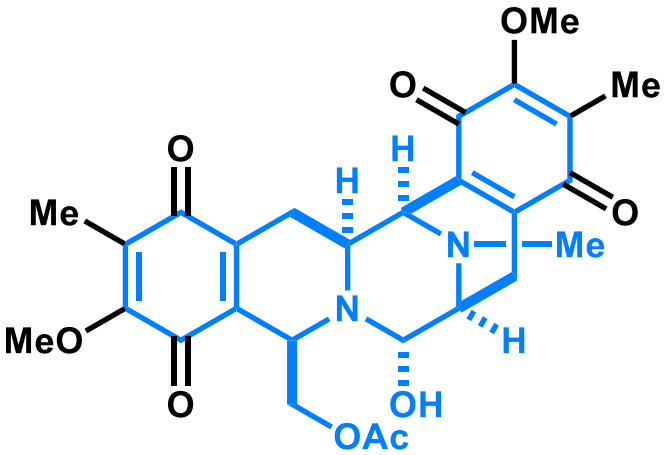
# Total Synthesis of (-)-Jorumycin

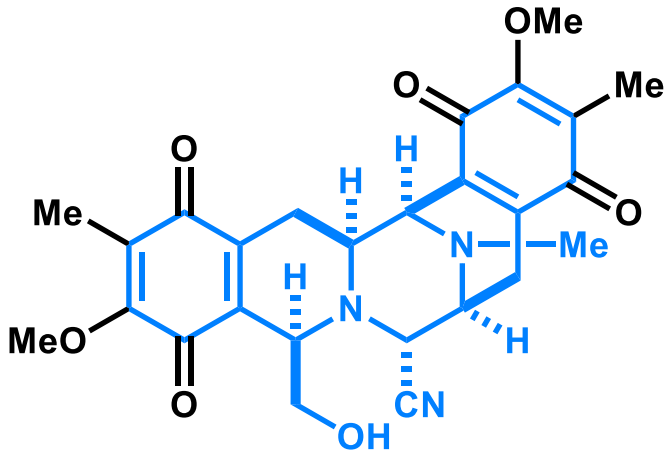
2019.11.30. Literature Seminar
B4 Shu Nakamura

# Contents

# Bis-Tetrahydroisoquinoline Alkaloids




(-)-Jorumycin




(-)-Jorunnamycin A

**Isolation:** ***Jorunna funebris*** **(2000)**

**Structural features: bis-tetrahydroisoquinoline skeleton**
**highly oxygenated ring**
**central pro-iminium ion**

**Total synthesis of (-)-jorumycin**
**: Wiiliams (2005), Zhu (2009), Liu (2012), Chen (2013), Stoltz (2019)**


1) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305.
2) Chrzanowska, Maria.; Grajewska, Agnieszka.; Rozwadowska, M. D. *Chem. Rev.* **2016**, *116*, 12369.
3) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.
4) Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558.
5) Liu, W. et al. *Tetrahedron* **2012**, *68*, 2759.
6) Chen, R.; Liu, H.; Chen, X. *J. Nat. Prod.* **2013**, *76*, 1789.

# Introduction of Prof. Williams and Stoltz

**Prof. Robert M. Williams**

**1975 B.S. @ Syracuse University (Prof. Ei-ichi Negishi)**
**1979 Ph.D @ MIT (Prof. William H. Rastetter)**
**1979 Postdoctral fellow**
**@ Harvard University (Prof. R.B. Woodward; Prof. Yoshito Kishi)**
**1980 @ Colorado State University**
**1985 Associate professor @ Colorado State University**
**1988 Professor @ Colorado State University**
**2002-Distinguished professor @ Colorado State University**

**Research topic: natural products synthesis**

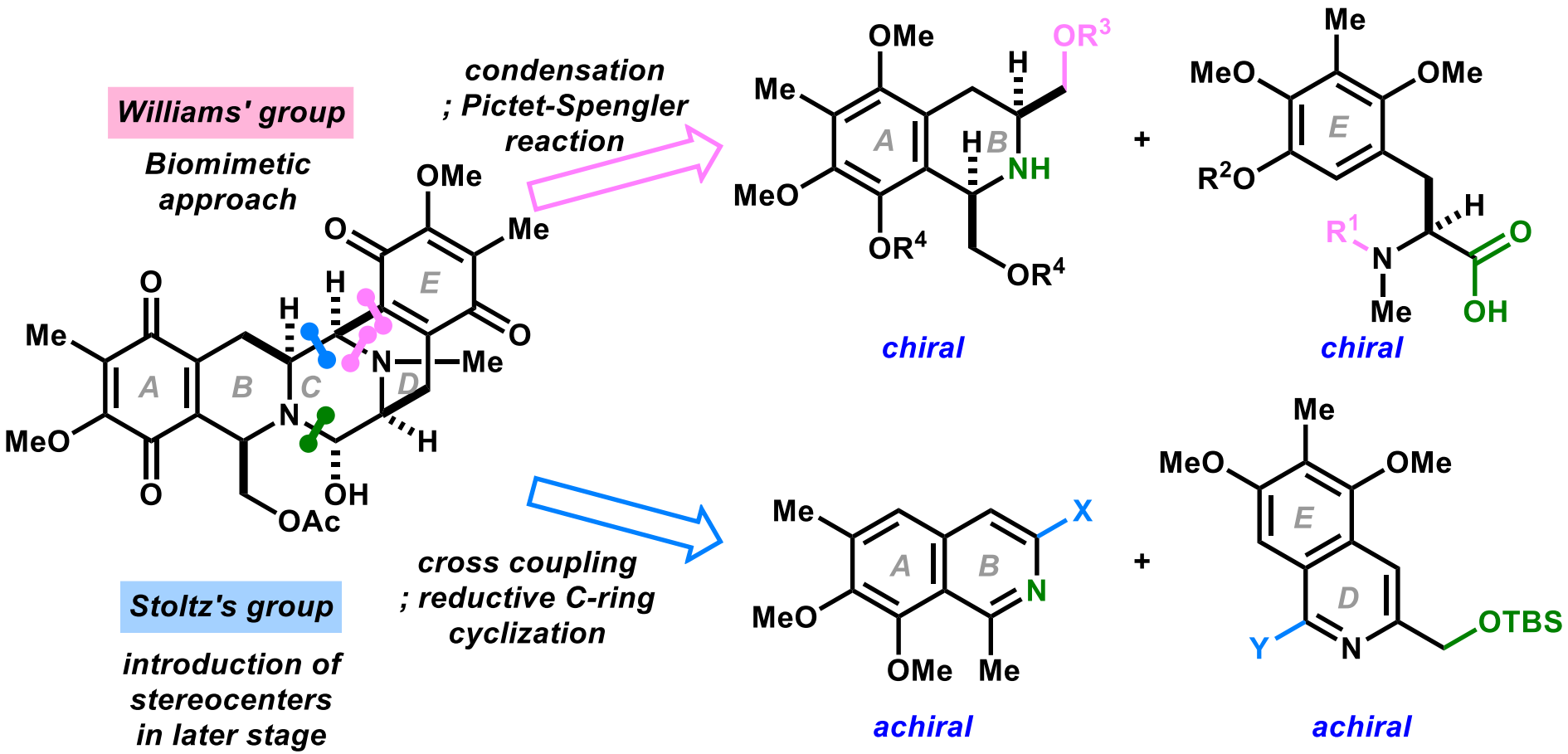
**Prof. Brian M. Stoltz**

**1993 B.S. @ Indiana University of Pennsylvania**
**1996 M.S. @ Yale University (Prof. John Wood)**
**1997 Ph.D @ Yale University (Prof. John Wood)**
**1998 NIH postdoctoral fellow @ Harvard University (Prof. Elias. J. Corey)**
**2000 Assistant professor @ California Institute of Technology**
**2006 Associate professor @ California Institute of Technology**
**2007-Professor @ California Institute of Technology**

**Research topic: natural products synthesis & methodology**

1) https://rmwilliamsgroup.wordpress.com/
2) http://www.stoltz.caltech.edu/
3) http://cce.caltech.edu/people/brian-m-stoltz

# Retrosynthetic Analysis of 2 Groups

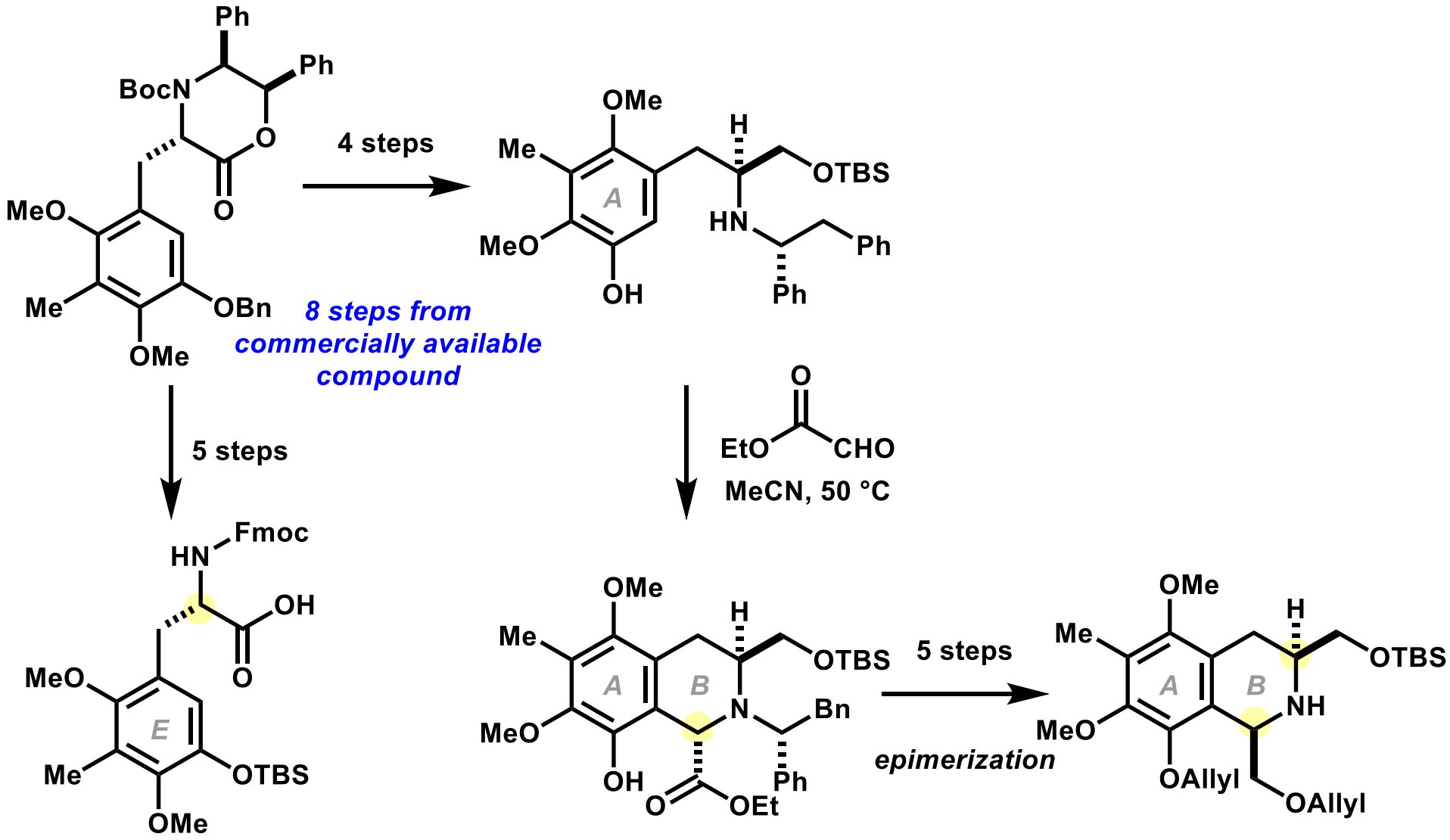




1) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.
2) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

