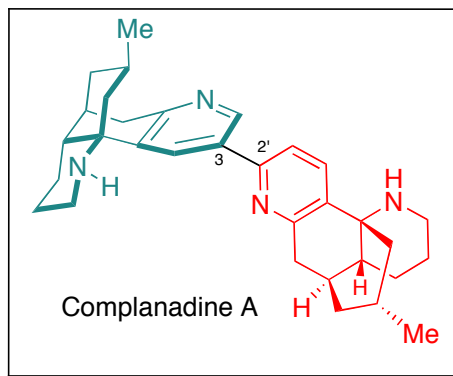


Total Synthesis of (+)-Complanadine A Using an Iridium-Catalyzed Pyridine C-H Functionalization

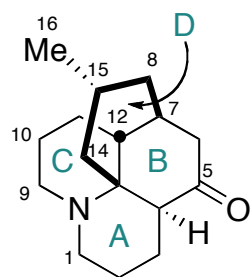
Daniel F. Fischer and Richmond Sarpong
J. Amer. Chem. Soc., ASAP



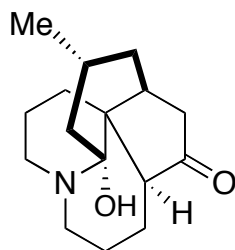
Synthesis of (+)-Complanadine A, an Inducer of Nerutrophic Factor Excretion

Changxia Yuan, Chih-Tsung Chang, Abram Axelrod, and Dionicio Siegel
J. Amer. Chem. Soc., ASAP

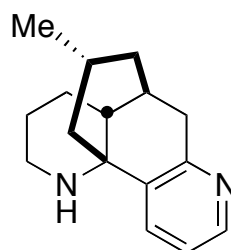
Lycopodium Alcaloids and Complanadine A



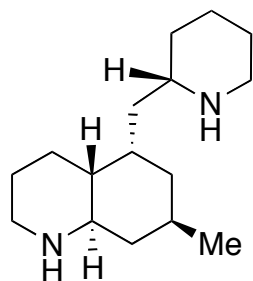
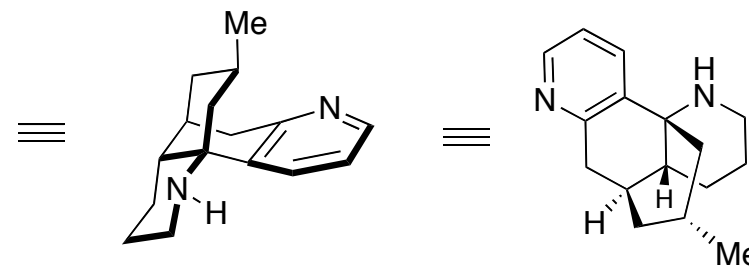
Lycopodine



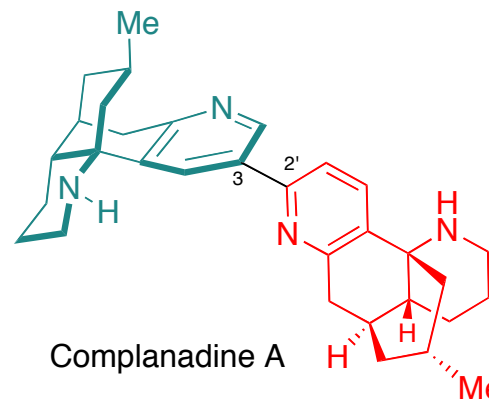
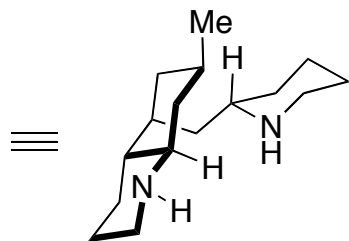
Fawcettimine



