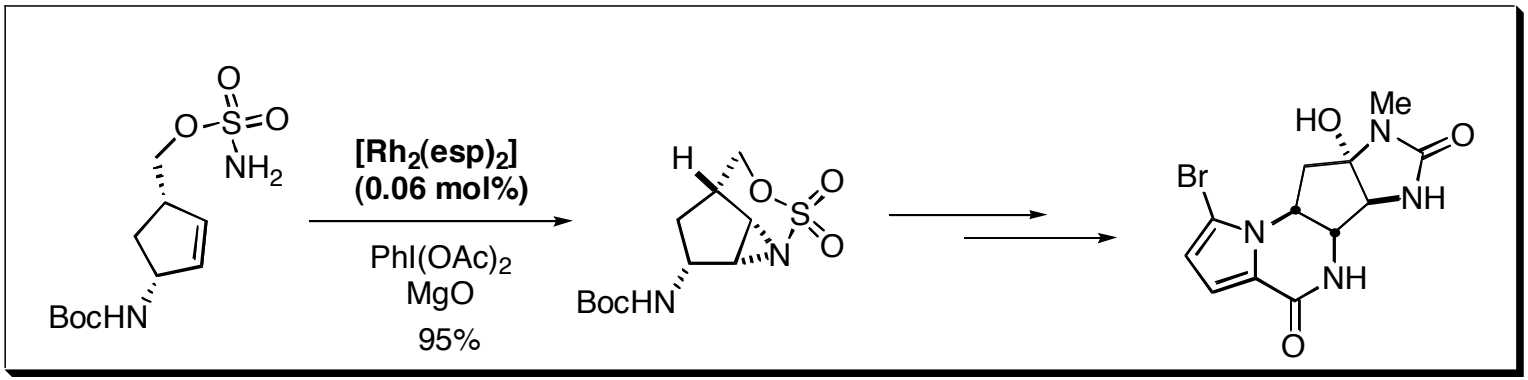
A Stereoselective Synthesis of the Bromopyrrole Natural Product (-)-Agelastatin A

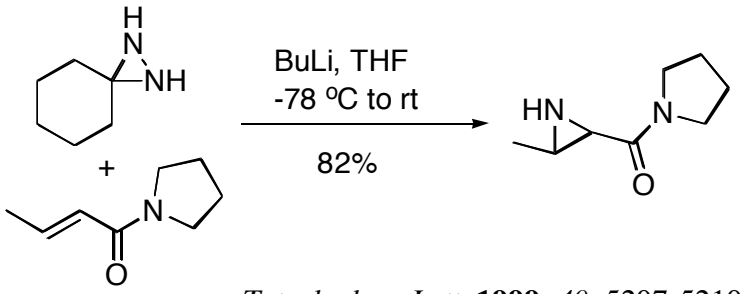
Paul M. When and J. Du Bois, *Angew. Chem. Int. Ed.* **2009,** *48,* 3802-3805.



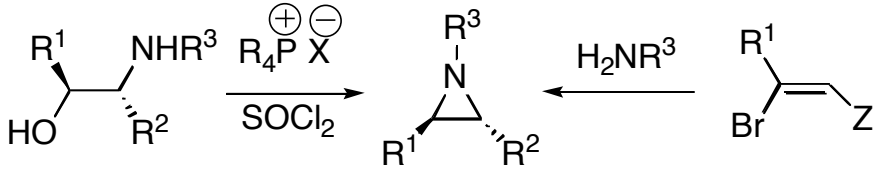
Melissa Sprachman

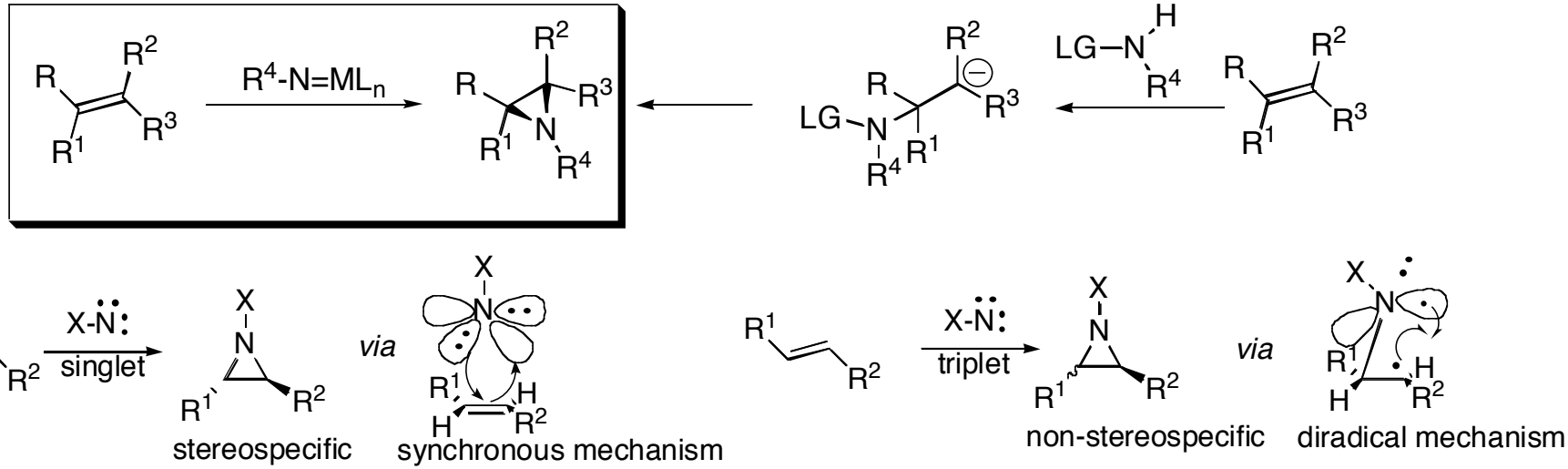
Current Literature: May 23, 2009

Aziridines: General Methods

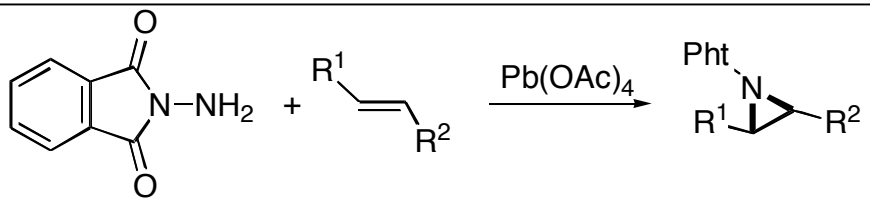


Tetrahedron Lett. **1999,** *40,* 5207-5210.





