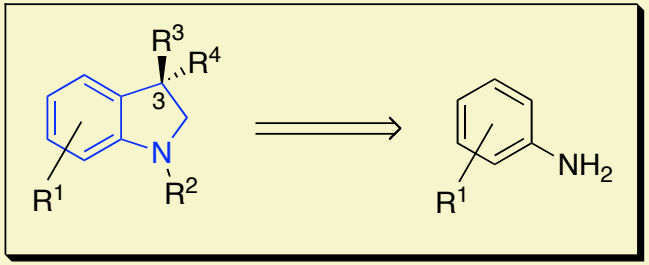
Formation of 3-Substituted Indoline Scaffolds Using Friedel-Crafts and Radical Mediated Processes

John Maciejewski

Research Topic Seminar
January 20th, 2007



Presentation Outline

- Recent approaches toward the indoline scaffold

- Important indoline natural products

- Synthesis of 3-substituted indolines

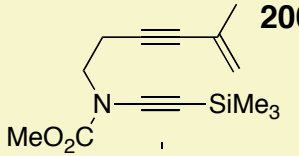
- Friedel-Crafts approach towards indoline synthesis

- Radical cyclization approach towards indoline synthesis

Approaches Toward the Indoline Scaffold

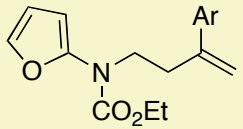
Danheiser, R. L.; Dunetz, J. R. *J. Am. Chem. Soc.* **2005,** *127*, 5776

[4+2] Cycloaddition



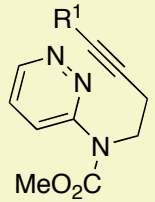
Padwa, A. et al. *J. Org. Chem.* **2001,** *66*, 3119

Intramolecular Diels-Alder reaction



BHT
Δ

Δ

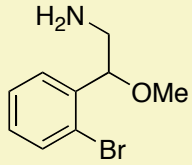


Intramolecular Diels-Alder cyclization

Δ

Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984,** *49*, 2240

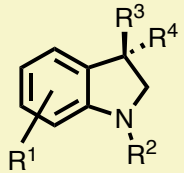
Johnston, J. N. et al. *Org. Lett.* **2001,** *3*, 1009



1) $Ph_2C{=}NH$

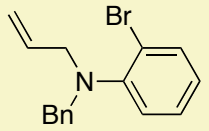
2) $^{n}Bu_3SnH$, AIBN

Aryl radical addition



$^{t}BuLi$

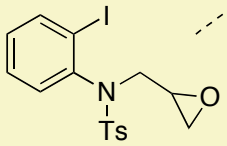
(-)-sparteine



Enantioselective Carbolithiation

Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000,** *122*, 6787

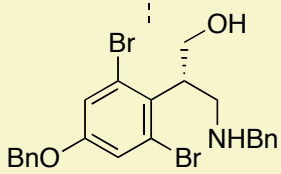
$Me_3Zn(SCN)Li_2$



Organozincate addition

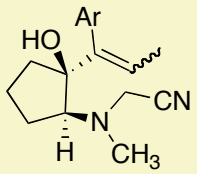
Sakamoto, T. et al. *J. Am. Chem. Soc.* **1998,** *120*, 4934

CuI (10%),
CsOAc (1.4 equiv)



Copper-mediated aryl amination

$Cu(OTf)_2$



Aza-Cope/Mannich rearrangement

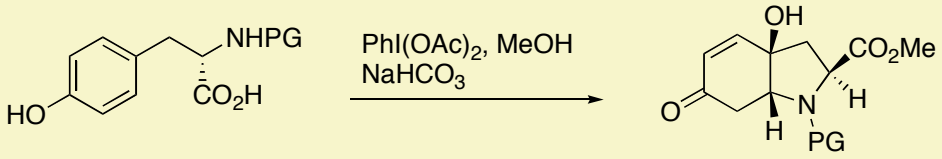
Overman, L. E.; Wild, H. *Tet. Lett.* **1989,** *30,* 647

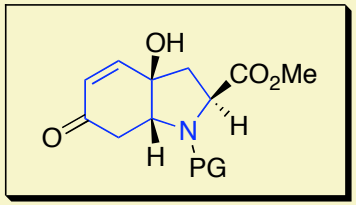
Fukuyama, T. et al. *J. Am. Chem. Soc.* **2003,** *125*, 6630

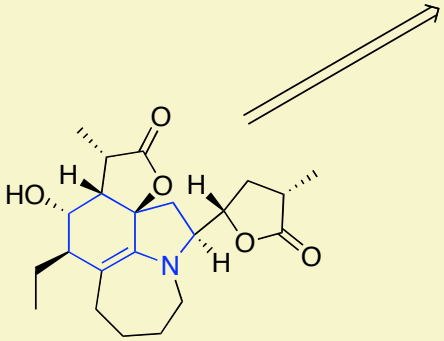
Wipf Group Interests

Stemona alkaloid core prepared by oxidative cyclization of *L*-tyrosine

Wipf, P.; Kim, Y. *Tet. Lett.* ***1992,*** 33, *5477*

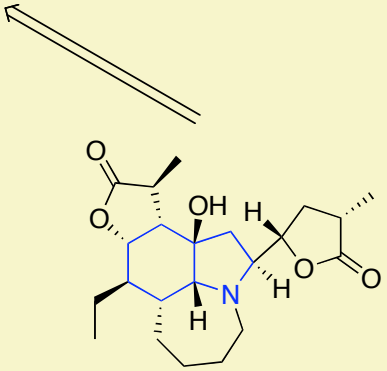






Oxotuberostemonine

No total synthesis to date



(-)-Tuberostemonine

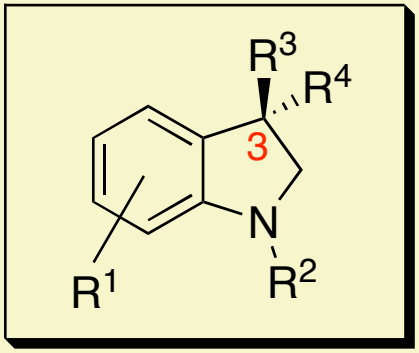
Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002,** *124*, 14848

