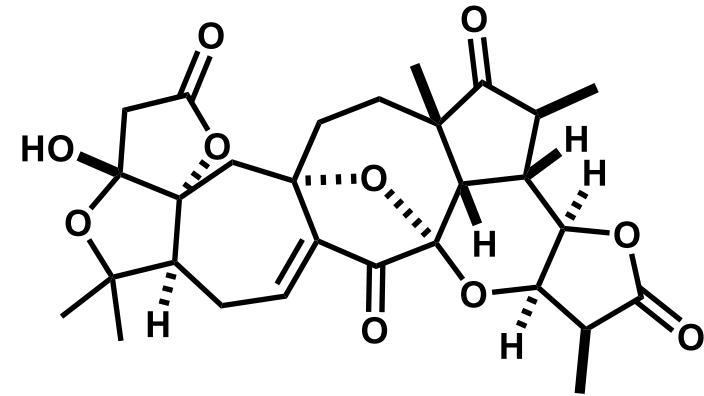


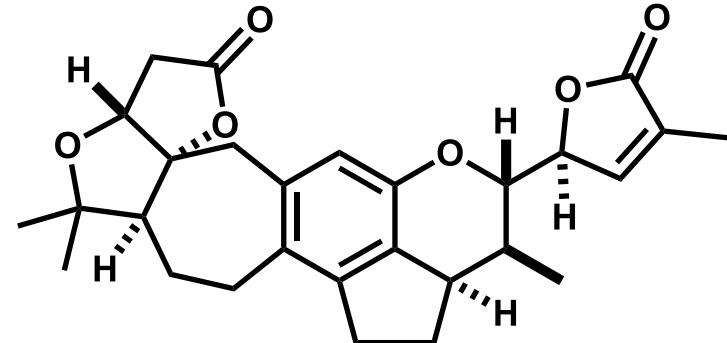
Total Syntheses of *Schisandraceae* Triterpenoids

2016.01.23

Yinghua Wang

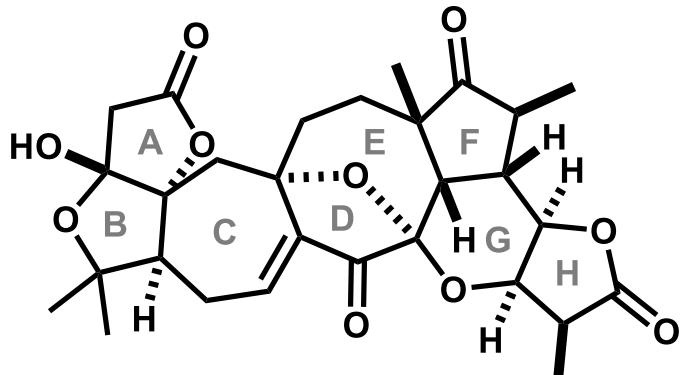


Schindilactone A

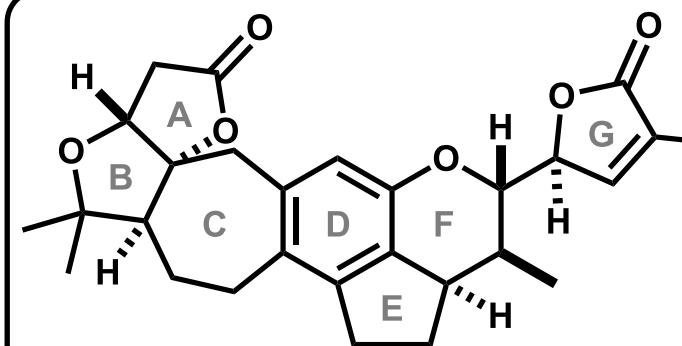


(+)-Rubriflordilactone A

Schisandraceae Triterpenoids



Schindilactone A



(+)-Rubriflordanolactone A

Isolation:

from *Schisandra chinensis*

Sun, H. D. et. al. *Org. Lett.* **2007**, 9, 2079

Biological activity:

weak anti-HIV-1 activity

Structural feature:

nortriterpenoid backbone

octacyclic framework

includes 5, 6, 7 and 8 membered rings

oxa-bridged ketal

12 stereocenters

Total Synthesis (racemic):

Yang, Z. et.al. *Angew. Chem. Int. Ed.* **2011**, 50, 7373

Isolation:

from *Schisandra rubriflora*

Sun, H. D. et. al. *Org. Lett.* **2006**, 8, 991

Biological activity:

weak anti-HIV-1 activity

Structural feature:

nortriterpenoid backbone

heptacyclic framework

includes 5, 6 and 7 membered rings

aromatic D-ring

7 stereocenters

Total Synthesis (enantiomor of natural product):

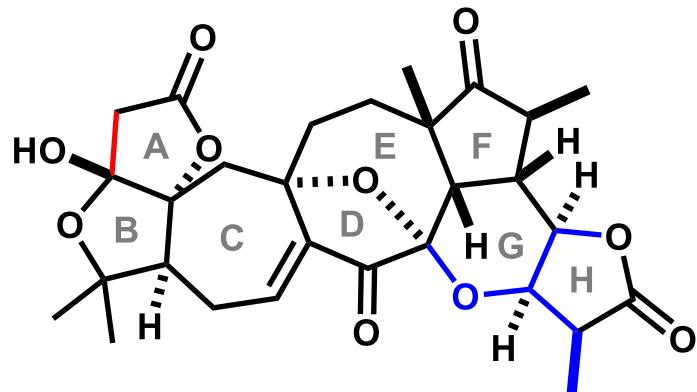
Li, A. et. al. *J. Am. Chem. Soc.* **2014**, 136, 16477

Anderson, E. A. et.al. *Angew. Chem. Int. Ed.* **2015**, 54, 12618

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(Li's study)
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5. Summary

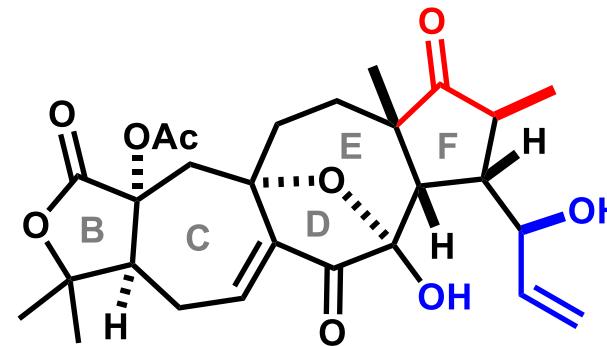
Retrosynthetic Analysis



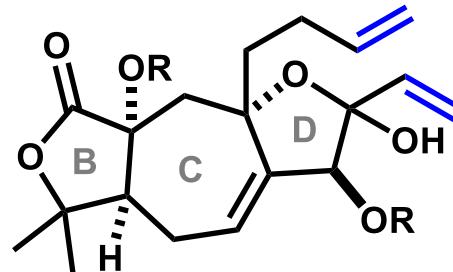
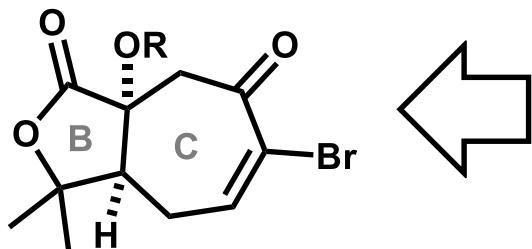
Schindilactone A

