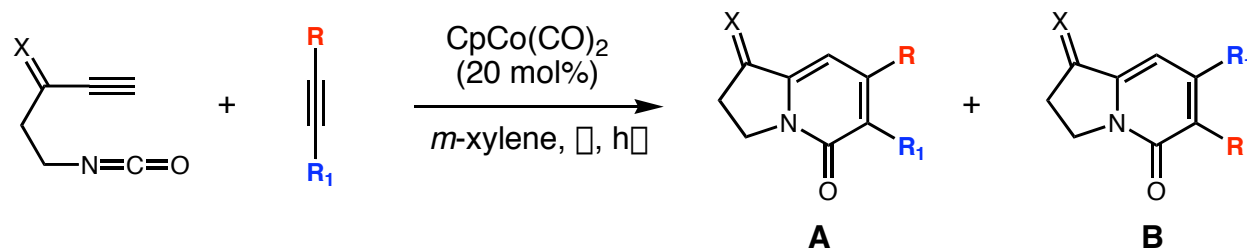
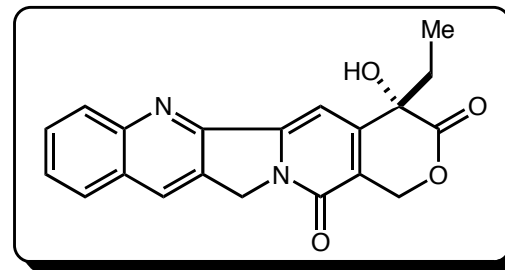
(R could not be an alcohol, aldehyde, or ester)

Heterocycle Synthesis



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

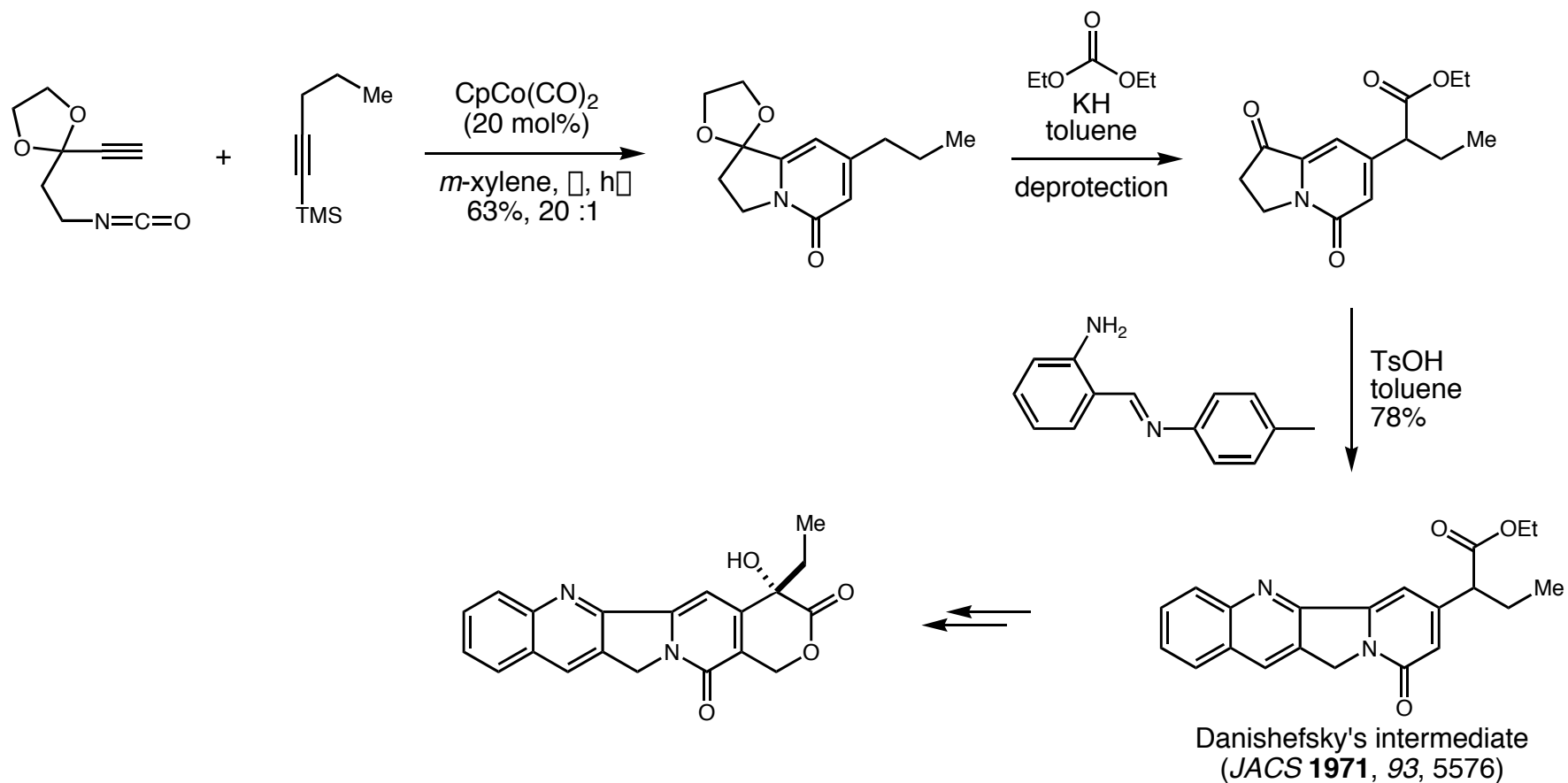
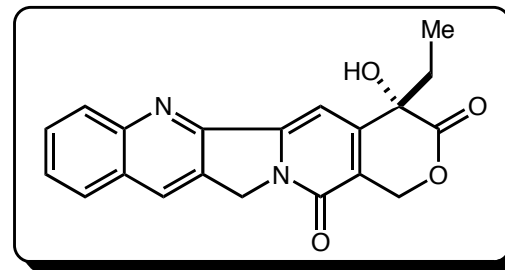
(±)-Camptothecin



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

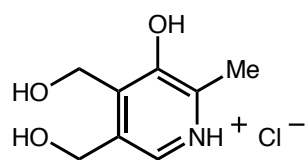
Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1983**, *105*, 6991.
 Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1984**, *49*, 4786.

(±)-Camptothecin

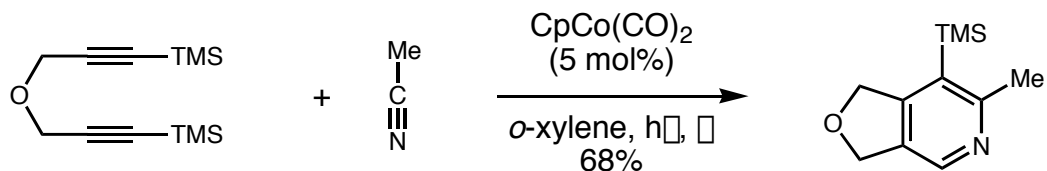


Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1983**, *105*, 6991.
Vollhardt, K. P. C. *et. al. J. Org. Chem.* **1984**, *49*, 4786.