3-Substituted Indoline Natural Products

- Few examples of enantioselective preparation in literature

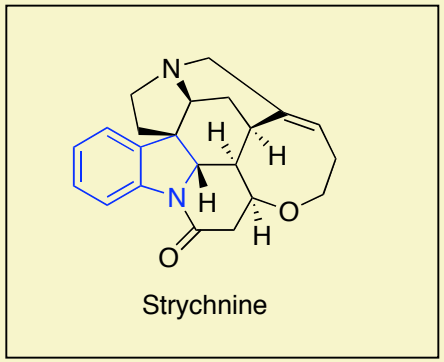
- Many biologically active indoline natural products are substituted at 3-position

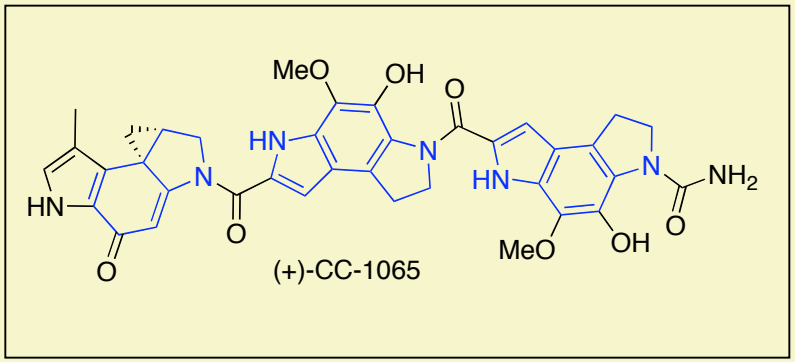
- Demand for mild, enantioselective method of construction

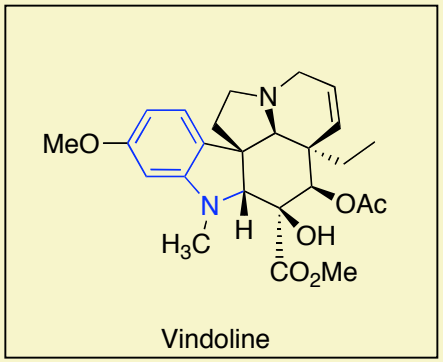


Difficult to enantioselectively form quaternary centers at 3-position

Examples of 3-Substituted Indoline Natural Products







Padwa, A. et al. *Org. Lett.* **2007,** *9*, 279

Boger, D. L. et al. *Chem. Rev.* **1997,** *97*, 787

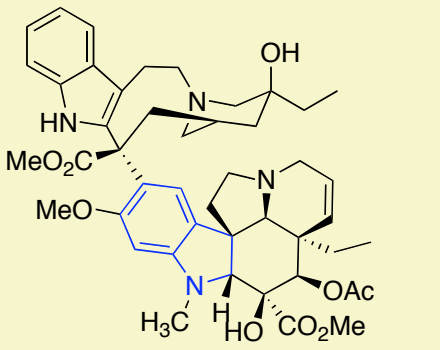
Fukuyama, T. et al. *Synlett* **2000,** *6*, 883

- Alkaloid of genus *Strychnos*
- Actively binds to glycine receptor site
- Disrupts nerve-cell signaling

- Alkaloid of genus *Streptomyces*
- Structure discovered in 1980
- Potent cytotoxin

- Alkaloid of genus *Catharanthus*
- Highly functionalized pentacyclic core
- Synthon for natural product Vinblastine

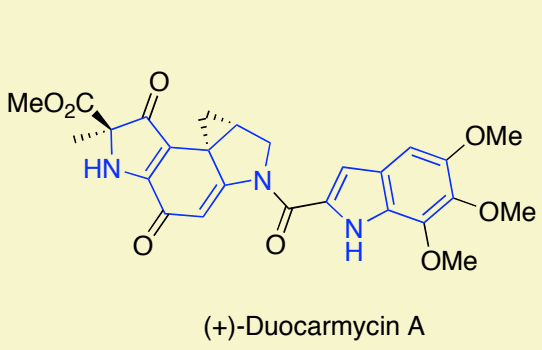
Examples of 3-Substituted Indoline Natural Products



(+)-Vinblastine

Fukuyama, T. et al. *J. Am. Chem. Soc.* **2002,** *124*, 2137

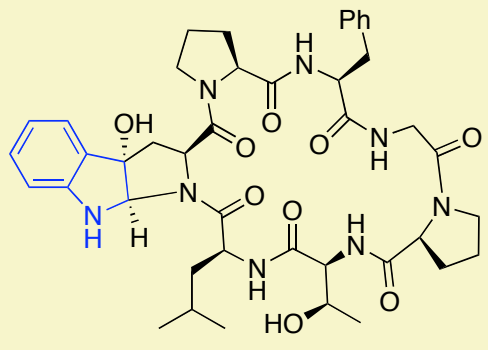
- Alkaloid of genus *Catharanthus*
- Binds to tubulin, inhibits cell division
- Potent chemotherapy agent