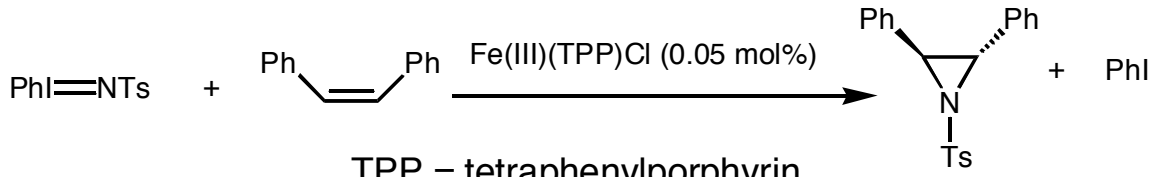
Aziridines and Epoxides in Organic Synthesis; Yudin, A. K. ed.; Wiley-VCH:Weinheim, 2006.



J. Chem. Soc. (C), **1970,** 576-582.

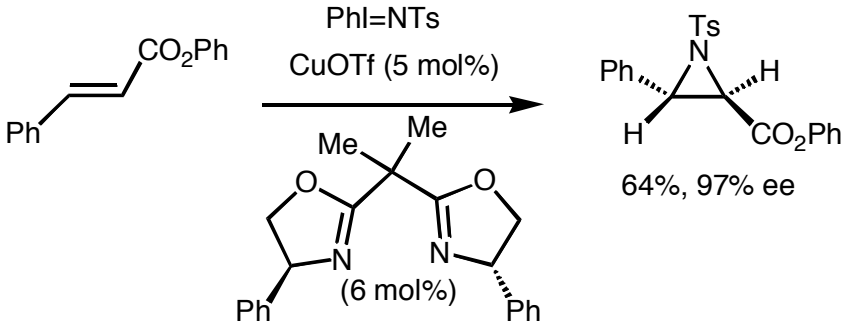
Synthesis of Aziridines via Metal-Catalyzed Nitrene Addition

Aziridation Using TsN=IPh:

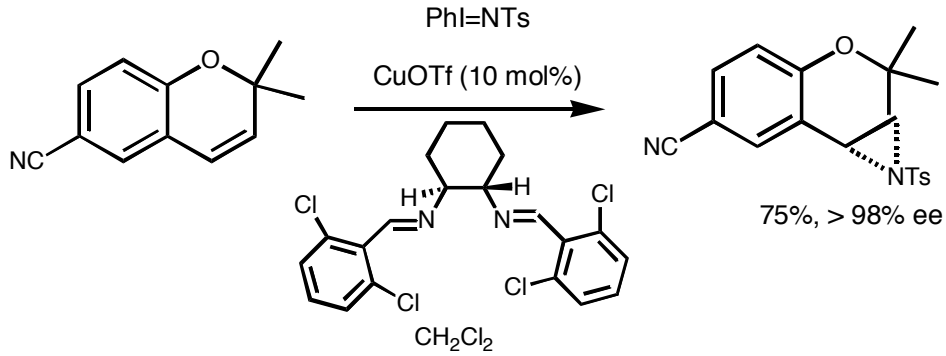


J. Chem. Soc., Chem. Commun. **1984,** 1161-1163.

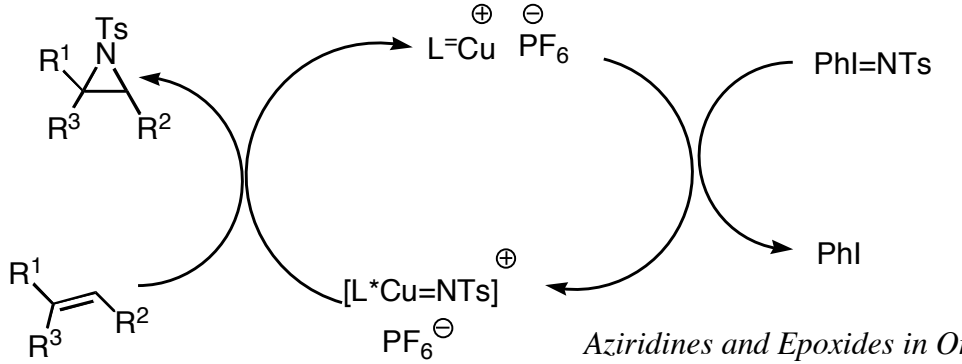
Evans and Jacobsen: Enantioselective aziridination using chiral Cu catalysts:



J. Am. Chem. Soc. **1993,** *115,* 5328-5329.

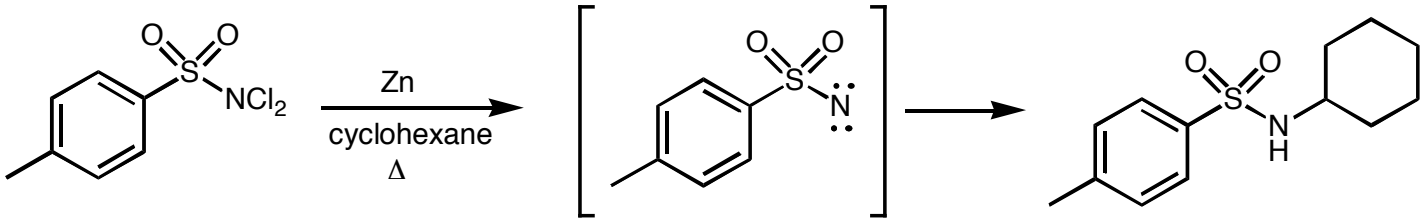


J. Am. Chem. Soc. **1993,** *115,* 5326-5327.

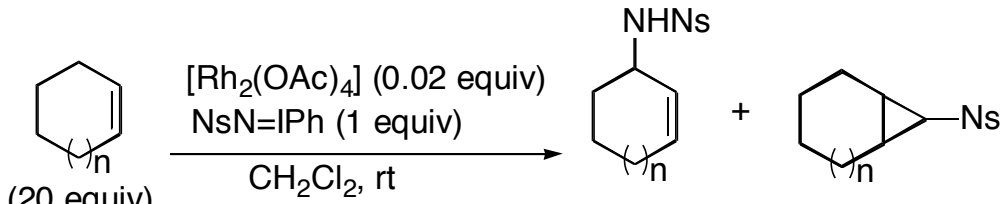


Aziridines and Epoxides in Organic Synthesis; Yudin, A. K. ed.; Wiley-VCH:Weinheim, 2006.