Lycodine



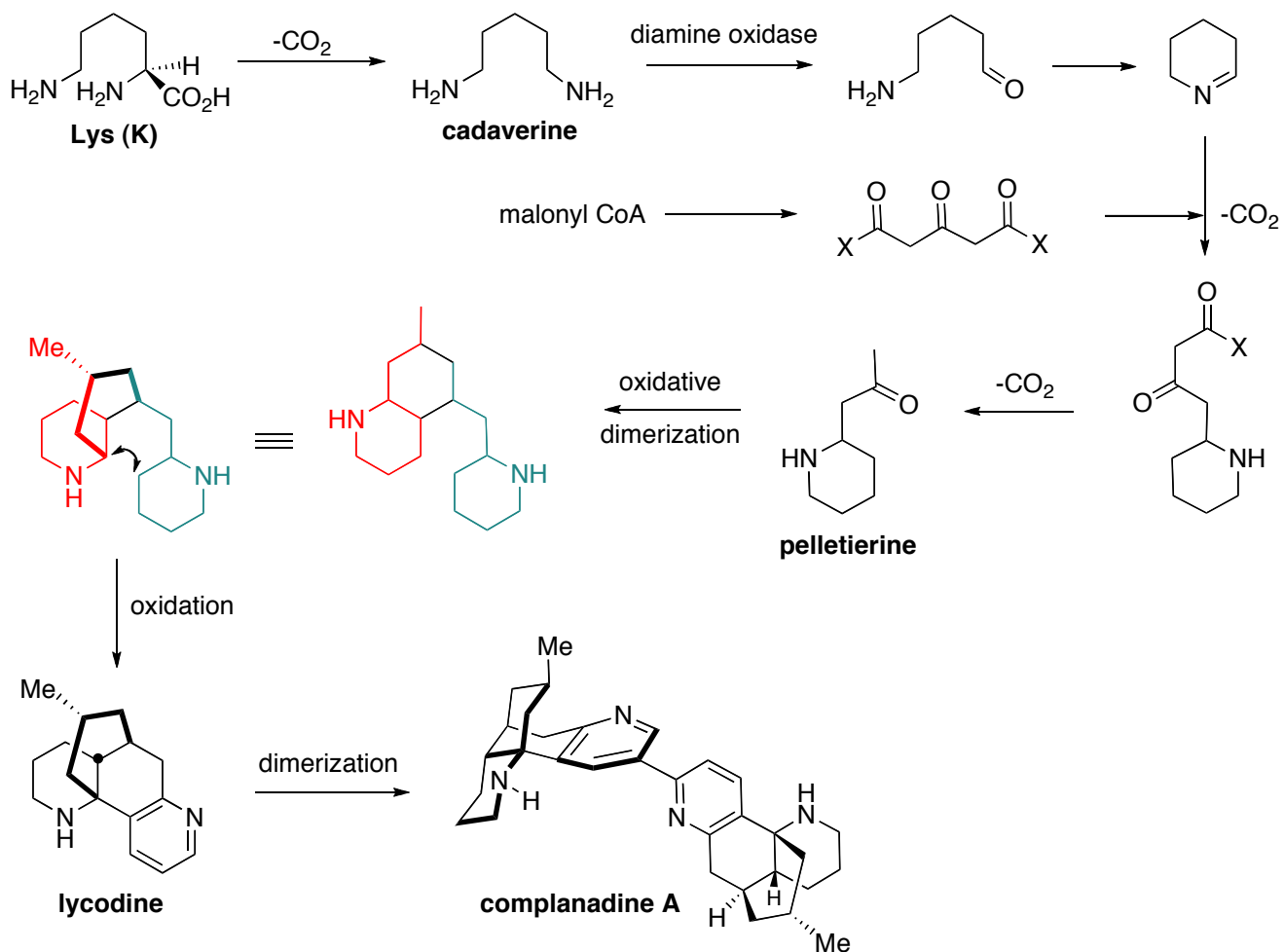
Phlegmarine



Complanadine A

For review see: Hudlicky, T.; and Reed, J.W. In *The Way of Synthesis*, 1st ed.; Wiley-VCH, 2007; pp 573-602..
Conroy, H.J. *Tetrahedron Lett.* **1960**, *10*, 34.
Fisher, D.; Sarpong, R.J. *Amer. Chem. Soc.* ASAP.

How Does Nature Make Complanadine A: Biosynthesis of *Lycopodium* Alkaloids

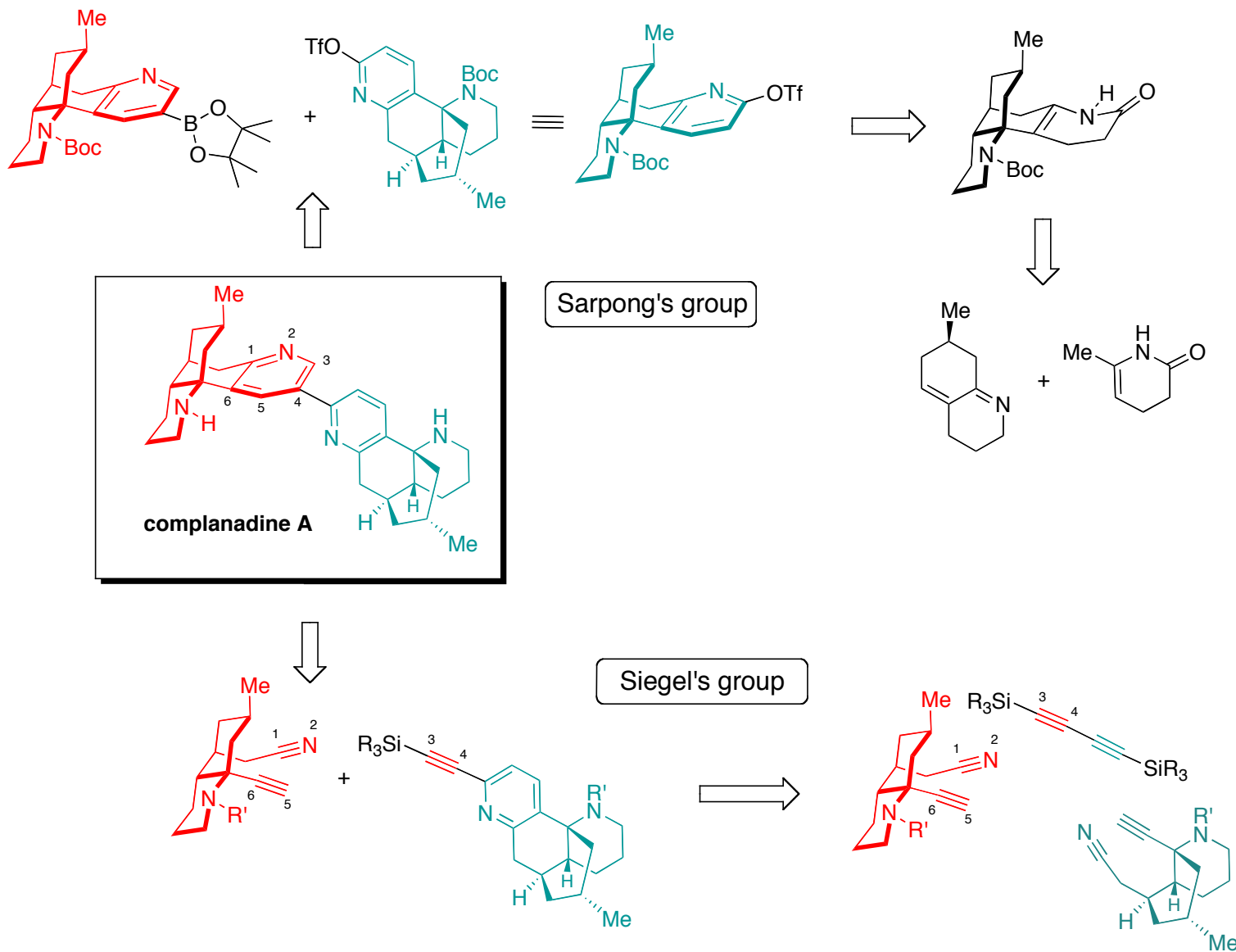


Hudlicky, T.; Reed, J.W. In *The Way of Synthesis*, 1st ed.; Wiley-VCH, 2007; pp 573-602 and references therein.

