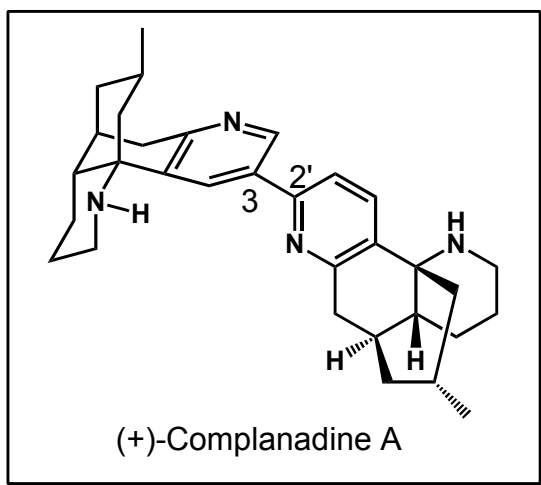


# Total Synthesis of (+)-Complanadine A



isolated from *Lycopodium complanatum*  
Ref. *Tetrahedron Lett.* **2000** 41 9069

An Inducer of Neurotrophic Factor Excretion

Pseudosymmetry

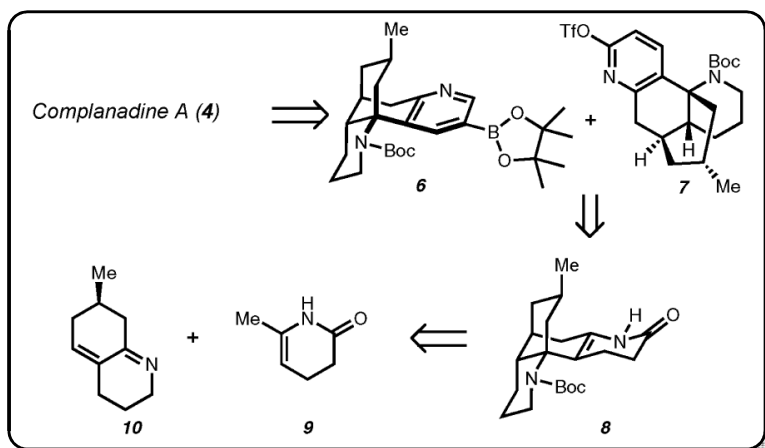
Total Synthesis by Sarpong and Siegel  
Ref. *JACS* **2010** 132 5926 (Sarpong et al)  
*JACS* **2010** 132 5924 (Siegel et al)

## Contents :

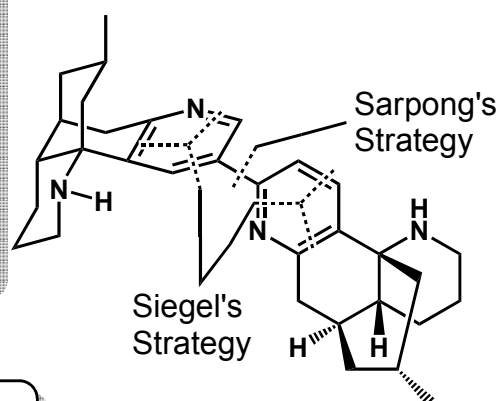
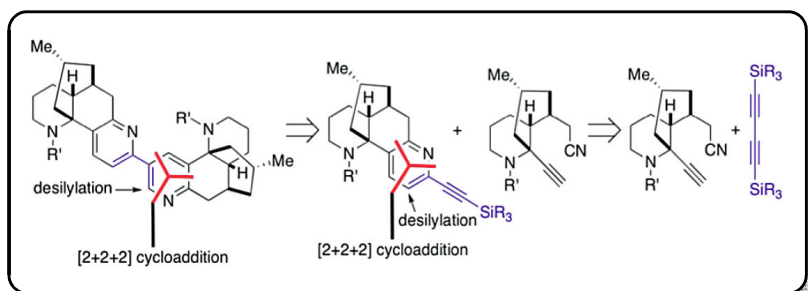
- 1 : Synthetic Strategies by Sarpong and Siegel
- 2 : Ir-catalyzed C-H Boryration
- 3 : Cobalt-catalyzed [2+2+2] cycloaddition
- 4 : Sarpong's Total Synthesis
- 5 : Siegel's Total Synthesis

## 1 : Synthetic Strategies by Sarpong and Siegel

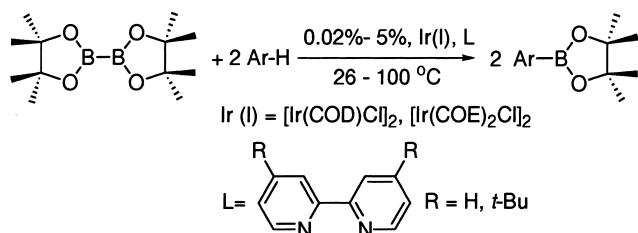
### Sarpong's Strategy



### Siegel's Strategy



## 2 : Ir-Catalyzed Borylation



Miyaura, Hartwig et al *JACS*, **2002**, *124*, 390

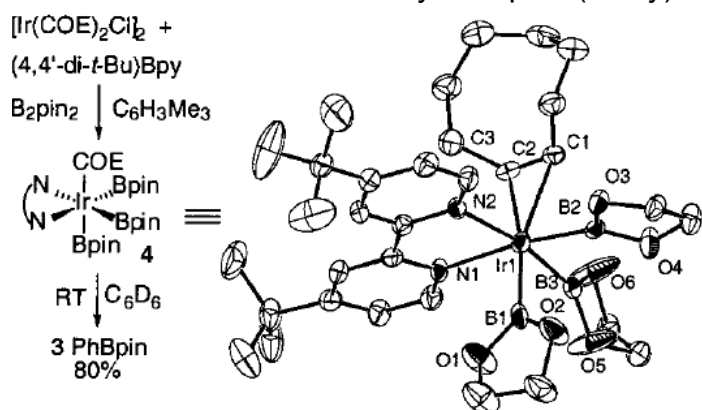
Miyaura, Hartwig et al *JACS*, **2005**, *127*, 14263

### (i) Introduction

$\text{ArH} + \text{B}_2\text{pin}_2 \xrightarrow[80^\circ\text{C}, 16\text{h}]{1.5 \text{ mol}\% [\text{Ir}(\text{COD})\text{Cl}]_2, 3.0 \text{ mol}\% \text{bpy}}$ 
 $2 \text{ArBpin} + \text{H}_2$

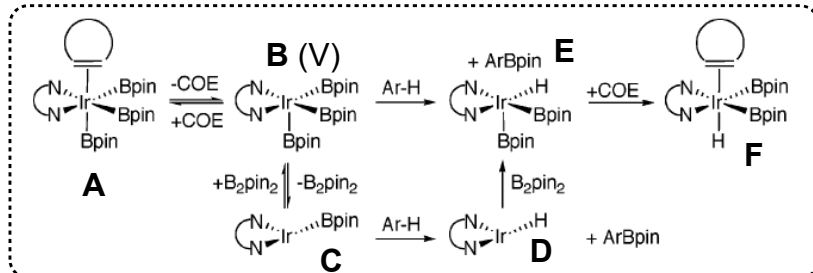
product	yield %	product	yield %	product	yield %
	95		83		86
	95 (1:74:25) (o:m:p)		86		72
	82 (0:69:31) (o:m:p)		83		73
	80 (0:70:30) (o:m:p)		58		73

### Scheme and Tris-boryl complex (X-ray)



$\text{Ir-N1} = 2.177 \text{ \AA}$ ,  $\text{Ir-N2} = 2.221 \text{ \AA}$ ,  $\text{Ir-B1} = 2.055 \text{ \AA}$ ,  $\text{Ir-B2} = 2.057 \text{ \AA}$ ,  
 $\text{Ir-B3} = 2.027 \text{ \AA}$ ,  $\text{Ir-C1} = 2.308 \text{ \AA}$ ,  $\text{Ir-C2} = 2.318 \text{ \AA}$  Pinacol methyl groups and hydrogens have been removed for clarity.

### (ii) Mechanistic study : determination of catalyst system

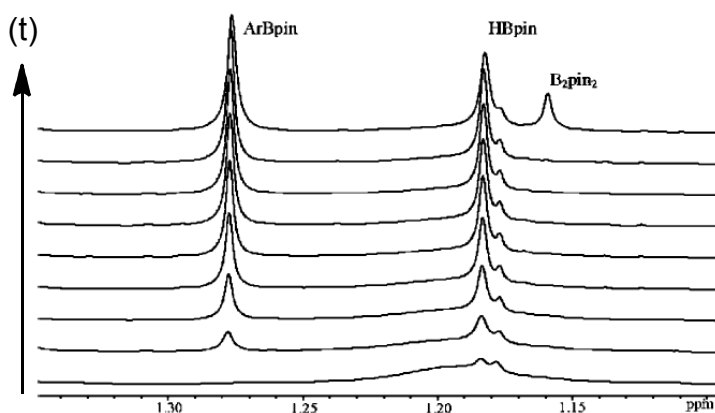


Two possible catalytic cycles

possible catalyst system :

- 1) Ir(III)  $\leftrightarrow$  Ir(V)
- 2) Ir(I)  $\leftrightarrow$  Ir(III)

### $^1\text{H}$ NMR spectra tracing



**Figure 4.**  $^1\text{H}$  NMR spectra of pinacol methyl region during the reaction of **1** with 1,2-dichlorobenzene at  $7.5^\circ\text{C}$  in the presence of  $\text{B}_2\text{pin}_2\text{-}d_{24}$ . The final spectrum contains added  $\text{B}_2\text{pin}_2$  for reference. Small amounts of HBpin ( $\delta$  1.184) and pinBOBpin ( $\delta$  1.178) are present in solution at  $t = 0$ .