Dieckmann condensation

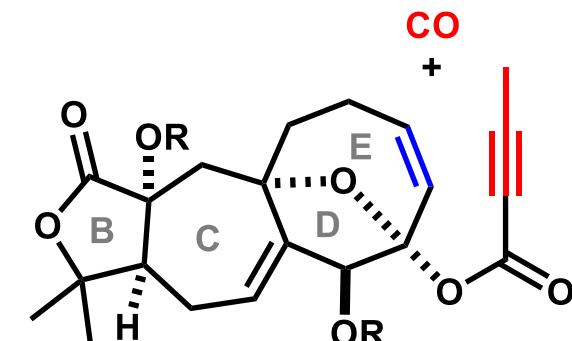
Pd-catalyzed
Carbonylative
annulation



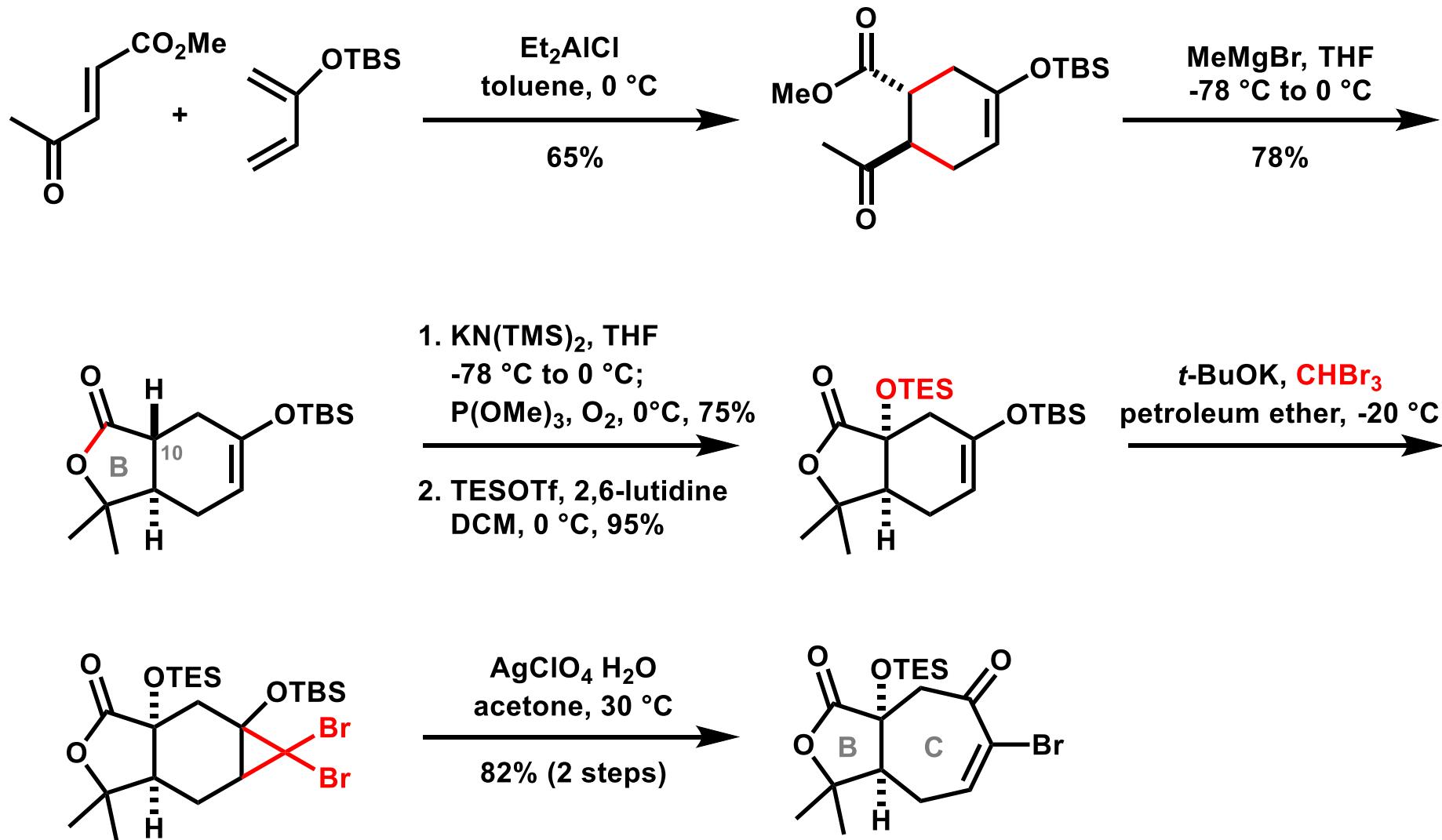
Pauson-Khand reaction



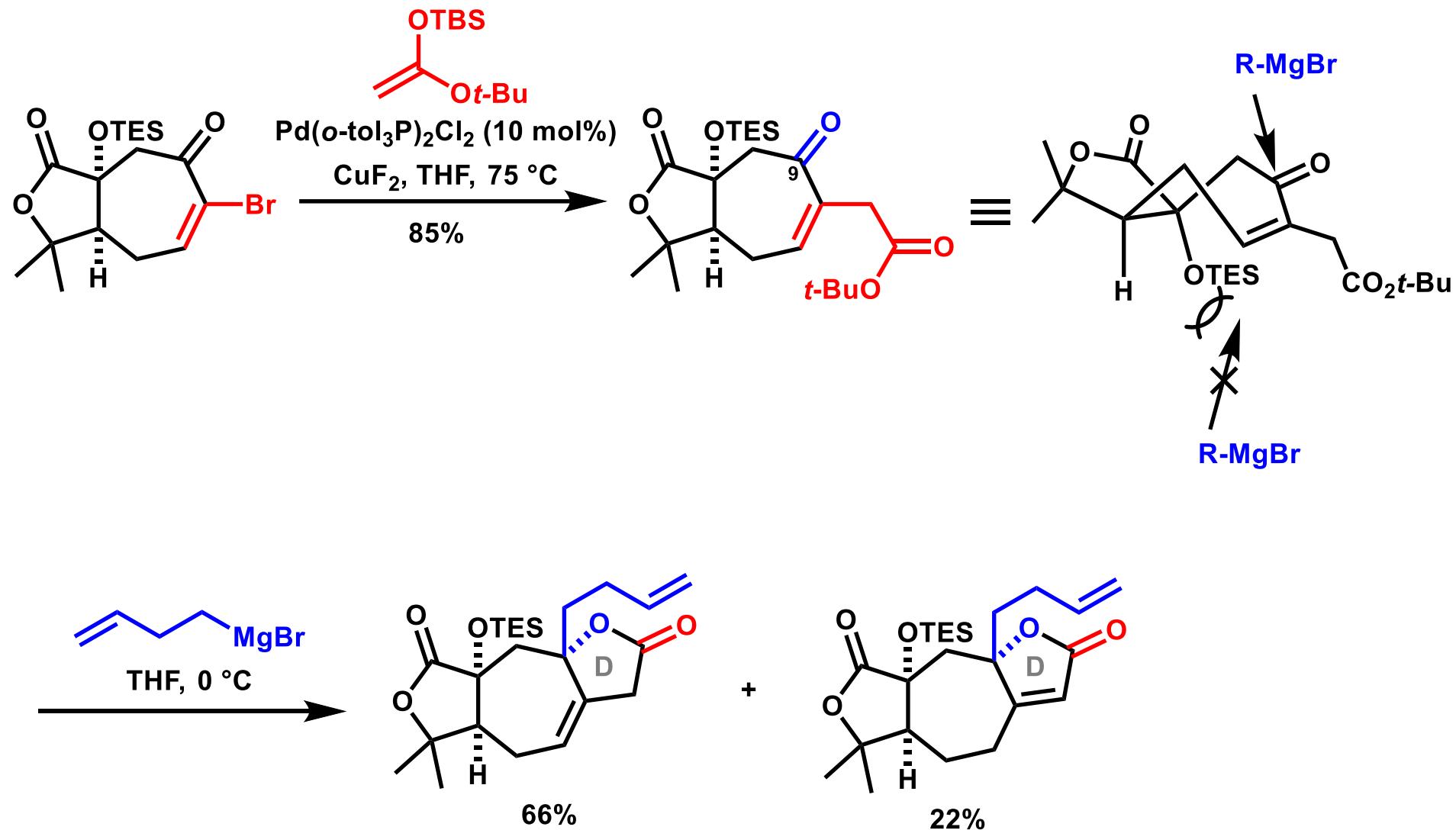
RCM



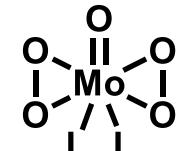
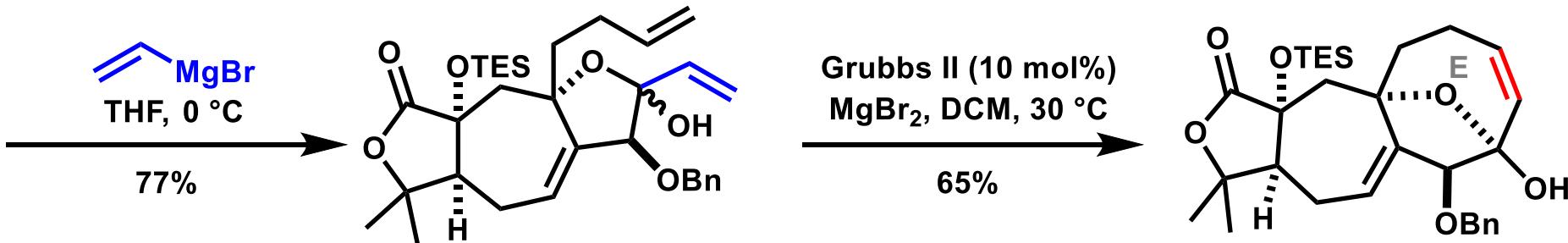
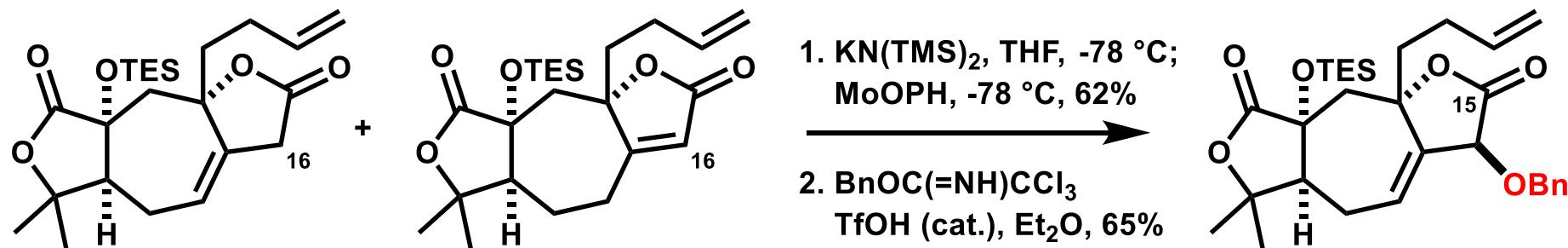
Construction of BC-rings



Construction of D-ring

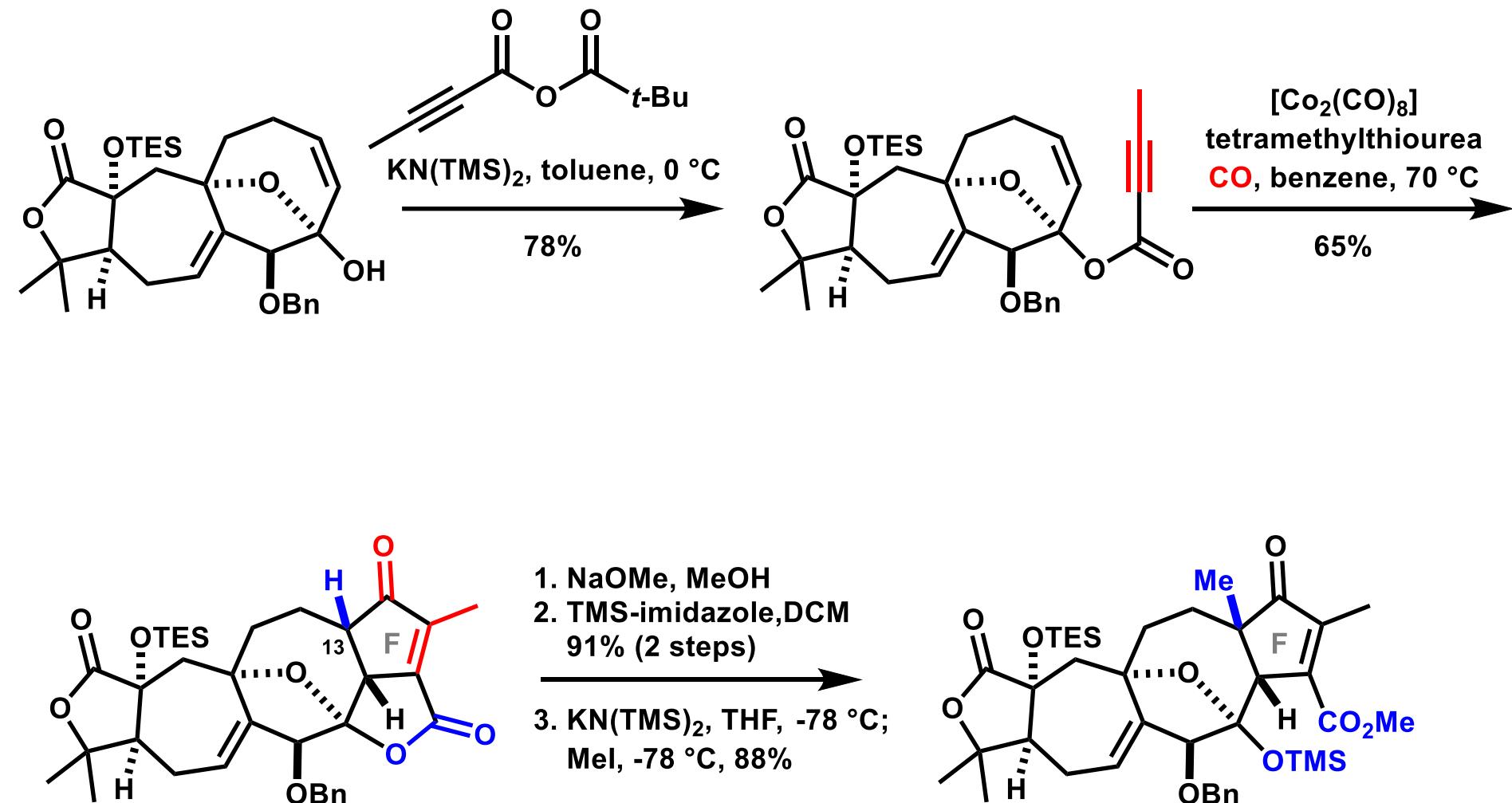


Construction of E-ring by RCM

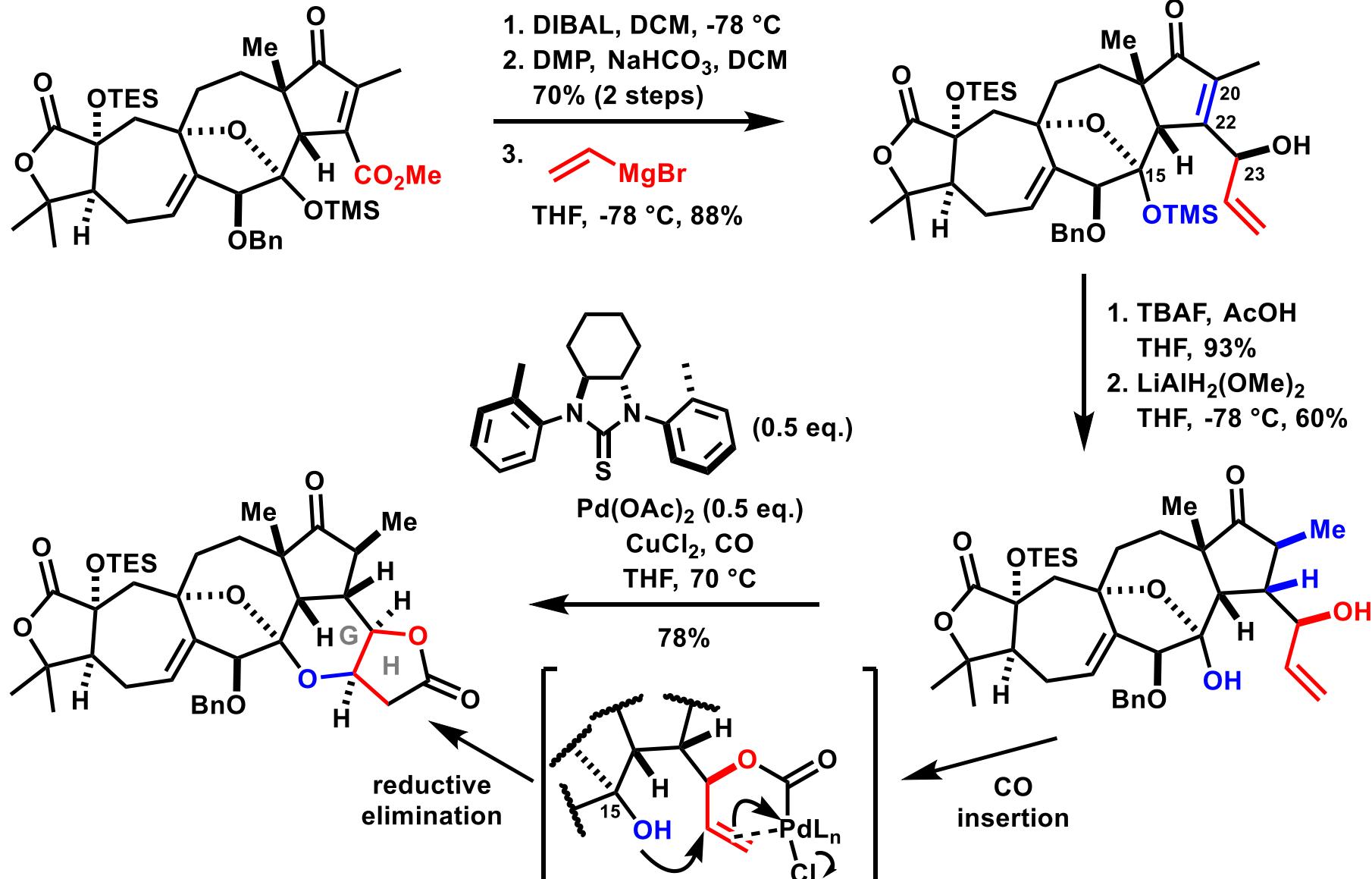


$\text{L} = \text{py, HMPA}$
 MoOPH

Construction of F-ring by Pauson-Khand Reaction



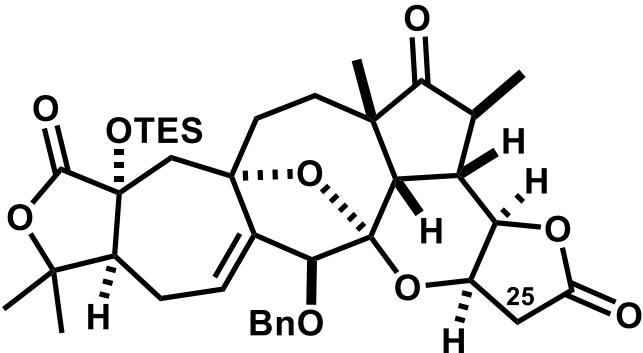
Construction of GH-rings via Pd-catalyzed Carbonylative annulation



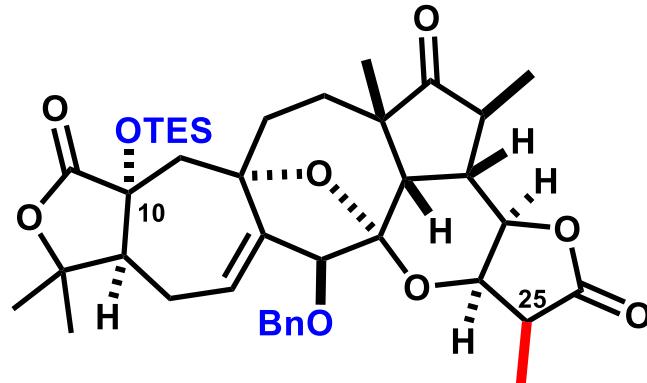
1) Xiao, Q.; Ren, W.; Chen, Z.; Sun, W.; Li, Y.; Ye, Q.; Gong, J.; Meng, F.; You, L.; Liu, Y.; Zhao, M.; Xu, L.; Shan, Z.; Shi, Y.; Tang, Y.; Chen, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 7373.

2) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 885.

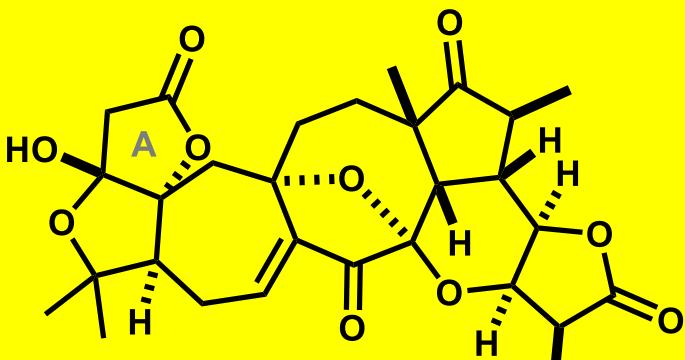
Completion of Total Synthesis



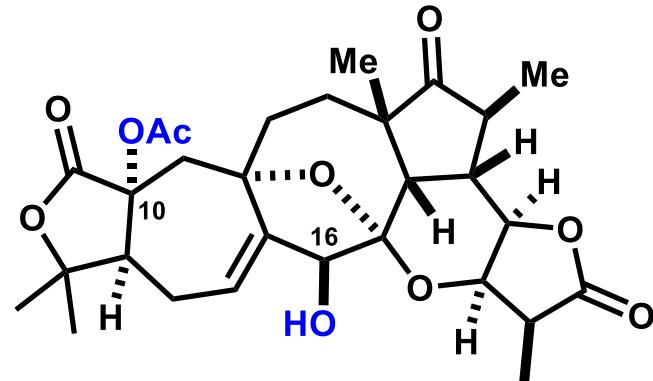
1. LiN(TMS)₂, THF, -78 °C;
MeI, -78 °C, 80%
2. LiTMP, THF, -78 °C;
sat. aq. NH₄Cl, 76%