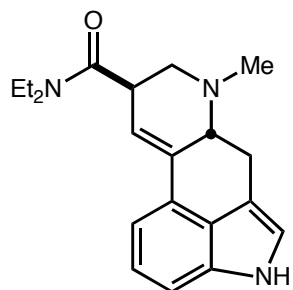
Alkaloids



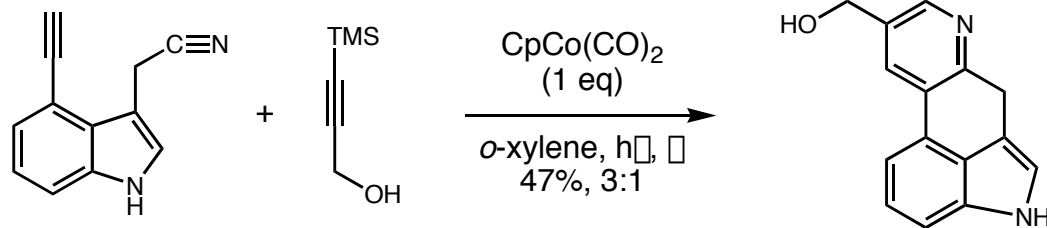
Vitamin B₆



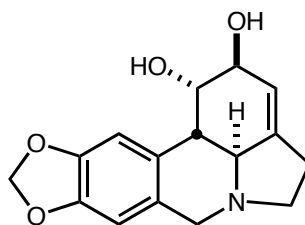
Vollhardt, K. P. C. *et. al. Tetrahedron* **1985**, 41, 5796.



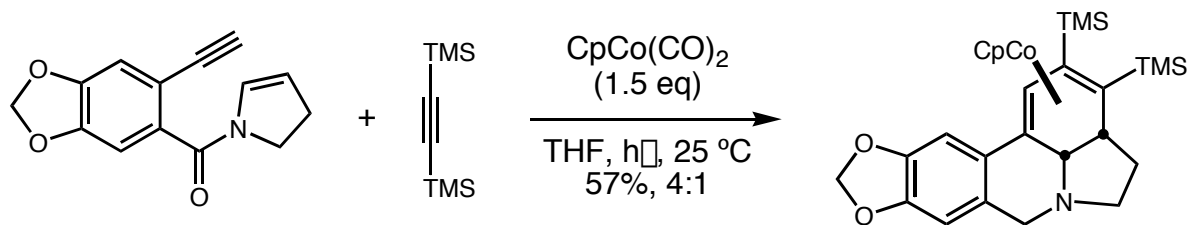
(±)-Lysergic acid diethylamide



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

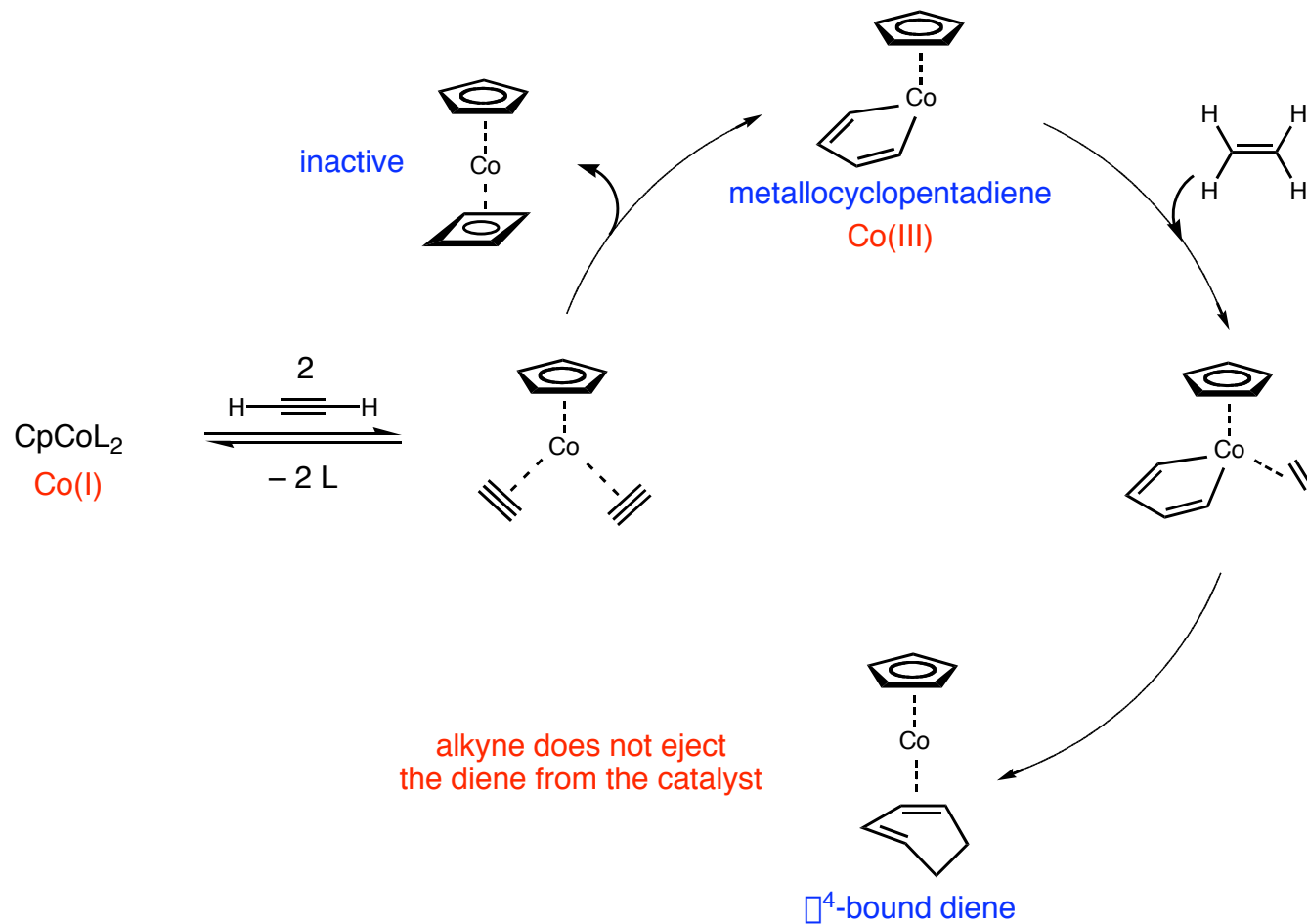


Lycorane

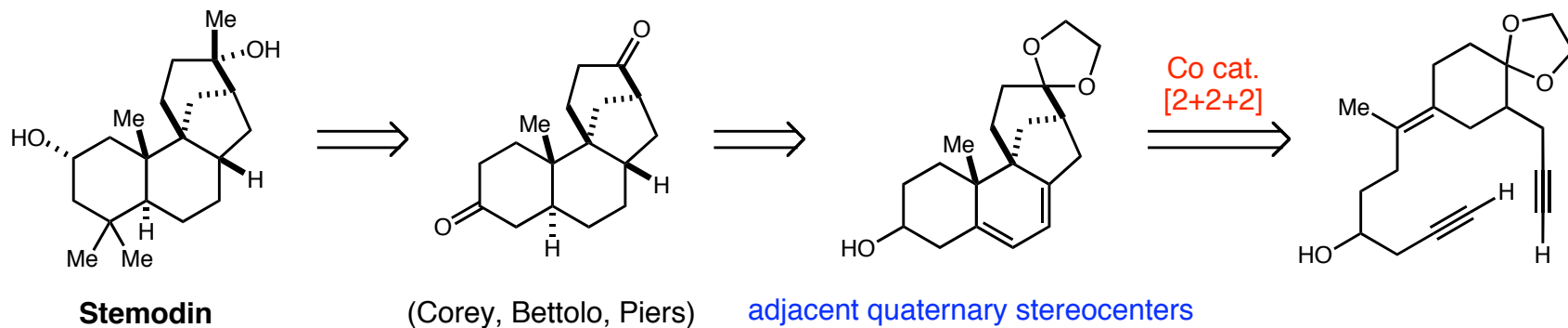


Vollhardt, K. P. C. *et. al. Synthesis* **1994**, 579.