Rh-catalyzed Aziridination was developed in tandem with C-H amination

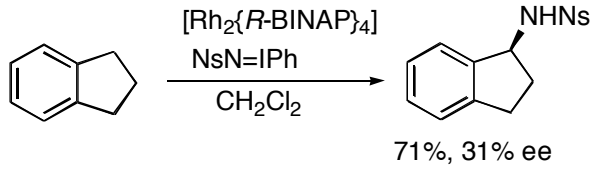


Tetrahedron Lett. **1968,** 5349-5352.

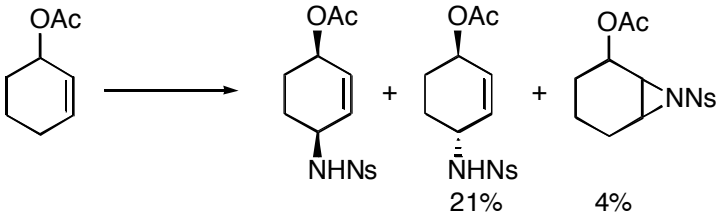


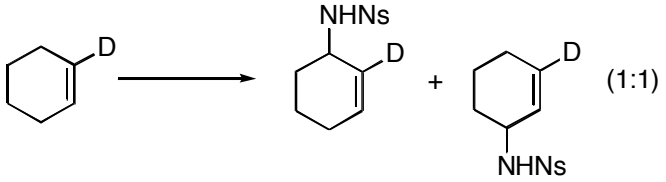
a) n = 0	44%	9%
b) n = 1	70%	4%
c) n = 2	17%	24%
d) n = 3	0%	54%

Preliminary hope for enantioselective insertion:



Mechanistic Aspects:

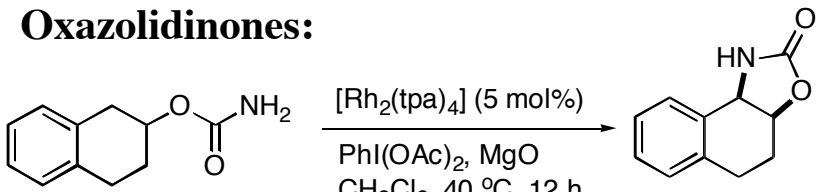




Helvetica Chim. Acta, **1997,** *80,* 1087-1105.

Du Bois Group Contributions: Early Developments and Mechanistic Considerations

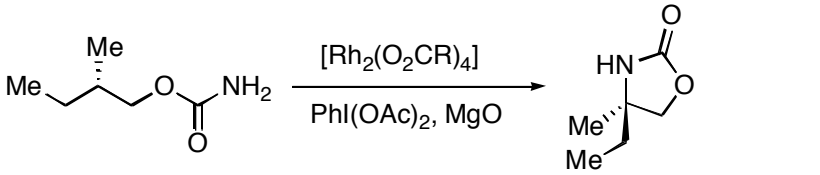
Conversion of Carbamates to Oxazolidinones:



77%, single diastereomer

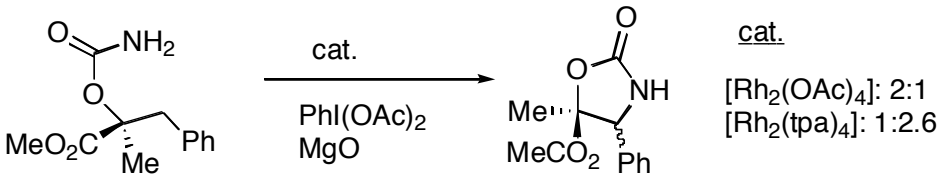
tpa = triphenylacetate

Evidence for direct insertion:



single enantiomer (GC)

Evidence for a metallo-nitrene:

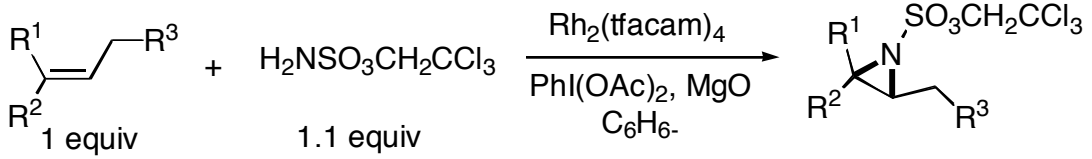


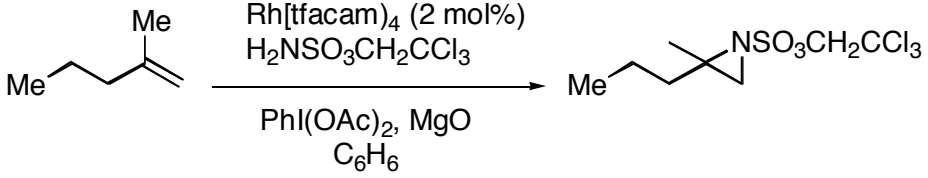
cat.

$[Rh_2(OAc)_4]$: 2:1
$[Rh_2(tpa)_4]$: 1:2.6

Angew. Chem. Int. Ed. **2001,** *40,* 598-560.

