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Total Synthesis of the Daphniphyllum Alkaloids

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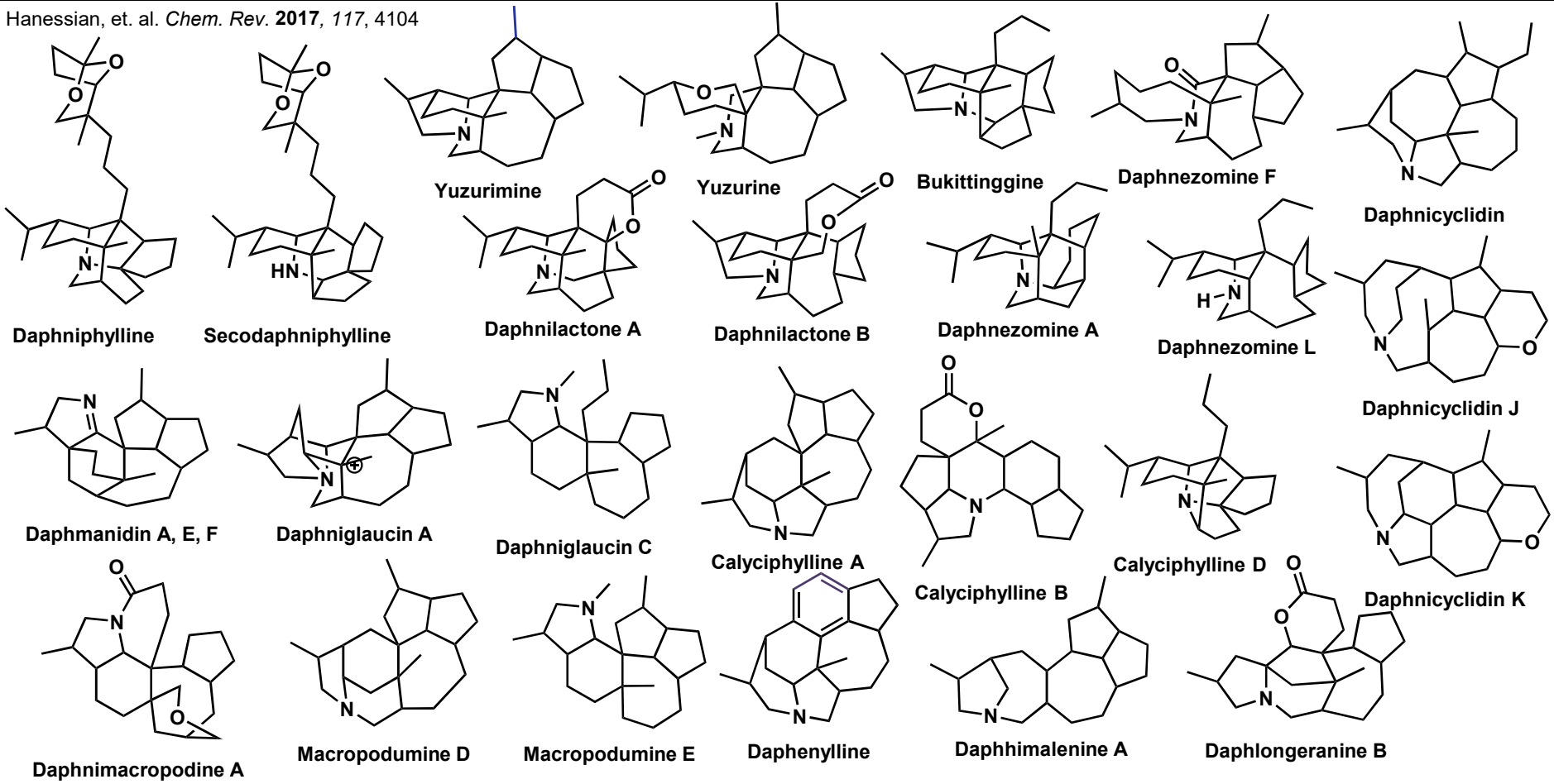
Hanessian, et. al. *Chem. Rev.* **2017**, *117*, 4104



Quick Facts

- **The Daphniphyllum Alkaloids consist of > 300 members with rich structural diversity**
- **Squalene derived**

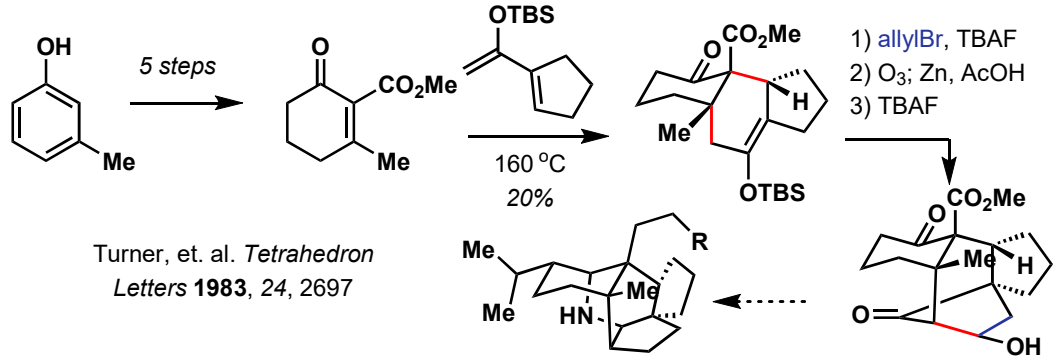
Topic for today:

- **Early synthetic studies**
- **Heathcock's Campaign**
- **Modern syntheses & synthetic studies**

Resources:

Biosynthesis: Kubota, et. al. *Natural Product Reports* **2009**, *26*, 936
Bioactivity: Xu, et. al. *Planta Med* **2013**, *79*, 1589

Early Synthetic Studies: Orban & Turner's DA approach towards secodaphniphylline (1983)



Turner, et. al. *Tetrahedron Letters* **1983**, *24*, 2697

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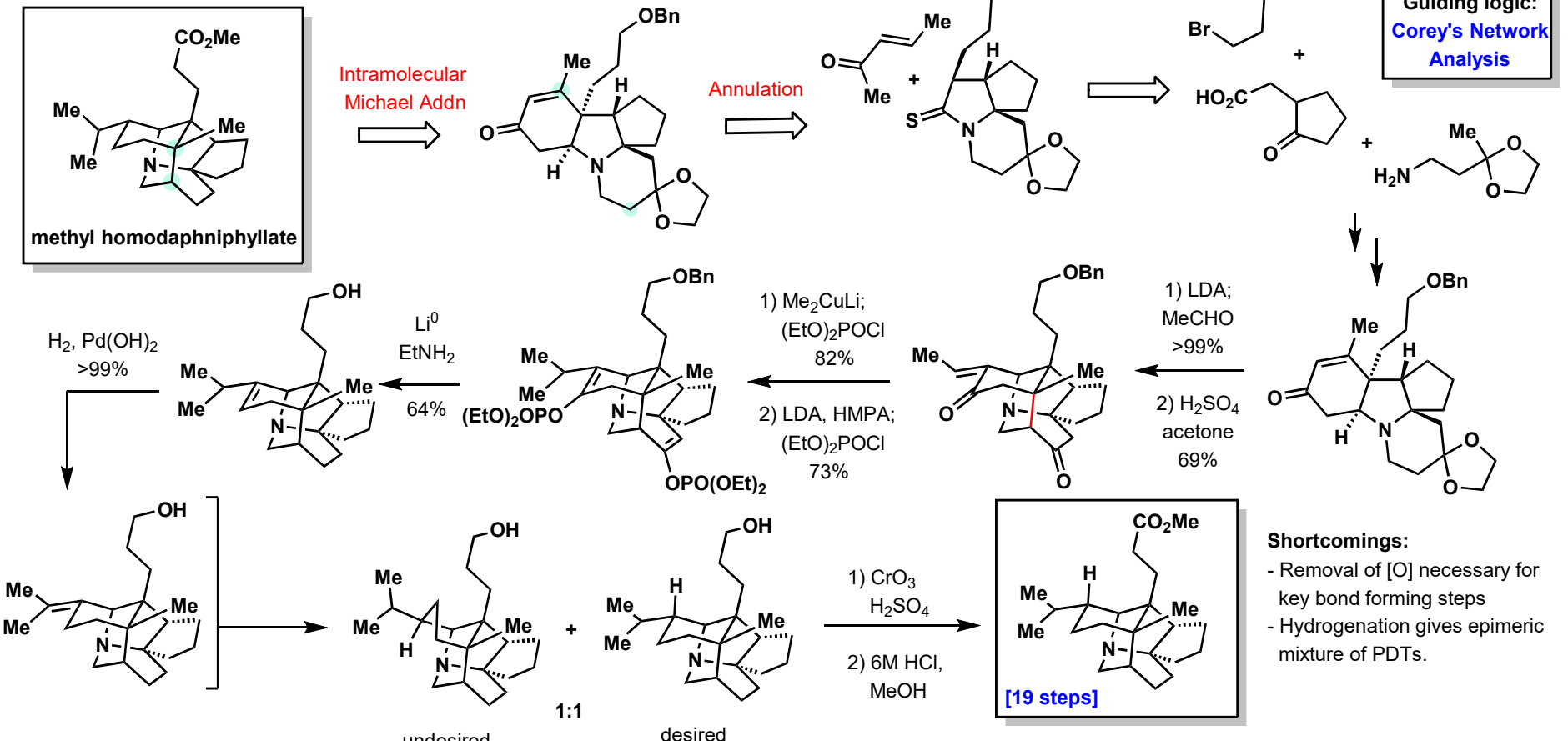
Heathcock's first synthesis of methyl homodaphniphyllate (1986)