Conroy, H.J. *Tetrahedron Lett.* **1960**, *10*, 34.

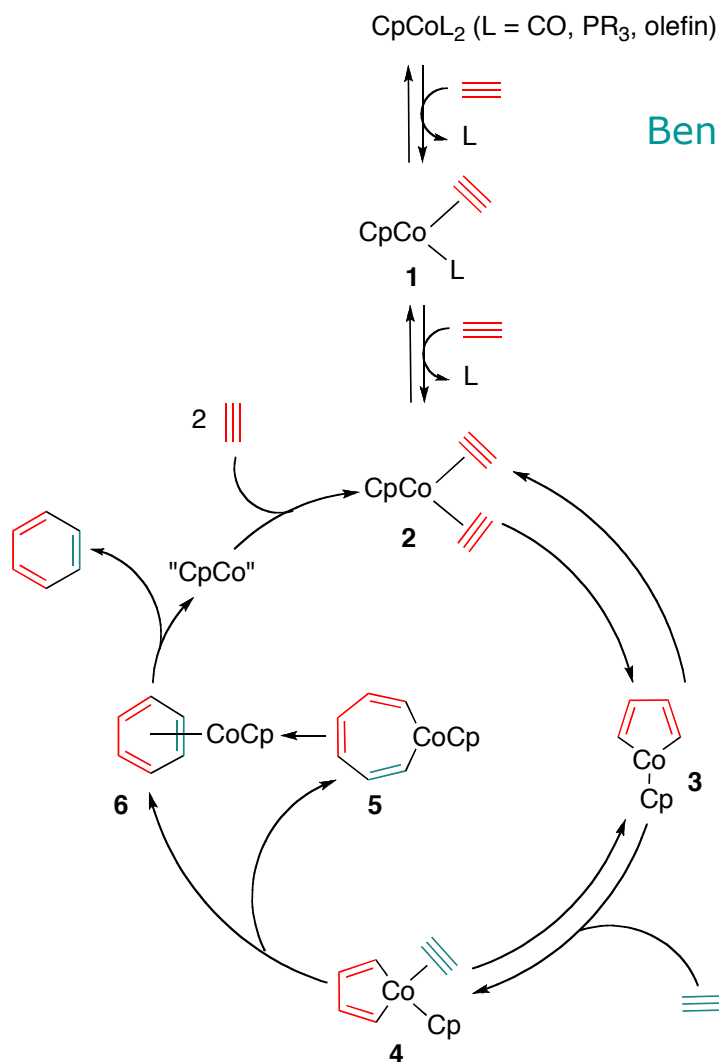
Stork, G. *Pure Appl. Chem.* **1968**, *17*, 383.

Retrosynthetic Approaches in the Sarpong and Siegel Groups

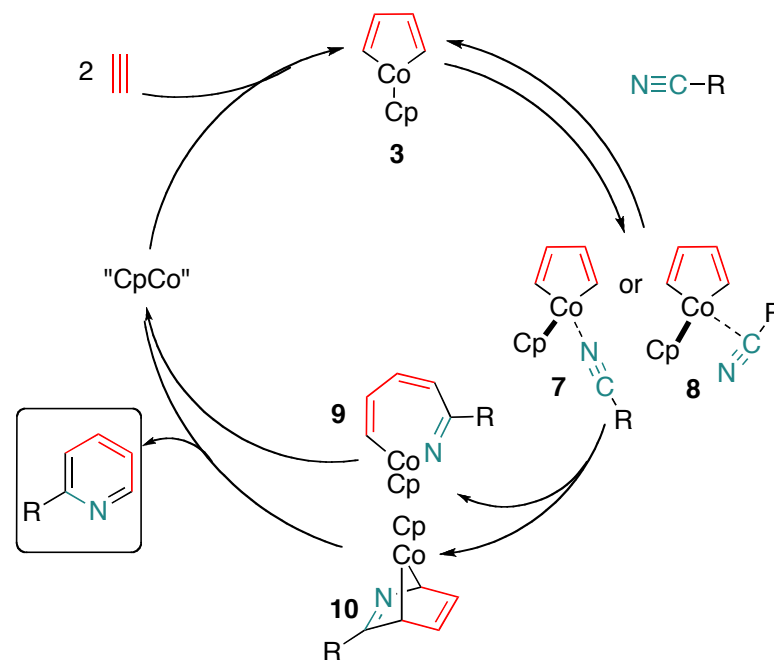


Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Amer. Chem. Soc.* ASAP.
 Fisher, D.; Sarpong, R. *J. Amer. Chem. Soc.* ASAP.