(+)-Duocarmycin A

Ichimura, M. et al. *J. Am. Chem. Soc.* **2003,** *125*, 6630

- Alkaloid of genus *Streptomyces*
- More potent subunit of CC-1065
- Functions as DNA alkylating agent

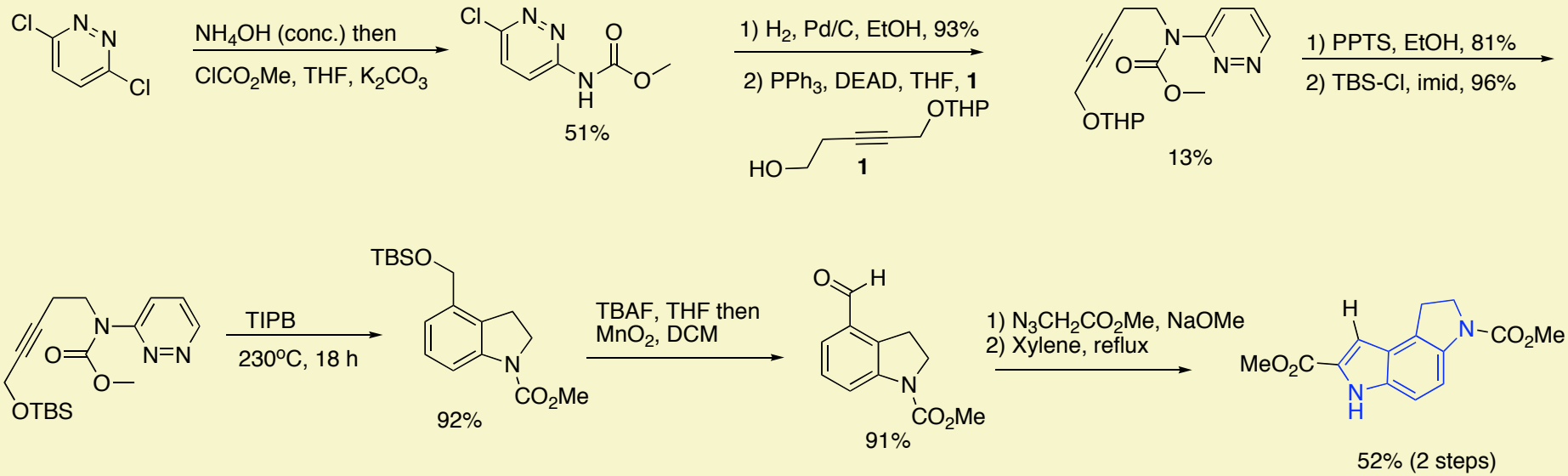


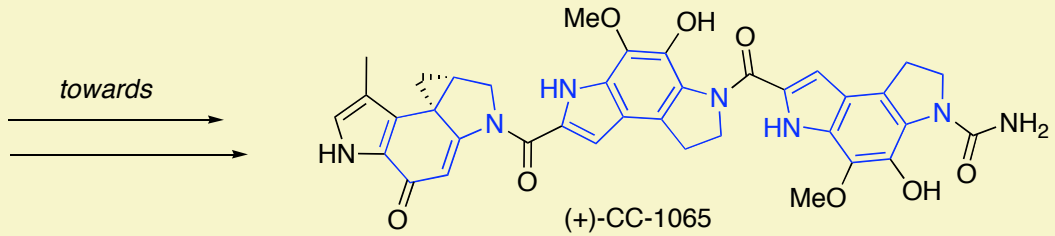
Phakellistatin 3

Van Vranken, D. L. et al *Org. Lett.* **2004,** *6*, 1713

- Alkaloid of genus *Phakellia*
- Unique moiety derived from photooxidation of Trp
- Activity against leukemia cell lines under investigation

Indoline Scaffolds Through Diels-Alder Chemistry

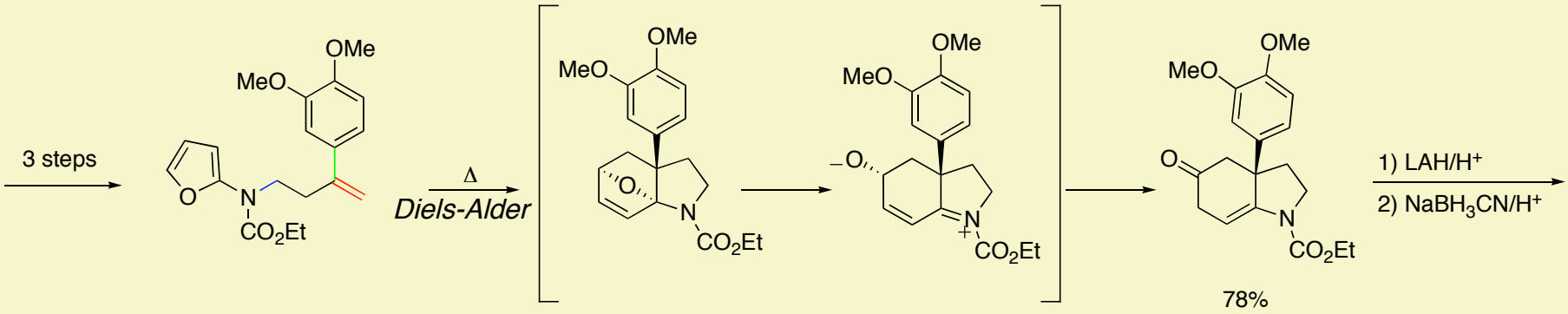


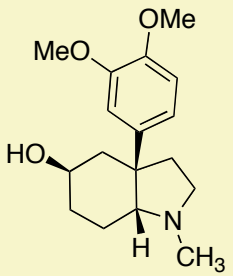


Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984,** *49*, 2240

Synthesis of (±)-Mesembrane

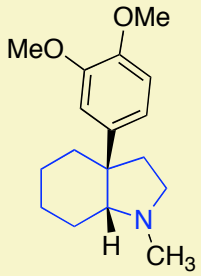
Methodology used to synthesize natural products (±)-dendrobine and (±)-crinane