1. Ac₂O, Sc(OTf)₃
MeCN, 92%
2. Pd(OH)₂ (10 mol%)
H₂, EtOAc, 90%



1. LiN(TMS)₂, THF
-78 °C to 0 °C
 2. DMP, NaHCO₃, DCM
- 60% (2 steps)
- Dieckmann condensation*

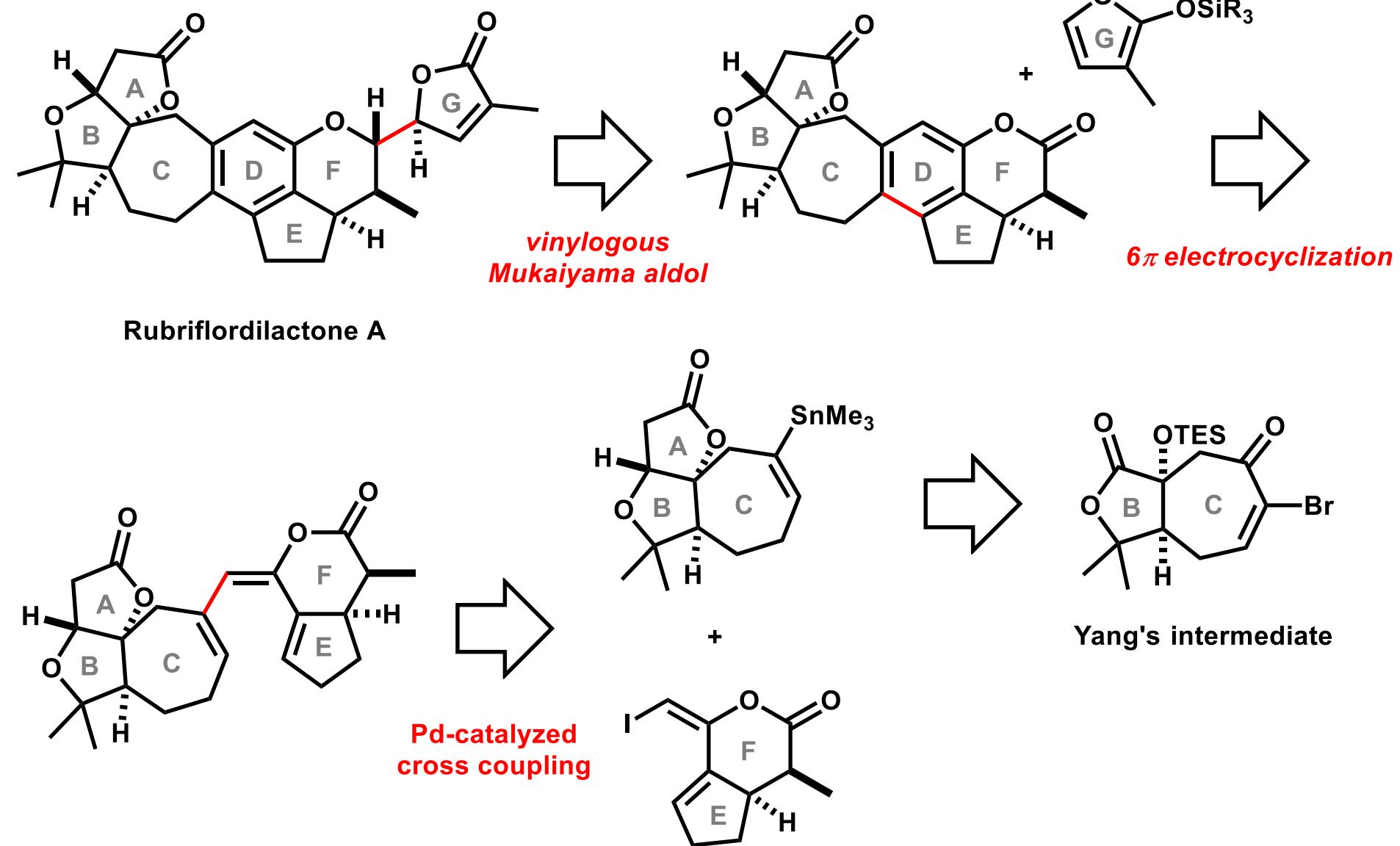


(±)-Schindilactone A
29 steps, <0.17%

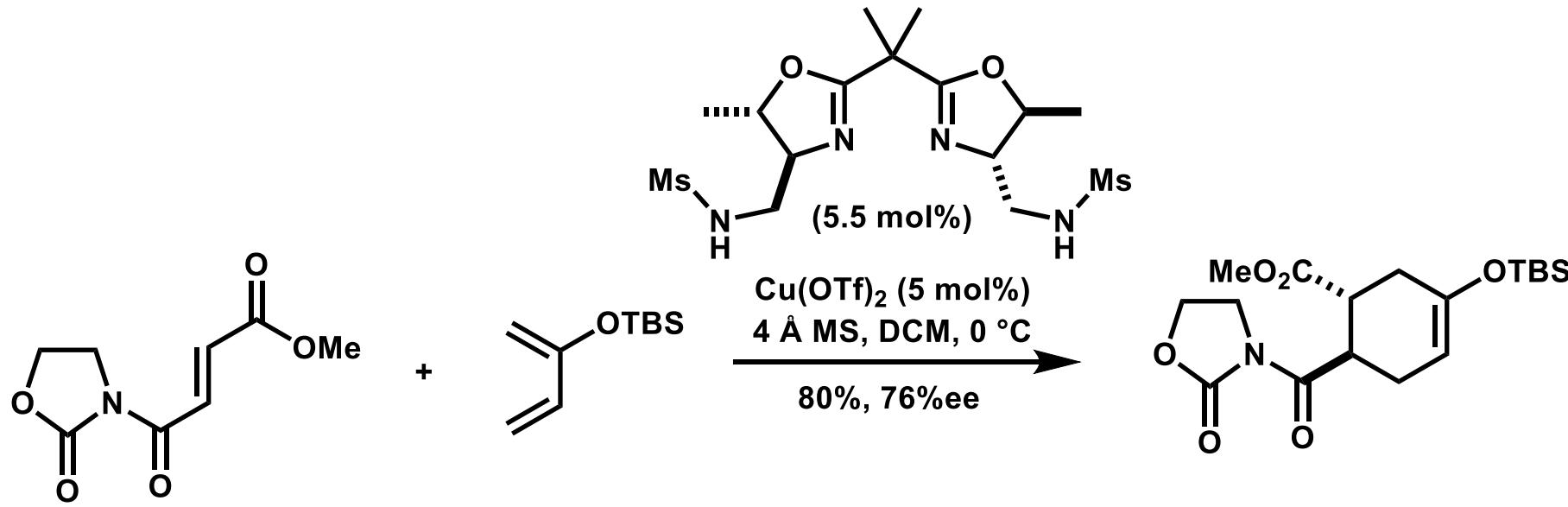
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(Li's study)
4. Total Synthesis of (+)-Rubriflordilactone A
(Anderson's study, main paper)
5. Summary

Retrosynthetic Analysis

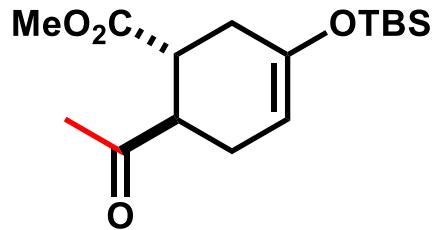


Asymmetric Synthesis of BC-rings



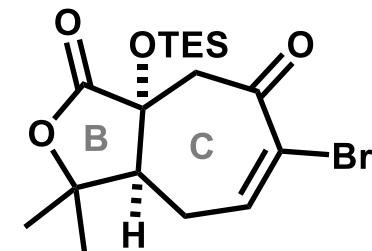
1. EtSH, BuLi
THF, 0 °C, 96%

2. $\text{Pd}_2(\text{dba})_3$ (1 mmol%)
S-Phos (5 mmol%)
 MeZnI , NMP/THF
-40 °C to -20 °C, 80%



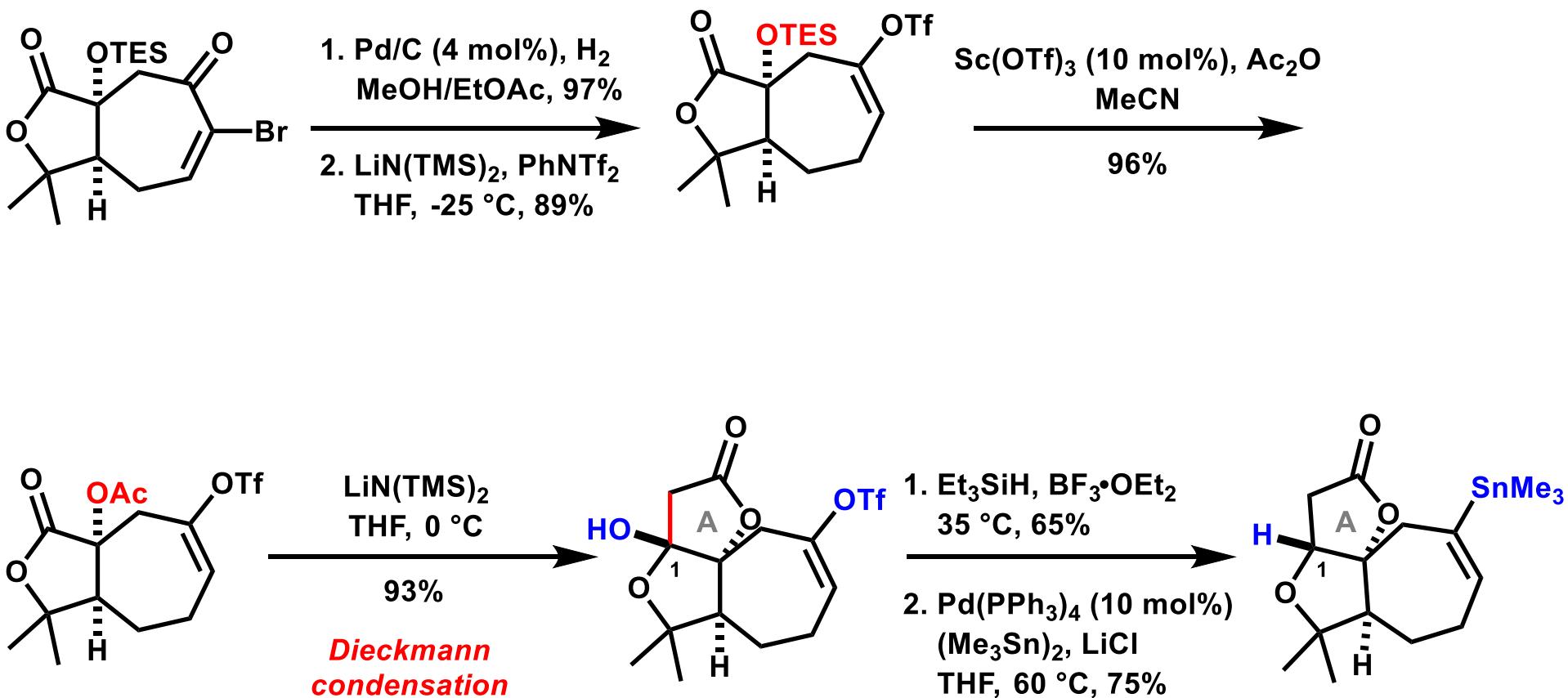
5 steps

same as
Yang's procedure

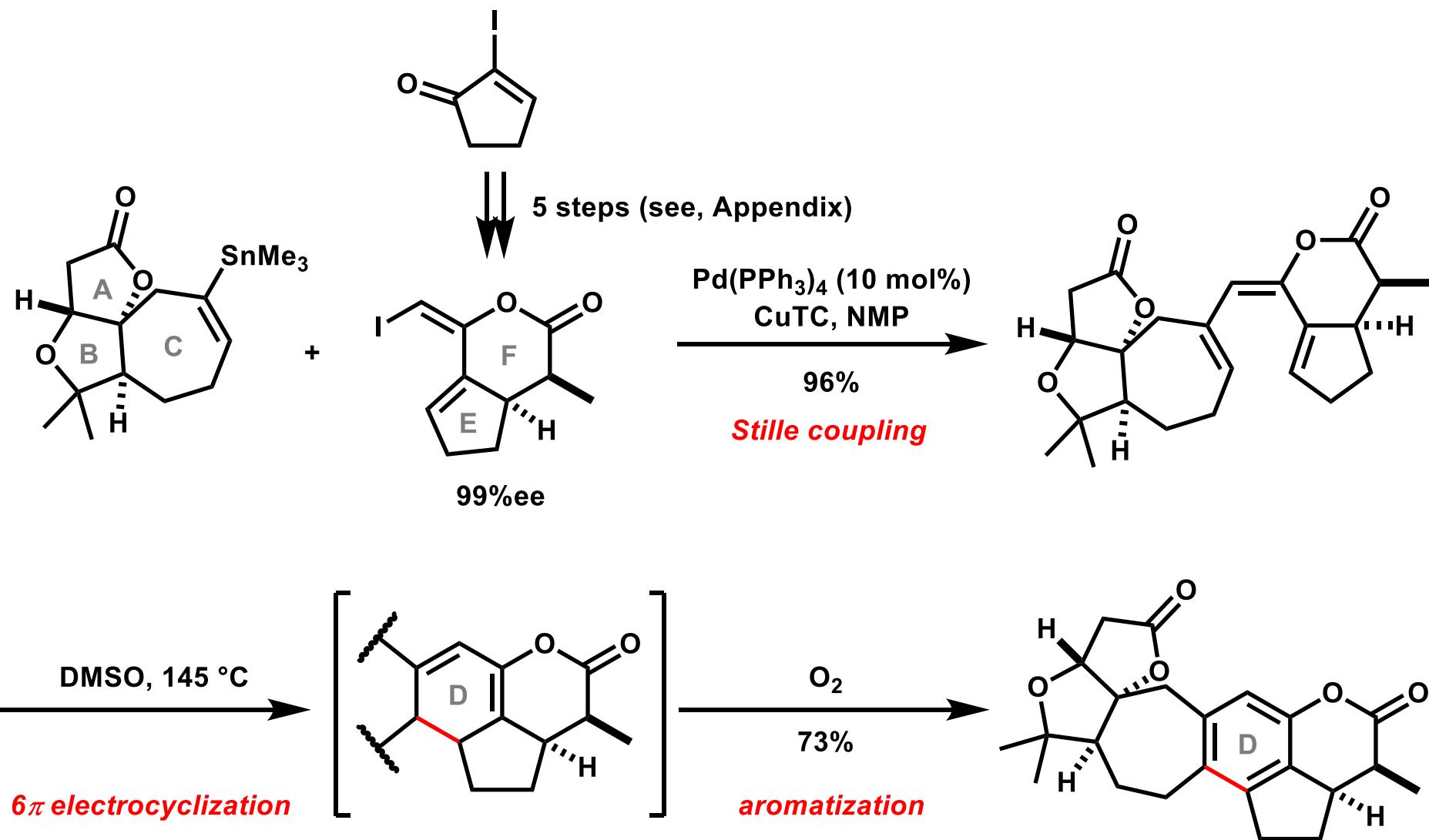


73% for recrystallization
>99%ee
(Yang's intermediate)

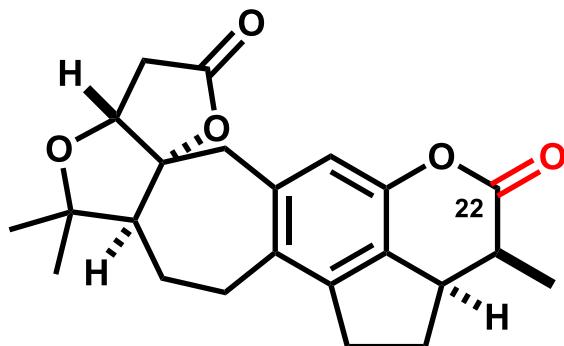
Construction of A-ring by Dieckmann Condensation



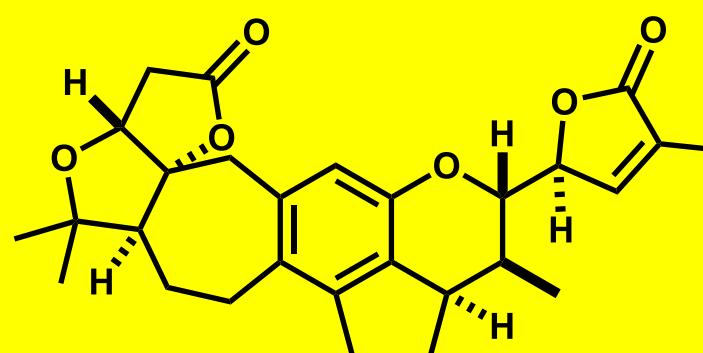
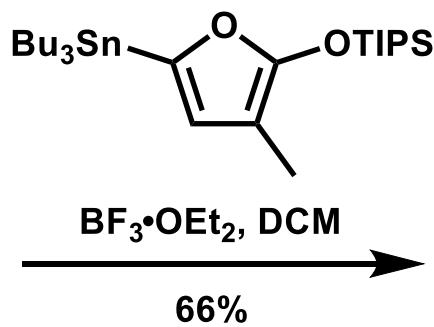
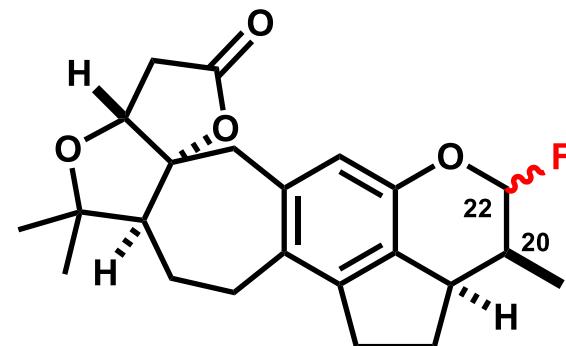
Construction of D-ring by 6π -Electrocyclization