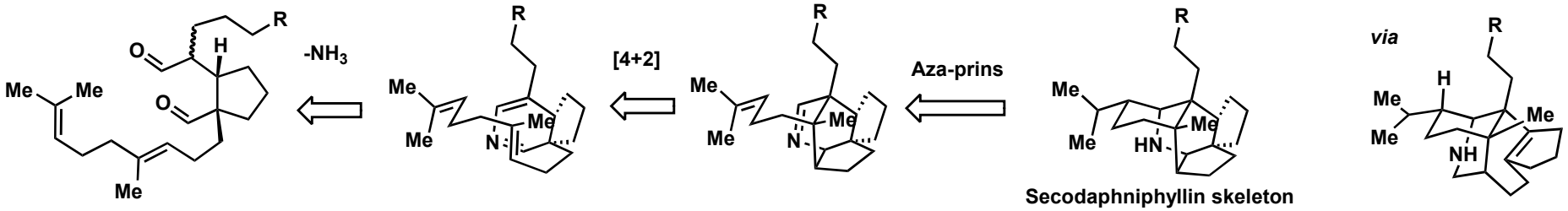
Shortcomings:

- Removal of [O] necessary for key bond forming steps
- Hydrogenation gives epimeric mixture of PDTs.

Heathcock, et. al. *JACS* **1986**, *108*, 5650

Biomimetic Retrosynthesis

New synthetic strategy?



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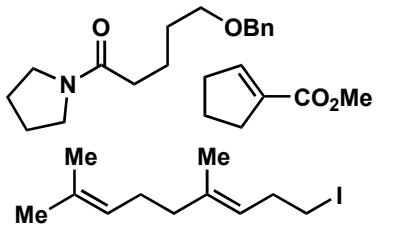
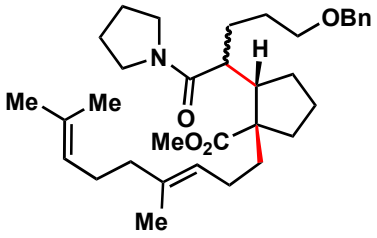
Heathcock's Biomimetic Approaches

Heathcock, et. al. *JACS* **1988**, *110*, 8734



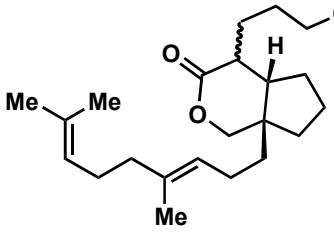
LDA

87%



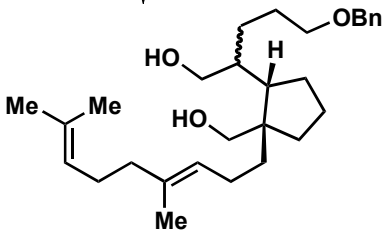
1) DIBAL
2) NaOH, H_2O
EtOH, 95°C

80%



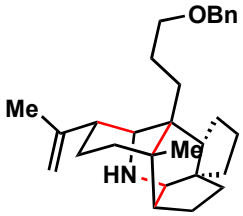
$LiAlH_4$

96%



1) $(COCl)_2$, DMSO
Et_3N, DCM

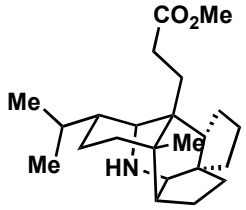
2) NH_3; AcOH
77% over 2 steps



1) H_2, Pd/C, HCl
2) CrO_3, H_2SO_4

3) MeOH, H_2SO_4
85% over 3 steps

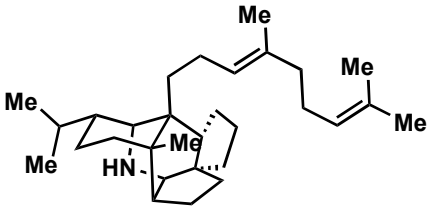
[9 steps from iodide]



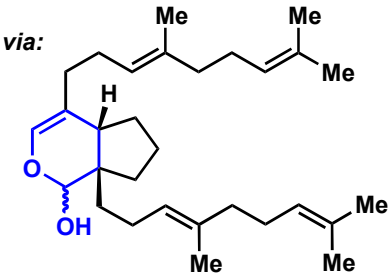
(rac)-Methyl Homosecodaphniphyllate

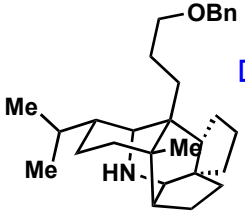
1) H_2SO_4
2) O_3, -78°C

3) CrO_3
4) MeOH, H_2SO_4
67%



via:



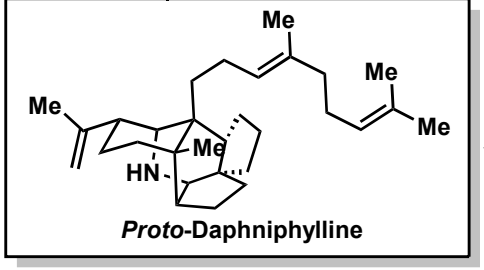


[Mechanism?]

1) $(COCl)_2$, DMSO
Et_3N, DCM
2) **$MeNH_2$**
3) AcOH, NH_4OAc
85°C
75% over 3 steps

A happy accident Heathcock, et. al. *ACIE* **1992**, *31*, 665

$(PPh_3)_3RhCl$
H_2
88%

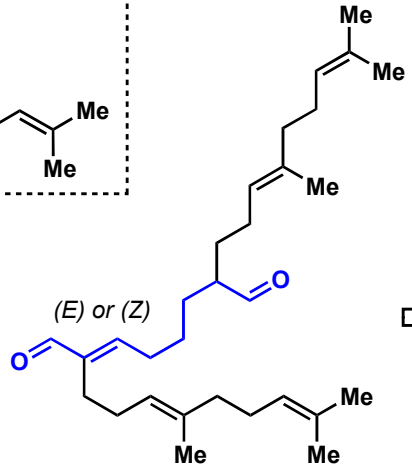


***Proto*-Daphniphylline**

[10 steps]

1) KOH, $TBA(HSO_4)$
2) NH_3, NH_4OAc
DMSO, 80°C

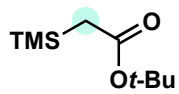
3) HOAc, 80°C
50% over 3 steps



(E) or (Z)

Works equally well with other geometric isomer

Access to *(Z)* through:



then Peterson olefination
(E/Z = 3:7)

Heathcock, et. al. *Science* **1990**, *248*, 1532

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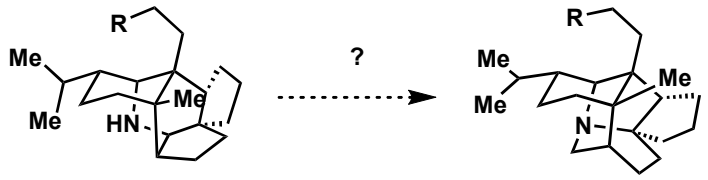
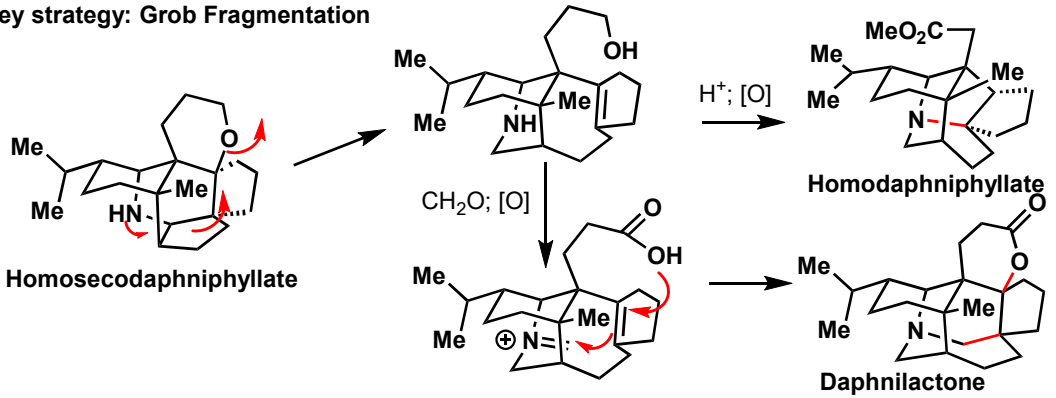
Heathcock's Biomimetic Approach Cont: Skeletal Converions