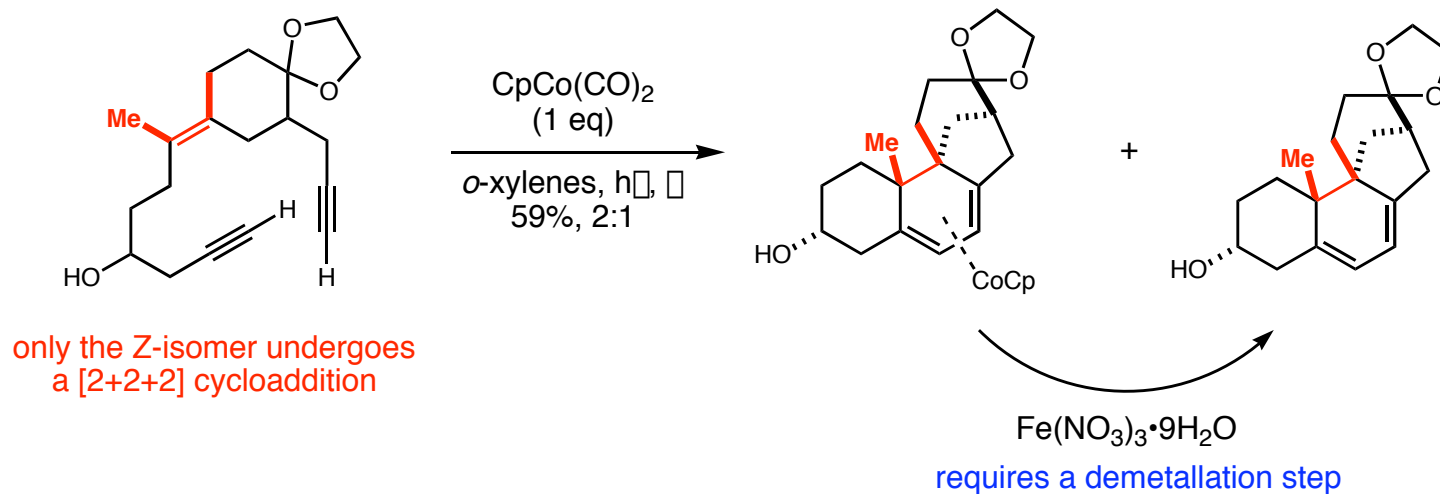
Cobalt Eneidyne [2+2+2] Mechanism



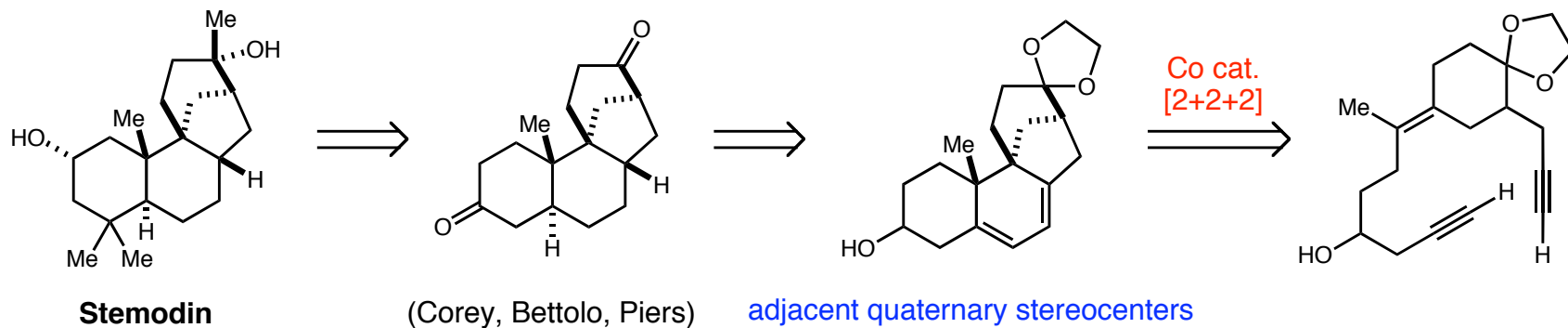
Enediyne [2+2+2] Cyclizations



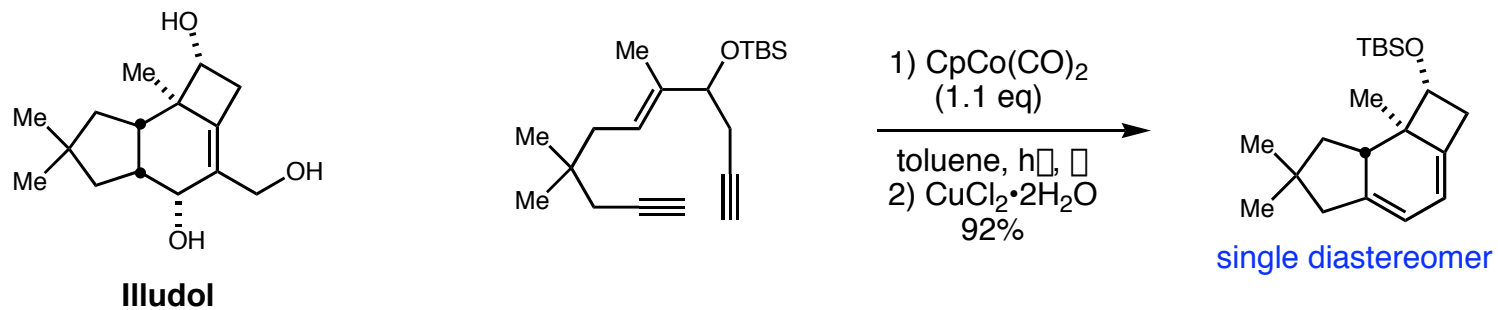
Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1991**, 113, 4006.



Enediyne [2+2+2] Cyclizations

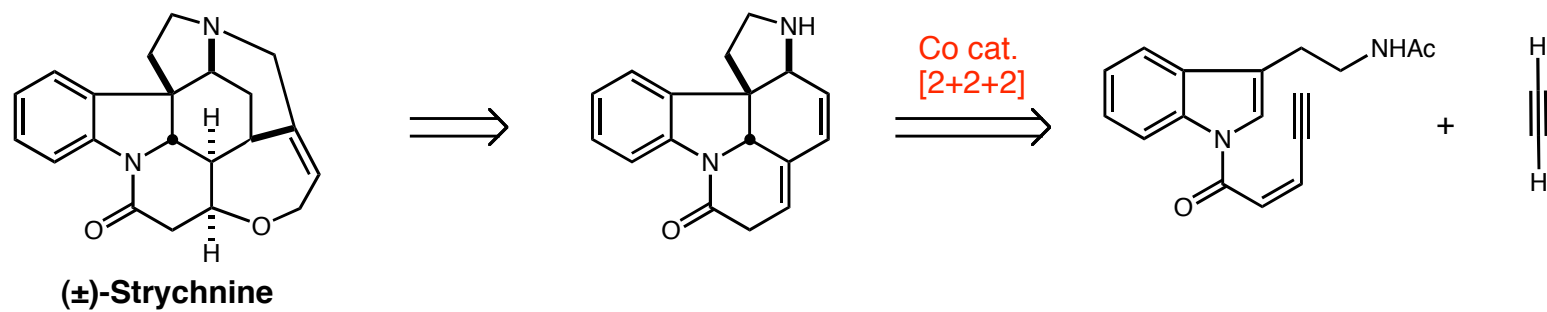


Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **1991**, *113*, 4006.



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.)