The Key Step in Siegel's Synthesis: [2+2+2] Cycloaddition

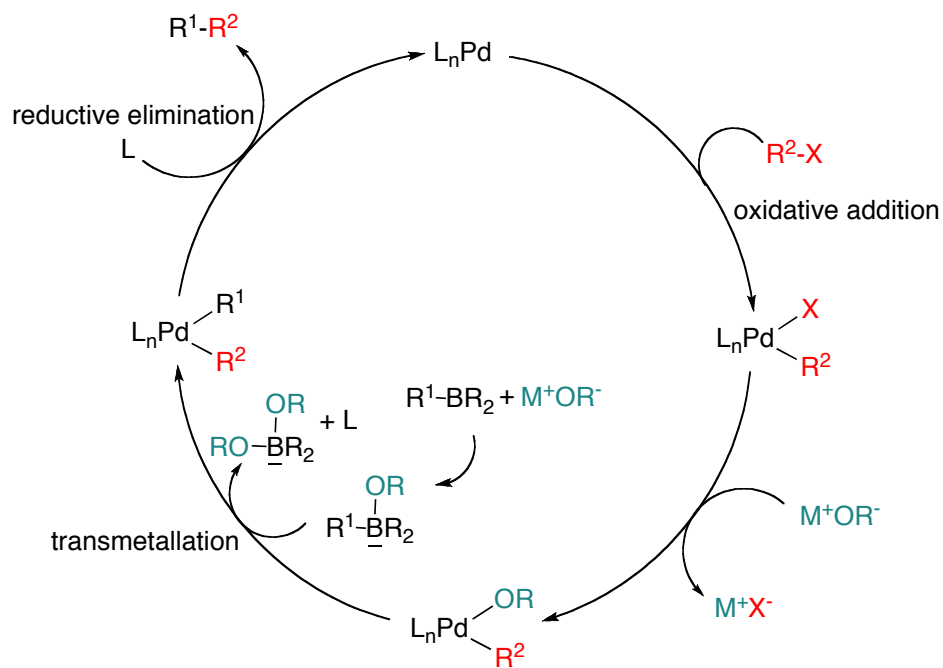


Benzene and Pyridine Synthesis by Cyclotrimerization



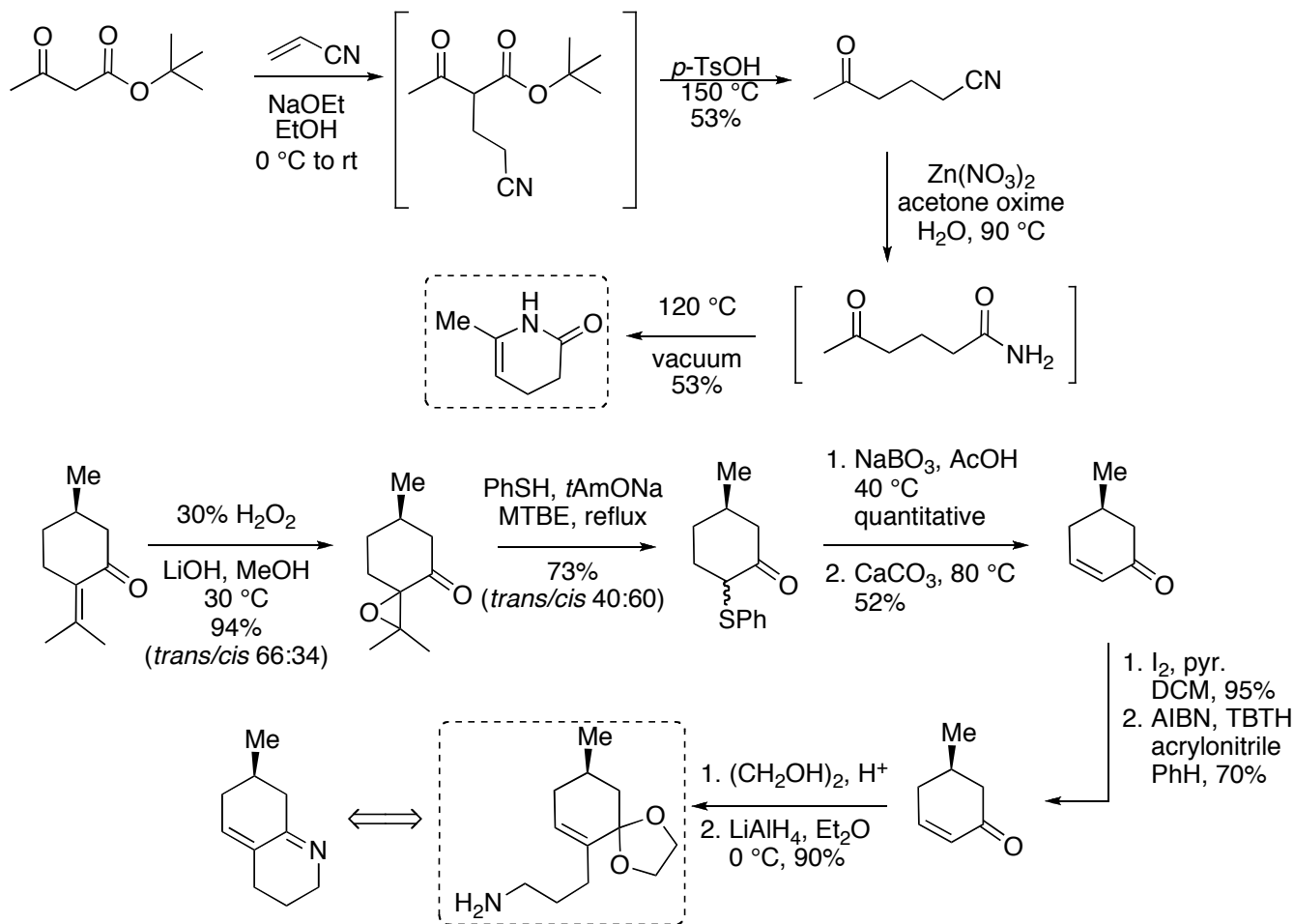
For an excellent review on pyridine synthesis by metal
Mediated cyclotrimerization, see: Varela, J.A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787.
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The Key Step in Sarpong's Synthesis: Suzuki Reaction



Kurti, L.; Czako, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; pp 448-449.