This shows ...  
the reductive elimination of  $\text{B}_2\text{pin}_2$  doesn't occur.

### Isotope tracing Part 1

(for determination of "key" complex)

Benzene- $d_6$  +  $\text{B}_2\text{pin}_2\text{-}d_{24}$  (catalyzed by **A**)

**A** is unlabelled

Results : (conversion)

PhBpin- $d_5$  : PhBpin- $d_{17}$  = 68 : 32 (10%)

PhBpin- $d_5$  : PhBpin- $d_{17}$  = 47 : 53 (50%)

PhBpin- $d_5$  : PhBpin- $d_{17}$  = 17 : 83 (100%)

This reaction occurred directly from **A** or boryl complex generated from **A**.

## Isotope tracing Part 2

(for determination of "key" complex)

$B_2pin_2-d_{24} + A$  (absence of arene) at RT  
**A** is unlabelled

Unlabelled  $B_2pin_2$  is generated slowly ...

However,

1,2-dichlorobenzene +  $B_2pin_2-d_{24}$  at RT  
(catalyzed by unlabelled **A**)

monoboryl arene is generated faster  
(even at below RT)

Isotope tracing examinations show the rate of elimination of  $B_2pin_2$  to generate a monoboryl complex is much slower than the rate of reaction of **A** with arene.

**Ir(I) isn't an intermediate.**

## Kinetic study

An exchange between  $B_2pin_2-d_{24}$  and **A** occurs at higher temperature.  
This exchange process is degenerate.

This shows ...

Ir(I)  $\leftrightarrow$  Ir(III) system : an exchange process depends only reductive elimination of  $B_2pin_2$  from **A**. The reaction would be zero-order in added  $[B_2pin_2-d_{24}]$ .

Ir(III)  $\leftrightarrow$  Ir(V) system : The reaction would be first-order added  $[B_2pin_2-d_{24}]$ .

result : the rate constant for the exchange process depended linearly on  $[B_2pin_2-d_{24}]$ .

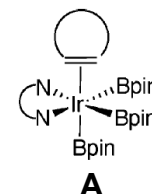
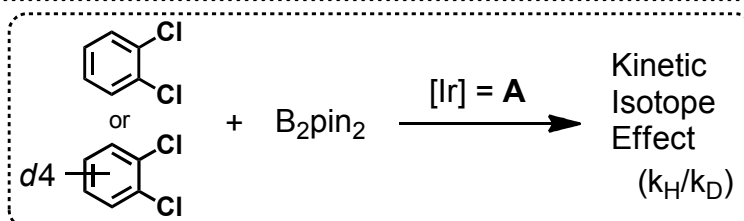


This shows the exchange process occurs by reaction of  $B_2pin_2-d_{24}$  with **A**.

**Conclusion :** This catalyst system is Ir(III)  $\leftrightarrow$  Ir(V).

### (iii) Rate limiting step

measuring isotope effect



using two separate reactions of 1,2-dichlorobenzene and 1,2-dichlorobenzene- $d_4$

(  $[A] = 4.0 \times 10^{-3} M$  ,  $[B_2pin_2] = 0.315 M$  ,  $[arene] = 0.284 M$  )

**result : isotope effect is  $3.3 \pm 0.6$**

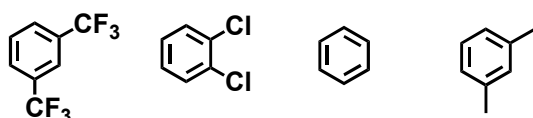
**Conclusion :** C-H bond cleavage is turnover-limiting and is consistent with the first-order dependence of the catalytic reaction on the concentration of arene.

### (iv) Kinetic study

Plots of  $\ln[arene]$  vs time

These are linear 3-4 half lives.

using four arenes in catalytic reaction



1,3-bis(trifluoromethyl)-benzene ,  $t_{1/2}=1h$  ,  $0^\circ C$

1,2-dichlorobenzene ,  $t_{1/2}=1h$  ,  $10^\circ C$

benzene ,  $t_{1/2}=1h$  ,  $25^\circ C$

m-xylene ,  $t_{1/2}=1h$  ,  $40^\circ C$

Reaction of two-different concentration of  $B_2pin_2$

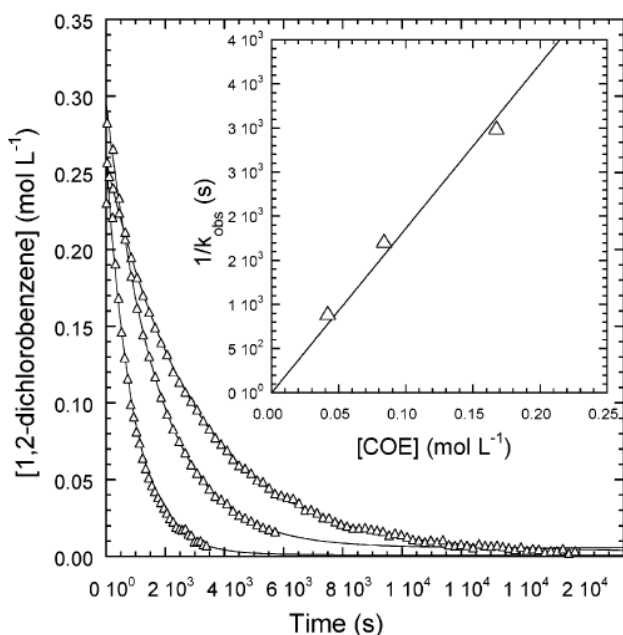
containing arene (0.299 M)

**$B_2pin_2$  (0.492 M and 1.38 M)**  
others (10 mol%)

result :  $k_{obs} = 1.9 \pm 0.2 \times 10^{-4} s^{-1}$  (0.492 M)

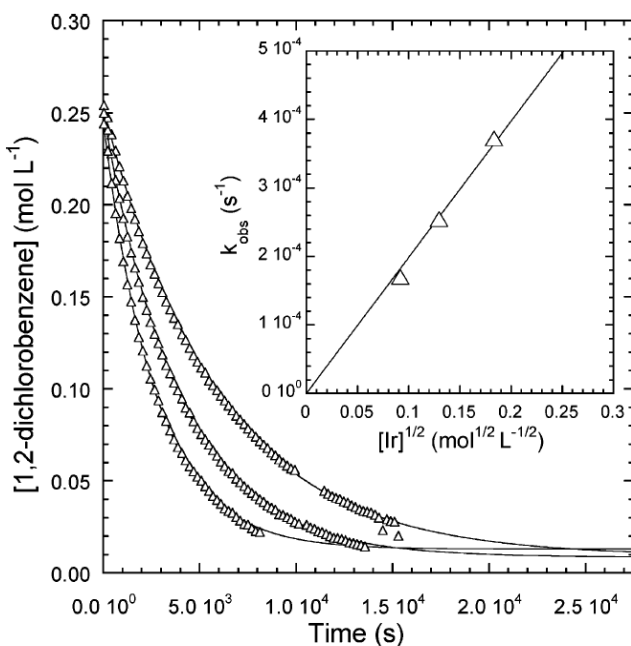
$k_{obs} = 1.7 \pm 0.2 \times 10^{-4} s^{-1}$  (1.38 M)

**The reaction is zero-order in  $B_2pin_2$ .  
first-order in arene**



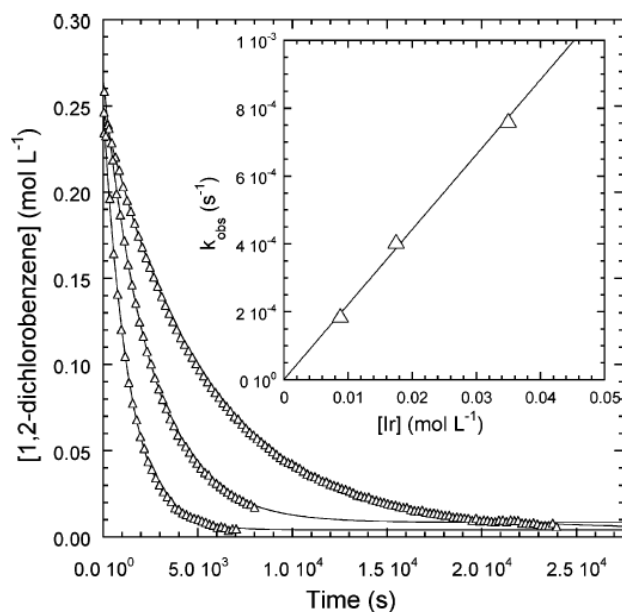
**Figure 6.** Decay of 1,2-dichlorobenzene during the reaction with  $B_2pin_2$  catalyzed by **1** at 40 °C. Inset: Relationship between  $1/k_{obs}$  and  $[COE]$  for the reaction of 1,2-dichlorobenzene with  $B_2pin_2$  catalyzed by **1**.

