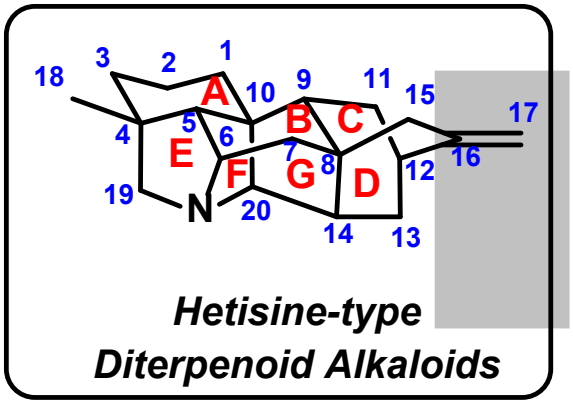
Synthesis towards Hetisine-type Diterpenoid Alkaloids

Fanrui Wu
College of Chemistry and Molecular Engineering
October 7th 2023

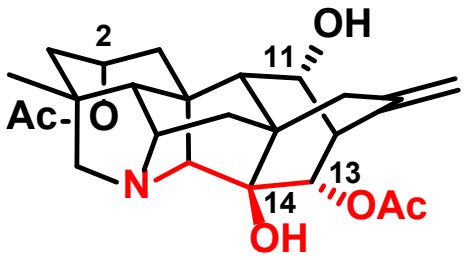
Outline

- Introduction
- Constructing G Ring First
- Constructing F Ring First
- Constructing F&G Ring Simultaneously
- Summary and Outlook

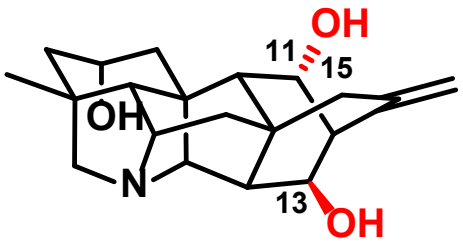
Hetisine-type C20-diterpenoid Alkaloids



Hetisine-type Diterpenoid Alkaloids

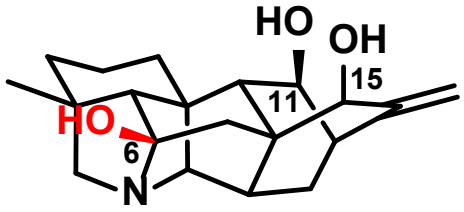


Guan-fu base A
antiarrhythmic
multi-ion channel blocker



Hetisine
antifeedant

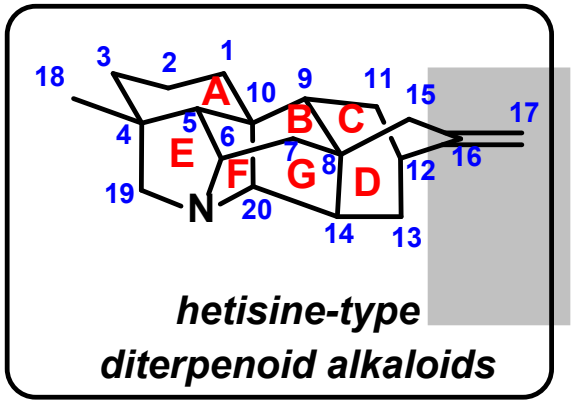
Mostly isolated from the genera *Aconitum* and *Delphinium* in the Ranunculaceae family



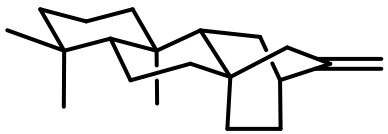
Pseudokobusine
antitumor
peripheral vasculature activities

Yin, T. *et al*. *RSC Adv*. **2021**,*11*, 36023.

Hetisine-type and its Related C20-DAs

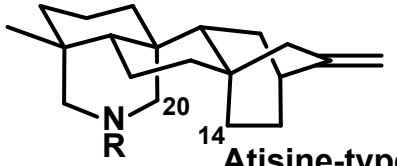


hetisine-type diterpenoid alkaloids



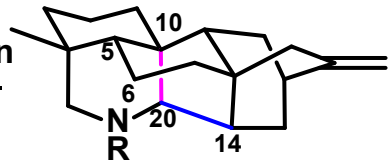
Atisane-type diterpenoids

amination



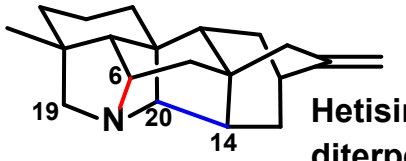
Atisine-type diterpenoid alkaloids

C20-C14 bond formation



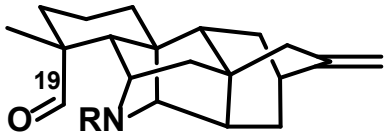
Hetidine-type diterpenoid alkaloids

N-C6 bond formation



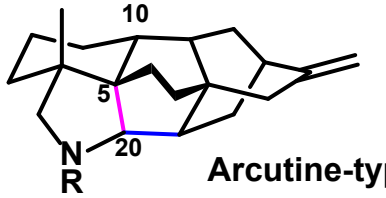
Hetisine-type diterpenoid alkaloids

N-C19 bond cleavage



Vakognavine-type diterpenoid alkaloids

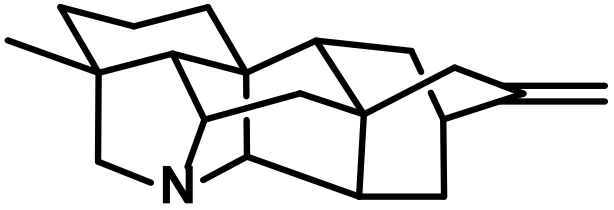
[1,2]-shift

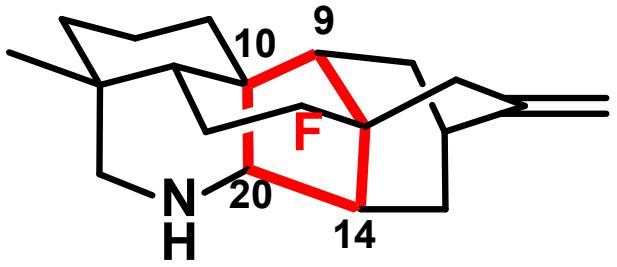


Arcutine-type diterpenoid alkaloids

Yin, T. *et al*. *RSC Adv*. **2021**,*11*, 36023.

Logic in Hetisine Synthesis

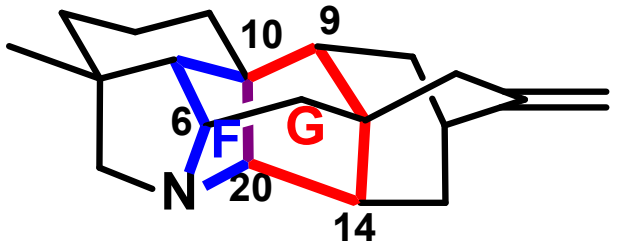




Highly congested cage-like polycyclic ring

Highly continuous bridged ring system:
2 × [3.3.1]; 1 × [2.2.2]; 1 × [2.2.1]
3 × [3.2.1]

Moderate strain



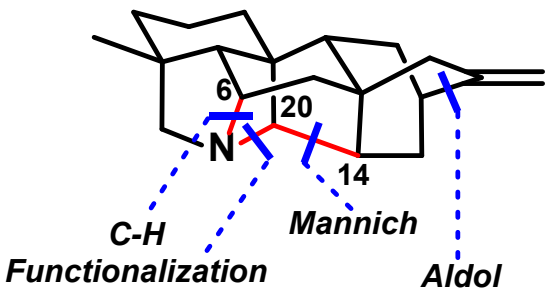
Bond-network analysis of the maximally bridged ring of the hetidine and hetisine skeleton

Doering, N. A. *et al*. *Angew. Chem., Int. Ed.* **2020**, *59*, 10722.