Aziridination Chemistry:

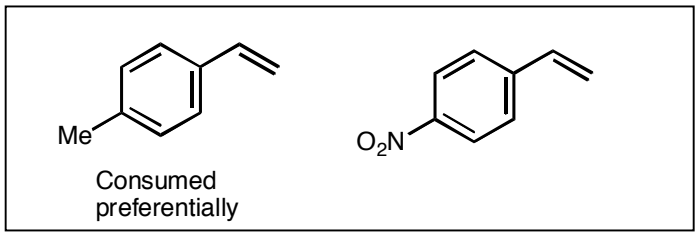




tfacam = CF_3CONH

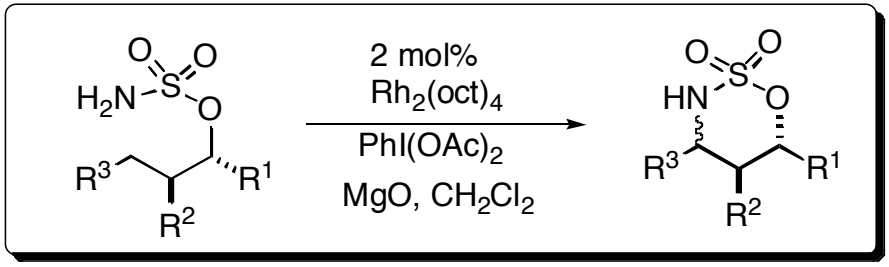
72%

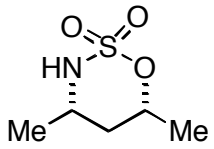
J. Am. Chem. Soc. **2002,** *124,* 13672-13673.



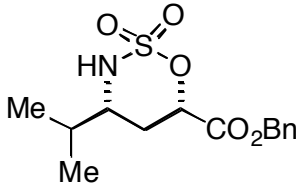
For related work using Cu and PhIO, see *J. Am. Chem. Soc.* **2001,** *123,* 7707-7708 and *Org. Lett.,* **2002,** *4,* 2481-3..

Rh-Catalyzed Amination Reactions of Chiral Sulfamates

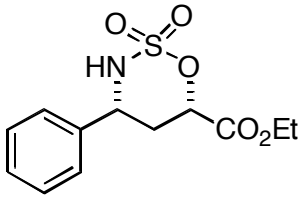




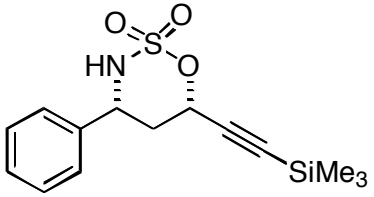
88%, 3:1 dr



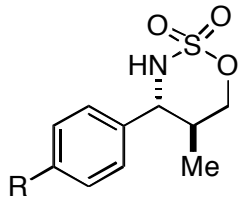
55%, 8:1 dr



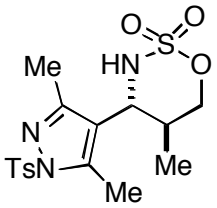
91%, 15:1 dr



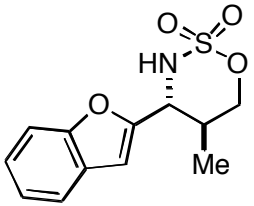
62%, 20:1 dr



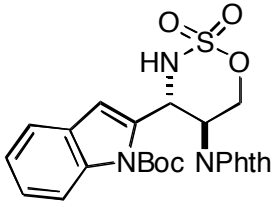
R = CF_3, 70%, 20:1 dr
R = OMe, 85%, 20:1 dr



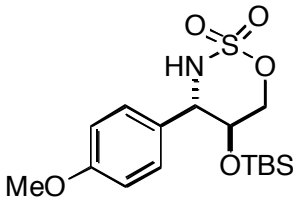
84%, 20:1 dr



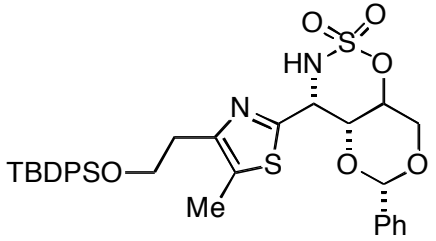
65%, 20:1 dr



85%, 12:1 dr



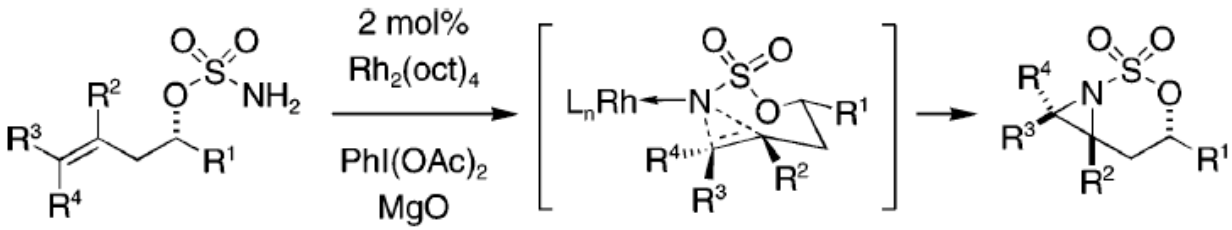
77%, 10:1 dr

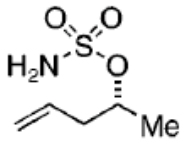
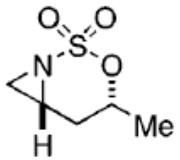
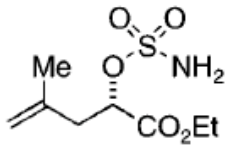
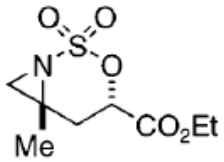
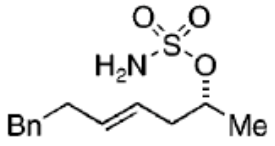
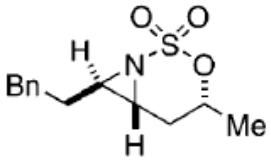
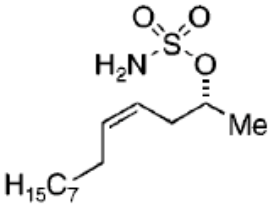
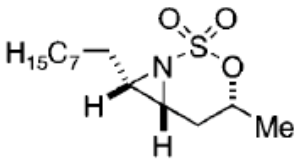


92%, 20:1 dr

Org. Lett. **2003,** *5,* 4823-4826.