The reaction is inverse first-order in  $[COE]$ .



**Figure 8.** Decay of 1,2-dichlorobenzene during the reaction with  $B_2pin_2$  catalyzed by **1** at 10 °C. Inset: Relationship between  $k_{obs}$  and  $[Ir]$  for the reaction of 1,2-dichlorobenzene with  $B_2pin_2$  catalyzed by **1** in the absence of COE.

The reaction is half-order in  $[Ir]$ .  
(COE is absence)



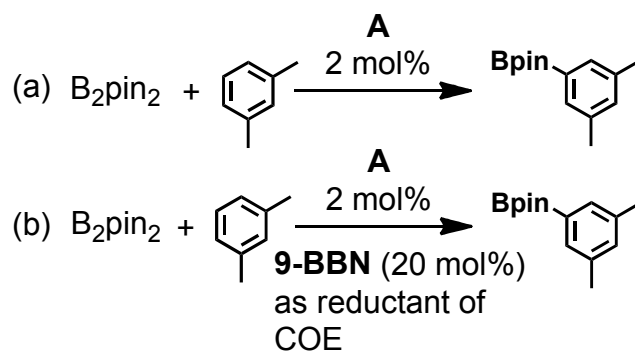
**Figure 7.** Decay of 1,2-dichlorobenzene during the reaction with  $B_2pin_2$  catalyzed by **1** at 40 °C in the presence of added COE. Inset: Relationship between  $k_{obs}$  and  $[Ir]$  for the reaction of 1,2-dichlorobenzene with  $B_2pin_2$  catalyzed by **1** with added COE.

The reaction is first-order in  $[Ir]$ .  
(COE is added)

These kinetic studies show COE inhibits the reaction.

therefore, removing COE after catalyst is generated would promote the reaction.

Experimental condition :

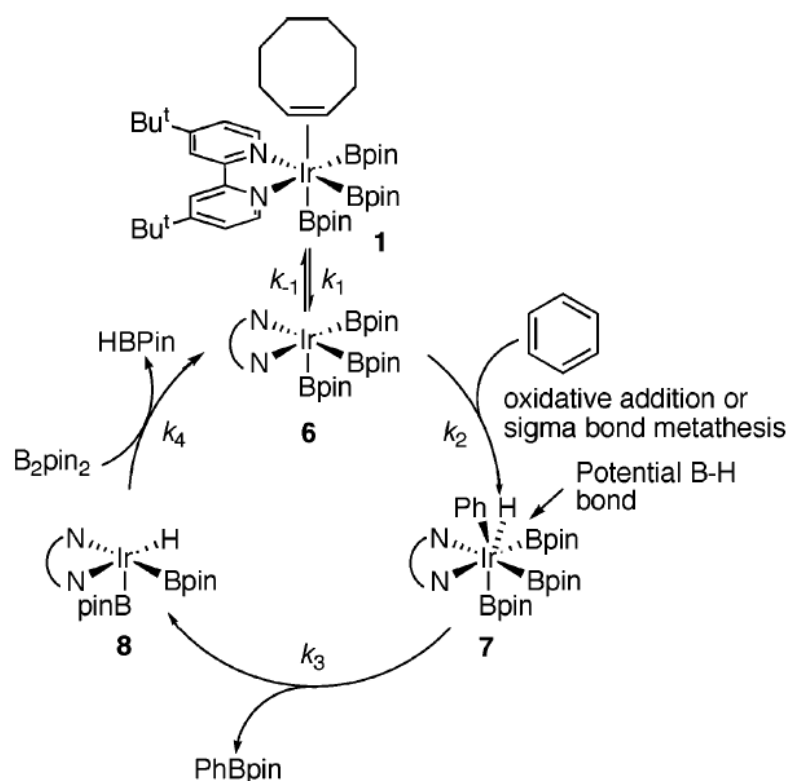


Results : (a) 15% (8h) , 25% (20h)  
 (b) 44% (8h) , 80% (20h)

Consuming the COE ligand does lead to significant rate enhancements.

## (v) Catalytic cycle

The reaction's catalytic cycle proposed based on these mechanistic studies below.



The reasons that complex **1** is this reaction's catalyst are shown below.

- 1) induction period is observed when the catalyst is generated in situ from  $[\text{Ir}(\text{COE})_2(\text{OMe})]_2$  and dtbpy, but induction period is absent when the reactions are initiated with isolated complex **1**.
- 2) the isotope effects are similar for the catalytic reactions and the stoichiometric reactions of complex **1**.
- 3) the selectivities for reactions of  $\text{B}_2\text{pin}_2$  with different arenes and heteroarenes are similar for the catalytic reactions and the stoichiometric reactions of complex **1**.

## (vi) Reactivity and selectivity of substrates

### a) reactivity of arene

#### a1) electronic-rich arenes vs electron-poor arenes

The catalytic reaction occurs faster with electron-poor arenes than with electronic-rich arenes. (see. (iv) Kinetic study)

The precursor to C-H bond cleavage is known to be a  $\eta^2$ - $\pi$ -complex.

The stability of the  $\eta^2$ - $\pi$ -complexes contributes to reactivity.

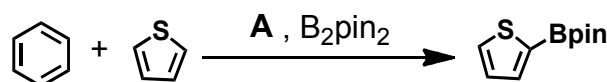
Ref : Jones , Perutz *JACS*, **1993**, *115*, 7685

However...

#### a2) electronic-rich five-membered heteroarene vs electron-neutral arene

The catalyst reaction occurs faster with electron-rich heteroarenes than with arenes.

competing with reactions of benzene and thiophene, 2-thienyl pinacol boronate ester is major product.



Five-membered  $\eta^2$ -heteroarene complexes are more stable than  $\eta^2$ -arene complexes.

### b) site selectivity or regioselectivity in arene

steric effect vs  $\pi$ -complexes stability effect

In the reaction of phenanthrene, borylation would occur at the 9-position.

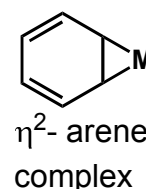
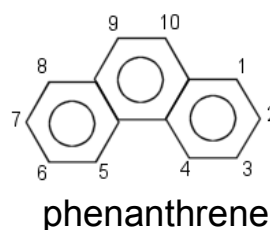
( $\pi$ -complexes)

borylation would occur at the 2 and 3-position.

(steric effects)

result : 2- and 3-borylated isomers are observed

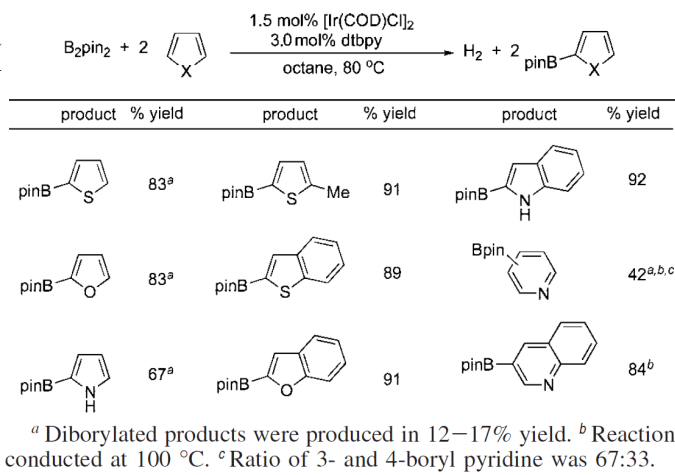
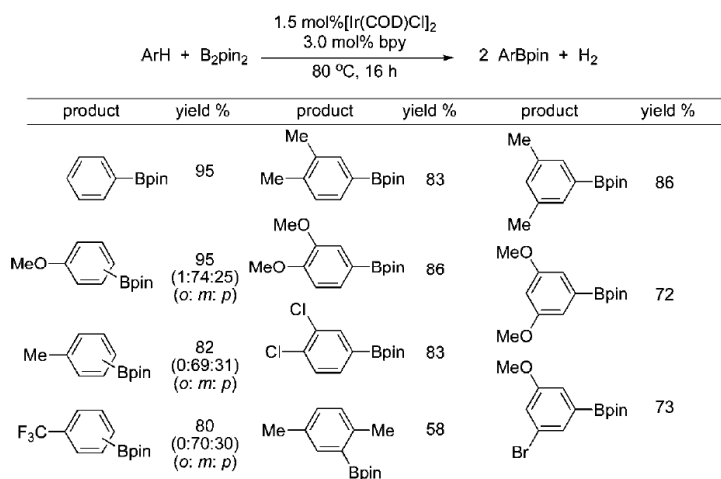
the steric effect on regioselectivity is stronger than the stability of the  $\pi$ -complexes.