Addressing the original synthetic question:

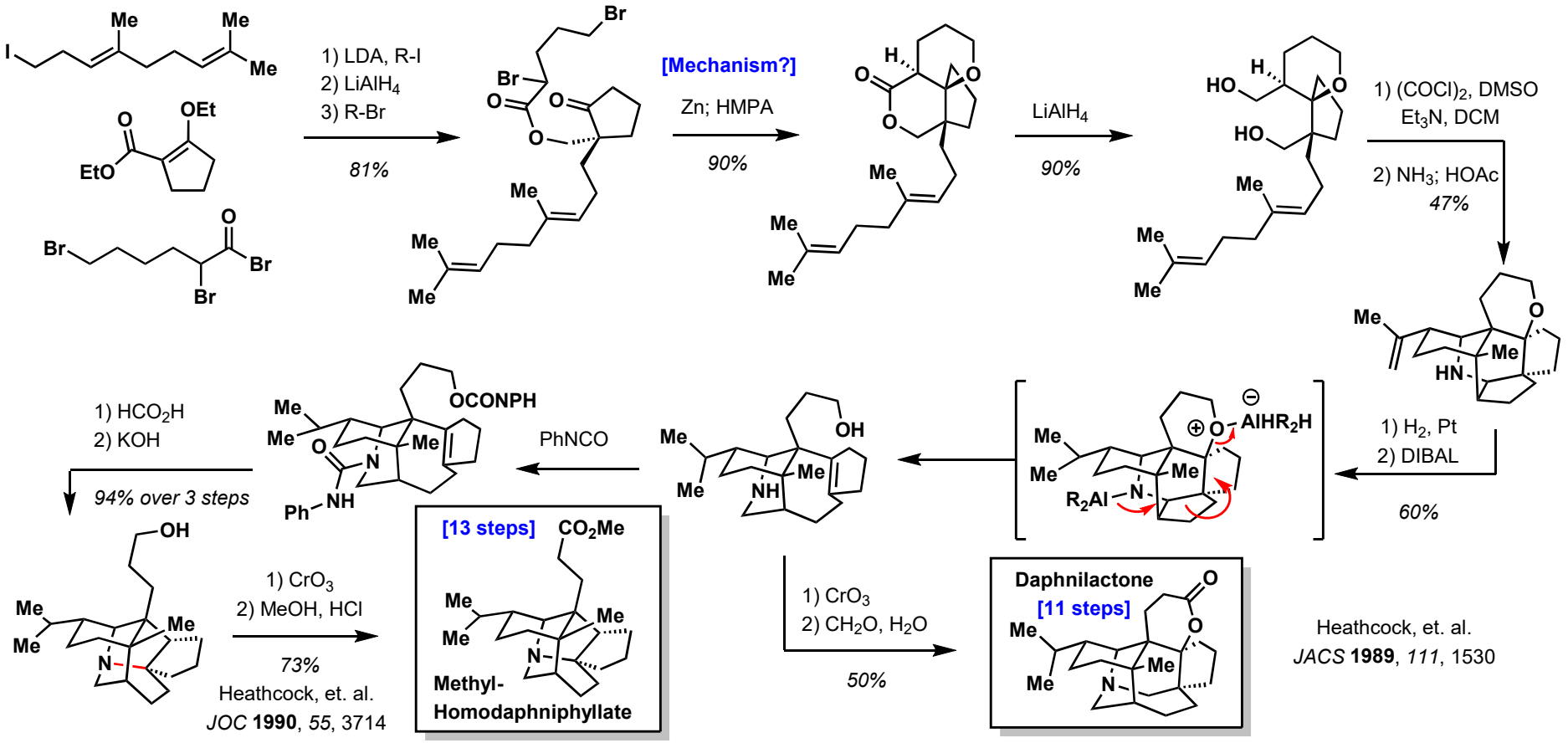


Homosecodaphniphyllate — Homodaphniphyllate

Key strategy: Grob Fragmentation



Total Synthesis of Daphnilactone & Homodaphniphyllate



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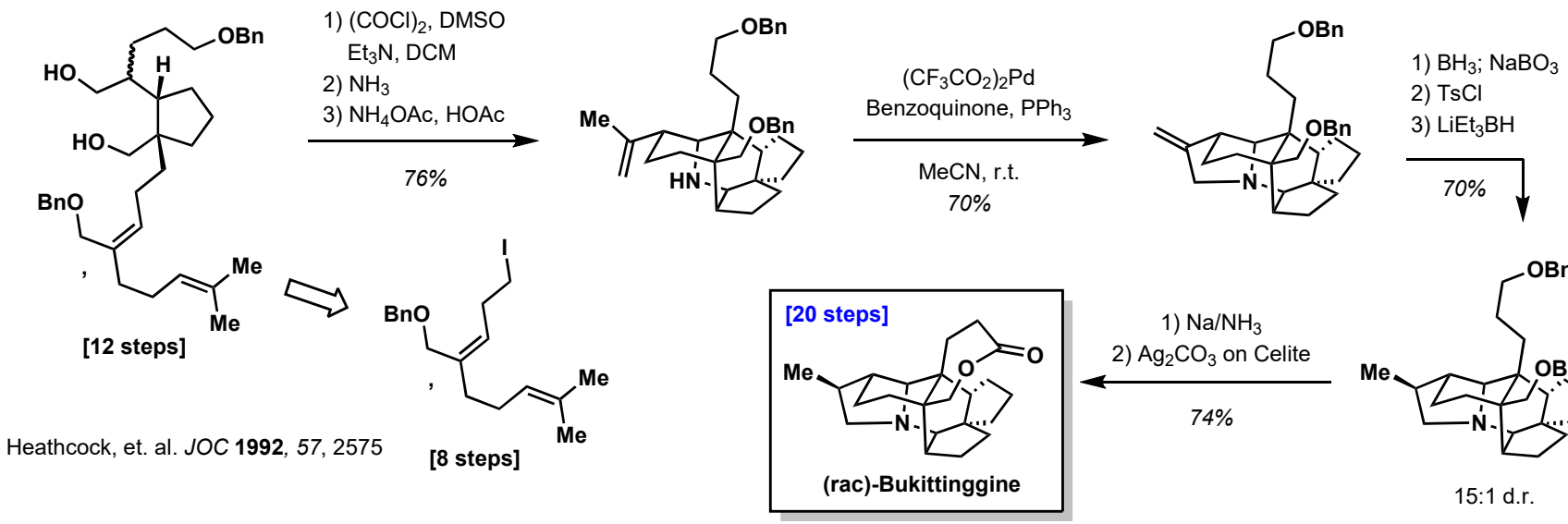
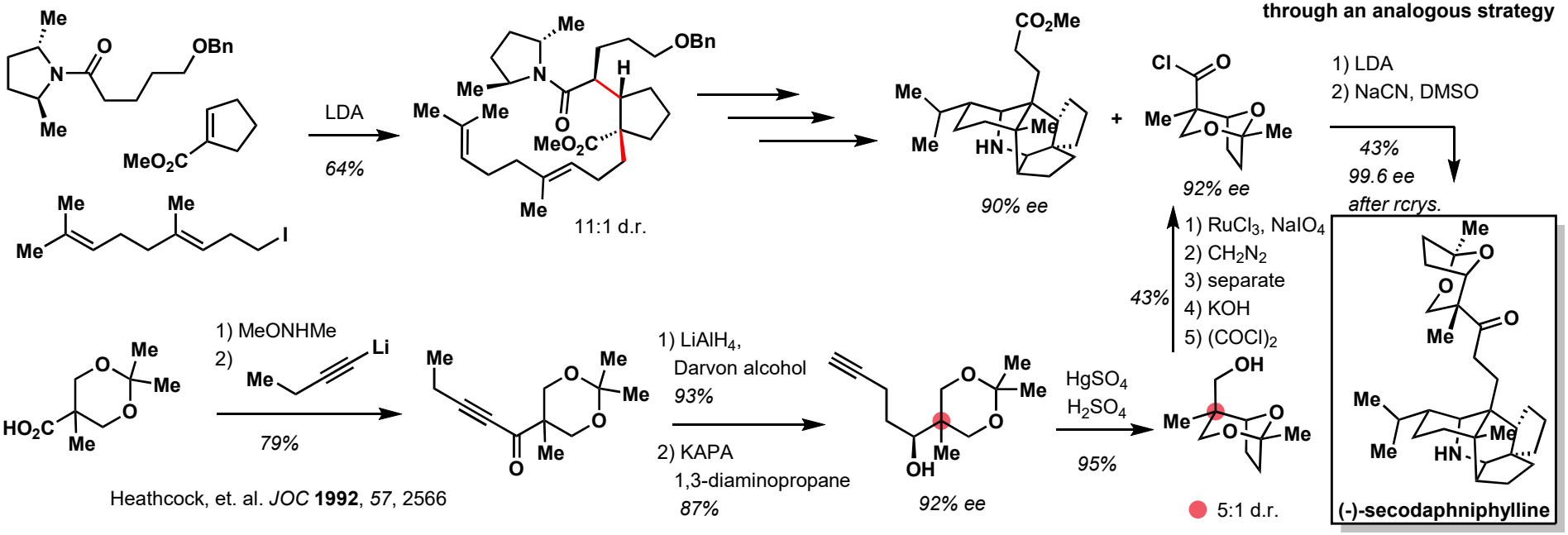
Heathcock's synthesis of (rac)-Bukittinggine