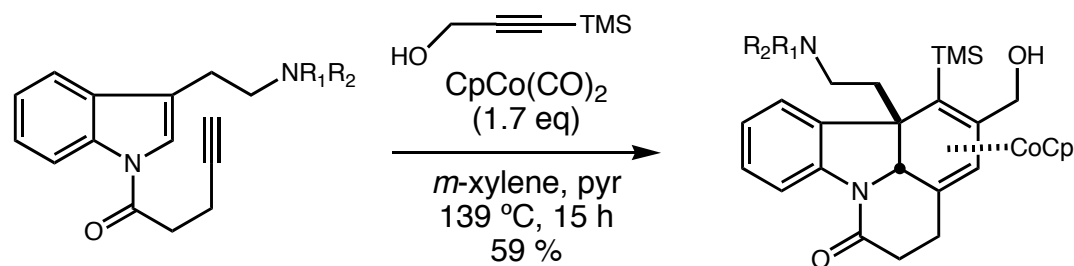
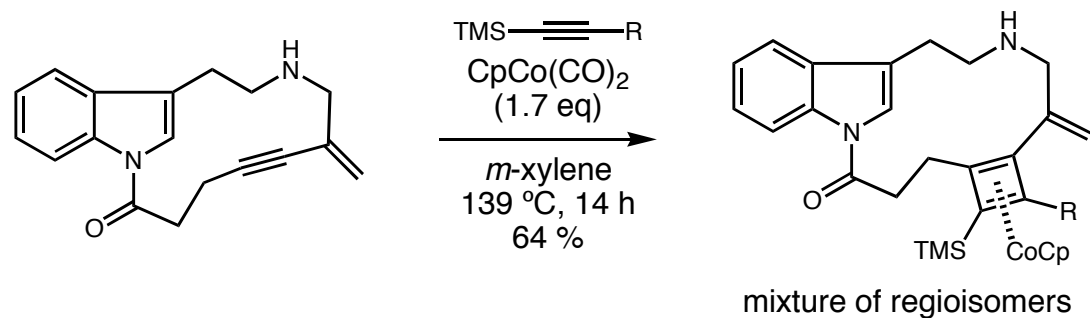
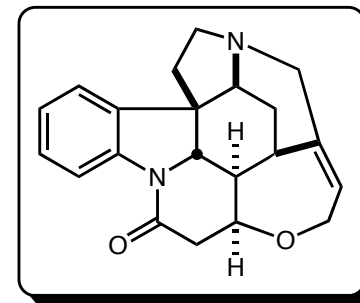
Racemic syntheses: Magnus (1992), Stork (1992), Kuehne (1993), Rawal (1994), Martin (1996)

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

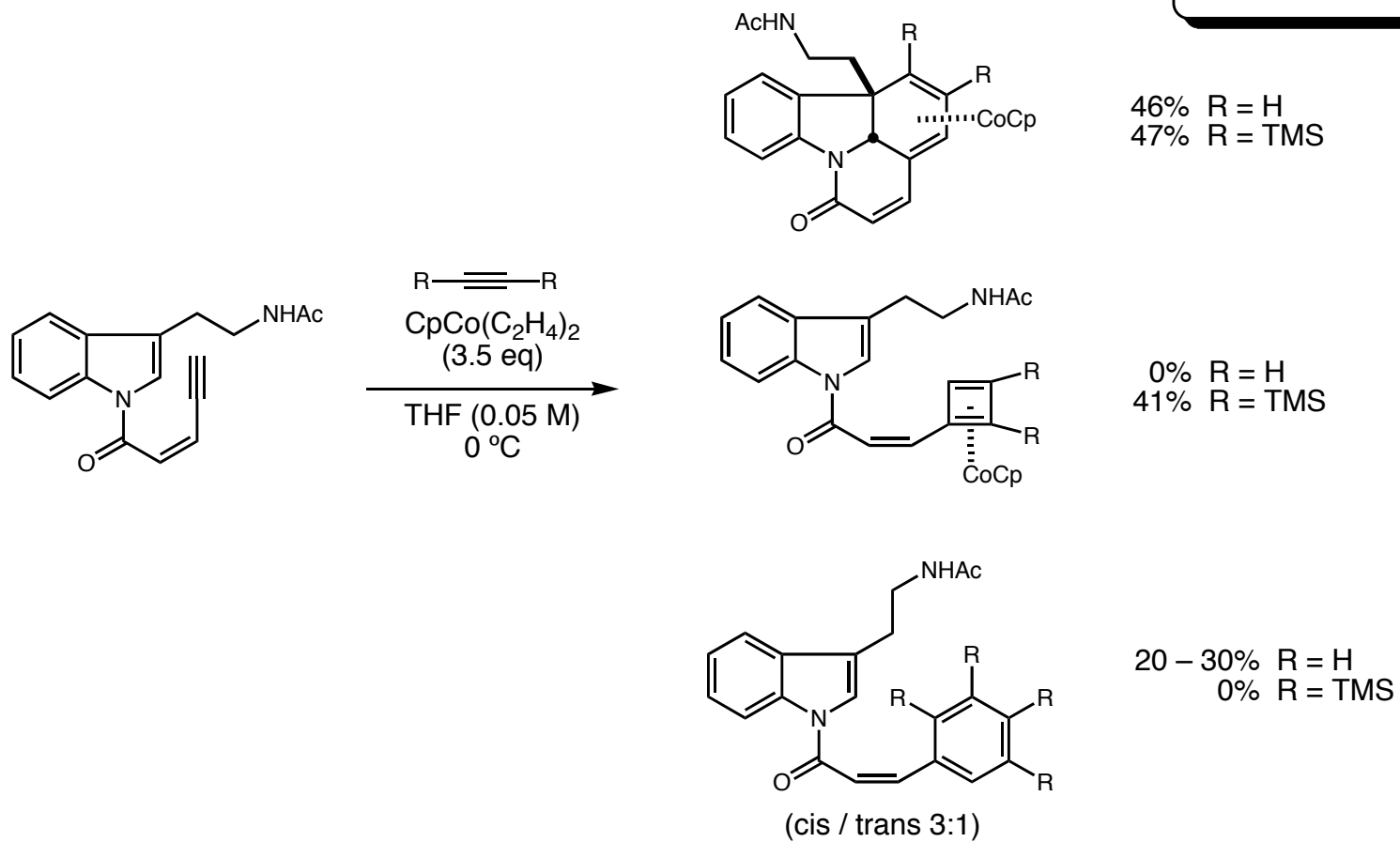
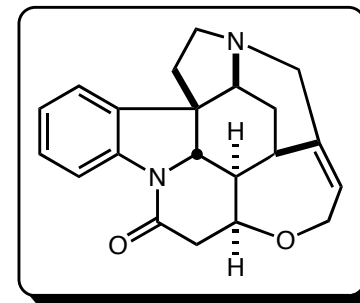
Vollhardt, K. P. C. *et. al. Org. Lett.* **2000**, 2, 2479.

