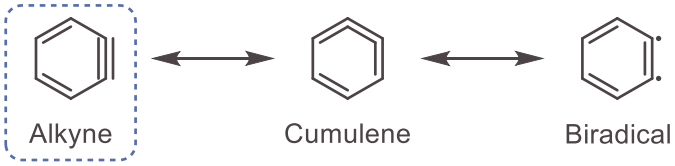
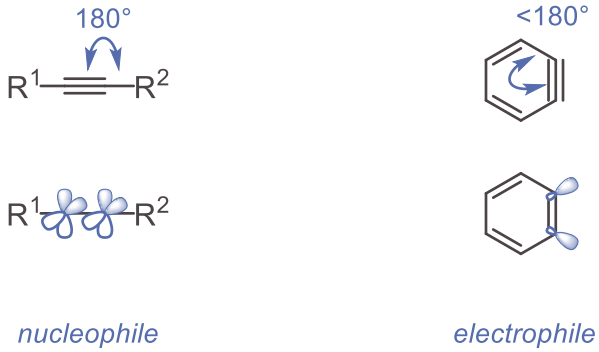
Arynes as Tools in Natural Product Synthesis

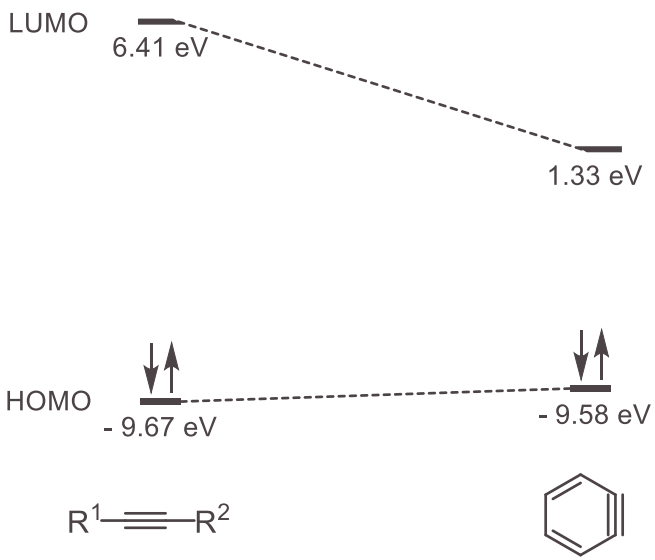
Synthesis Club ♦ Jamie Allen ♦ July 31st, 2017

What is an aryne?



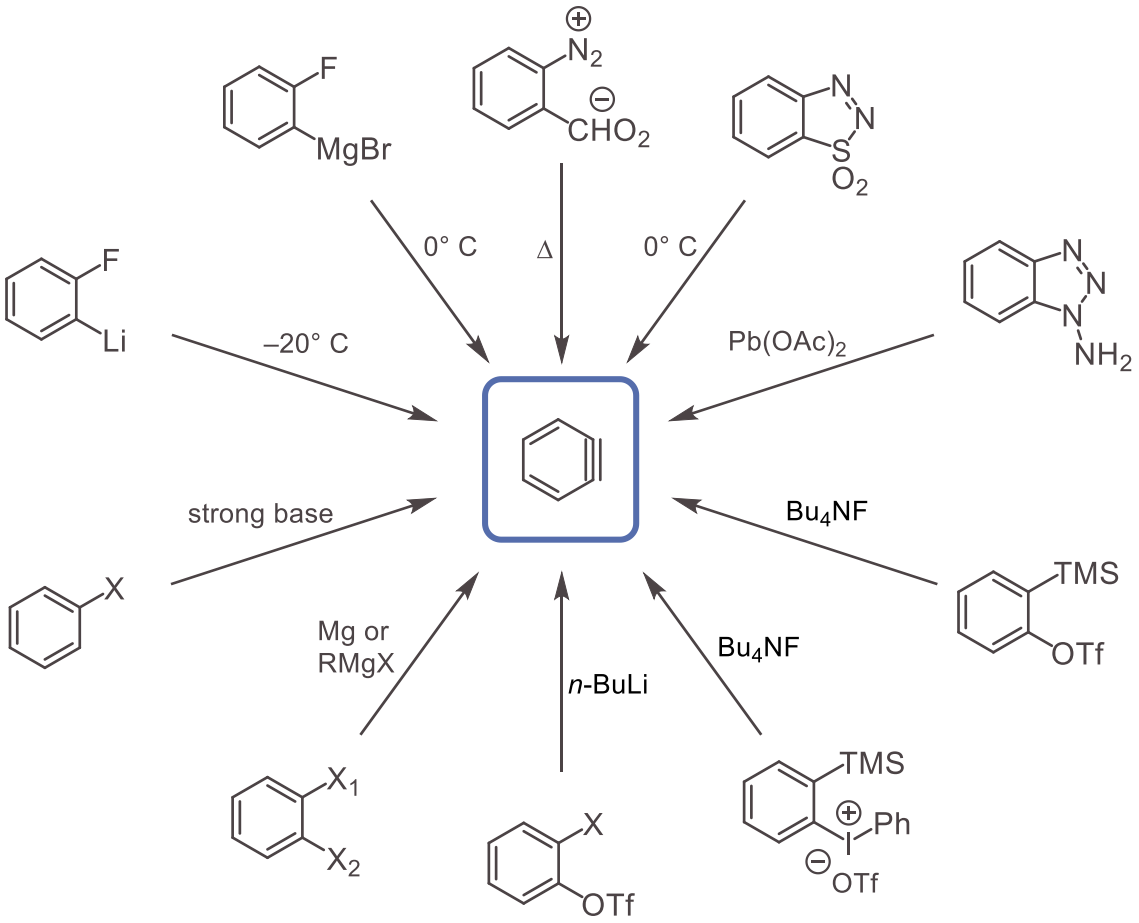
unstrained alkyne ***vs.*** ***benzyne***





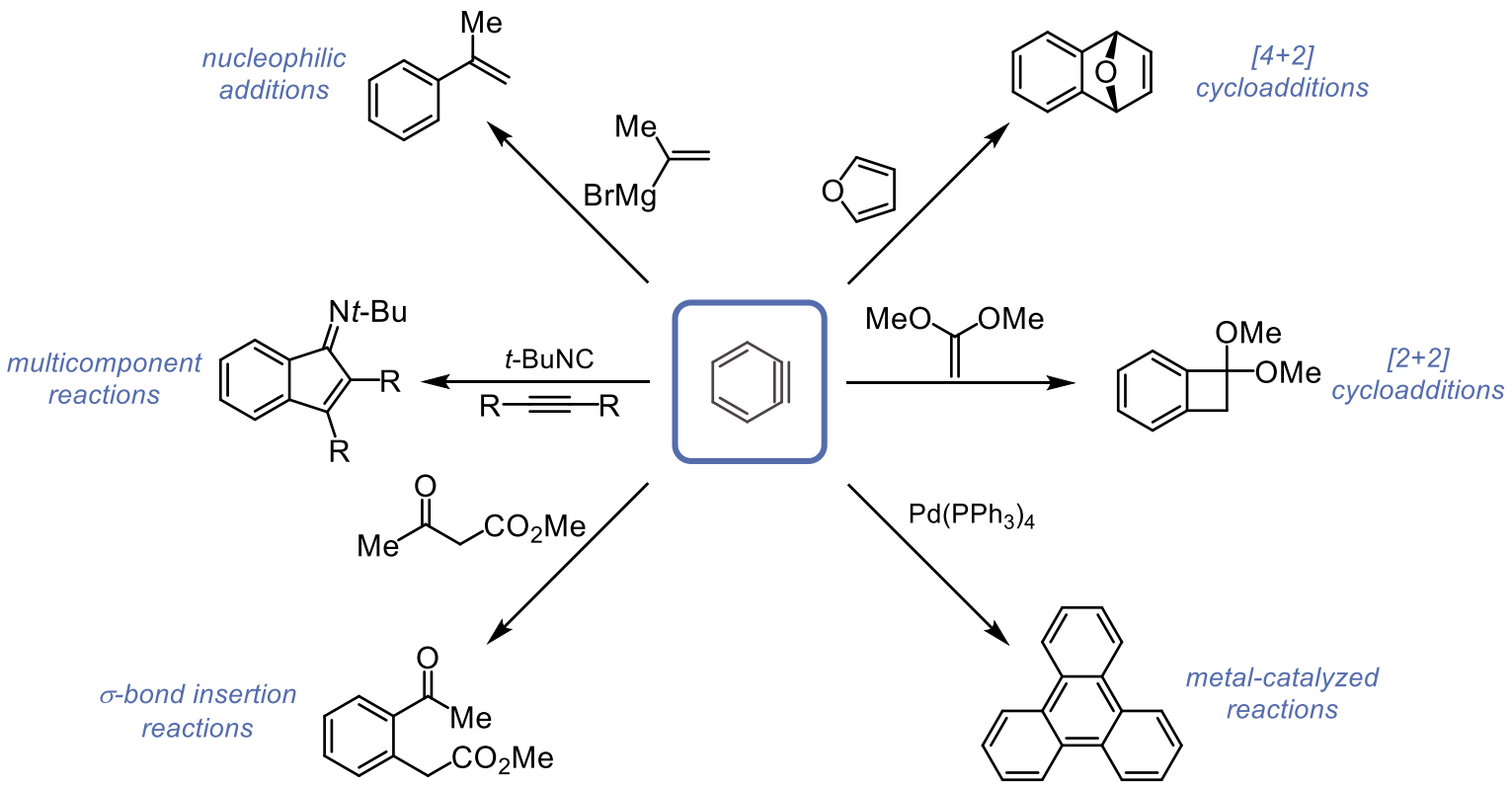
Gampe, C. M.; Carreira, E. M. *Angew Chem. Int. Ed.* **2012**, *51*, 3766

How are arynes made?



