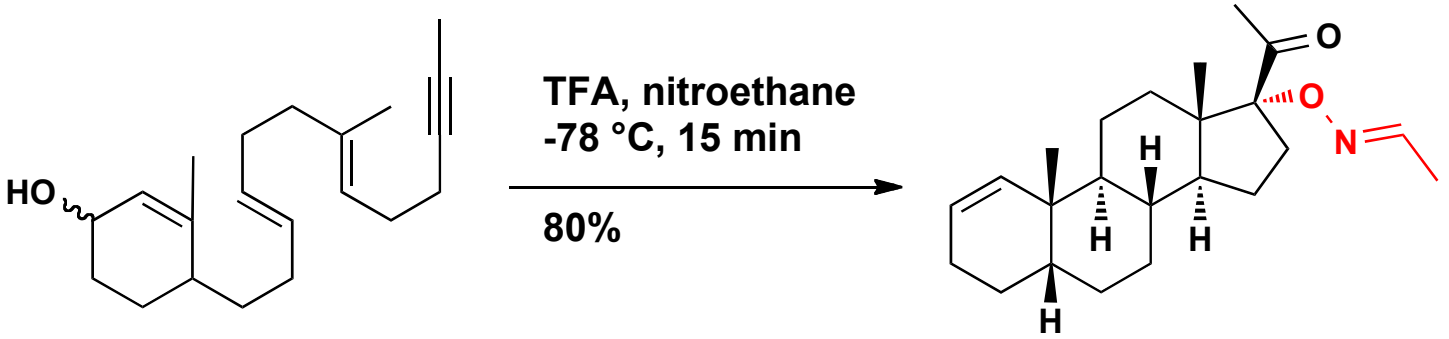
Domino Process in Organic Synthesis

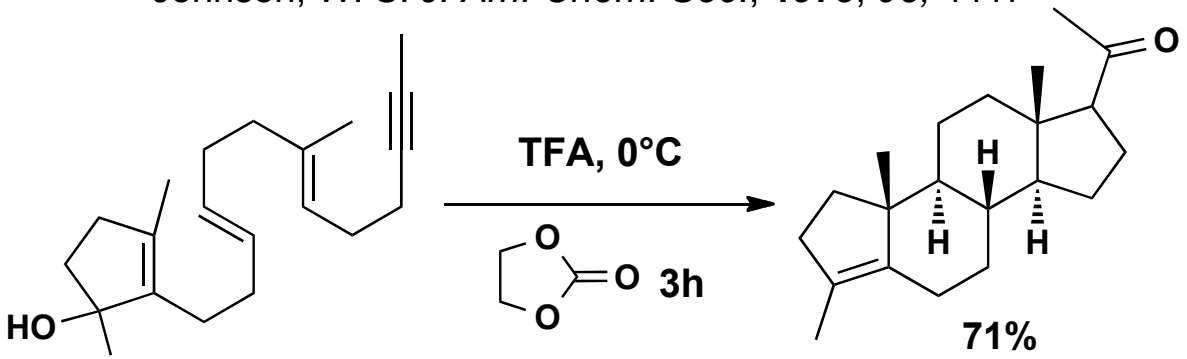
Domino process: a combination of two or more bond-forming reactions under identical conditions *wherein the subsequent reactions result as a consequence of the functionality formed in the previous step*.
Could be: Uni-molecular (Intramolecular), Bi-molecular and Multi-component
***Related terms*: Cascade reaction, Tandem reaction**

a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136;
b) Domino Reactions in Organic Synthesis; L. F. Tietze, G. Brasche, K. Gericke, Eds.; Wiley-VCH, Weinheim, **2006**.
c) Domino recations, Ed: L. F. Tietze, Wiley-VCH, Weinheim, **2014**.
c) In natural product synthesis: Nicolaou, K. C. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134--7186.

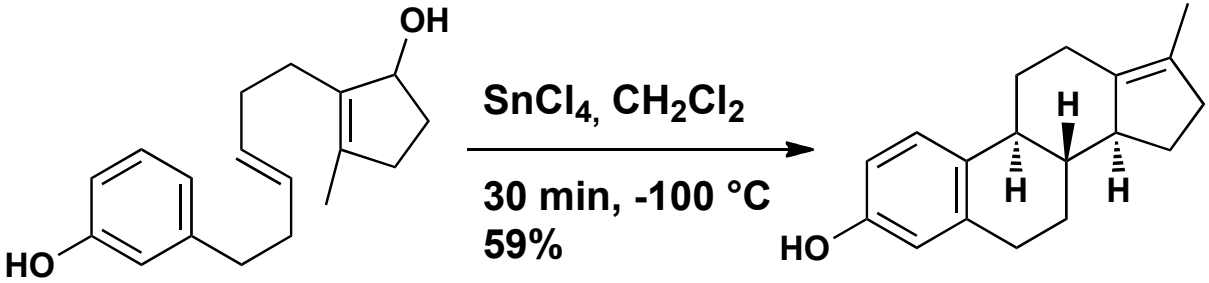
Classical Examples: Johnson's Synthesis of Steroids



Johnson, W. S. *J. Am. Chem. Soc.*, **1973**, *95,* 4417

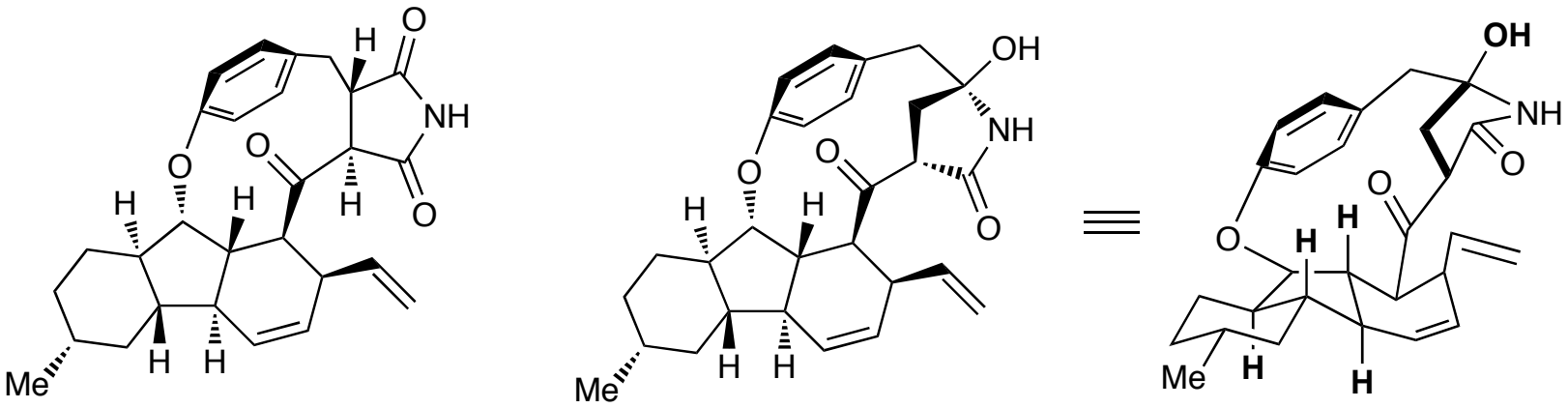


Johnson, W. S. *Angew. Chem. Int. Ed*. **1976,** *15,* 9



Johnson, W. S. *J. Am. Chem. Soc.*, **1973**, *95,* 7501.

Hirsutellone A and B

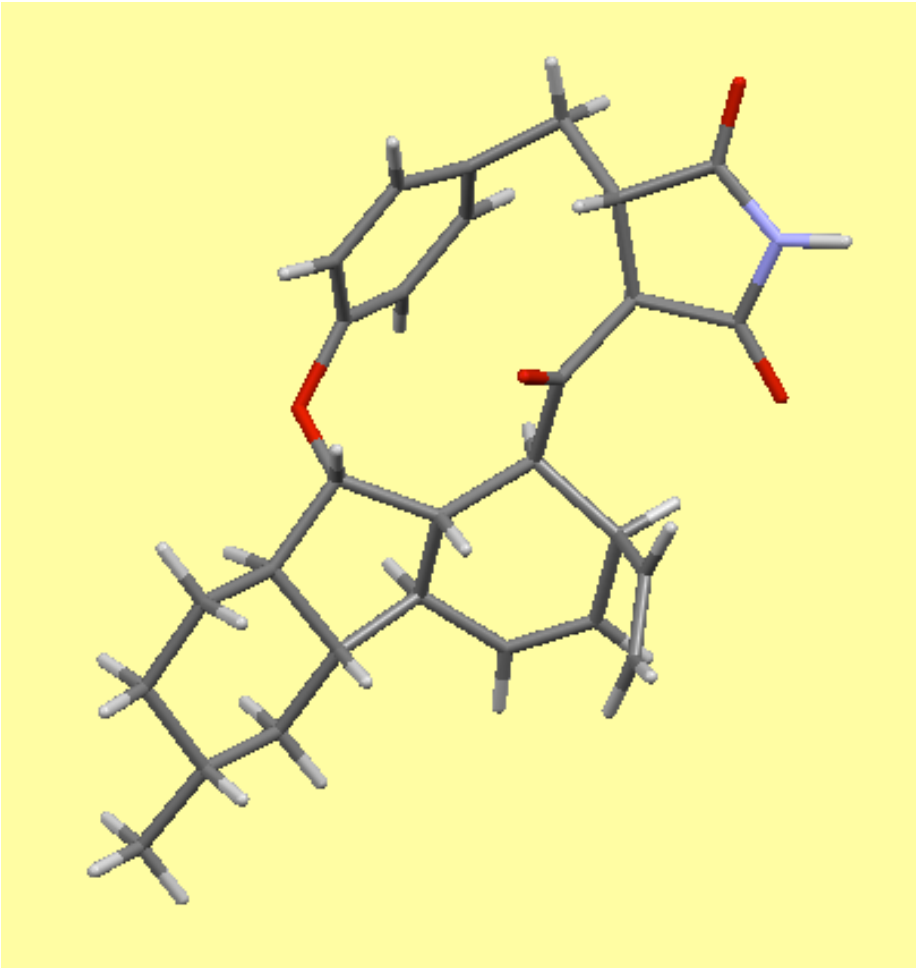


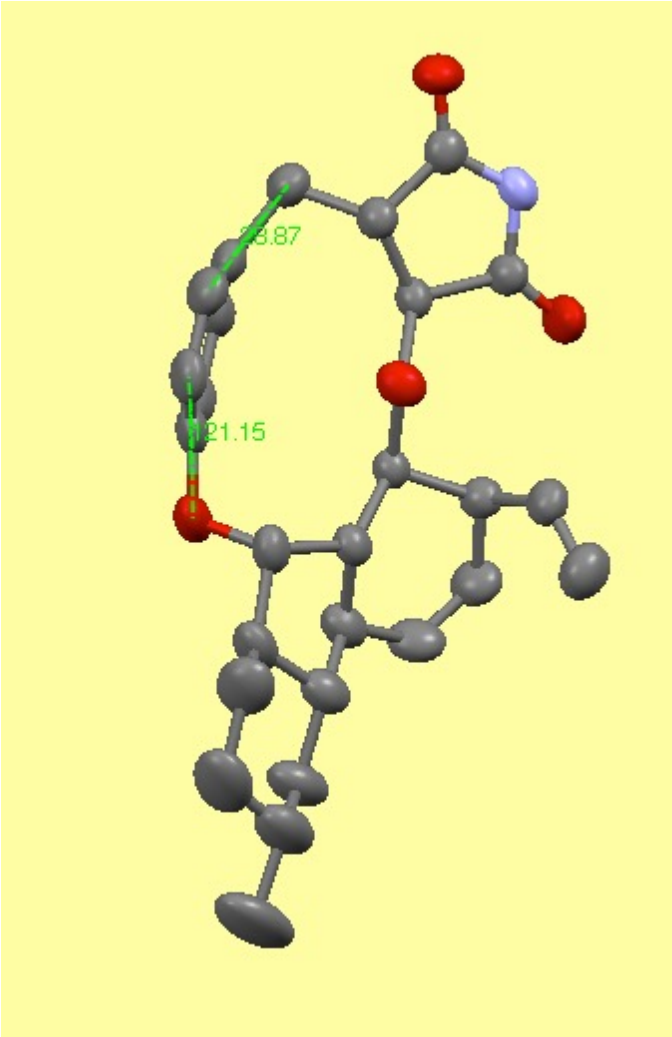
Isolated from *Hirsutella nivea* BCC 2594
Fungal Secondary metabolites with antifungal, antibiotic activities
MIC = 0.78 mg/L against *Mycobacterium tuberculosis*

6,5,6-fused trans, trans-tricycle, a γ-lactam, a 12- (hirsutellon A) or 13-membered (hirsutellon B) *para*-cyclophane, an ando ary-alkyl ether linkage.
10 stereocenters, 7 of them are contiguous

Isaka, M. et al. *Tetrahedron* **2005**, *61*, 5577-5583.

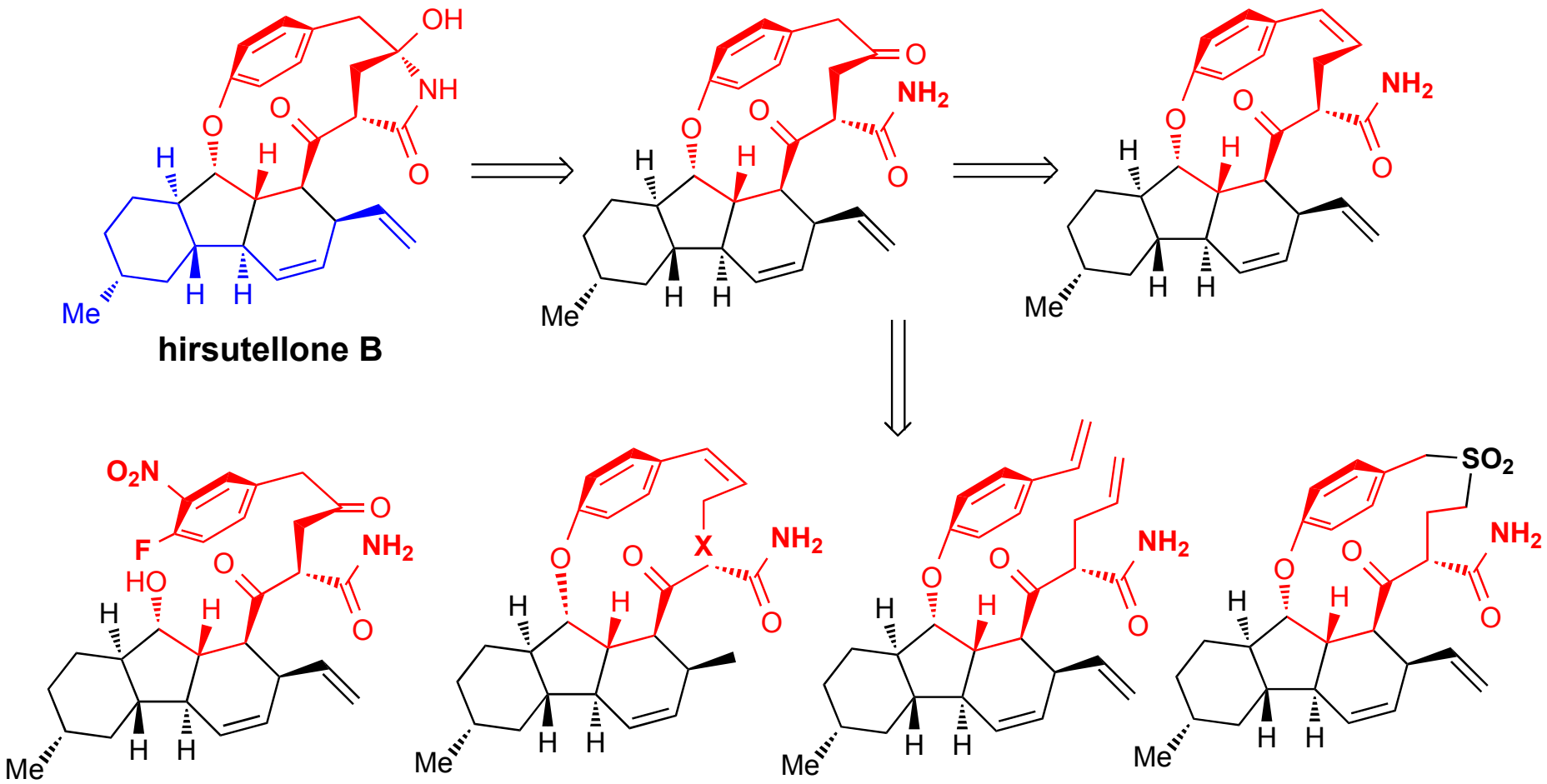
X-ray Structure of Hirsutellone A





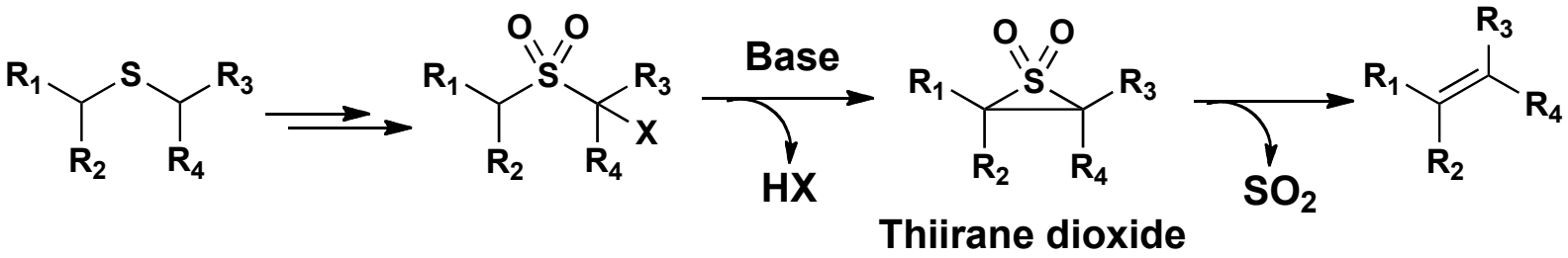
A clearly bent cyclophane unit

Access to 13-Membered *p*-cyclophane: Possible Disconnections



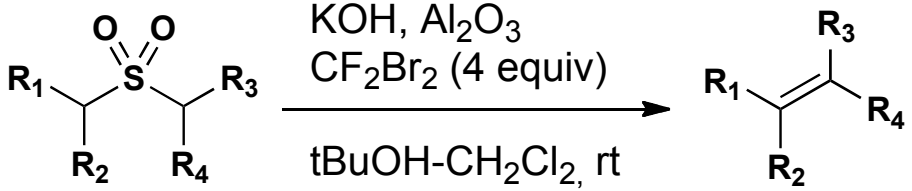
Rev on synthesis of strained cyclophane: Baran, P. *Nat. Prod. Rep*. **2012**, *29*, 899-934.

Ramberg-Bäcklund Reaction



L. Ramberg; B. Bäcklund, A*rk. Kern. Mineral. Geol.,* **1940**, *13A*, 50.
L.A. Paquette, A*cc. Chem. Res.,* **1968**, *1*, 209.

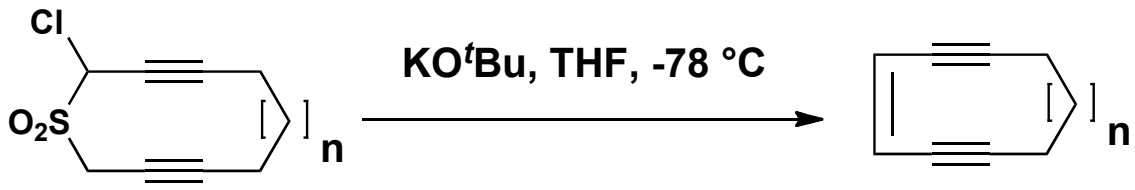
Chan's modification:



T.-L. Chan, et al *Chem. Commun*. **1994,** 1771-1772.
J. Org. Chem., **2003,** *68,* 2948.

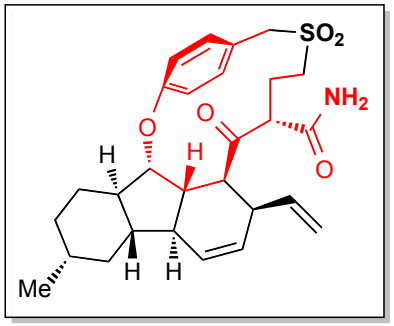
***Cheletropic reaction*: processes in which two σ bonds terminating at a single atom are made, or broken, in concert.**
Ramberg-Bäcklund reaction is a cheletropic reaction

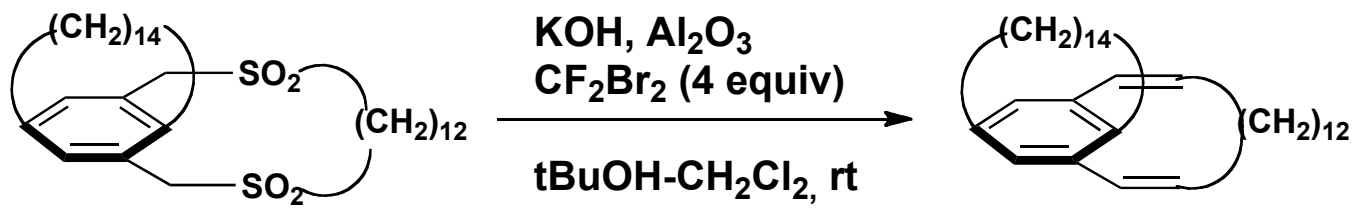
Background Search— Ramberg-Bäcklund Reaction



n = 3-8, yield: 32-52%

Nicolaouk K. C. *J. Am. Chem. SOC.* **1992,** ***114,*** 7360-7371





T.-L. Chan, et al *J. Org. Chem.*, **2003,** *68,* 2948.

Powerful methode for generating the strained molecules

Macrocyclization: Entropic Factor

Macrocyclization: generally disfavored entropically, disfavored enthapically as well if the macrocycle is strained.

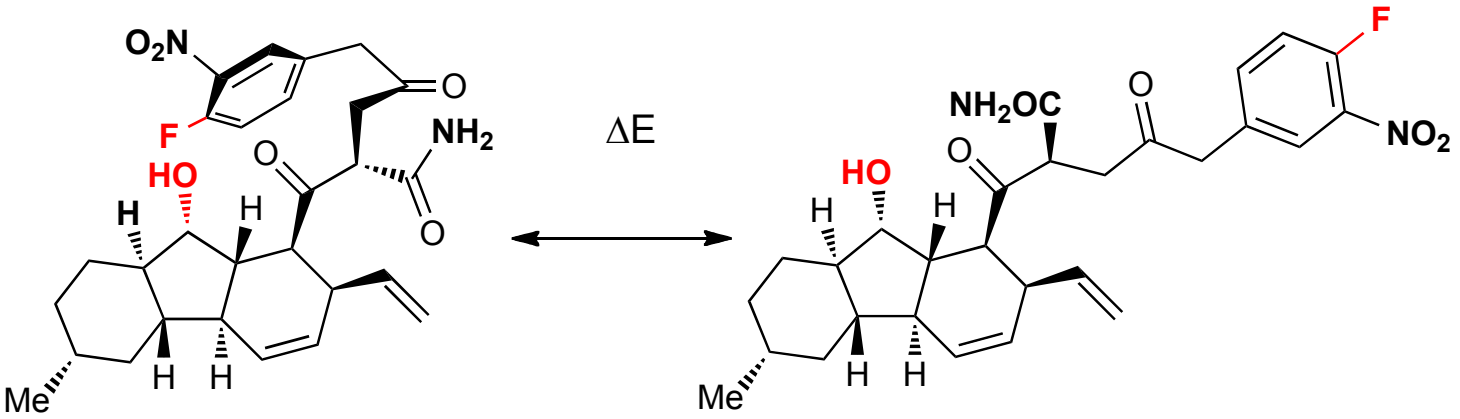
***"Solutions"*:**

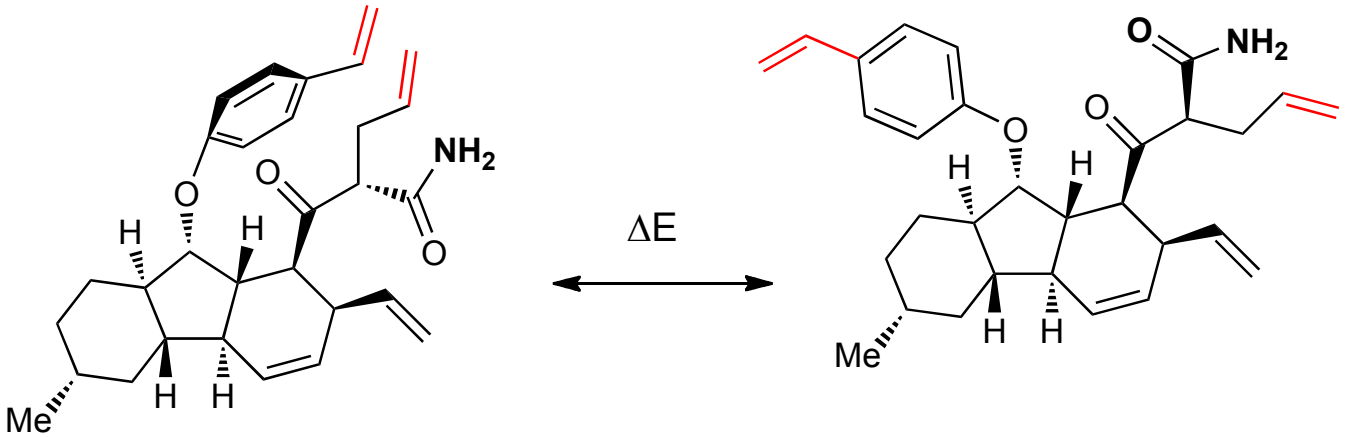
a) **Perform the reaction at high dilution**
b) **Via ring contraction (eg: Ramberg-Bäcklund reaction)**
c) **Conformational pre-organization**
   *** Intrinsic conformational preference: Low energy conformation is conducive to macrocyclization**
   *** Template effect**
   and so on……

Macrocyclization: Reactivity match, Steric effect, and…*conformation of substrate*…needed to be considered

Conformation-directed macrocyclization:
Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem*. **2005**, 1949-1964.
Rev on synthesis of strained cyclophane: Baran, P. *Nat. Prod. Rep*. **2012**, *29*, 899-934.