# Contents

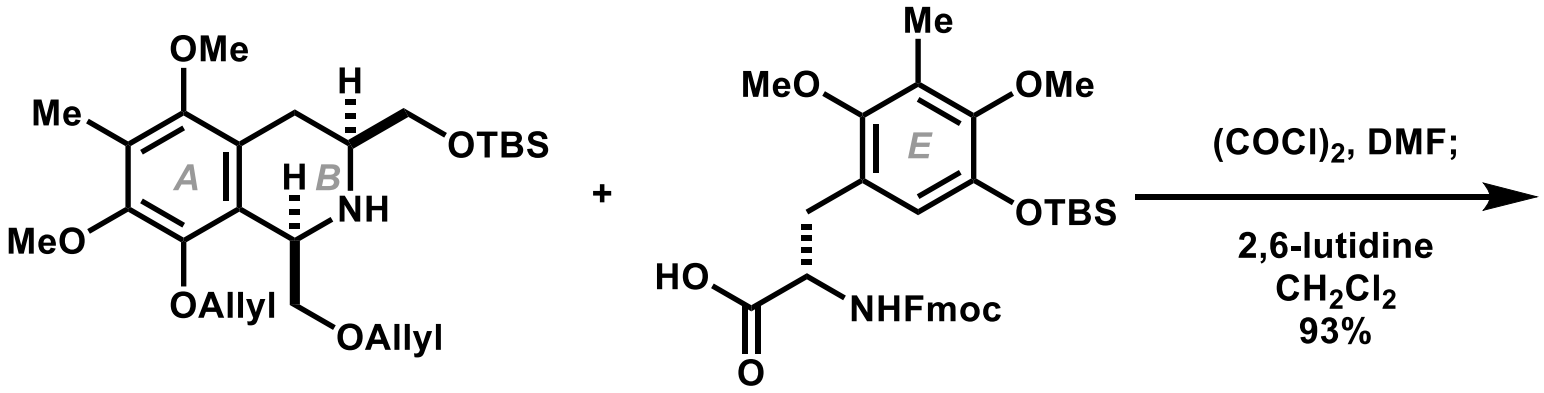
# Synthesis of Chiral Fragments

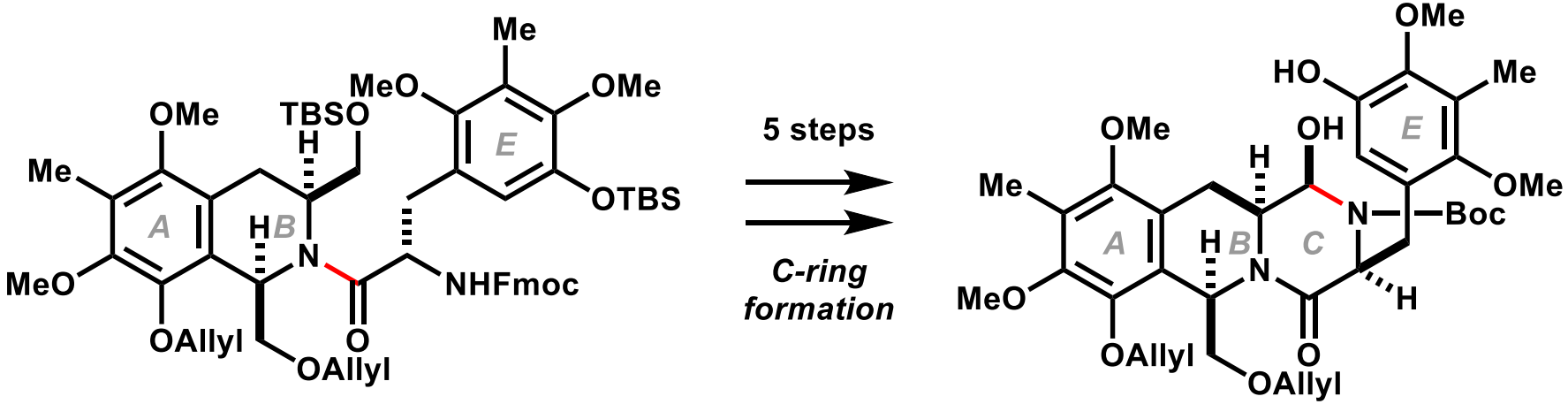




1) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.
2) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957

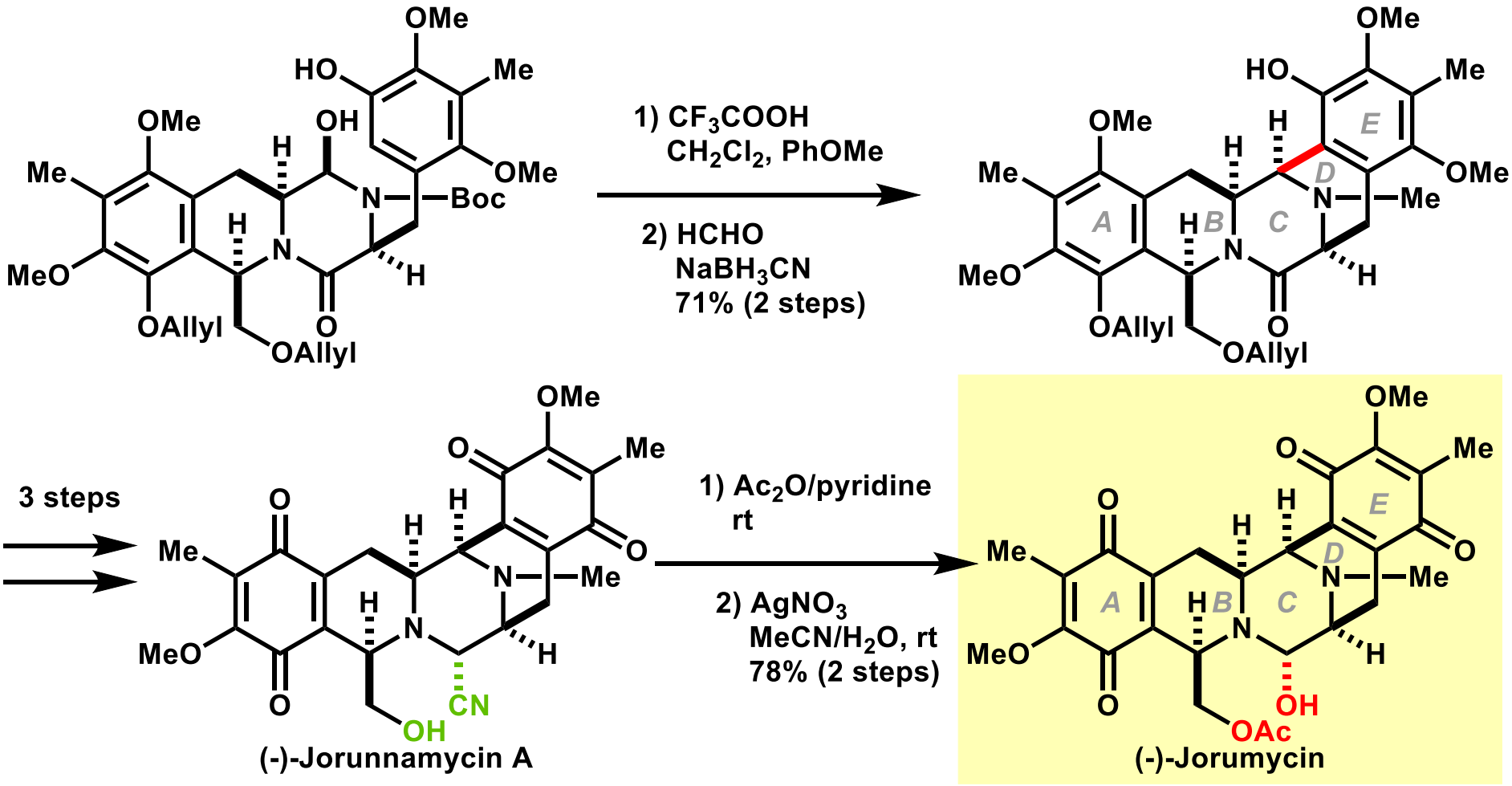
# Condensation of two fragments




1) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.

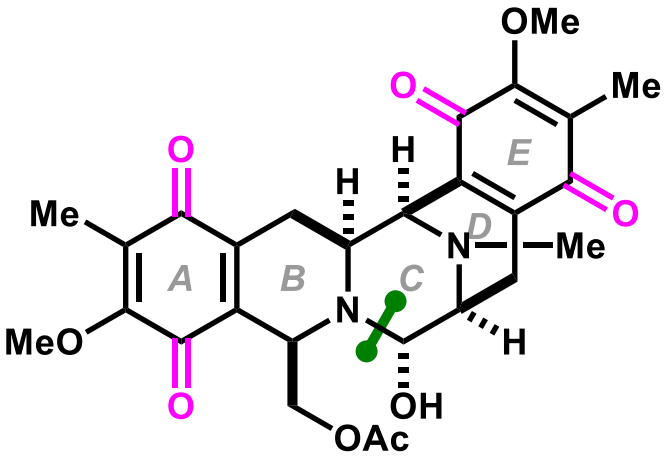
# Total synthesis of (-)-Jorumycin




1) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.