5

## (vii) Regioselectivity of arene and heteroarene

Hartwig et al *Chem. Rev.*, **2010**, *110*, 890



In arene, meta product is major.

In 5-membered heteroarene, 2-borylated products are major. However, in 6-membered heteroarene (ex. pyridine, quinoline), 3-borylated products are major and 2-borylated products aren't obtained.

*"The regioselectivity of the borylation of pyridine and quinoline to give 3-borylated products is perplexing. One possibility is that an iridium complex or a boron compound binds reversibly to the basic nitrogen and both activates the substrate for reaction and blocks borylation at the 2-position."*

Hartwig et al *Tetrahedron Lett.*, **2002**, *43*, 5649

### 3 : Cobalt-catalyzed [2+2+2] cycloaddition

#### (i) Introduction

Omae et al *Appl. Organometal.. Chem*, 2007, 21, 318

Organocobalt compounds in organic synthesis have three characteristic reactions.

- A) A high affinity to C-C  $\pi$ -bonds or C-N  $\pi$ -bonds.
- B) A high affinity to carbonyl groups.
- C) Easily tending to form square-planar bipyramidal six-coordination structures at the square-planar position, and to bond with one or two carbon atoms at axial position.

Nicholas reaction, Pauson-Khand reaction and [2+2+2] cyclization are based on character A. (Pauson-Khand reaction is also based on character B)

#### (ii) Nicholas reaction (character A)

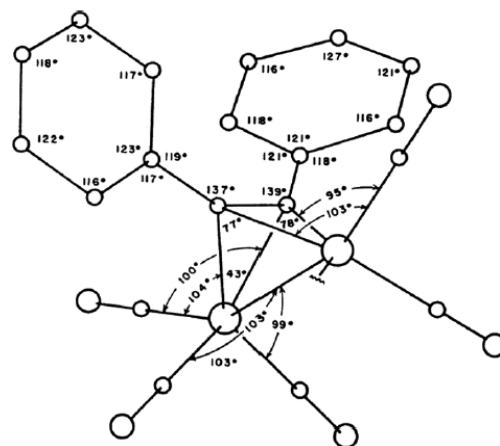
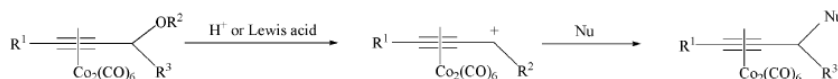
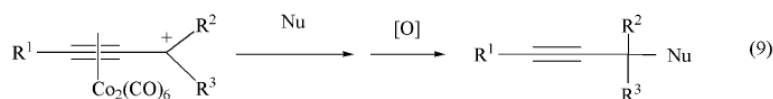
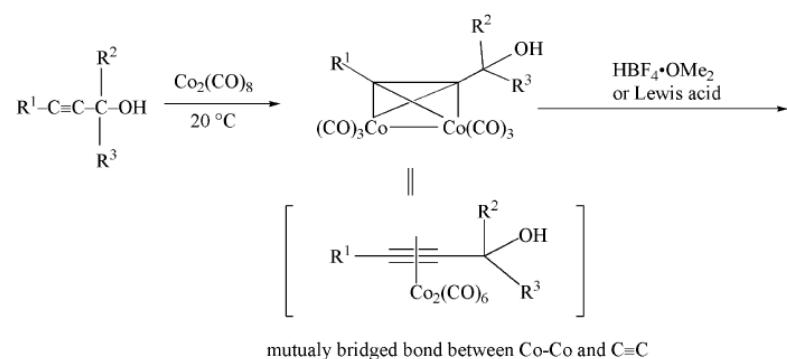


Figure 1. Structure of dicobalt hexacarbonyl diphenylacetylene.<sup>69</sup>

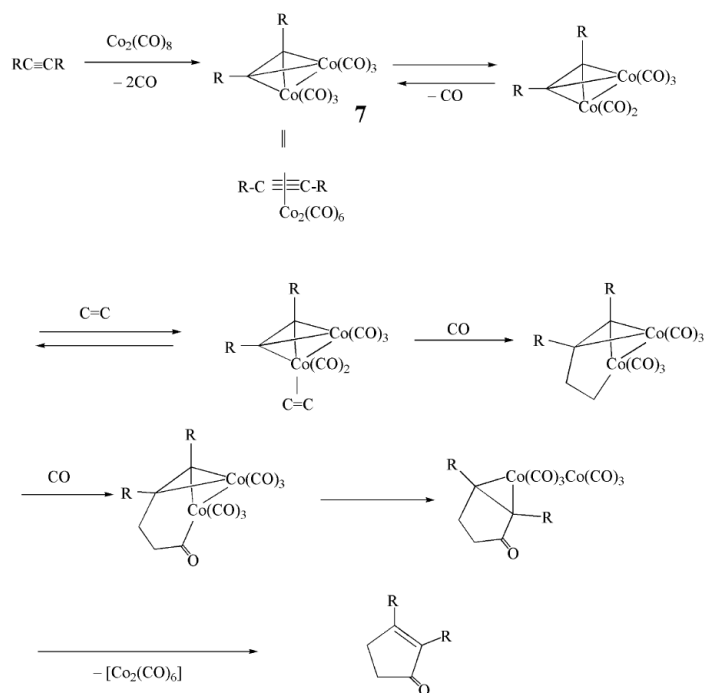
The cation at the  $\alpha$ -position of the alkynes is stabilized by dicobalt hexacarbonyl acetylene moiety.

Ref : Mayr et al *JACS*, 1998, 120, 900

Cobalt-alkyne complex is stable, so this is also used for protection of alkyne.

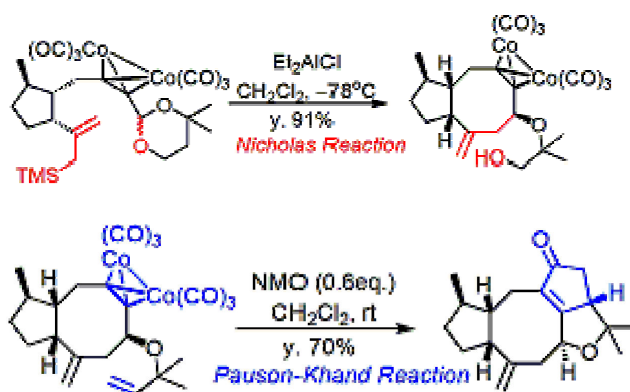
Alkyne's  $\pi$ -bonds are used for forming cobalt-alkyne complex. This alkyne isn't active.

### (iii) Pauson-Khand reaction (character A , B)



The cobalt-alkyne complex same as Nicholas reaction is revealing.

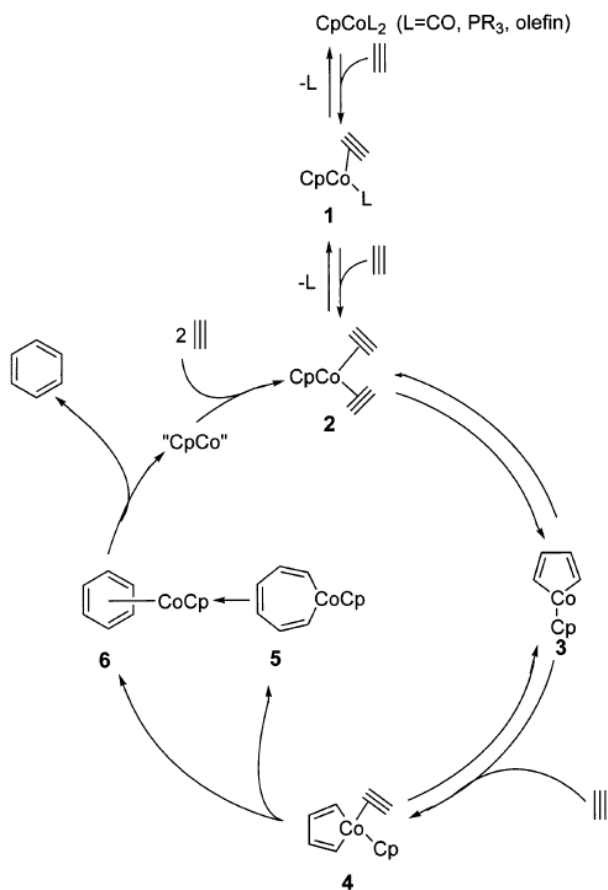
### ex) Nicholas reaction and Pauson-Khand reaction