Heathcock, et. al. *JOC* **1992**, *57*, 2575

Heathcock's asymmetric synthesis of (-)-secodaphniphylline



Heathcock, et. al. *JOC* **1992**, *57*, 2566

(+)-Codapnhiphylline synthesized through an analogous strategy

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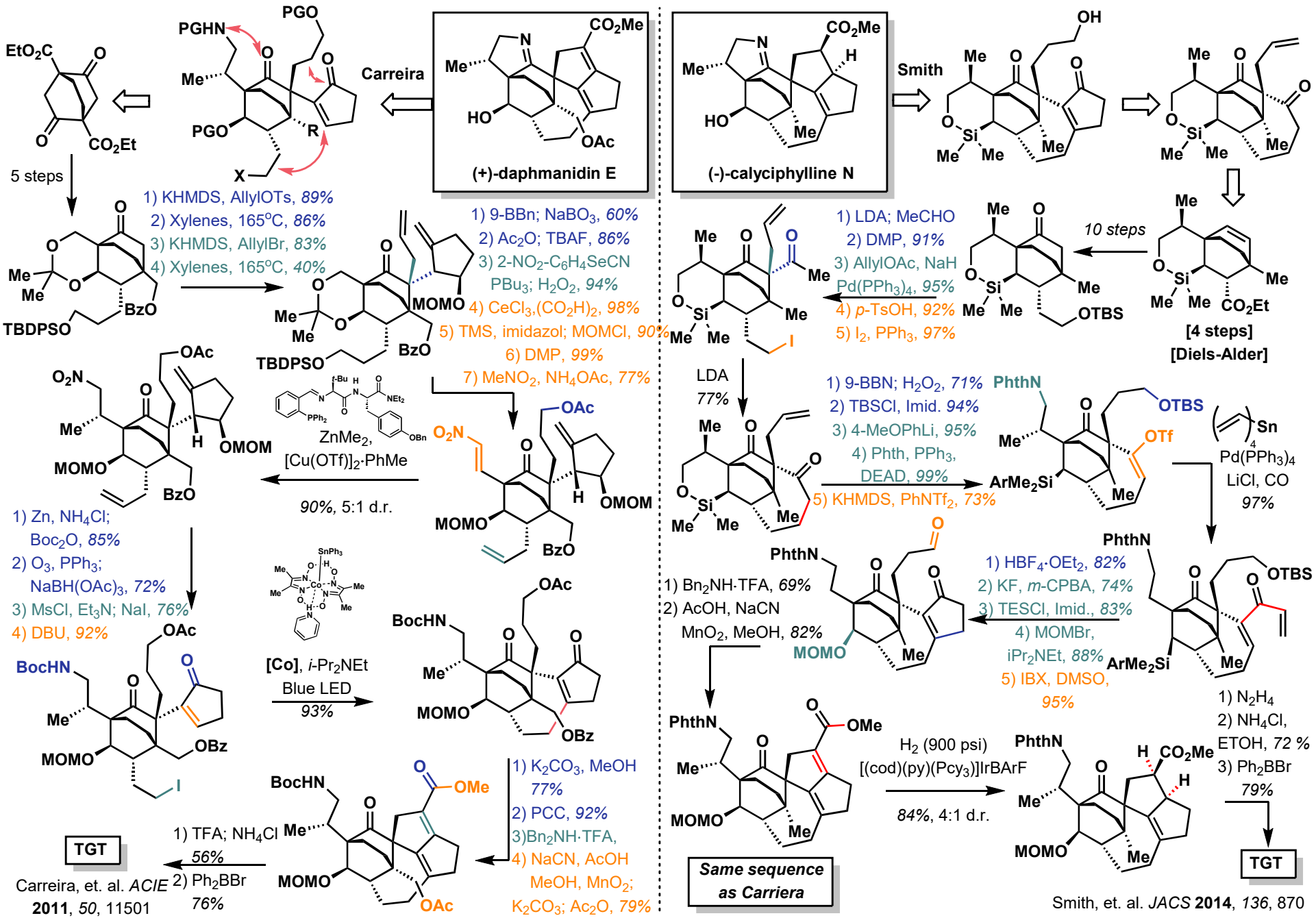

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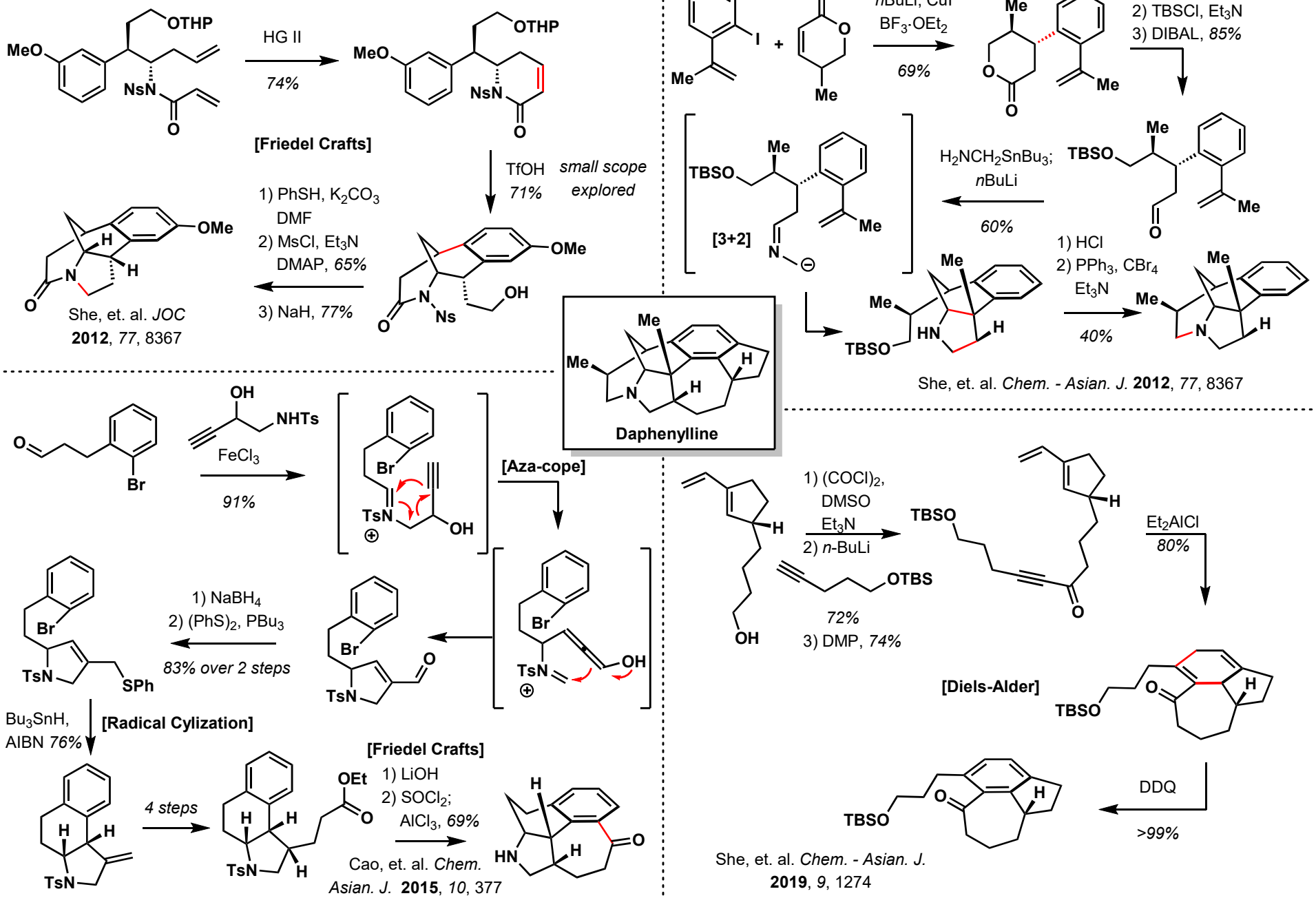
Highlights of Synthetic Studies Towards Daphenylline Alkaloids