# Contents

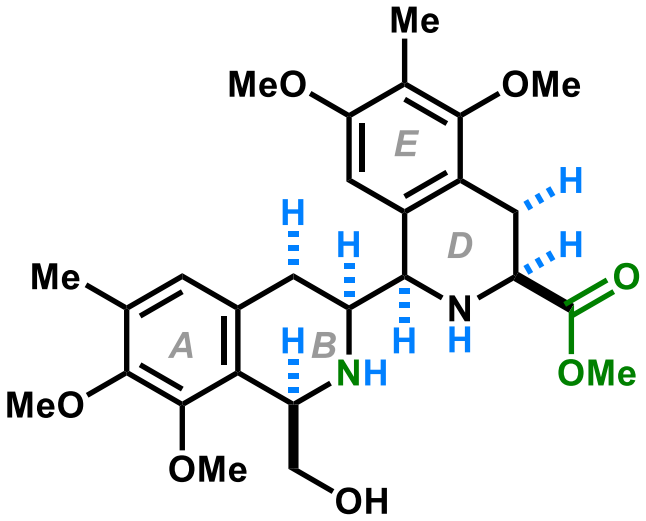
# Retrosynthesis




(-)-Jorumycin

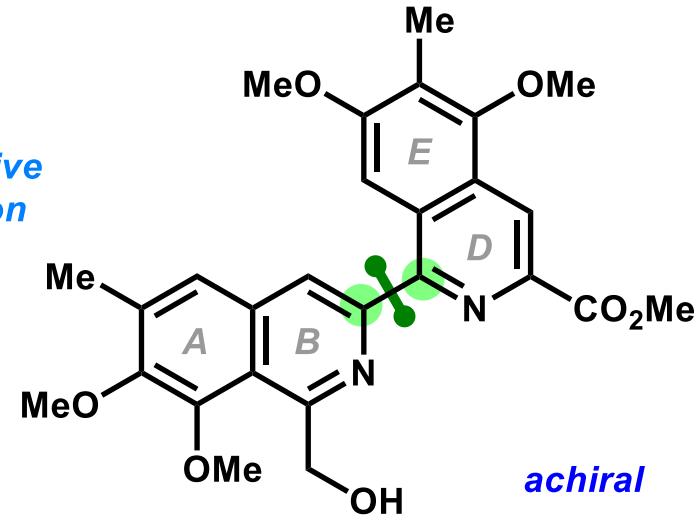
*A,E-ring oxidation*

*C-ring formation*



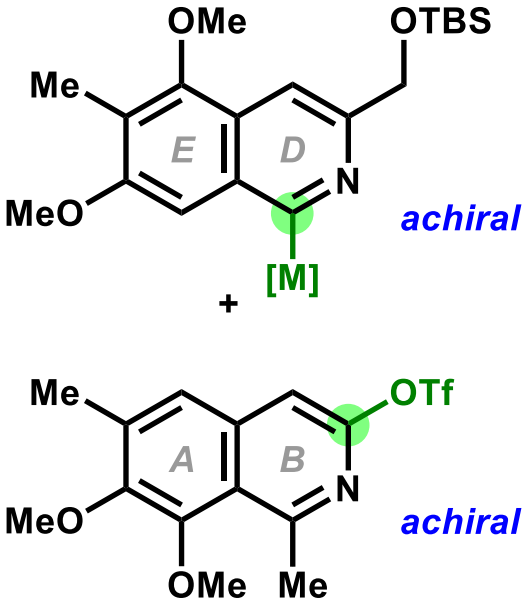

*enantiopure*

*enantioselective hydrogenation*




*achiral*

*cross coupling*

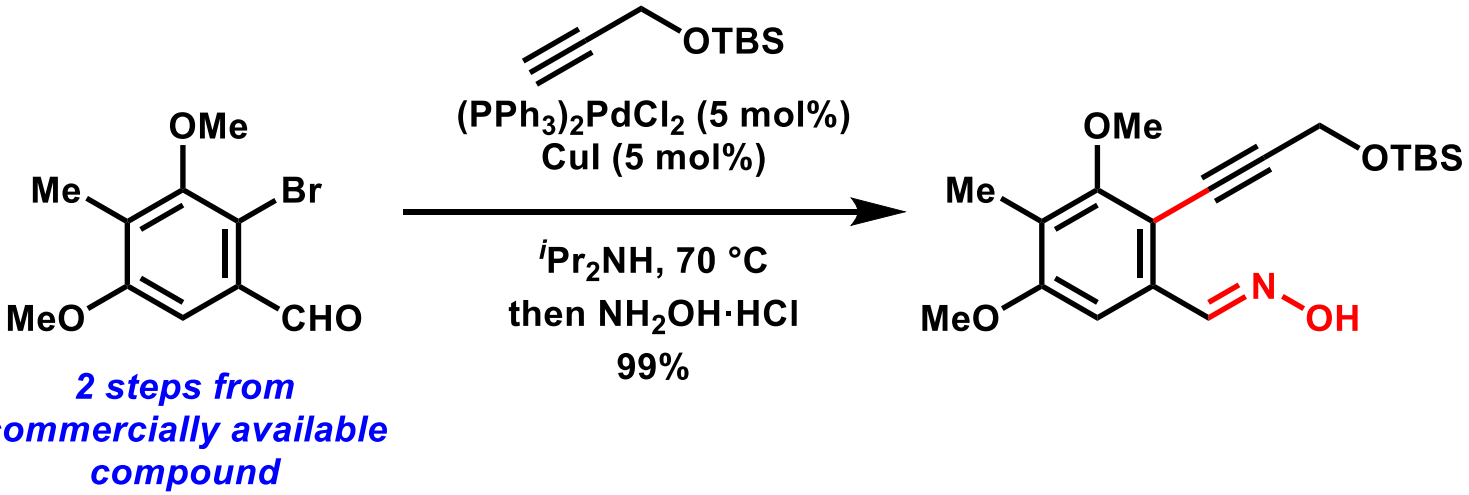



*achiral*

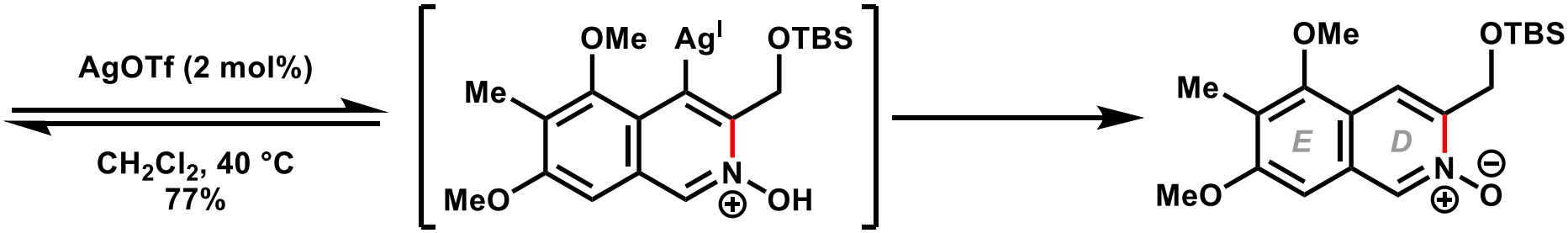
*achiral*

1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

# Synthesis of *D*,*E*-ring Fragment

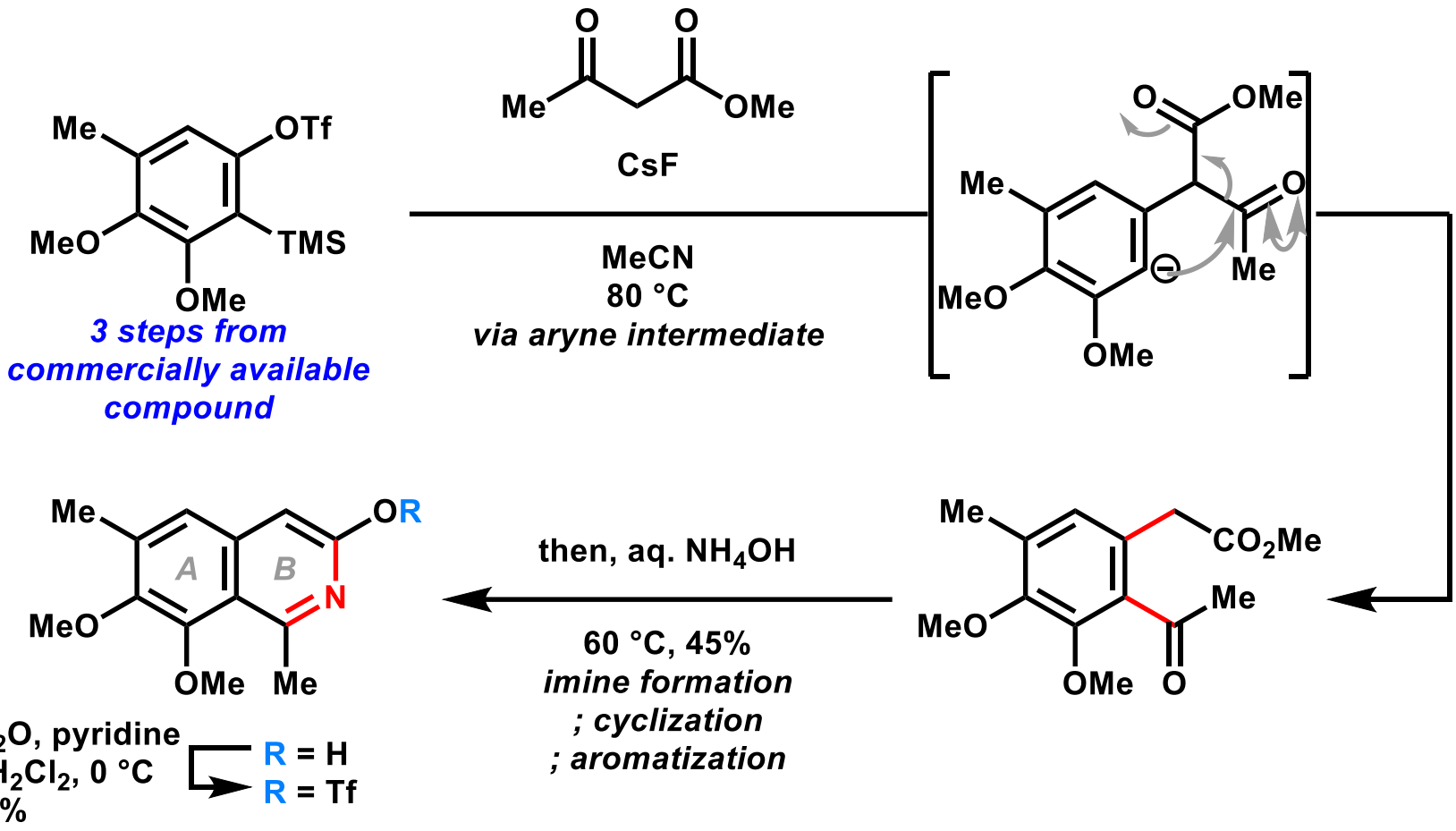



***2 steps from commercially available compound***



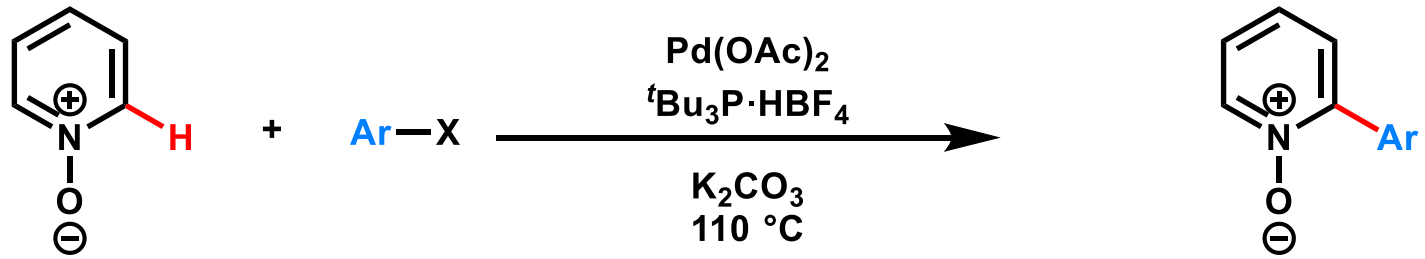

1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

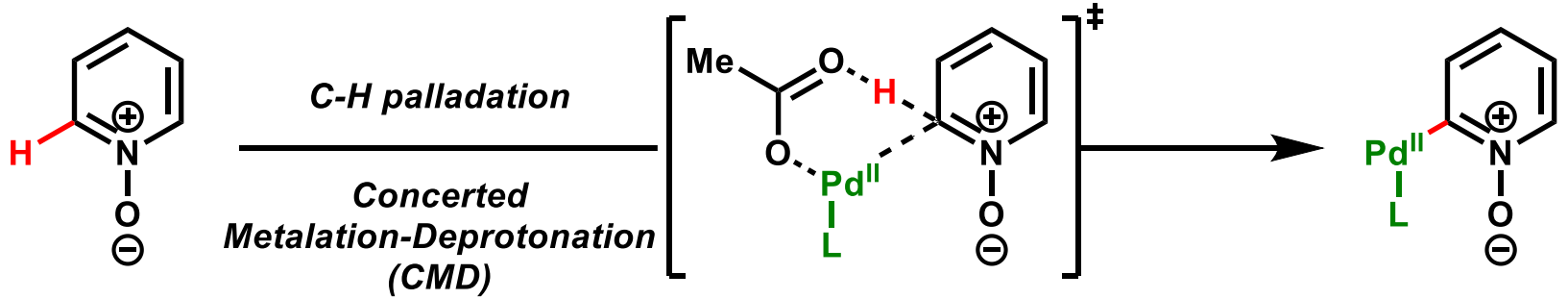
# Synthesis of *A,B*-ring Fragment

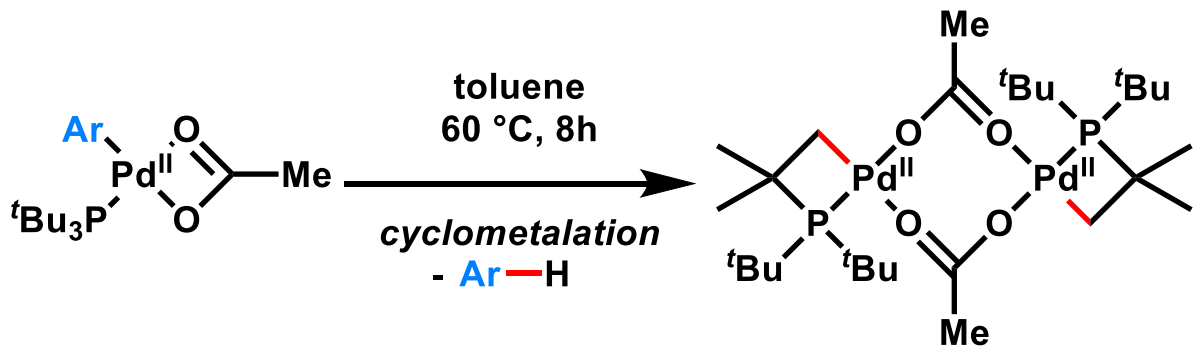



1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

# Fagnou coupling (I)



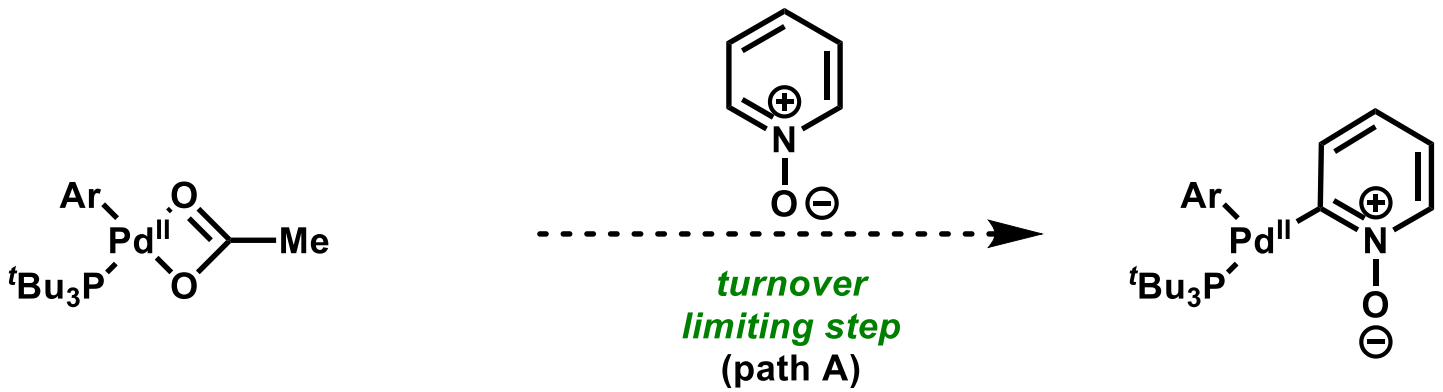



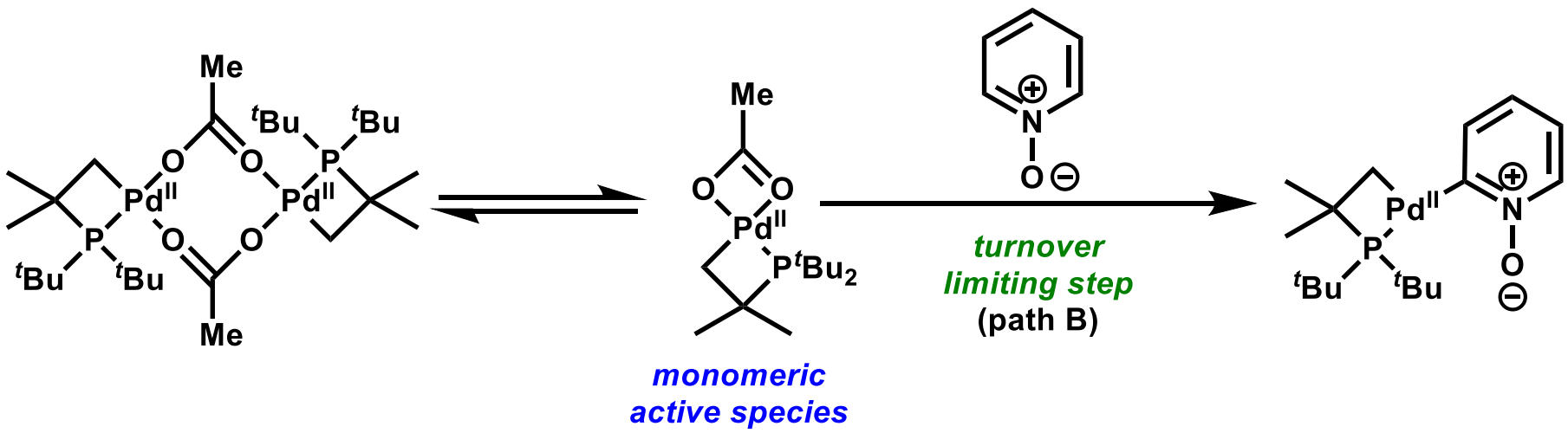


1) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc*. **2007**, *130*, 3266.
2) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.
3) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