Schreiber et al *JACS*, **1997**, *119*, 4353

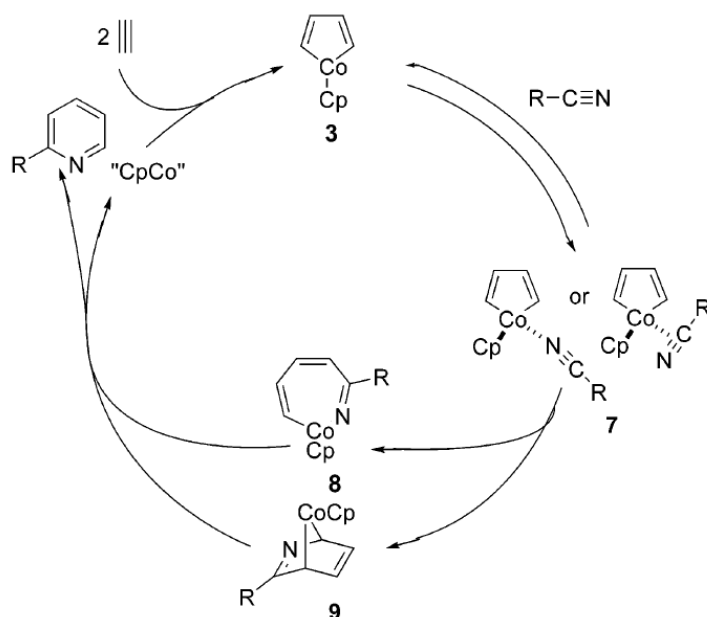
### (iv) [2+2+2] cyclization

catalytic cycle



Oxidative coupling of two coordinated alkynes to afford cobaltacyclopentadiene

Ref : Varela , Saa et al  
*Chem. Rev.* **2003**, *103*, 3787

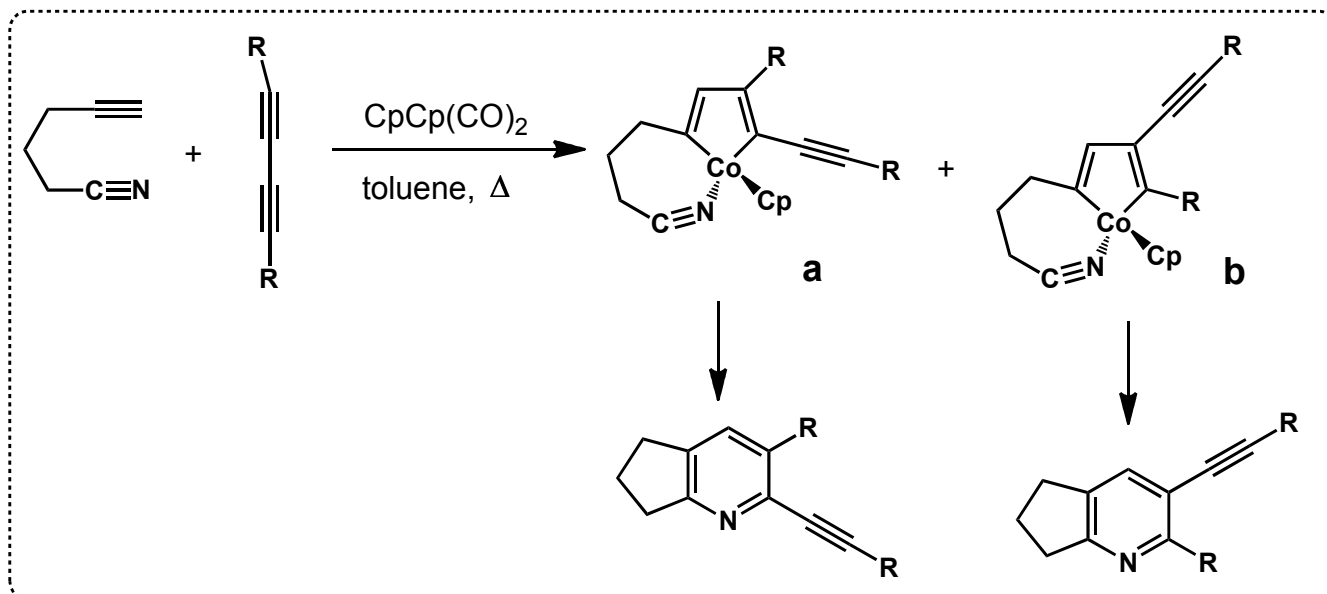


CpCoL<sub>2</sub>-catalyzed pyridine synthesis 8



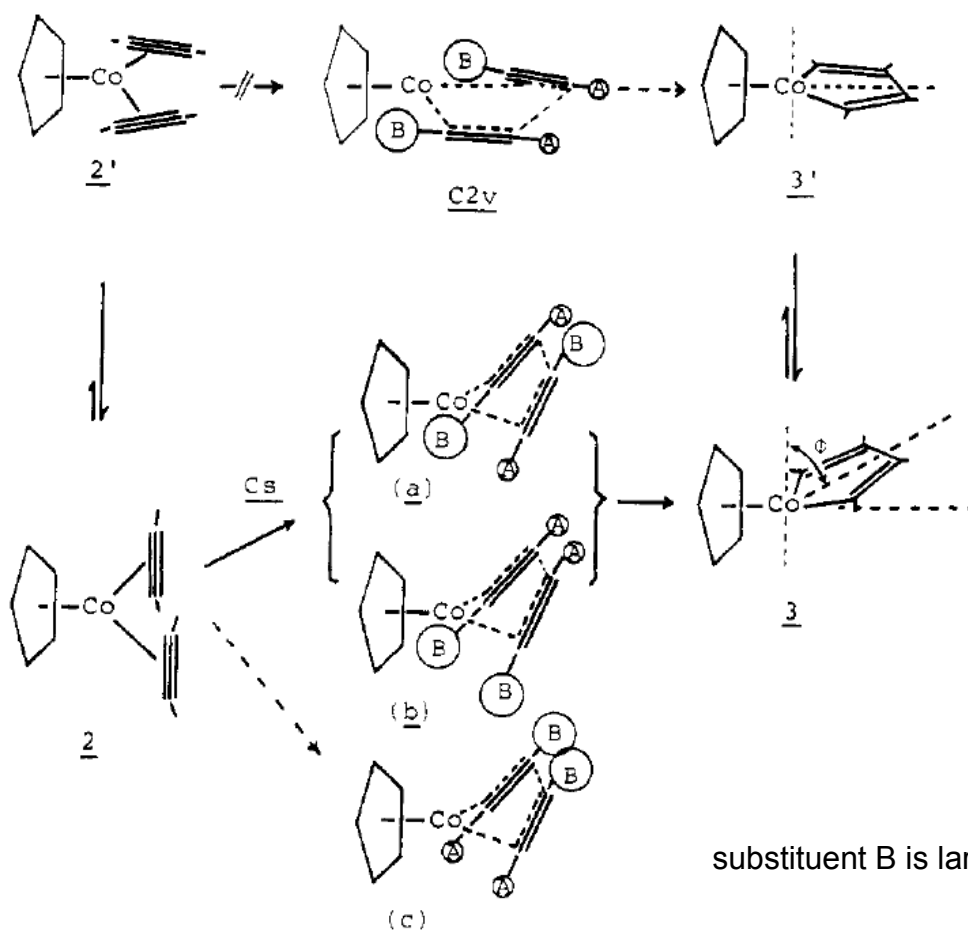
(iv) Steric effect vs electronic effect

Saa et al *JACS*, 1998, 120, 12147



If steric effect is important...  
complex **b** is major.

Ref : Wakatsuki et al *JACS*, 1983, 105, 1907



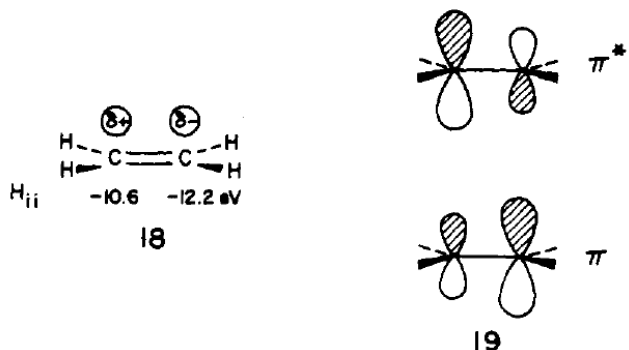
substituent B is larger than A

**Path Cs-b** is favorable because the bulkier substituent B is directed to the most vacant site.

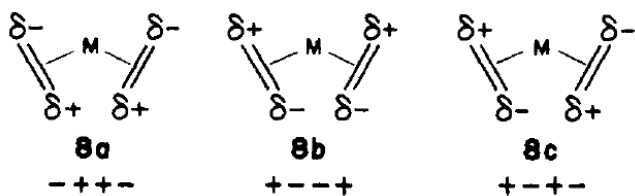
However, **path Cs-c** is unfavorable because a large steric repulsion between two bulky B at the  $\beta$ -positions.

If electronic effect is important...

complex **a** is major.