Outline

- Introduction
- **Constructing G Ring First**：Baran, Murakate and Ding
- **Constructing F Ring First**
- **Constructing F&G Ring Simultaneously**
- **Summary and Outlook**

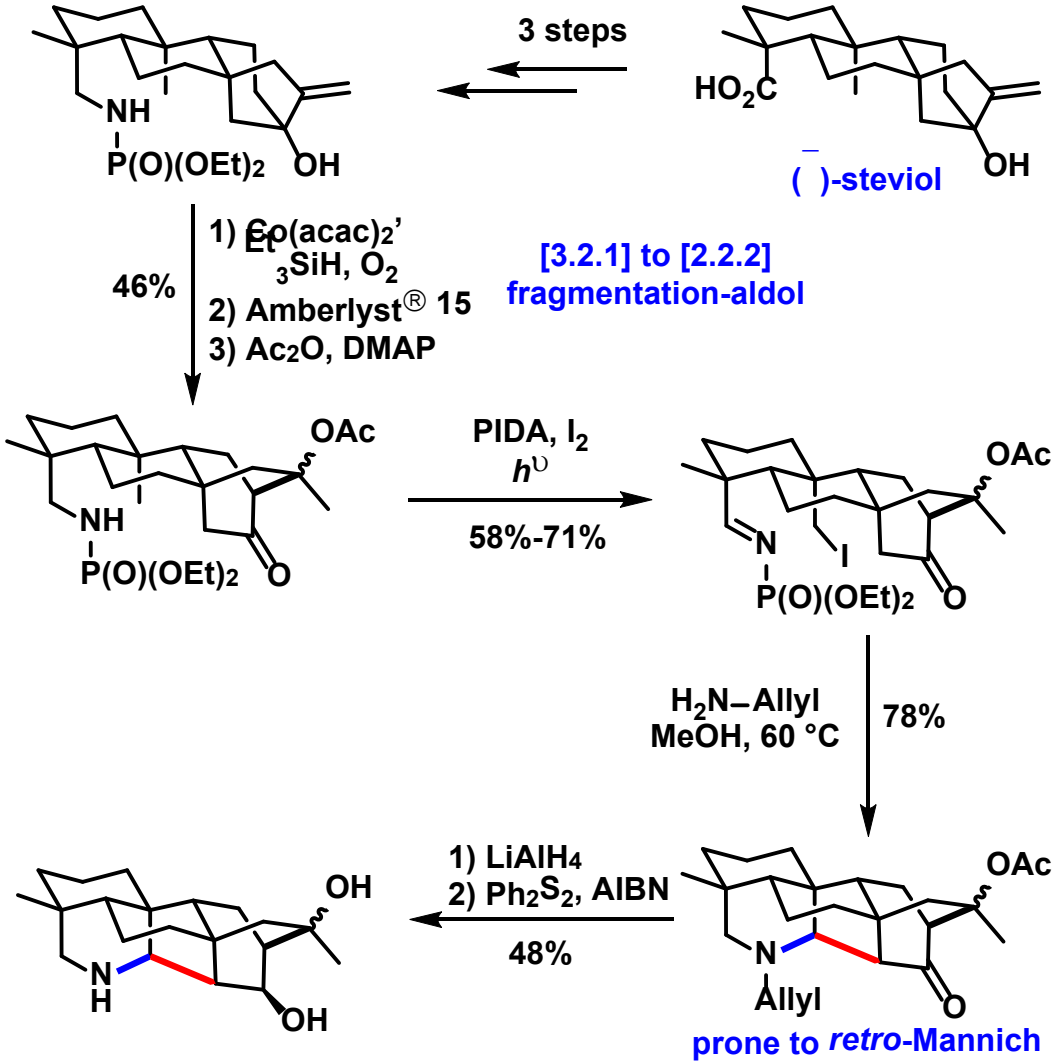
Baran(2014): From Hetidine to Hetisine



Atisine-Hetidine-Hetisine bond-by-bond construction

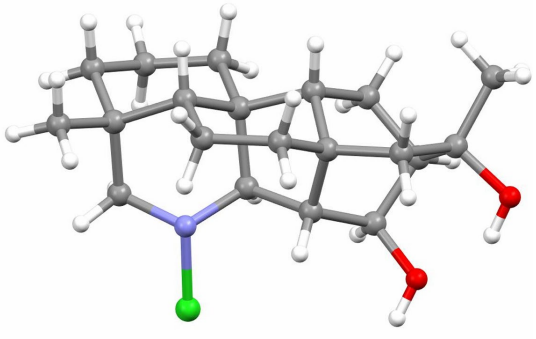
[3.2.1] to [2.2.2]

C-H fuctionalization for aza-[2.2.1]

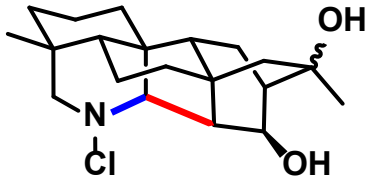


Cherney, E. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12592.