Different Bond-disconnections Give Cyclization Precursor with Different Conformational Properties





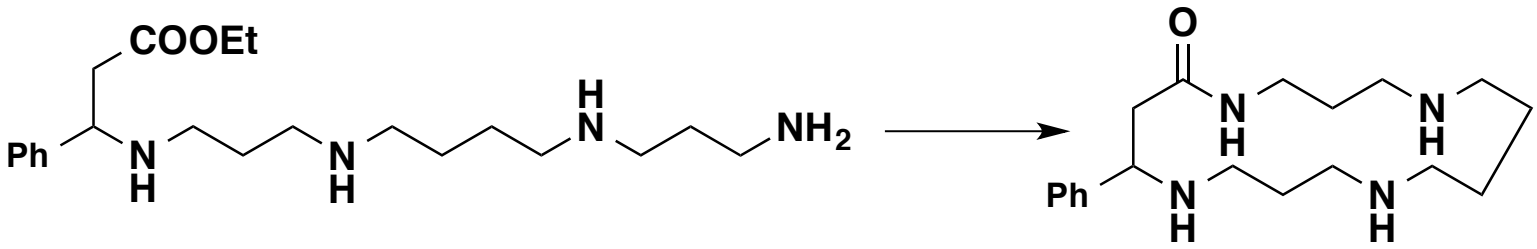
Conformation conducive to macrocyclization

Conformation conducive to oligomarization

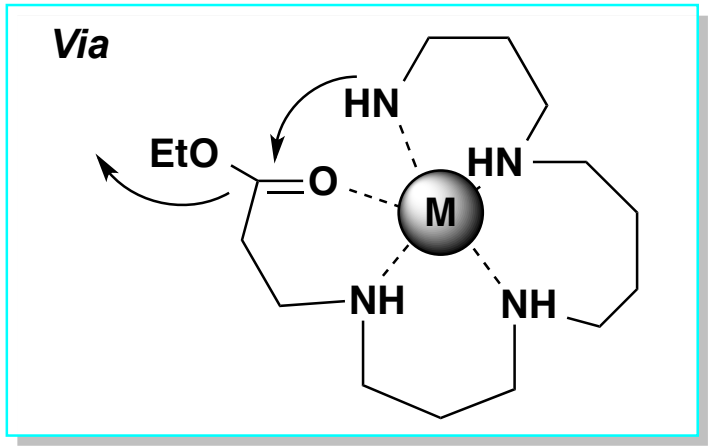
Computational study: **Useful tool to "predict" the conformational preference of a given compound**

Rev on synthesis of strained cyclophane: Baran, P. *Nat. Prod. Rep*. **2012**, *29*, 899-934.

Metal-templated Macrocyclization

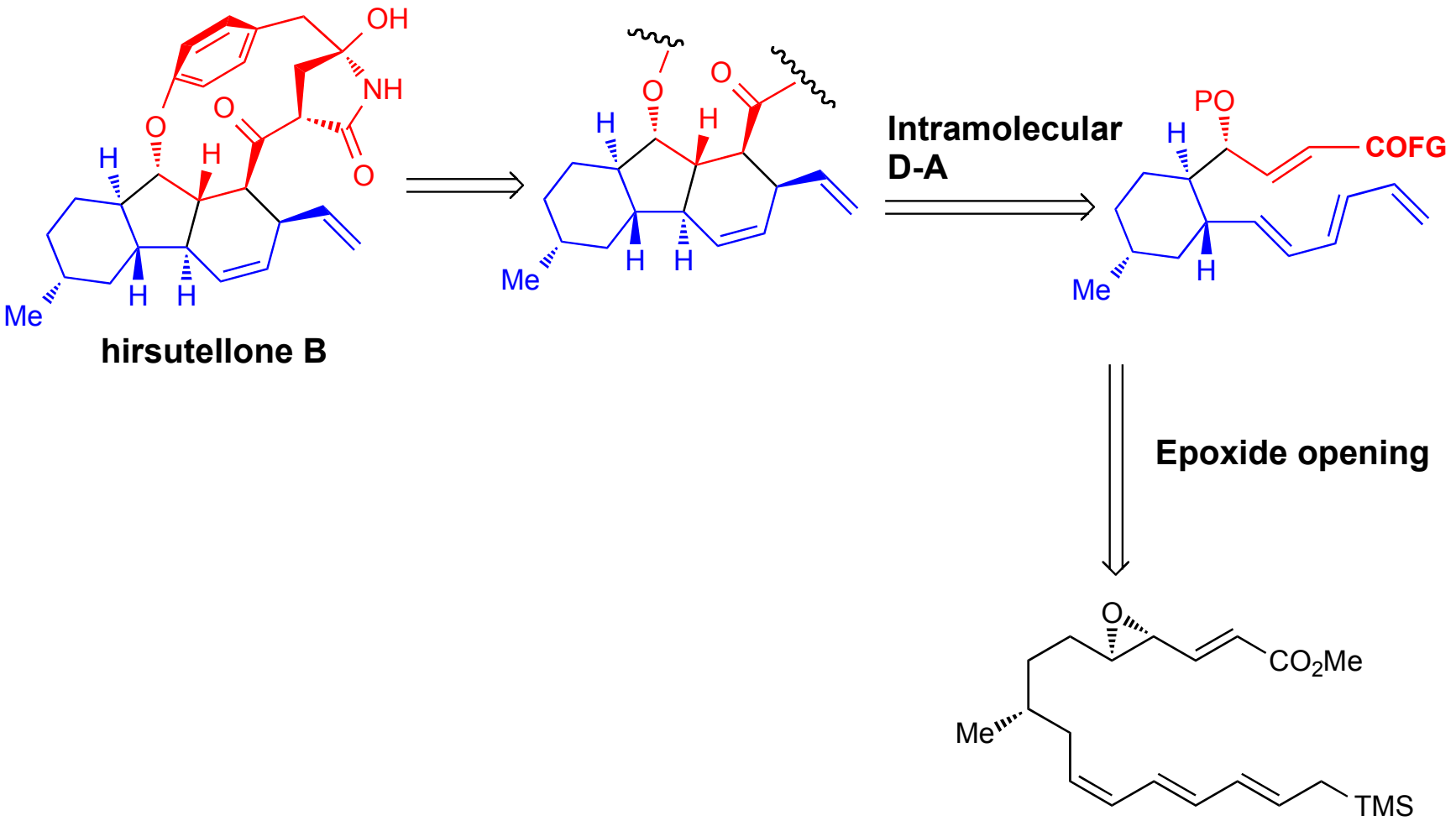


a) benzene, reflux, no cyclization
b) benzene, reflux, $Sb(OEt)_3$, 90%

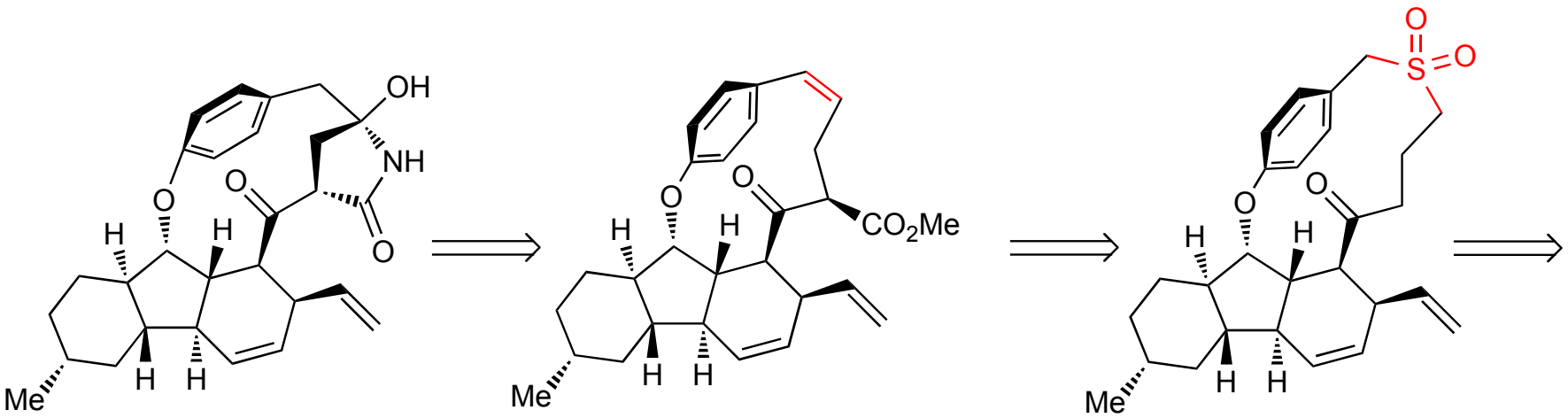


Yamamoto, H. *J. Am. Chem. Soc.*, **1996**, *118*, 1569-70.

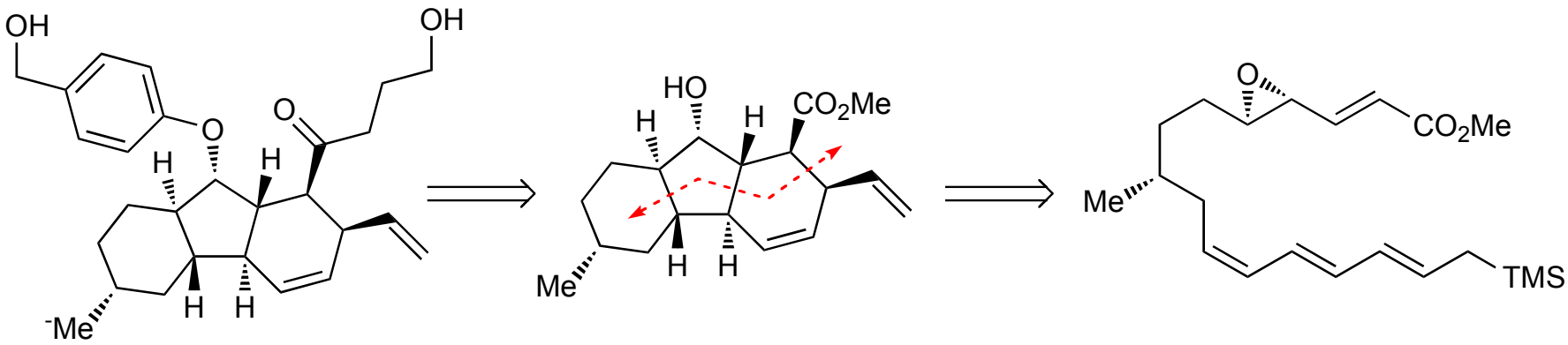
Access to Tricyclic Ring System



Nicolaou's Synthesis of Hirsutellone B



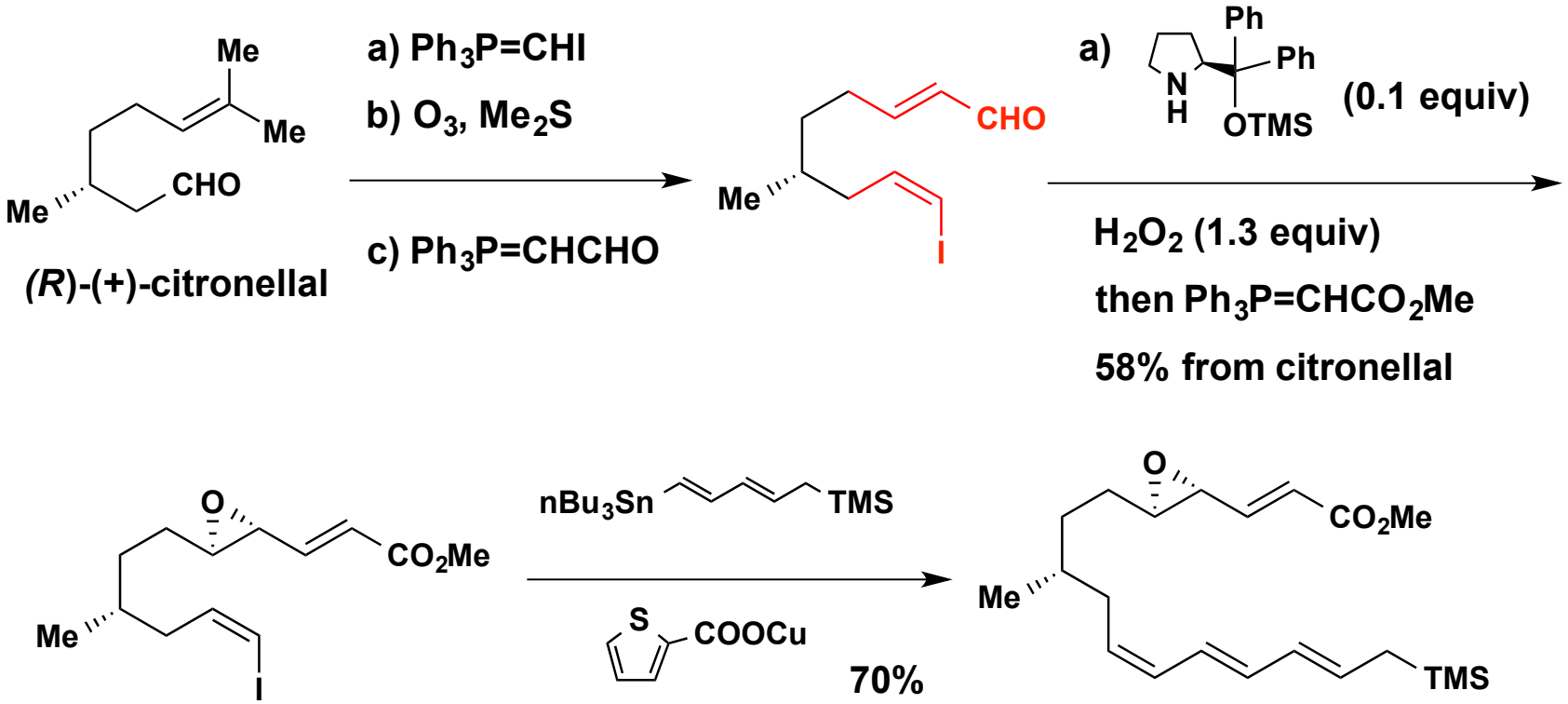
Ramberg-Bâcklund reaction



Domino Epoxide opening/intramolecular Diels-Alder reaction

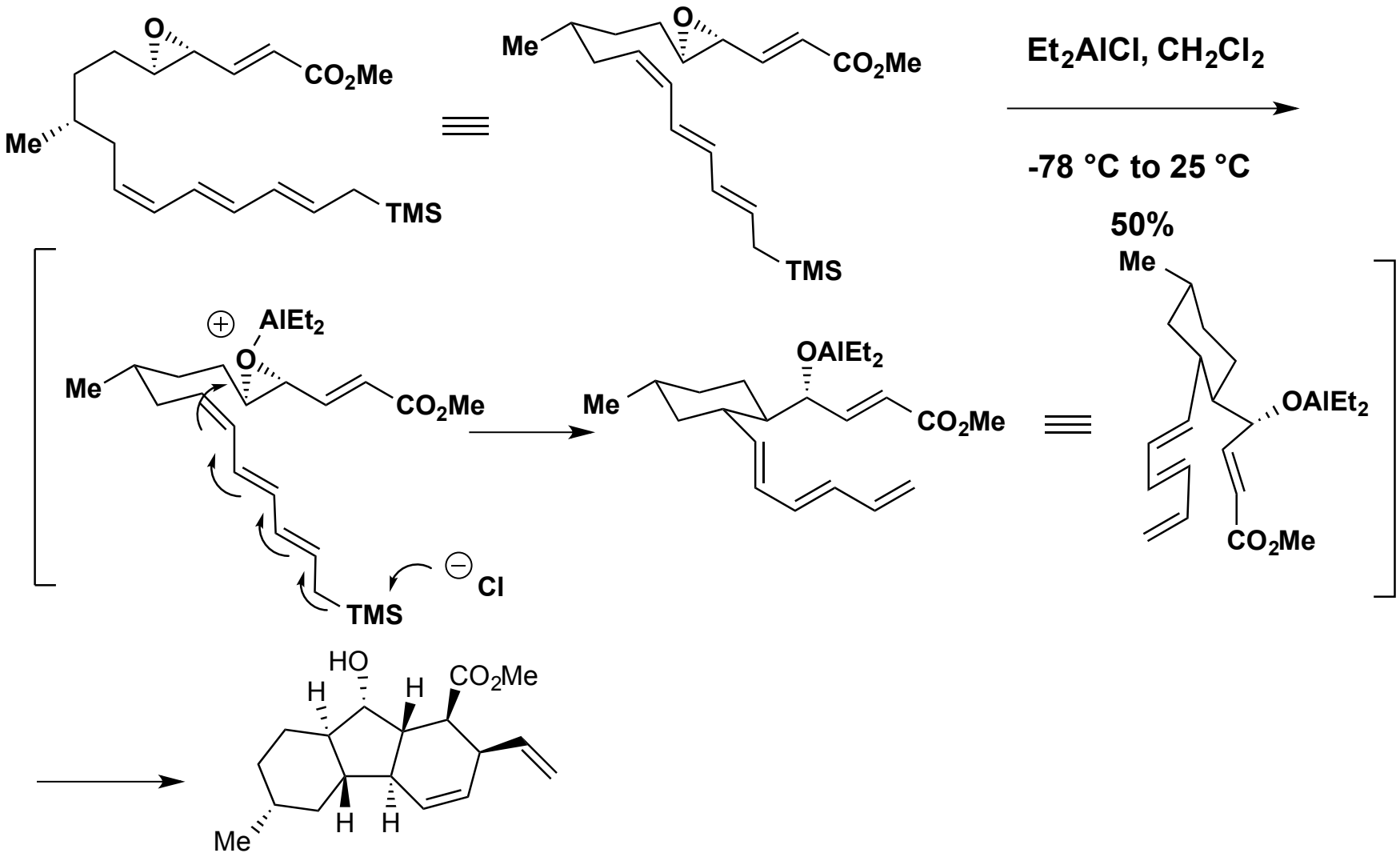
K. C. Nicolaou, D. Sarlah, T. R. Wu, W. Zhan, *Angew. Chem. Int. Ed*. **2009**, *48*, 6870-6874.

Nicolaou's Synthesis of Hirsutellone B: Access to Cyclization Precursor

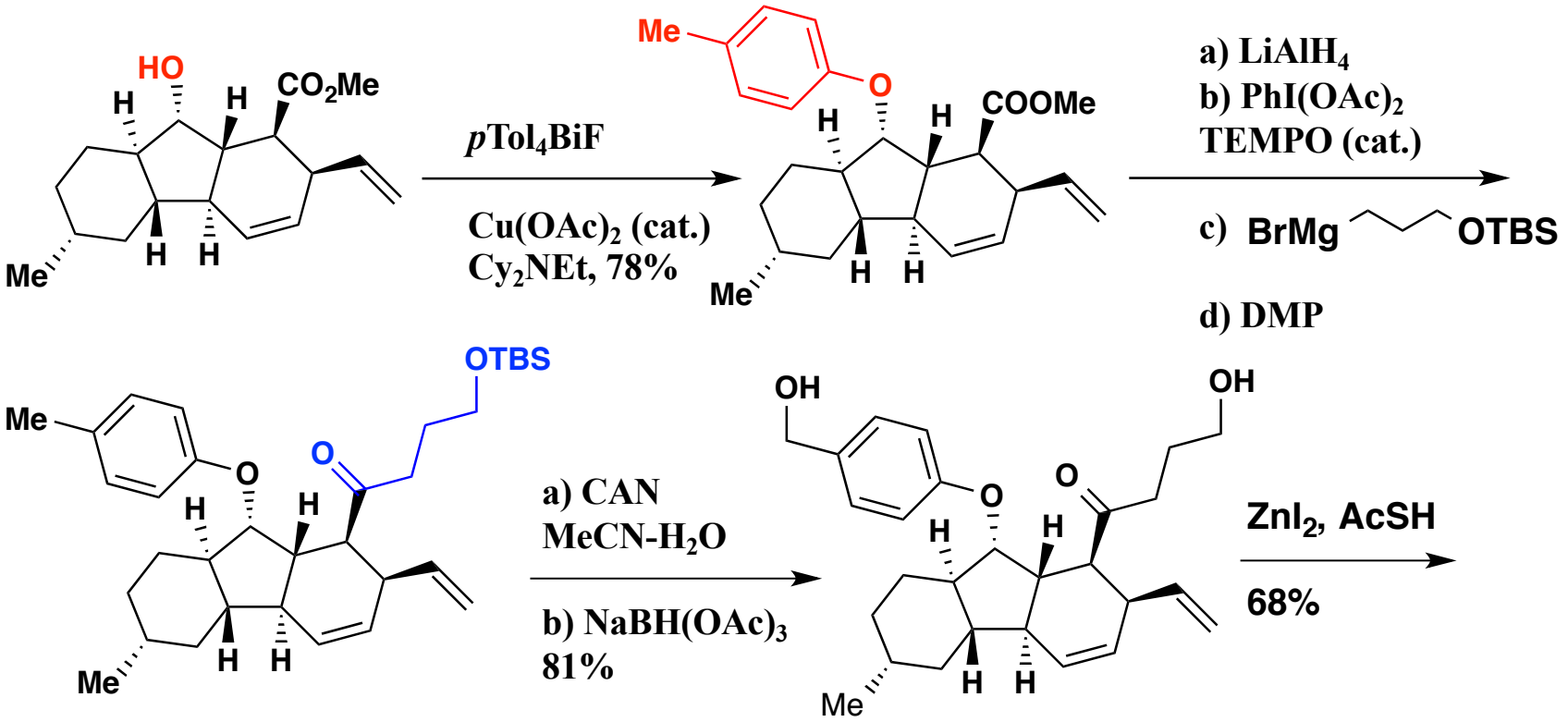


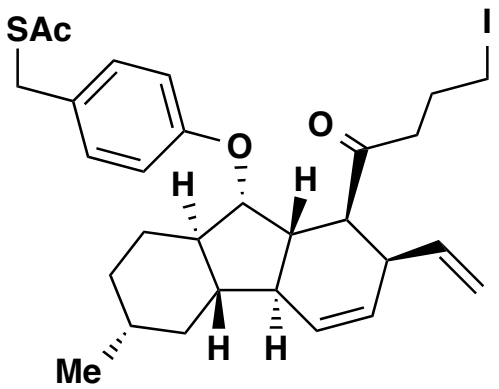
Organocatalytic enantioselective epoxidation: K. A. Jorgensen, *J. Am. Chem. Soc*. **2005**, *127*, 6964-6965.
Cu-mediated cross coupling of organostanne: Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748-2749.

Nicolaou's Synthesis of Hirsutellone B: Domino Epoxide Opening/Intramolecular D-A Reaction



Nicolaou's Synthesis of Hirsutellone B: Elaboration of Tricycle





CAN = Ceric Ammonium Nitrate $(NH_4)_2Ce(NO_3)_6$
Ce^{4+} is a stronger one-electron oxidant.

Barton etherification:

Barton, D. H. R. *Tetrahedron* **1988,** *44,* 3039-3071 (Rev).