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

(±)-Strychnine

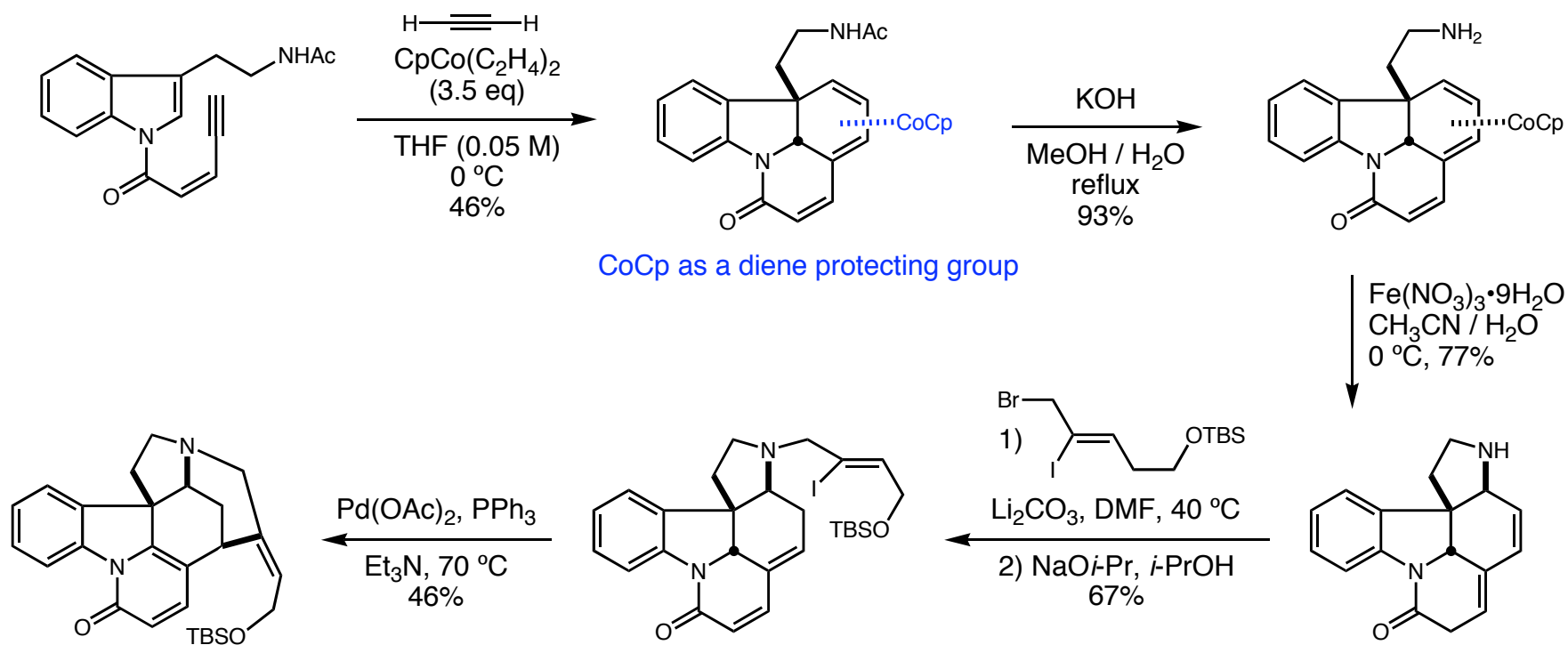
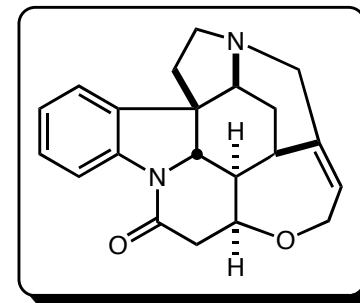


(±)-Strychnine



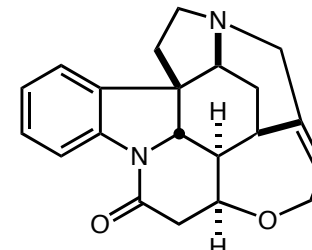
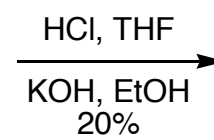
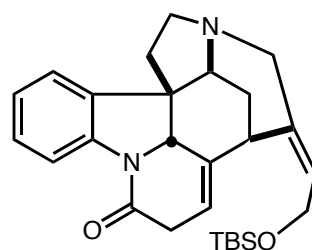
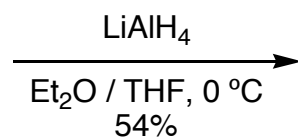
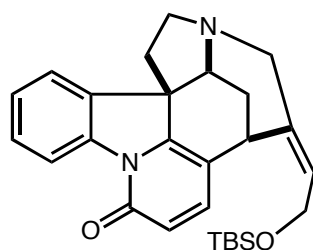
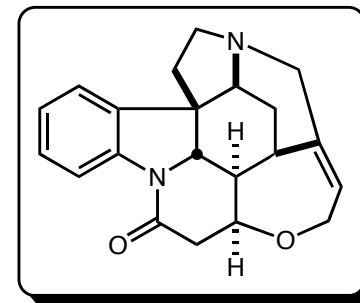
Vollhardt, K. P. C. *et. al. Org. Lett.* **2000**, 2, 2479.
 Vollhardt, K. P. C. *et. al. J. Am. Chem. Soc.* **2001**, 123, 9324.

(±)-Strychnine



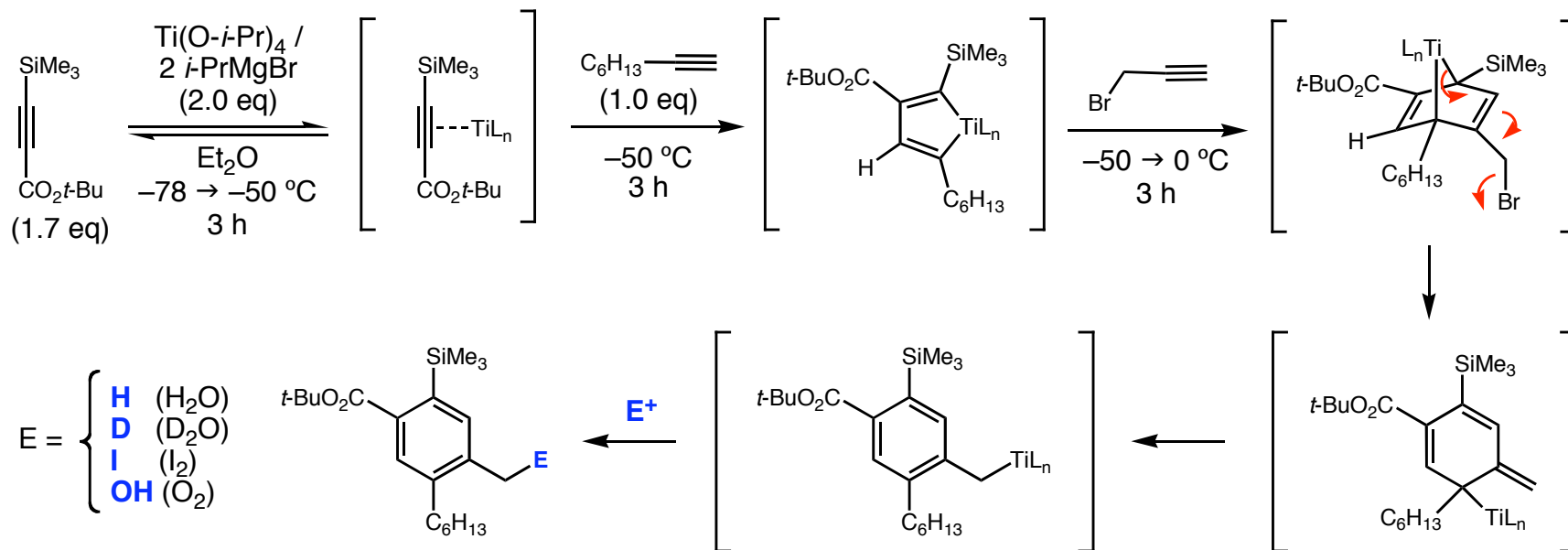
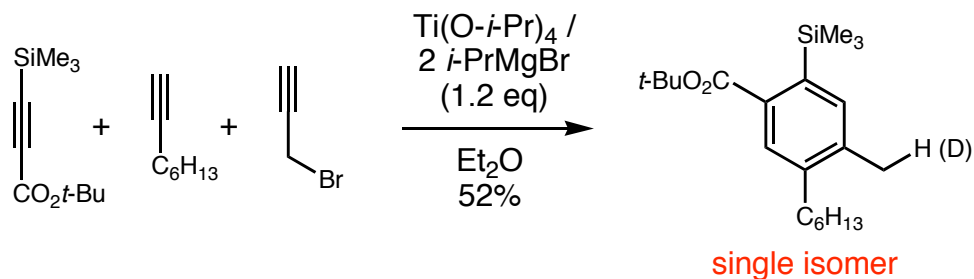
Vollhardt, K. P. C. *et al. Org. Lett.* **2000**, 2, 2479.
Vollhardt, K. P. C. *et al. J. Am. Chem. Soc.* **2001**, 123, 9324.