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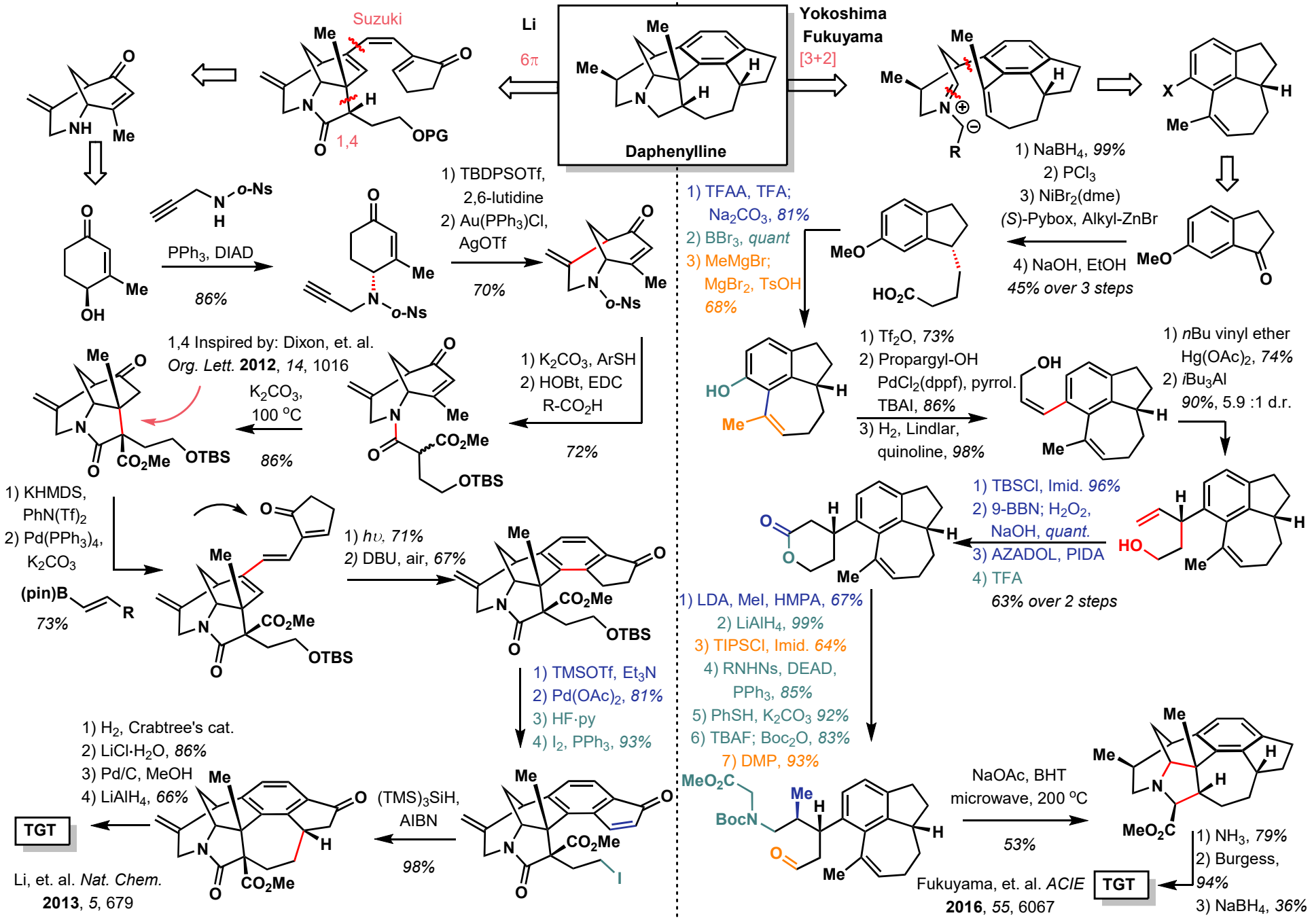

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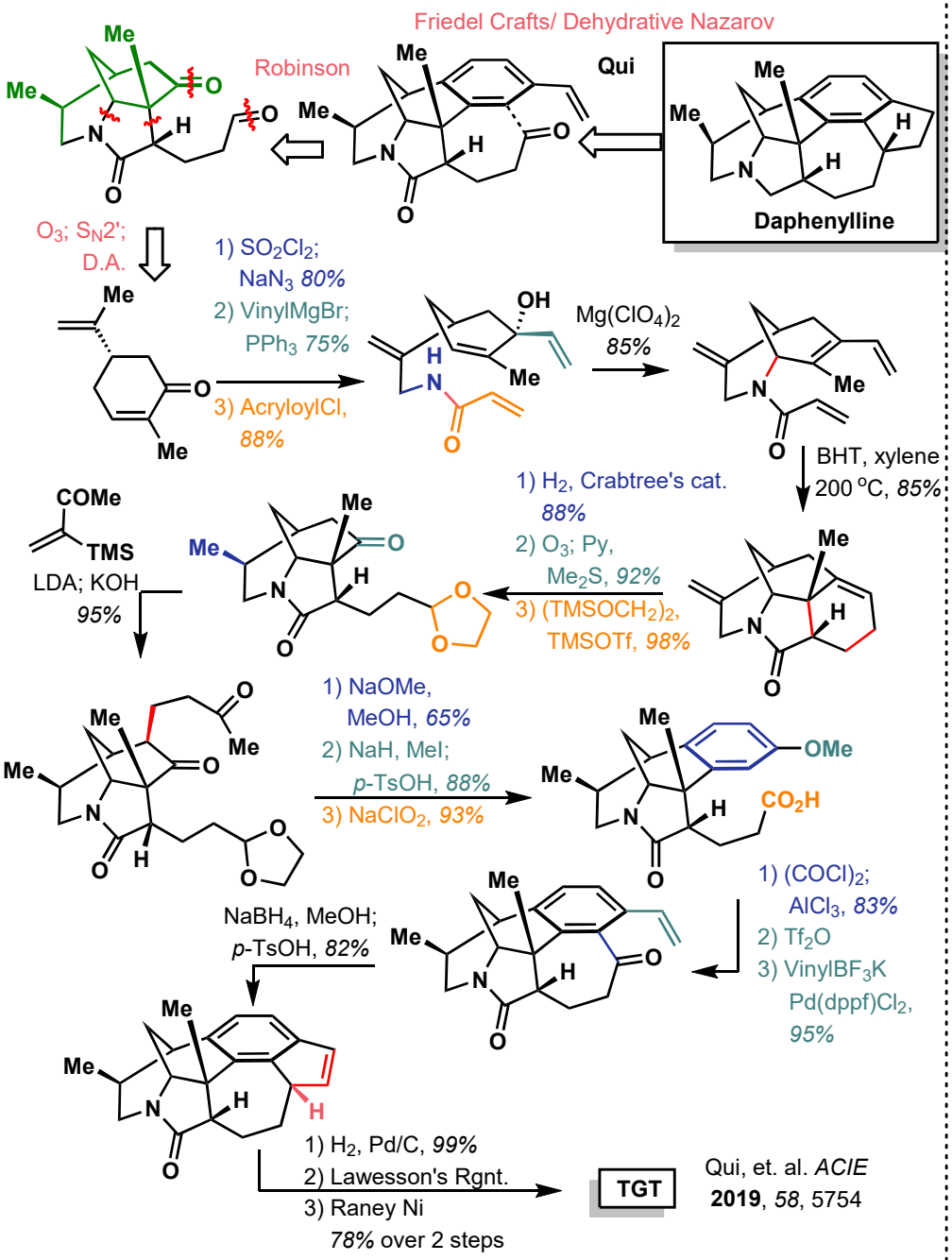
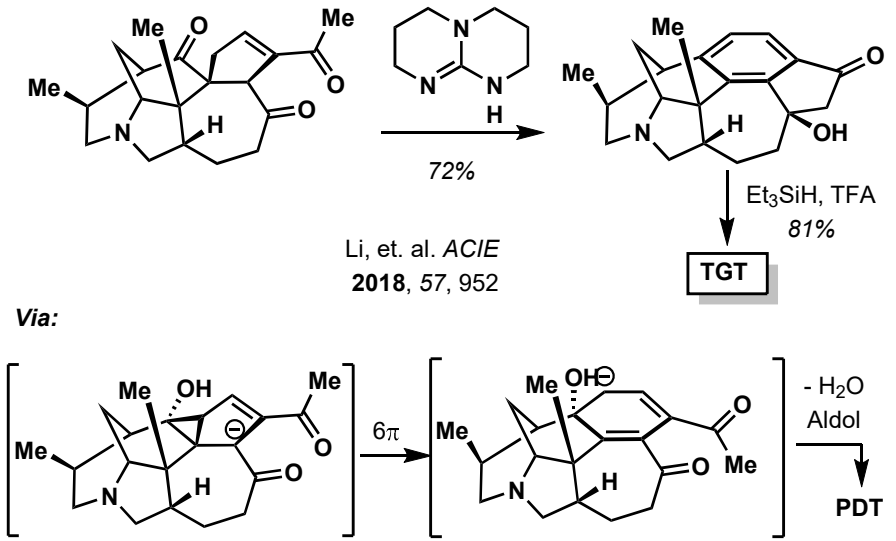
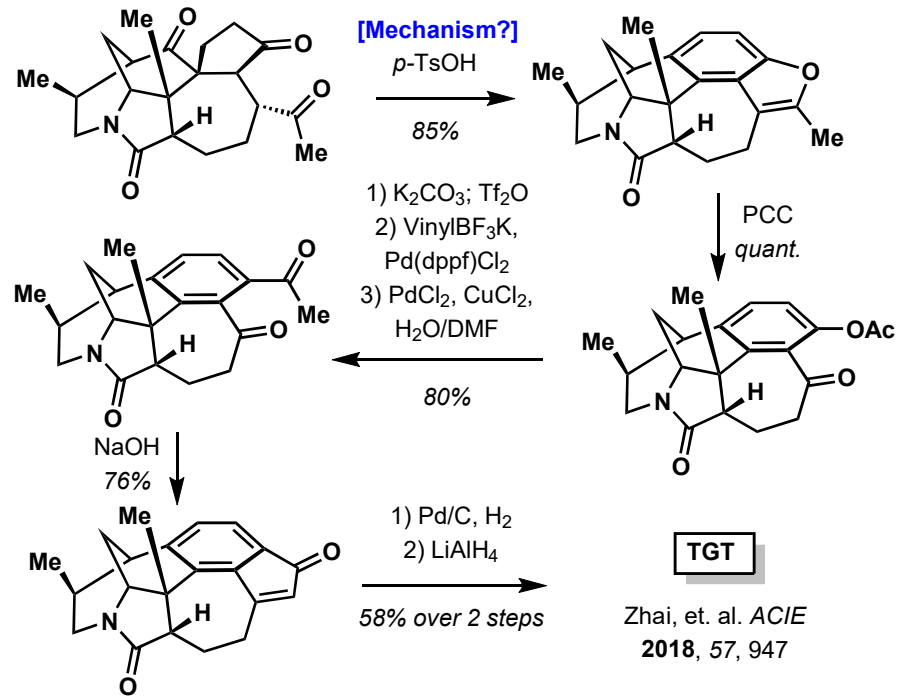