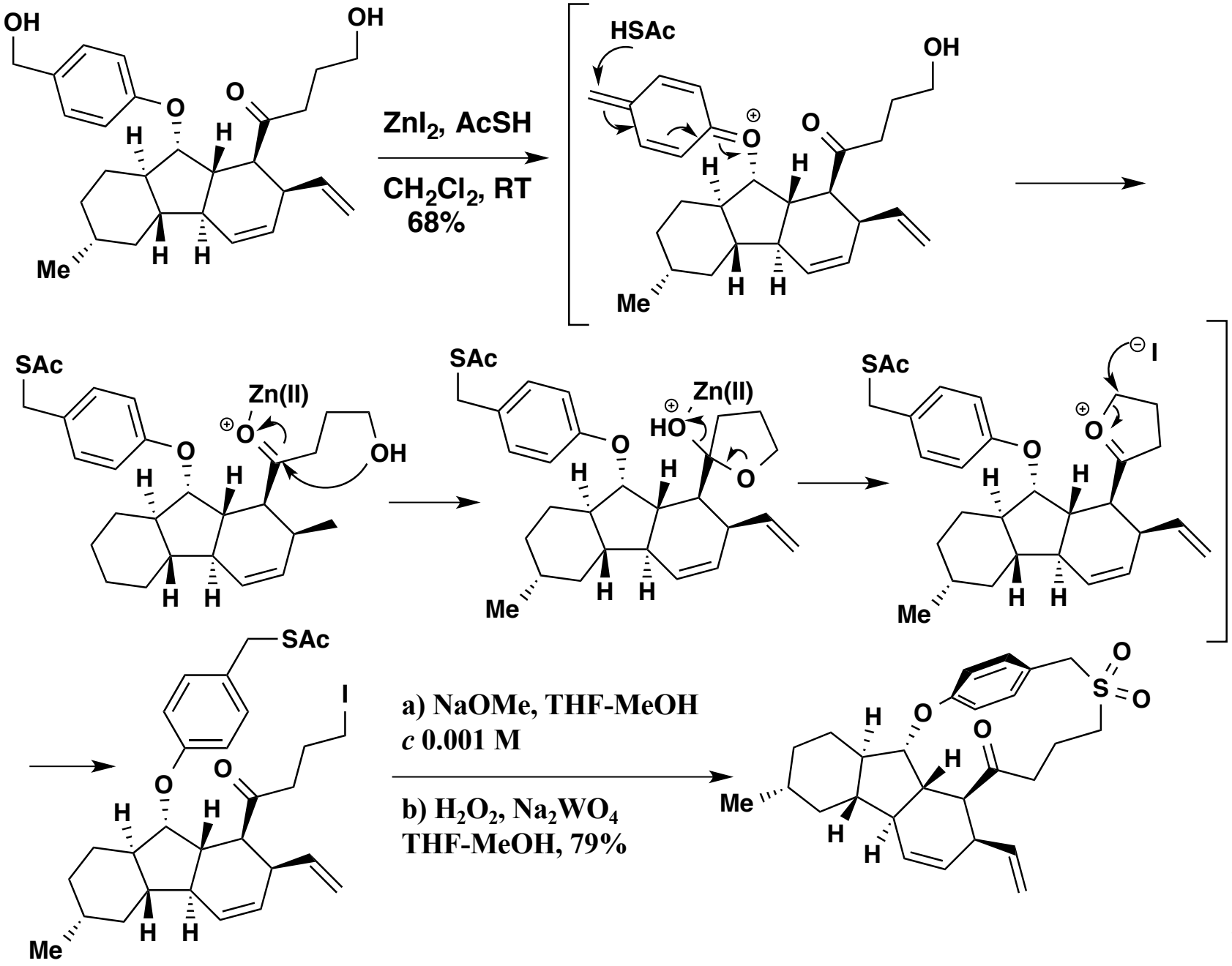
Mukayama modification:

Mukayama, T. *Chem. Lett*. **2006,** *35,* 1140-1141 (Cu-catalyzed)

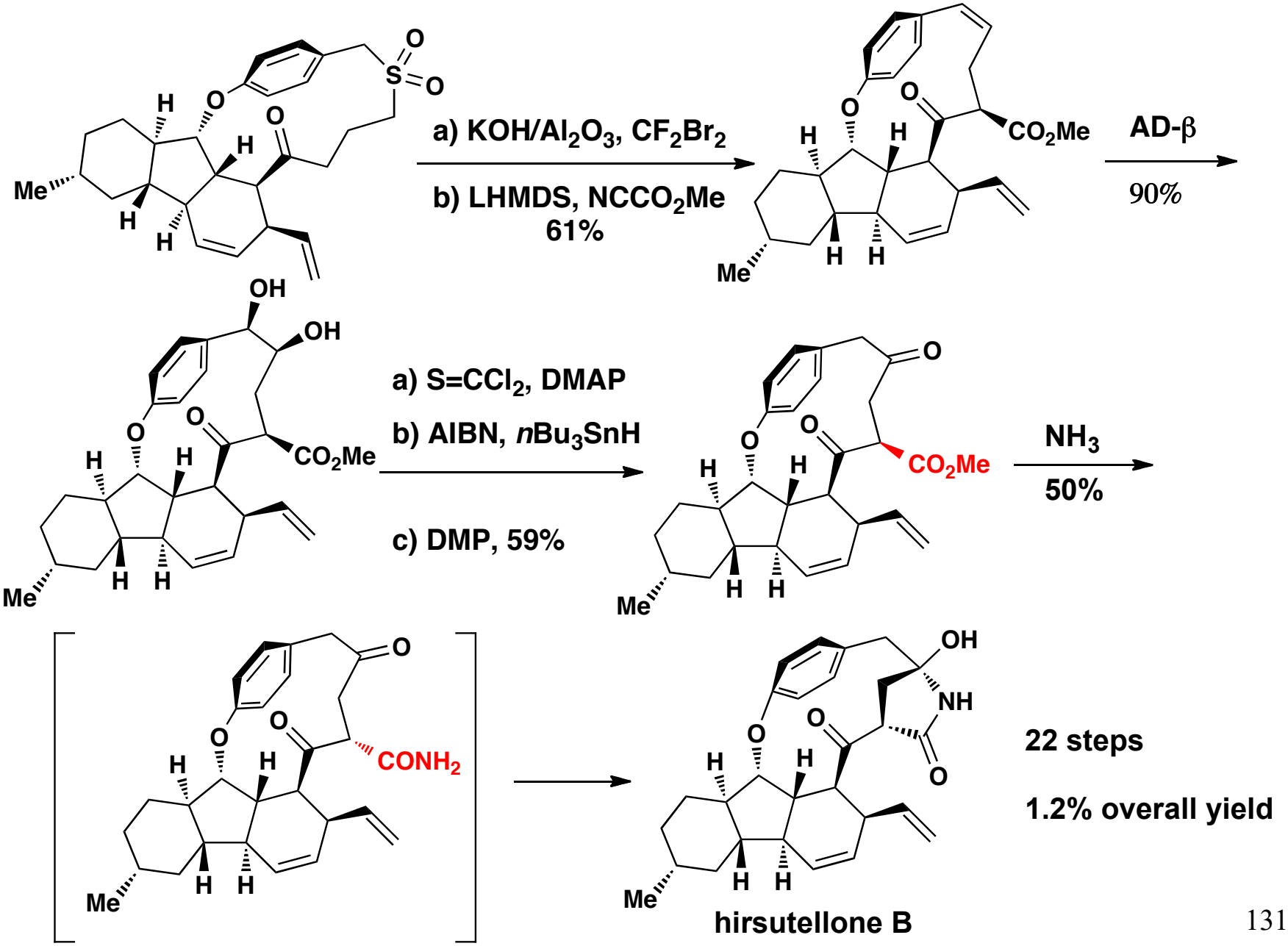
Synthesis and characterization of Ph_4BiF:

Maruoka, K. *J. Am. Chem. Soc*. **2003,** *125,* 10494-10495.

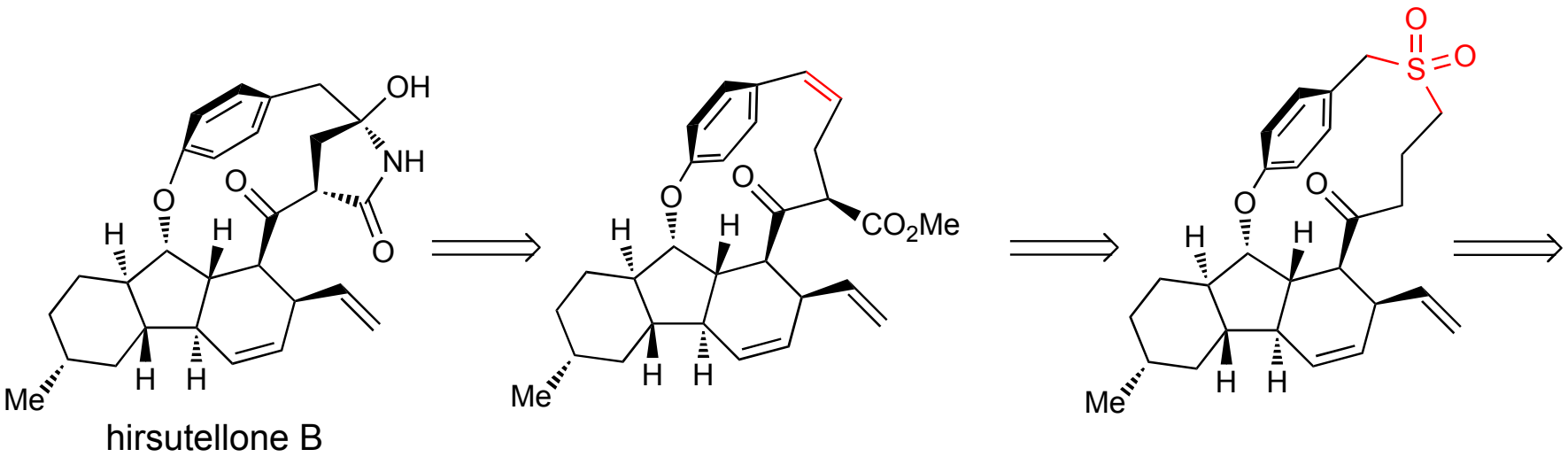
Nicolaou's Synthesis of Hirsutellone B: Formation of Macrocycle

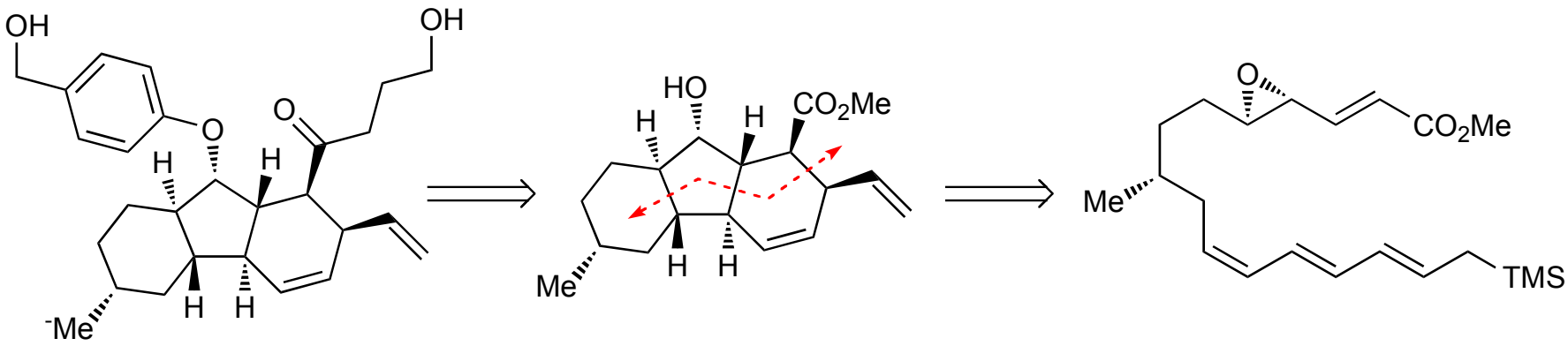


Nicolaou's Synthesis of Hirsutellone B: End game



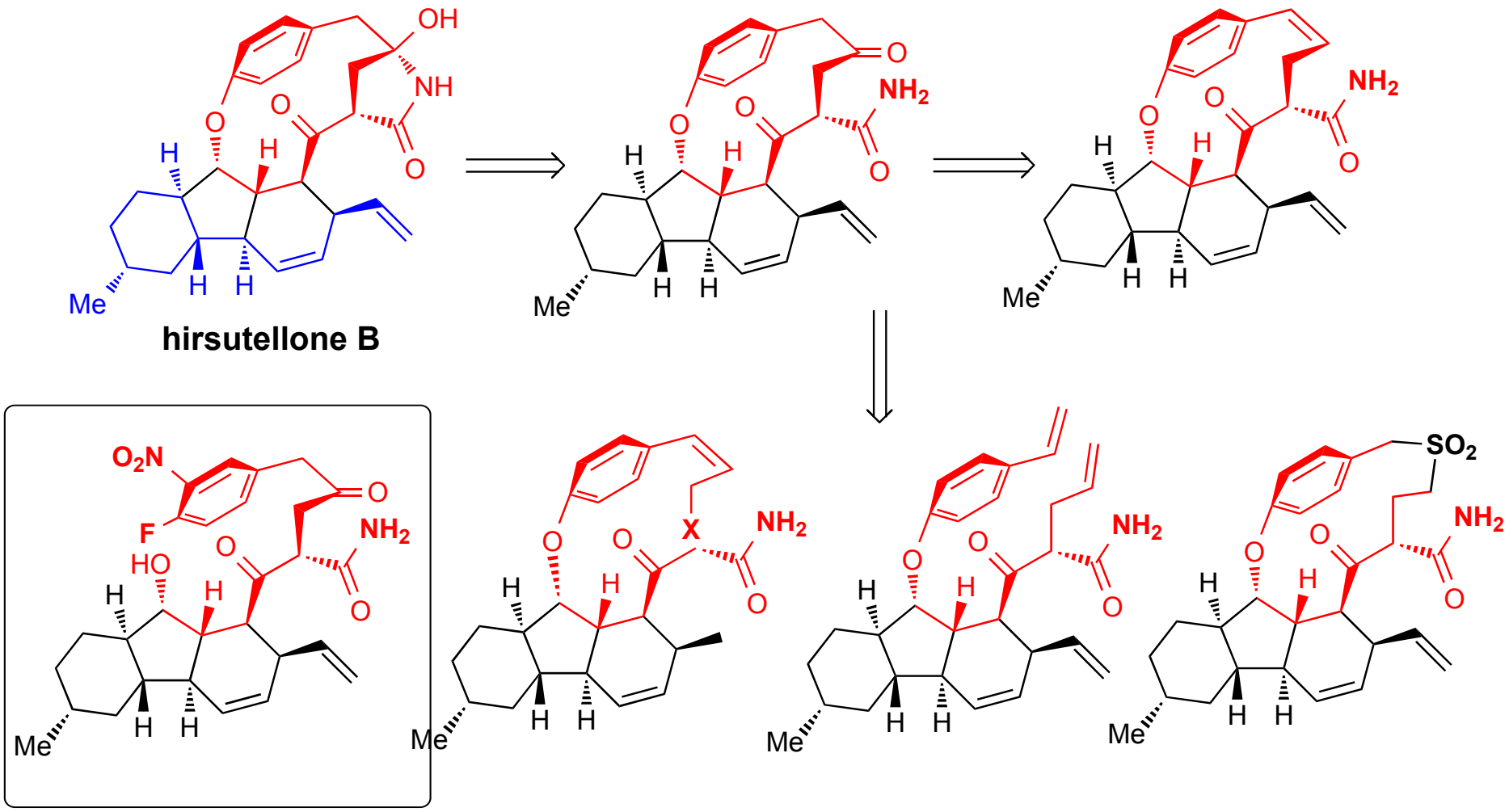
Nicolaou's Synthesis of Hirsutellone B-Summary





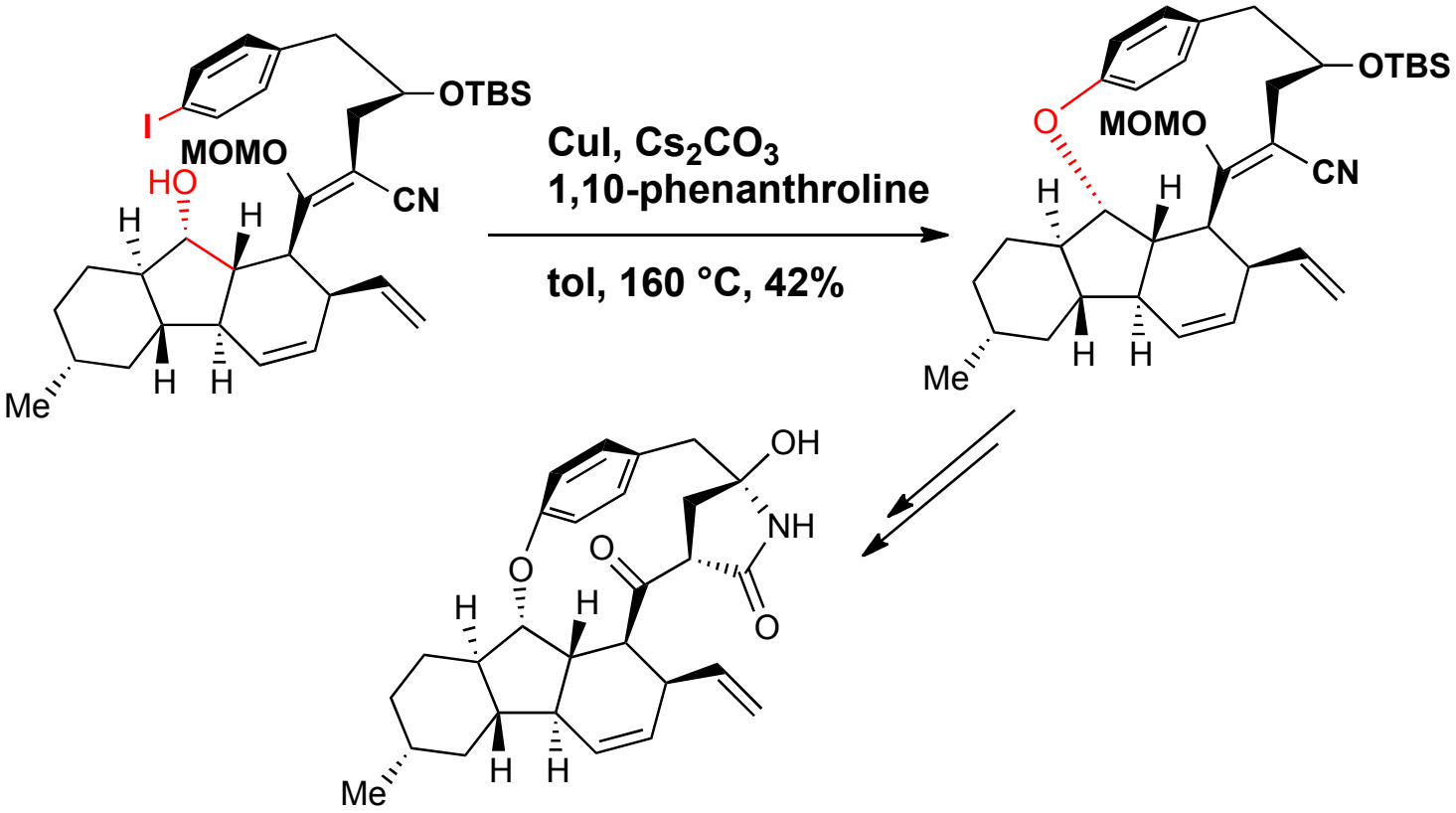
K. C. Nicolaou, D. Sarlah, T. R. Wu, W. Zhan, *Angew. Chem. Int. Ed.* **2009**, *48*, 6870-6874.

Access to 13-Membered *p*-cyclophane: Possible Disconnections



Rev on synthesis of strained cyclophane: Baran, P. *Nat. Prod. Rep*. **2012**, *29*, 899-934.[133]

Uchiro's Synthesis: Cycloetherification Strategy



hirsutellone B

Uchiro, H. *Org. Lett*. **2011**, *13*, 6268-6271.

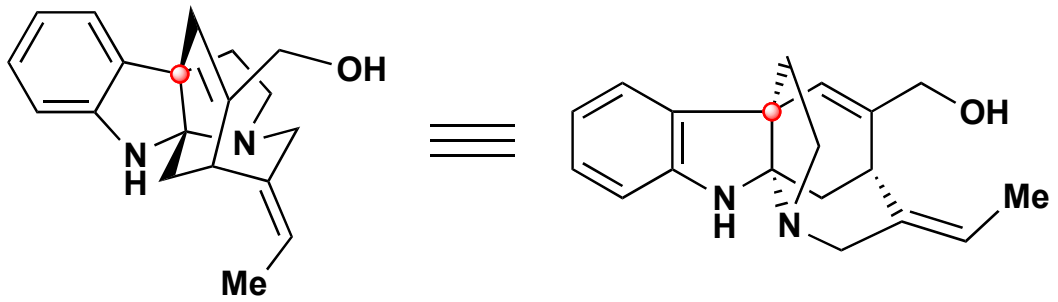
Rev on synthesis of strained cyclophane: Baran, P. *Nat. Prod. Rep*. **2012**, *29*, 899-934.

Summary of Nicolaou's Synthesis: Reactions and Tactics

1) **Organocatalytic enantioselective Epoxidation**
2) **Liebeskind's modification of Stille Coupling**
3) **Domino Epoxide opening/intramolecular D-A reaction**
4) **Barton etherification, Organobismuth compounds**
5) **Barton-McCombie Deoxygenation**
6) **Sharpless Asymmetric dihydroylation**
7) **Ramberg-Bäcklund Reaction**

Macrocyclization: Important factors to be considered (conformational preorganization, template effet, psudodilution etc…)

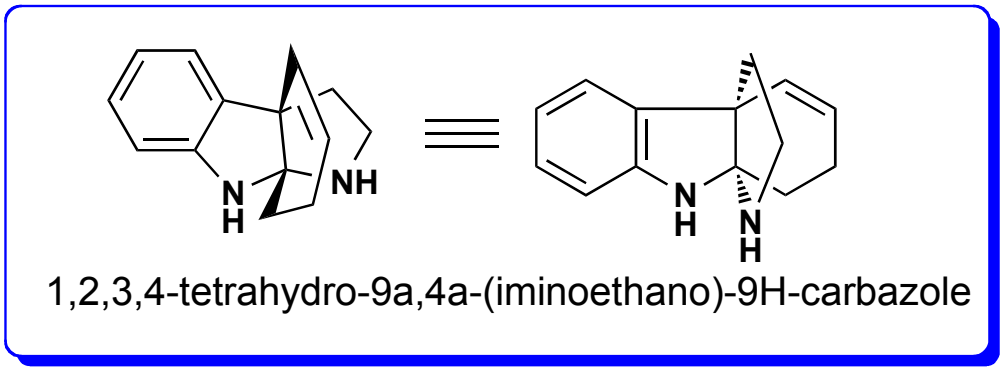
Minfiensine



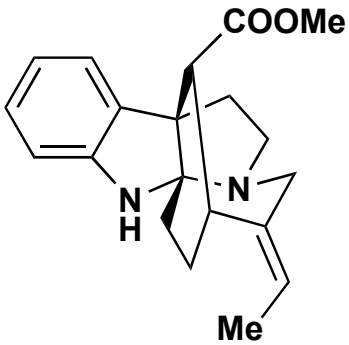
Minfiensine

G. Massiot, et al. *Heterocycles*, **1989**, *29*, 1435-1438.

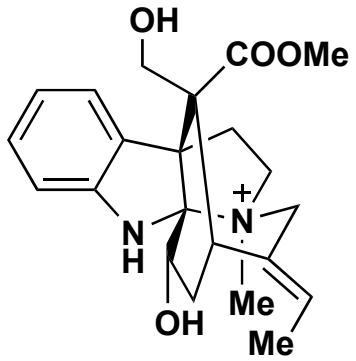
*** Isolated from *Strychnos minfiensis*, a member of the akuammiline family alkaloids.**
*** A highly congested pentacyclic ring system.**
*** Antitumor activity.**



1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9H-carbazole

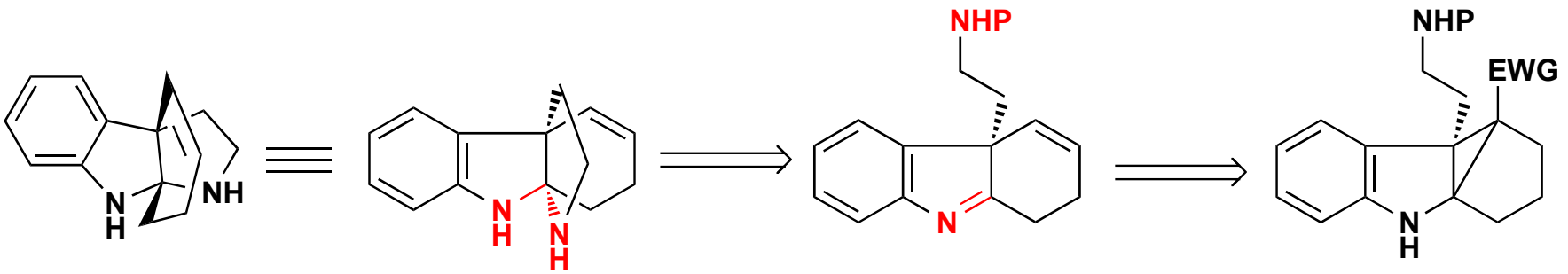


Vincorine



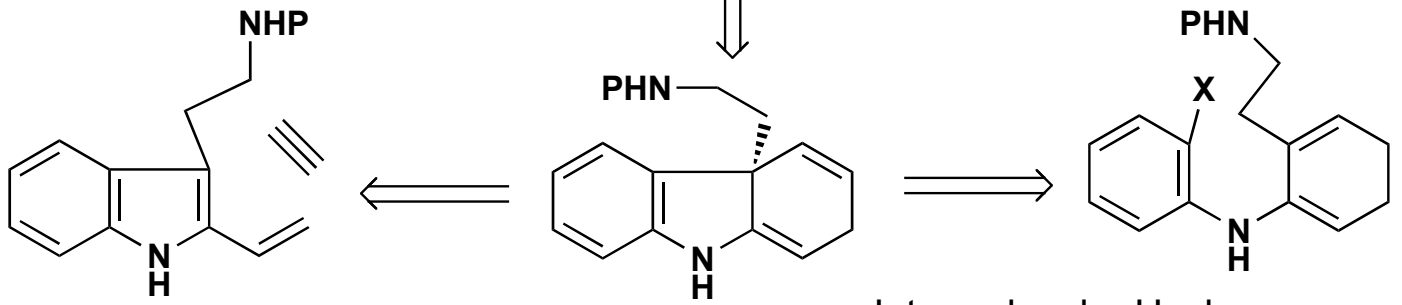
Echitamine

General Consideration-Construction of Tetracycle



Disconnect the easiest bond (function) here: Aminal !!!