(±)-Strychnine

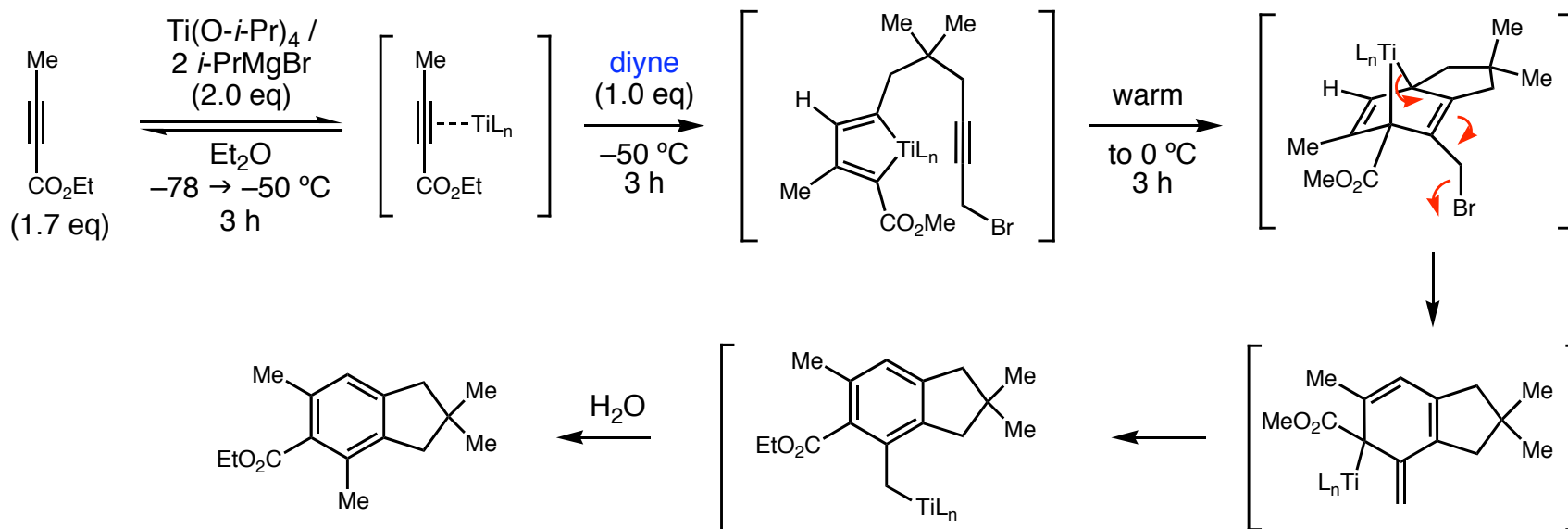
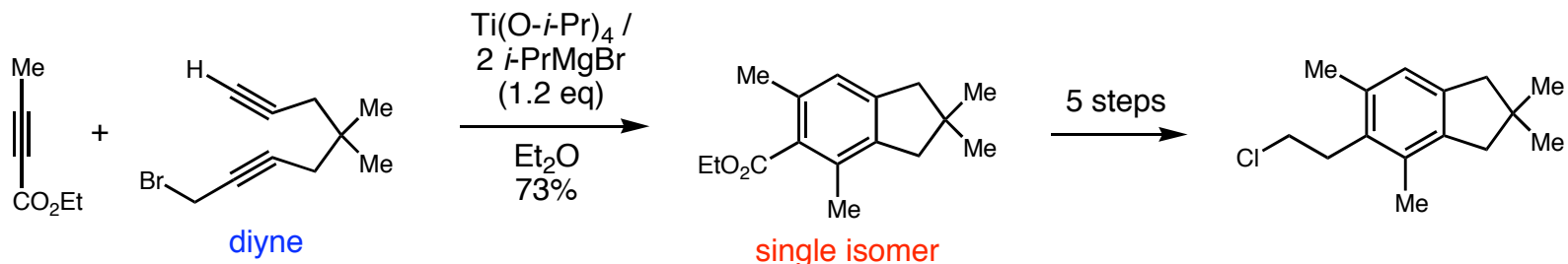
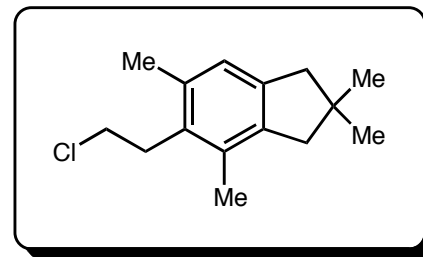


14 linear steps

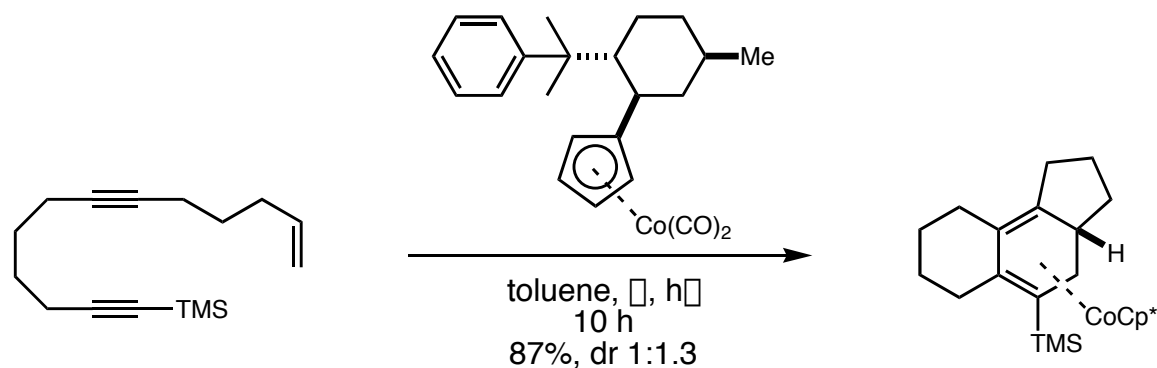
[2+2+2] Cycloaddition of Three Unsymmetrical Alkynes



Alcyopterosin A

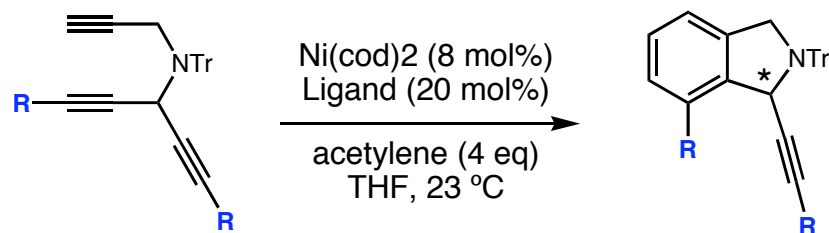


Enantioselective [2+2+2] Cyclotrimerizations

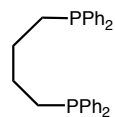


this was the only [2+2+2] cycloaddition reported in the paper

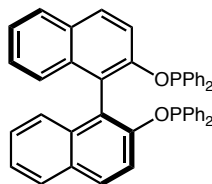
Enantioselective [2+2+2] Cyclotrimerizations