Tadross, P. M.; Stoltz, B. M. *Chem. Rev.*, 2012, *112*, pp 3550–3577

What do arynes do?



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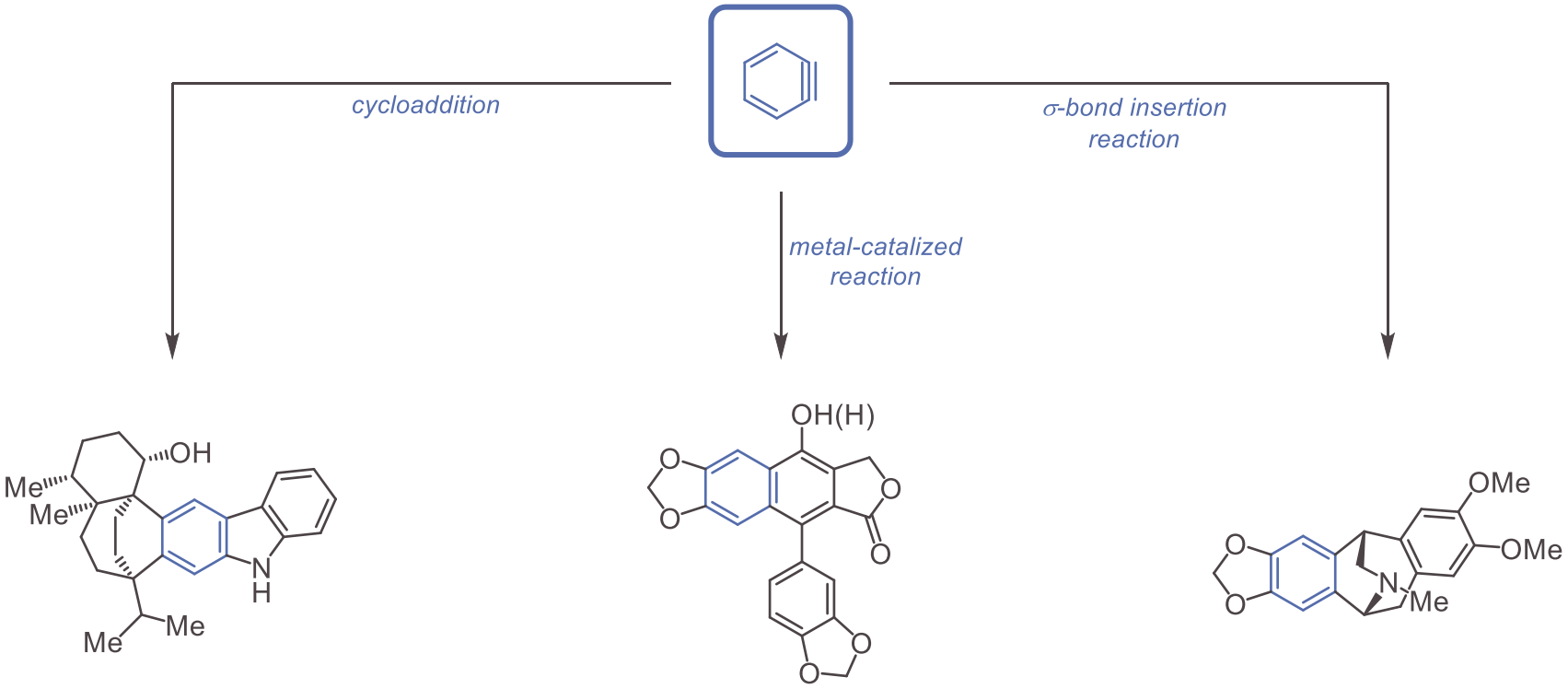
Arynes in Total Synthesis



(–)-Tubingensin B
Garg, 2017

Taiwanin E/G
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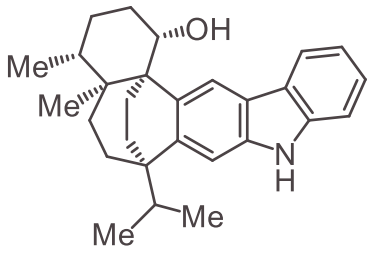
Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem. Int. Ed.* 2004, *43*, 2436 –2440

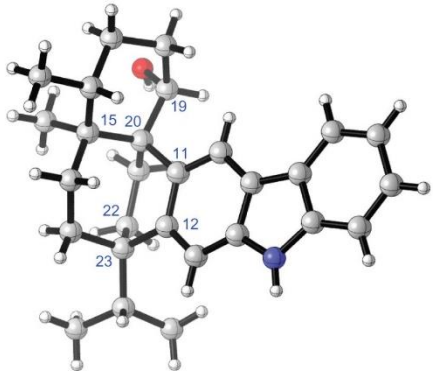
What is (-)-Tubingensin B?



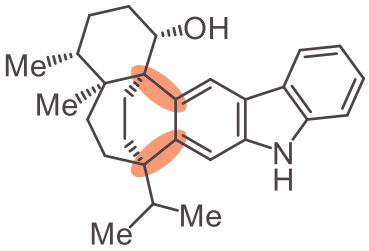
(–)-Tubingensin B
Garg, 2017

Biological Relevance

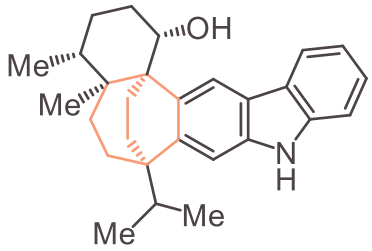
- Isolated from the fungus *Aspergillus tubingensis* in 1989.
- Absolute structure determined by X-ray crystollagraphy in 1989.
- Acts as a secondary metabolite; it is believed to help protect the producing fungus from natural predators.
- Displays cytotoxicity against cervical cancer cells (HeLa) with an IC_{50} of 4 μg ml^{-1}.
- Demonstrate *in vitro* antiviral activity against herpes simplex virus type 1 (HSV-1) with an IC_{50} of 9 μg ml^{-1}.



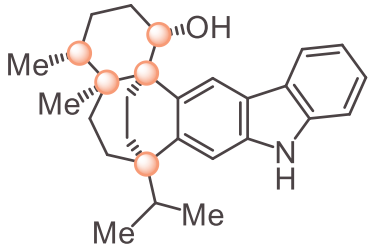
Structural Challenges:



- 2 adjacent sp^2–sp^3 C–C bond linkages
- quaternary stereocenters stemming from the carbazole