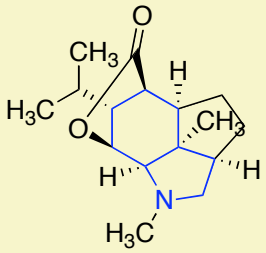
49% (2 steps)

1) PCC
2) $HSCH_2CH_2SH$
3) Raney-Ni

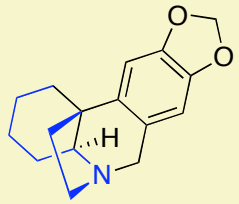


85% (3 steps)

(±)-mesembrane



(±)-dendrobine

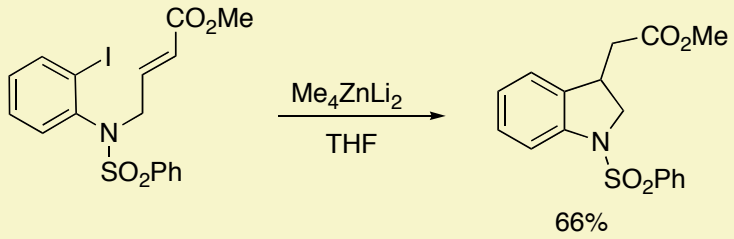


(±)-crinane

Padwa, A. et al. *J. Org. Chem.* **2001,** *66*, 3119

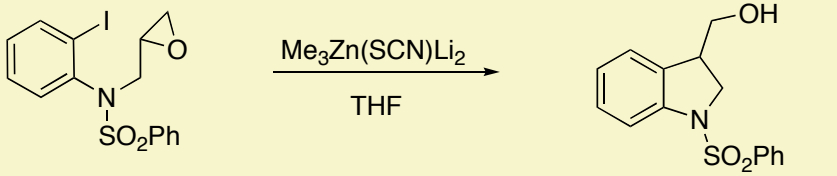
Synthesis of 3-Substituted Indolines

Intramolecular Michael addition



66%

Intramolecular substitution



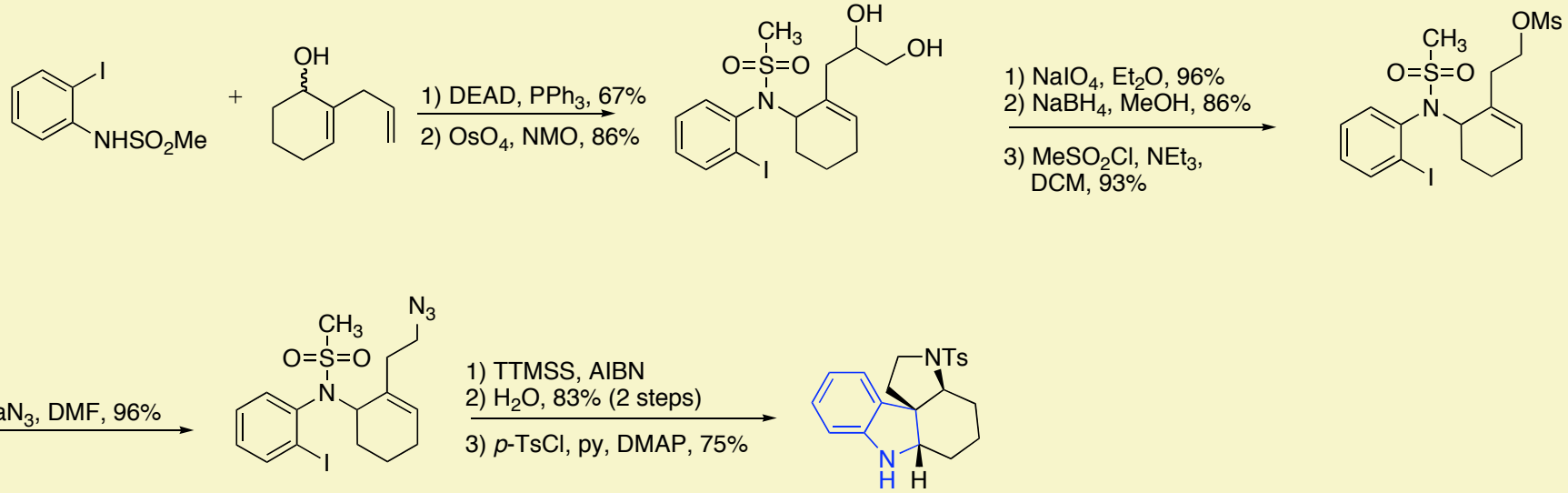
92%

97 (5-exo) : 3 (6-endo)