Completion of Total Synthesis



1. LiAlH(O*t*-Bu)₃
THF, 5 °C
2. Et₂NSF₃ (DAST)
DCM
62% in 2 steps



(+)-Rubriflorldilactone A

longest linear 19 steps, <2.1%

Short Summary

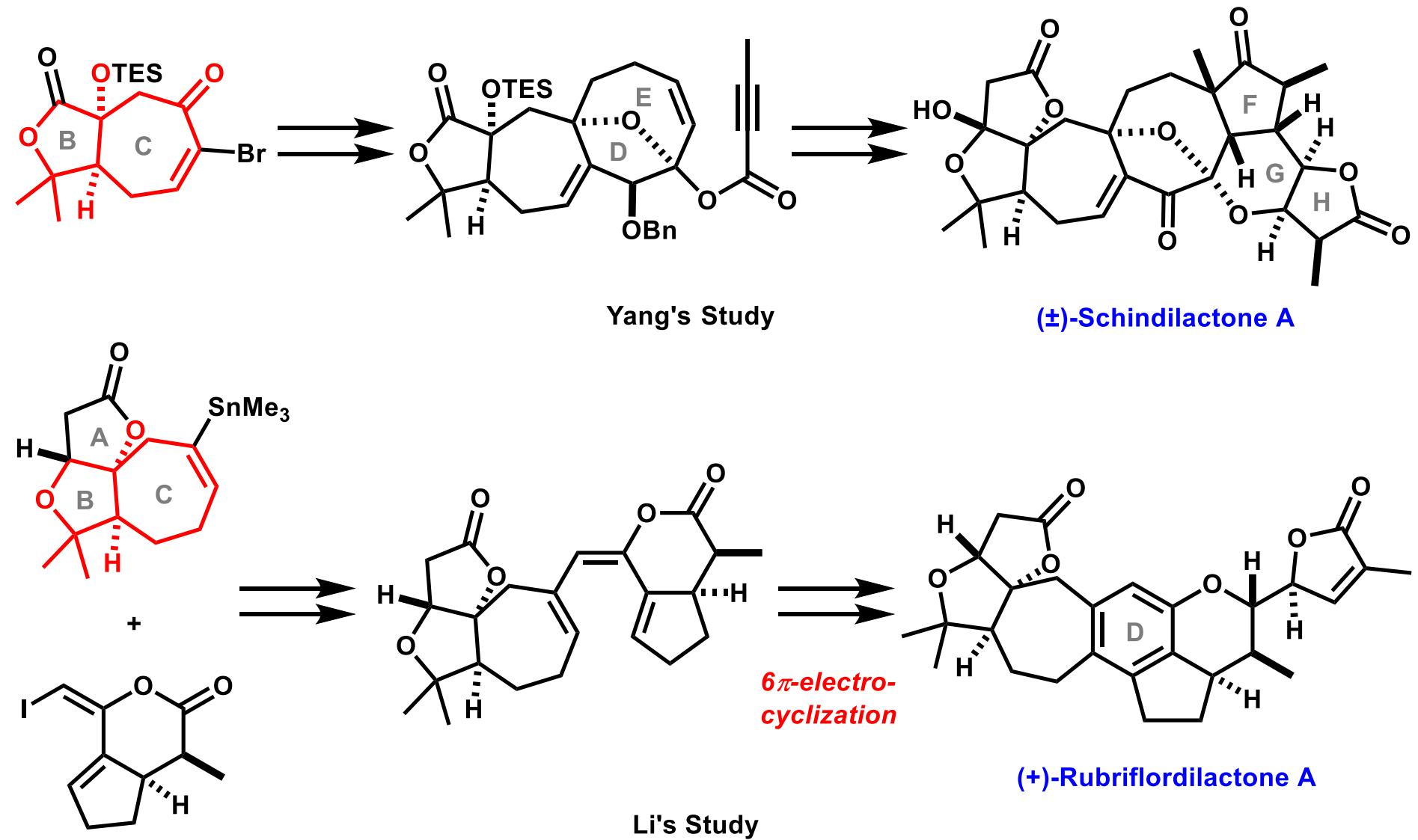
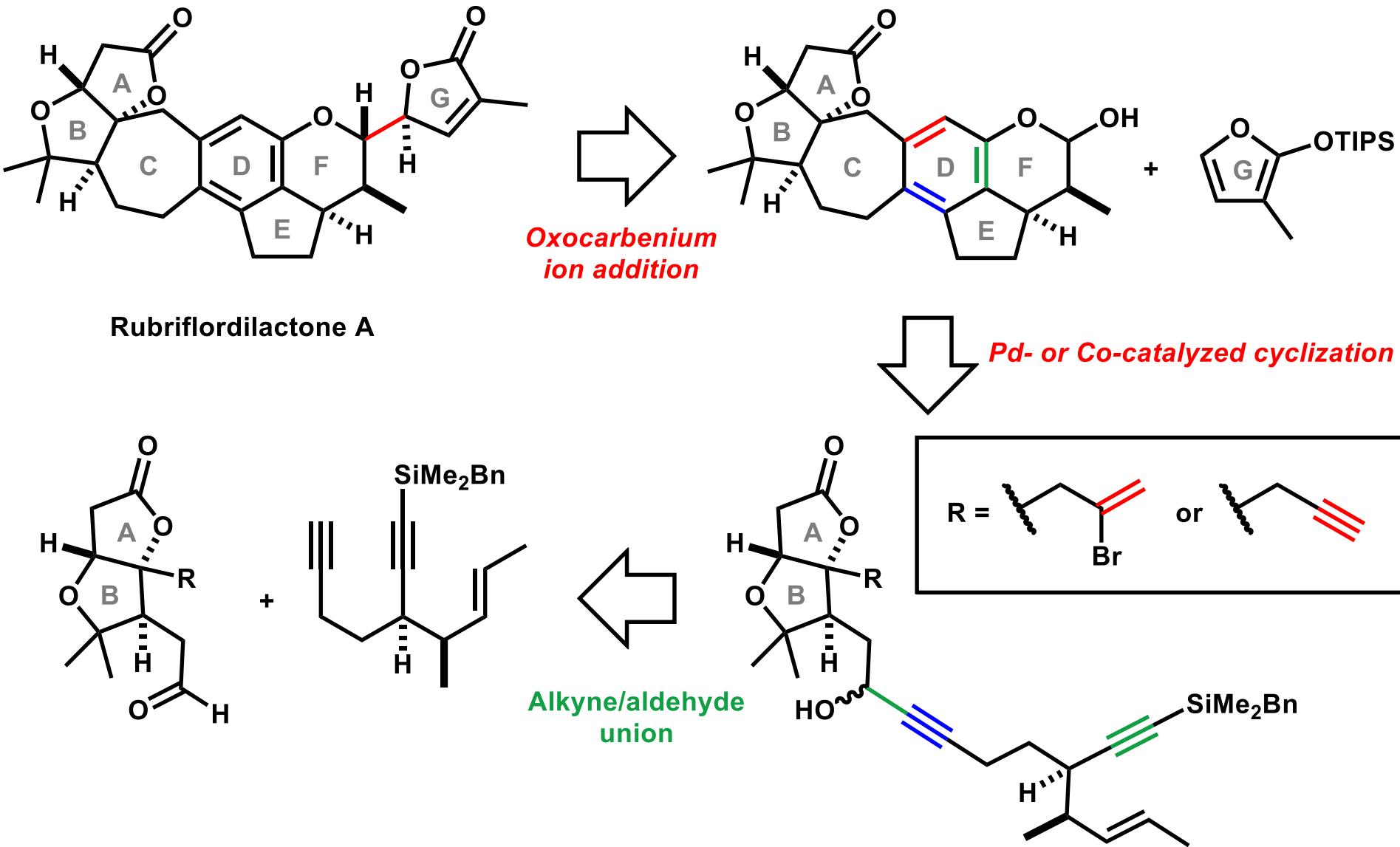


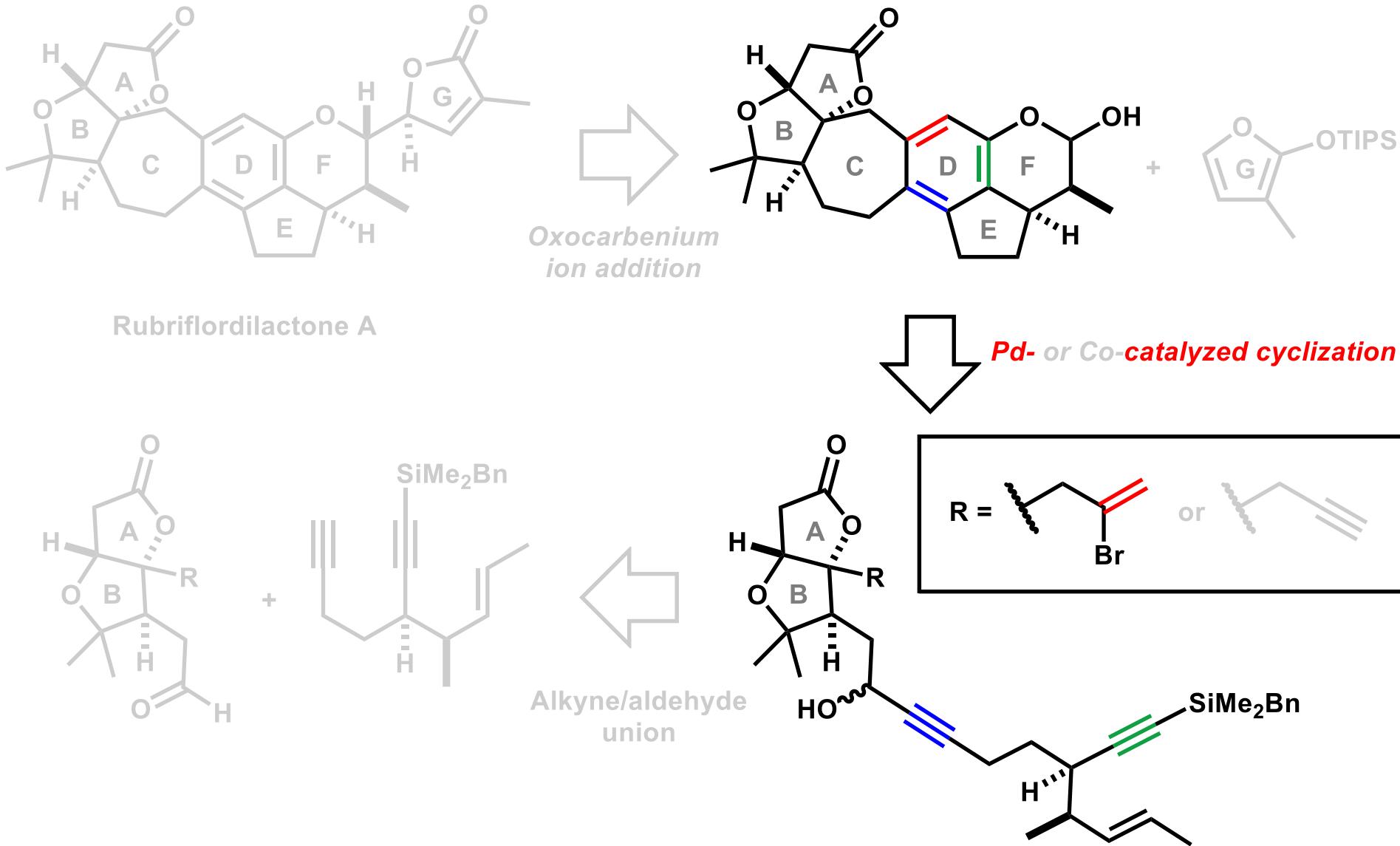
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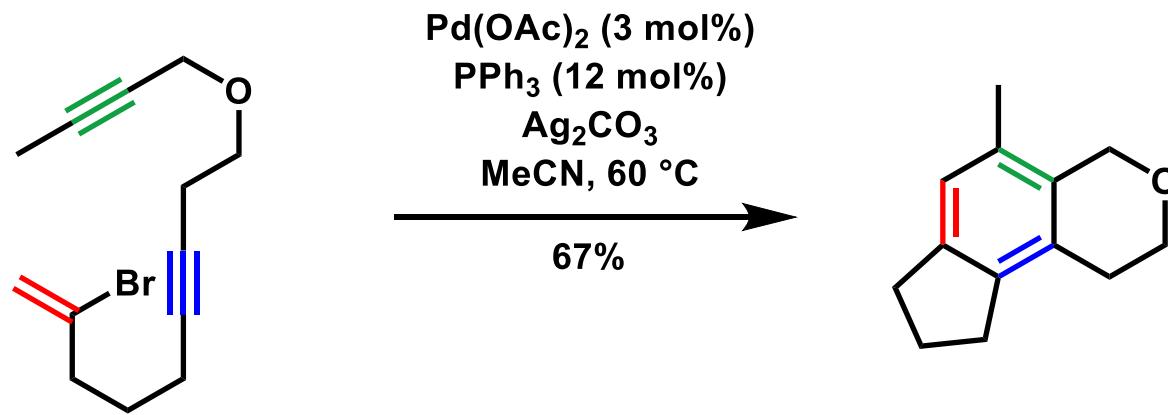
Retrosynthetic Analysis