# Fagnou coupling (II)



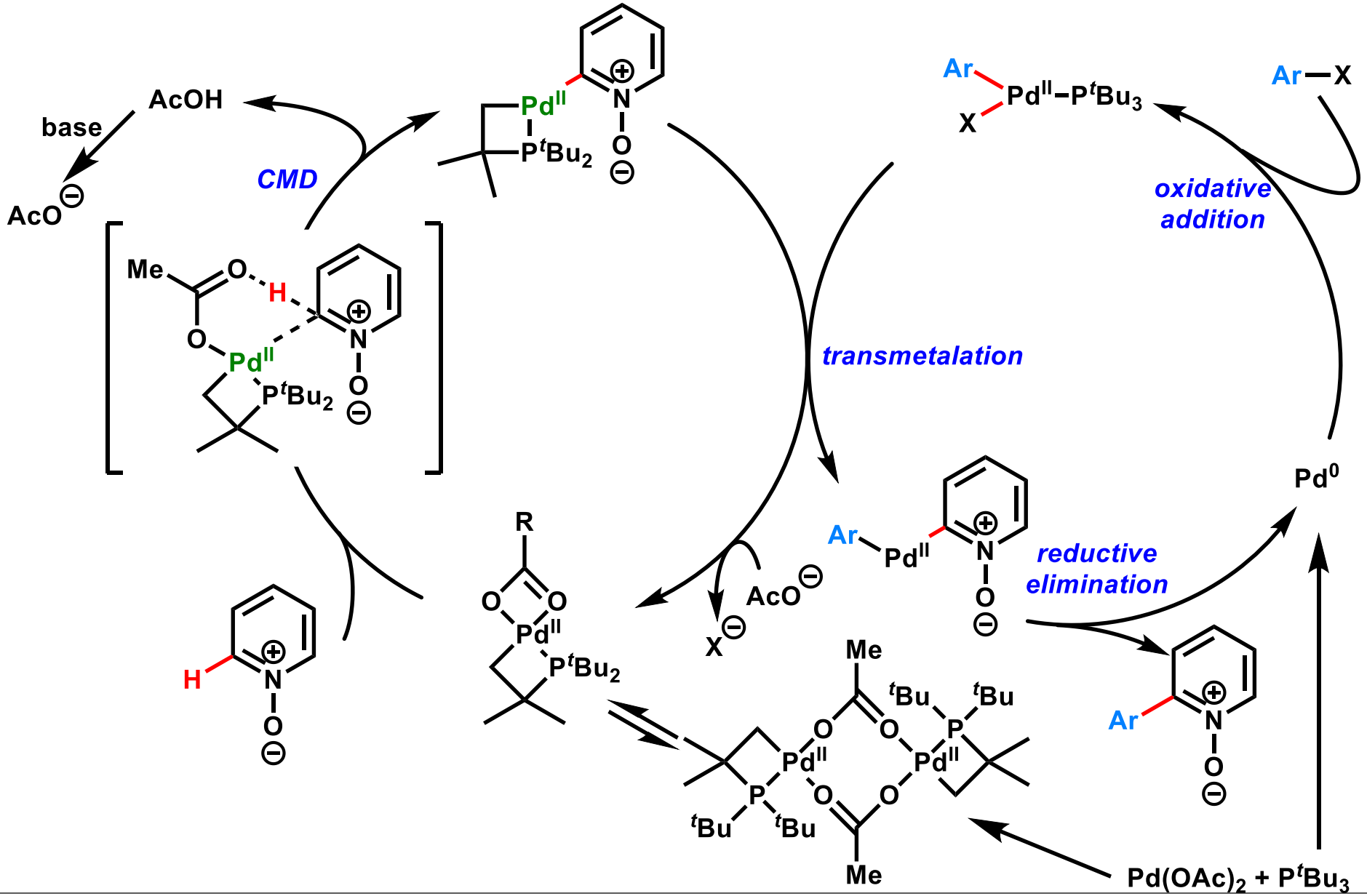

**1) CMD is turnover limiting step.**
**2) 0.5th-order in $Pd^{II}$**
**→ path B would be plausible.**





1) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *130*, 3266.
2) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.
3) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

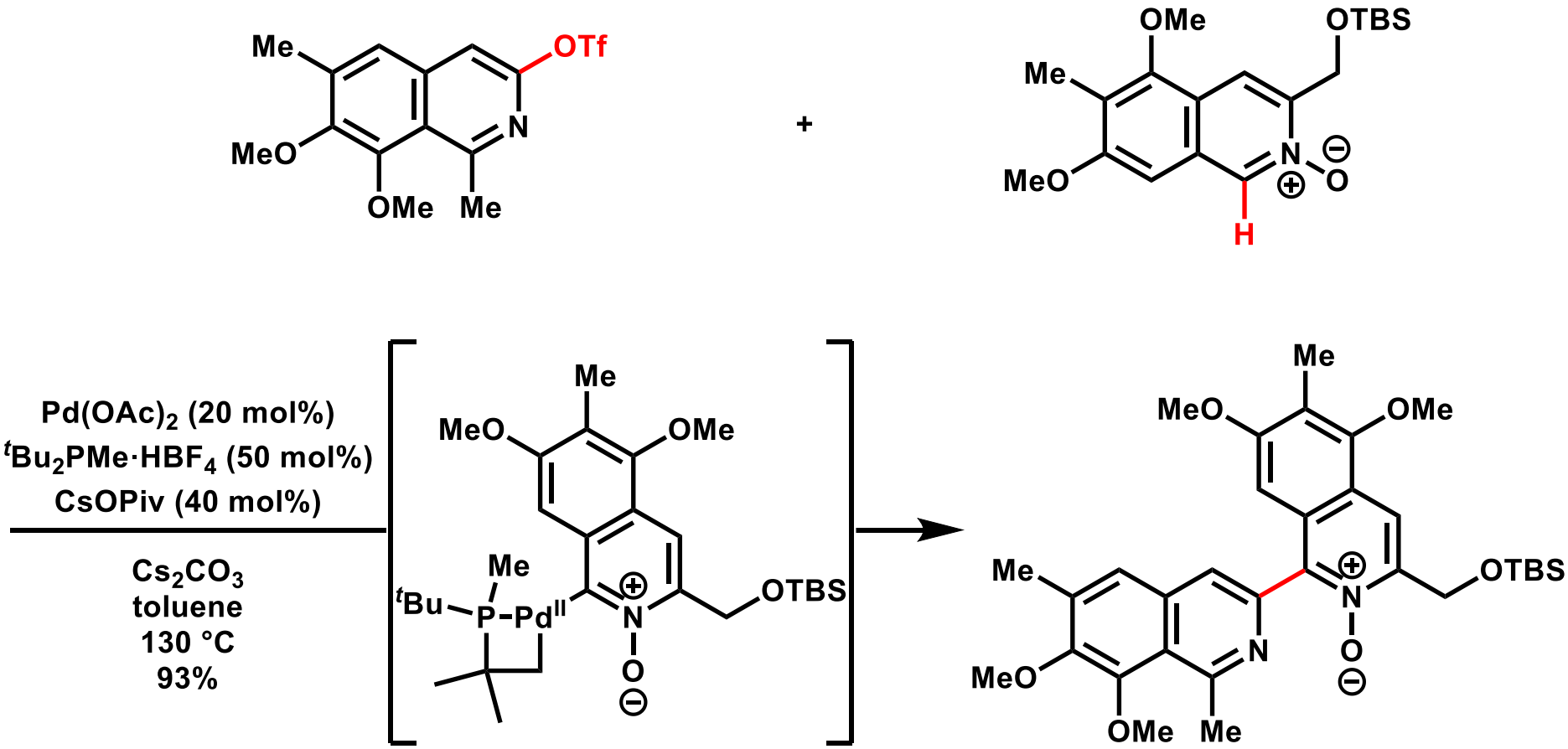
# Fagnou coupling (III)





1) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc*. **2007**, *130*, 3266.
2) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.
3) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

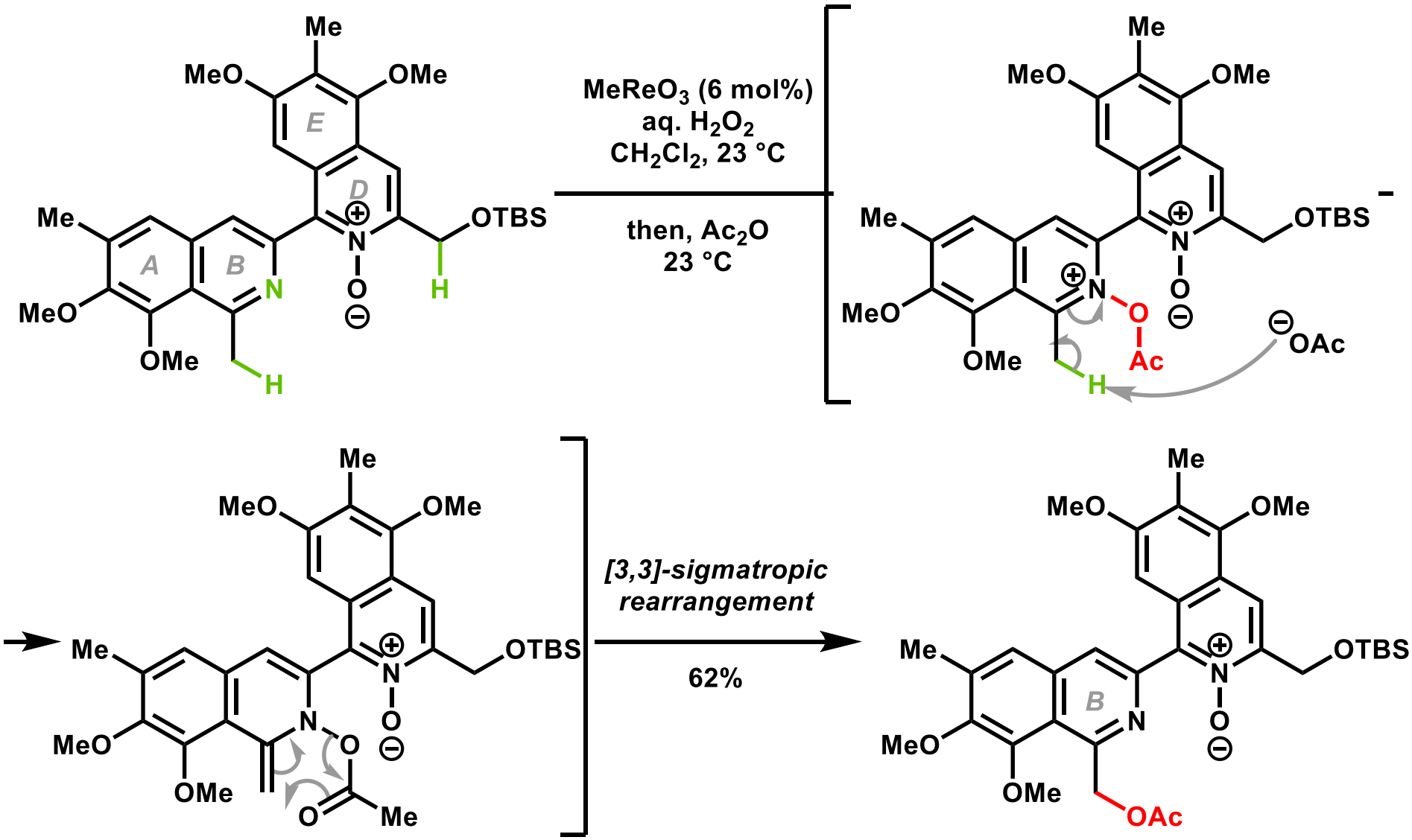
# Fagnou coupling: synthesis of bis-isoquinoline