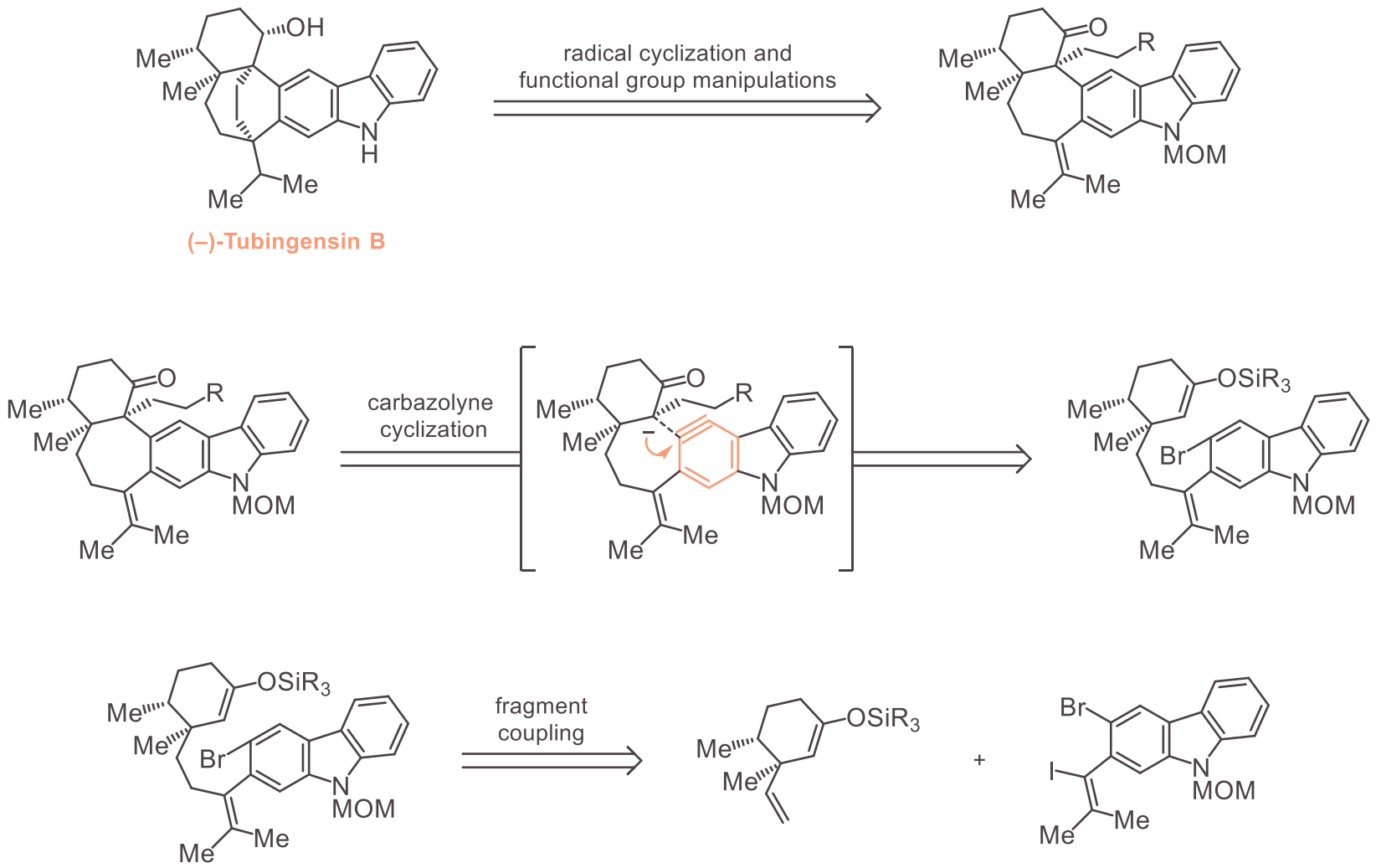
bicyclo[3.2.2]nonane core



5 stereogenic centers:
- 4 are contiguous
- 3 are quaternary

Corsello, M. A.; Kim, J.; Garg, N. K. *Nature Chemistry*, 2017, advance online publication

The plan for synthesizing (-)-Tubingensin B



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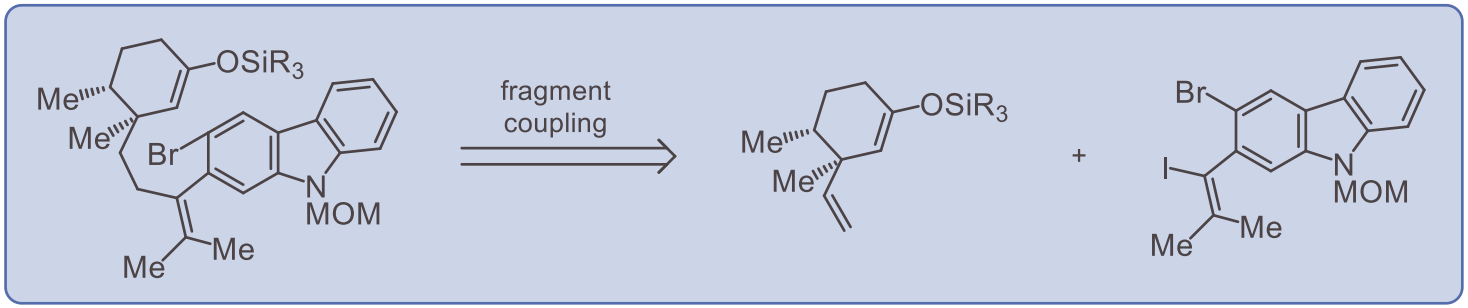
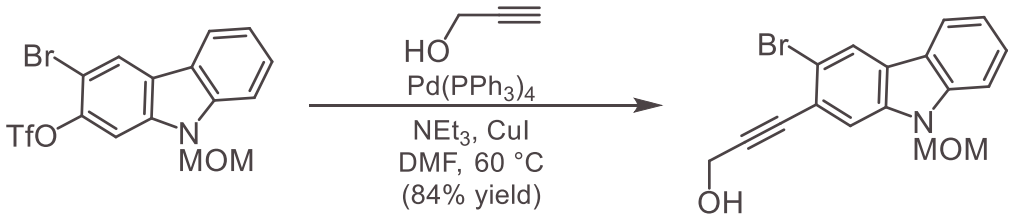
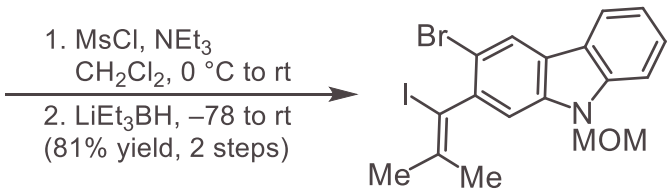
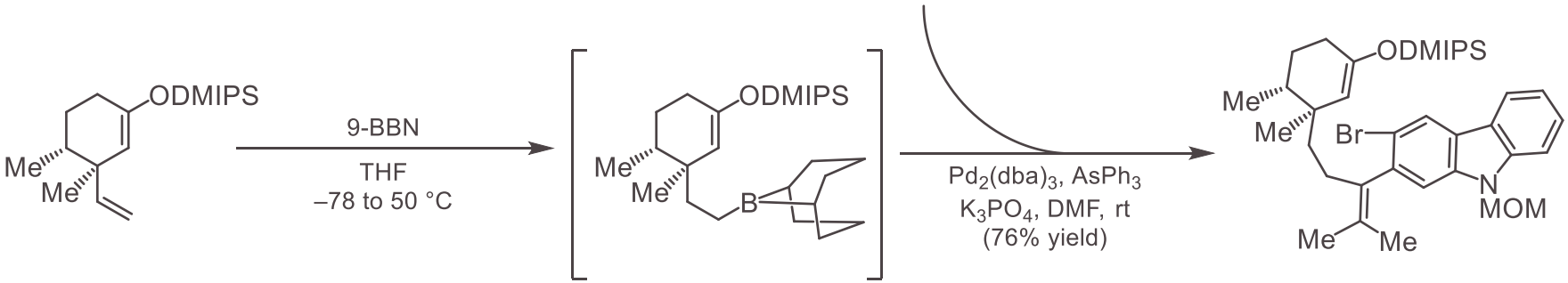
Synthesis of (-)-Tubingensin B









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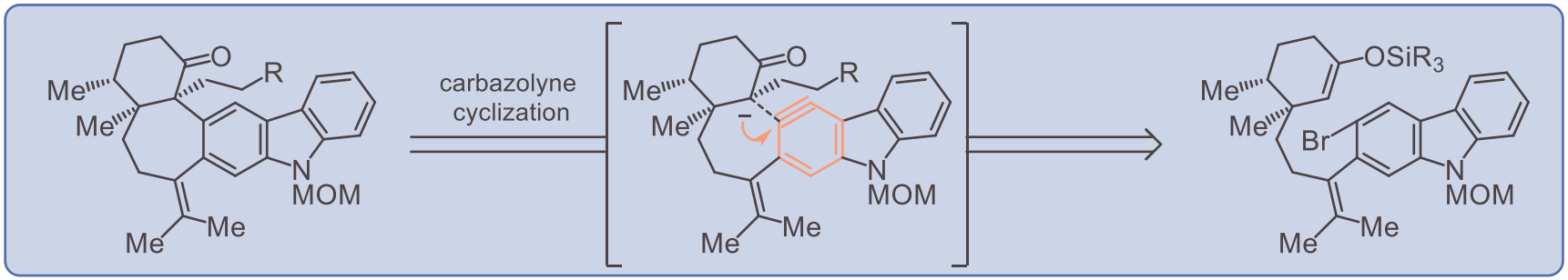