Divergent Syntheses Intercepting Daphenylline (details on further slides)





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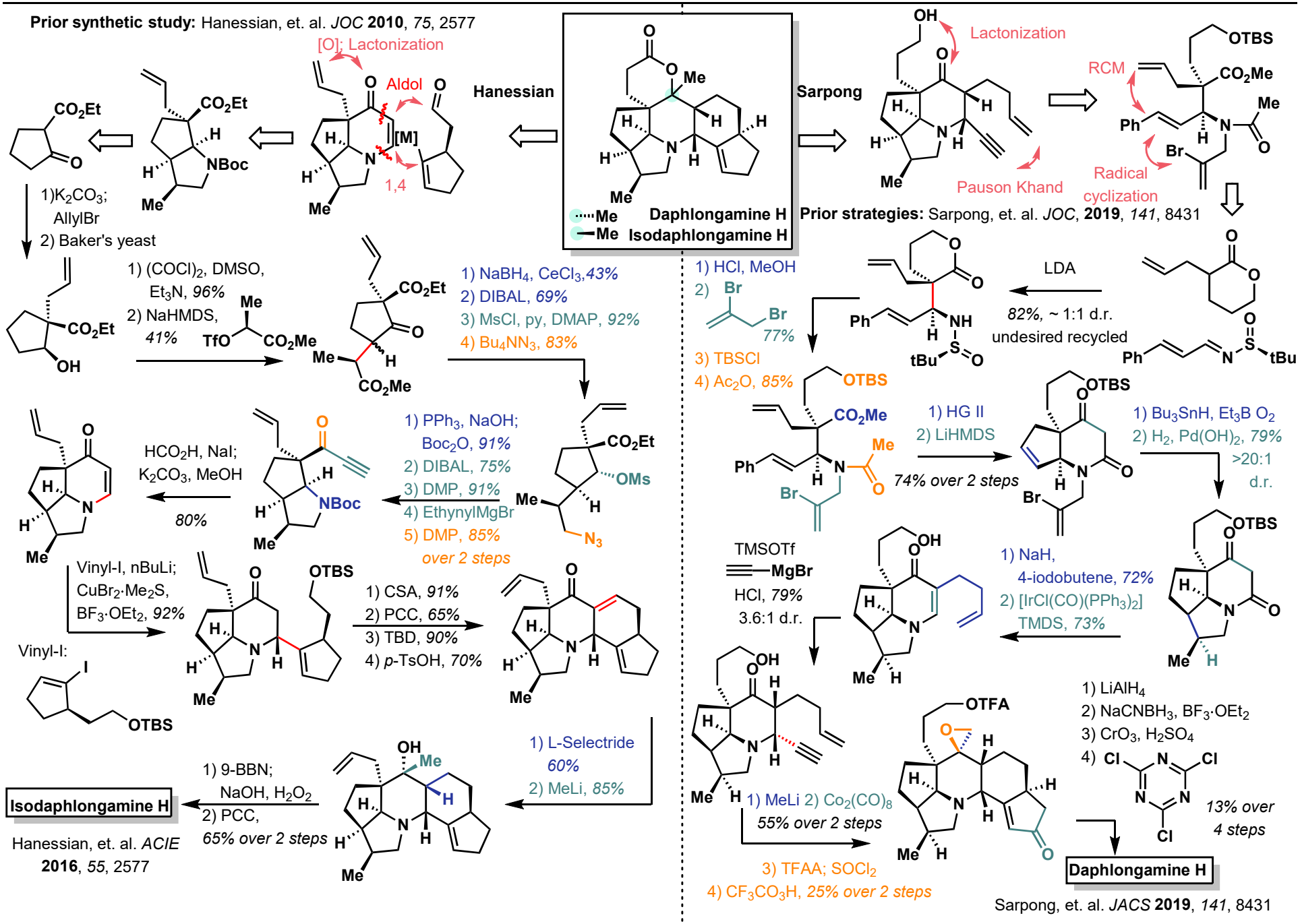
Prior synthetic study: Hanessian, et. al. *JOC* **2010**, *75*, 2577



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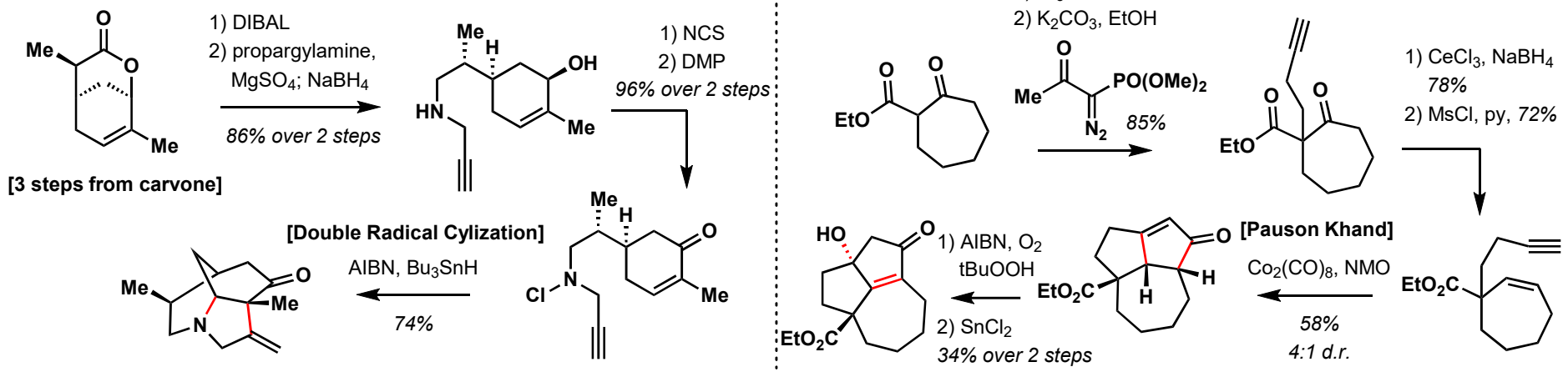
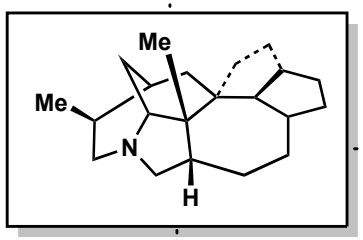
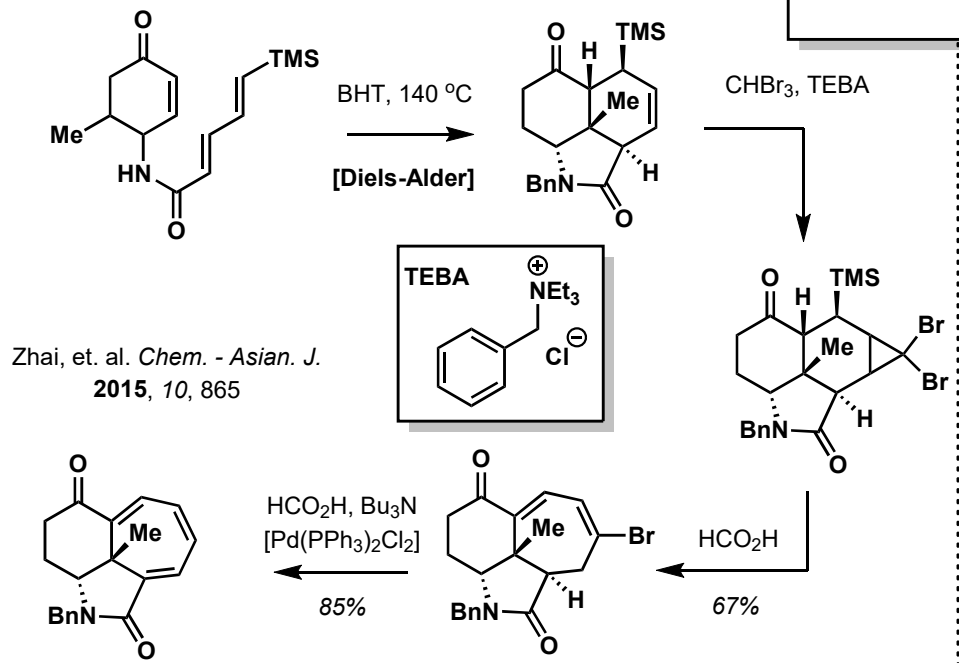
Highlights of Synthetic Studies Towards Longeracinphyllin A and Calyciphyline A Alkaloids