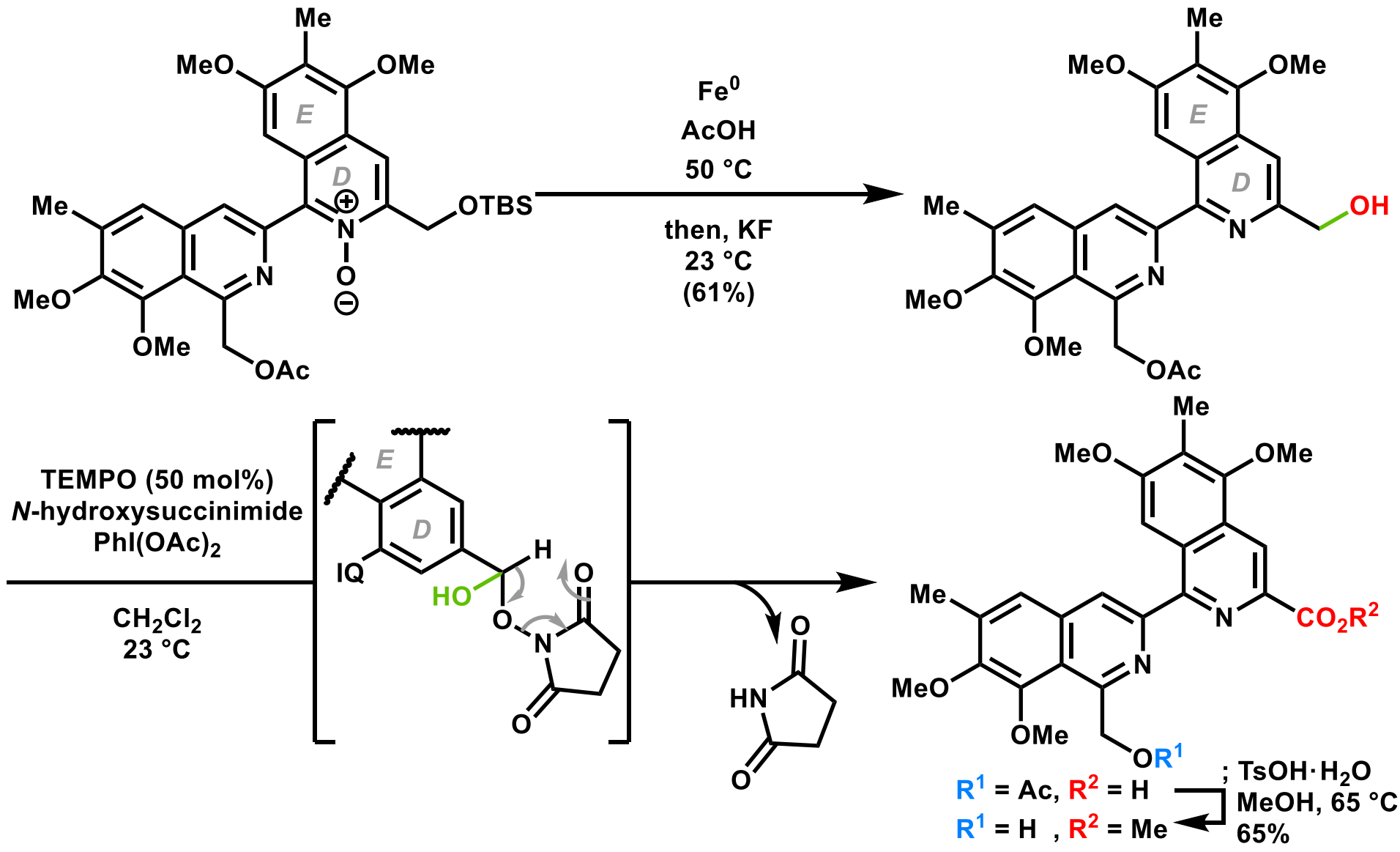
1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc*. **2007**, *130*, 3266.
3) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.
4) Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

# Formal C-H oxidation




1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

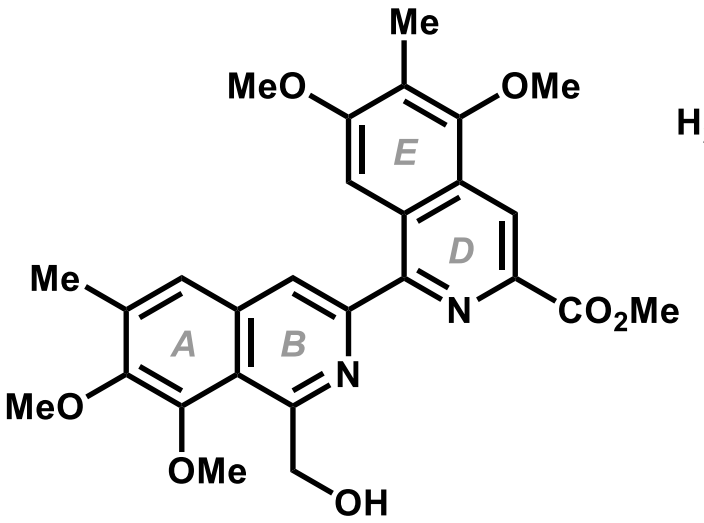
# Synthesis of hydrogenation precursor





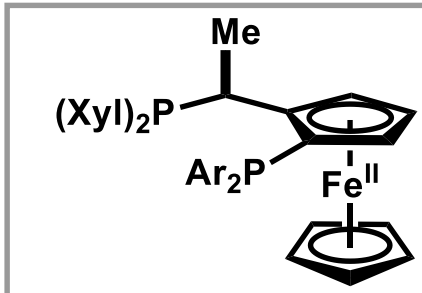
1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Wang, N.; Liu, R.; Xu, Q.; Liang, X. *Chem. Lett.* **2006**, *35*, 566.

# Attempted Enantioselective Hydrogenation



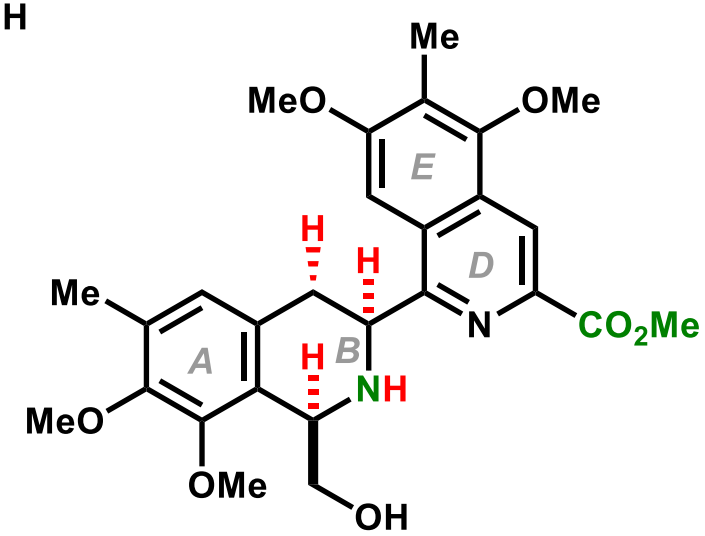

$H_2$ (60 bar), $[Ir(cod)Cl]_2$ (5 mol%)
$^nBu_4NI$ (30 mol%)
L* (12 mol%)

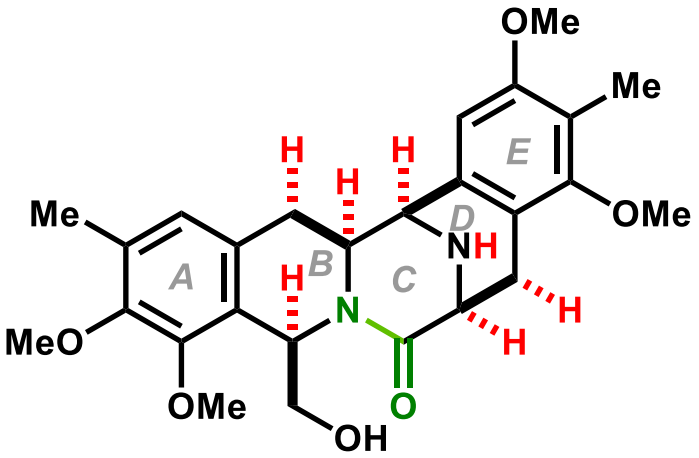
toluene/AcOH
60 °C




($S$,$R_p$)-Xyliphos (Ar = Ph)

($S$,$R_p$)-BTFM-Xyliphos
[Ar = 3,5-$(CF_3)_2C_6H_3$]



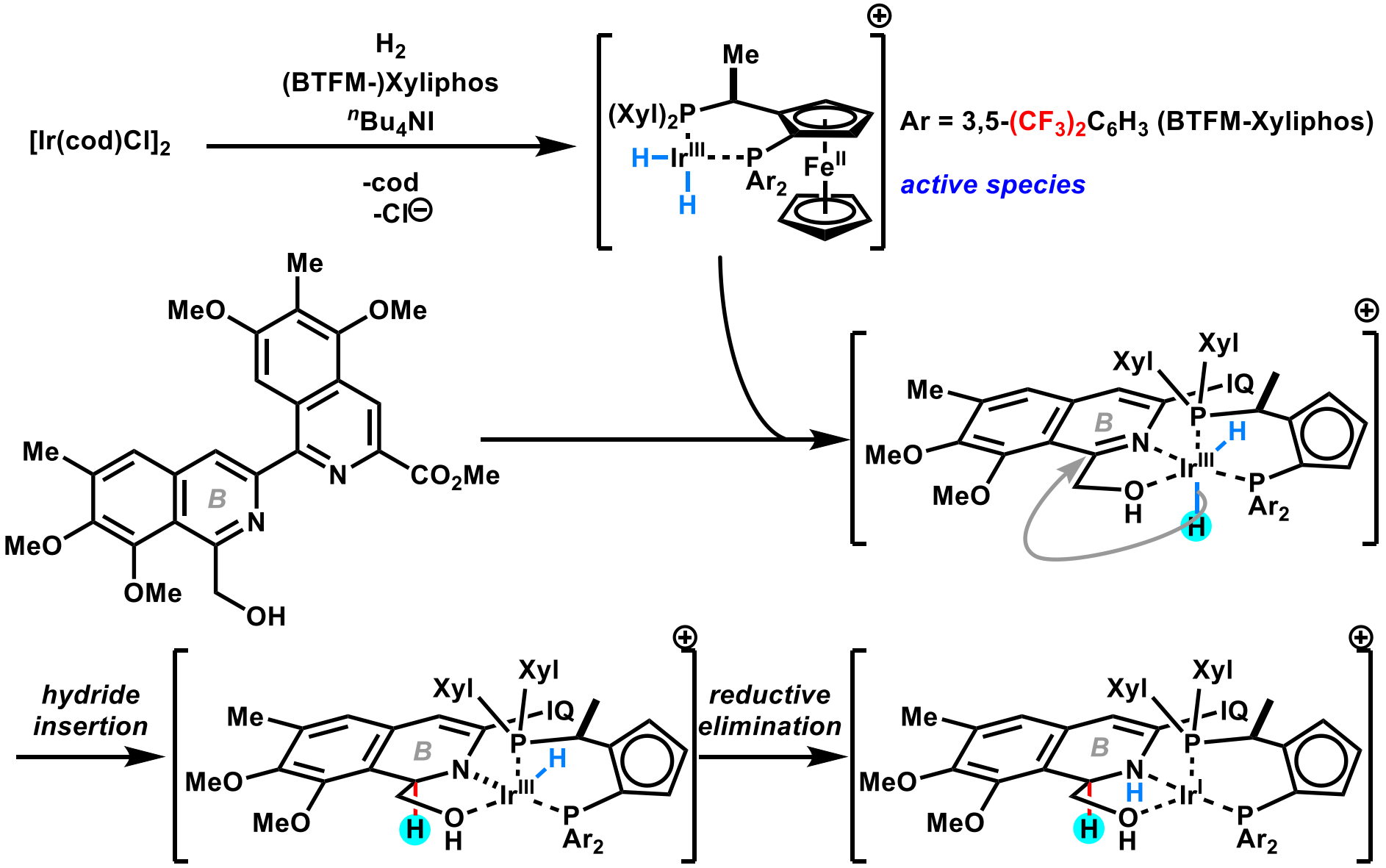




| L* | | |
|---|---|---|
| ($S$,$R_p$)-Xyliphos | 30% (80%ee) | 0% |
| ($S$,$R_p$)-BTFM-Xyliphos | 83% (94%ee) | 10% (dr >20:1) |

**Reduction of *B*-ring is faster than that of *D*-ring**


1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Dorta, R. et al. *Chem. Eur. J*. **2004**, *10*, 267.