Qin, *Angew. Chem. Int. Ed.* **2008**, *47*, 3618-3621.



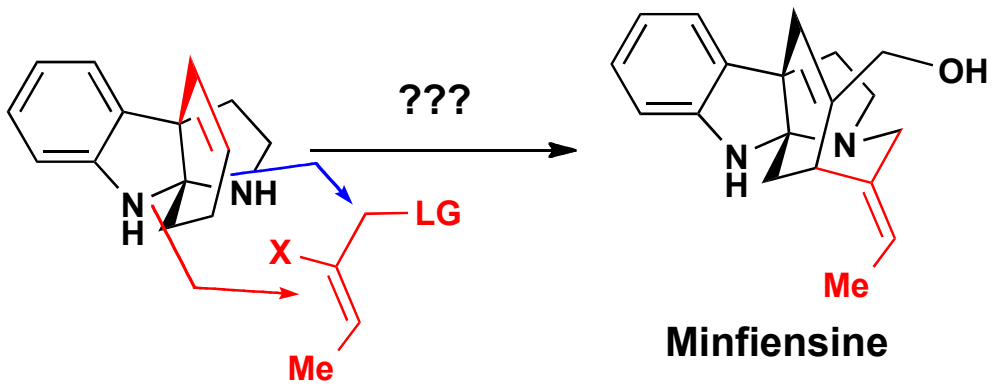
Diels-Alder

Lévy, J. *Synlett* **1992,** 601.
MacMillan, D.W. C.
J. Am. Che. Soc. **2009,** *131,* 13606

Intramolecular Heck

Oveman, L. E.
J. Am. Che. Soc. **2008,** *130,* 5369

General Consideration-From Tetracycle to Pentacycle



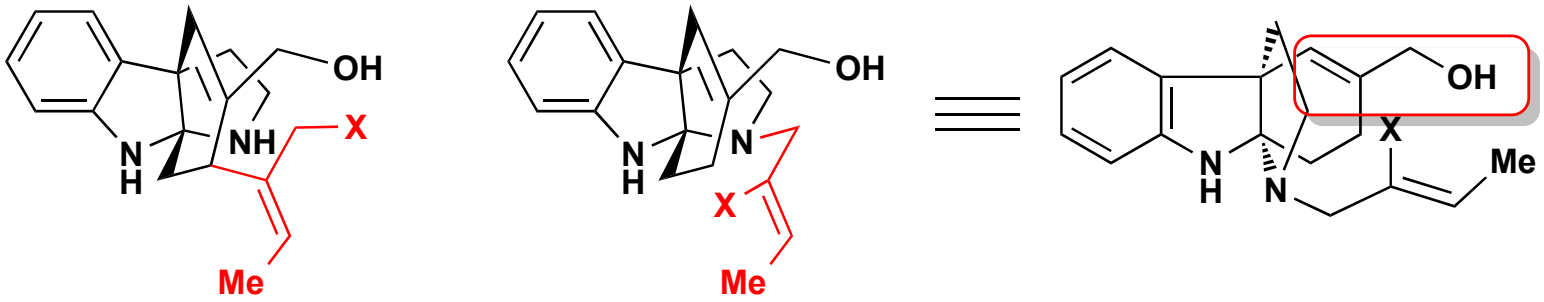
Minfiensine

C-N bond formation: easy (from synthesis perspective)
Csp3-Csp2 bond formation: Large panel of reactions available, depending on the funcationality of the vicinal carbon

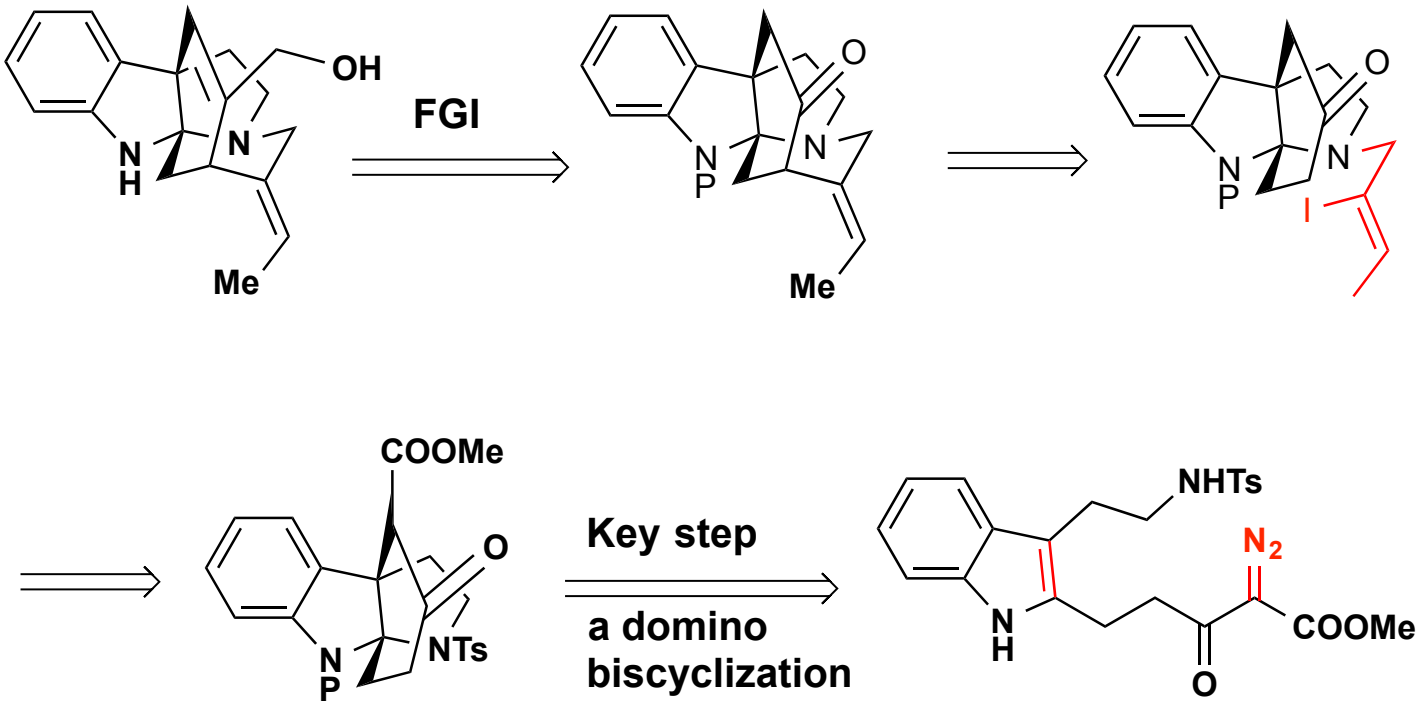
The order of bond forming processes:

a) Second reaction will be intramolecular, so will be facilitated.

b) Stereochemical issue if one considered the creation of the Csp3-Csp2 first

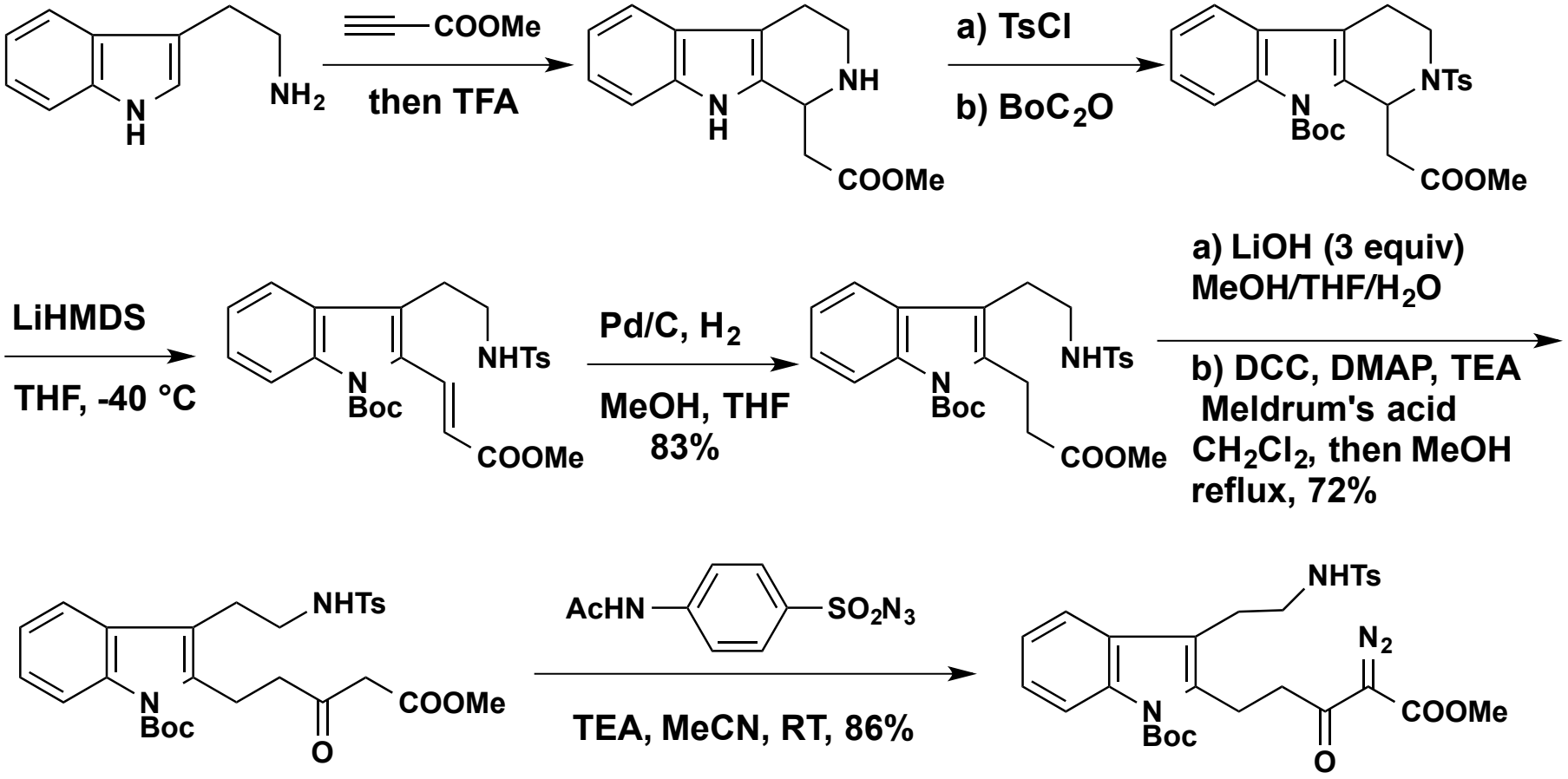


Qin's Synthesis of (±)-Minfiensine: Retro Synthetic Analysis



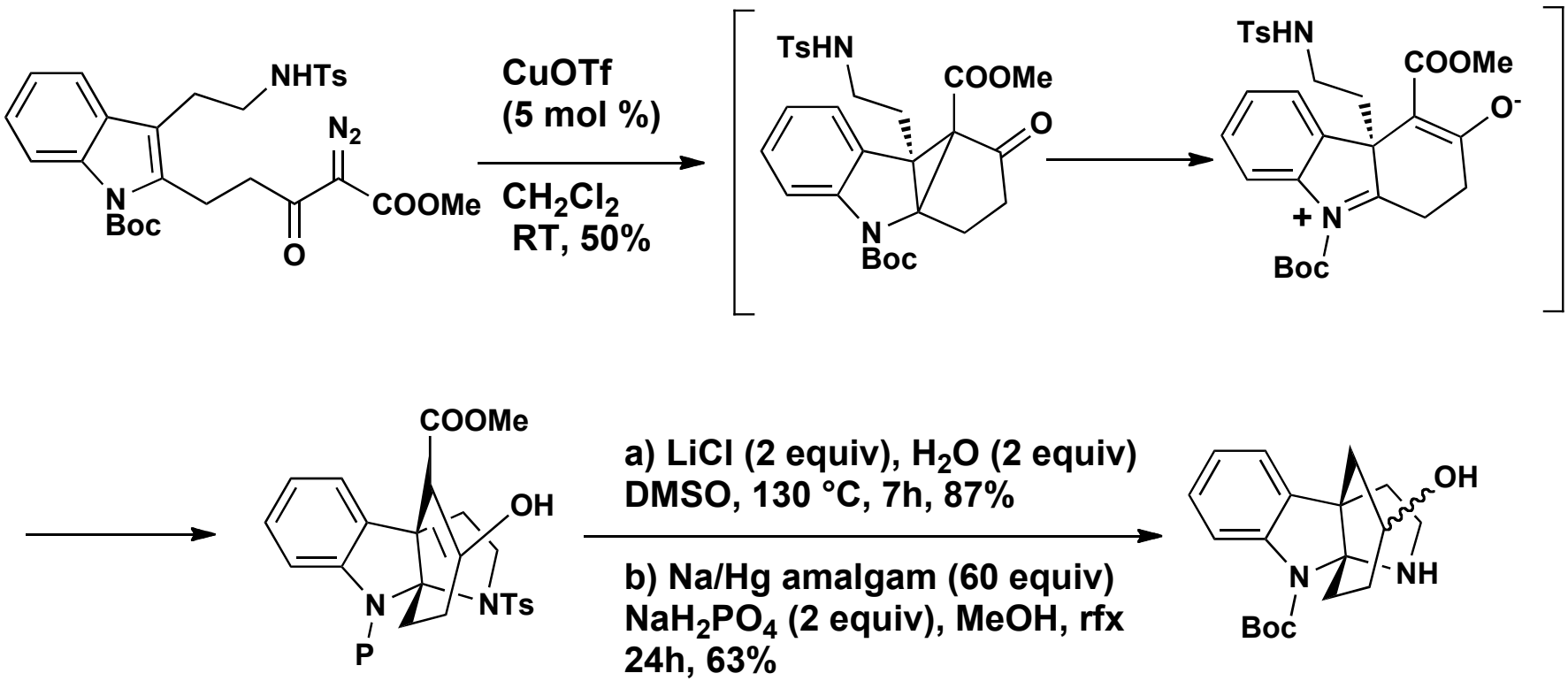
L. Shen, M. Zhang, Y. Wu, Y. Qin, *Angew. Chem. Int. Ed*. **2008**, *47*, 3618-3621.

Qin's Synthesis of (±)-Minfiensine: Synthesis of 2,3-disubstituted Indole



(Regitz's Diazo transfer reaction)

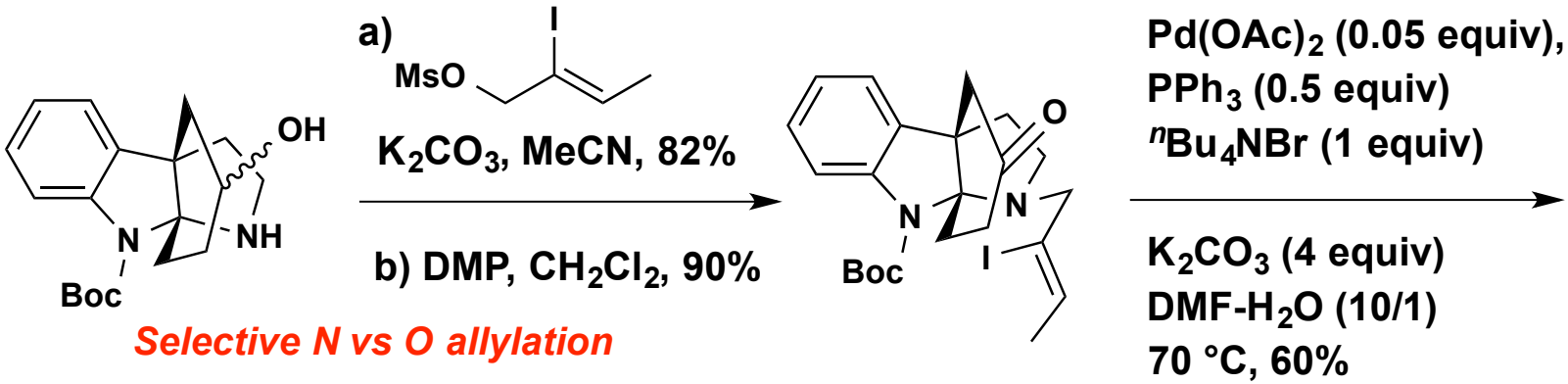
Qin's Synthesis of (±)-Minfiensine: Domino cyclization



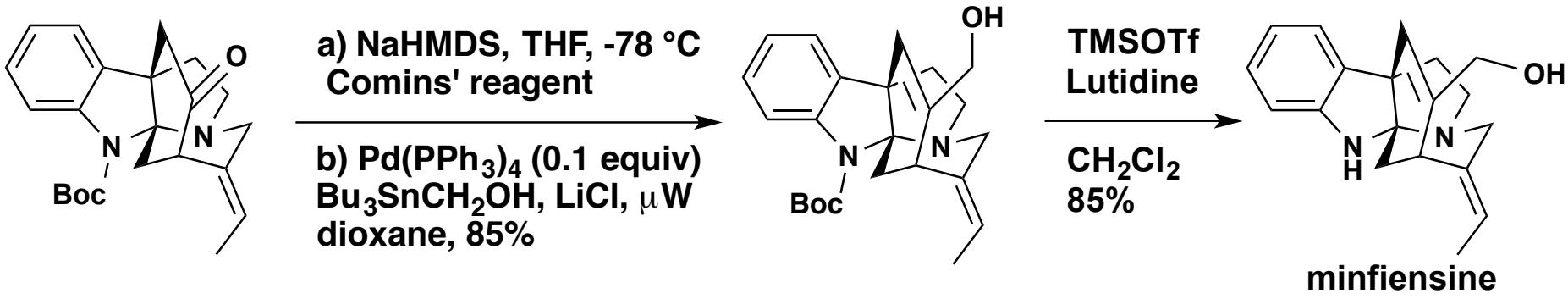
Krapcho Decarboxylation

L. Shen, M. Zhang, Y. Wu, Y. Qin, *Angew. Chem. Int. Ed.* **2008**, *47*, 3618-3621.

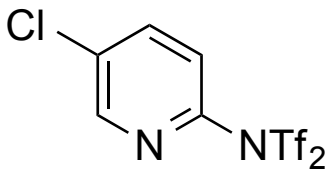
Qin's Synthesis of (±)-Minfiensine: End Game