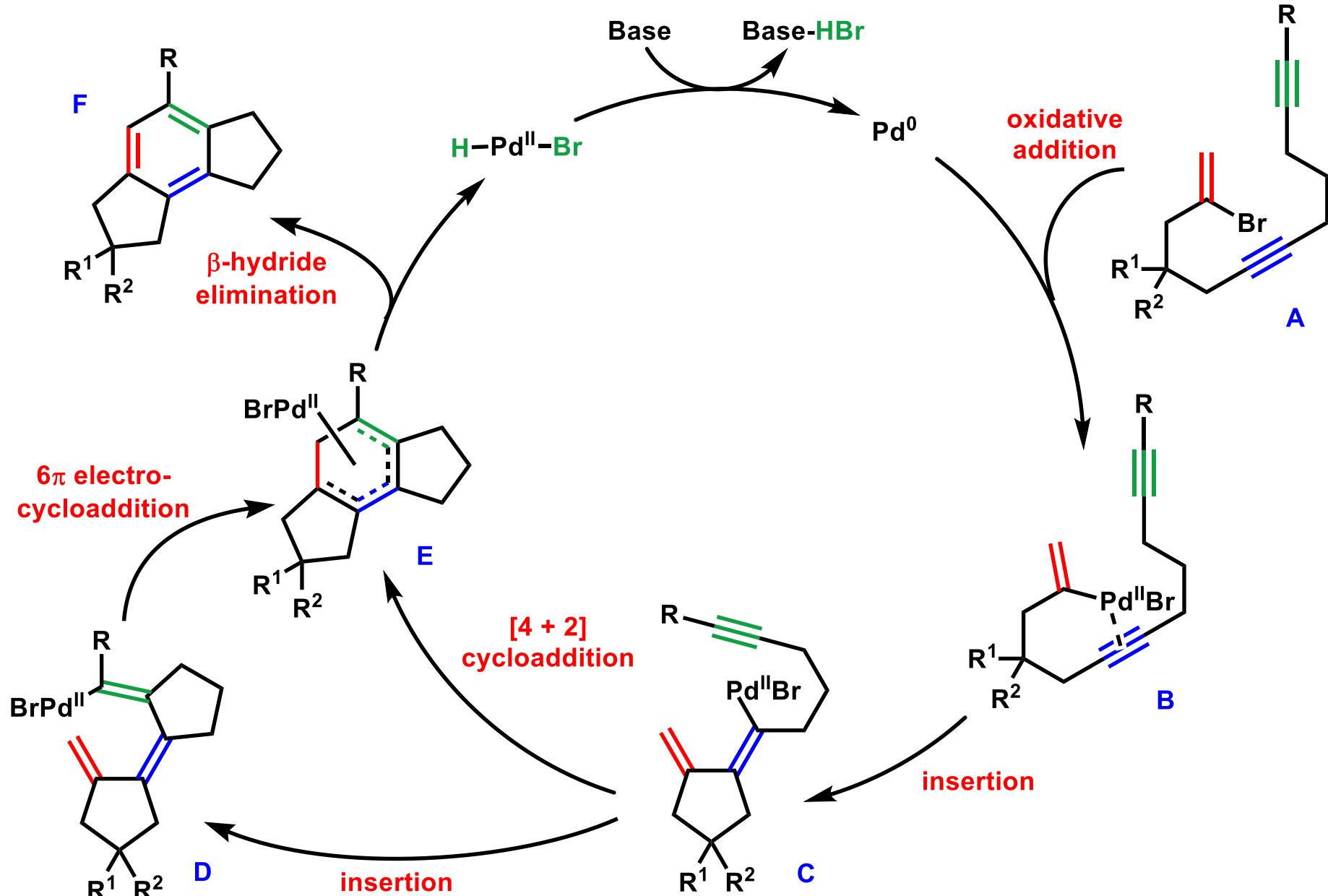
Retrosynthetic Analysis



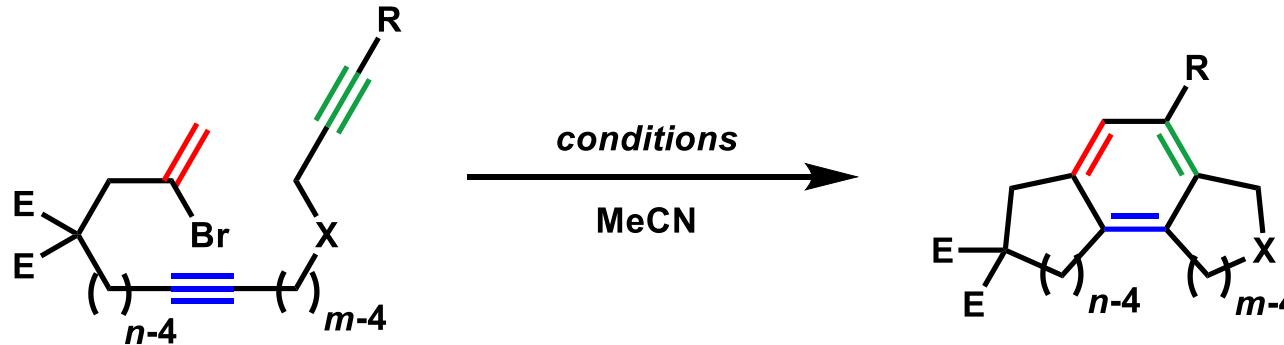
Pd-catalyzed Bromoendiyne Cyclization



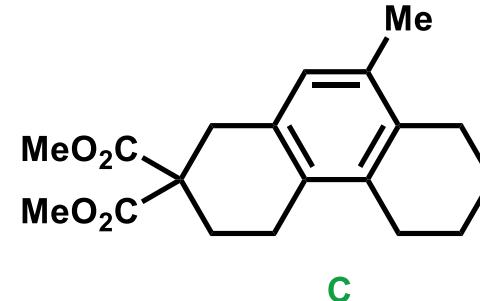
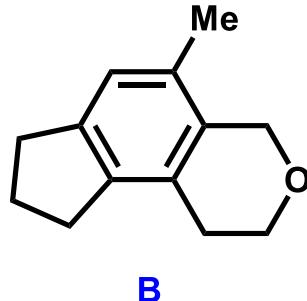
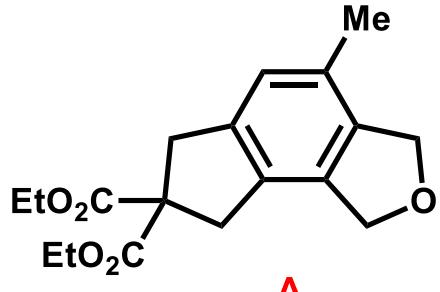
Pd-catalyzed Bromoendiyne Cyclization



Pd-catalyzed Bromoendiyne Cyclization



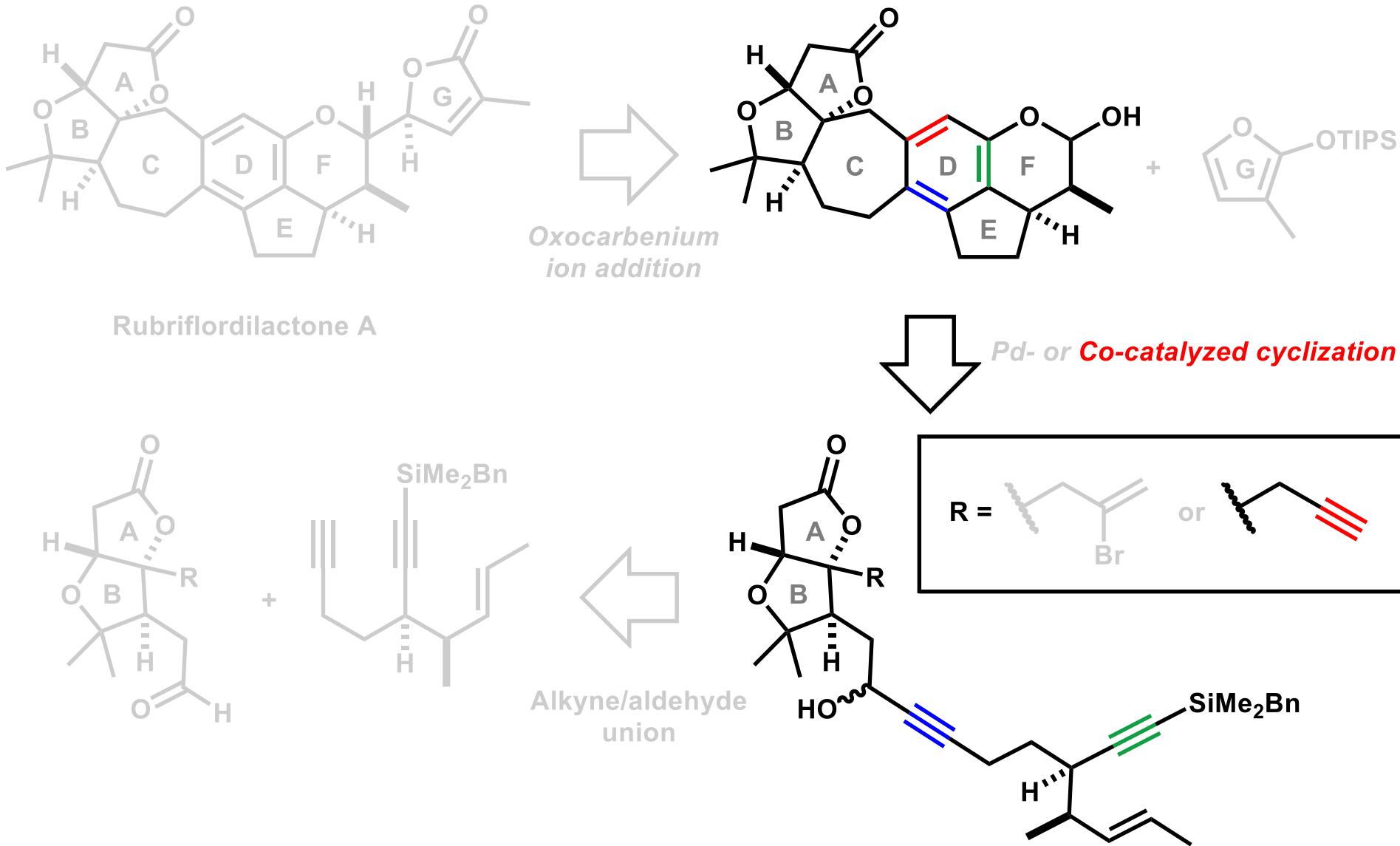
<i>m</i>	<i>n</i>	E	X	R	conditions	Product	Yield (%)
5	5	CO ₂ Et	O	Me	Pd(PPh ₃) ₄ (3 mol%) Et ₃ N, reflux	A	85
5	6	H	O	Me	Pd(OAc) ₂ (3 mol%) PPh ₃ (12 mol%), Ag ₂ CO ₃ , 60 °C	B	67
6	6	CO ₂ Me	CH ₂	TBS	Pd(OAc) ₂ (10 mol%) PPh ₃ (25 mol%), K ₂ CO ₃ , 60 °C	C	79



1) Meyer, F. E.; de Meijere, A. *Synlett*. **1991**, 777.

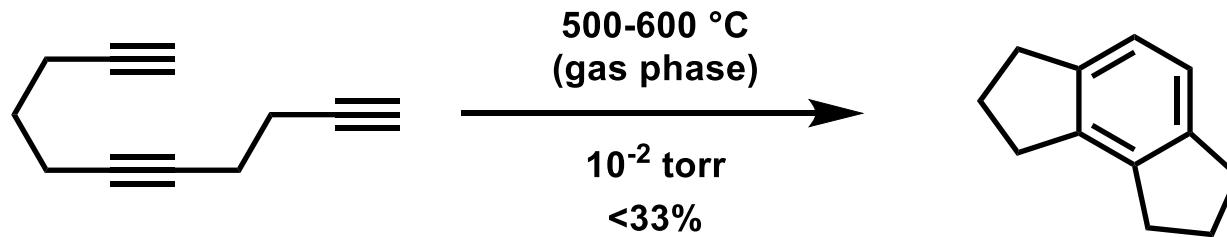
2) Tokan, W. M.; Meyer, F. E.; Schweizer, S.; Parsons, P. J.; de Meijere, A. *Eur. J. Org. Chem.* **2008**, 6152.

Retrosynthetic Analysis



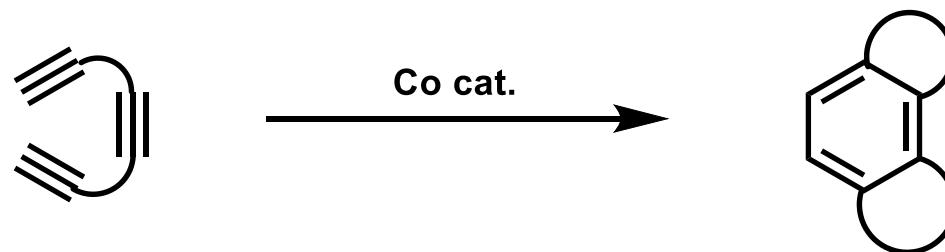
[2+2+2] Cycloaddition

Thermal [2+2+2]