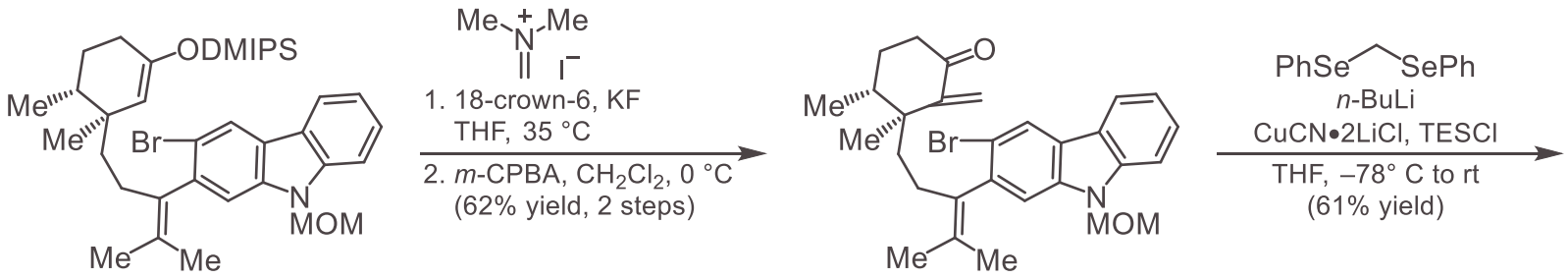

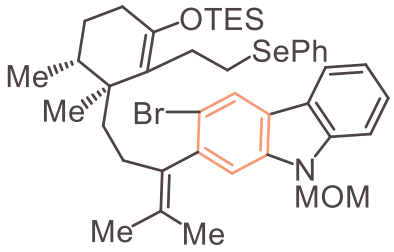

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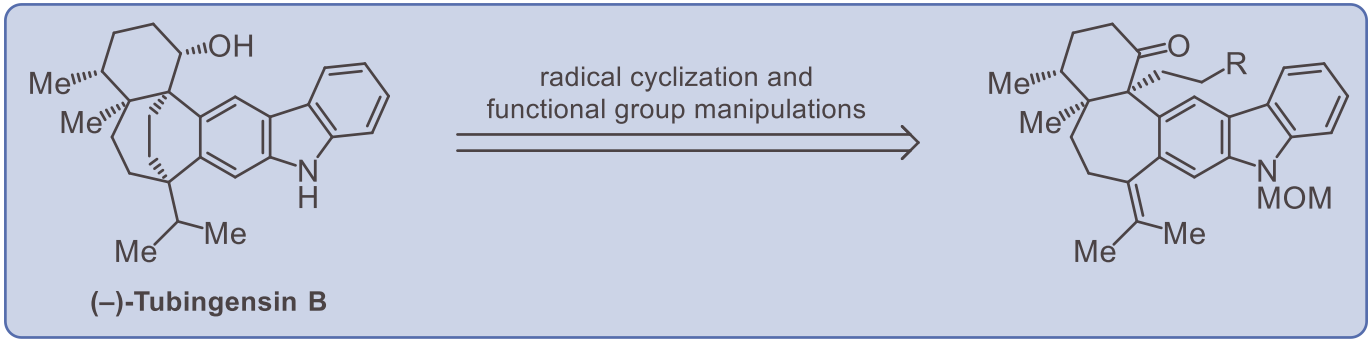

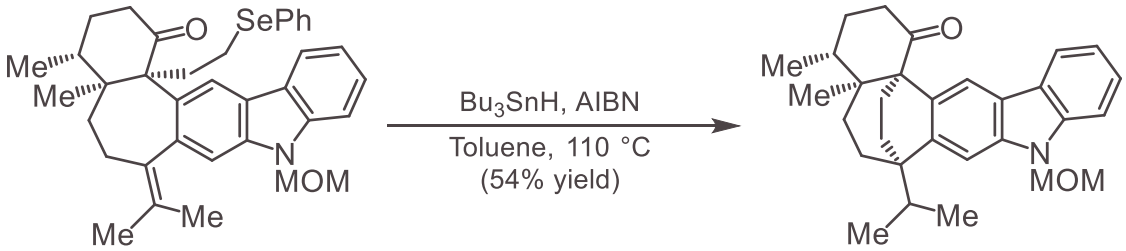

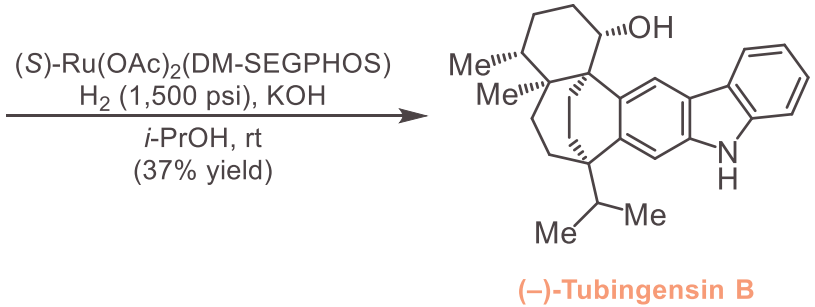

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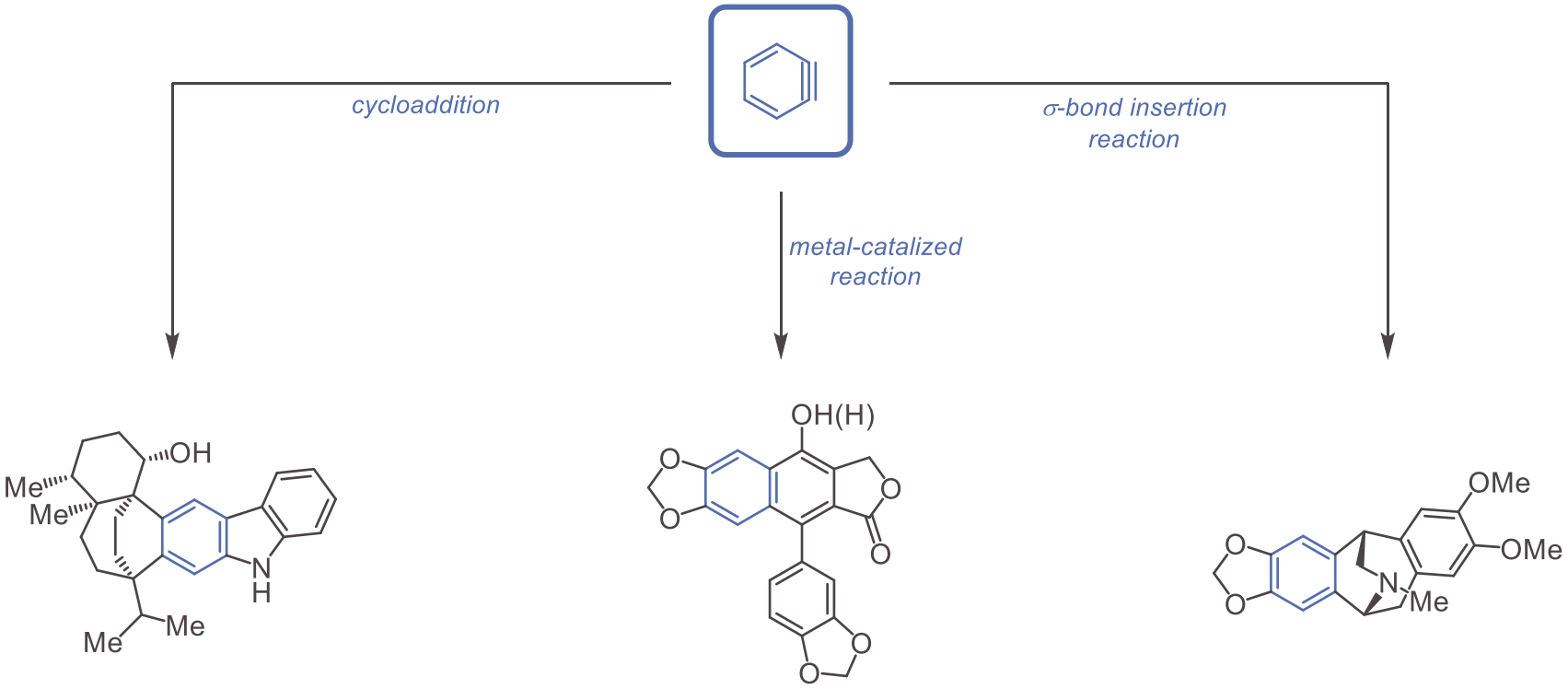

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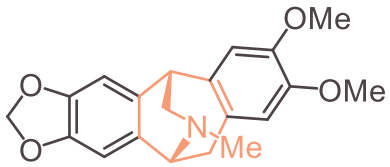
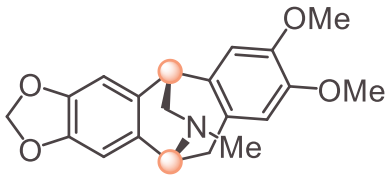
Synthesis of (+)-Amurensinine

Structural Challenges:



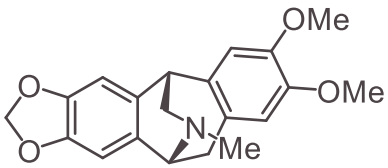
aza-bicyclo[3.2.2]nonane



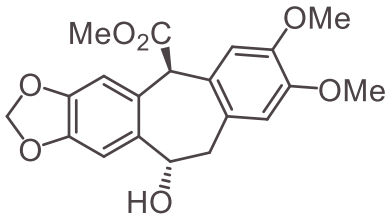
2 stereocenters

Biological Relevance

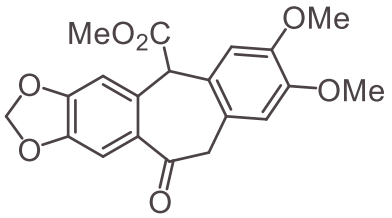
- Exhibit biological properties for the treatment of neurological disorders, such as Parkinson's and Alzheimer's disease.