Sarpong: Precursors Syntheses



Näslund, G.; Senning, A.; Lawesson, S.-O. *Act. Chem. Scand.* **1962**, *16*, 1324.

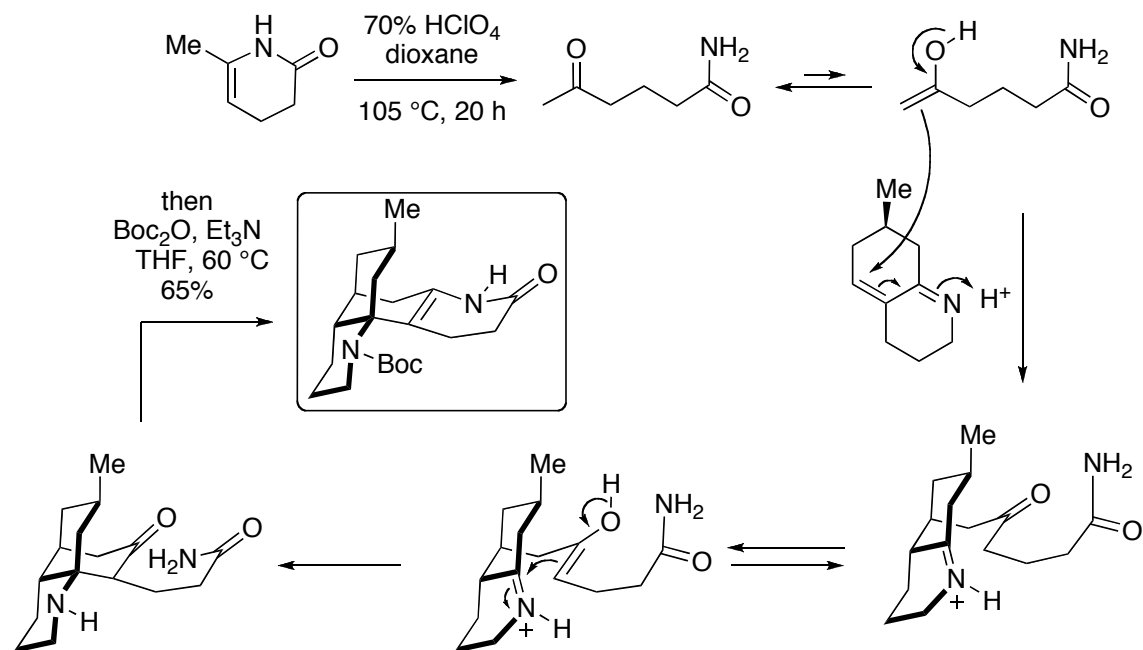
Koylovich, M.N.; Kukushkin, V.Y.; Haukka, M.; Fransto da Silu, J.J.R.; Pombeiro, A.J.L. *Inorg. Chem.* **2002**, *41*, 4798.

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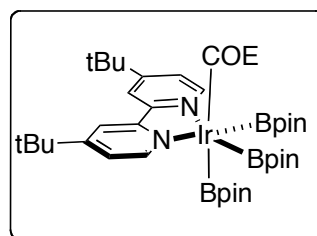
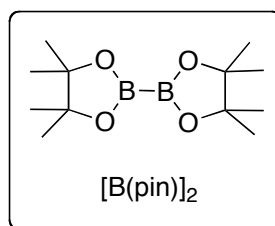
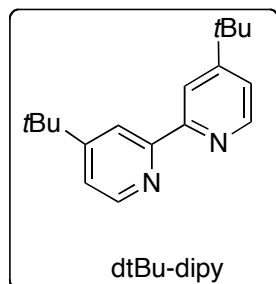
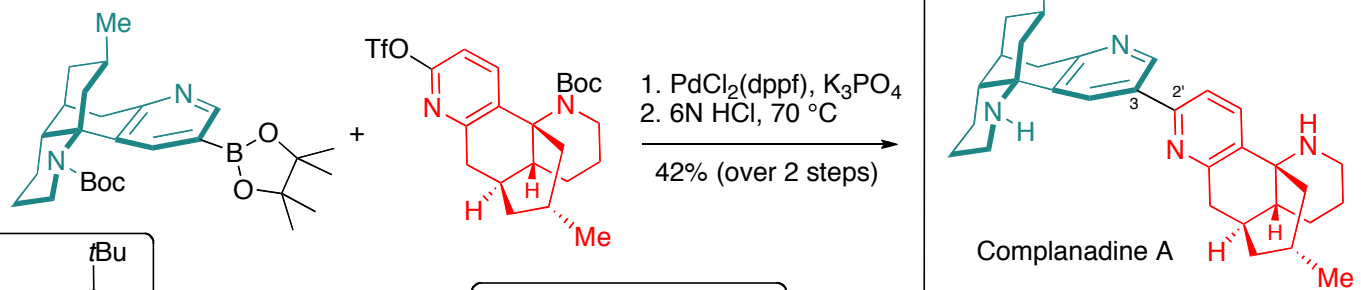
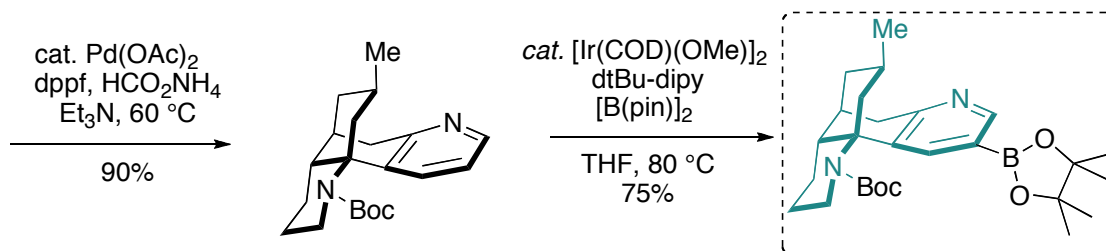
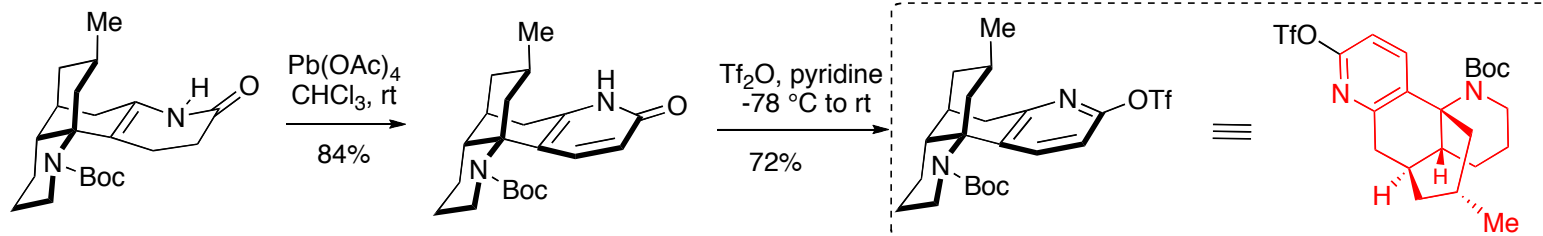
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Sarpong: Tricyclic Intermediate Synthesis