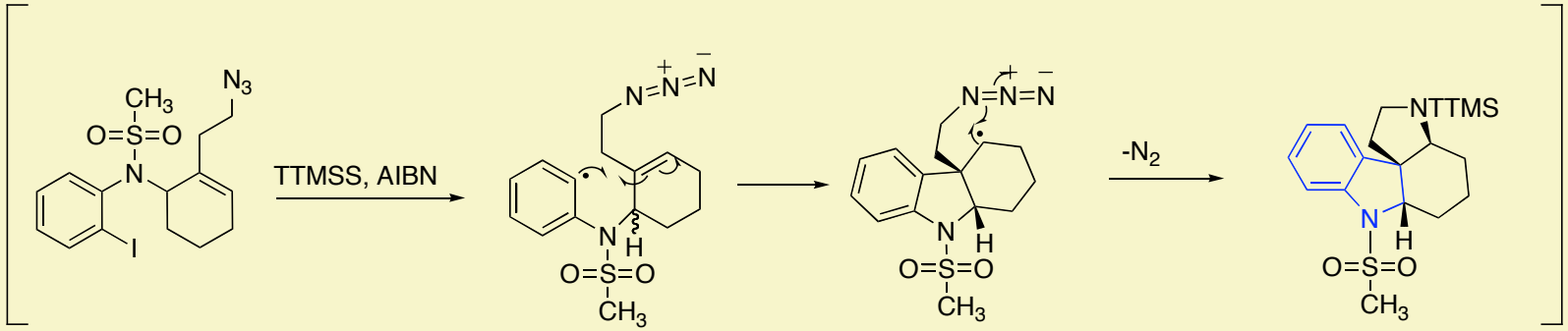
Sakamoto, T. et al. *J. Am. Chem. Soc.* **1998,** *120*, 4934

Synthesis of 3-Substituted Indolines

Tandem Radical Cyclization Reactions



Synthesis of core for Aspidosperma alkaloids

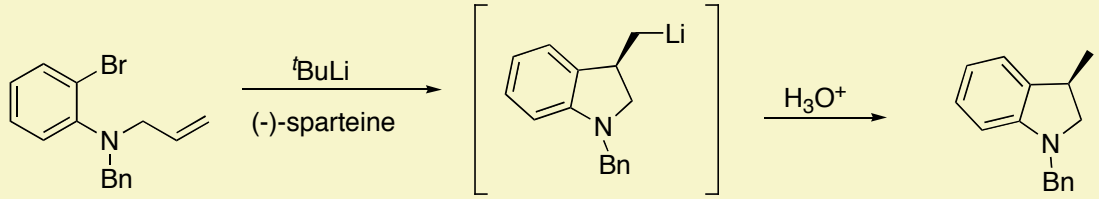


Mechanism for radical cyclization

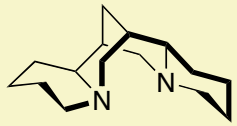
Hibbs, D. et al. *J. Org. Chem.* **1999,** *64*, 7856

Enantioselective Synthesis of 3-Substituted Indolines

Carbolithiation in the presence of (-)-sparteine



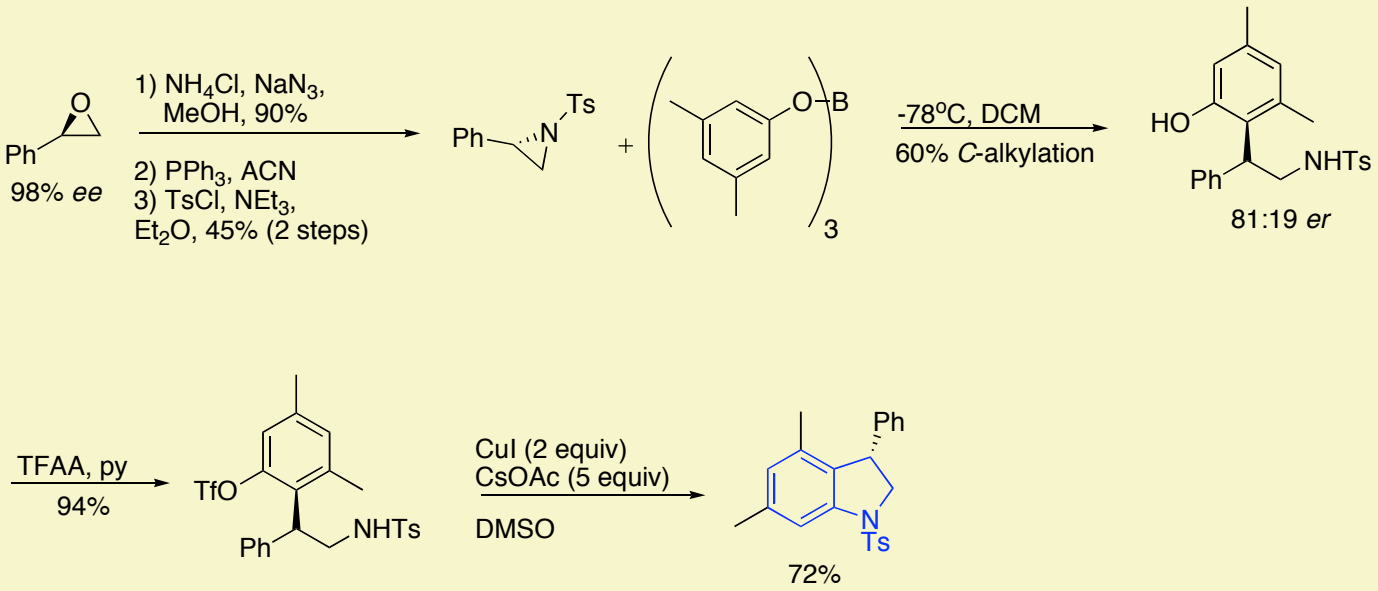
Entry	Solvent	Temp. °C	Yield, %	*ee*, %
1	Et_2O	-78	60	65
2	THF	-78	80	0
3	Toluene	-78	90	80
4	Toluene	-90	85	87
5	Cumene	-90	84	75