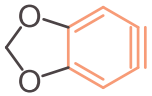


(+)-Amurensinine

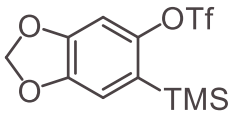


Oxidative Kinetic Resolution

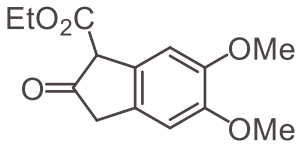




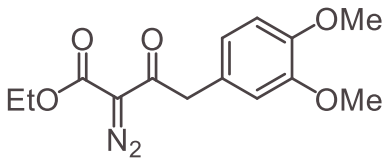
+



C–C Insertion



C–H Insertion



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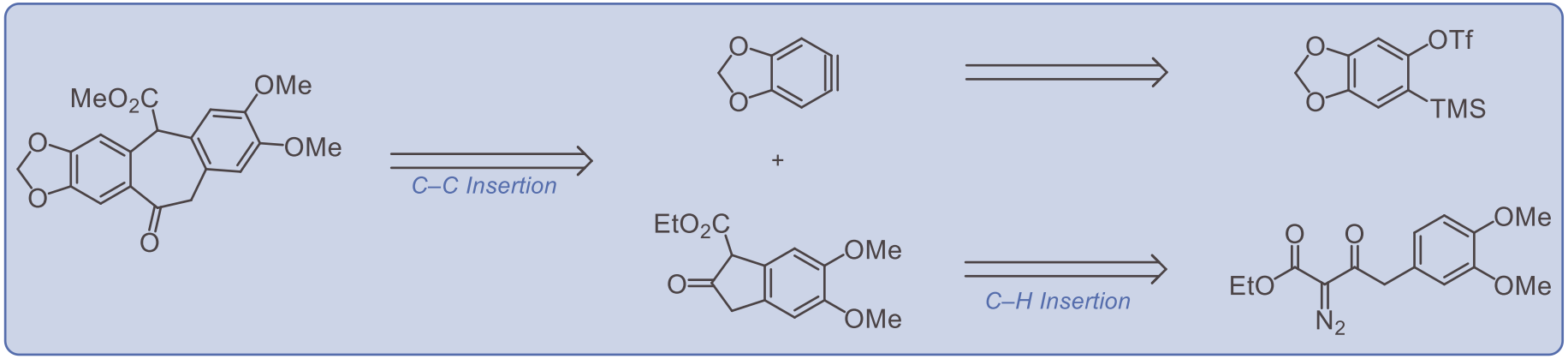
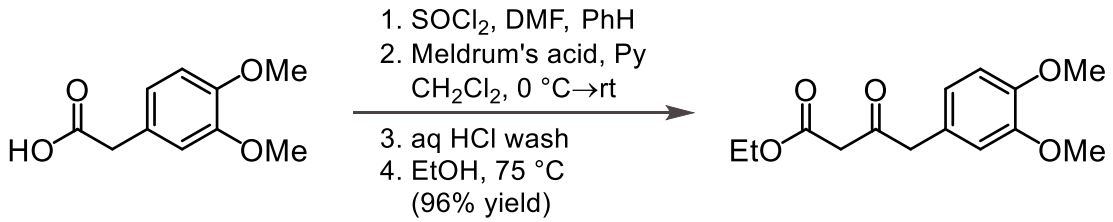
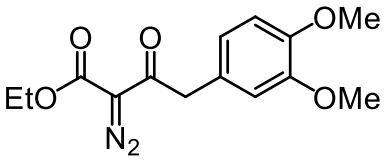
Synthesis of (+)-Amurensinine







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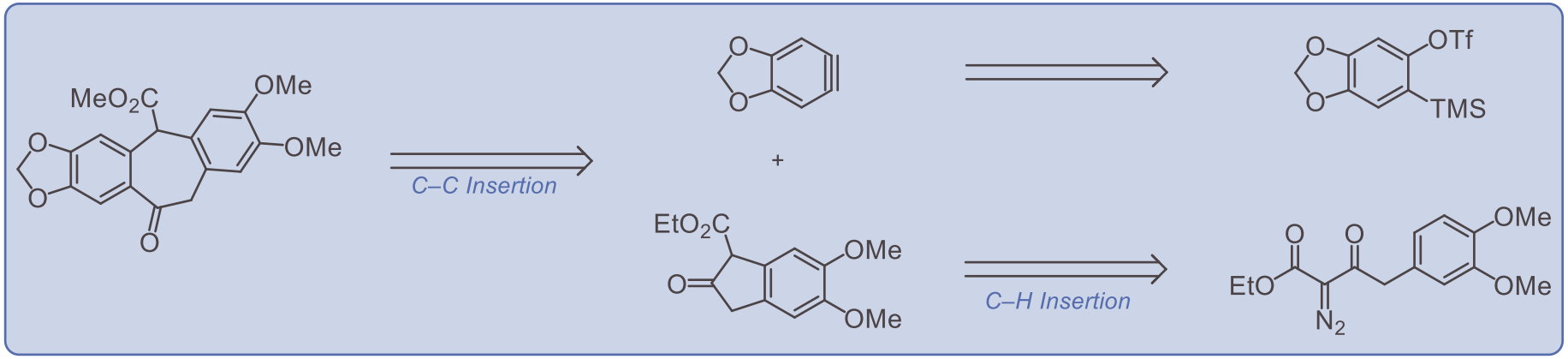

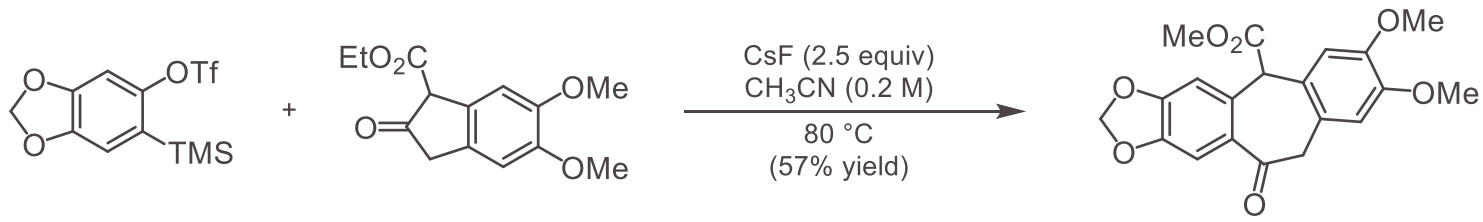

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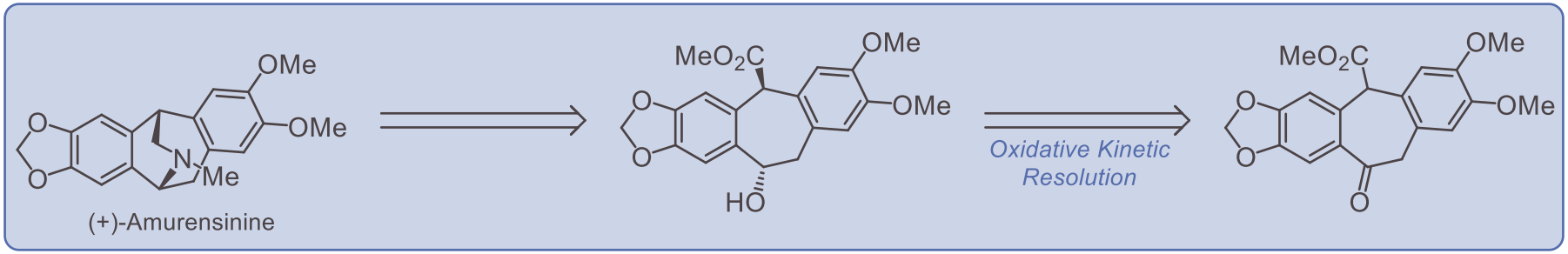