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Sarpong's Synthesis: Complandine A Formation



Takagi, J.; Sato, K.; Hartwig, J.F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, 43, 5649.

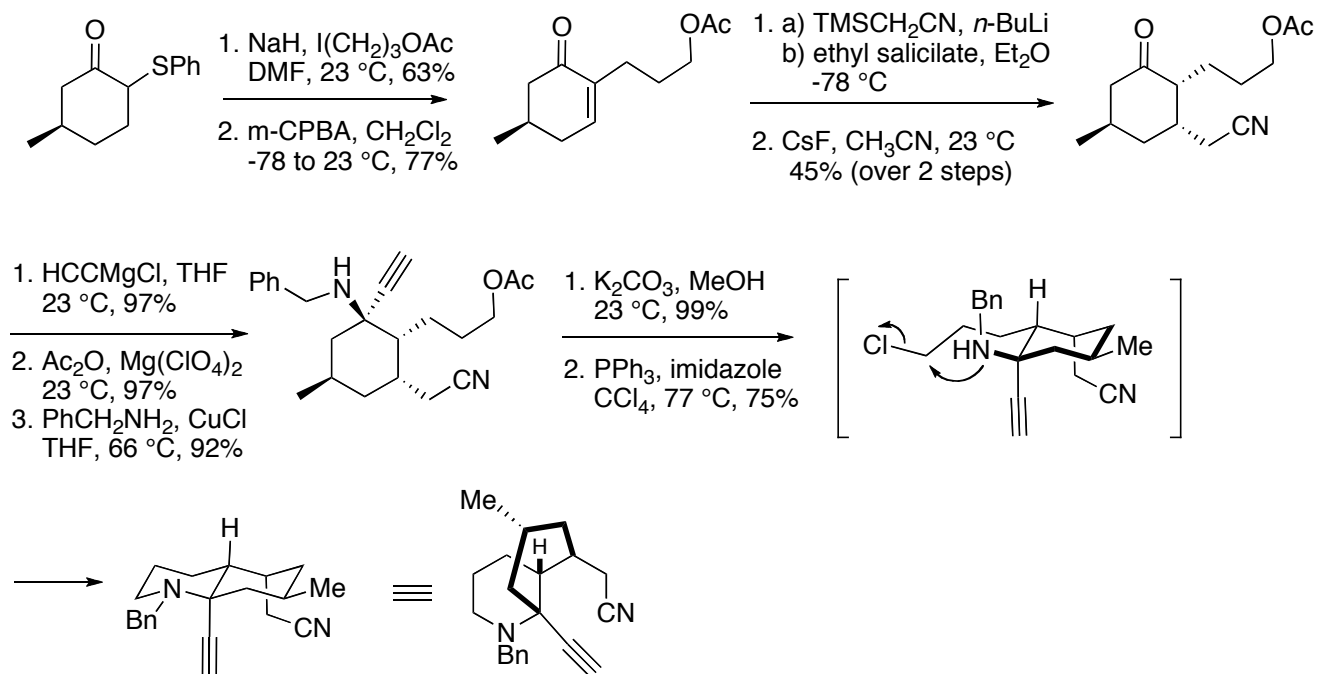
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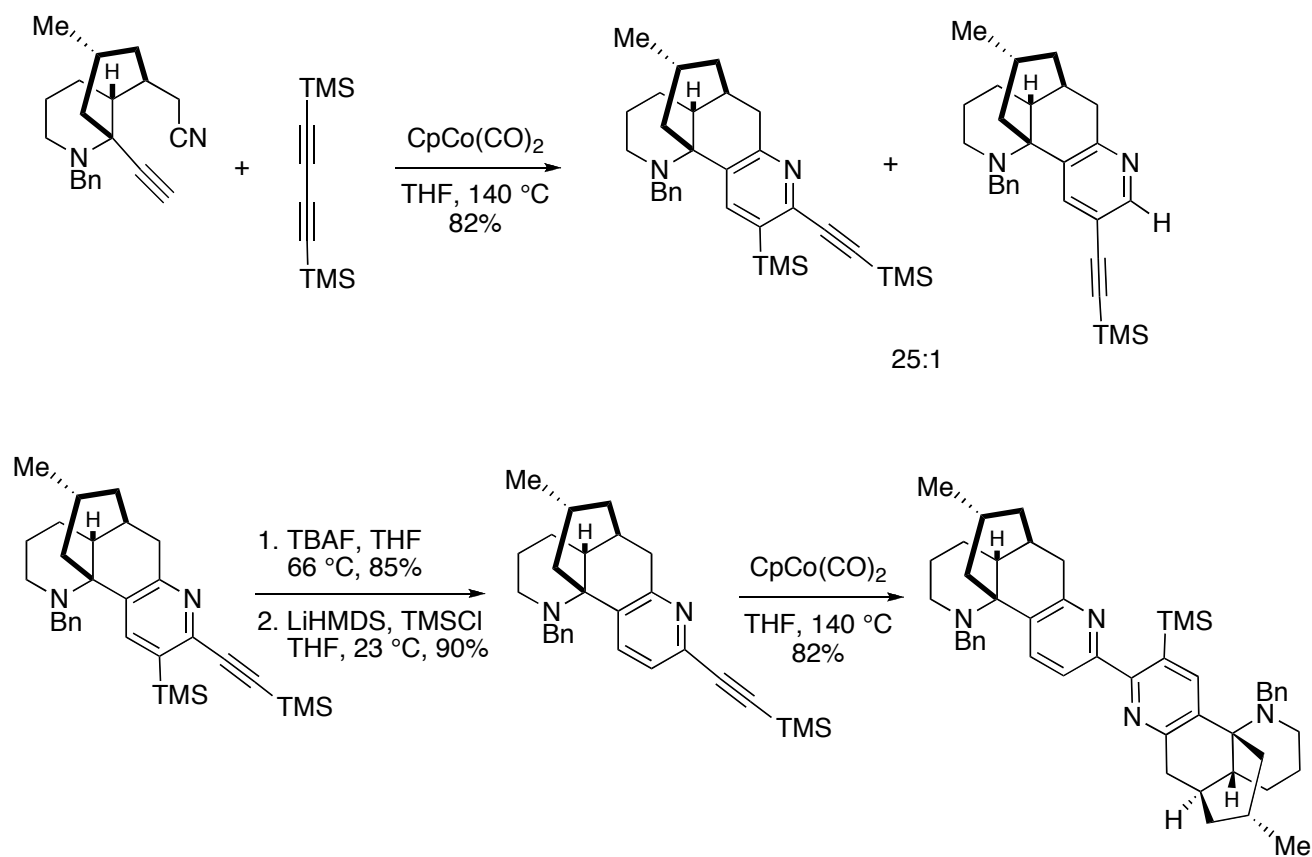
Fisher, D.; Sarpong, R. *J. Amer. Chem. Soc. ASAP*.