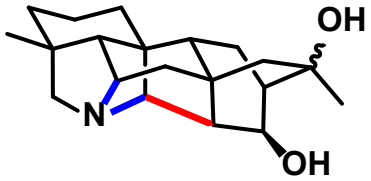
Construction N-C6 Bond: Failed



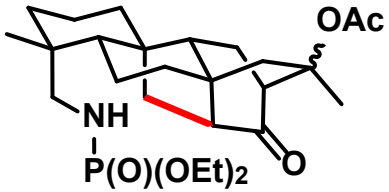
≡



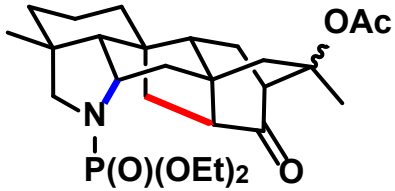
HLF
or Ag(I)
or NaOMe



Failed to get any chlorinated product

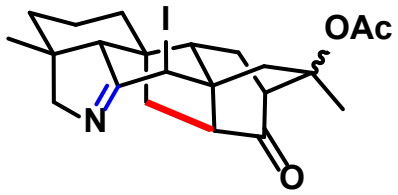


PIDA, I_2
$h\upsilon$

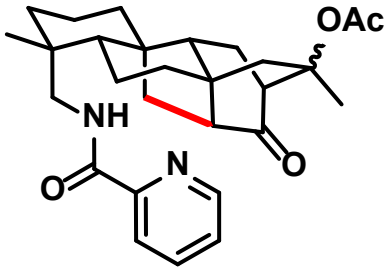


56%

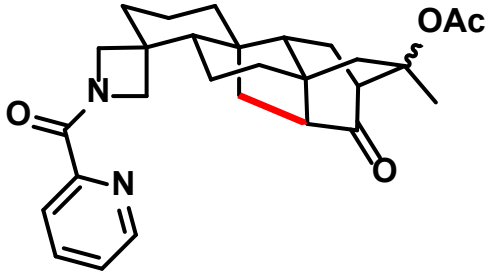
+



14%

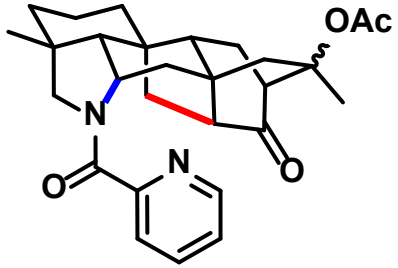


$Pd(OAc)_2$'
PIDA



60%

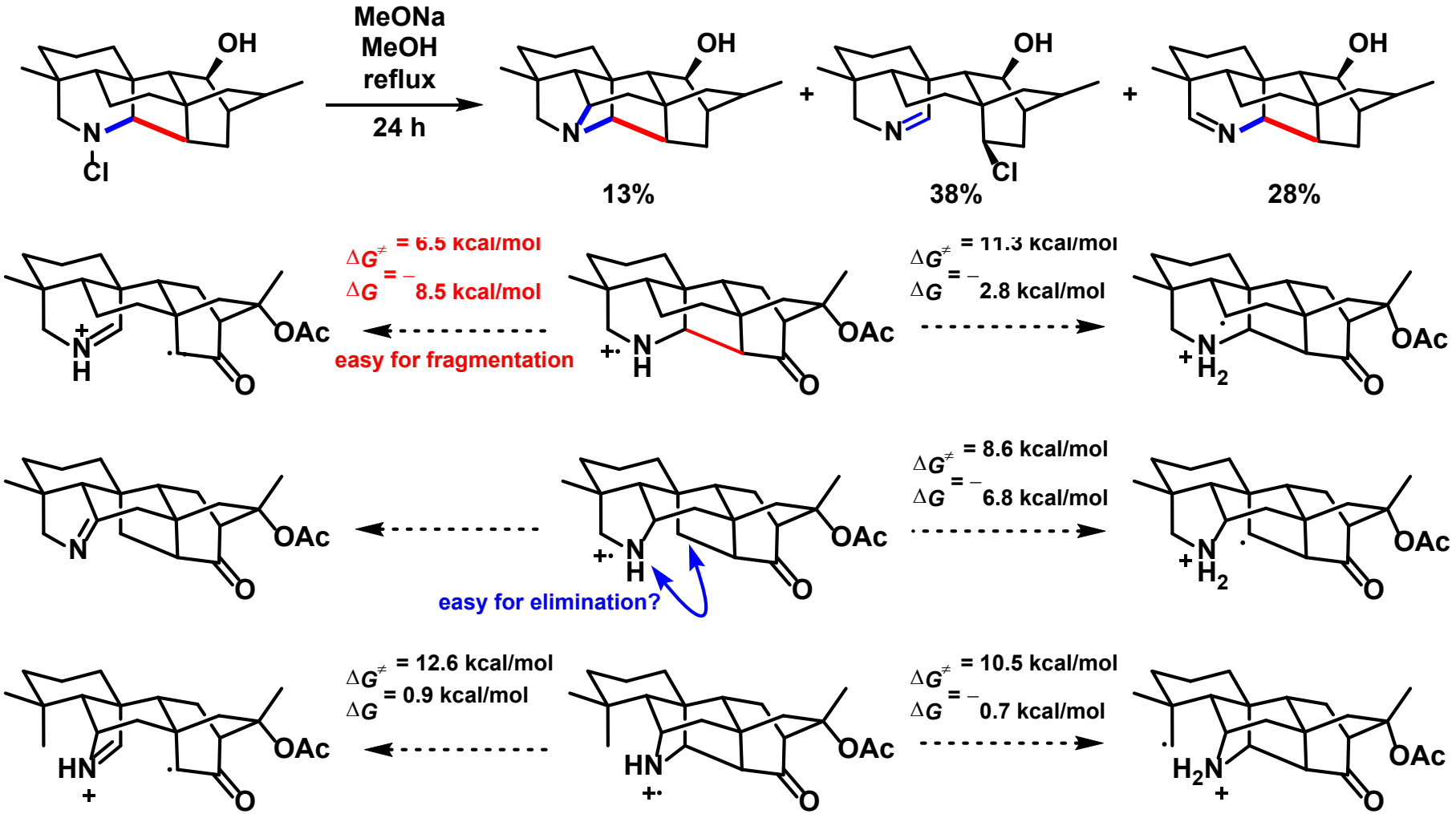
+



14%

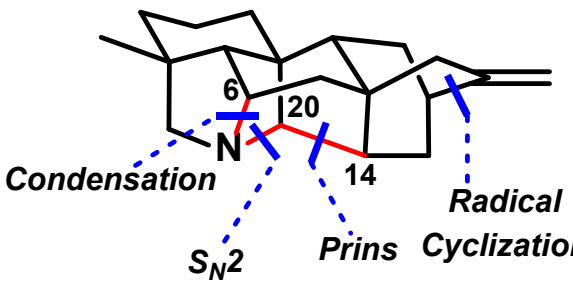
Cherney, E. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12592.

Late-stage C-H Activation: Too Strained?



Yatsunami, T. *et al. Chem. Pharm. Bull*. **1975**, 3030.