(-)-sparteine

Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000,** *122*, 6787
Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000,** *122*, 6789

Enantioselective Synthesis of 3-Substituted Indolines



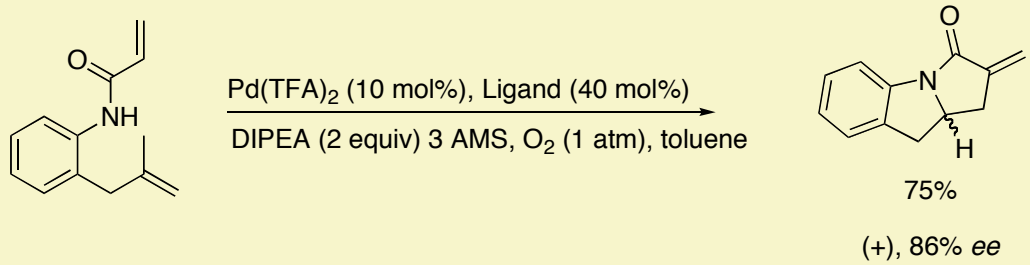
- *Stereochemistry is relayed from enantioenriched starting material*

- *Friedel-Crafts alkylation preserves enantioenrichment moderately*

Macchia, F. et al. *Org. Lett.* **2006,** *8*, 2627

Enantioselective Synthesis of Indolines

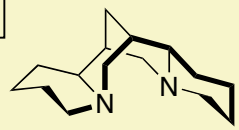
Demonstrates tandem C-N and C-C bond formation



75%

(+), 86% *ee*

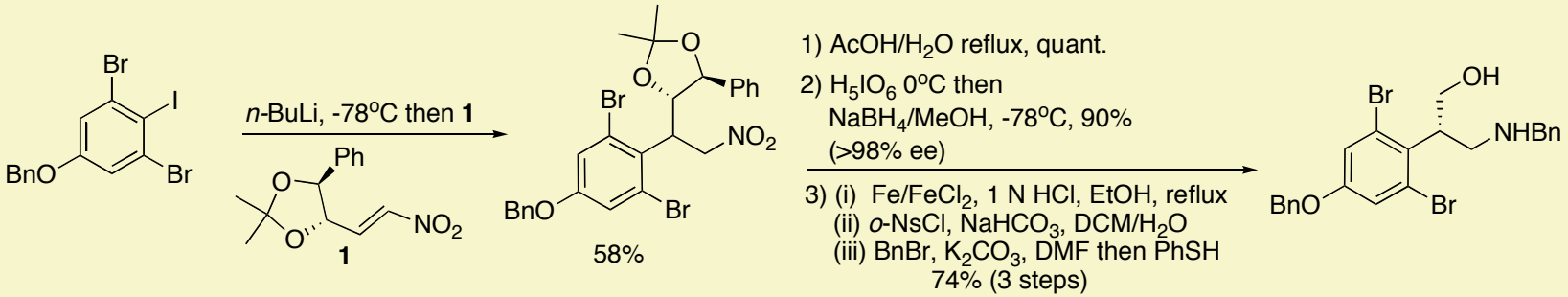
Ligand	yield (%)	ee (%)
1) $(DHQ)_2PHAL$	89	12
2) $(DHQ)_2AQN$	94	12
3) $(DHQD)_2PYR$	98	8
4) (-)-cinchonidine	40	7
5) Hydroxyquinine	47	11
6) (S,S)-Ph-box	55	9
7) (-)-sparteine	**75**	**86**



(-)-sparteine

Yang, D. et al. *J. Am. Chem. Soc.* **2006,** *128*, 3130

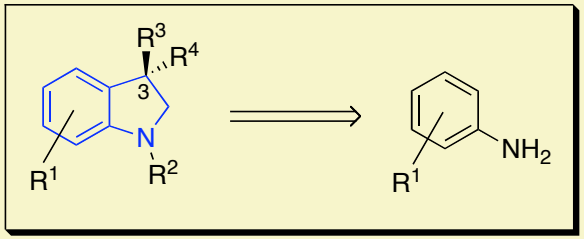
Enantioselective Synthesis of (+)-Duocarmycin A



Fukuyama, T. et al. *J. Am. Chem. Soc.* **2003,** *125*, 6630

Part 1:

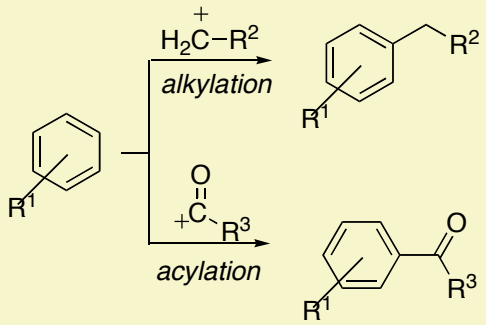
Using Intramolecular Friedel-Crafts Reactions to Form Indoline Scaffolds



Aromatic Friedel-Crafts (FC) Reactions

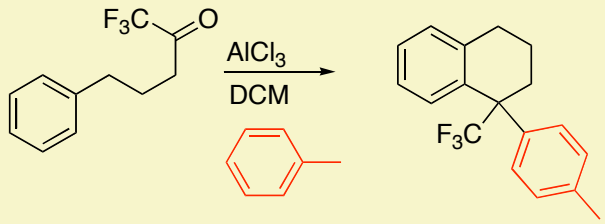
Use Brønsted or Lewis acids to generate electrophilic species