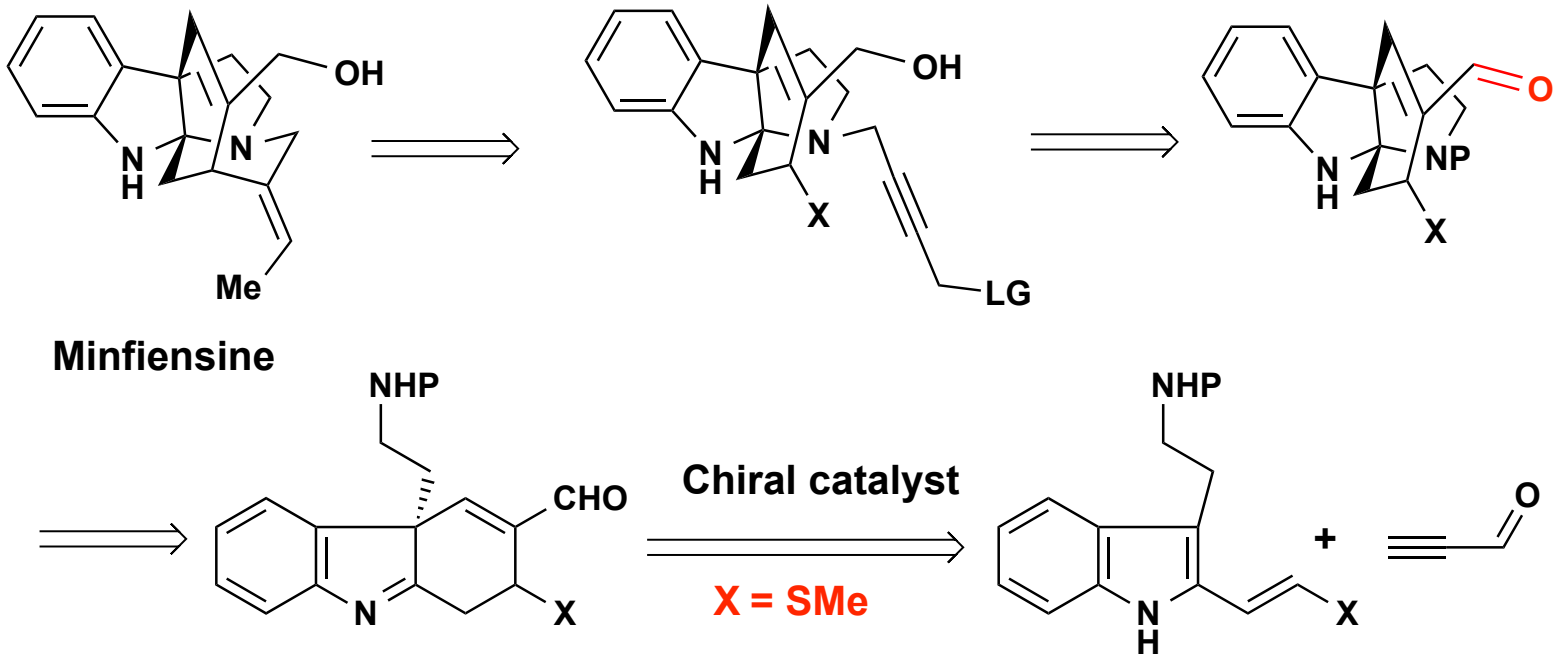
Selective N vs O allylation

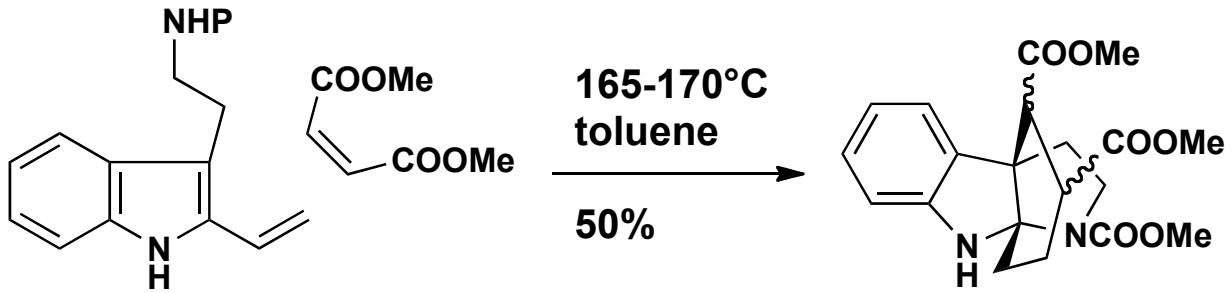


Comin's reagent



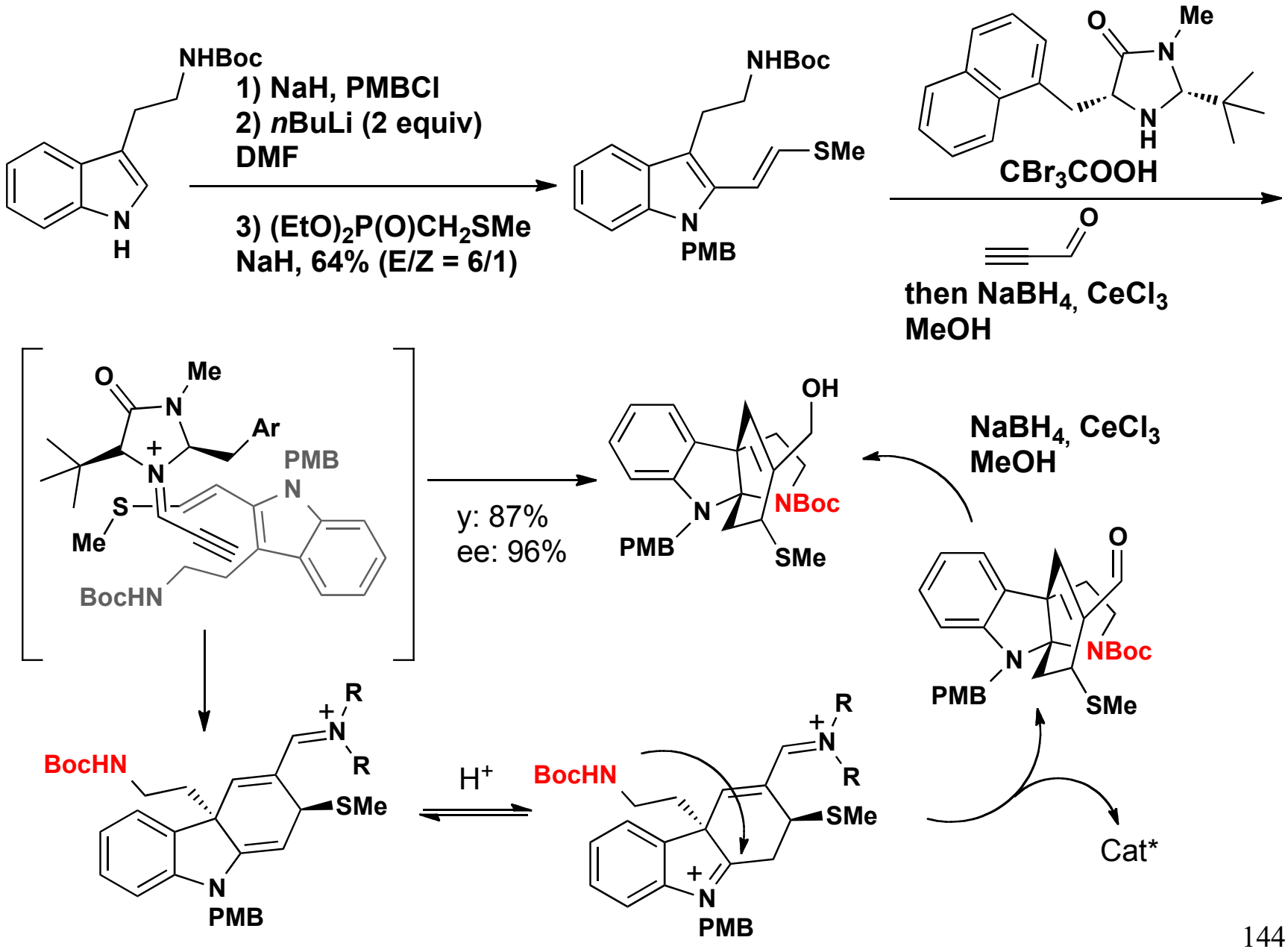
MacMillan's Synthesis of (+)-Minfiensine—Retro Analysis



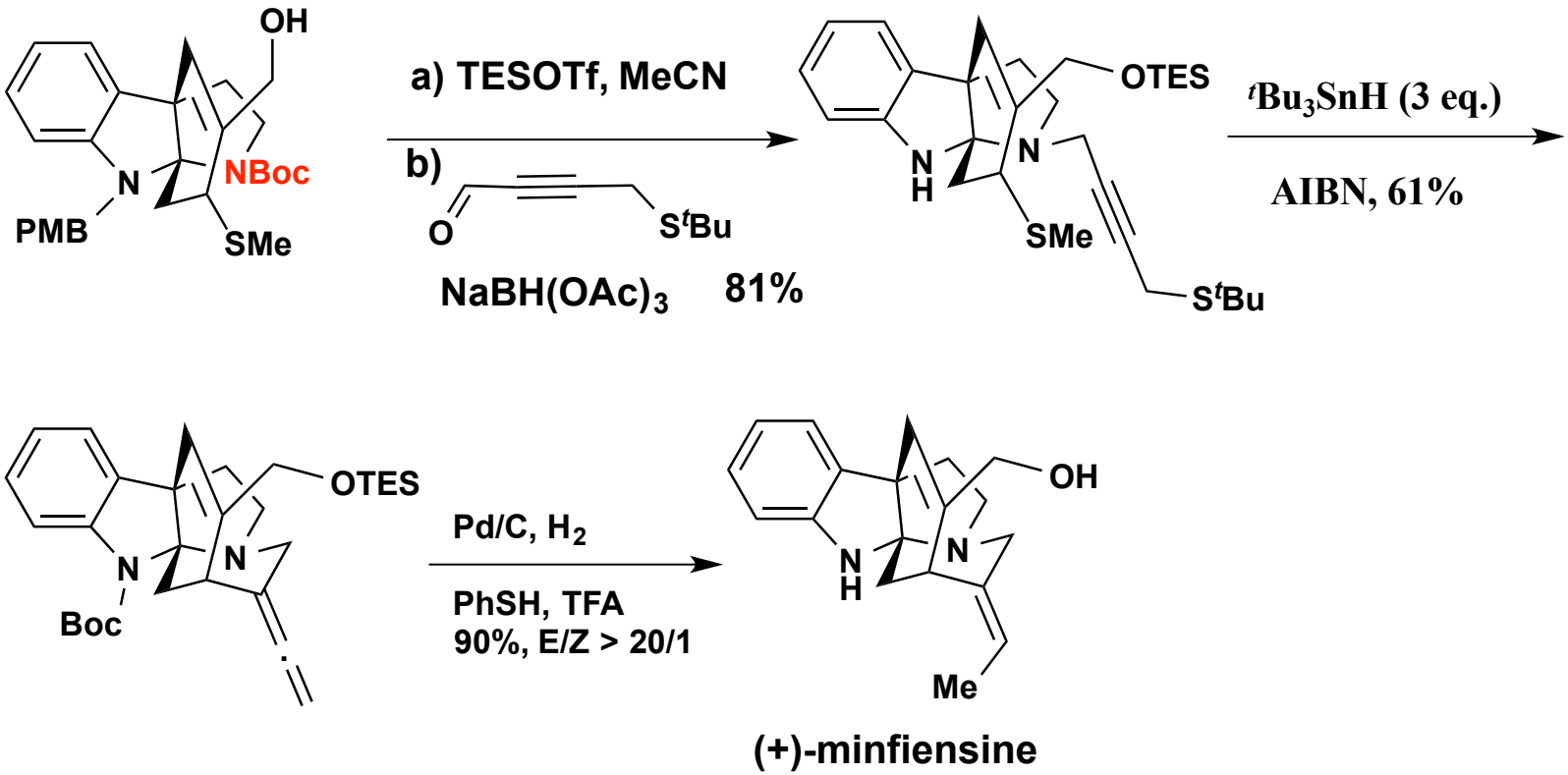


Lévy, J. et al. *Synlett* **1992,** *7*, 601.

MacMillan's Synthesis of (+)-Minfiensine—Access to Tetracycle



MacMillan's Synthesis of (+)-Minfiensine—End Game



9 steps, 21% overall yield

*** Organocatalytic Domino process for the construction of tetracyclic pyrroloindoline unit**

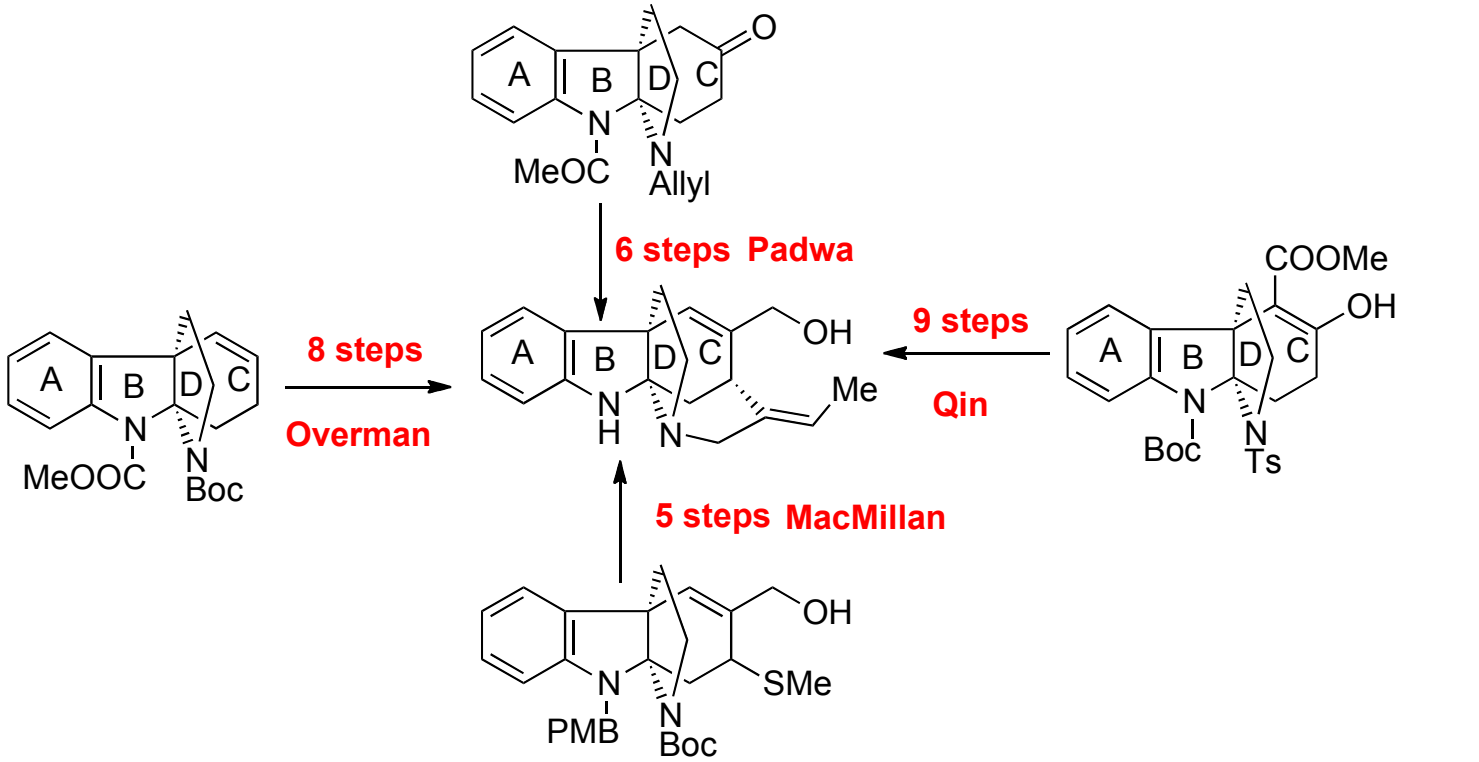
*** 6-Exo-dig radical cyclization for the formation of piperidine ring.**

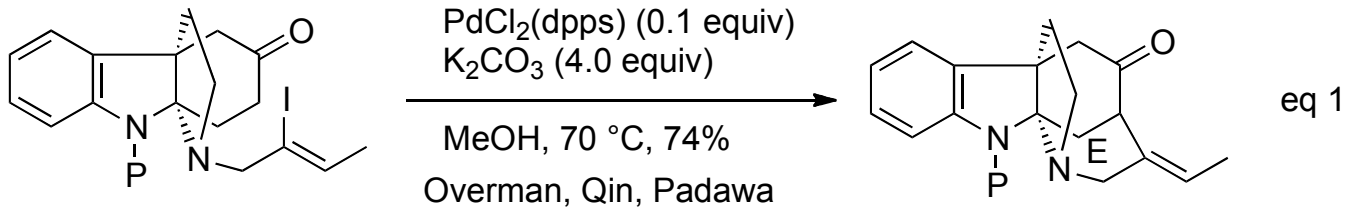
D. W. C. MacMillan, *J. Am. Chem. Soc*. **2009**, *131*, 13606-13607.

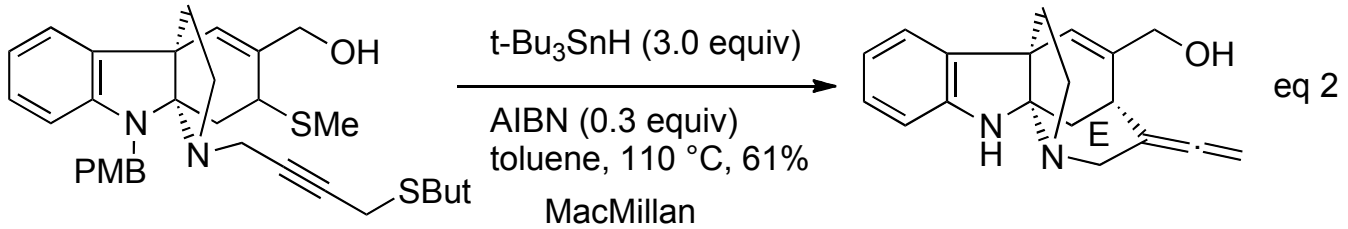
Summary of Qin's and MacMillan's Syntheses

1) **Regitz's diazo transfer**
2) **Domino cyclopropanantion/fragmentation/intramolecular trapping**
3) **Palladium-catalyzed α-vinylation of ketone**
4) **Vinyl triflate, Comin's reagent**
5) **Stille cross-coupling**
6) **Homologation of ketone to allylic alcohol**
7) **Organocatalytic enantioselective Diels-Alder reaction**
8) **Radical cyclization**

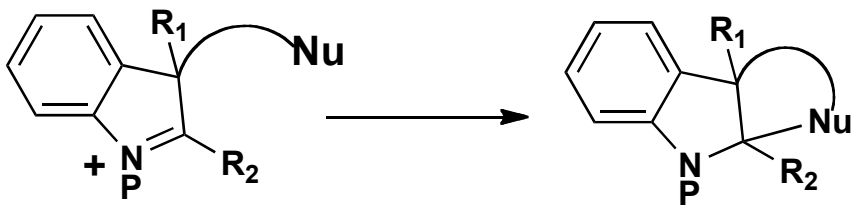
Total Synthesis of Minfiensine-Summary

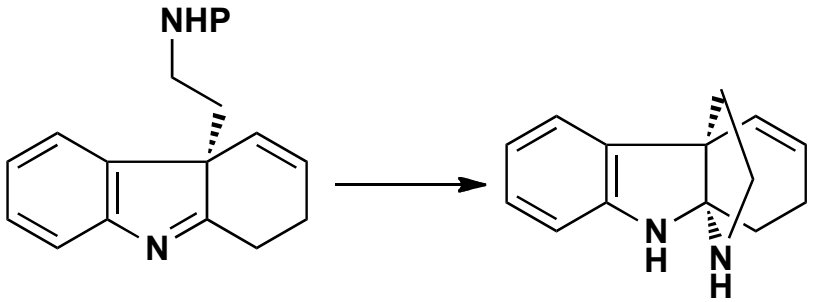


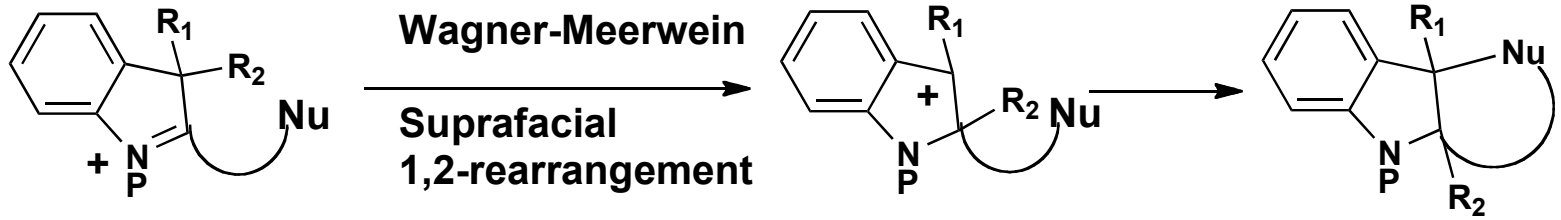




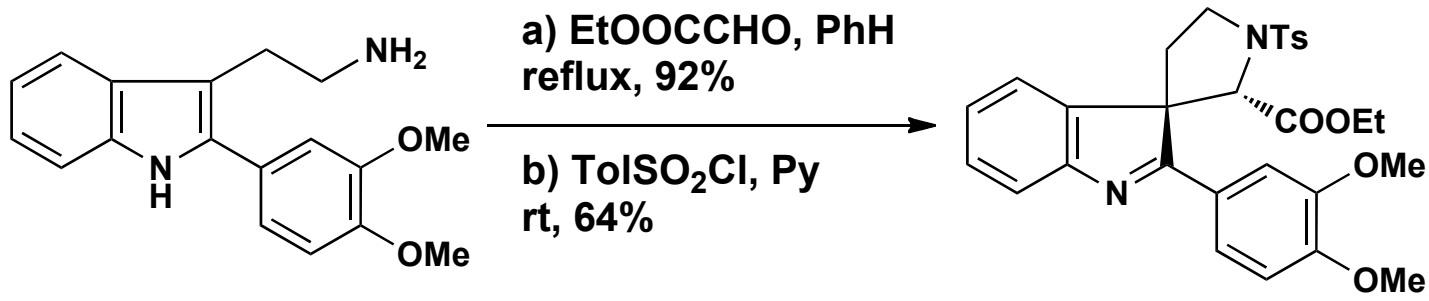
Exploiting the Reactivity of Indole



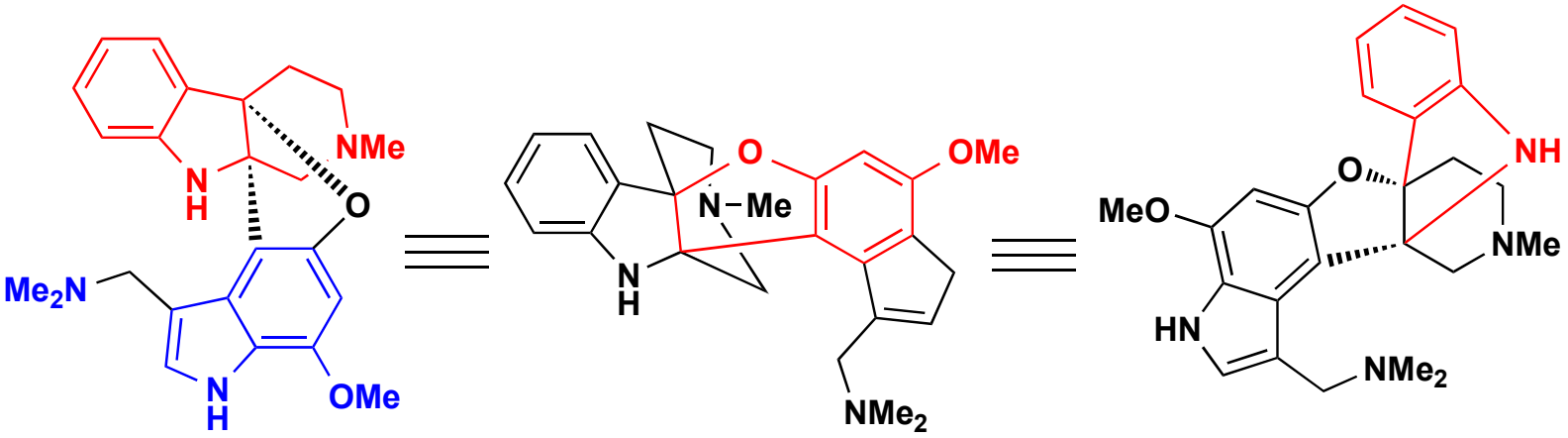




However, in Woodward's synthesis of Strychnine, no Wagner-Meerwein rearrangement



Phalarine



phalarine

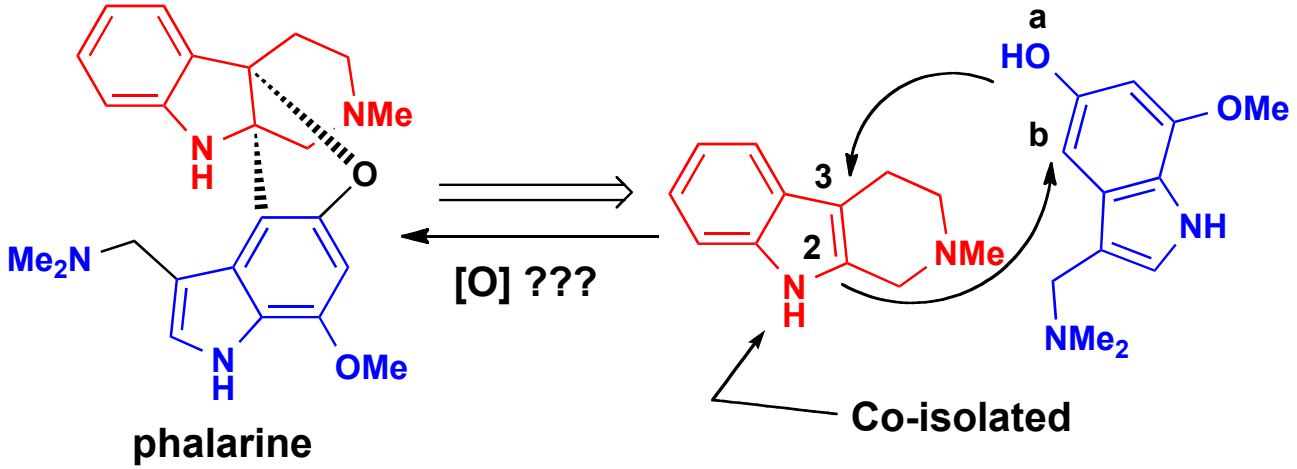
Isolation: Colegaten J. A. et al. *Phytochemistry* **1999**, *51*, 153-157.