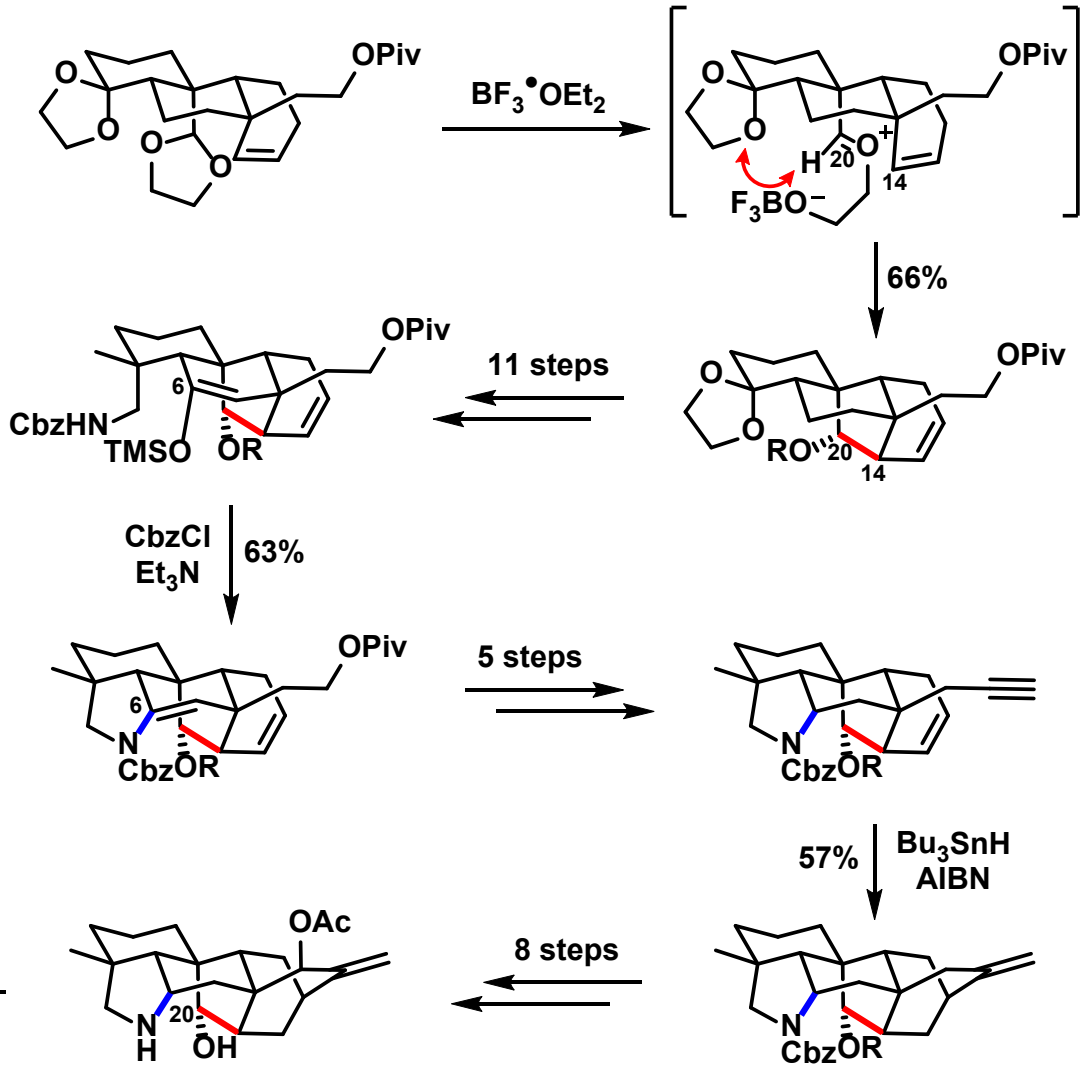
Muratake&Natsume(2004): Prins



Construct G ring early

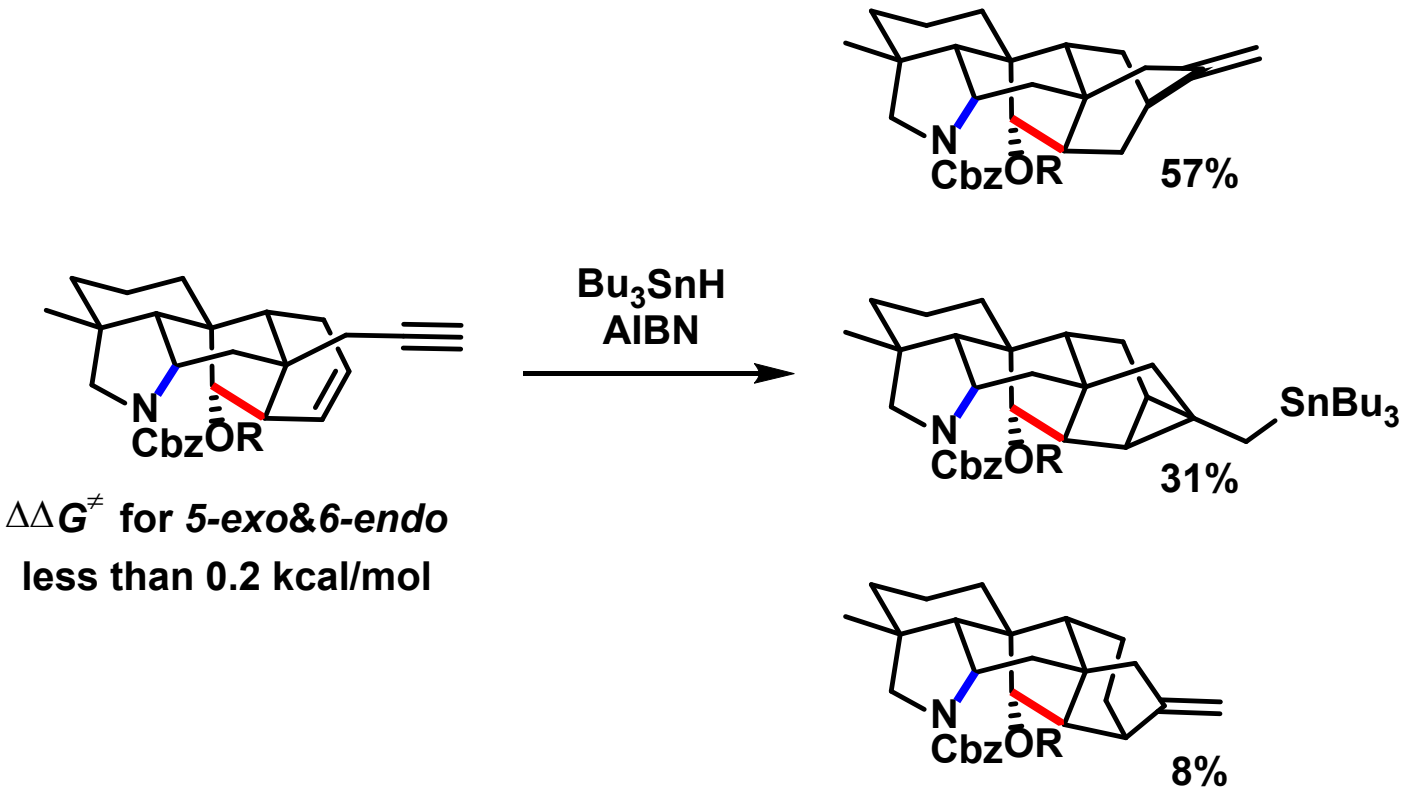
Radical cyclization for [2.2.2]: 1 bond disconnection

S_N2 for aza-[2.2.1]



Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4646.

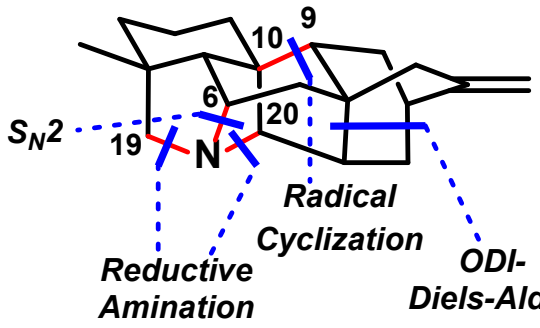
Radical Cyclization: C-H Principle



$\Delta\Delta G^{\neq}$ for *5-exo*&*6-endo*
less than 0.2 kcal/mol

Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4646.