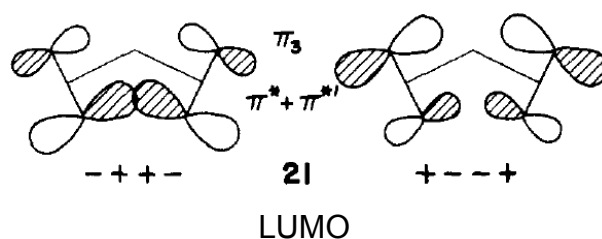
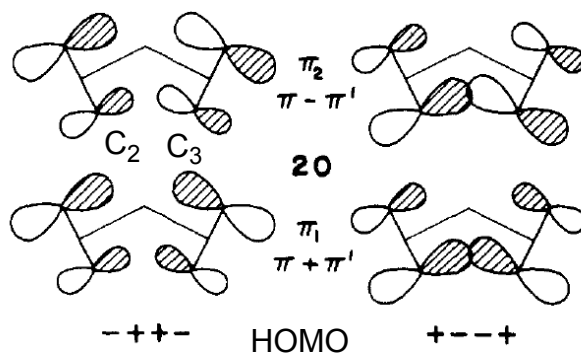


model of ethylene polarization

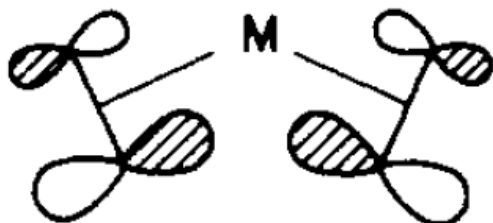


two ethylene and metal

Ref : Hoffmann et al *JACS*, 1980, 102, 2952



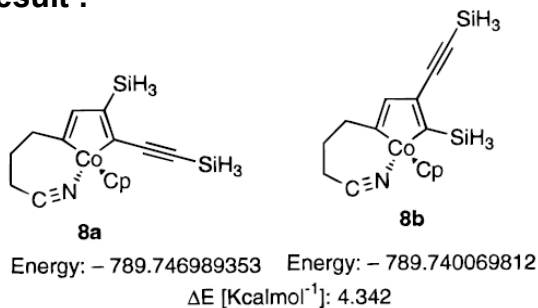
Summary,



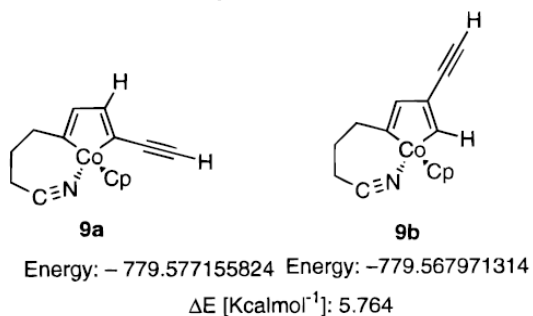
The activation energy is dominated by C<sub>2</sub>-C<sub>3</sub> bond formation.

The  $\pi^*$  mixing is enhanced when the large lobes of the polarized  $\pi^*$  face each other in the  $\beta$  positions.

Result :

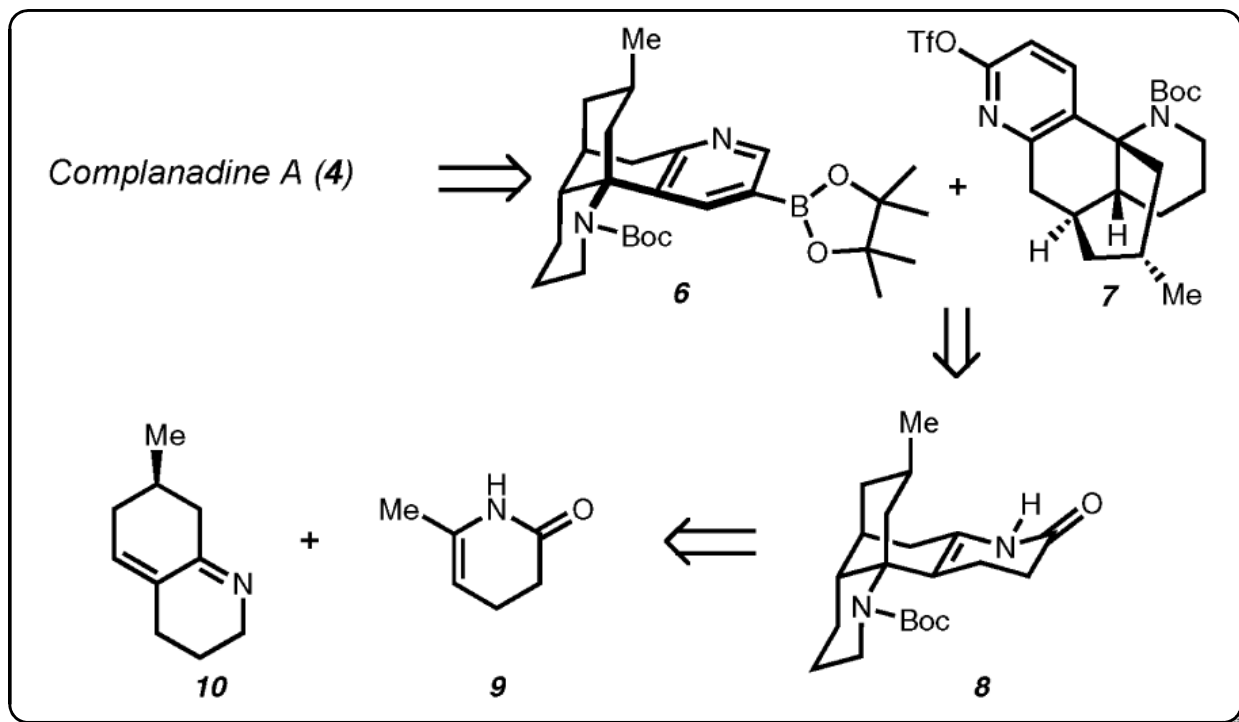


electronic effect is stronger than steric effect.