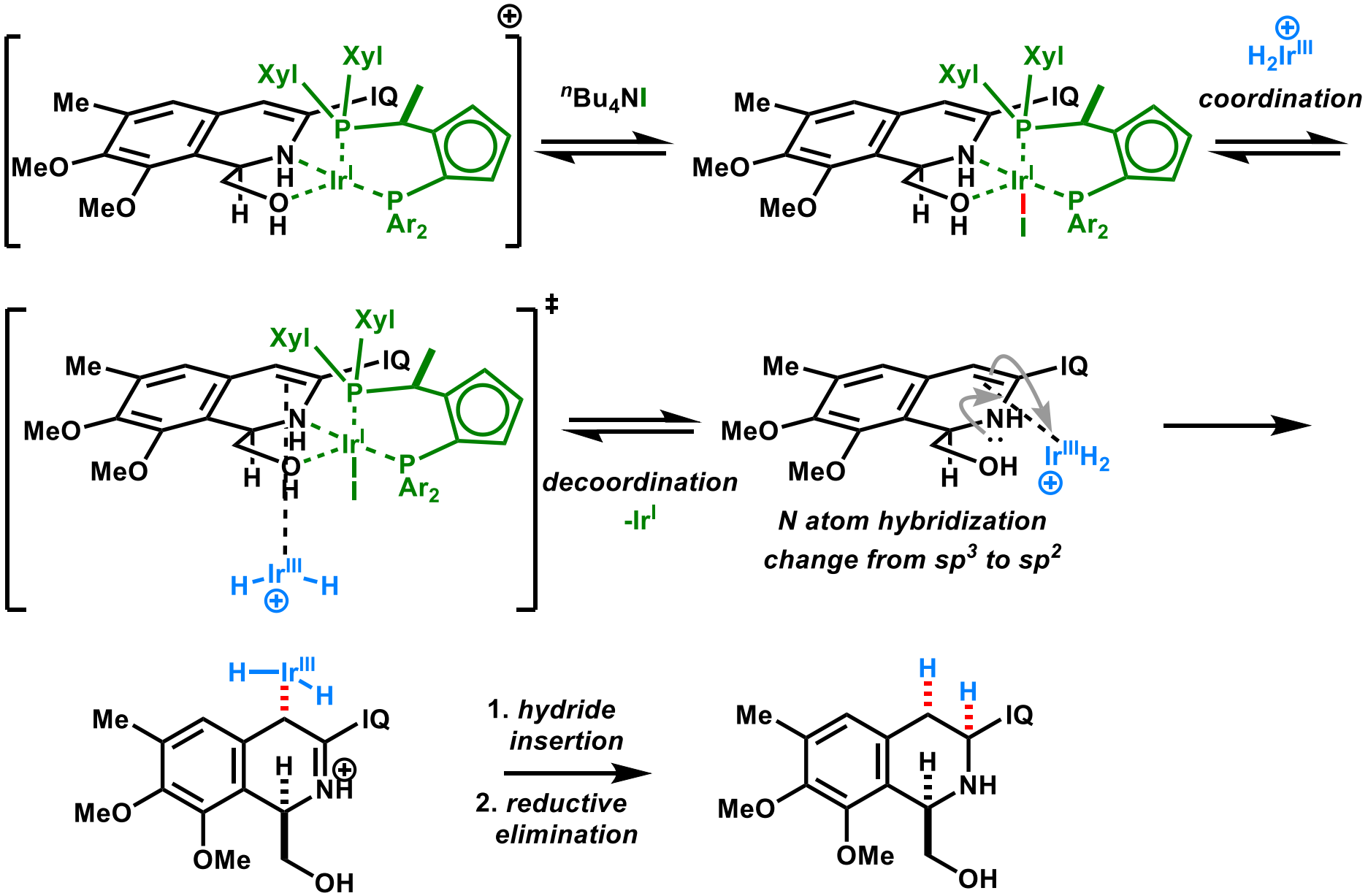
# Hydrogenation of *B*-ring (I)





1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Dorta, R. et al. *Chem. Eur. J*. **2004**, *10*, 267.

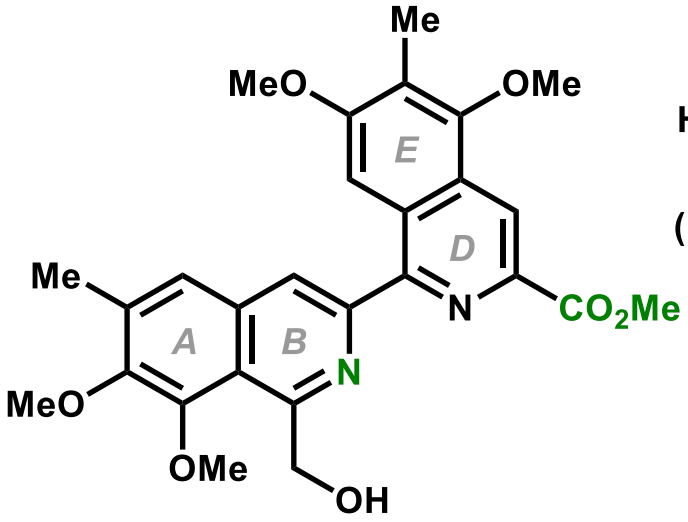
# Hydrogenation of *B*-ring (II)





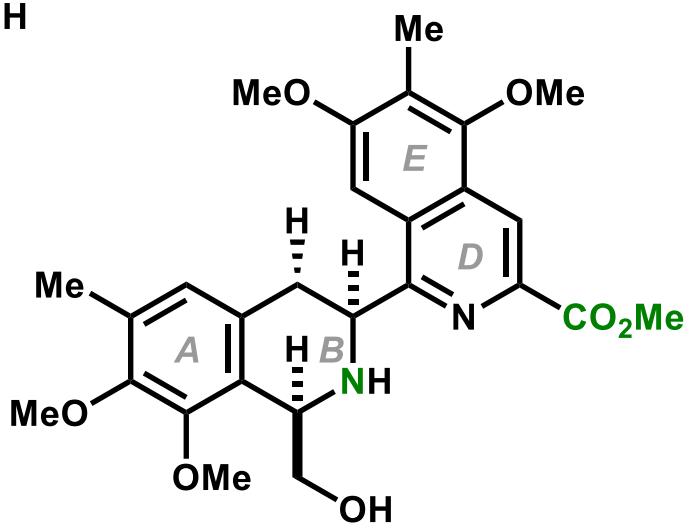
1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Dorta, R. et al. *Chem. Eur. J*. **2004**, *10*, 267.

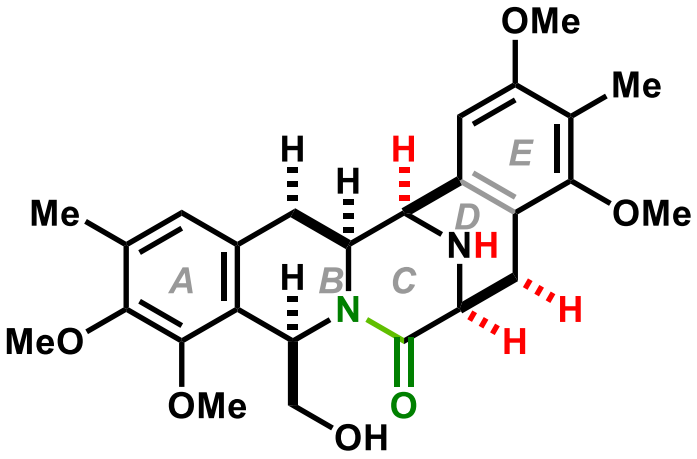
# Attempted Hydrogenation of *D*-ring




$H_2$ (60 bar), $[Ir(cod)Cl]_2$ (5 mol%)
$^nBu_4NI$ (30 mol%)
($S$,$R_p$)-BTFM-Xyliphos (12 mol%)

toluene/AcOH
*temp.*



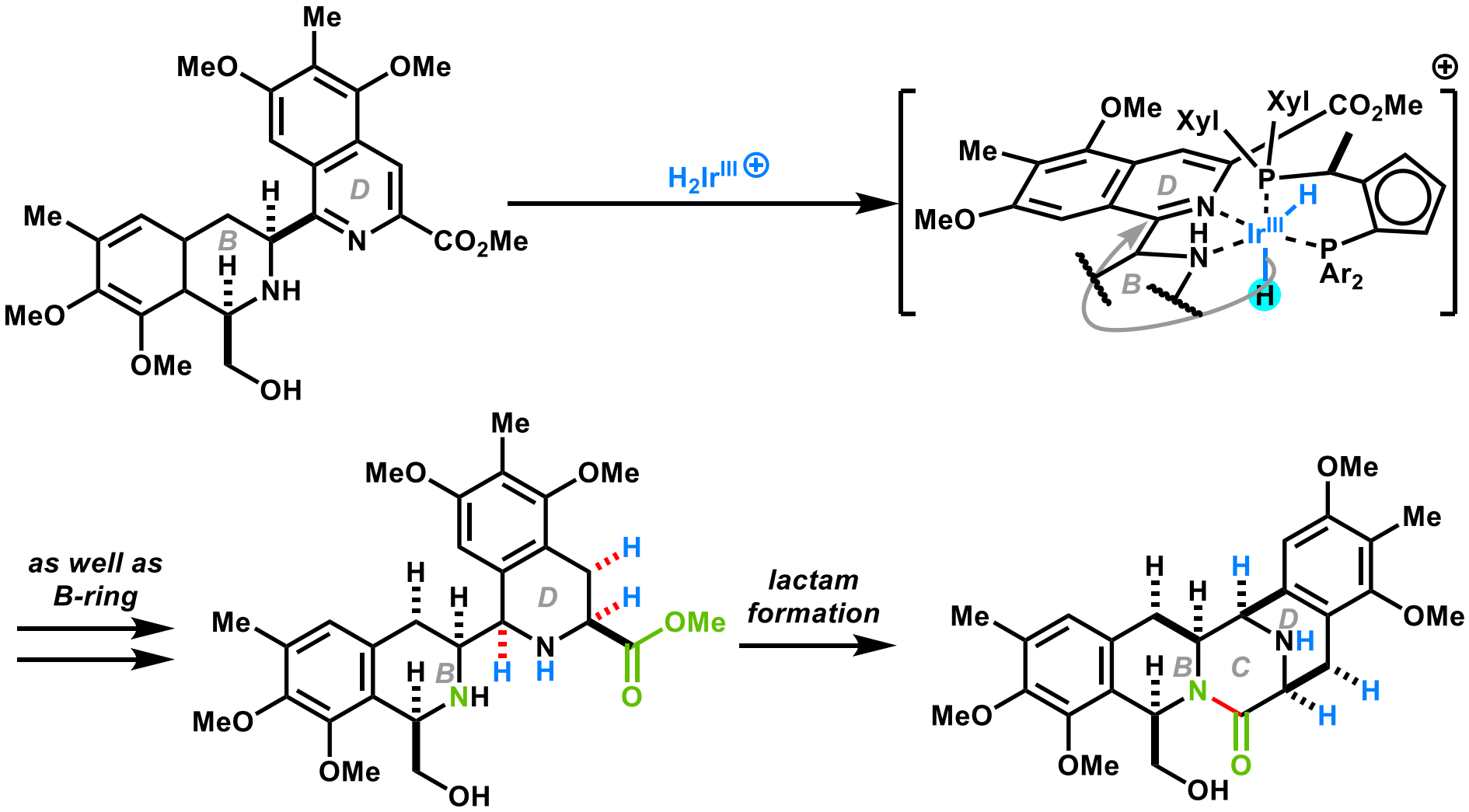




| *temp.* | 83% | desired |
|---|---|---|
| 60 °C | 7% | 10% |
| 60 to 80 °C | | 59% |

***High temperature is required for hydrogenation of D-ring.***

1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

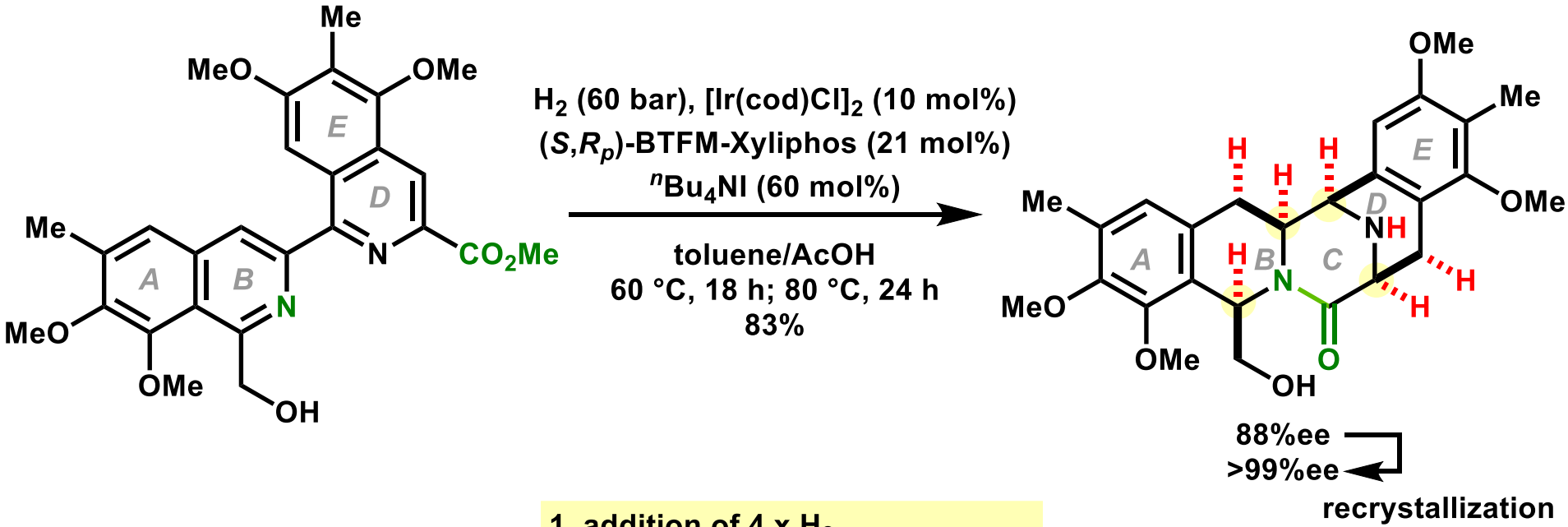
# Hydrogenation of *D*-ring





1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Dorta, R. et al. *Chem. Eur. J*. **2004**, *10*, 267.