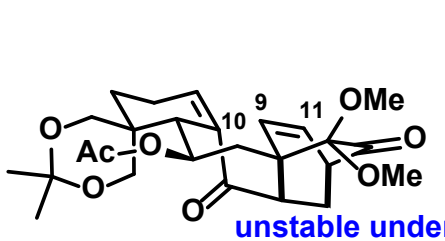
Ding(2021): C9-C10 Disconnection



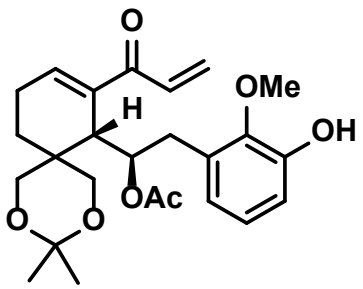
C9-C10 disconnection

ODI-DA for [2.2.2]:
2 bond disconnection

Late-stage introduction of N-atom



$PhI(OAc)_2$
MeOH
72%

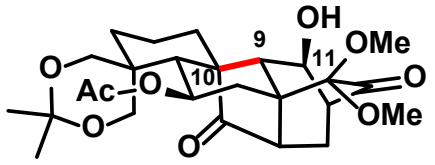


unstable under various epoxidation conditions

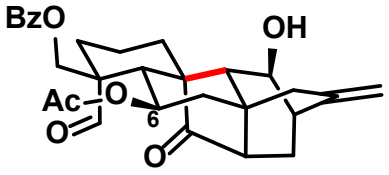
$Co(acac)_2$'
TMDSO
O_2, 4A MS

83%

Forming G ring and oxidation state at C11 simultaneously

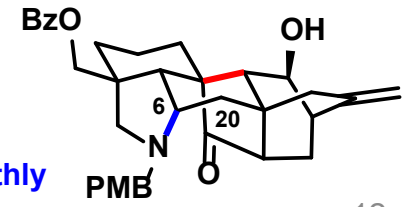


4 steps



$PMBNH_2$, AcOH, DCE
then $NaBH_4$, $NaCO_3$
N-C6 formed smmothly

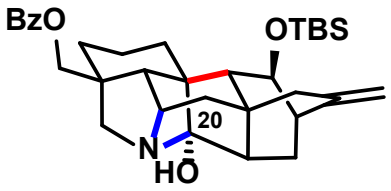
85%



TBSOTf, Et_3N
then DDQ

55%

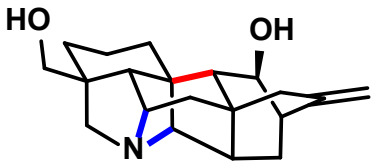
N-C20 formed smoothly



1) TCDI, DMAP
2) AIBN, Bu_3SnH
then TFA

3) K_2CO_3, MeOH

46%

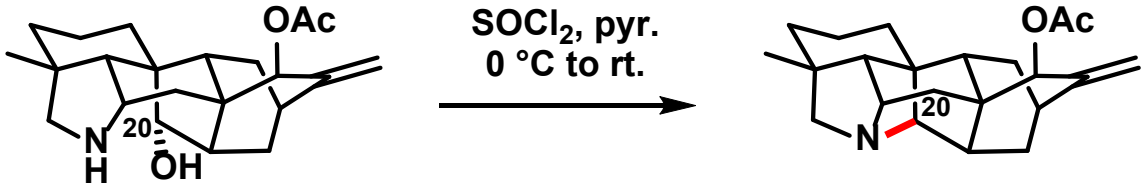


Davisinol

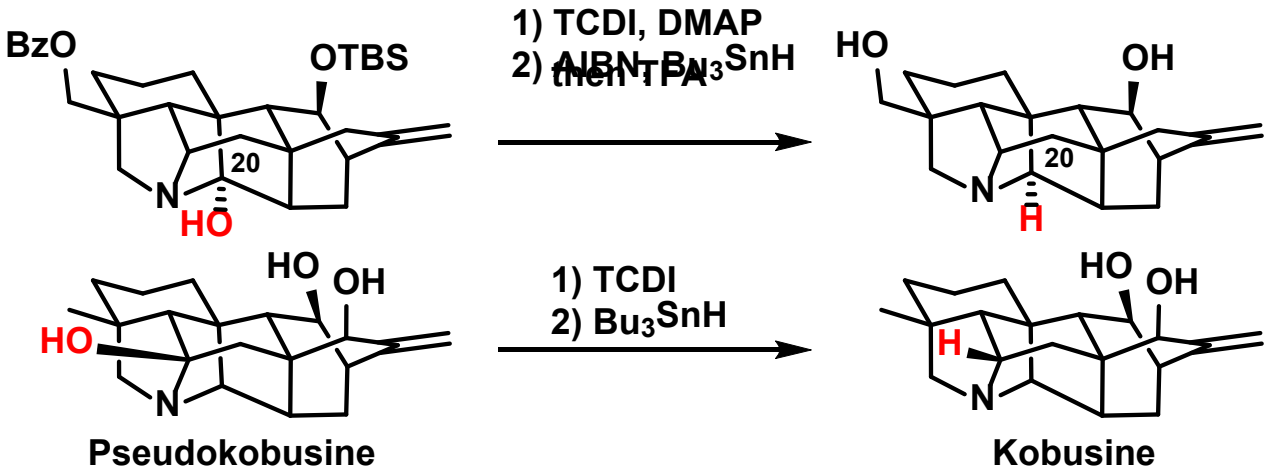
Yu, K. *et al*. *J. Am. Chem. Soc.* **2021**, *143*, 10576.

Brief Summary: F Ring Construction

- Mild S_N2: moderate strain, prone to close



- Closure-Barton deoxygenation strategy



- C-H functionalization: hard

Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4646.

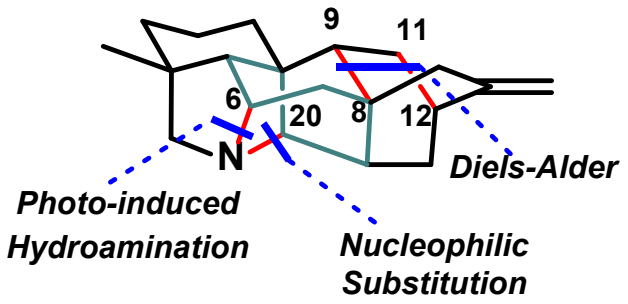
Yu, K. *et al*. *J. Am. Chem. Soc.* **2021**, *143*, 10576.

Koji, W. *et al*. *Heterocycles.* **1991**, *32*, 1297.

Outline

- Introduction
- Constructing G Ring First
- **Constructing F Ring First:** Sarpong and Gin
- **Constructing F&G Ring Simultaneously**
- **Summary and Outlook**

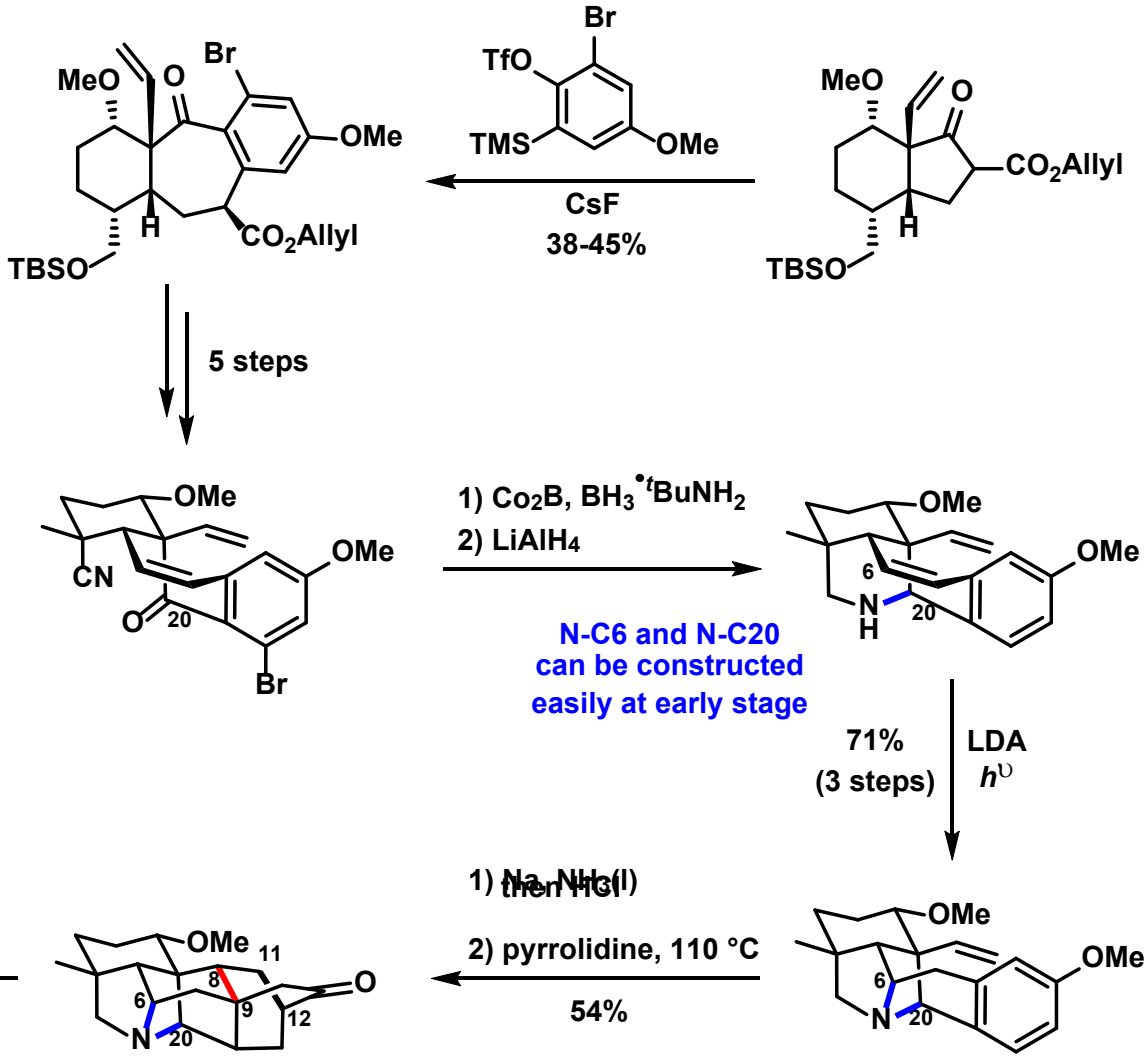
Sarpong(2018): 7-membered Ring as Linker



7-membered ring as linker

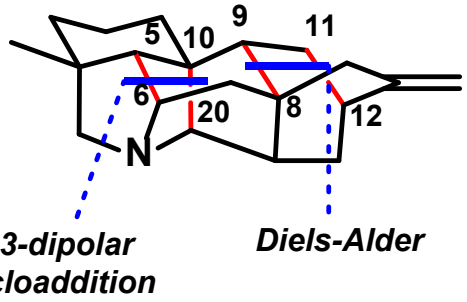
DA for [2.2.2]: 2 bond disconnection

Bond-by-bond construction of the aza[2.2.1]



Kou, K. G. M. *et al. J. Am. Chem. Soc.* **2018**, *140*, 8105.