Aziridination Chemistry

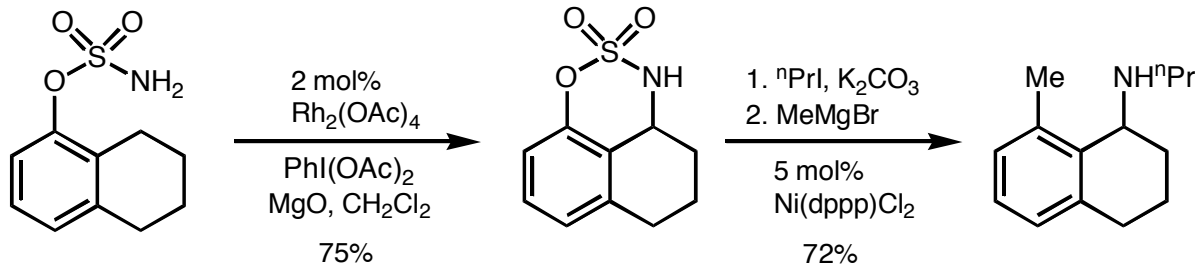


entry	substrate	major product	selectivity[a]	yield[b]
1			4:1	84
2			4:1	92
3			2.5:1	88
4			10:1	84

Org. Lett. **2003,** *5*, 4823-4826.

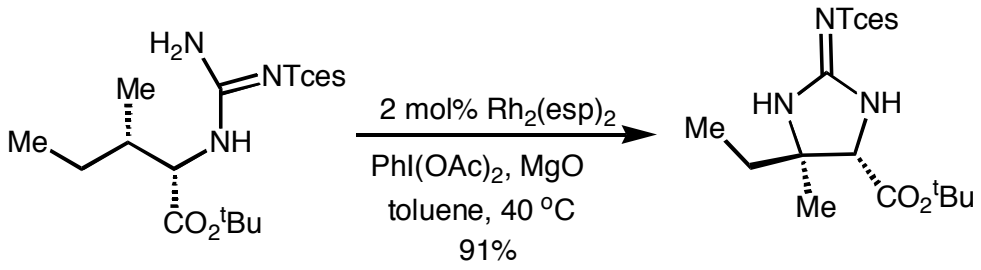
Extensions of Rh-Catalyzed Amination Reactions

Ni-catalyzed cross-coupling of cyclic sulfamates:

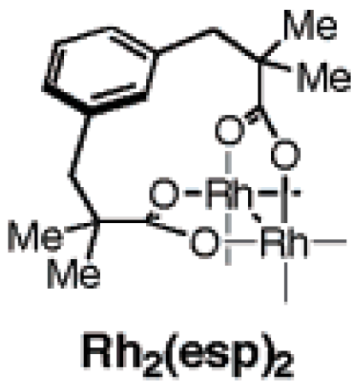


Org. Lett. **2005,** *7,* 4685-4688.

Oxidative Cyclization of Urea and Guanidine Derivatives:

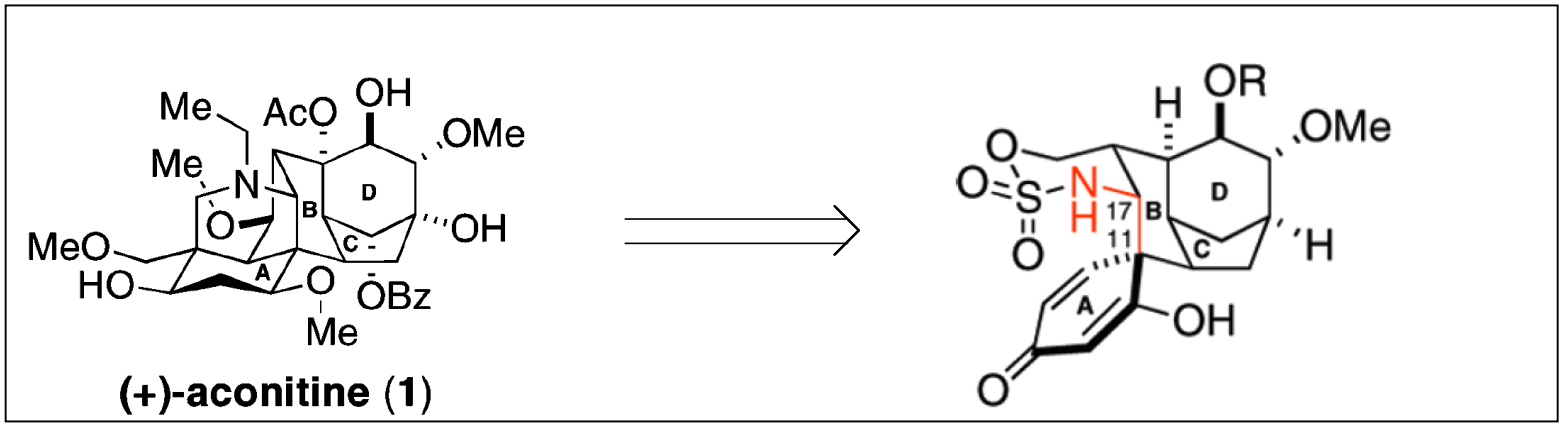


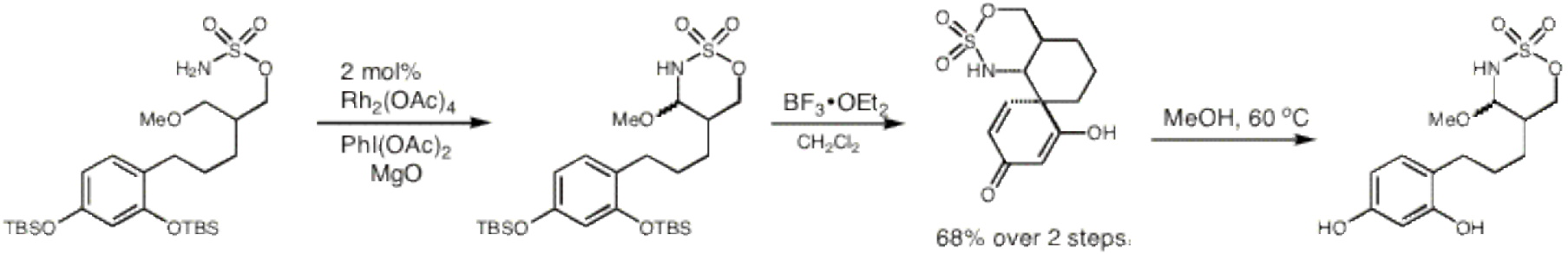
Org. Lett. **2006,** *8,* 1073-1076.

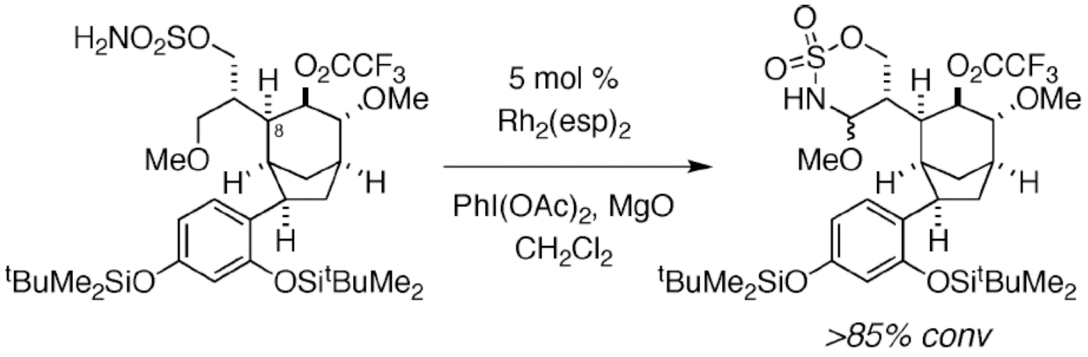


$Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate)$_2$

C-H Amination as an Application in Complex Molecule Synthesis

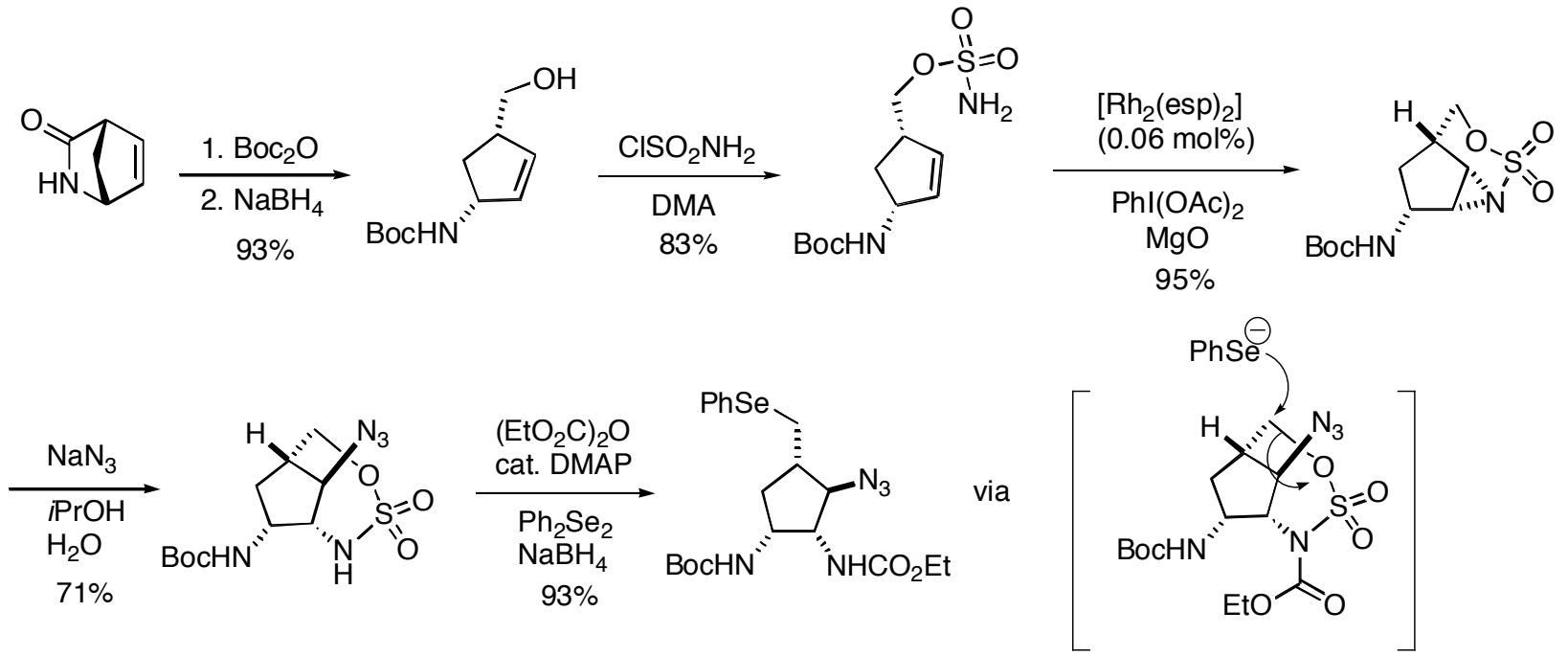




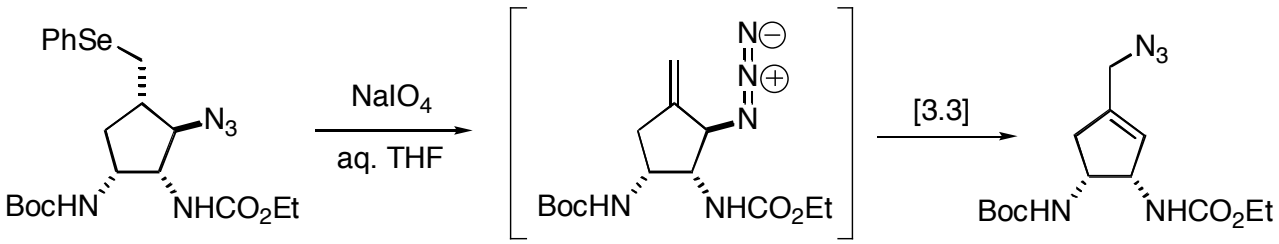


Org. Lett. **2007,** *9,* 5465-5468.