# Enantioselective Hydrogenation




1. addition of 4 x $H_2$

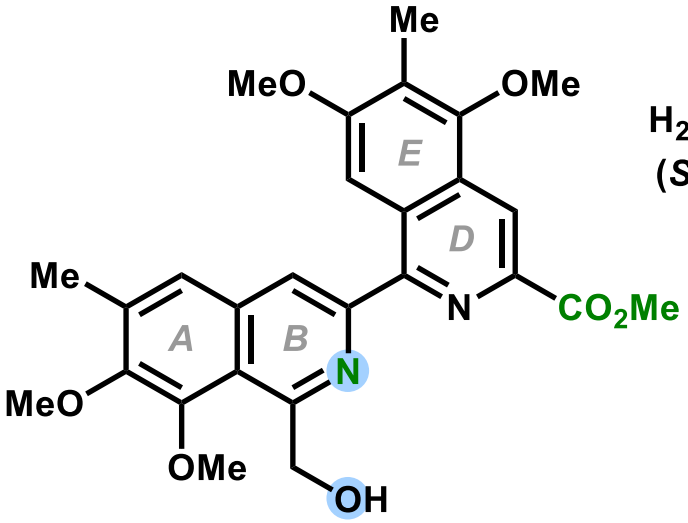
2. introduction of 4 stereocenters

3. *C*-ring formation

were realized in a single step

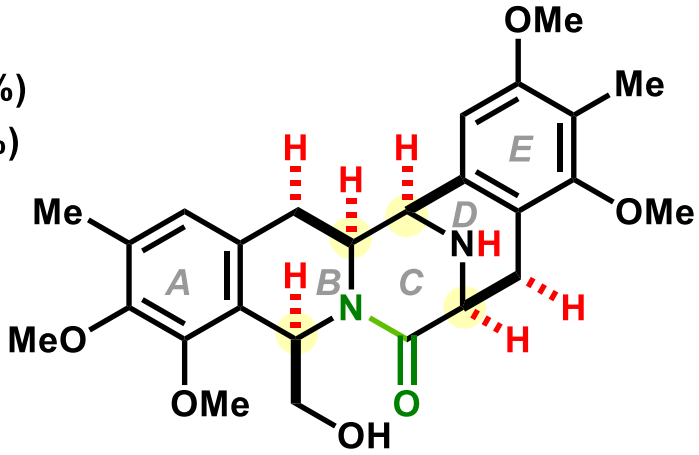
1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

# Key for Enantioselective Hydrogenation

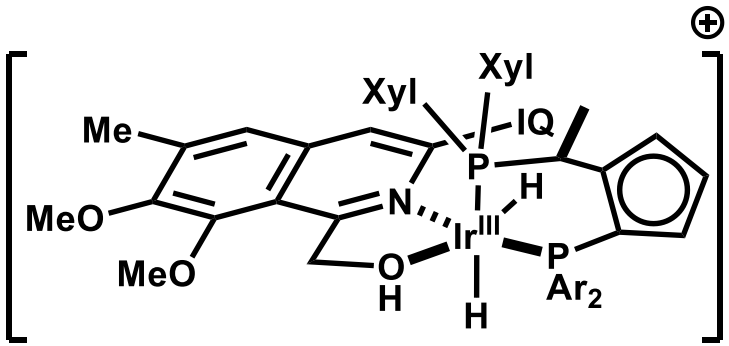



$H_2$ (60 bar), $[Ir(cod)Cl]_2$ (10 mol%)
$(S,R_p)$-BTFM-Xyliphos (21 mol%)
$^nBu_4NI$ (60 mol%)

toluene/AcOH
60 °C, 18 h; 80 °C, 24 h
83%



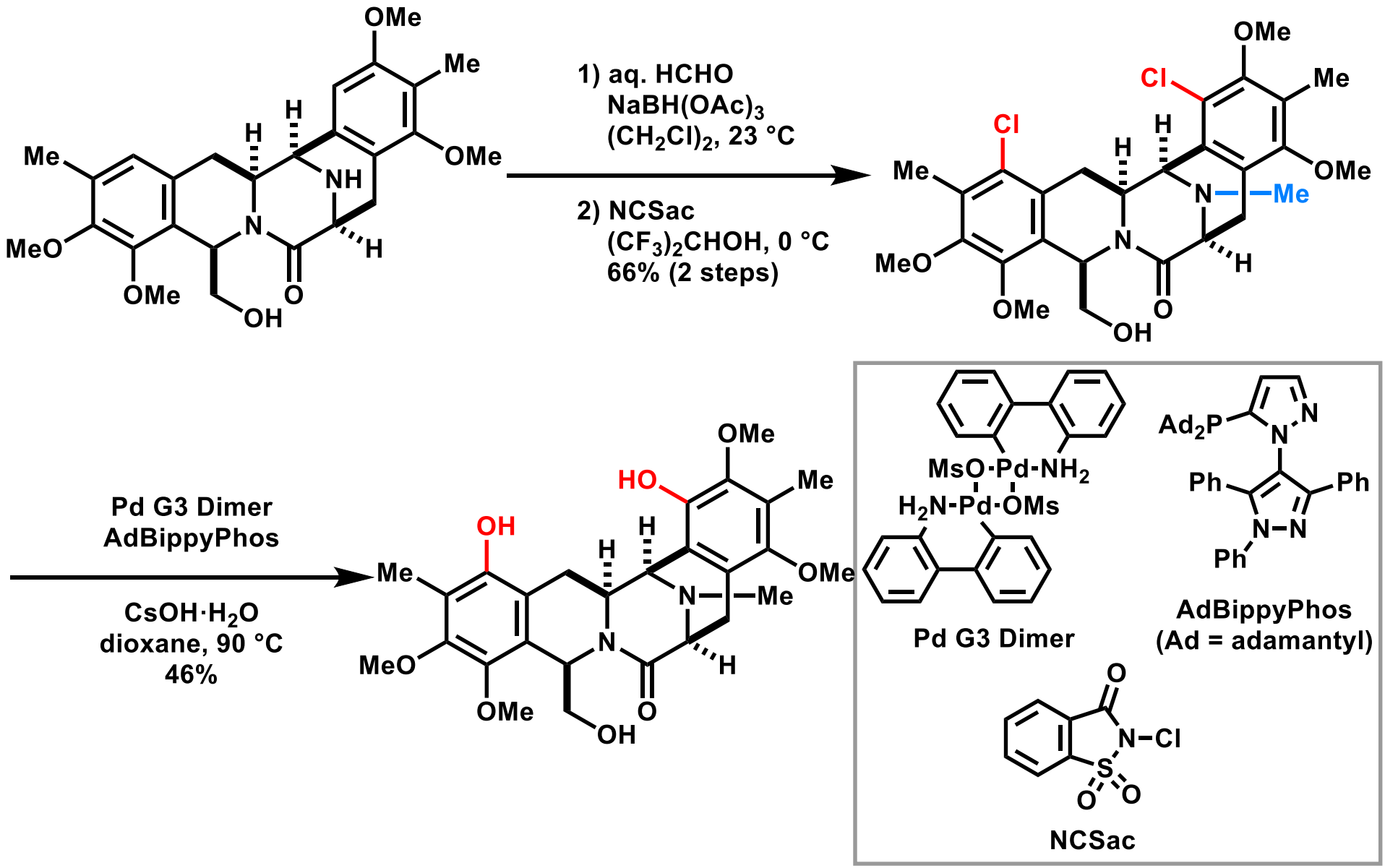

- **classify the reduction rate of *B*- and *D*- ring by directing group and temperature**
- **regulate the facial selectivity by Ir complex between metal and substrate**




***for enantioselective hydrogenation***

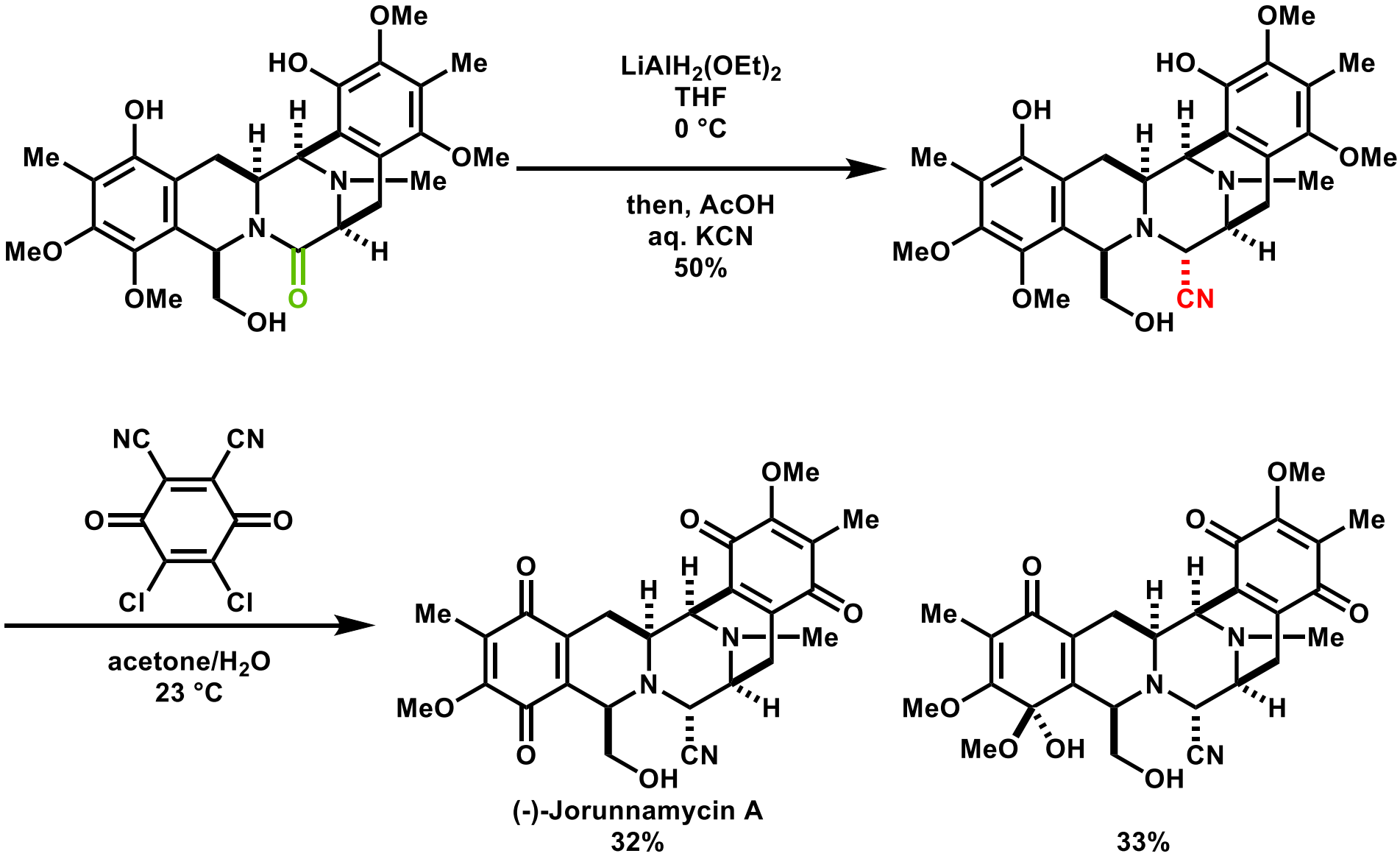

1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Dorta, R. et al. *Chem. Eur. J*. **2004**, *10*, 267.