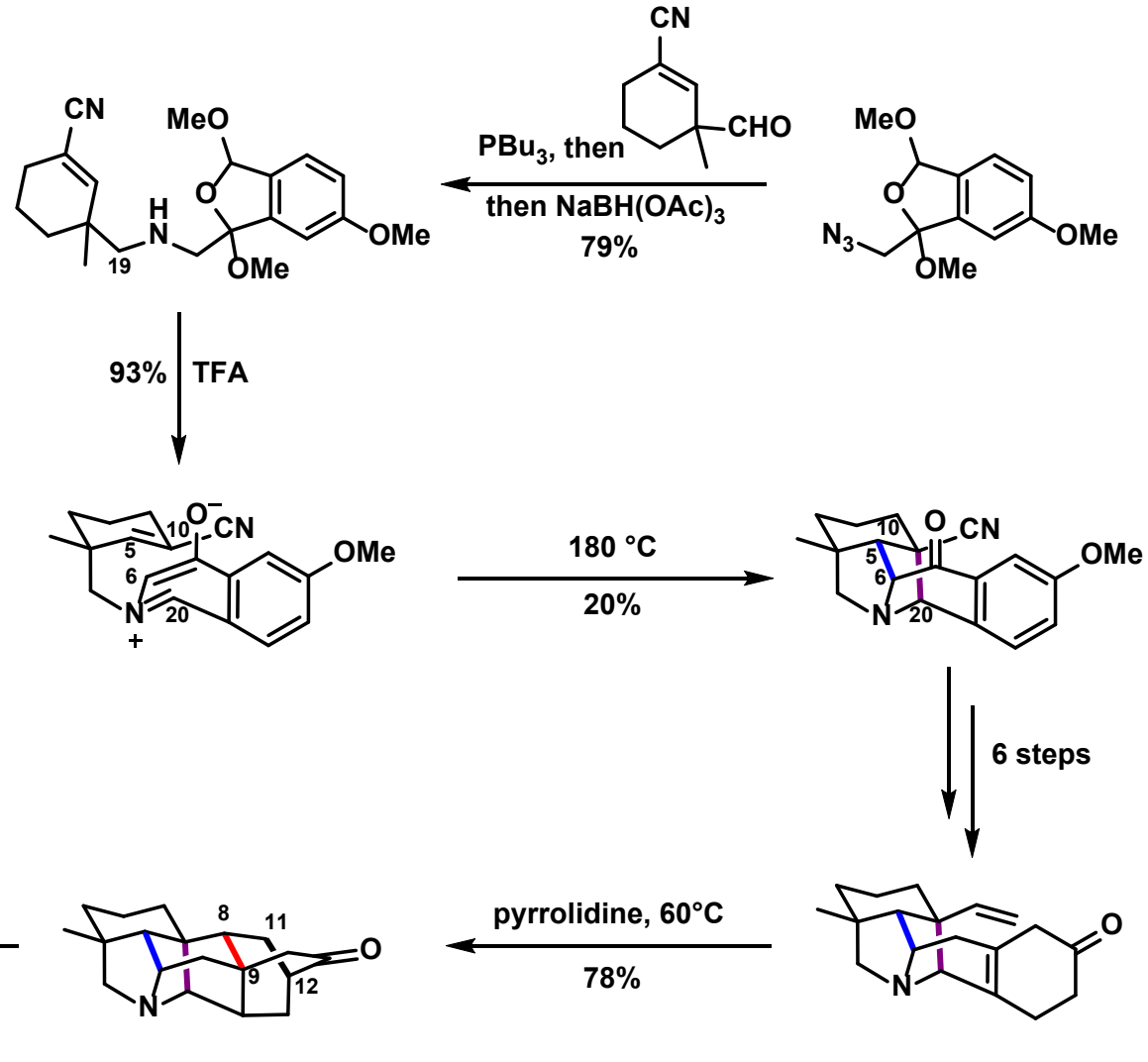
Gin(2006): Convergent Dual Cycloaddition