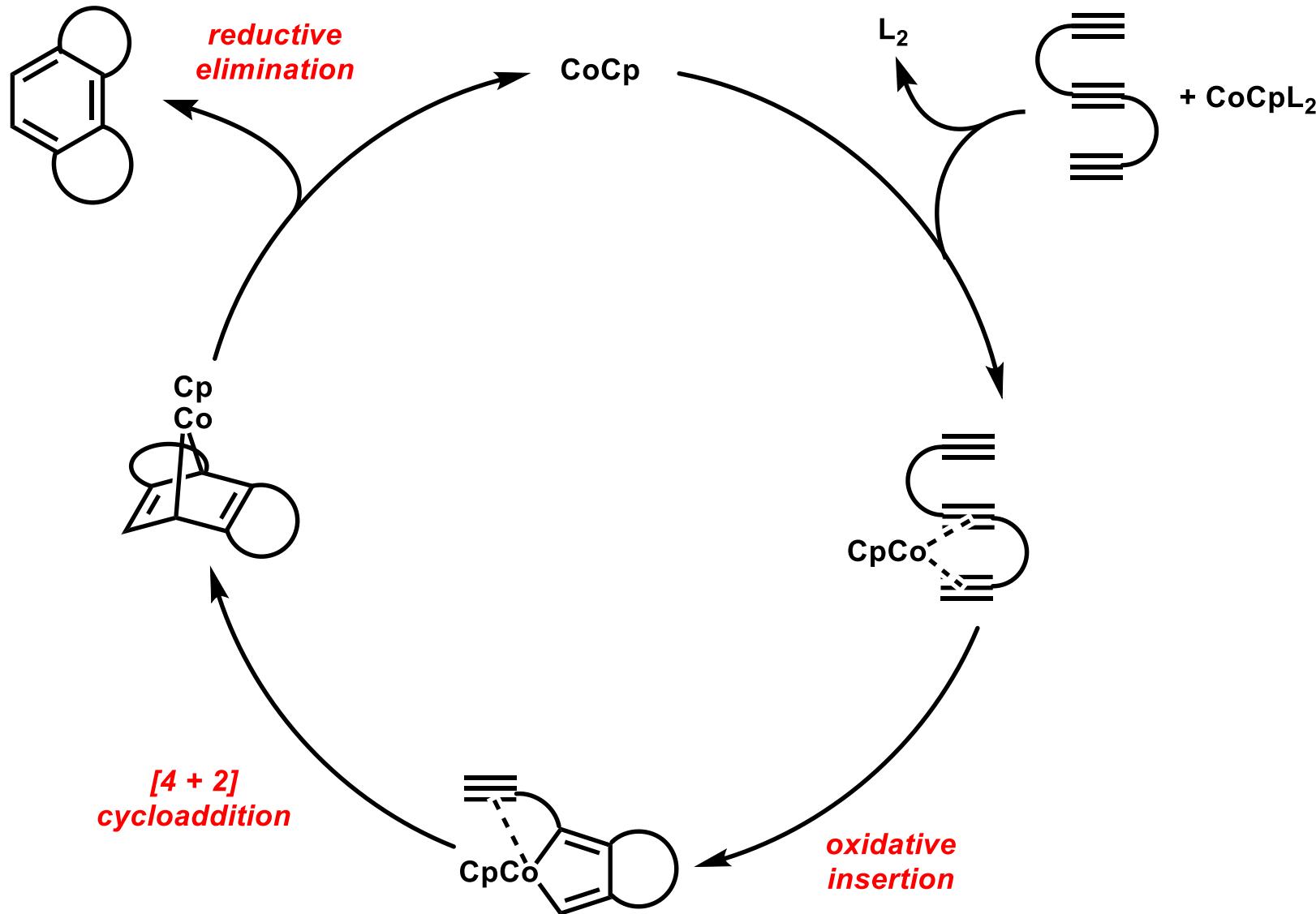


usually needs high temperature

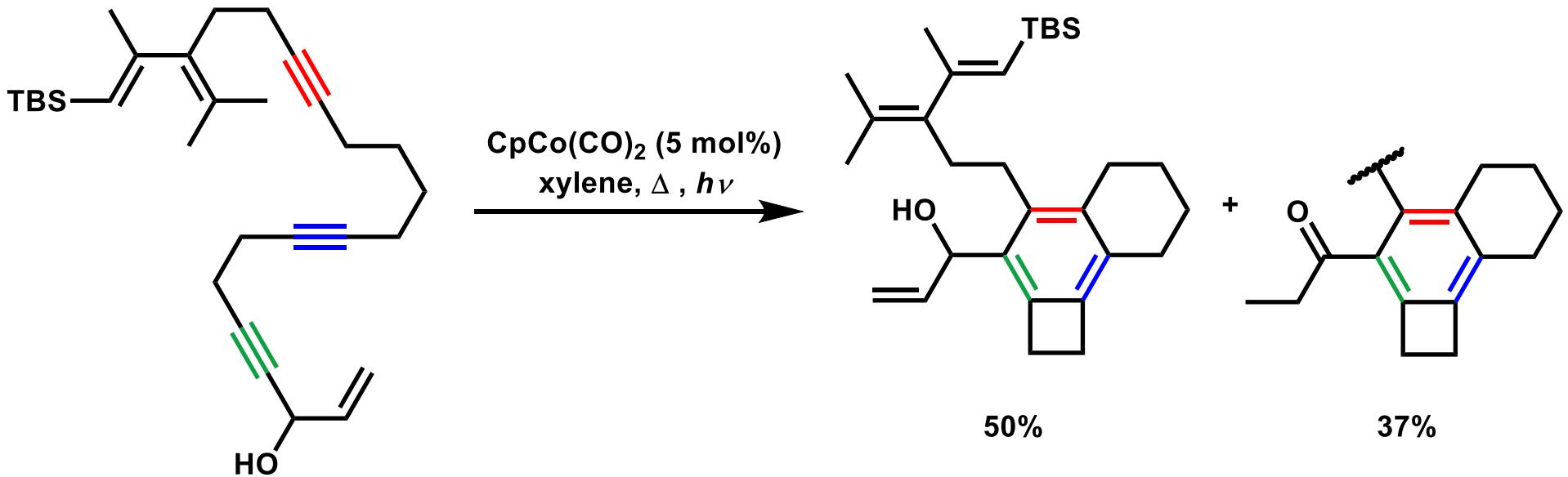
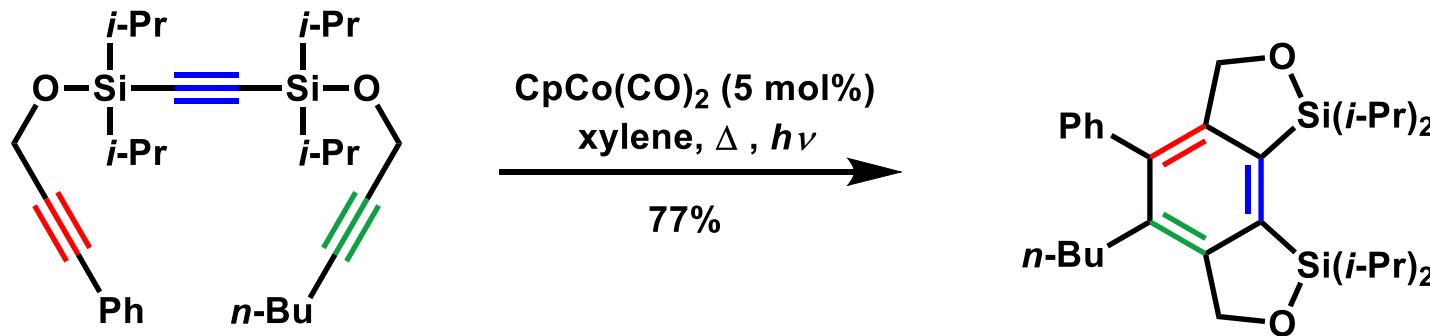
Co-catalyzed [2+2+2]



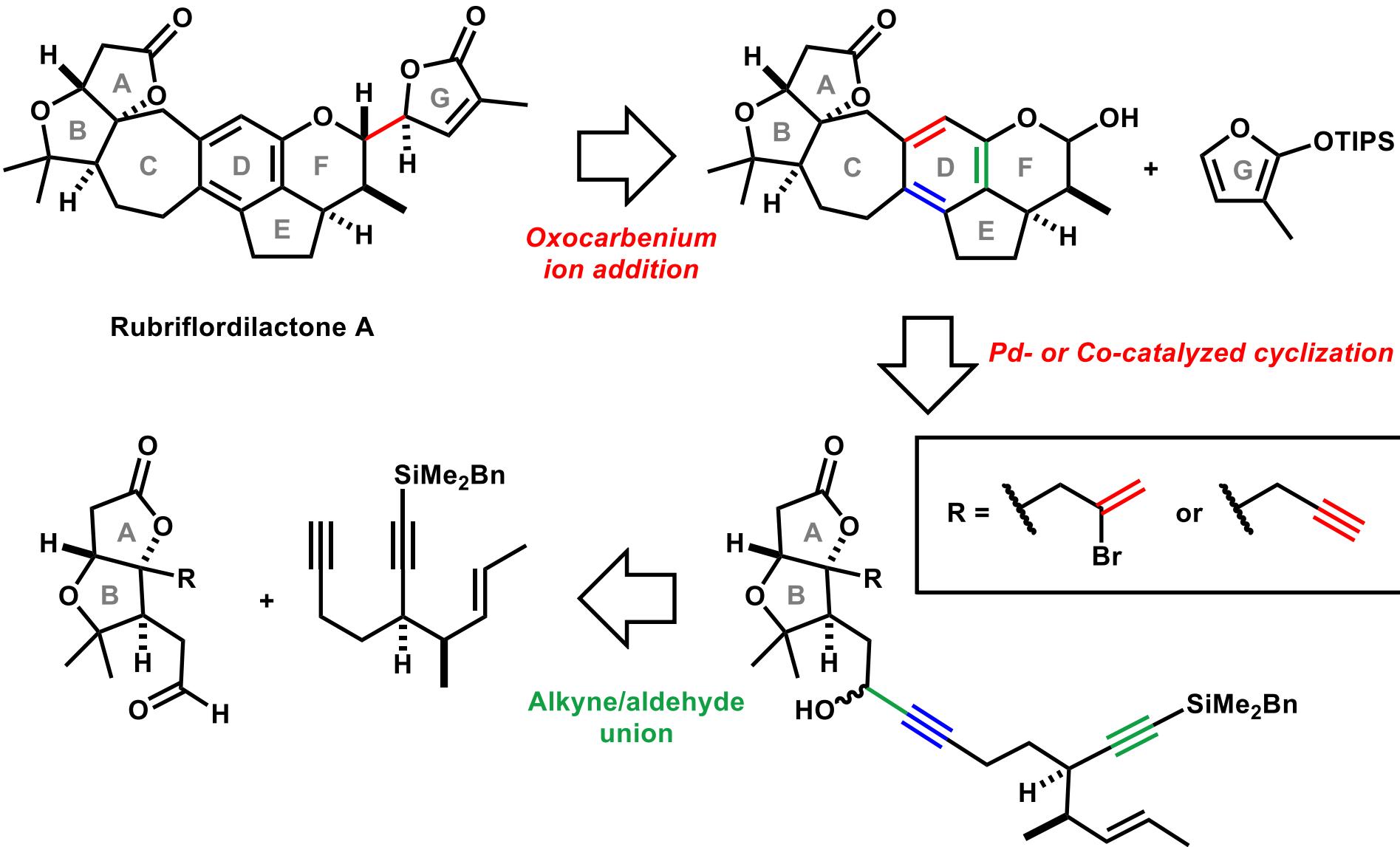
Proposed Mechanism for Co-catalyzed [2+2+2]