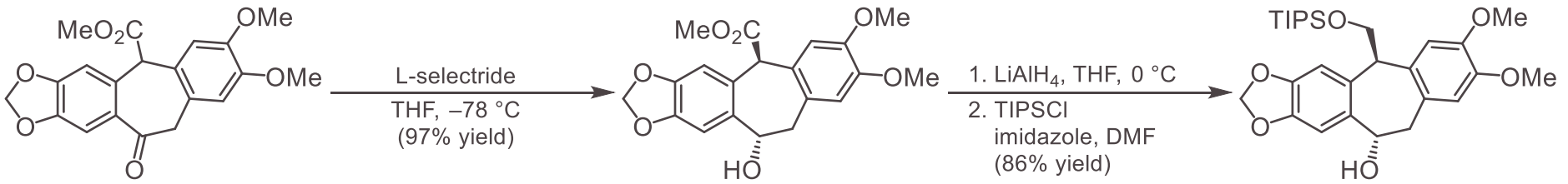

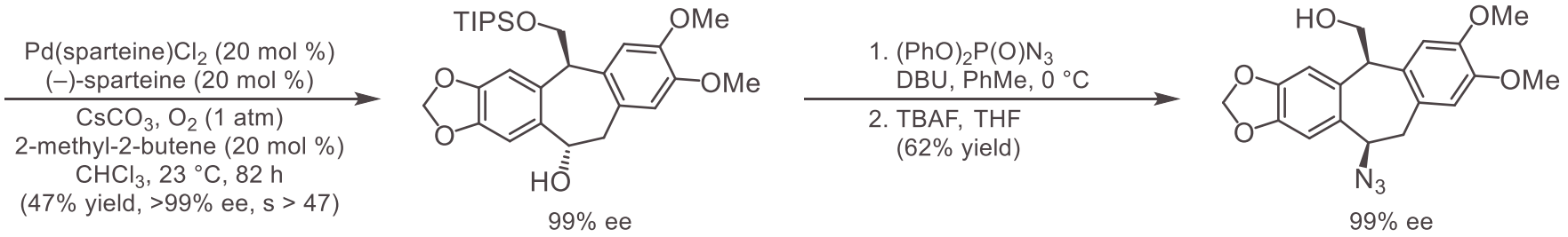

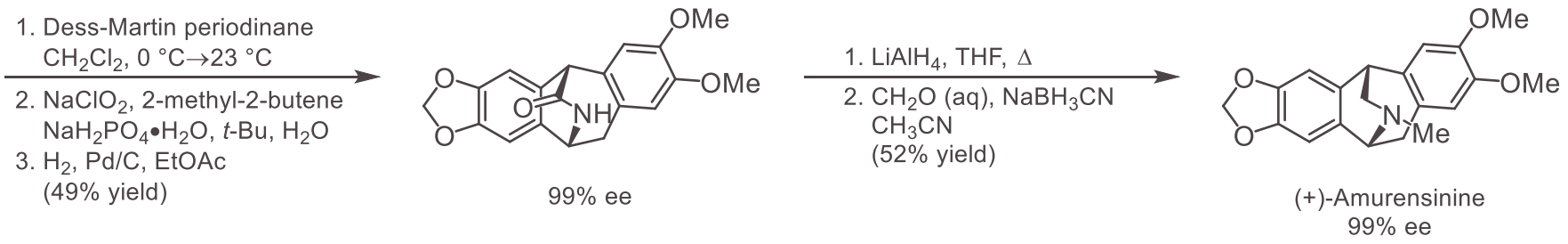

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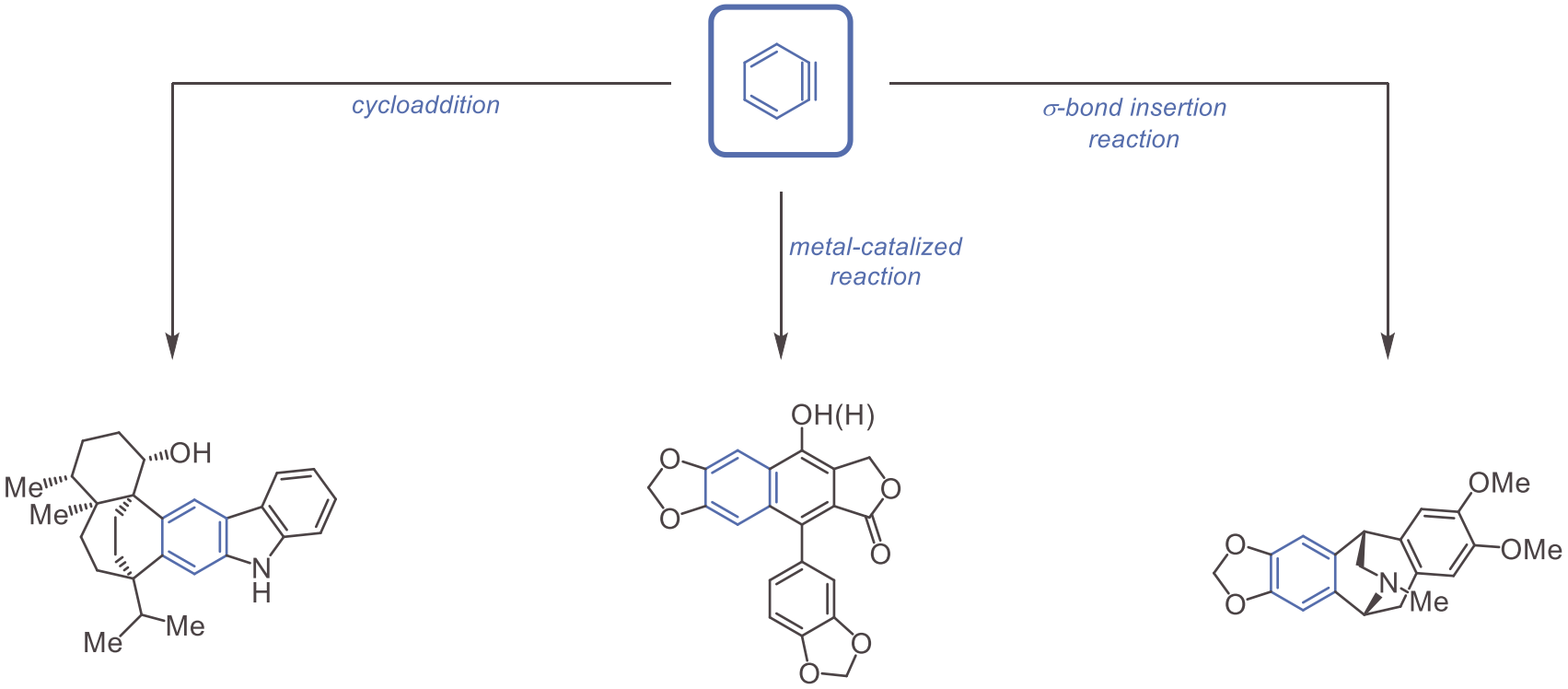

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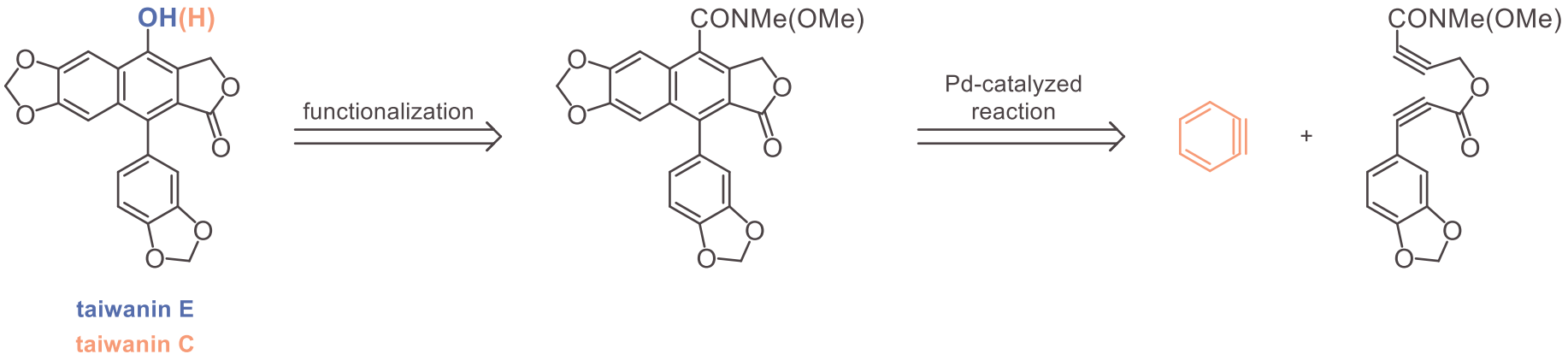
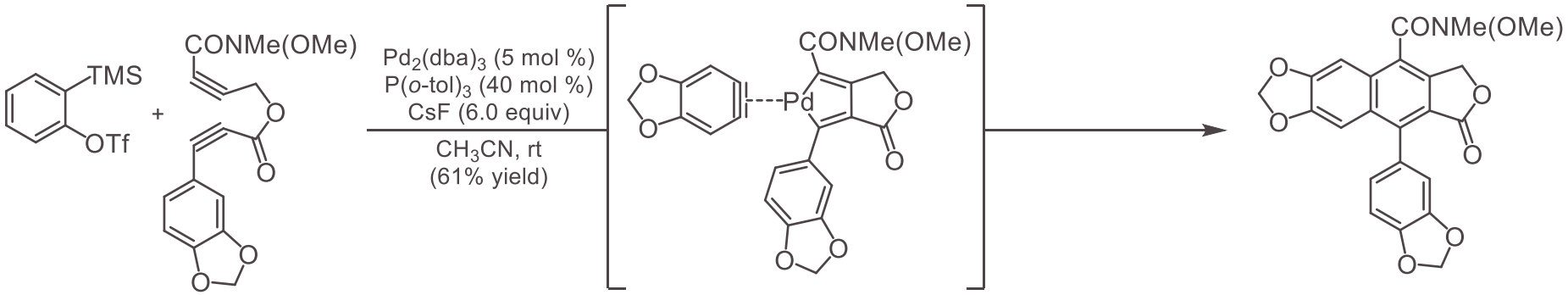
Synthesis of Taiwanin C & E