Bioactivity: Unknown

Structure: Interlocked tetrahydrocarbazole and a dihydrofuran-fused gramine,
Propeller-like structure, **absolute configuration unknown**

No degradation studies

Phalarine: Proposed biosynthetic pathway



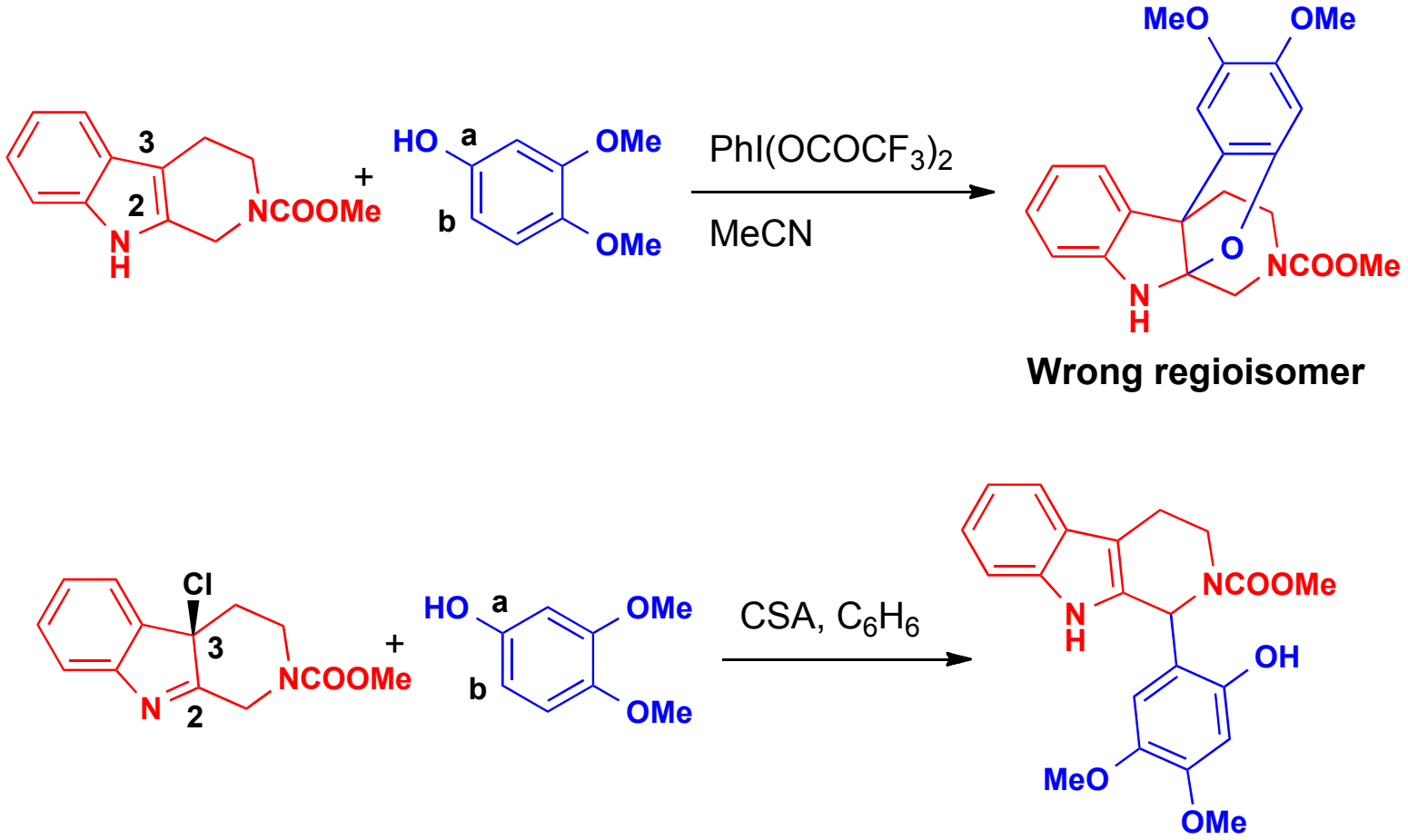
Potential problems

*** Cb is nucleophilic, need to inverse the polarity, using an oxidant to make aryloxenium ion**

*** C3 is generally more nucleophilic than C2**

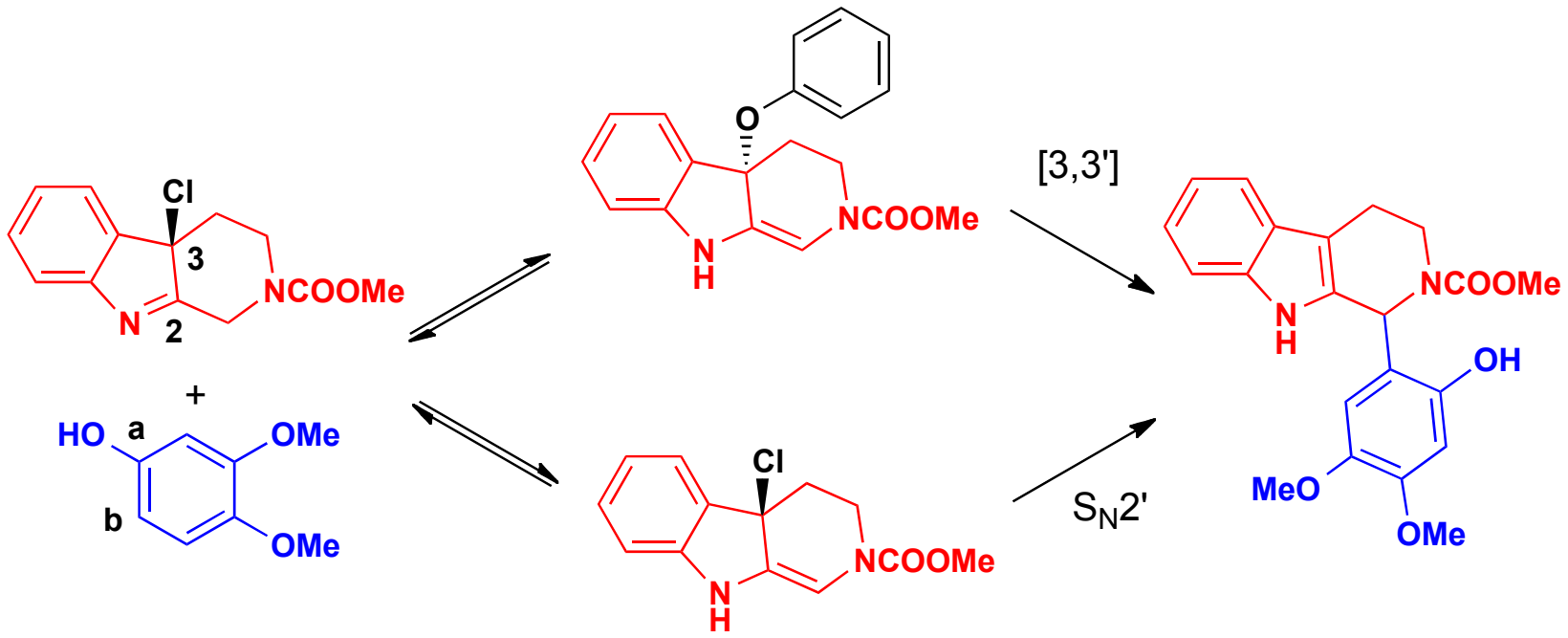
Aryloxenium ion: a positive charged monovalent oxygen intermediate, see for example: Abramovitch, R. A. J. Am. Chem. Soc. 1981, *103*, 4558-4565.

Phalarine—Attempted Biomimetic Synthesis

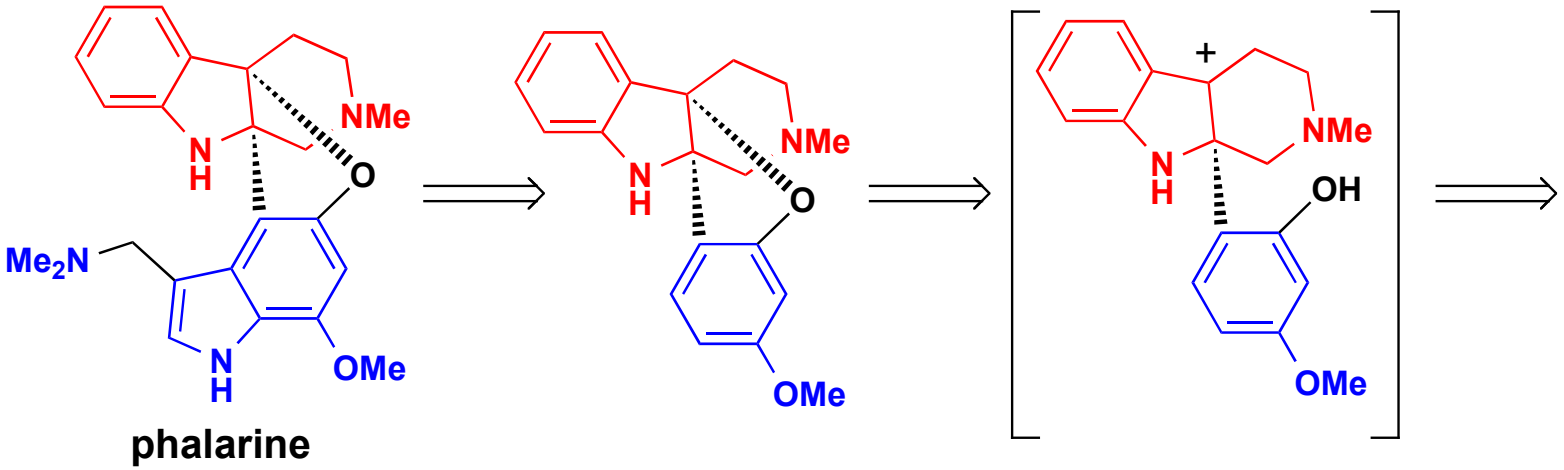


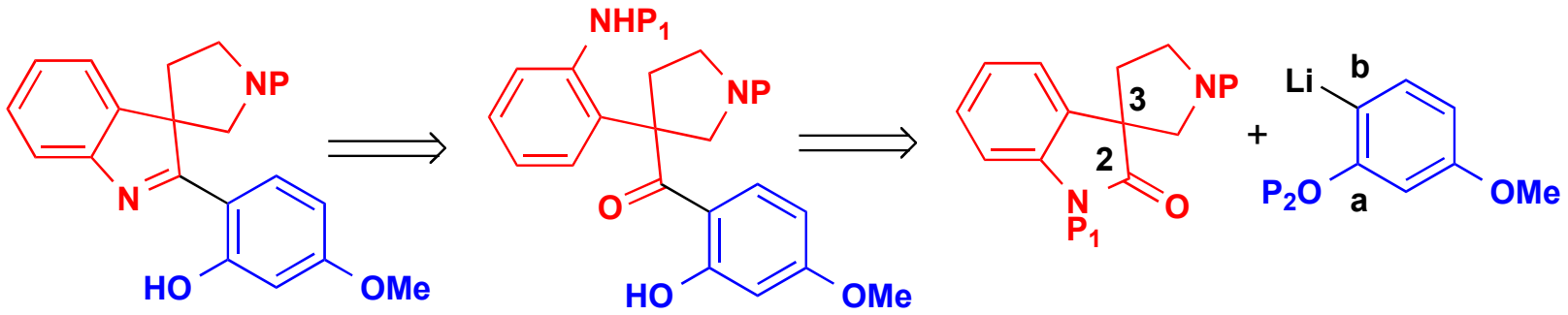
Danishefsky, S. J. *et al*. *Tetrahedron Lett*. **2006**, *47*, 4839-4841.

Formation of Tetrahydrocarbazole: Possible Mechanisms



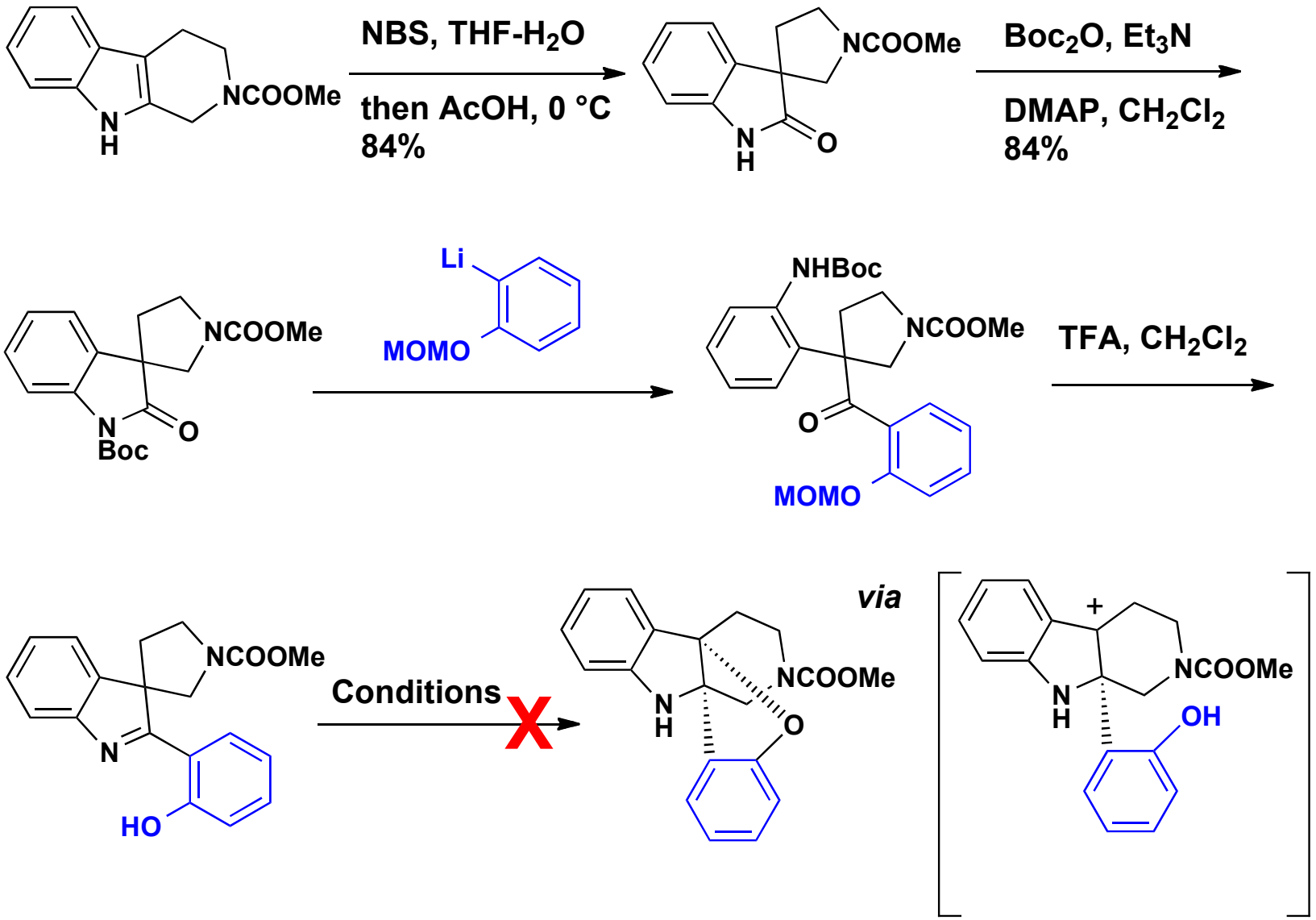
Phalarine: Retro Synthesis-1





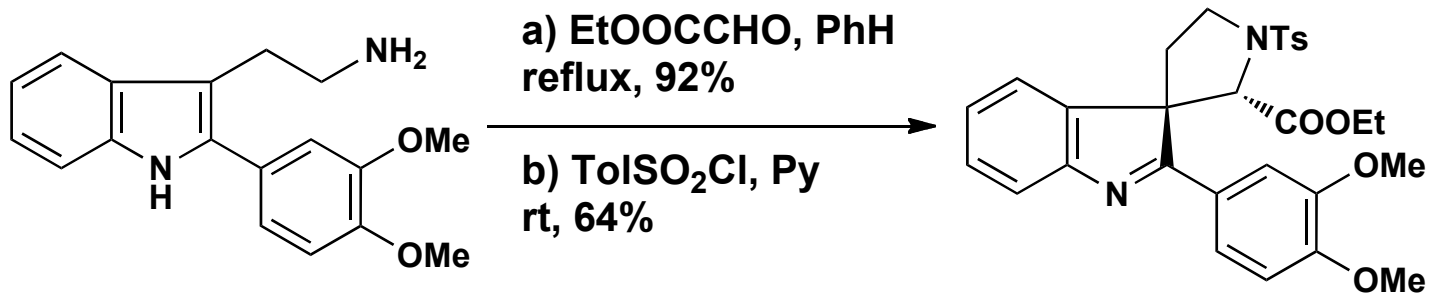
Formation of C_2-C_b bond priori to the creation of C_3-O_a ether bond

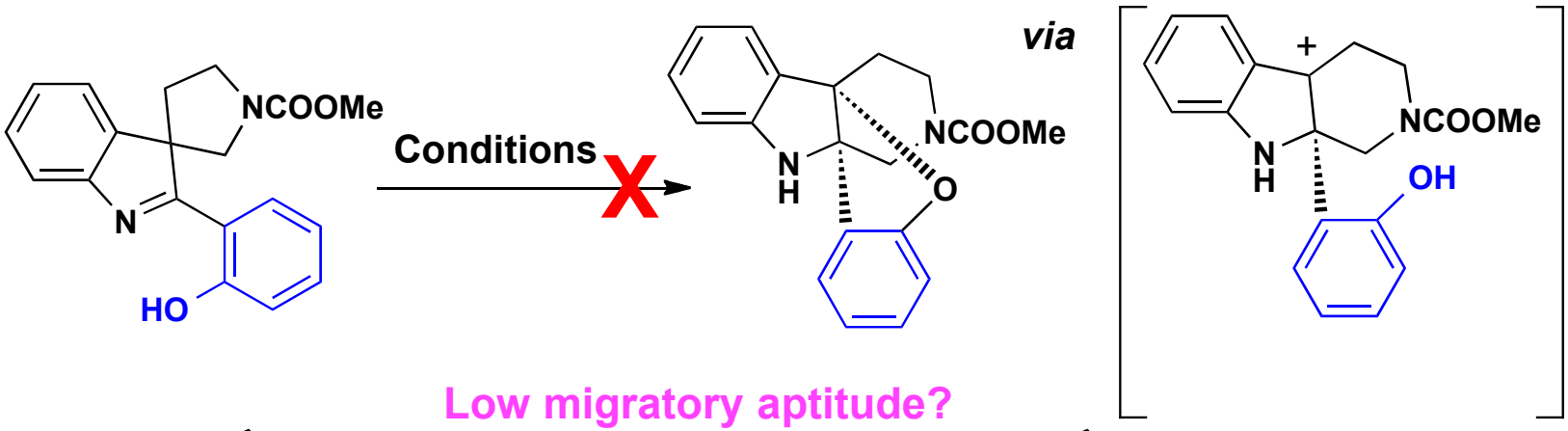
Phalarine: Synthesis of spiroindolenine



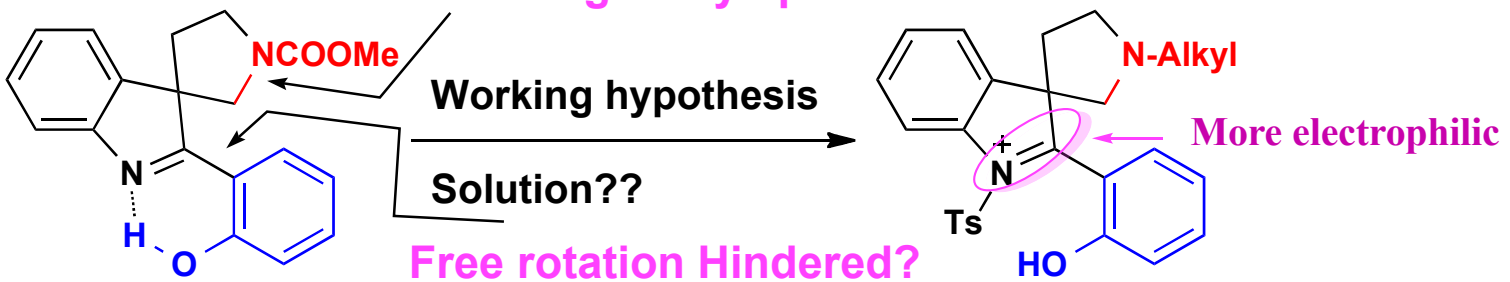
Wagner-Meerwein Rearrangement: How to make it work?

Woodward's synthesis of Strychnine





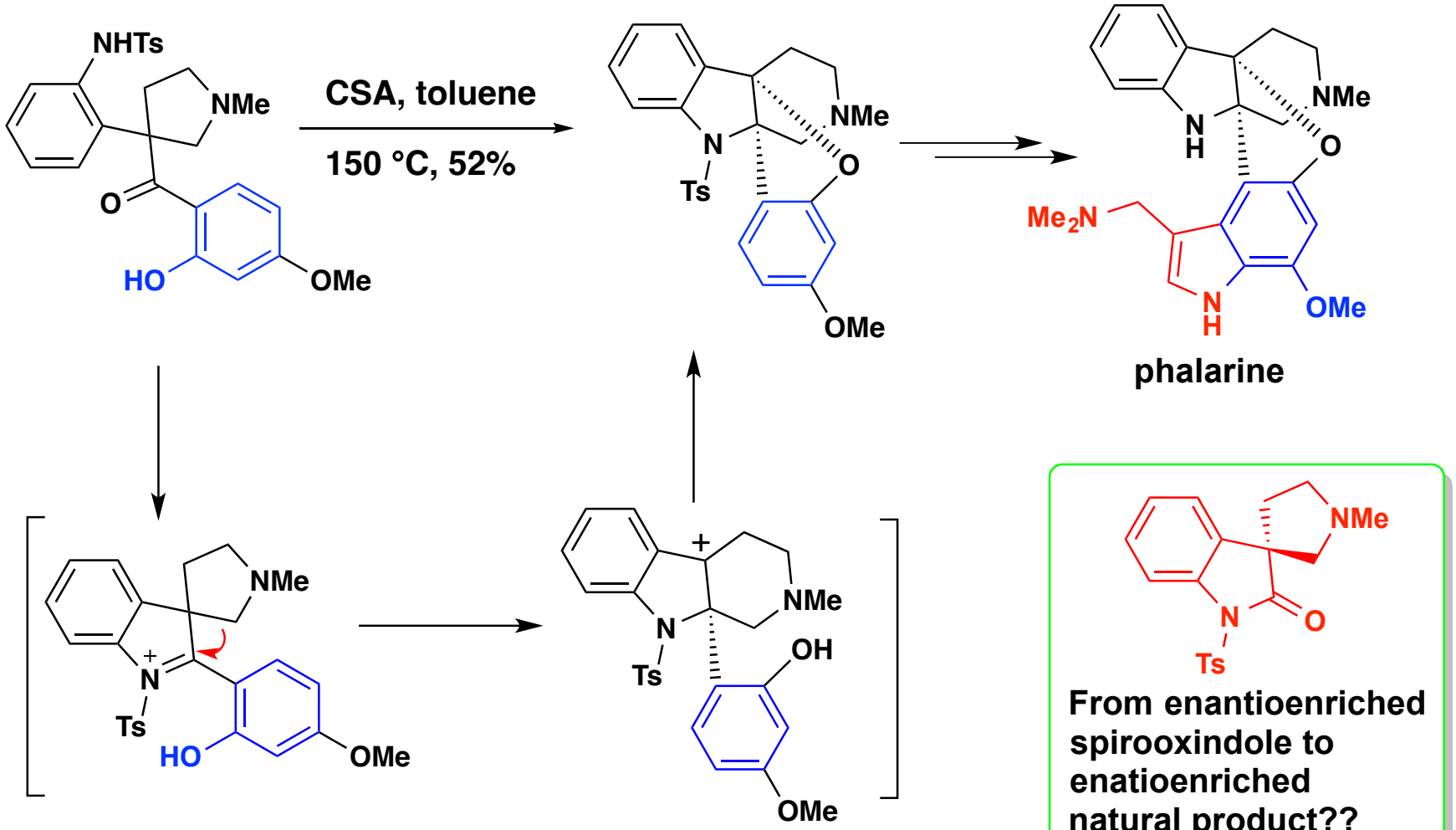
Low migratory aptitude?



Free rotation Hindered?

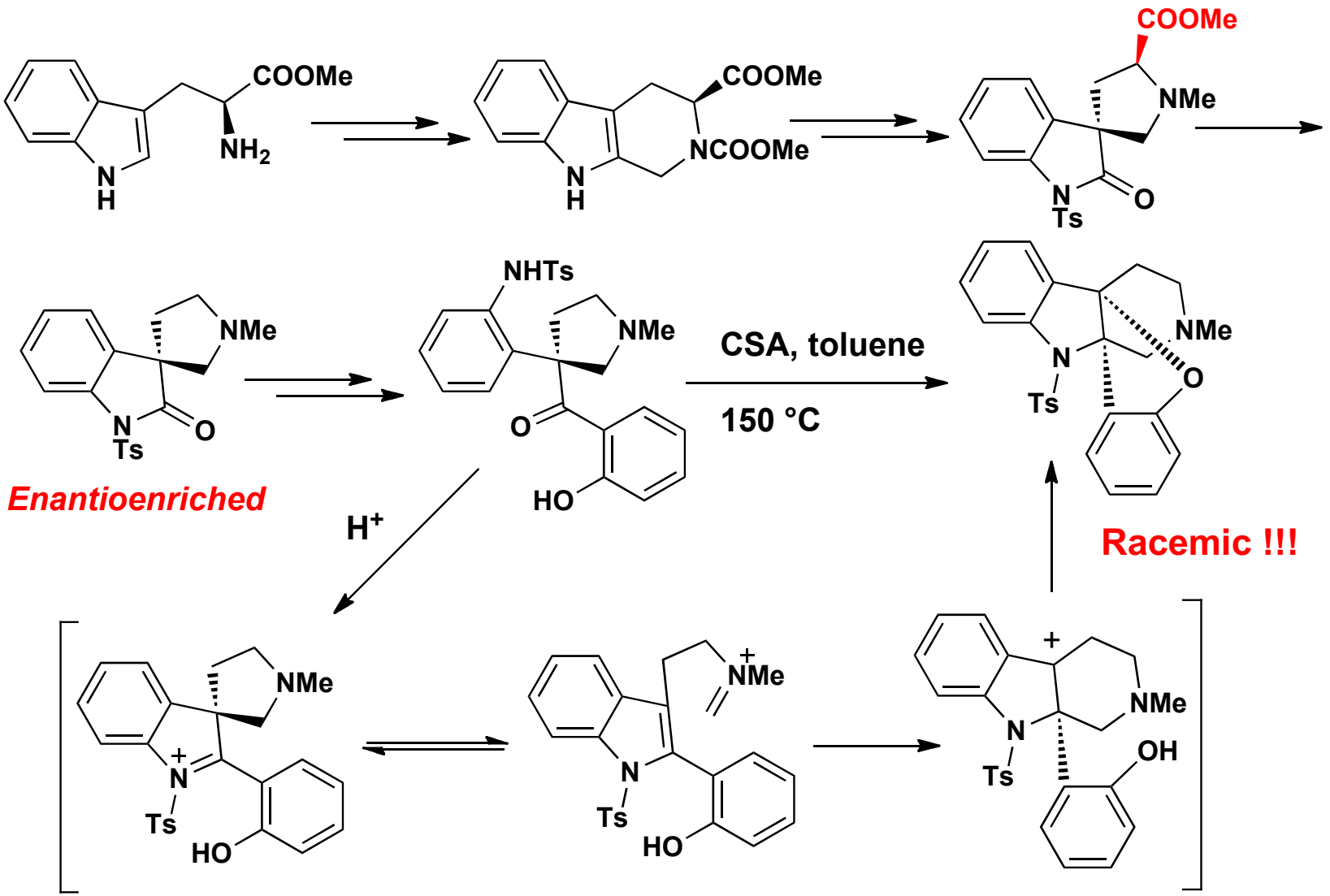
Free rotation hindered?