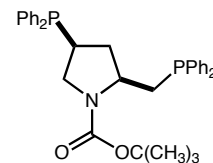
Ligand	R	Time (h)	Yield (%)	ee (%)
dppb	H	1.5	74	–
	TMS	5	83	–
(S)-BINAPO	H	16	66	12
	TMS	115	52	18
(S,S)-BPPM	H	2	82	45
	TMS	18	92	60



dppb



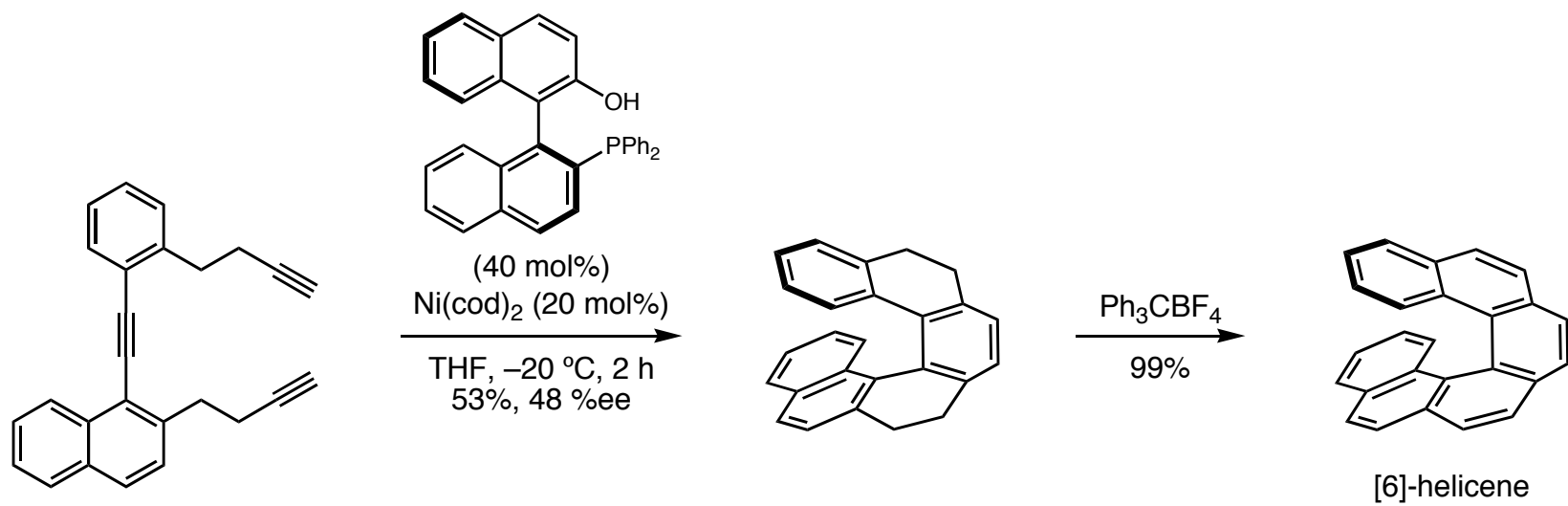
(S)-BINAPO



(S,S)-BPPM

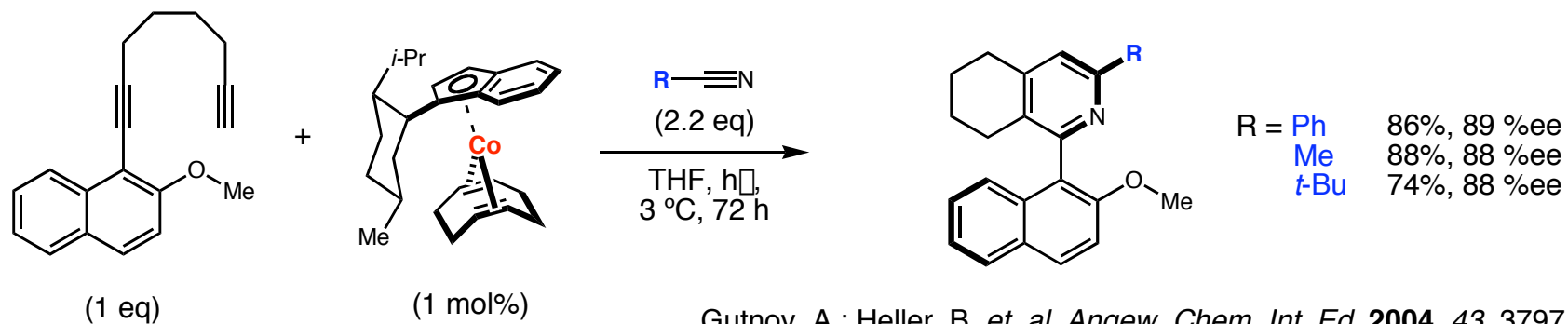
Mori, M. *et. al. J. Org. Chem.* **1994**, *59*, 6133.

Helicene

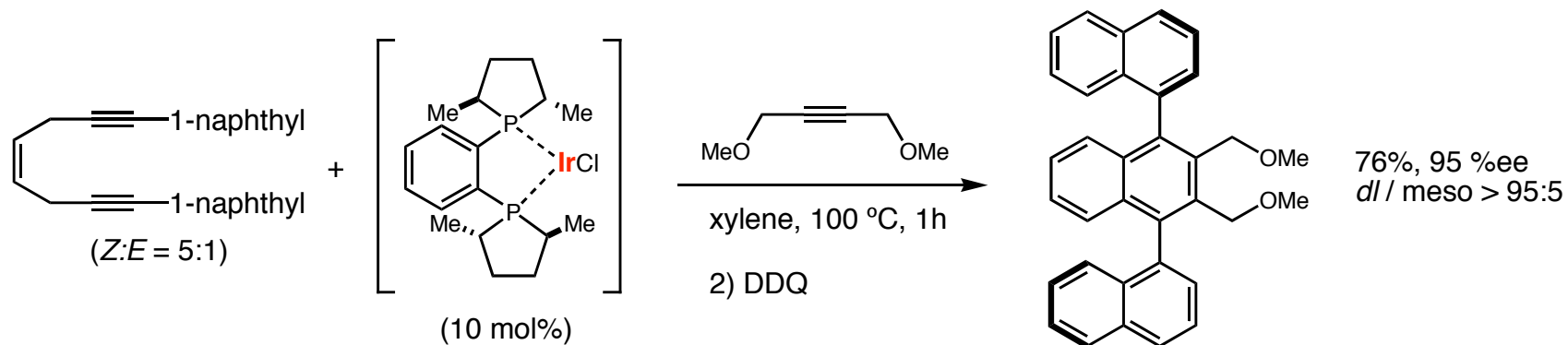


Stará, I. G. *et. al. Tetrahedron Lett.* **1999**, 40, 1993.
Stará, I. G. *et. al. J. Org. Chem.* **2003**, 68, 5193.