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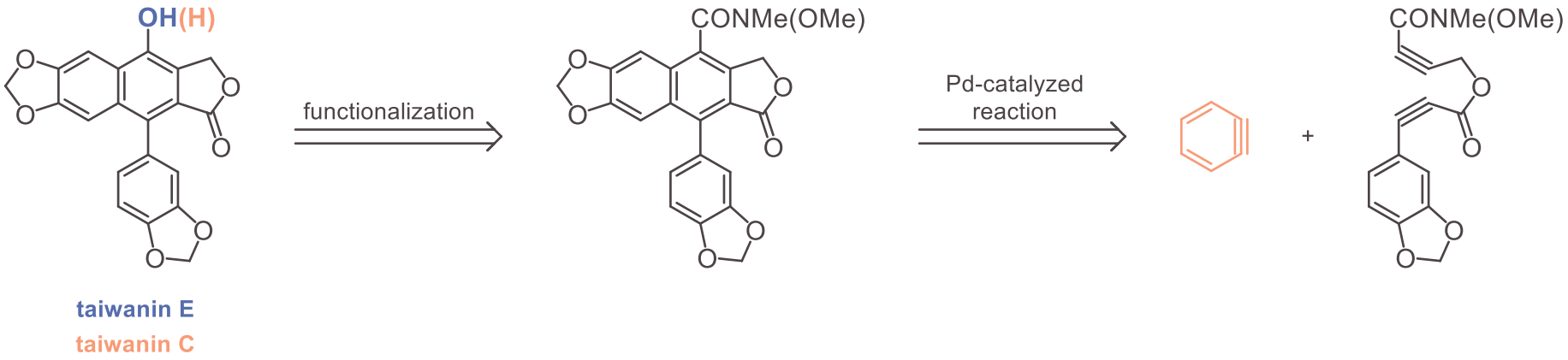

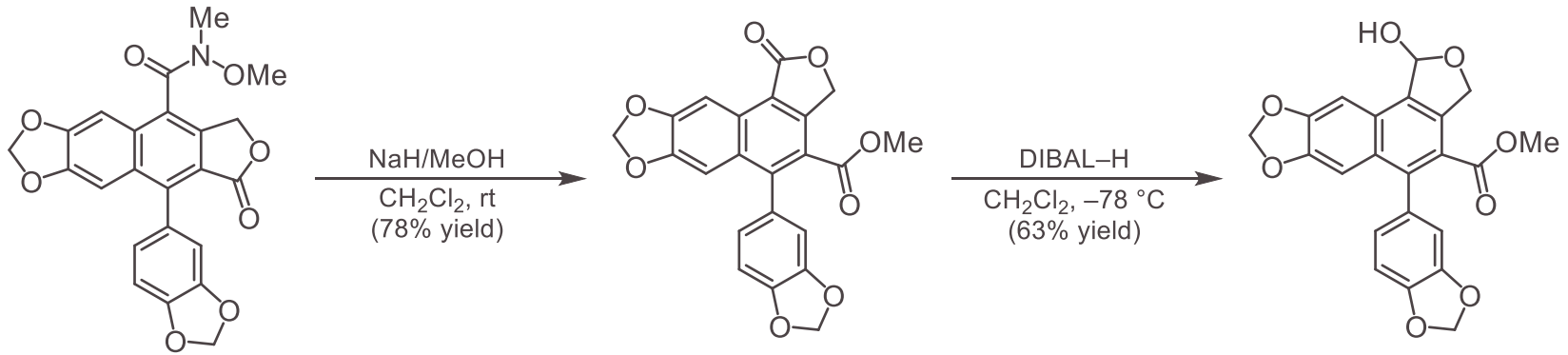

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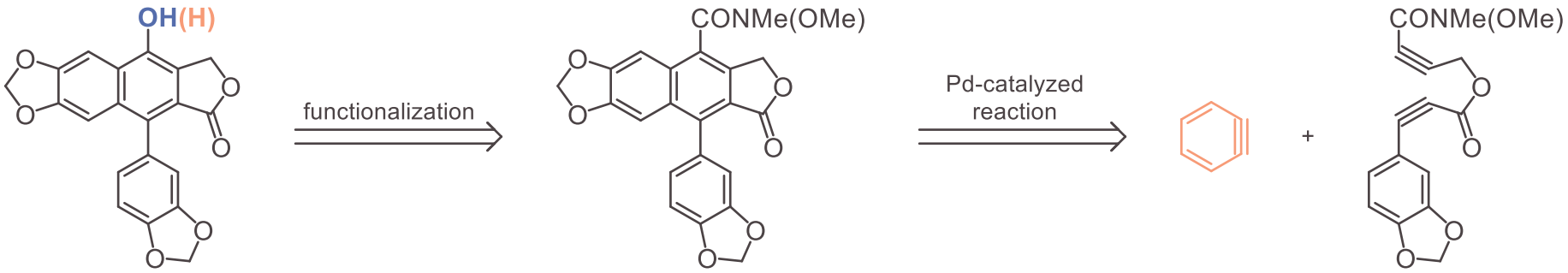
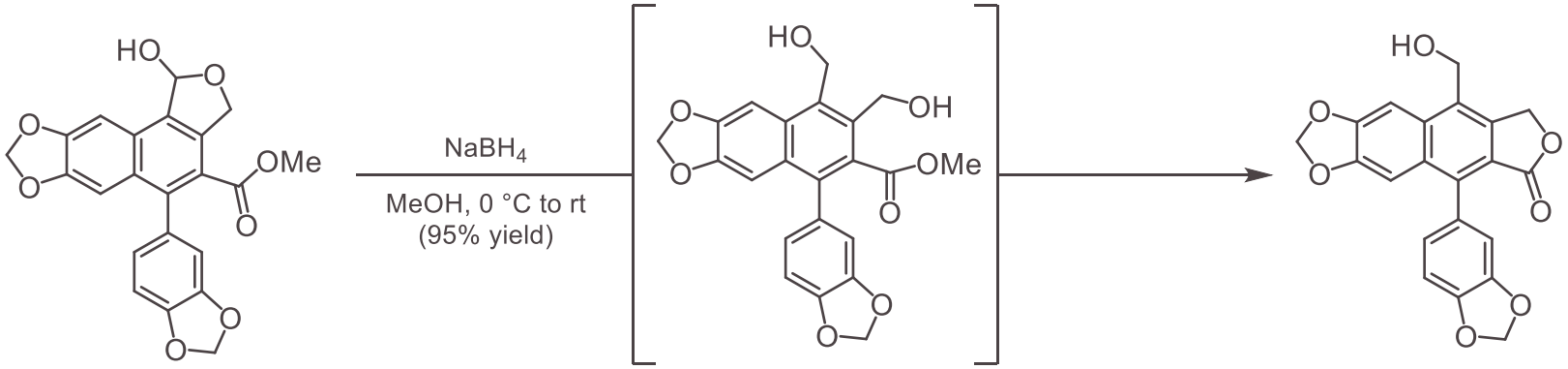