convergent synthesis

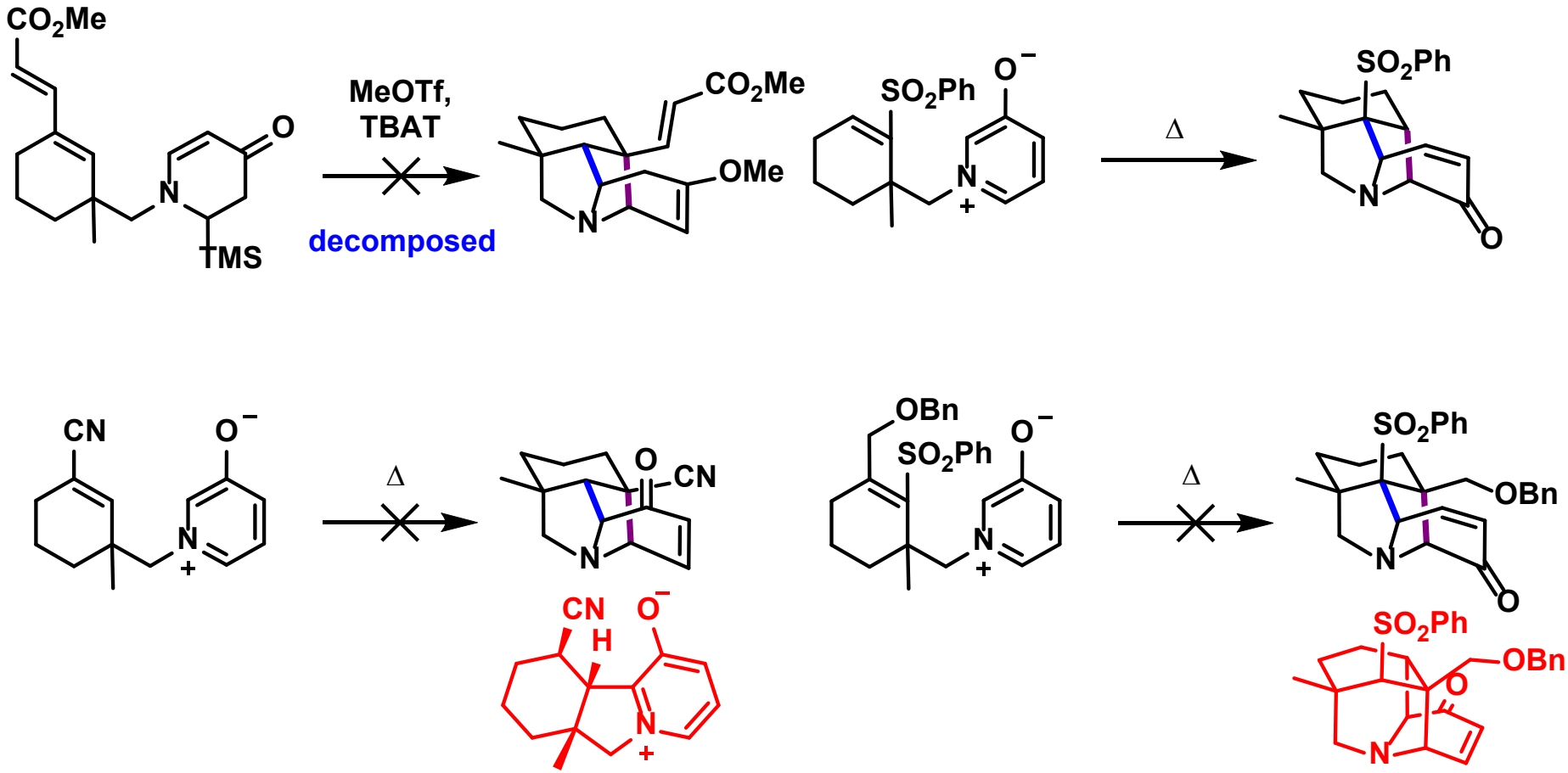
DA for [2.2.2]: 2 bond disconnection

constructing the aza[2.2.1] in one step: N as linker



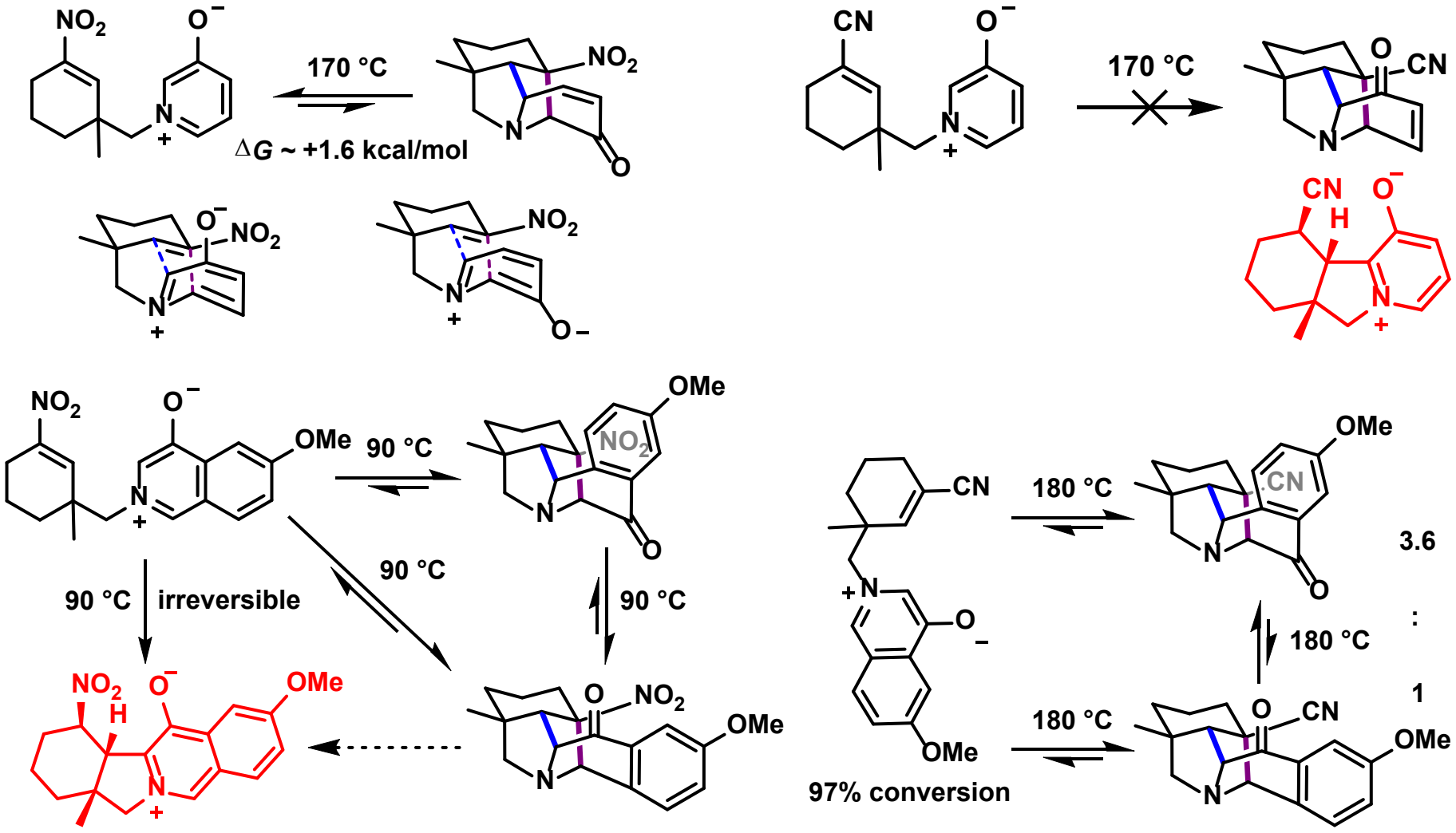
Peese, K. M.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 8734.

1,3-Dipolar Cycloaddition



Peese, K. M.; Gin, D. Y. *Chem. Eur. J.* **2008**, *14*, 1654.

Thermodynamic Solution

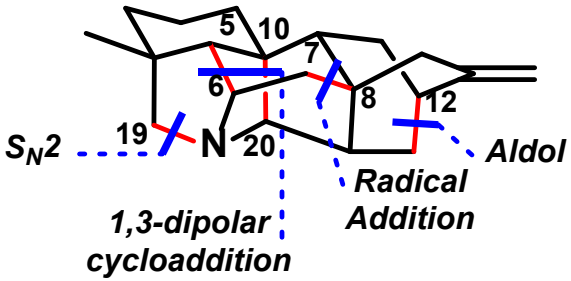


Peese, K. M.; Gin, D. Y. *Chem. Eur. J.* **2008**, *14*, 1654.

Outline

- Introduction
- Constructing G Ring First
- Constructing F Ring First
- **Constructing F&G Ring Simultaneously:** Zhang
- **Summary and Outlook**