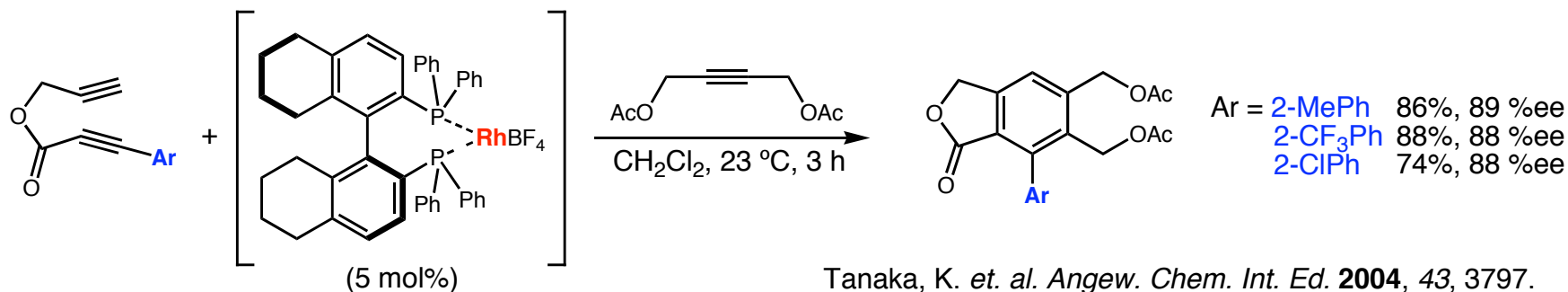
Enantioselective Biphenyl Synthesis



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

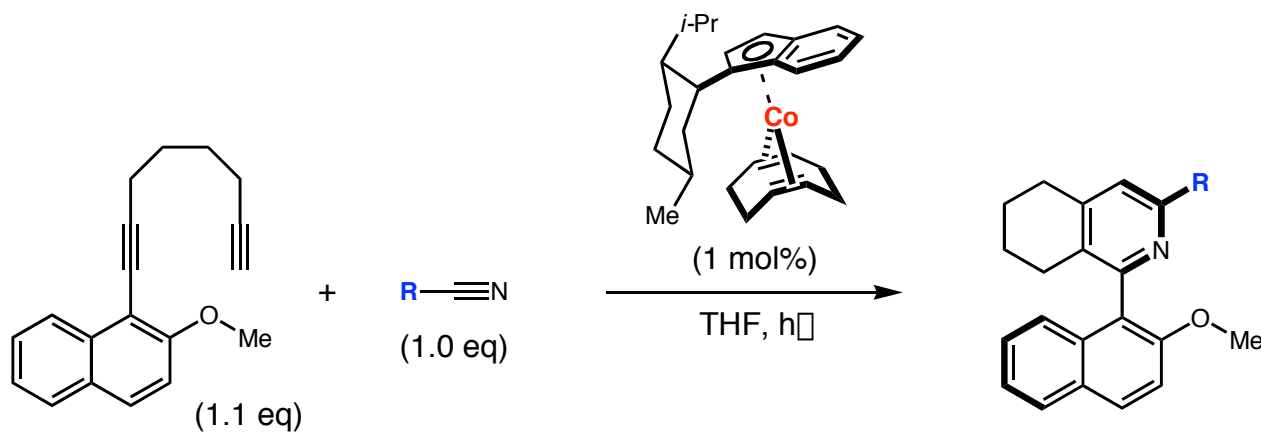


Shibata, T. *et. al. J. Am. Chem. Soc.* **2004**, 126, 8383.



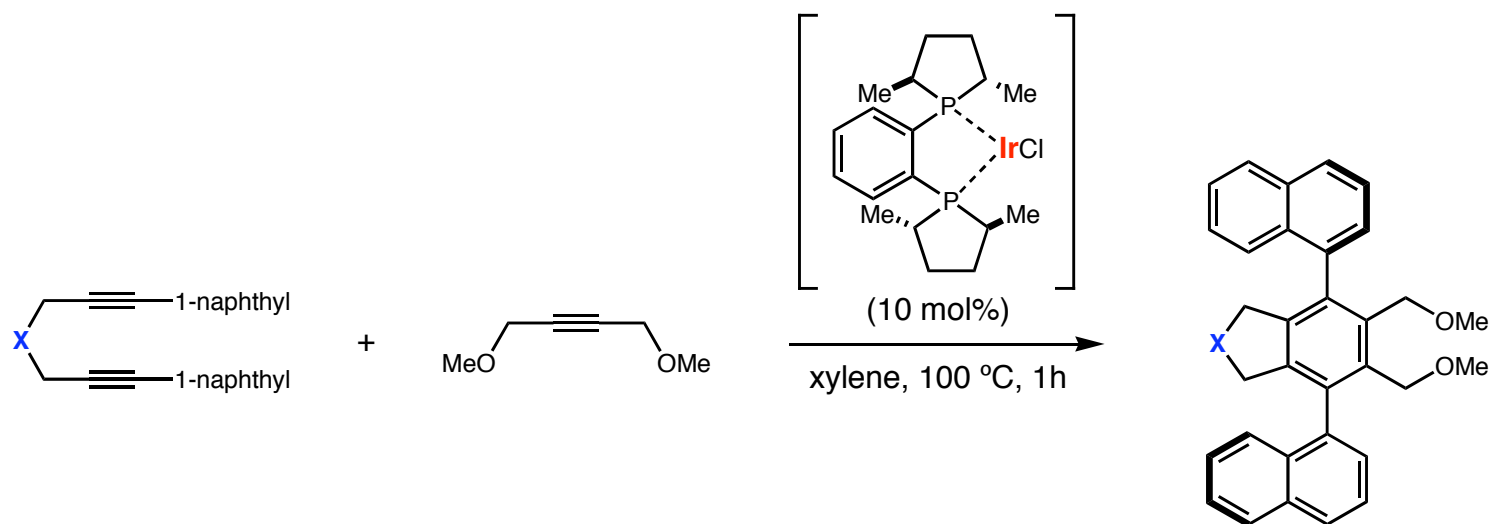
Tanaka, K. *et. al. Angew. Chem. Int. Ed.* **2004**, 43, 3797.

Enantioselective Biphenyl Synthesis



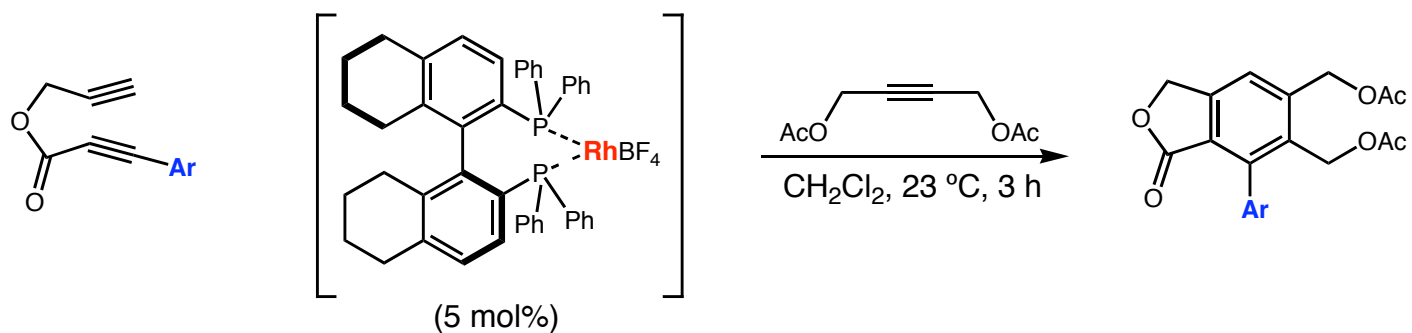
R	Temp (°C)	Time (h)	Yield (%)	ee (%)
Ph	20	24	79	82
Ph	3	24	86	89
Ph	-20	72	86	93
Me	3	24	88	88
<i>t</i> -Bu	3	24	74	88

Enantioselective Biphenyl Synthesis



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

Enantioselective Biphenyl Synthesis



Ar	Yield (%)	ee (%)
2-MeC₆H₄	67	>99
1-naphthyl	57	94
2-CF₃C₆H₄	73	>99
2-ClC₆H₄	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