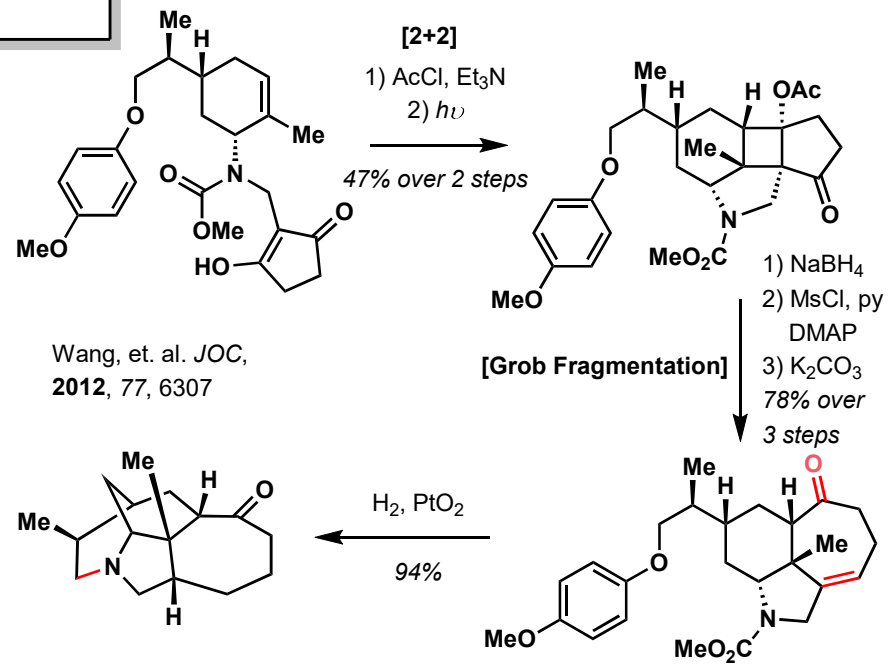
Stockdill, et. al. *Org. Lett.* **2014**, *16*, 1072

Dixon, et. al. *Org. Lett.* **2012**, *14*, 1684





Zhai, et. al. *Chem. - Asian. J.* **2015**, *10*, 865



Wang, et. al. *JOC*, **2012**, *77*, 6307

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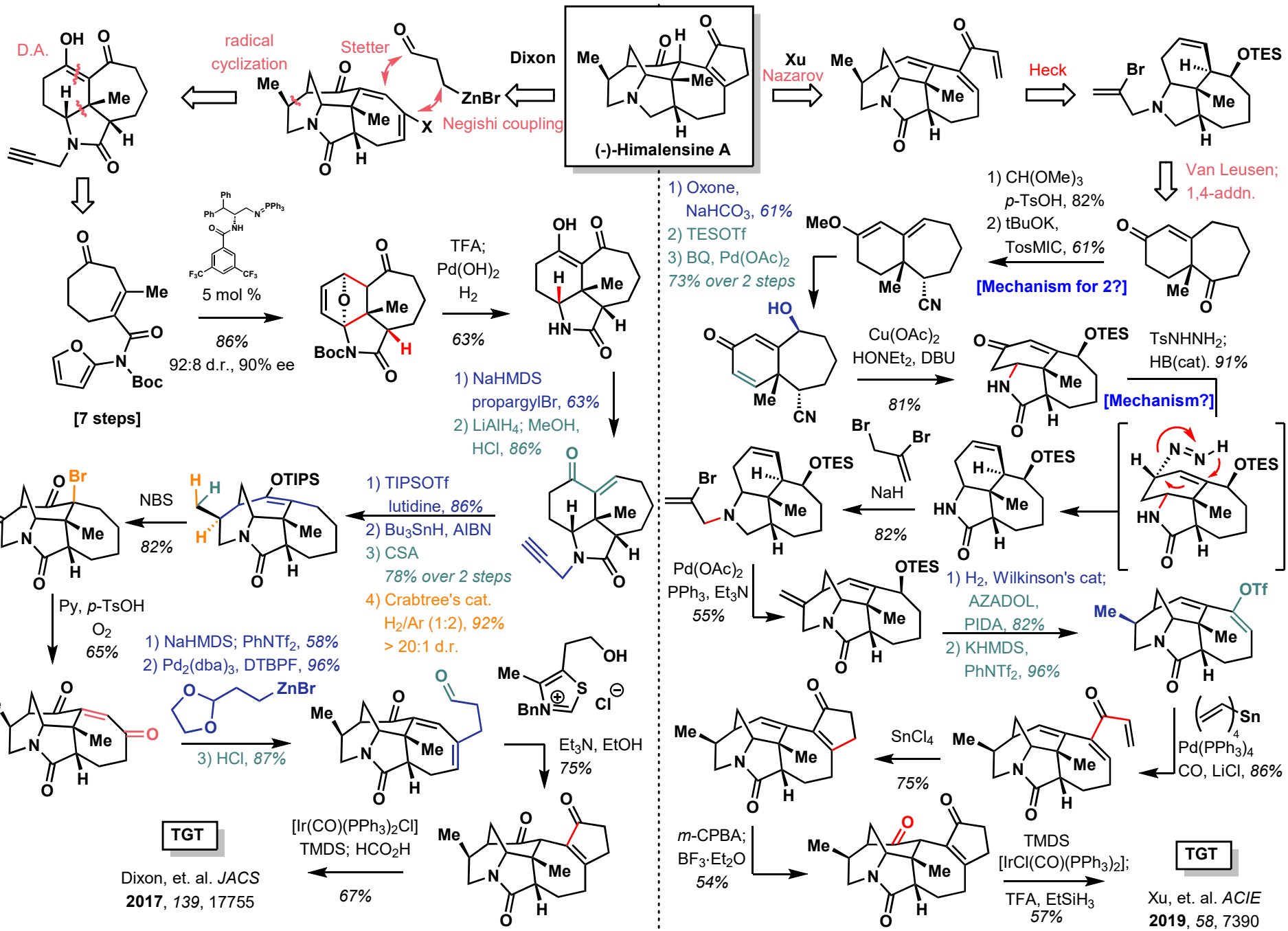