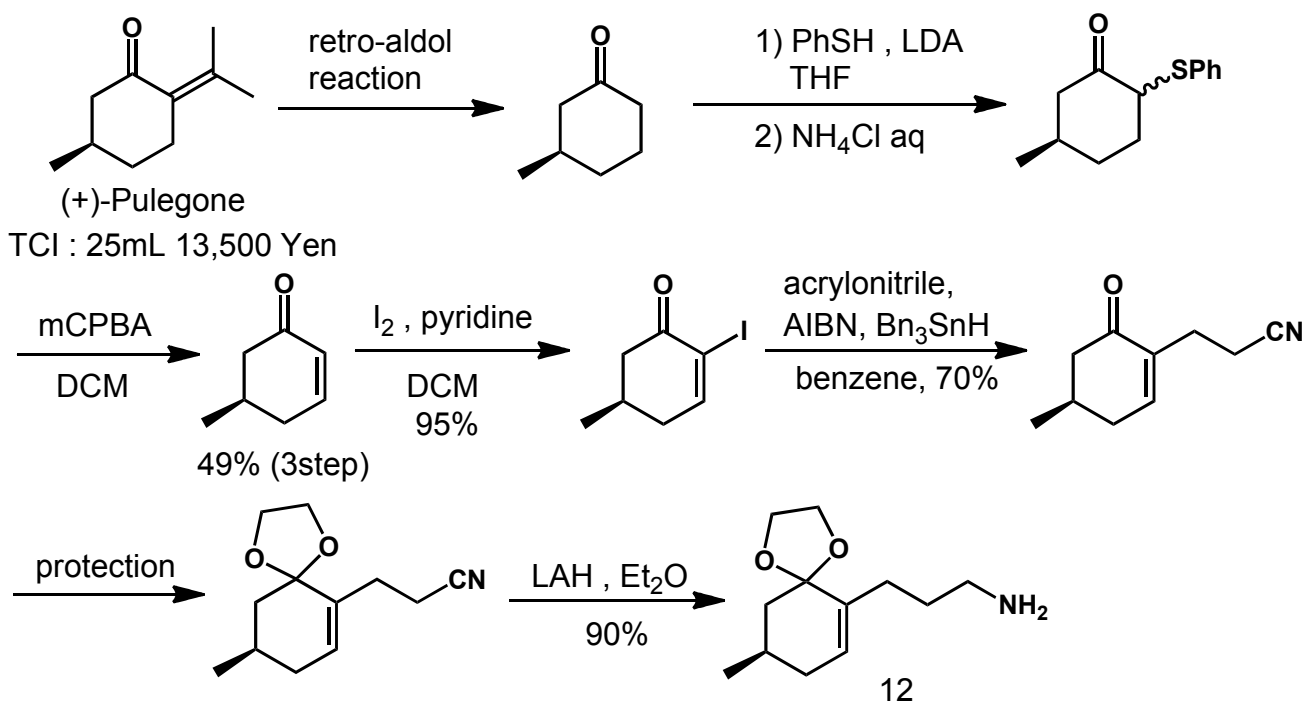


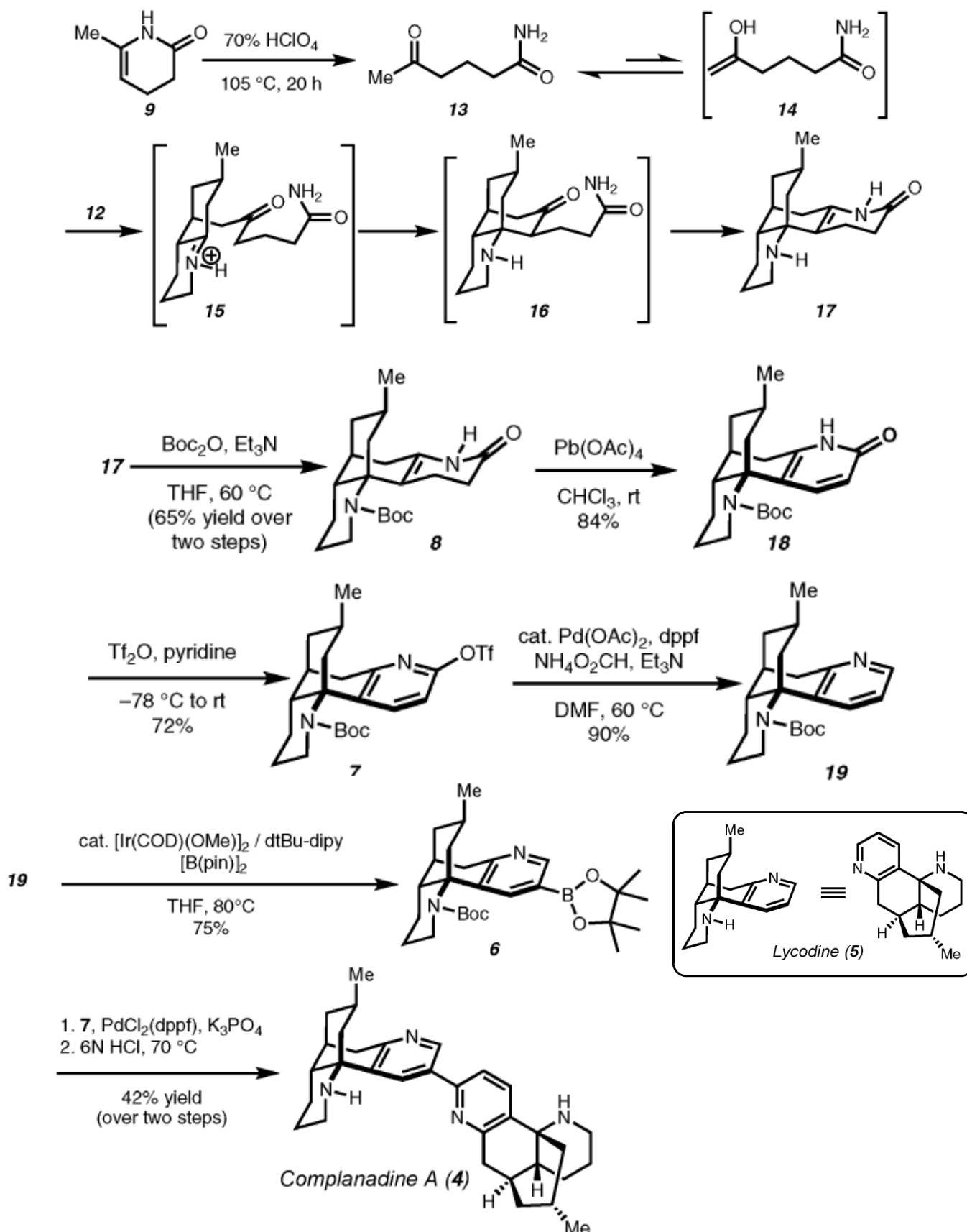
## 4 : Sarpong's Total Synthesis

### Retro-synthesis



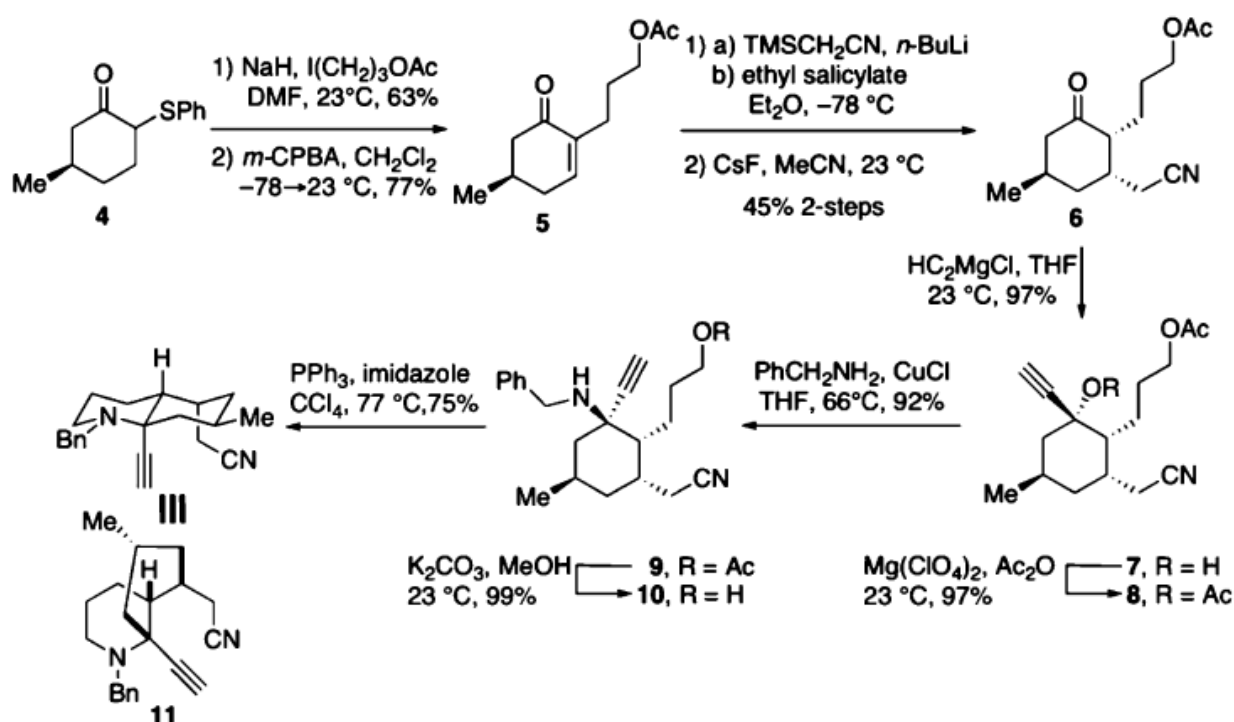
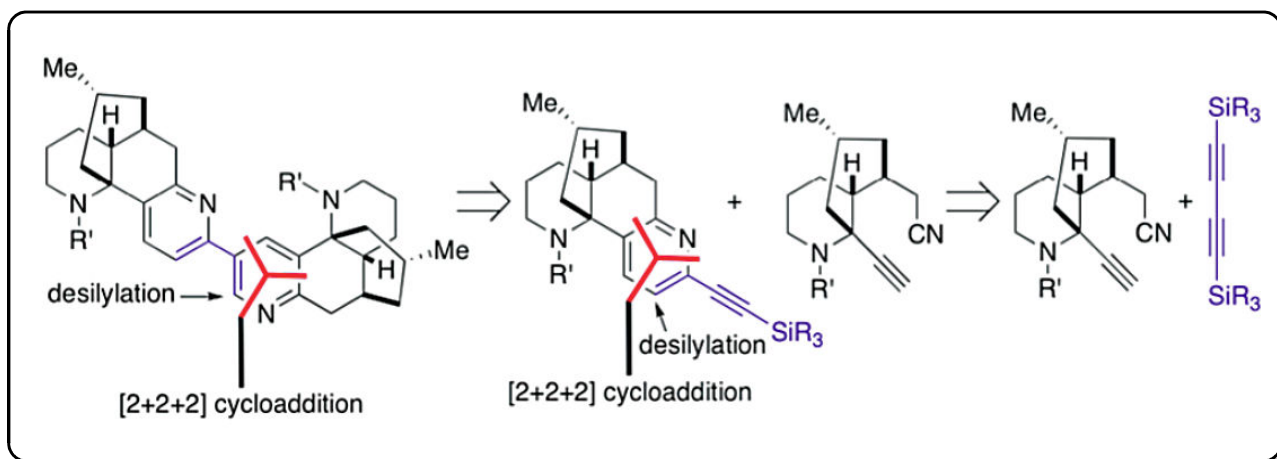
### Synthesis of 12