Intermolecular Friedel-Crafts reaction



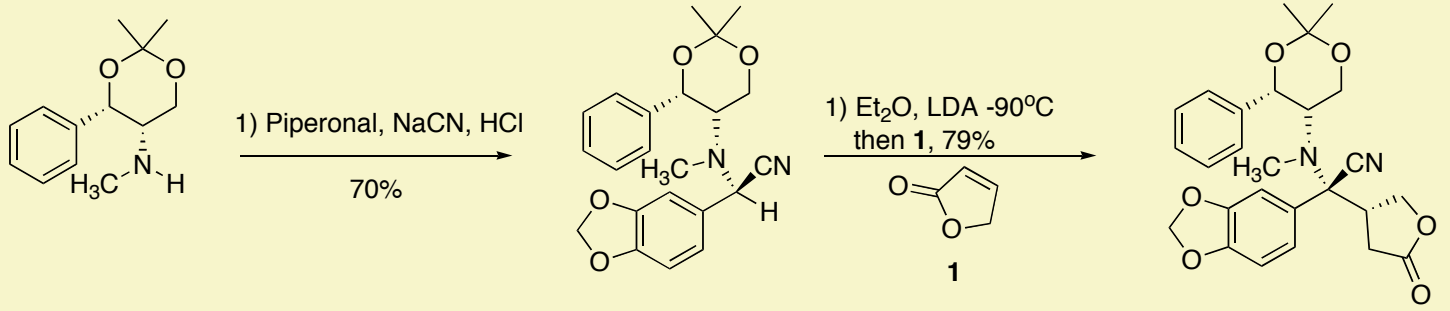
Gore. P. H. *Chem. Rev.* **1955,** *55, 2*29-281.

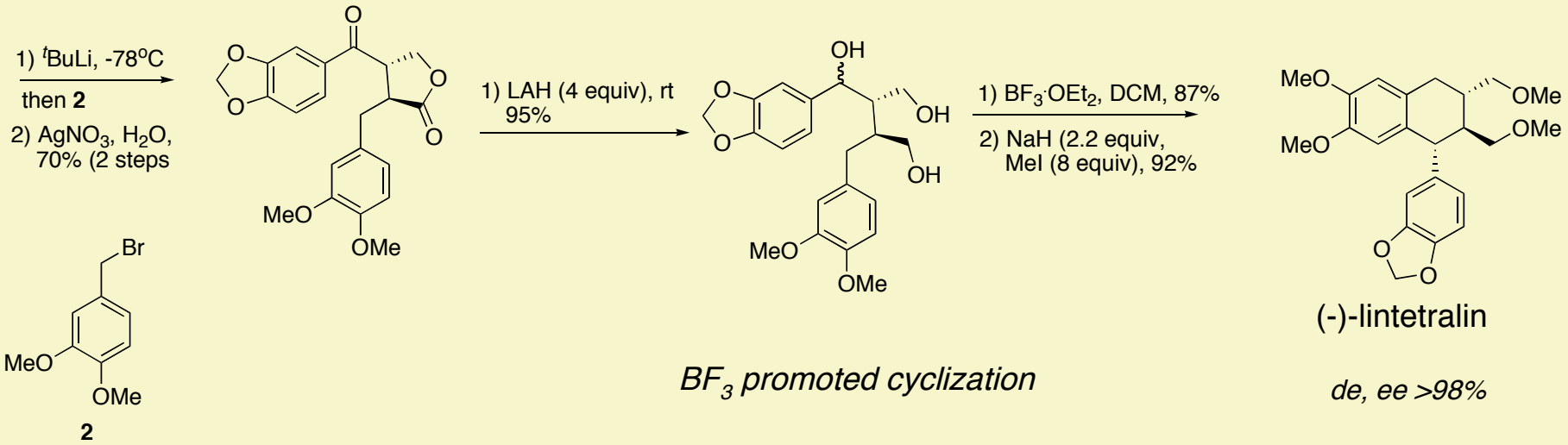
Intramolecular Friedel-Crafts cyclizations