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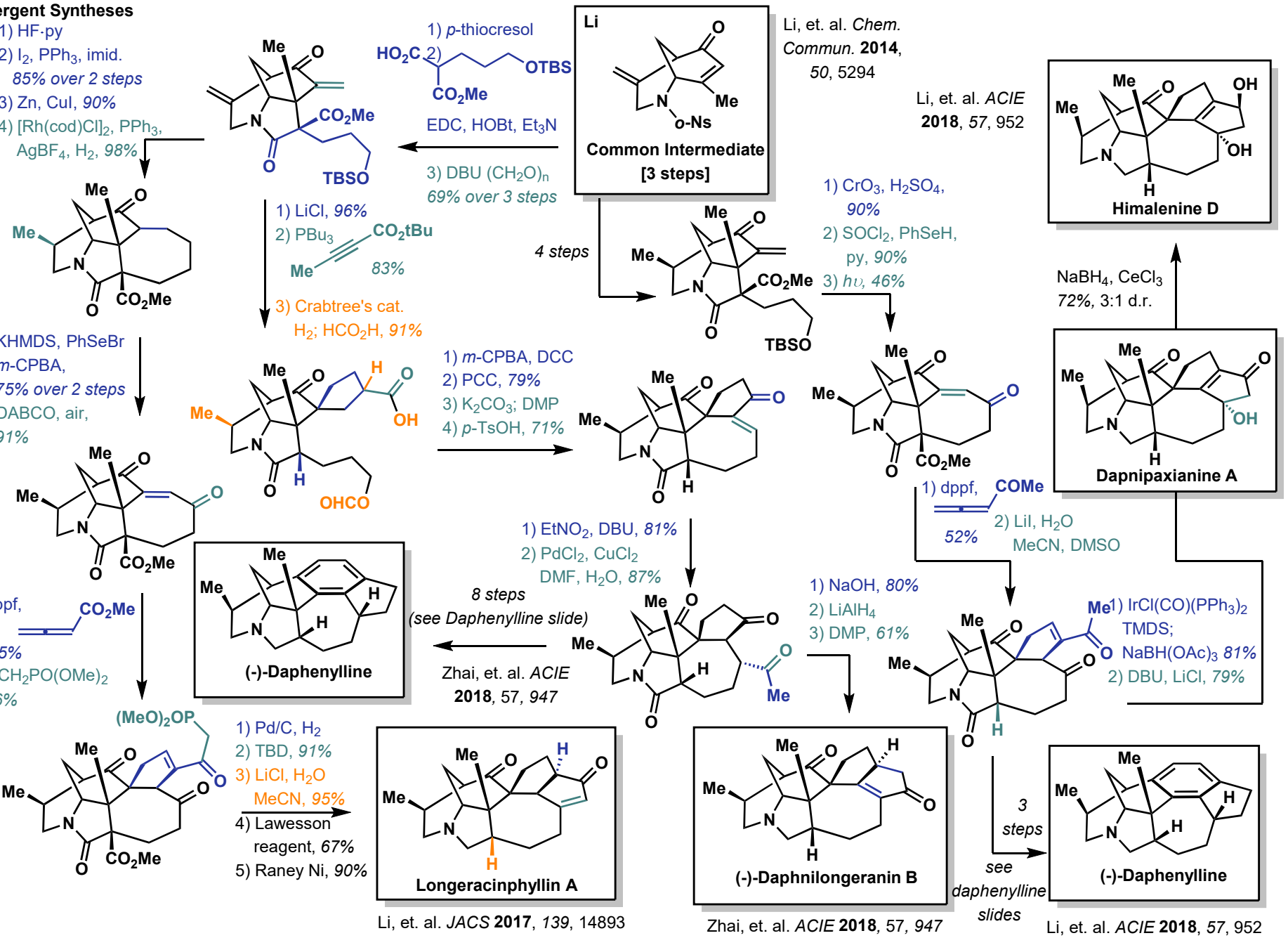
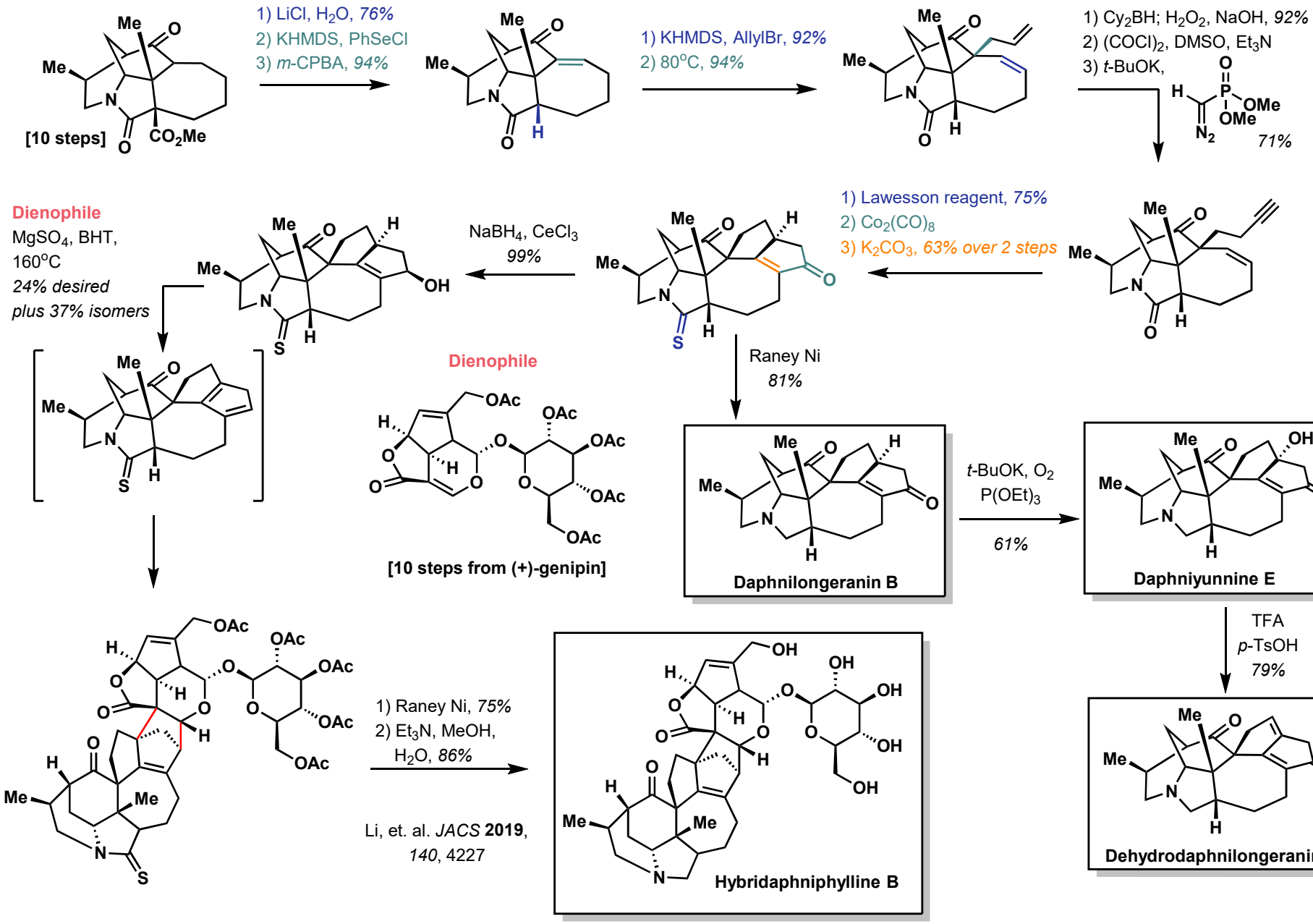
Divergent Syntheses



Divergent Syntheses Cont.

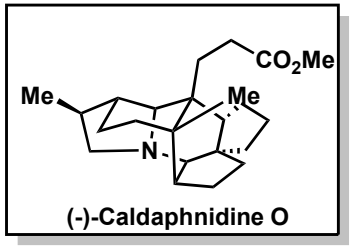


Total Synthesis of the Daphniphyllum Alkaloids

*"If progress in important fields such as medicine, biochemistry, and materials sceince is to continue, it is essential that we be able to synthesize literally any structure that the imagination can conceive....
Our textbooks are filled with hundreds of synthetic methods, all of which have limitations that will never be discovered unless the methods are tested in the challenging arena of [synthesis]. Although our approaches to problems have matured, we need even more mature strategies of synthesis. There is no reason that organic chemists should not be able to surpass nature's virtuosity in the synthesis of complex organic structures. In fact, we are still very far from this goal in most cases."*

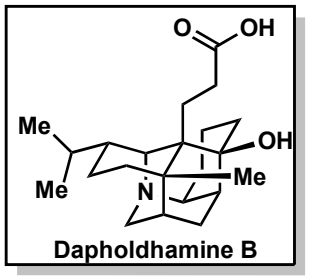
- Clayton Heathcock
ACIE **1992**, *31*, 665

Total syntheses not covered:



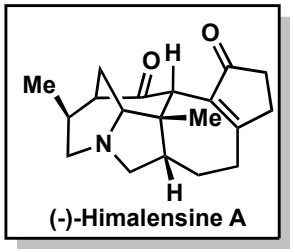
(-)-Caldaphnidine O

Xu. et. al. *JACS* **2019**, *141*, 13043



Dapholdhamine B

Xu, et. al. *JACS* **2019**, *141*, 11713



(-)-Himalensine A

Gau, et. al. *Org. Lett.* **2019**, *21*, 3741