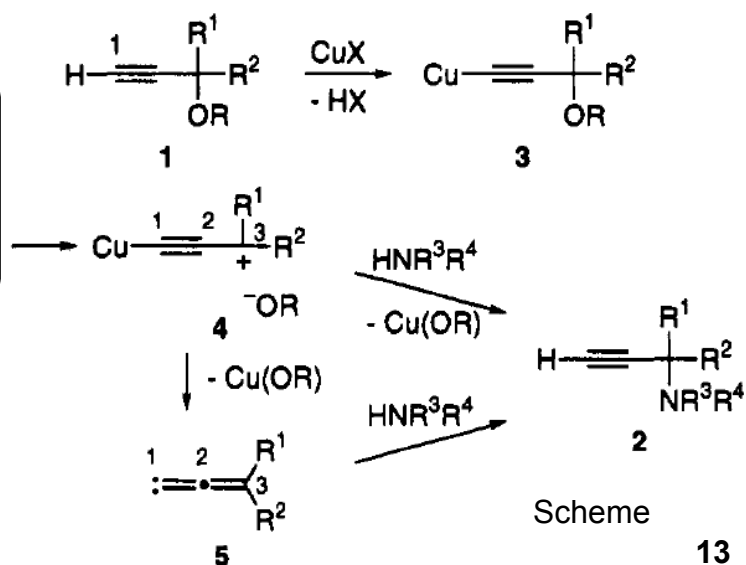
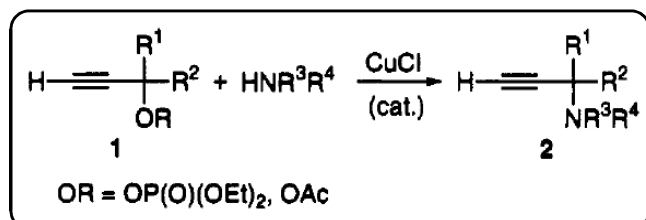


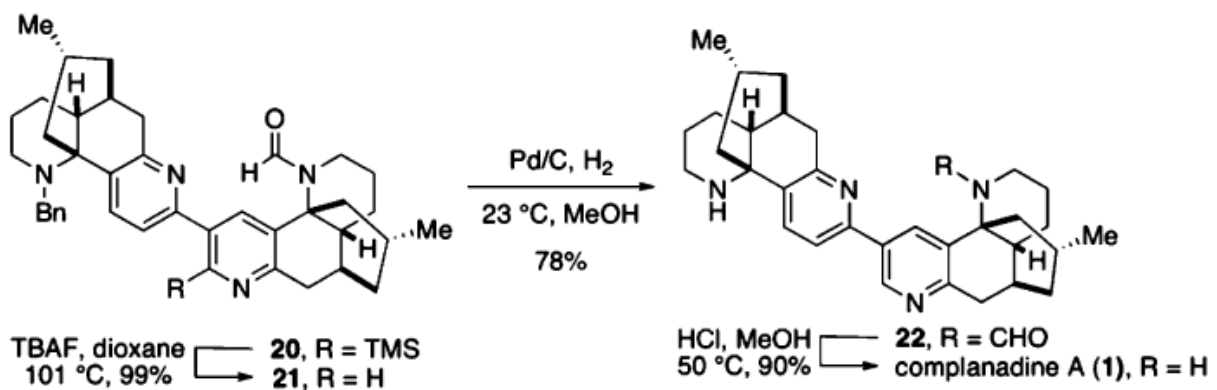
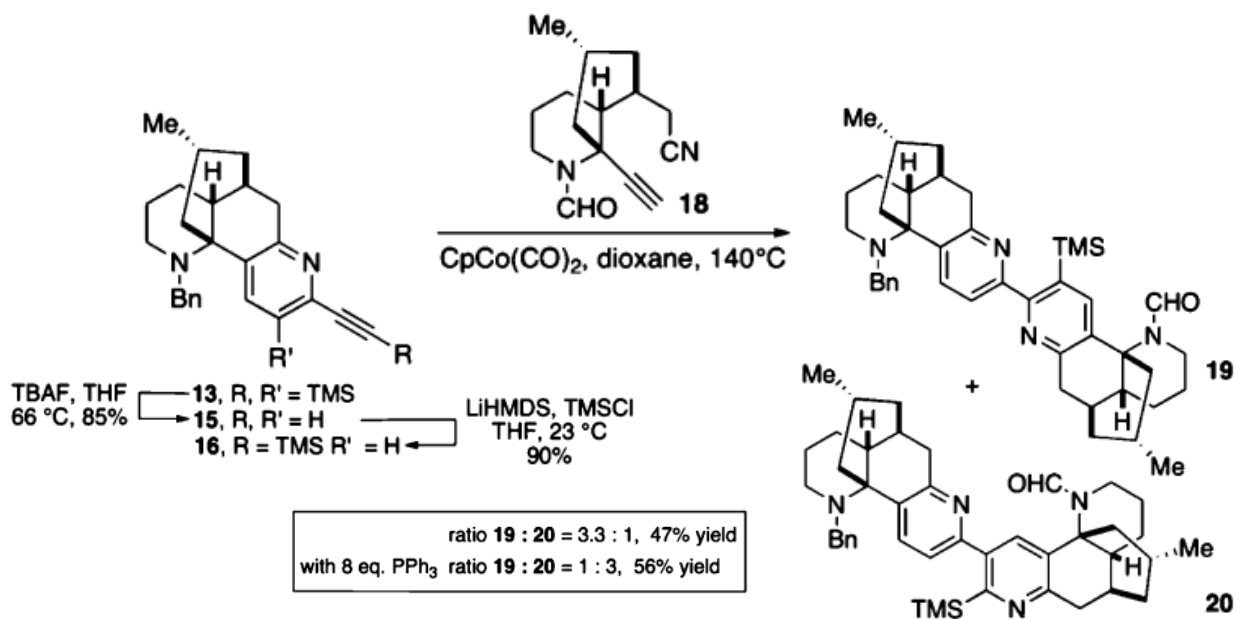
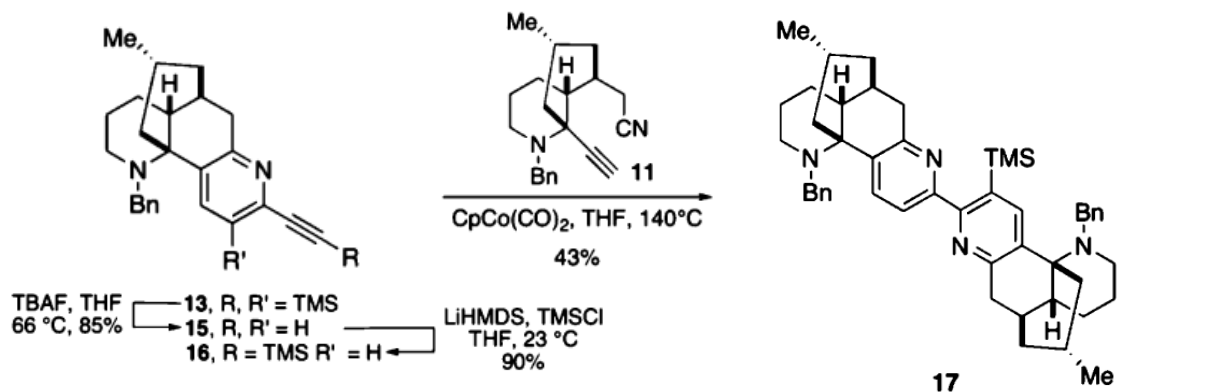
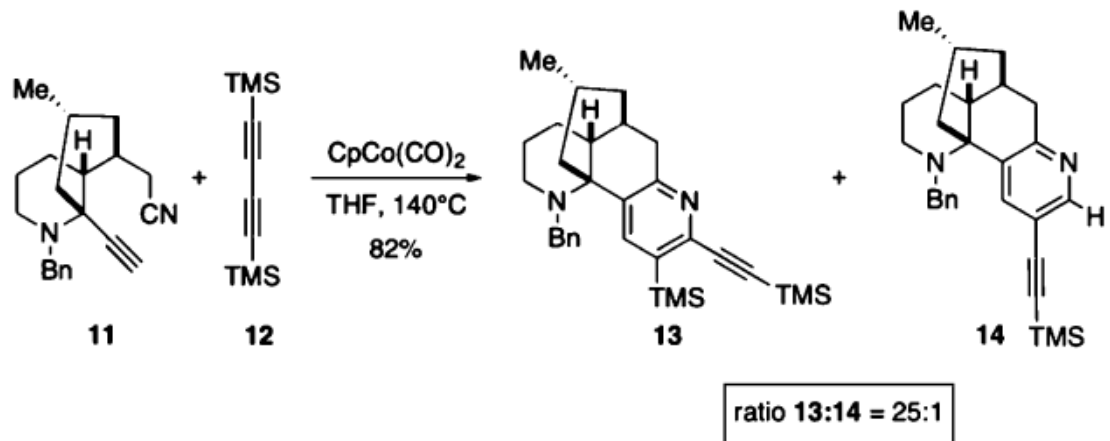
## 5 : Siegel's Total Synthesis

### Retro-synthesis



### Amidation of propargyl alcohol





## Summary

- 1) quaternary center : Cu-catalyzed amine substitution of propargyl amidation
- 2) pseudosymmetry : Late stage Cobalt-catalyzed [2+2+2] cyclization (regioselectivity by  $\text{PPh}_3$ )