Wagner-Meerwein Rearrangement: Validating the Working Hypothesis



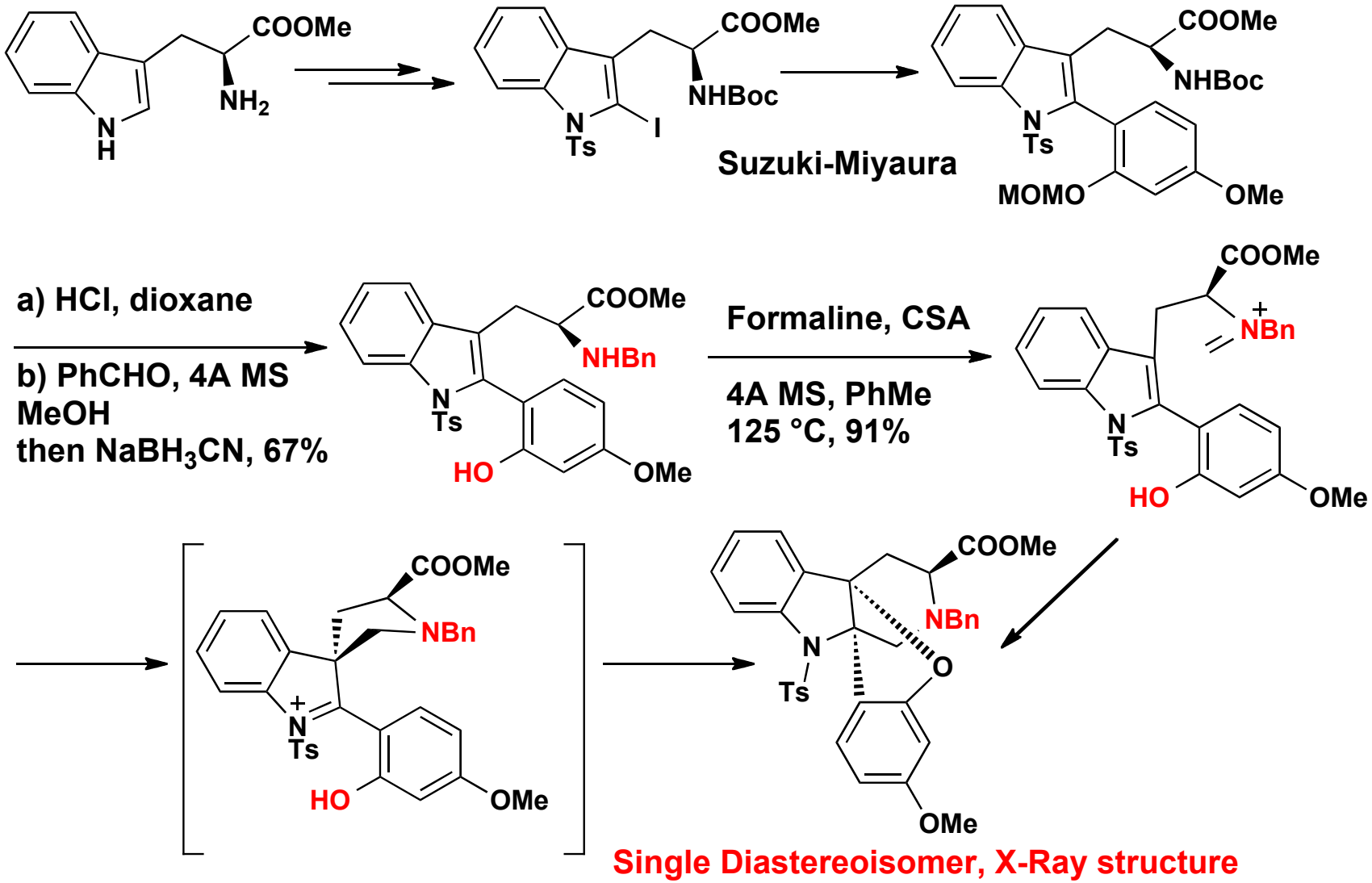
Danishefsky, S. J. *et al*. *Angew. Chem. Int. Ed*. **2007**, *46*, 1448-1450.

Attempted Enantioselective Synthesis of Phalarine

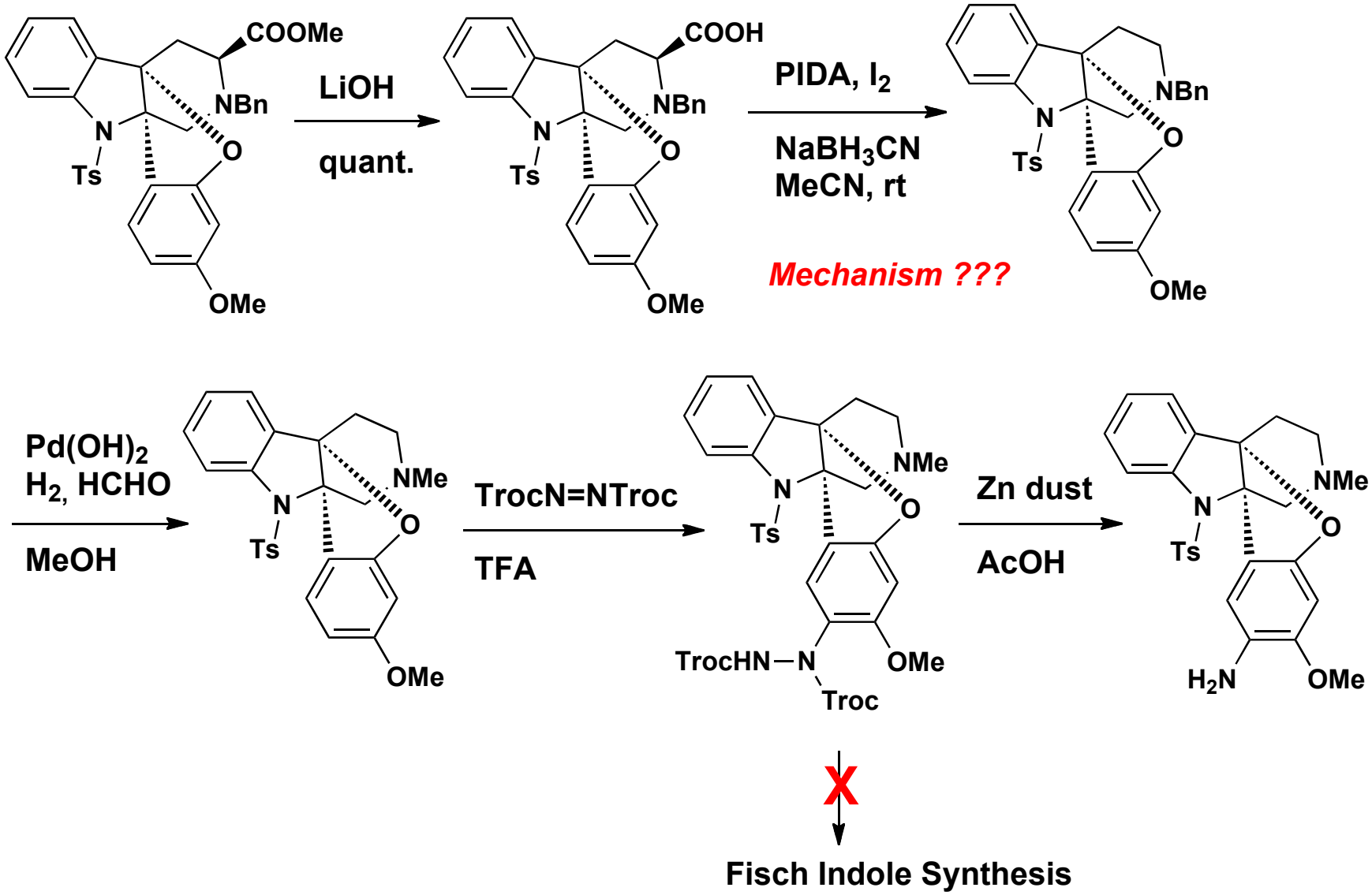


Danishefsky, S. J. *et al*. *Angew. Chem. Int. Ed*. **2007**, *46*, 1444-1447.

New Approach to Enantiomerically Enriched (-)-Phalarine

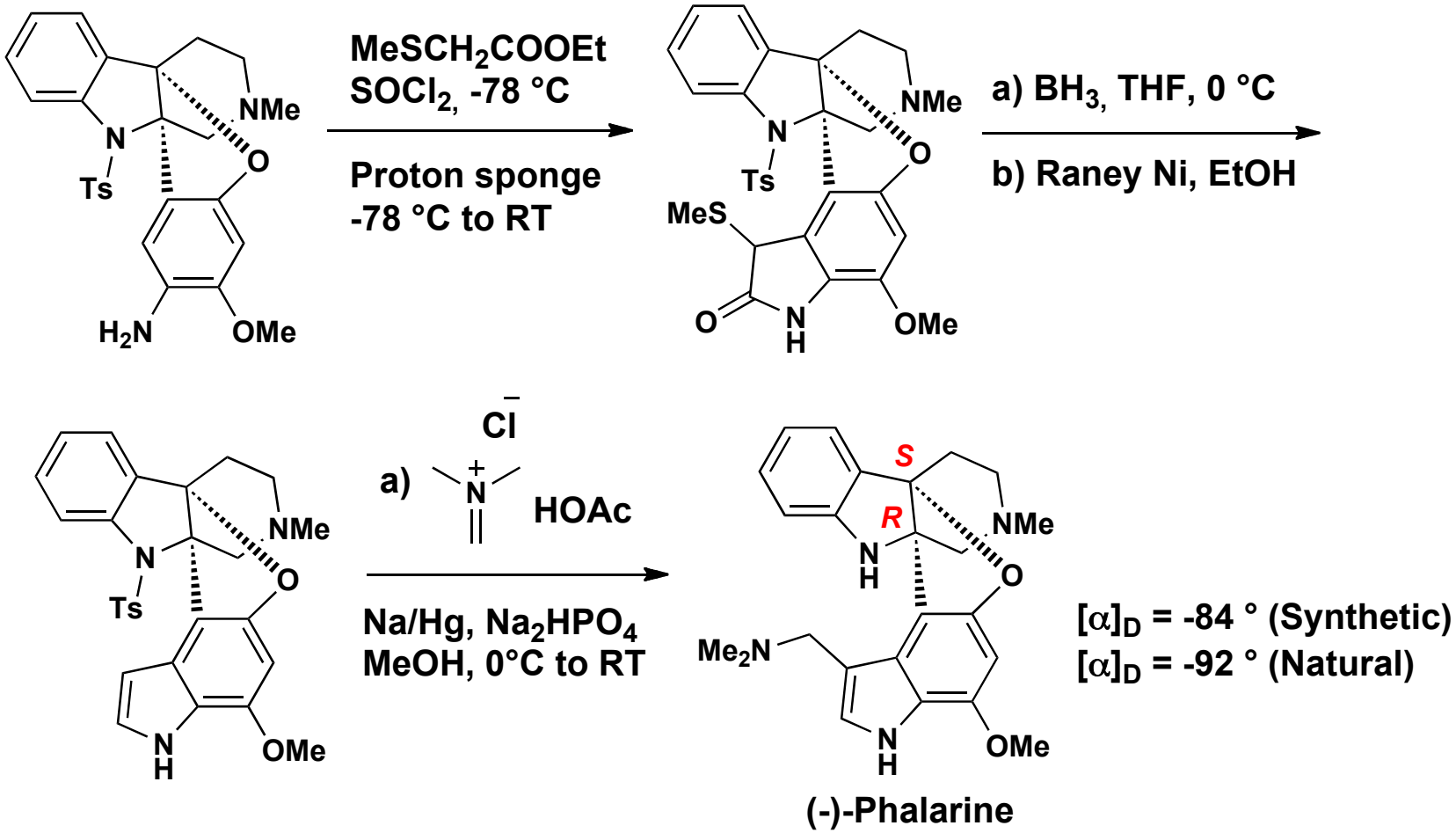


Functionalization of Tetracycle



Decarboxylation: Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930–4937.

Total Synthesis of (—)-Phalarine: End game



Absolute configuration of natural product confirmed

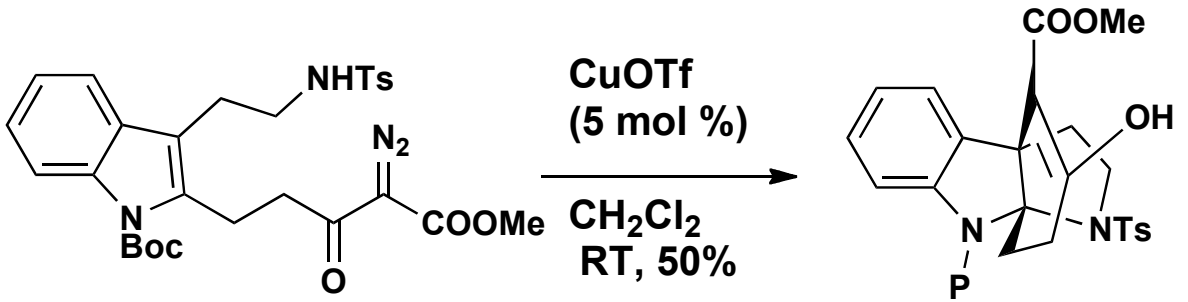
Danishefsky, S. J. *J. Am. Chem. Soc*. **2010**, *132*, 8506.
Alternative Formal total synthesis: Chen, D. Y.-K. *Angew. Chem. Int. Ed*. **2011**, 50, 676.
Jia, Y. *Angew. Chem. Int*. **2019**, *131*, 6135.

Gassman Indole synthesis: P.G. Gassman; T. J. van Bergen, *J. Am. Chem. Soc.* **1973**, *95*, 2718.

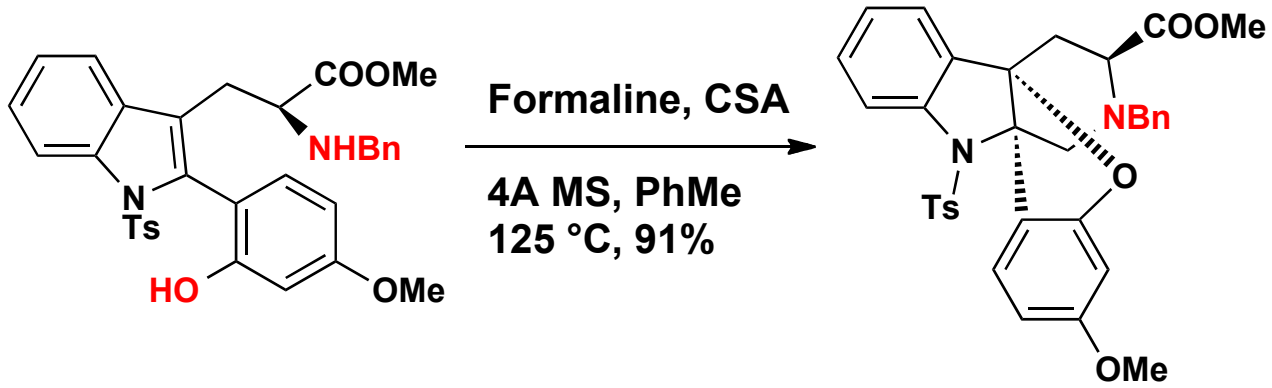
Summary of Danishefsky's Syntheses

1) Umpolung of phenol
2) Hypervalent iodine
3) Wagner-Meerwein rearrangement
4) Retro-Mannich/Mannich sequence
5) Suzuki-Miyaura cross coupling
6) Decarboxylation
7) Electrophilic amination
8) Gassman indole synthesis

Two Examples of Unimolecular Domino Process



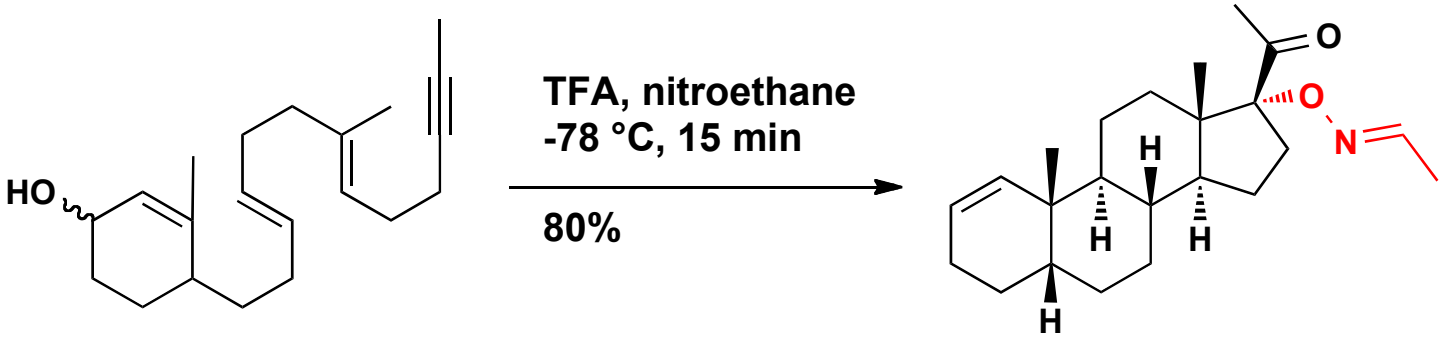
Y. Qin *et al. Angew. Chem. Int. Ed*. **2008**, *47*, 3618-3621.



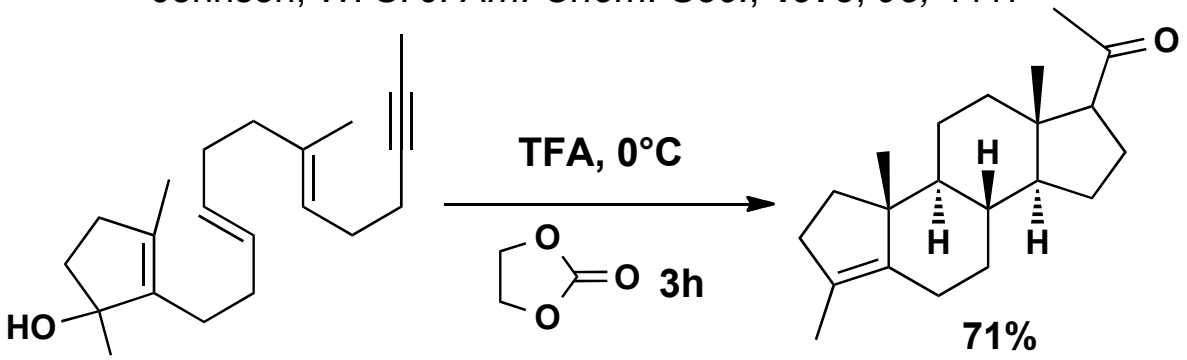
Danishefsky, S. J. *et al. J. Am. Chem. Soc*. **2010**, *132*, 8506-8512.

Domino processes initiated by a Bimolecular Reaction??

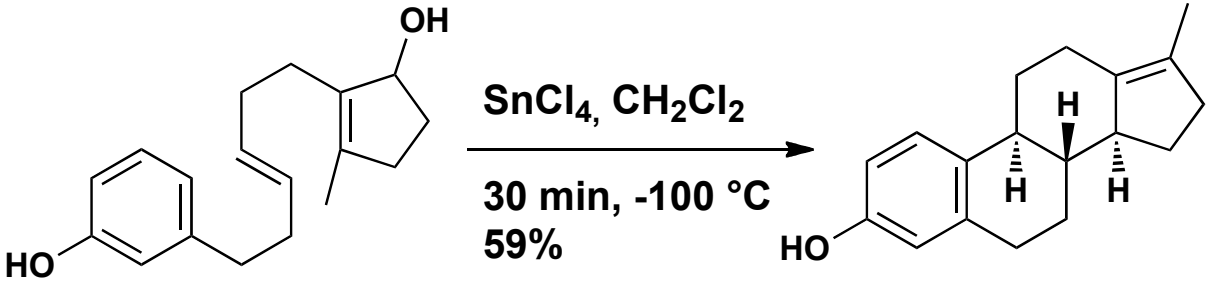
Classical Examples: Johnson's Synthesis of Steroids



Johnson, W. S. *J. Am. Chem. Soc.*, **1973**, *95,* 4417

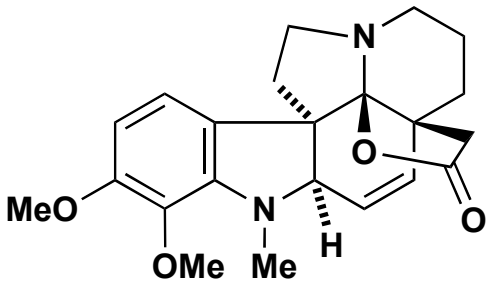


Johnson, W. S. *Angew. Chem. Int. Ed*. **1976,** *15,* 9

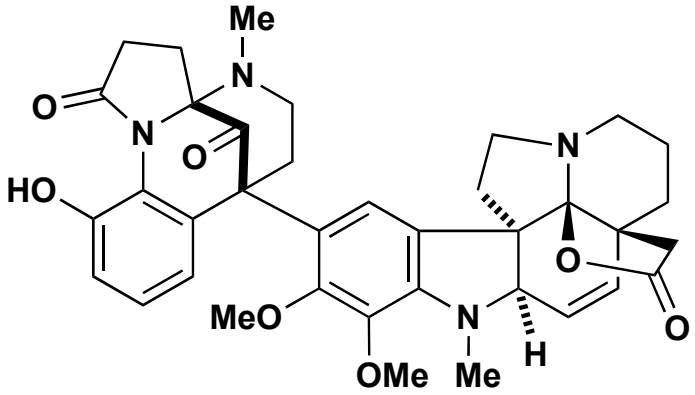


Johnson, W. S. *J. Am. Chem. Soc.*, **1973**, *95,* 7501.