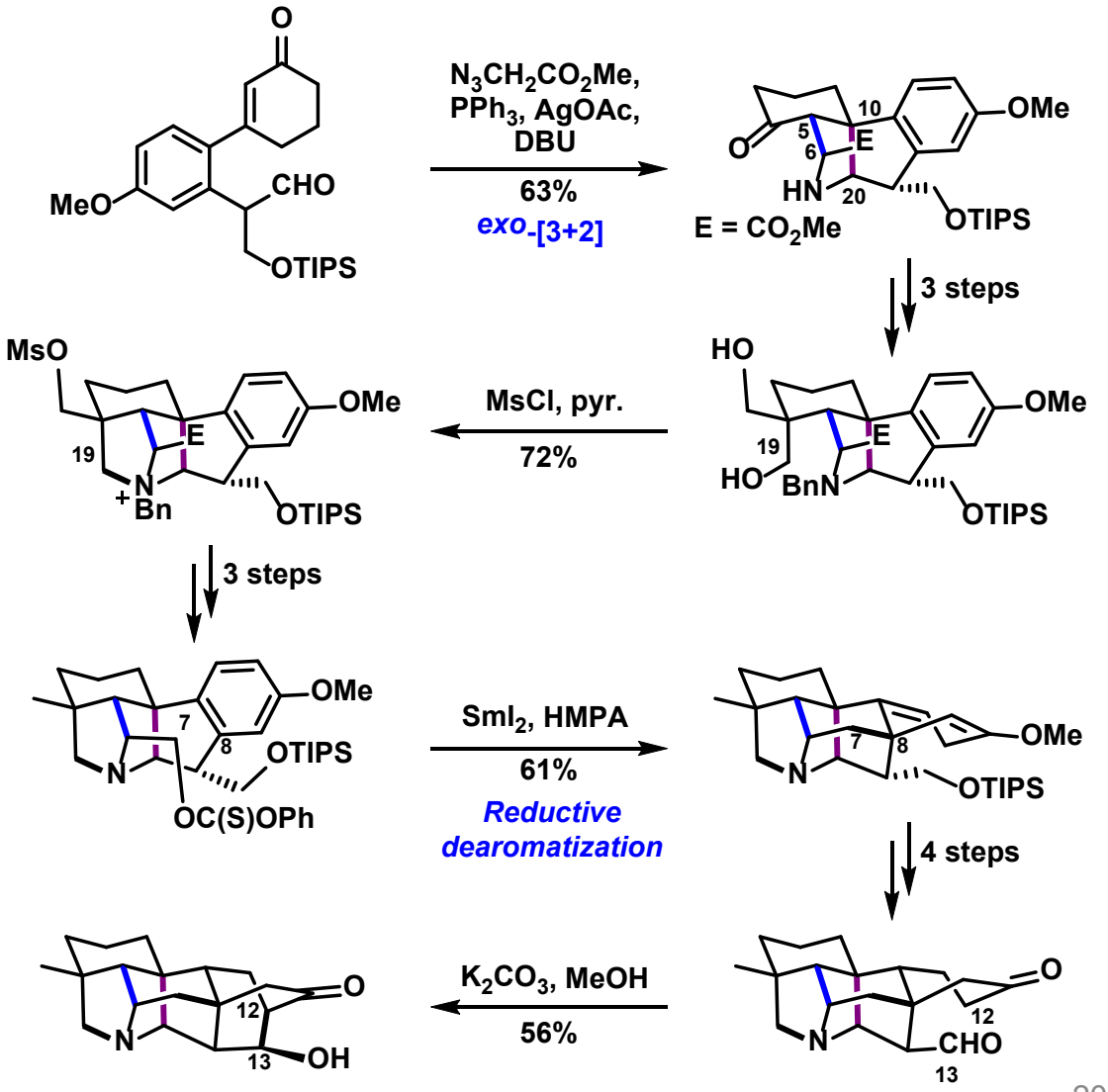
Zhang(2018): C7-C8 Disconnection



B ring disconnection

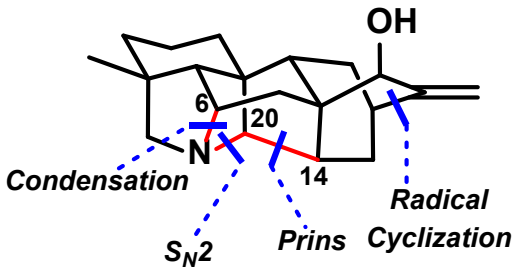
Aldol for [2.2.2]: 1 bond disconnection

Aza[2.2.1] : N-C19 disconnection

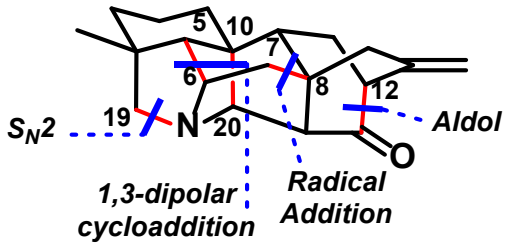


Zhang, Q. *et al*. *Angew. Chem., Int. Ed.* **2018**, *57*, 937.

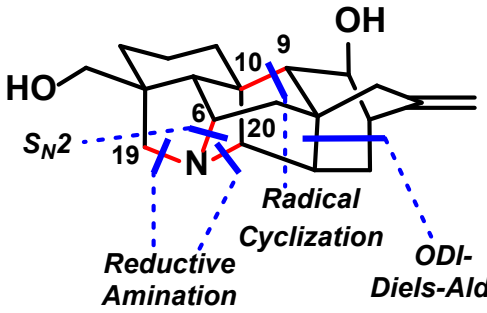
Summary



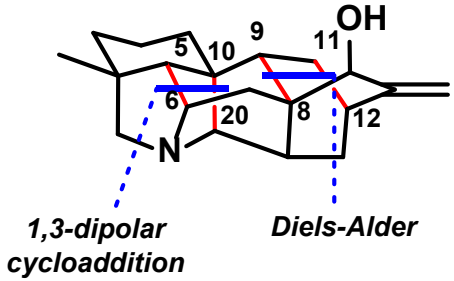
Nominine
Muratake&Natsume(2004)
40 steps



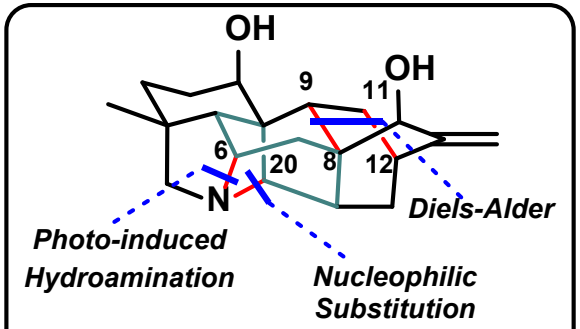
Spirasine IV
Zhang(2018)
22 steps



Davisinol
Ding(2021)
17 steps



Nominine
Gin(2006)
16 steps

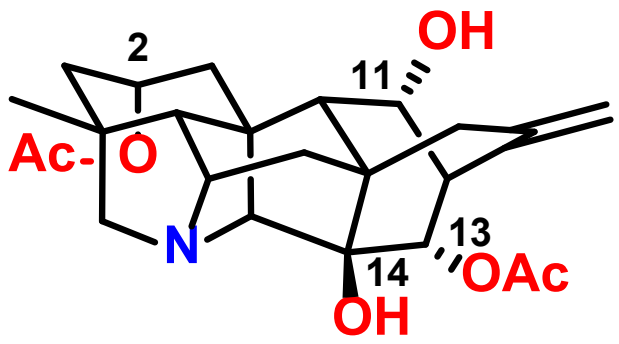


Cossonidine
Sarpong(2018)
21 steps

Outlook: Oxidation Level

Awkward position for higher oxidation state:

Synergy between skeleton and oxidation degree



Guan-fu base A

- **1,2-diol and 1,3-diol:**

  Easy for fragmentation

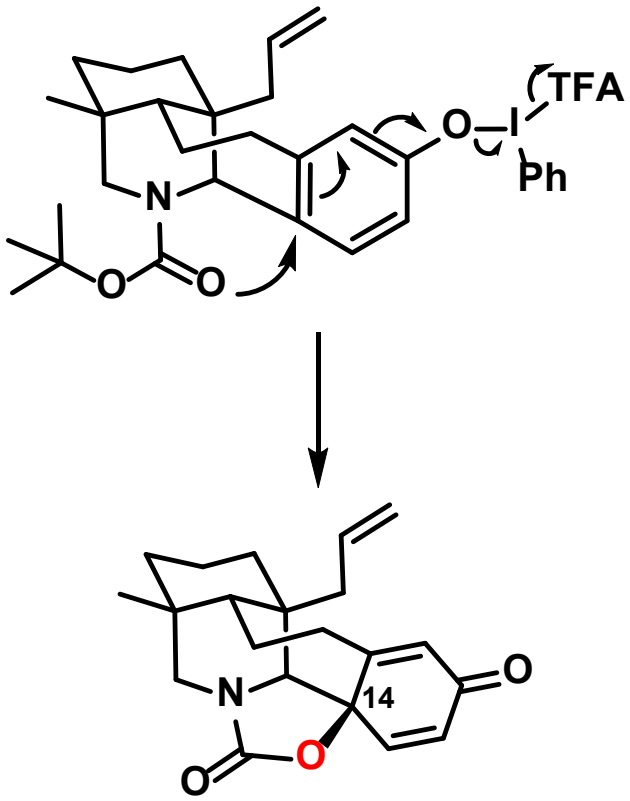
- **Bridgehead and relative separate -OH:**

  Call for convergent synthesis?

Outlook: Oxidation Level

Awkward position for higher oxidation state:

Synergy between skeleton and oxidation degree



- **1,2-diol and 1,3-diol:**

  Easy for fragmentation

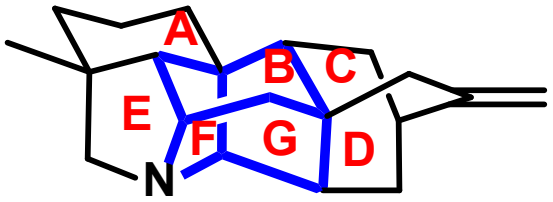
- **Bridgehead and relative separate -OH:**

  Call for convergent synthesis?

Hamlin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4854.

Outlook: Convergent Synthesis

- Highly continuous bridged-ring system



- BFG cage-like ring as the joint:

  How to design and connect

  fragments?

- Integral strain