Siegel's Synthesis: Starting Material Preparation



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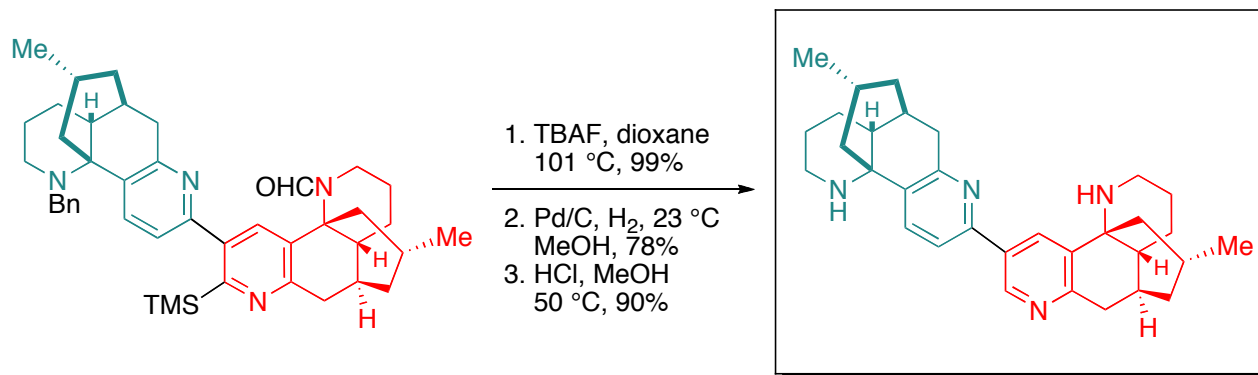
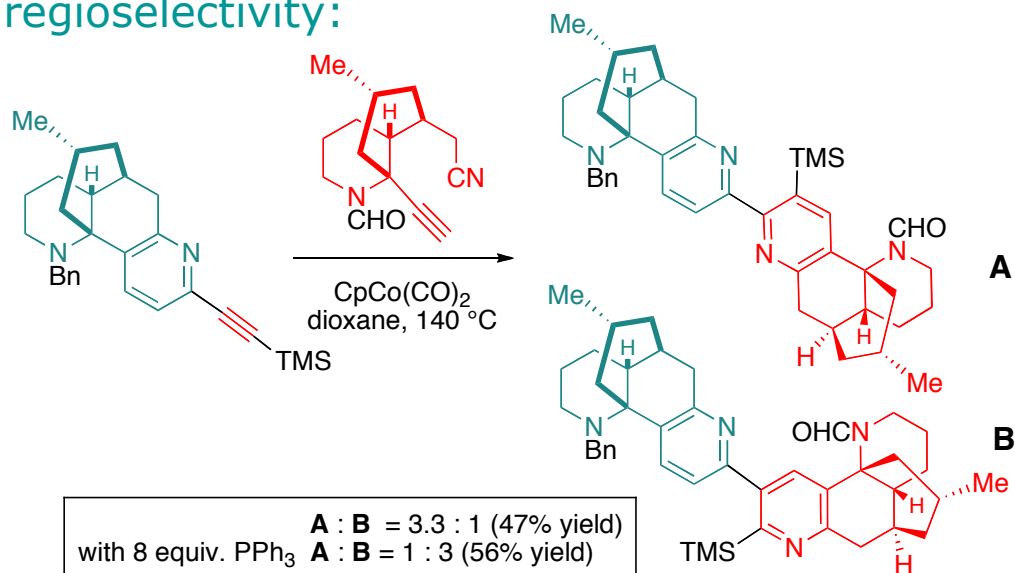
Siegel's Synthesis: Cyclotrimerization and Regioselectivity Problem



Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. J. *Amer. Chem. Soc. ASAP*

Siegel's Synthesis: End Game

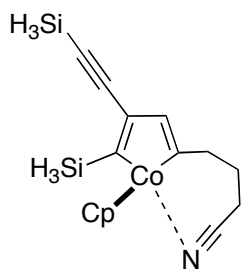
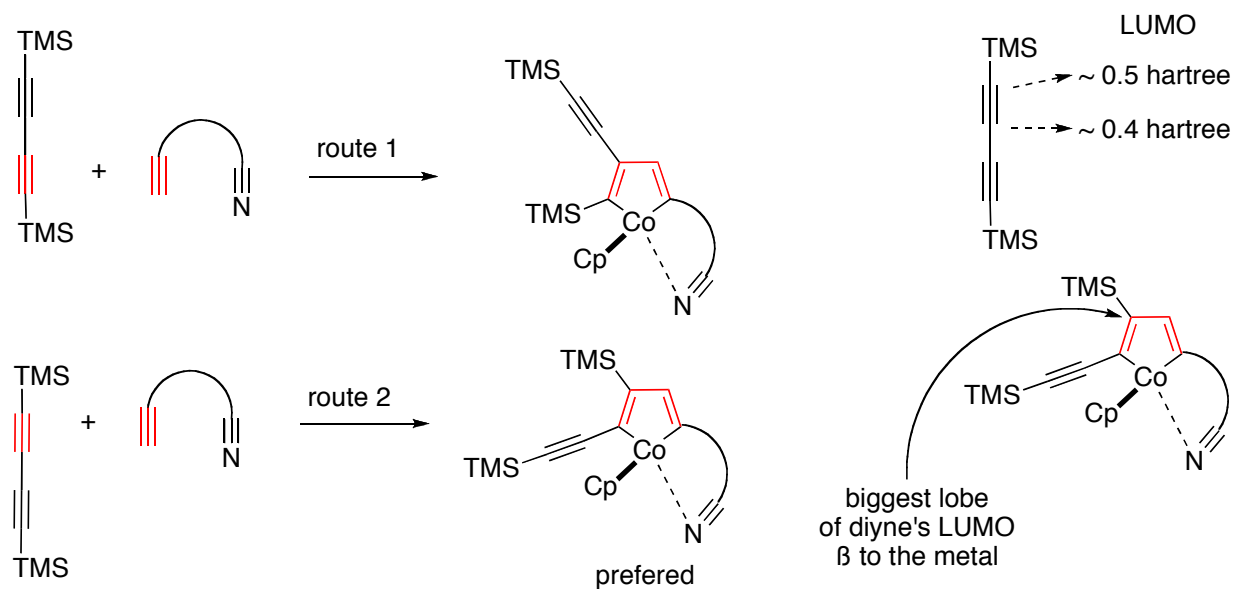
Changing the regioselectivity:



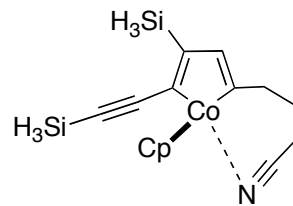
"The use of formyl in place of the benzyl group was required as "coupling partners" failed to react"
"The ability of PPh_3 to change the regioselectivity warrants further study"

Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Amer. Chem. Soc.* ASAP

Siegel's Synthesis: Cyclotrimerization Regioselectivity Explanation



Ab initio energies: -789.740069812

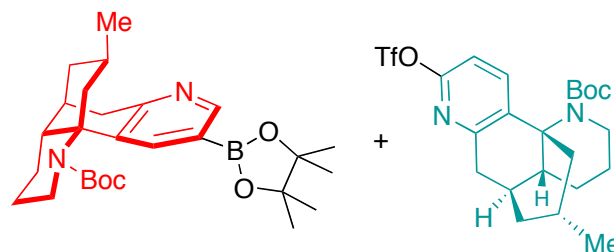


-789.746989353
preferred

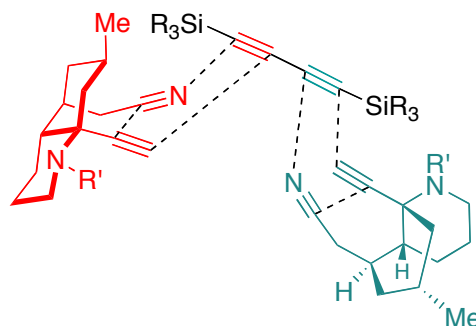
Varela, J.A.; Castedo, L.; Saá, C. *J. Amer. Chem. Soc.* **1998**, *120*, 12147.
Stockis, A.; Hoffmann, R. *J. Amer. Chem. Soc.* **1980**, *102*, 2952.

Conclusions

- Both syntheses are based on the “symmetry” of Complanadine A:
Nature mimicking approaches
- Sarpong’s key step: Hartwig-Miyaura Ir(I)-catalyzed borylation and Suzuki-Miyaura coupling



- Siegel’s key step: Co(I)-catalyzed [2+2+2] cycloaddition – cyclotrimerization



- Biological studies in progress: The influence of the compound on primary cultures of rat glial cells and examining the effects on the biosynthesis of neurotrophin mRNA