# Installation of Oxygen Atom



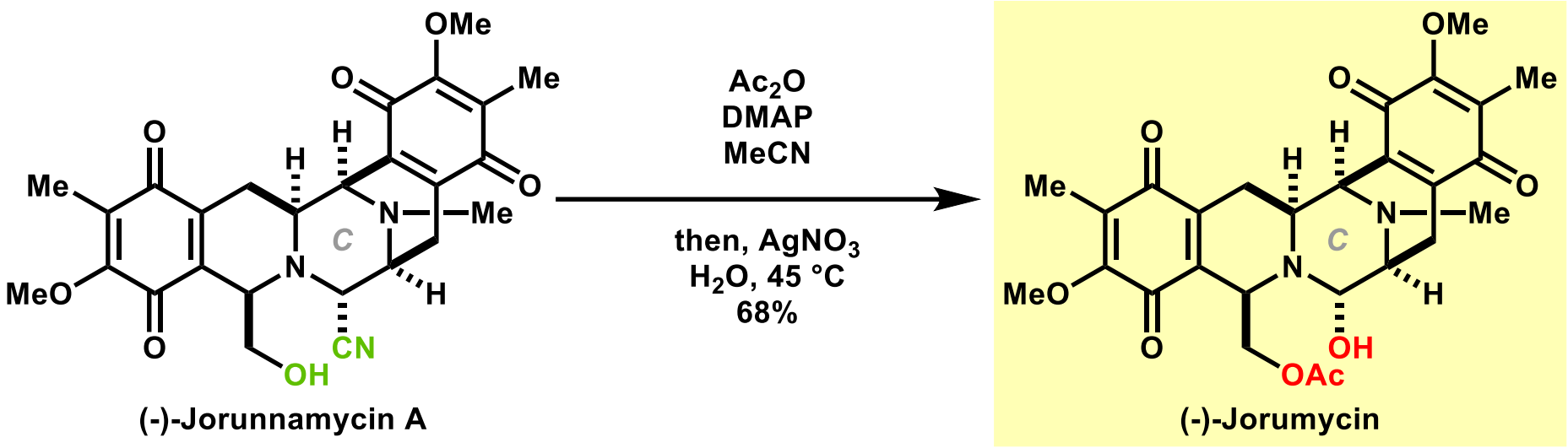

1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

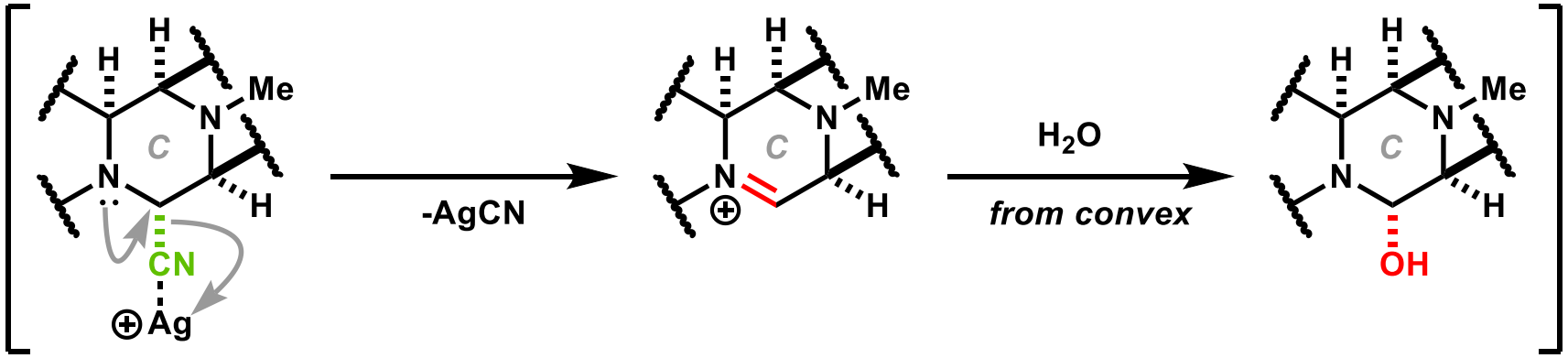
# Total Synthesis of (-)-Jorunnamycin A




1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.

# Total Synthesis of (-)-Jorumycin

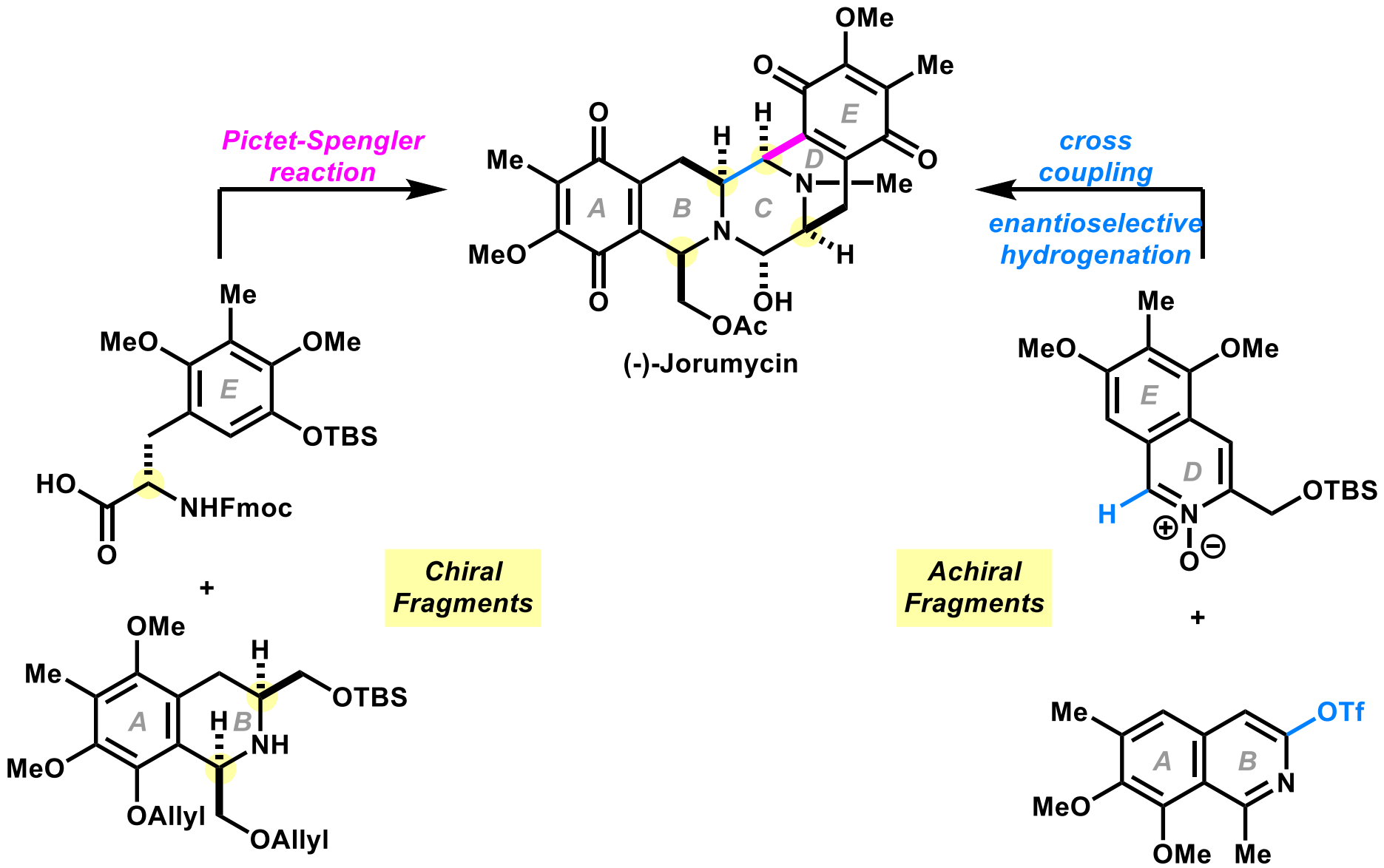




1) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270.
2) Chrzanowska, Maria.; Grajewska, Agnieszka.; Rozwadowska, M. D. *Chem. Rev.* **2016**, *116*, 12369.

# Summary

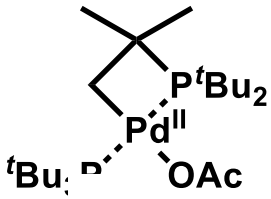




1) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.
2) Slamon, D. J.; Stoltz, B. M. et al. *Science*. **2019**, *363*, 270. .

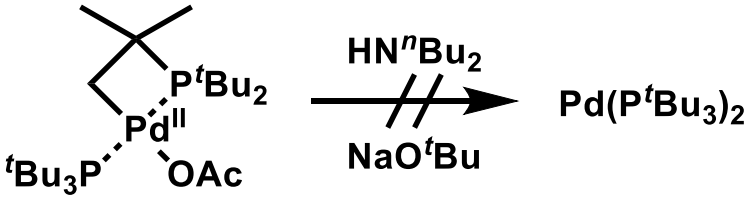
# Appendix

# 4-membered palladacycle

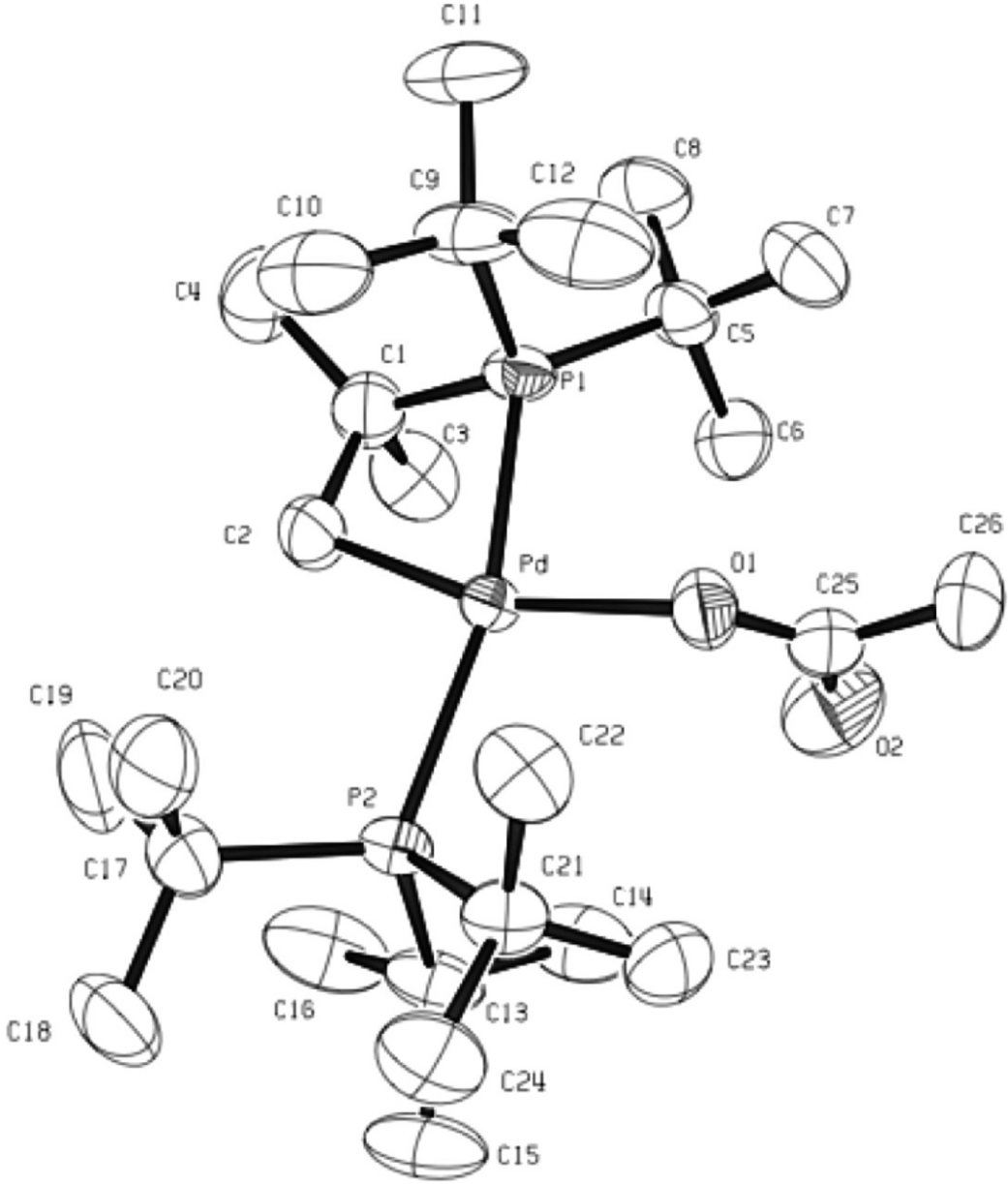



**small bite angle (∠P-Pd-C ~ 68°)**
**→ suppress reductive elimination**

**Reductive elimination of cyclic phosphine also seems to be suppressed.**




**probably due to its fixed small membered ring**




1) Henderson, W. H.; Alvarez,J. M.; Eichman, C. C.; Stambuli, J. P. *Organometallics* **2011**, *30*, 5038.