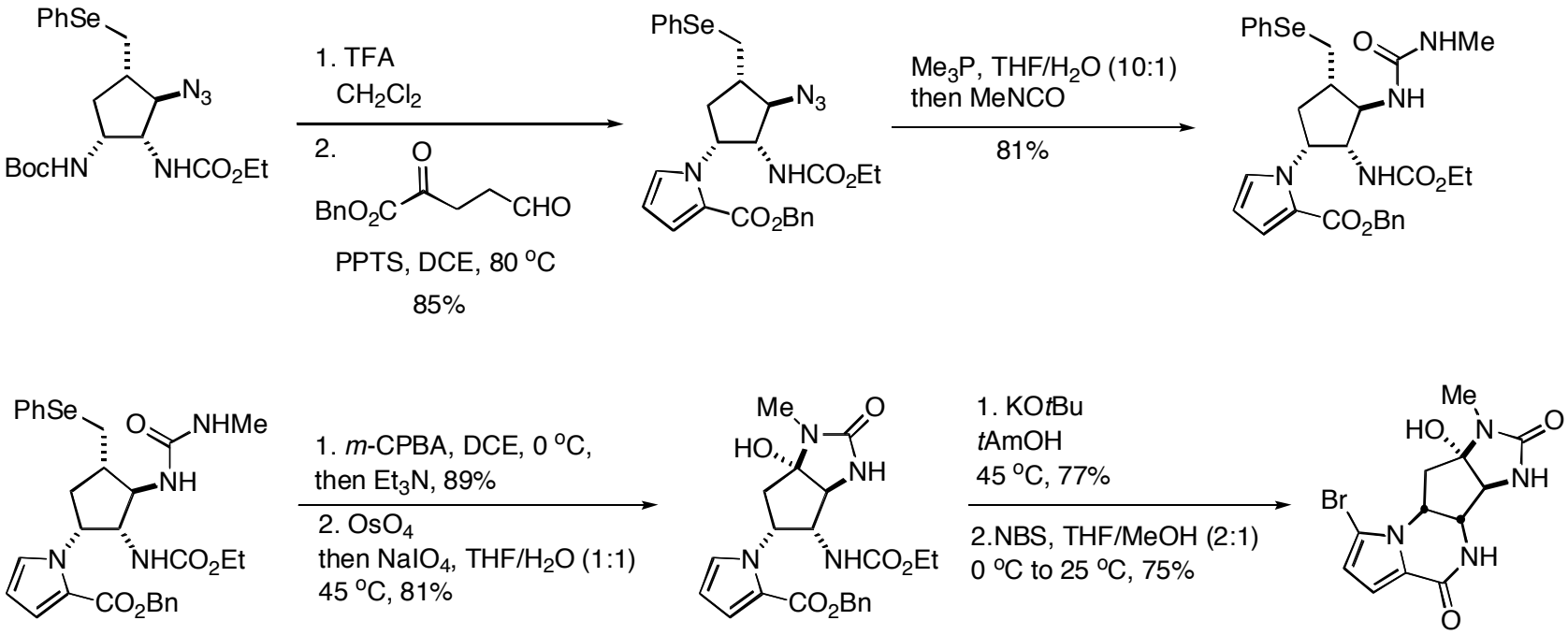
Synthesis of (-)-Agelastatin A



Problem with installation of the exocyclic olefin at this stage:

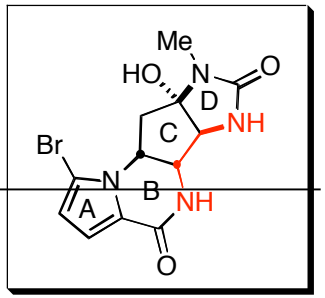


Synthesis of (-)-Agelastatin A

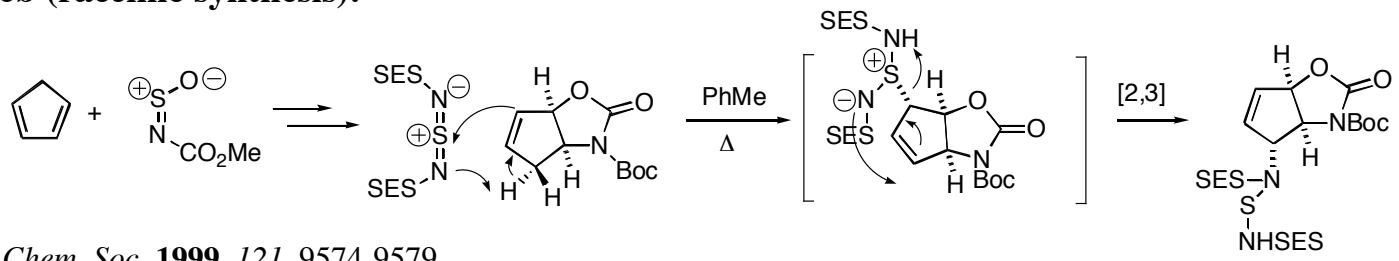


11 Steps, 15% overall yield (200 mg of natural product synthesized)

Other Routes to (-)-Agelastin A: A Comparison

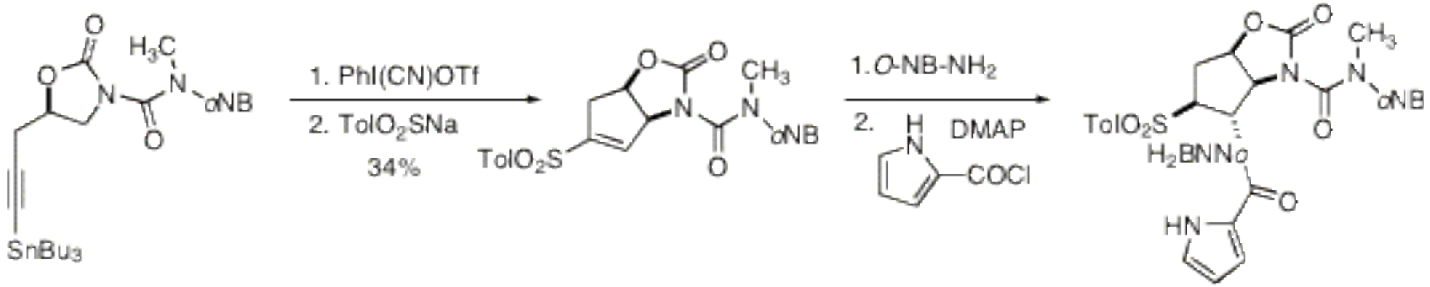


Weinreb (racemic synthesis):



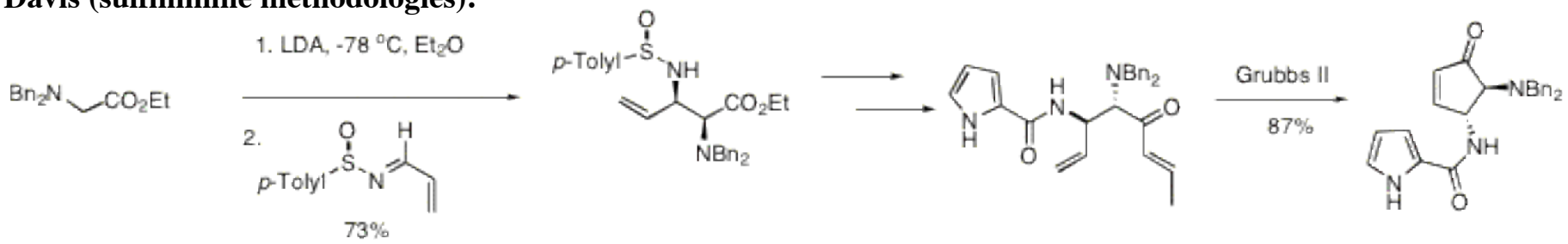
J. Am. Chem. Soc. **1999,** *121,* 9574-9579.

Feldman (via alkynyliodonium salts):

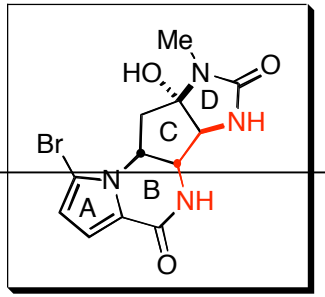


J. Org. Chem. **2002,** 67, 7096-7109.

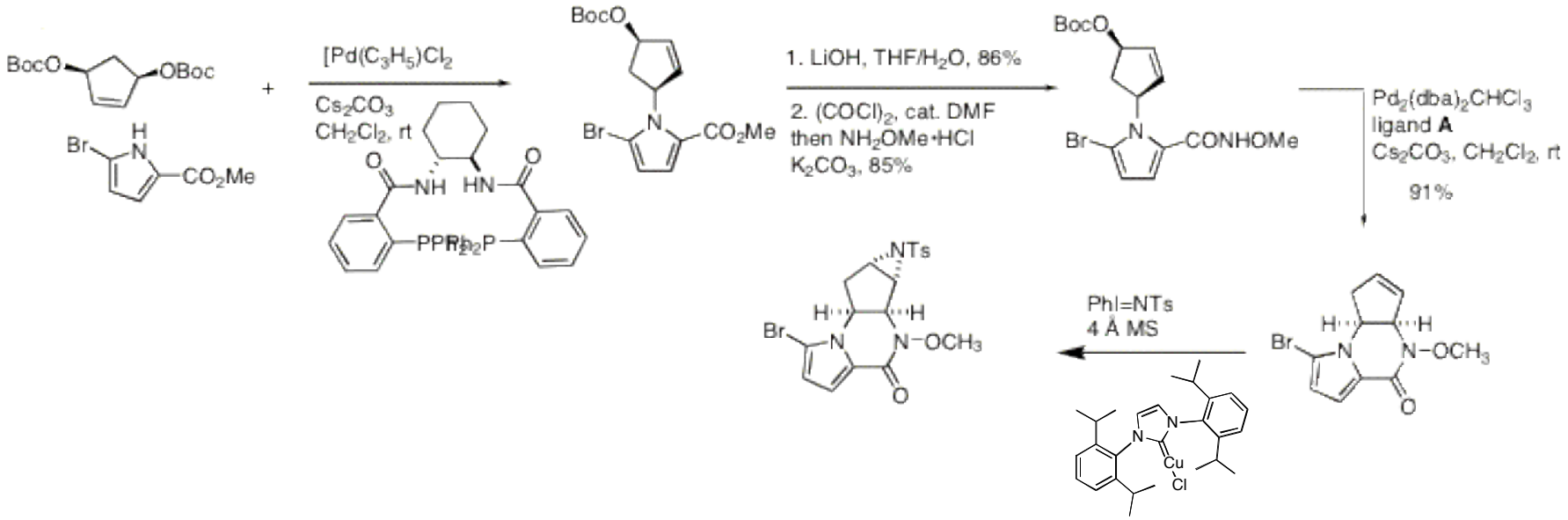
Davis (sulfinimine methodologies):



Other Routes to (-)-Agelastin A: A Comparison



Trost (Pd-catalyzed asymmetric allylic alkylation):



J. Am. Chem. Soc. **2006,** *128,* 6054-6055.

Summary and Outlook

-Rh-catalyzed selective C-H amination and olefin aziridination methods have been developed as useful tools for synthesis.

-Du Bois and co-workers have demonstrated the utility of their aziridination methodology through installation of a critical chiral C-N bond in the synthesis of (-)-Agelastatin A.