Domino Process Initiated by a Bimolecular Reaction: Example of Aspidophytine



Aspidophytine



Haplophytine

Insecticidal/Anti-cockroach activities

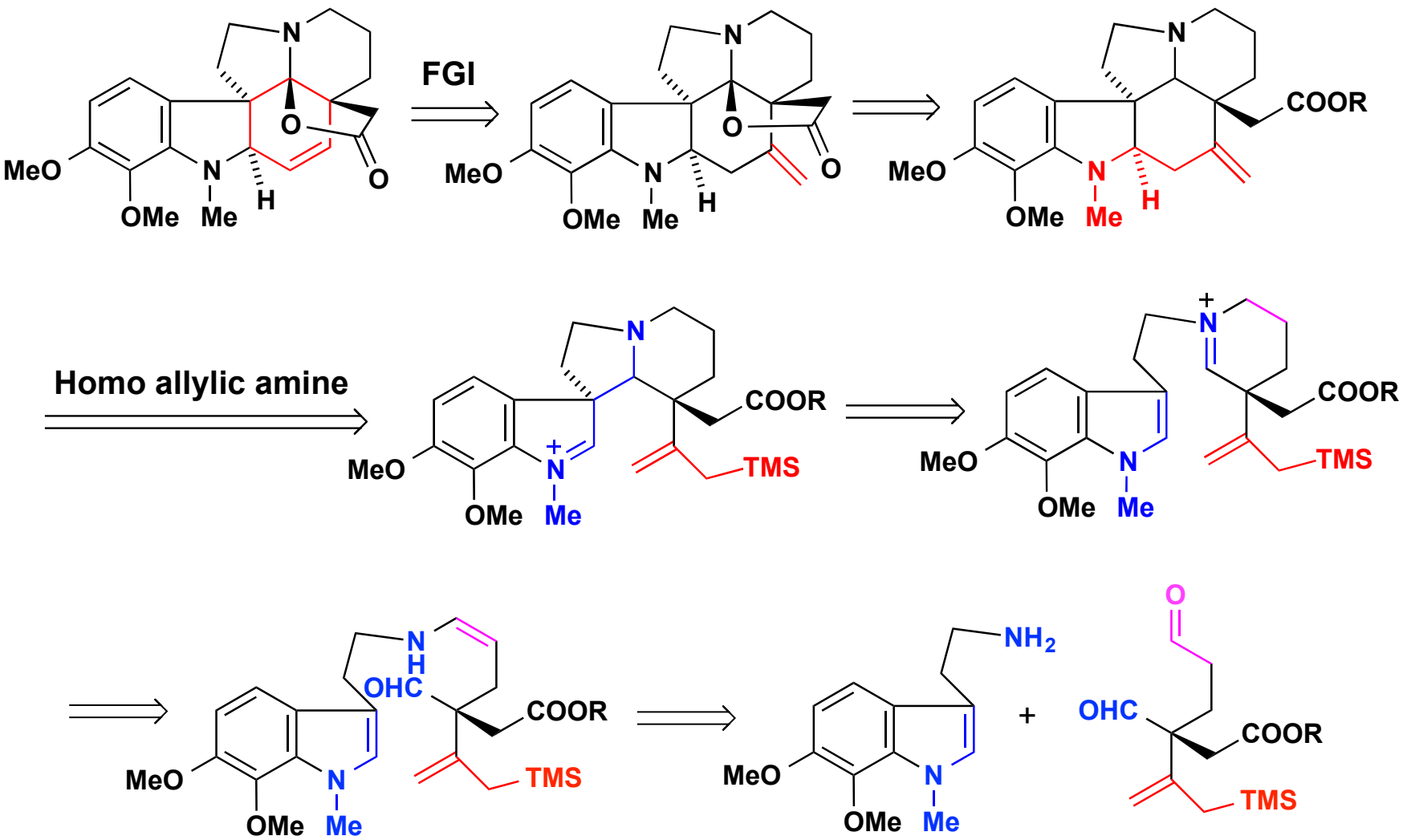
Isolation and structural identification:

Snyder, H. R. et al. *J. Am. Chem. Soc*. **1954**, *76*, 2819 and 4601.
Cava, M. P. *J. Am. Chem. Soc*. **1973**, *95*, 7842.

Total Synthesis of haplophytine:

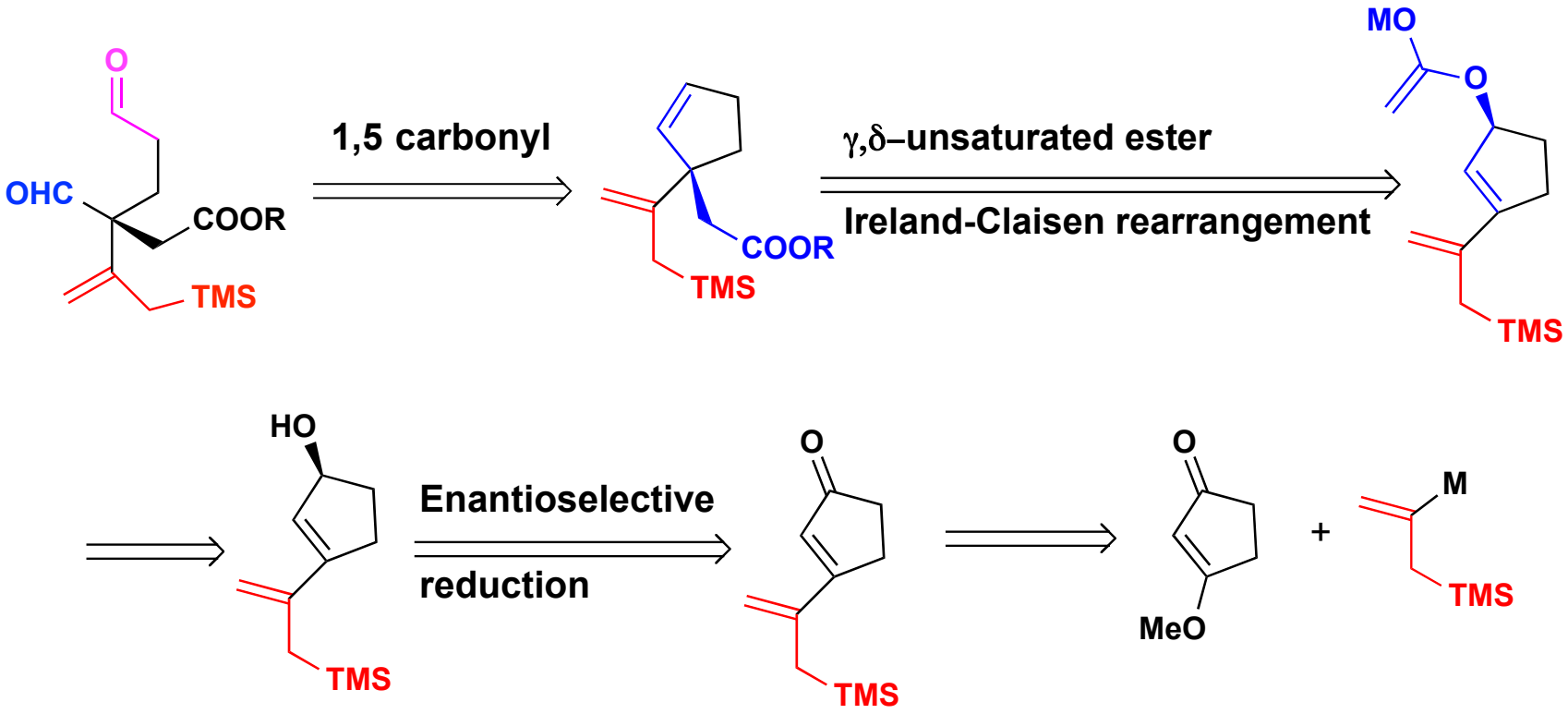
H. Ueda, H. Satoh, K. Matsumoto, K. Sugimoto, T. Fukuyama, H. Tokuyama, *Angew. Chem. Int. Ed*. **2009**, *48*, 7600 –7603;
K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, D. Y.-K. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 7752-7756.

Total Synthesis of Aspidophytine: Retro

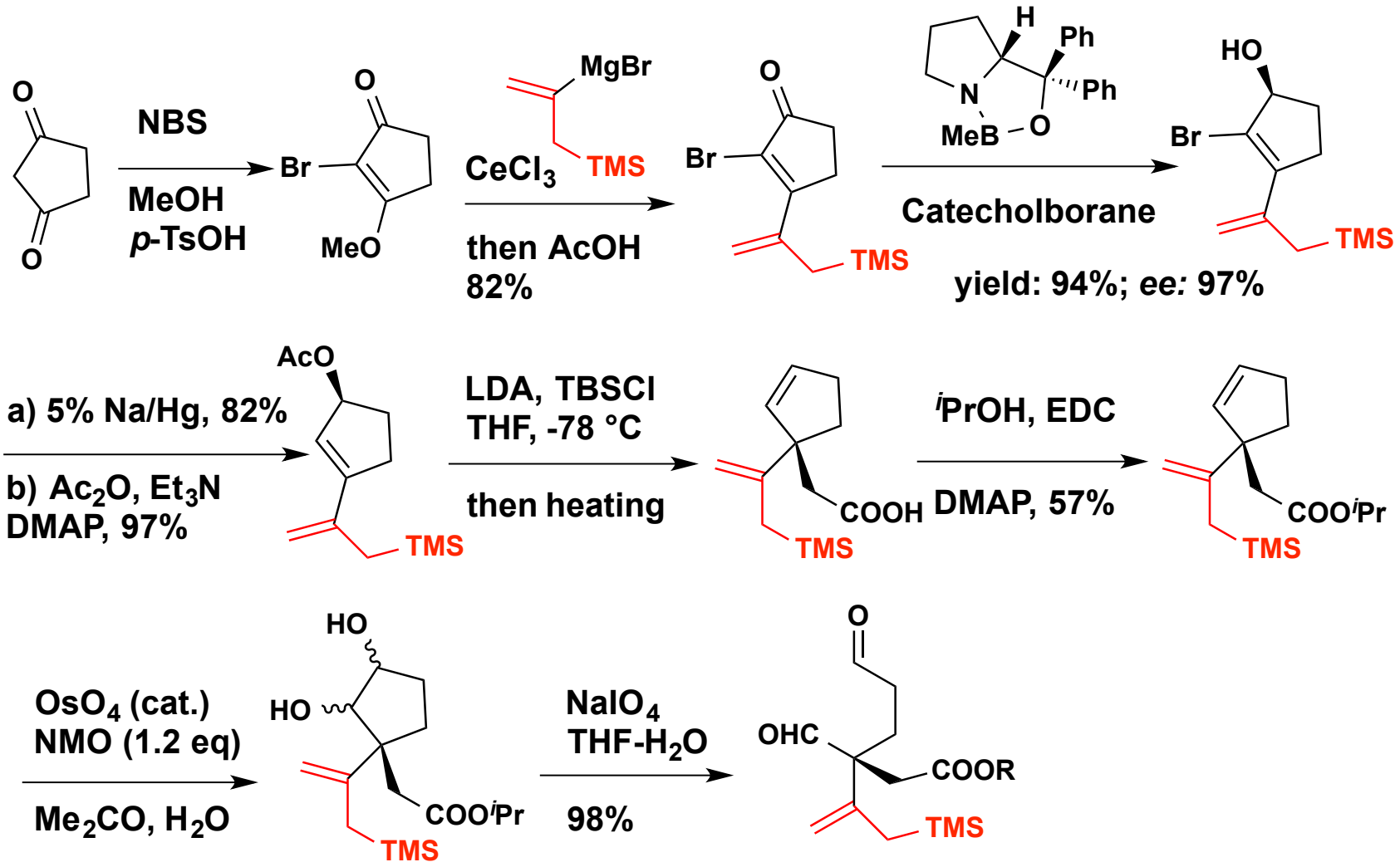


F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc*. **1999**, *121*, 6771-6772.

Enantioselective Synthesis of Dialdehyde—Retro



Enantioselective Synthesis of Dialdehyde

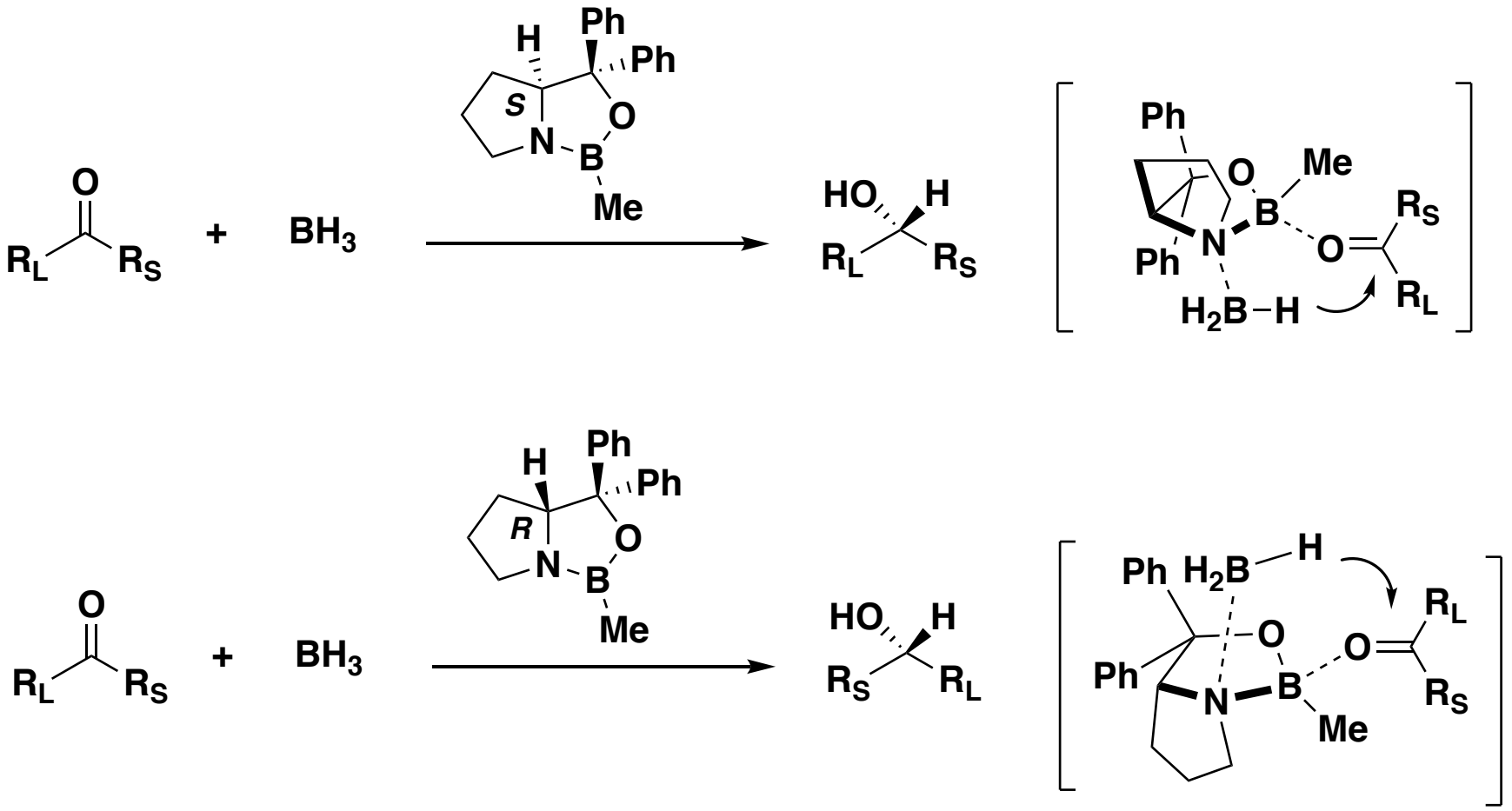


CBS method: Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551 and 7925.

Review: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.

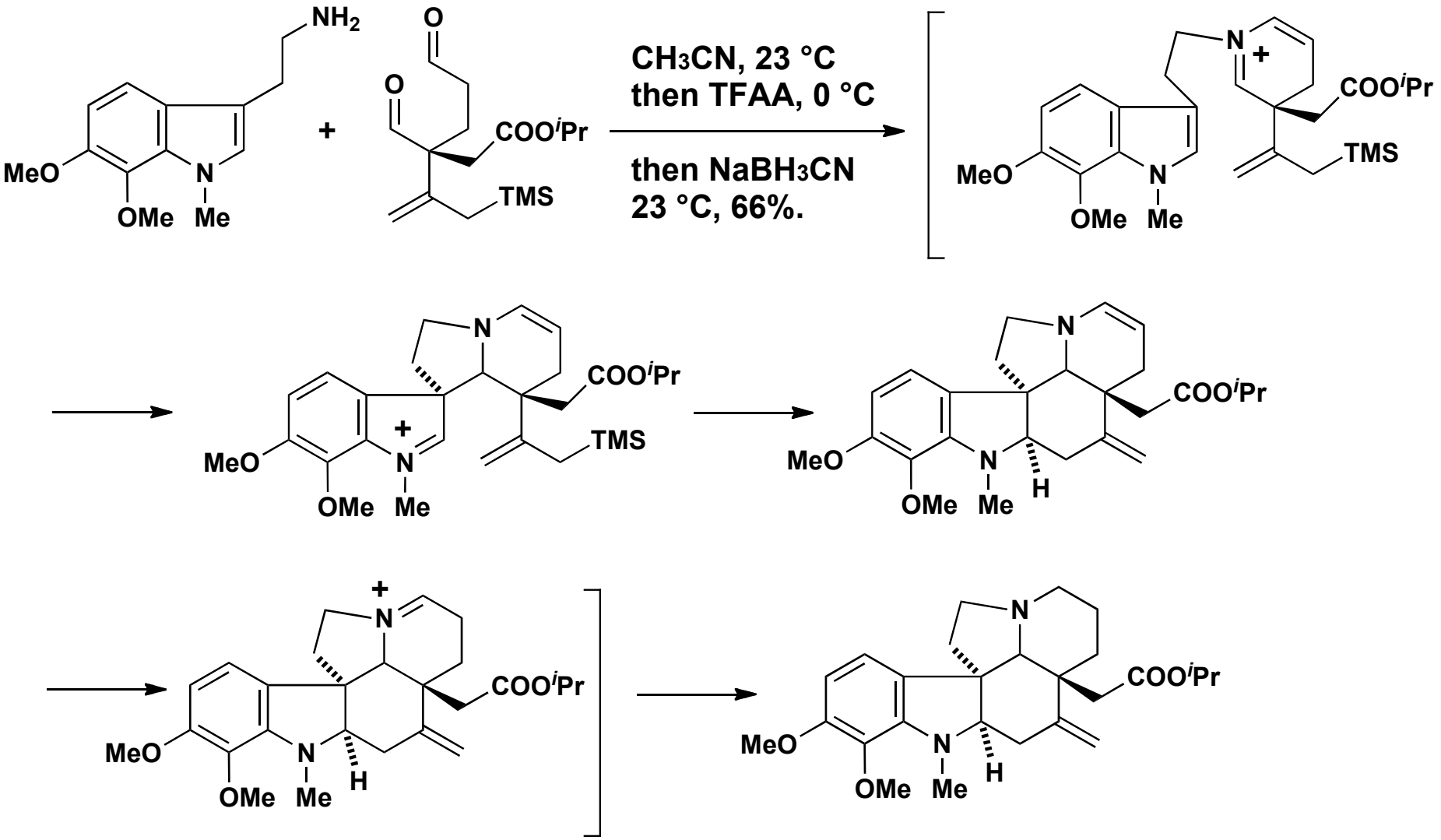
Strok-Danheiser Transposition: Stork, G.; Danheiser, R. L. *J. Org. Chem*. **1973**, *38*, 1775.

CBS Reduction: Stereochemical Model



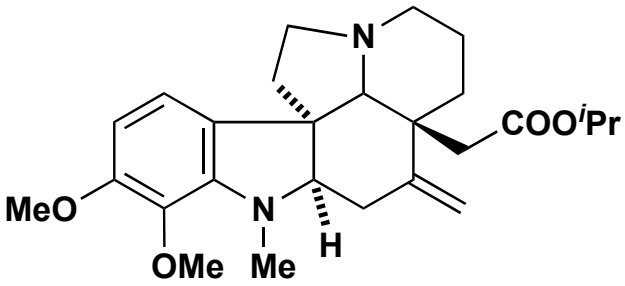
CBS method: Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551 and 7925.
Review: Corey, E. J.; Helas, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.

Domino Process for the Construction of Pentacycle



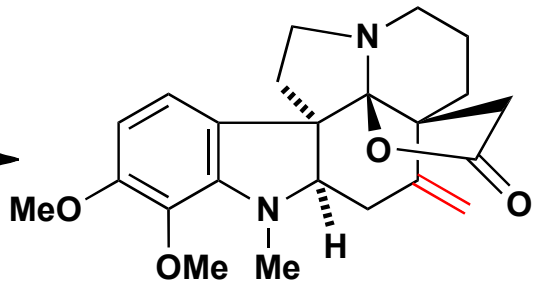
F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc*. **1999**, *121*, 6771-6772.

Total Synthesis of Aspidophytine: End game



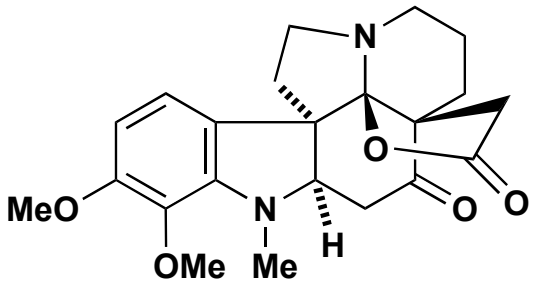
a) NaOH, EtOH, 75 °C
24 h, 88%

b) $K_3Fe(CN)_6$, $NaHCO_3$
t-BuOH-H_2O 1:2, 92%.



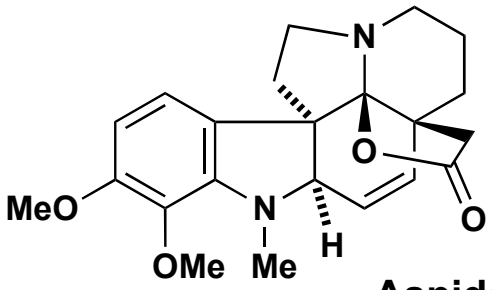
a) OsO_4 (1 equiv)
DMAP (2 equiv)
t-BuOH/H_2O (1:1)
then Na_2SO_3.

b) $Pb(OAc)_4$, AcOH
CH_2Cl_2, -20 °C
71% for two steps.



a) KHMDS, THF, -78 °C
then $PhNTf_2$, -78 °C, 54%

b) $Pd(PPh_3)_4$ (0.2 equiv)
Bu_3SnH (8 equiv)
THF, 23 °C, 1 h, 86%.



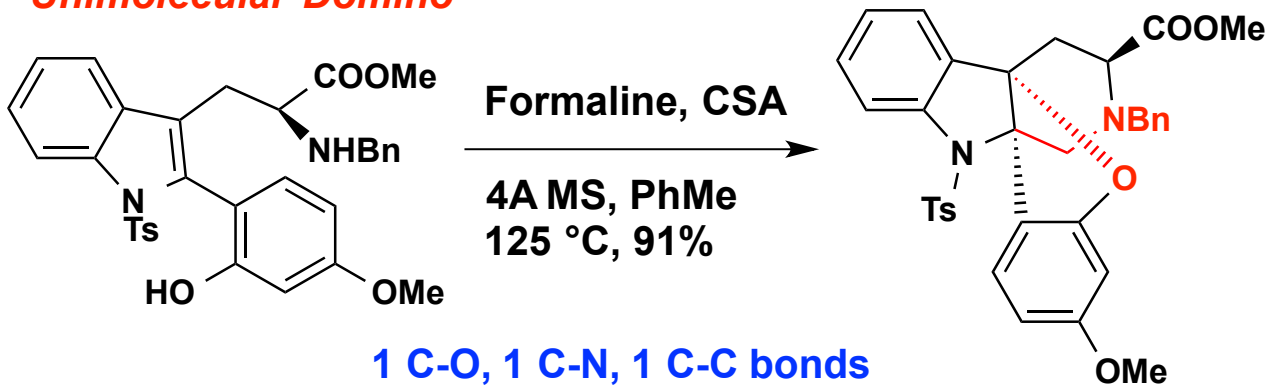
Aspidophytine

Summary of Corey's Syntheses

1) Enantioselective reduction of Ketone (CBS reduction)
2) Ireland-Claisen rearrangement
3) Domino Mannich/Allylation process
4) Oxidation of amine to imine
5) Conversion of ketone to alkene

Uni-, Bi-molecular Domino Processes

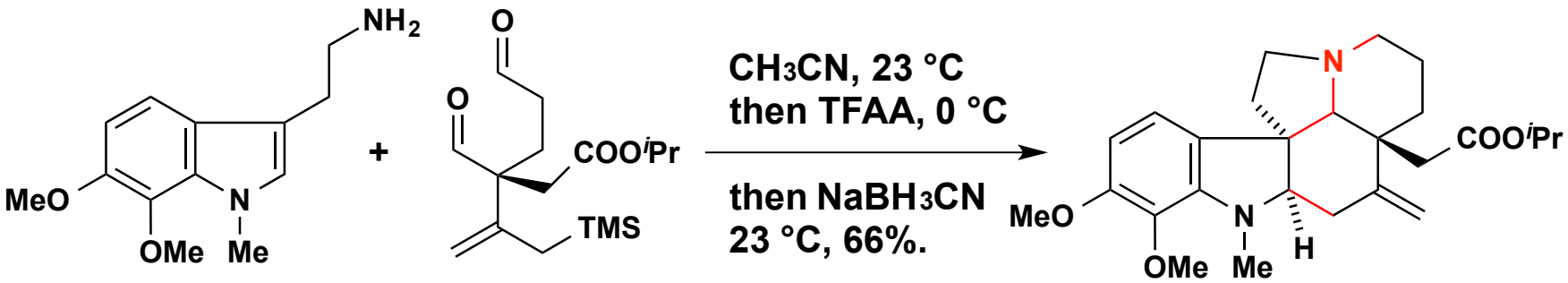
"Unimolecular Domino"



1 C-O, 1 C-N, 1 C-C bonds

Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **2010**, *132*, 8506-8512.

"Bimolecular Domino"



2 C-N, 2 C-C bonds

F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 6771-6772.

…and Multi-component Reaction…