taiwanin E

taiwanin C



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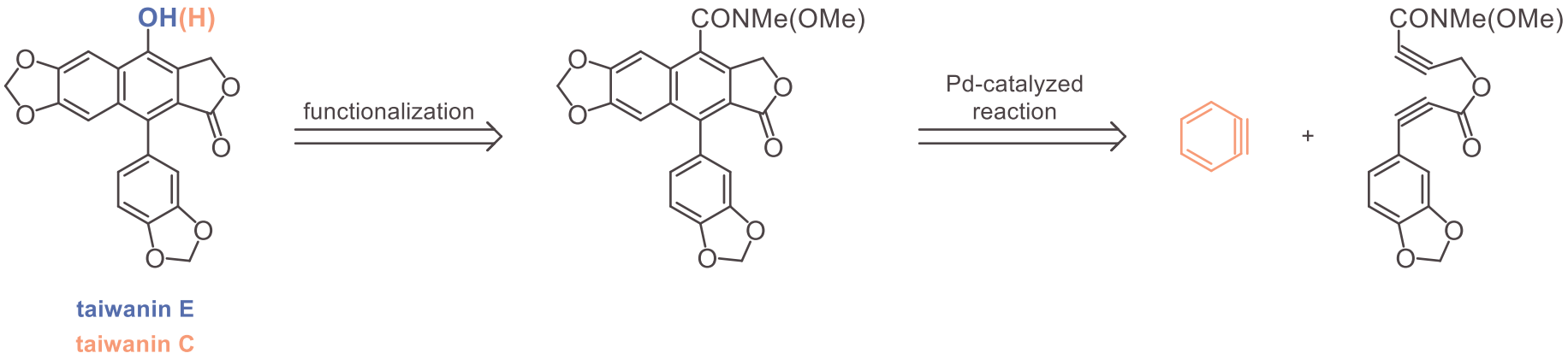

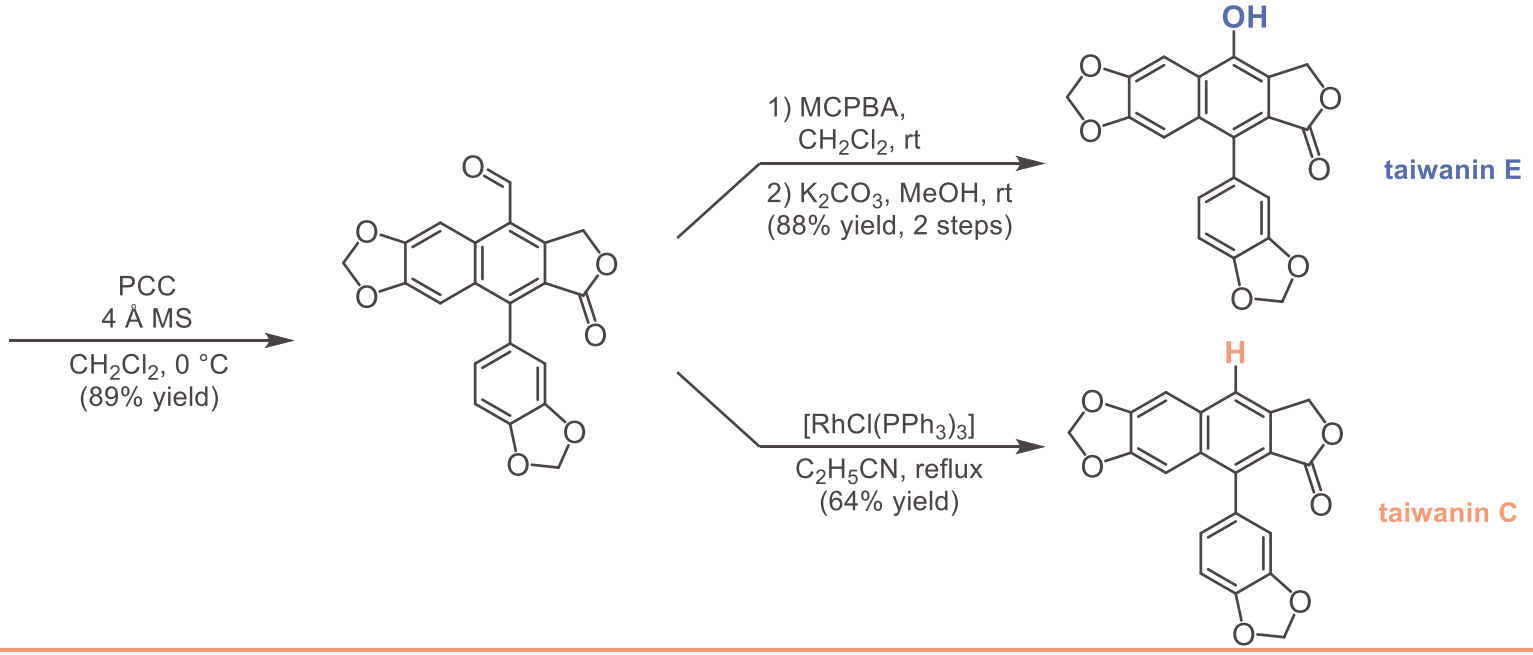

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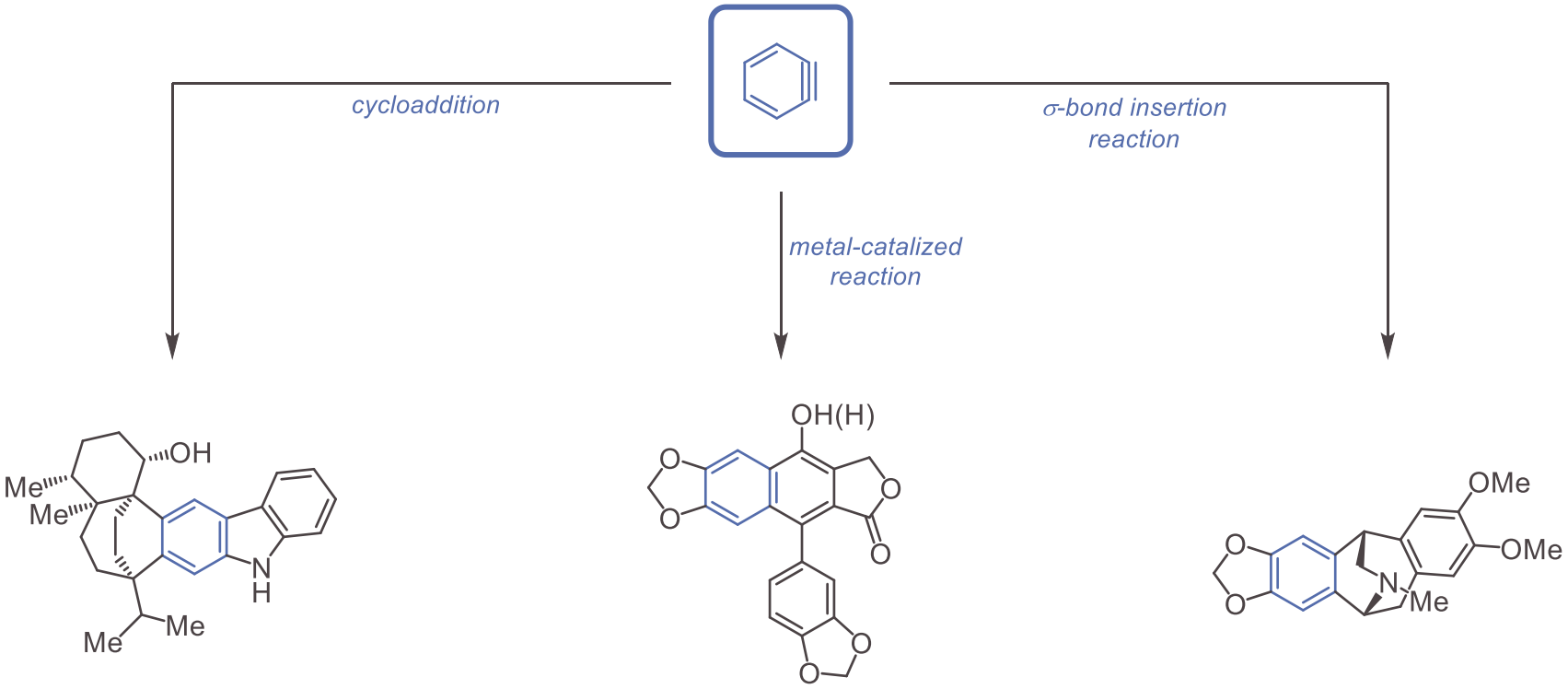
Arynes in Total Synthesis



(–)-Tubingensin B
Garg, 2017

Taiwanin E/G
Mori, 2004

(+)-Amurensinine
Stoltz, 2006

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Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* 2006, *128*, 11752-11753
Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem. Int. Ed.* 2004, *43*, 2436 –2440