Jacquot, R. et al. *J. Org. Chem.* **1988,** *53*, 759

Examples of Intramolecular FC Reactions





BF_3 promoted cyclization

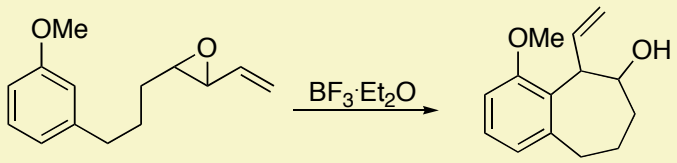
(-)-lintetralin

de, ee >98%

29% over seven steps

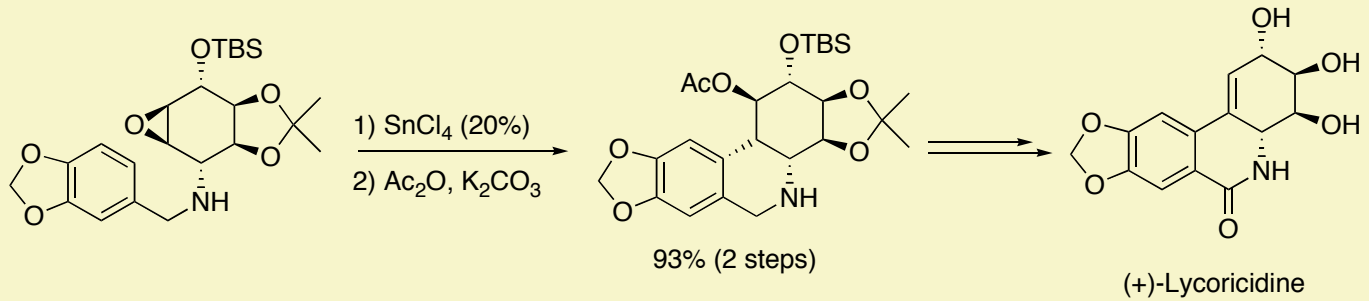
Examples of Intramolecular FC Reactions

Using epoxides as electrophiles



85%

Nagumo, S. et al. *Tet. Lett.* **2002,** *43*, 2223

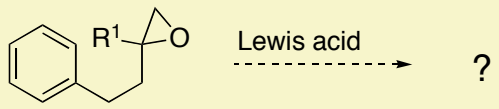


93% (2 steps)

(+)-Lycoricidine

Elango, S.; Yan, T-H. *Tetrahedron.* **2002,** *58*, 7335

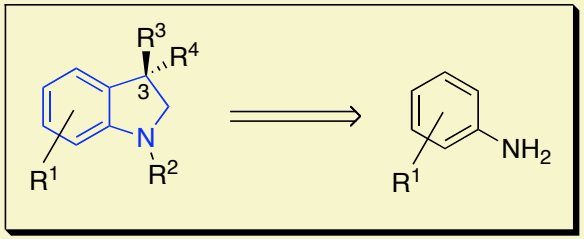
Few examples of 2,2-disubstituted epoxides used in Friedel-Crafts type alkylations



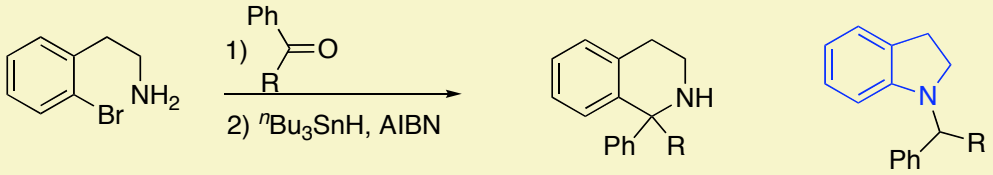
$R^1 \neq$ -H

Part 2:

Using Radical Mediated Processes to Form Indoline Scaffolds



Radical Processes to Form Indolines



yield, (*cyclized:ArH*)			
	R = H	72% (20:1)	<1%
	R = -CH_3	<1%	87% (10:1)

Johnston, J. N. et al. *Org. Lett.* **2001,** *3*, 1009

- Observed 5-*exo* cyclization onto nitrogen with ketimines

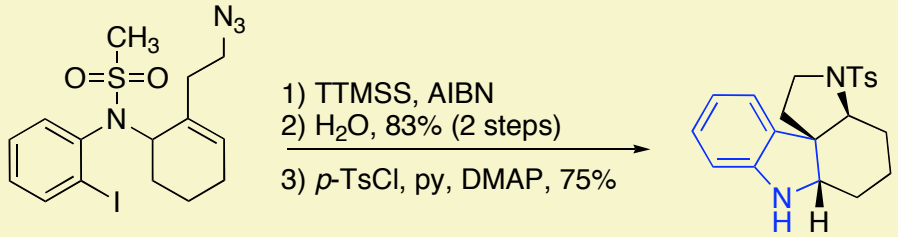
- Observed 6-*endo* cyclization onto carbon with aldimines

Review of radical additions to imines: Friestad, G. K. *Tetrahedron* **2001,** *57*, 5461

Radical Cyclization onto Olefins

Recall synthesis of *Aspidosperma* alkaloid core

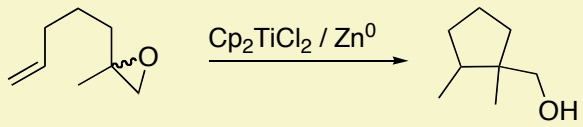
Tandem C-C and C-N bond formation via radical intermediate



Elegant method to form complex heterocycles

Hibbs, D. et al. *J. Org. Chem.* **1999,** *64*, 7856

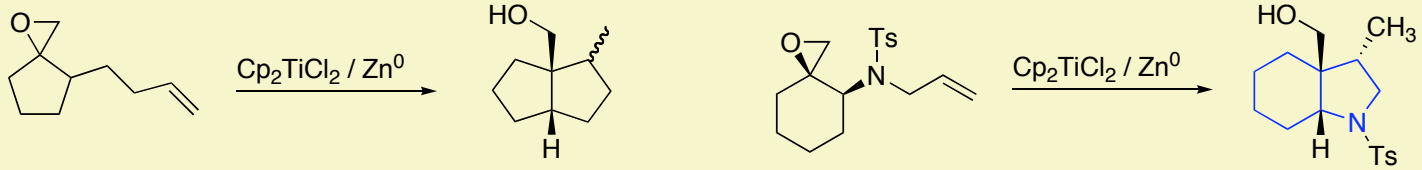
Literature Precedence for Titanocene Systems



94%

RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994,** *116*, 986

Examples of substrates tolerated



88%

endo : exo
90:10

64%

78:22 dr

Gansauer, A.; Pierobon, M.; Bluhm, H. *Synthesis,* **2001,** *16*, 2500

For recent review see: Arteaga, J. F. et al. *Eur. J. Org. Chem.* **2006,** 1627

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NIH

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