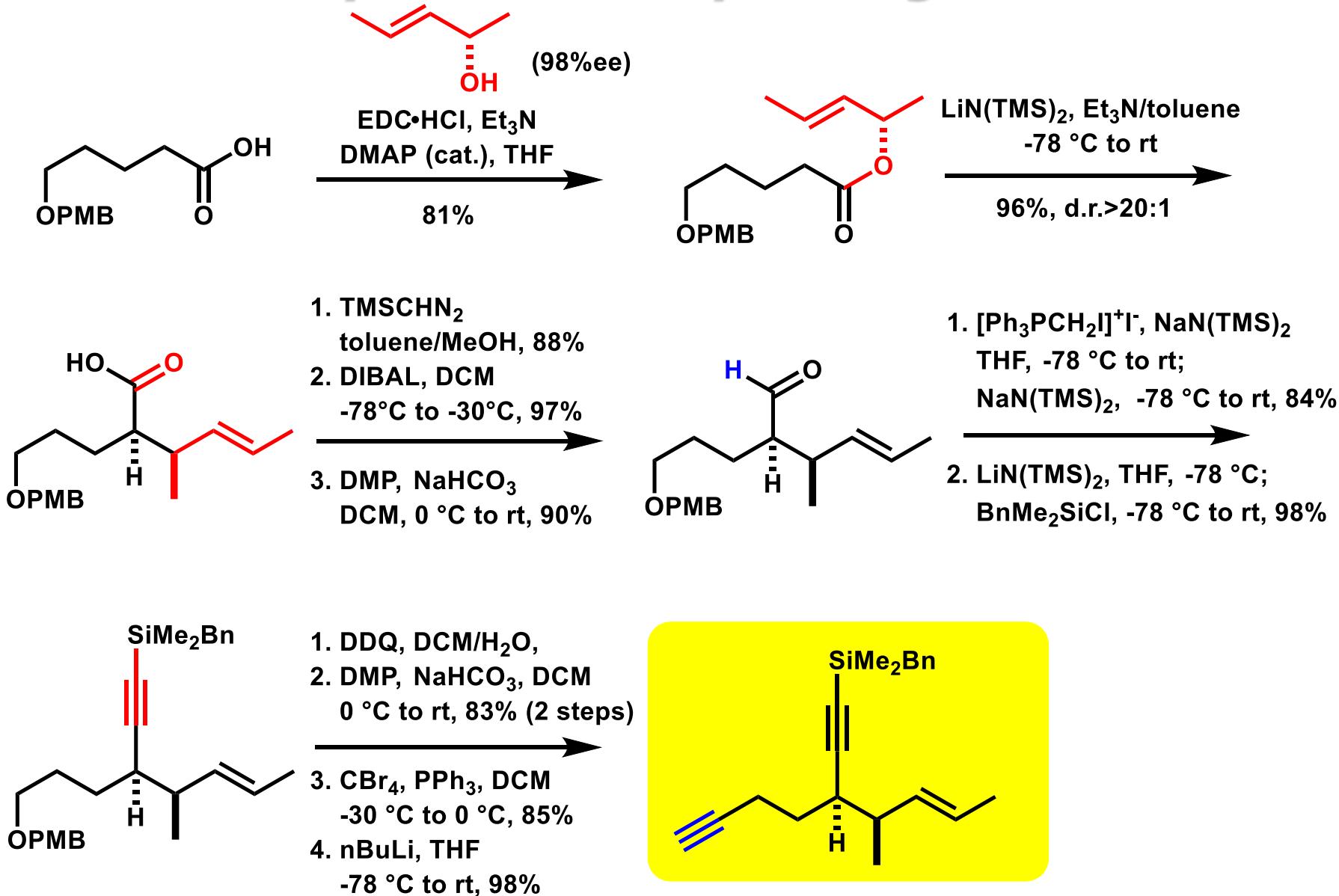
Co-catalyzed [2+2+2] Cycloaddition



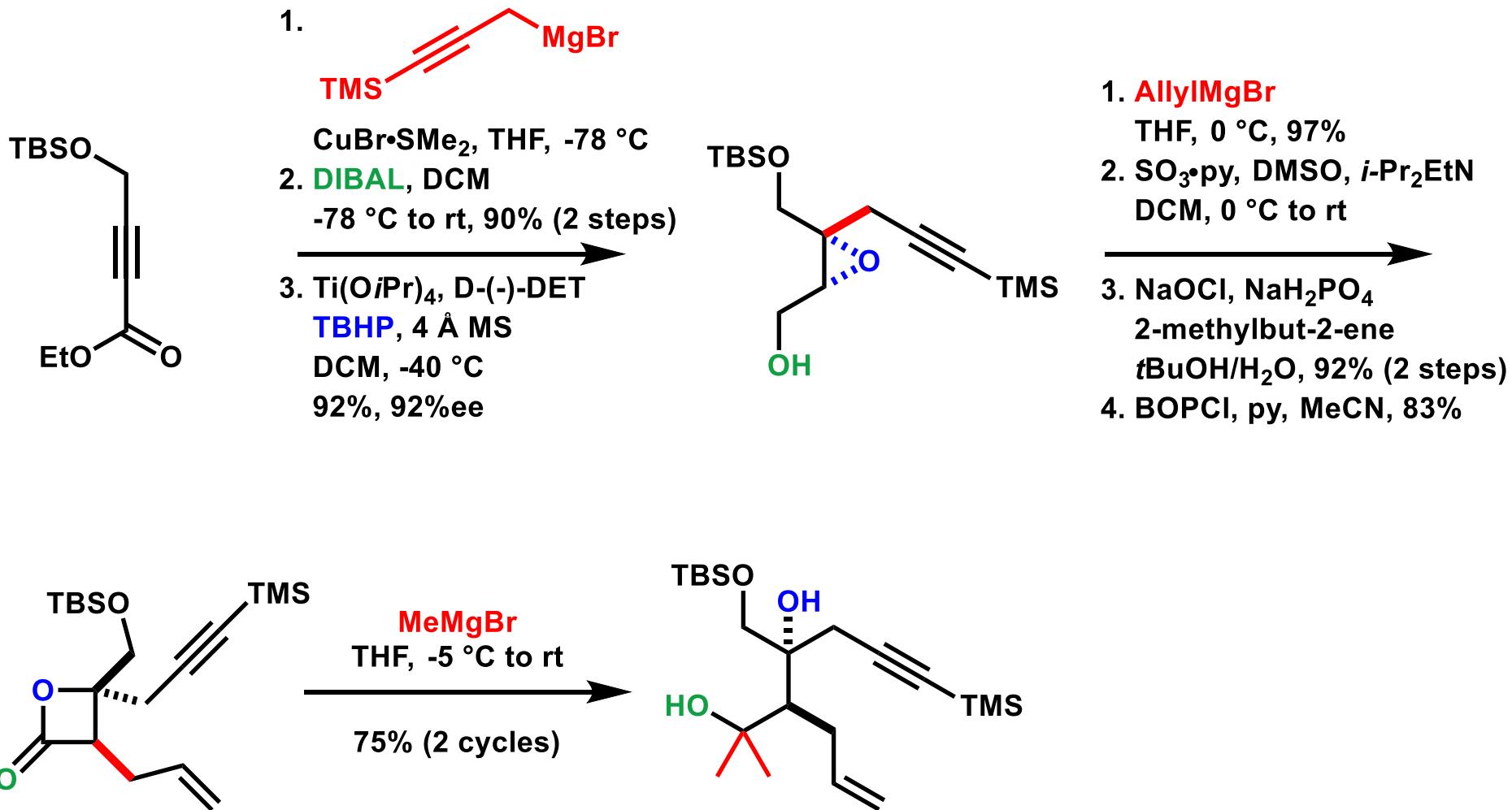
Retrosynthetic Analysis



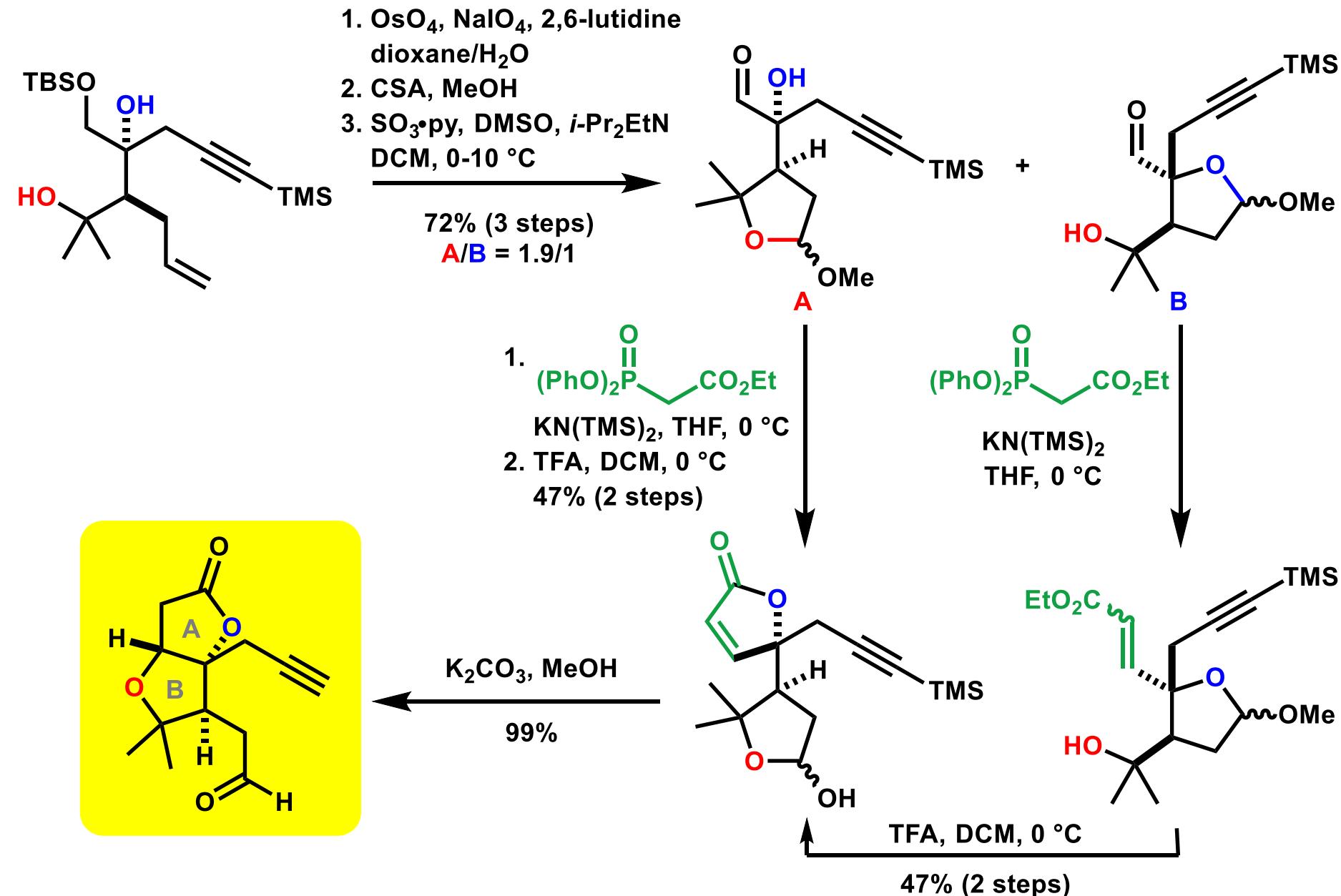
Synthesis of Diyne-fragment



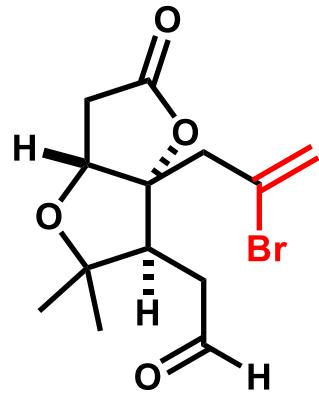
Construction of AB-rings



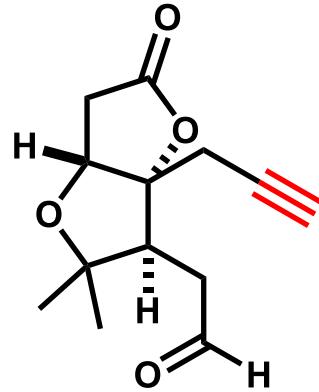
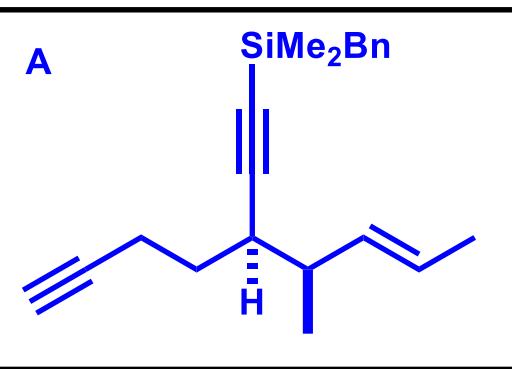
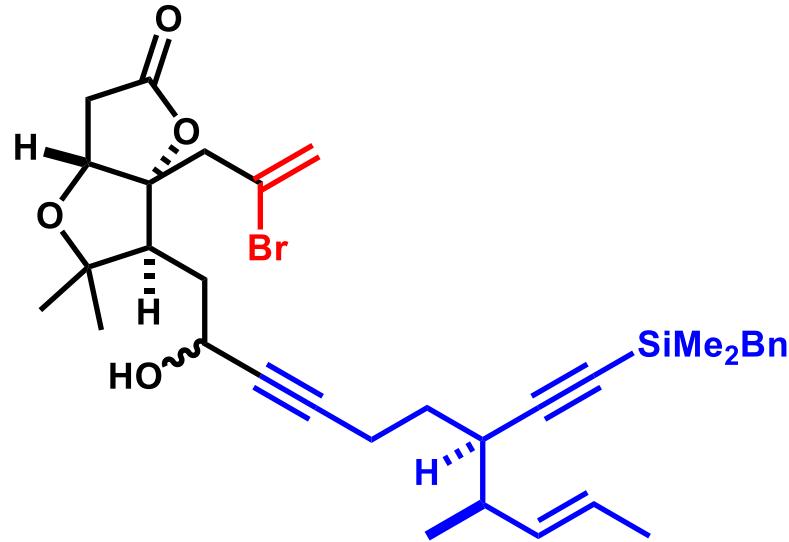
Construction of AB-rings



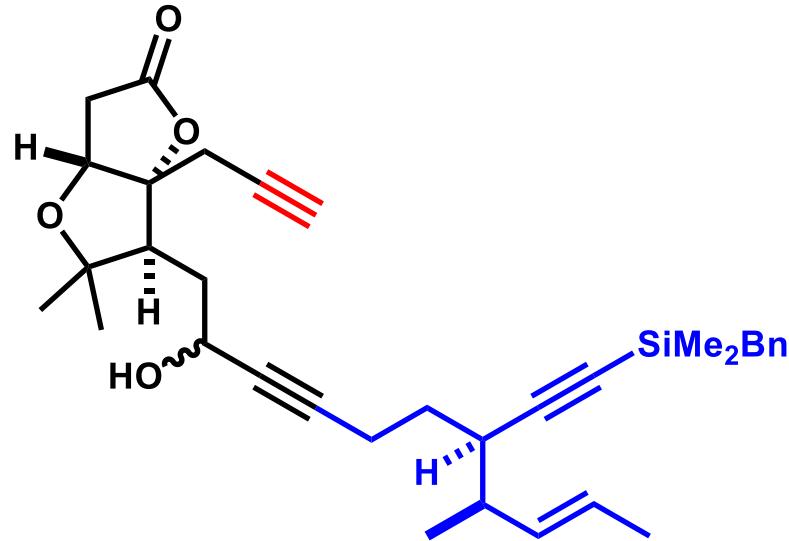
Syntheses of Substrates for Cyclization



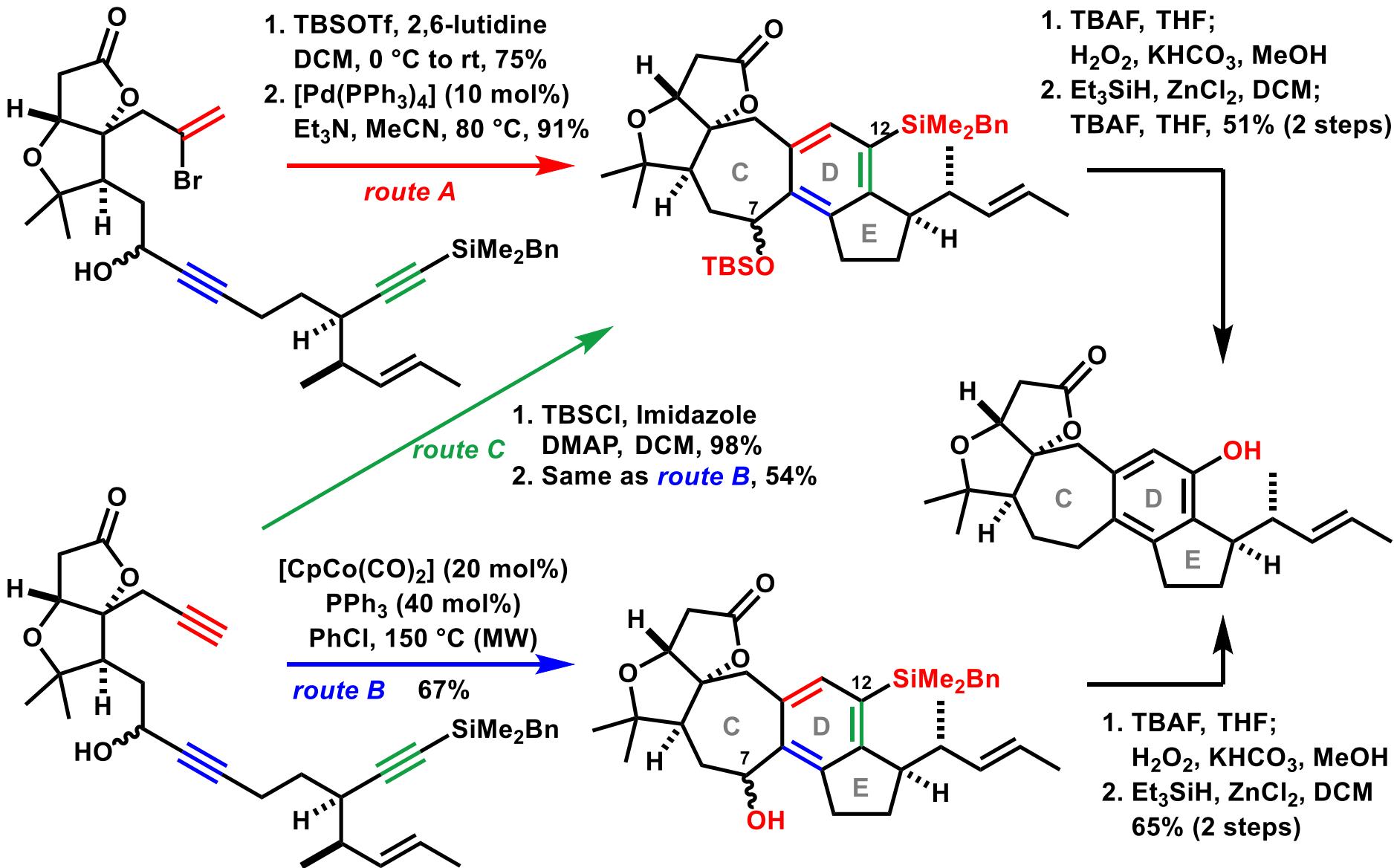
$n\text{BuLi}$, A
THF, -78 °C to -40 °C
67%



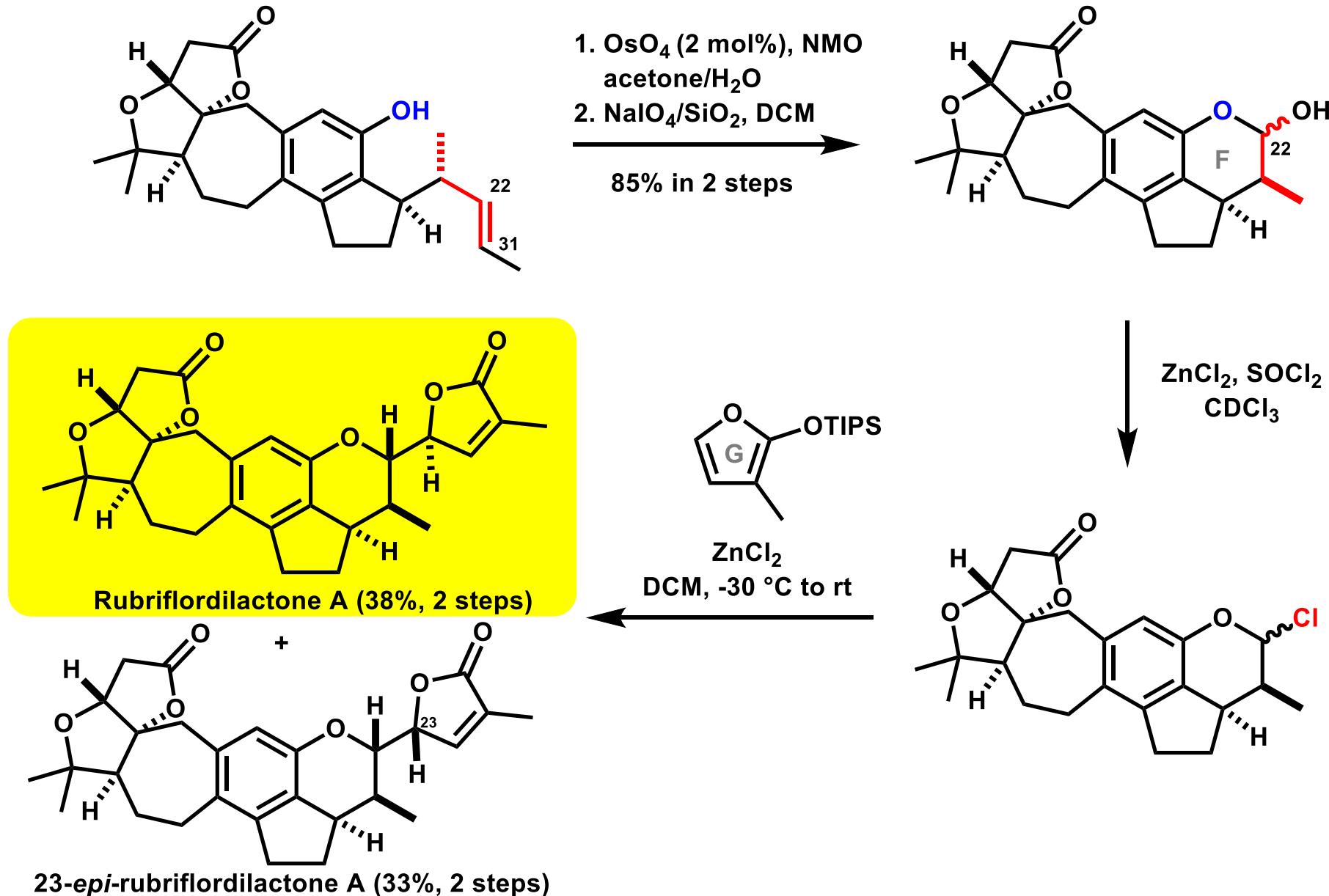
$n\text{BuLi}$, A
THF, -78 °C to -40 °C
85%



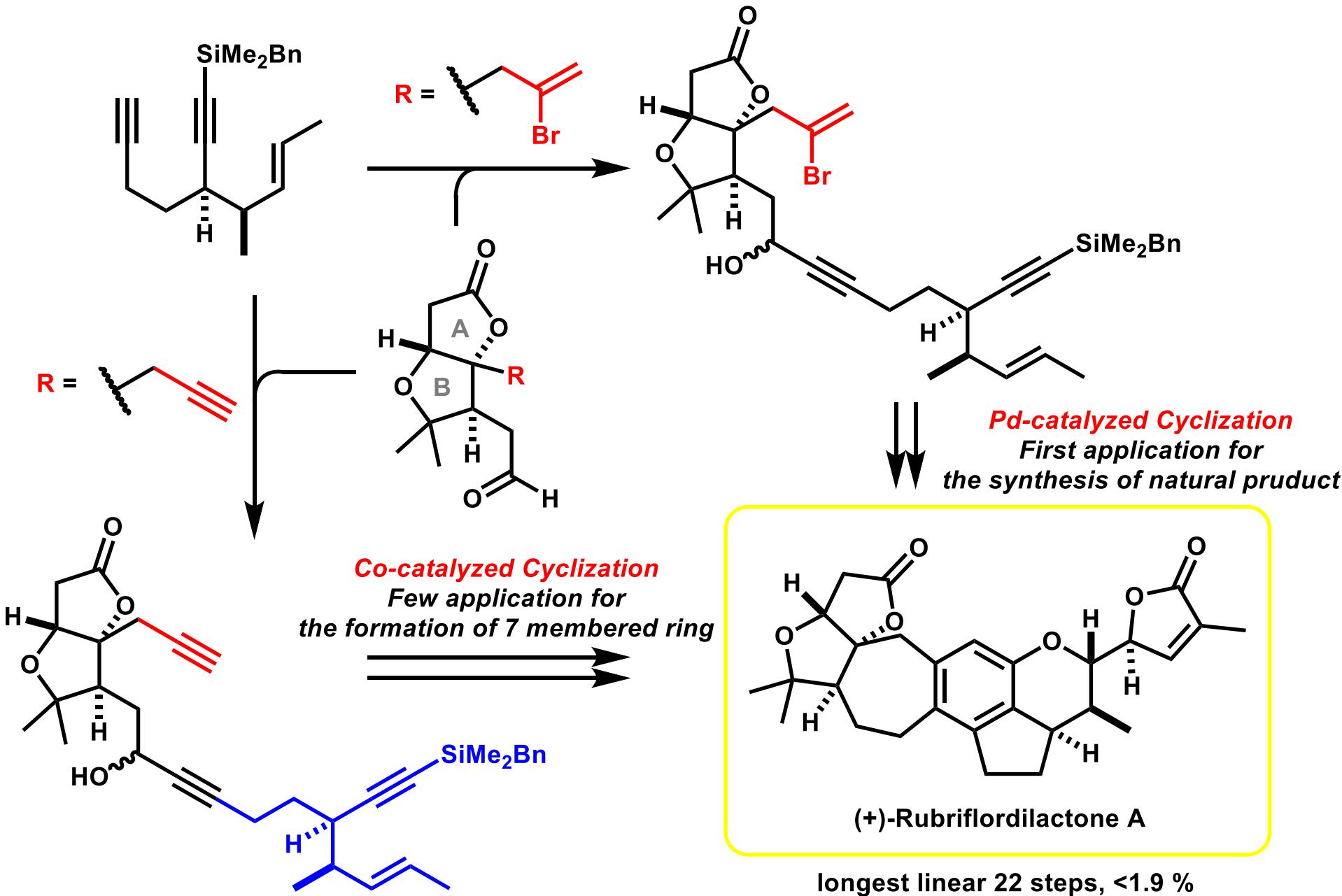
Construction of CDE-rings via Pd- or Co-catalyzed Cyclization



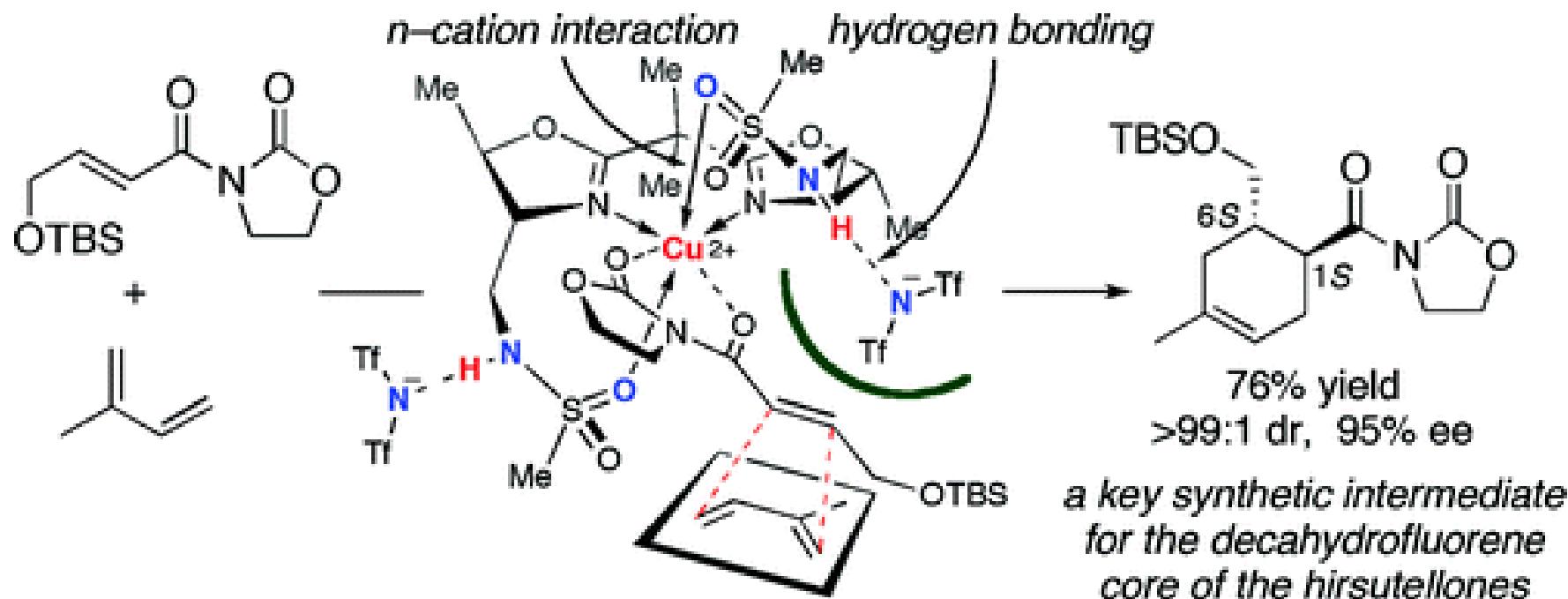
Completion of Total Synthesis



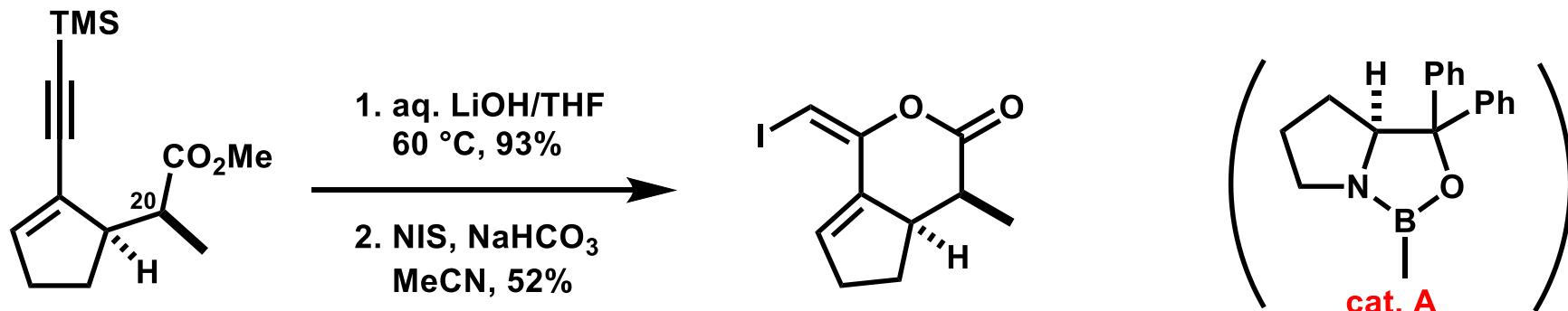
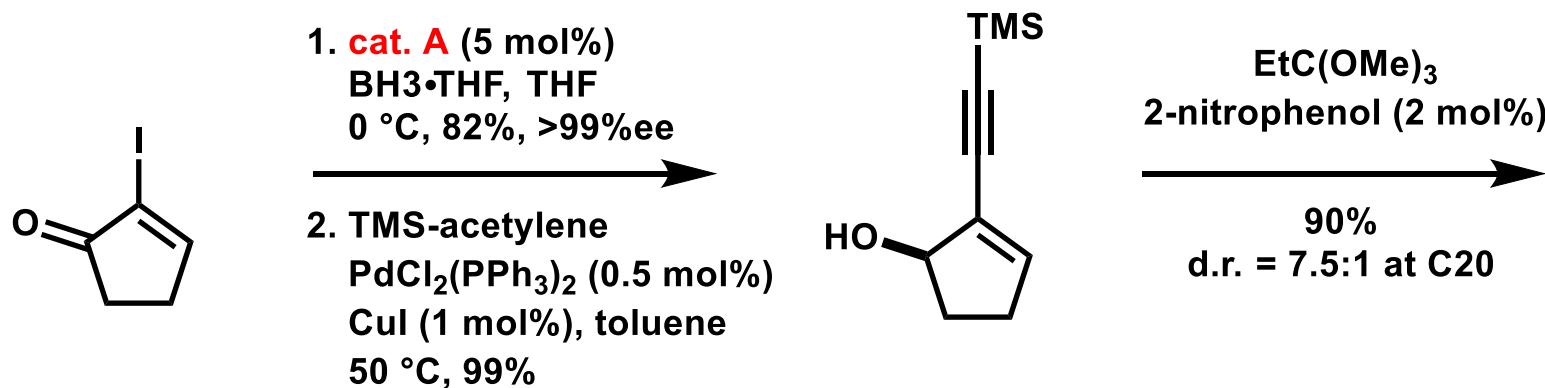
Summary



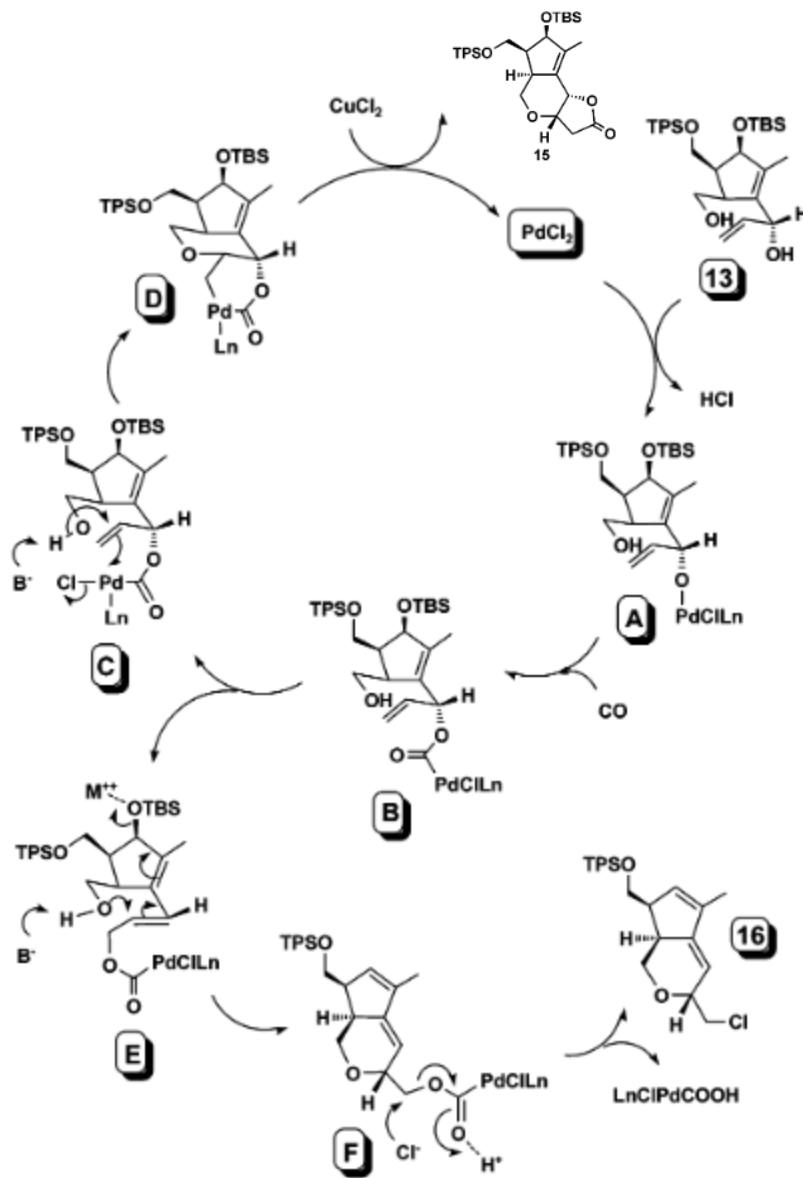
Appendix: Proposed Transition-state of Cu-catalyzed Diels-Alder Reaction



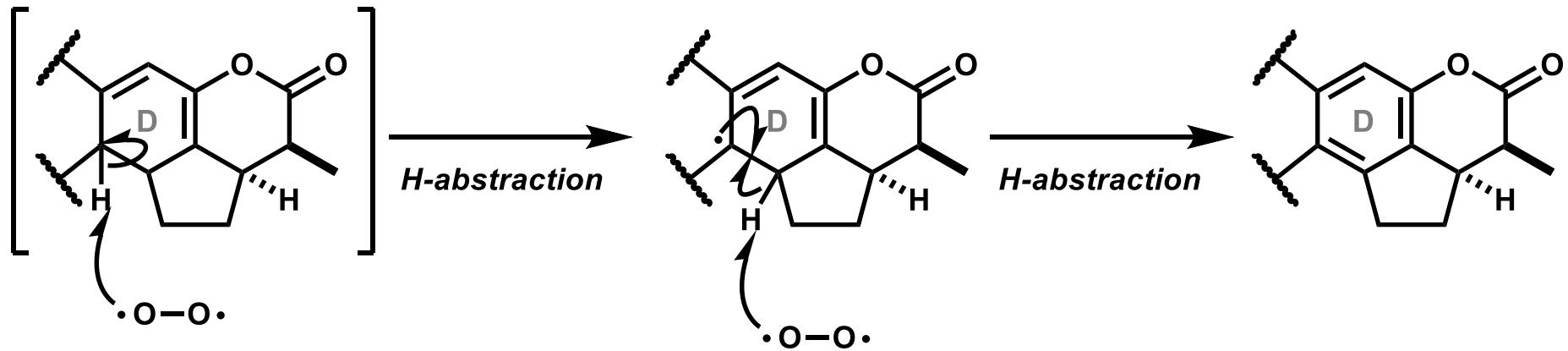
Appendix: Synthesis of EF-rings in Li's Study



Appendix: Proposed Mechanism of Pd-catalyzed Carboannulation



Appendix: Proposed Mechanism of Aromatization



Appendix: Pd-catalyzed Bromoendiyne Cyclization

