Synthetic Approaches to Pyrroloindoline Containing Natural Products

MacMillan Group Meeting
Joe Carpenter
February 18, 2009

Synthetic Approaches to Pyrroloindoline Natural Products

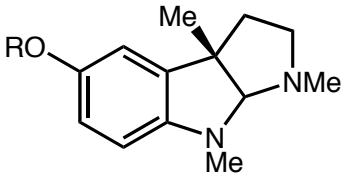
Presentation outline

- Introduction to pyrroloindolines
- Methods to construct the pyrroloindoline core
  - ***Biomimetic approach***
    i. Raceimc methods
    ii. Synthesis from chiral pool
    iii. Enantioselective synthesis
  - ***"Oxoindole" approach***
    i. Raceimc methods
    ii. Synthesis from chiral pool
    iii. Enantioselective synthesis
  - ***Other methods***
    i. Raceimc methods
    ii. Synthesis from chiral pool
    iii. Enantioselective synthesis
- Conclusions

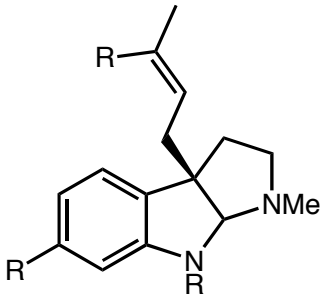
Synthetic Approaches to Pyrroloindoline Natural Products

Introduction

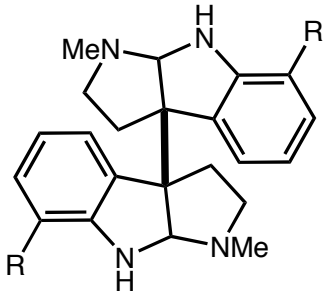
■ Diverse biological activity of pyrroloindolines



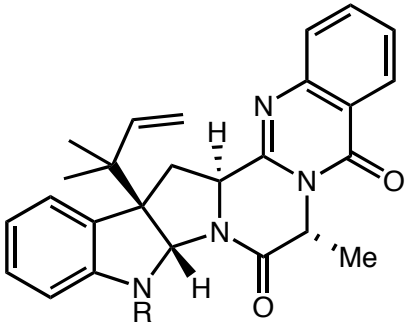
calabar alkaloids
Alzheimer's
anticholinergic
organophosphate poisoning

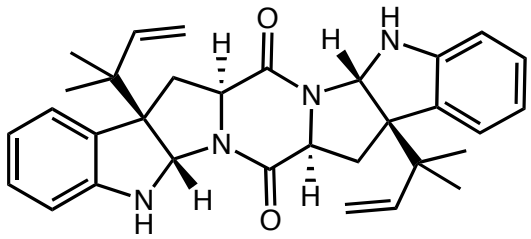


flustramines and pseudophyrnamines
anticancer activity
muscle relaxant
cholecystokinin antagonist

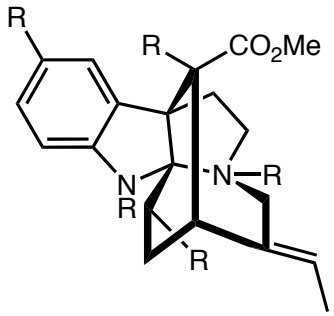


calycanthaceous alkaloids
analgesic
antibacterial
somatostatin agoinst





ardeemins and amauromine
reverse multi-drug resistance in cancer cells
vasodilator



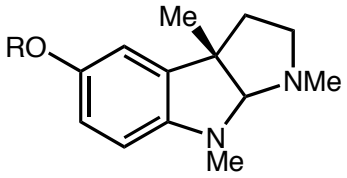
echitamine alkaloids
anticancer

■ Pyrroloindolines are isolated from amphibians, marine organisms and plant sources

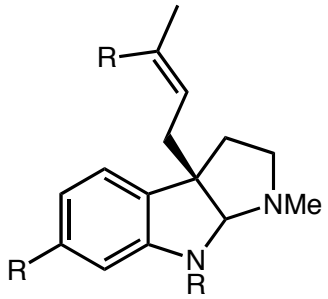
Synthetic Approaches to Pyrroloindoline Natural Products

Introduction

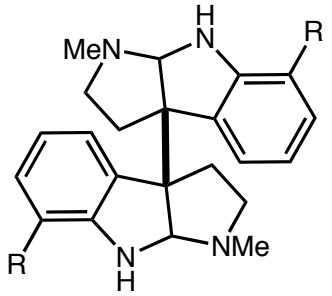
■ Substitution pattern around central pyrroloindoline varies greatly



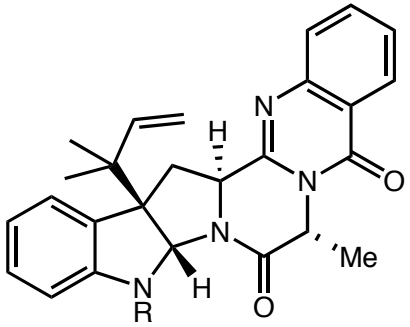
calabar alkaloids
esermethole R = Me
physostigmine R = CONMe
phenserine R = CONPh

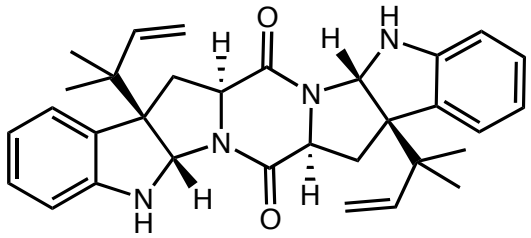


flustramines and pseudophyrnamines

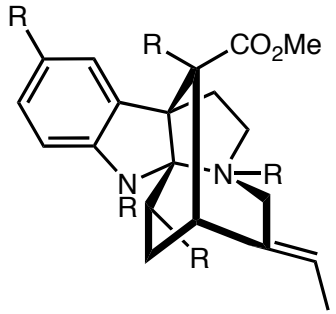


calycanthaceous alkaloids
chimonanthine R = H





ardeemins and amauromine

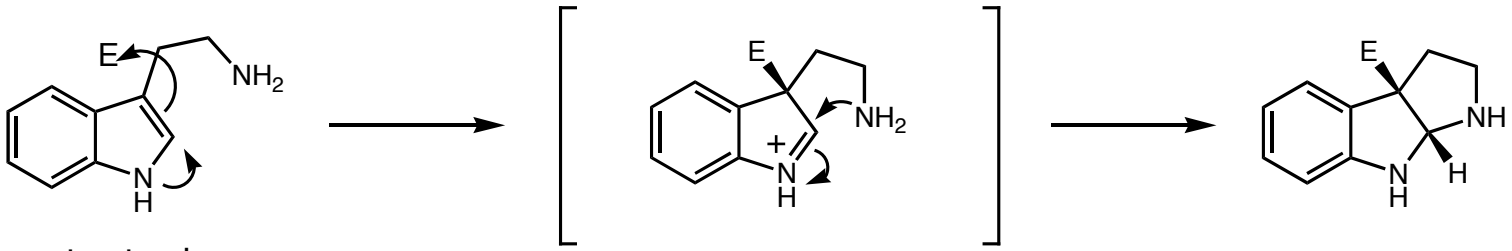


echitamine alkaloids
echitamine
vincorine

Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Perceived to arise via electrophilic attack at indole C-3 position of tryptophan or tryptamine



tryptamine

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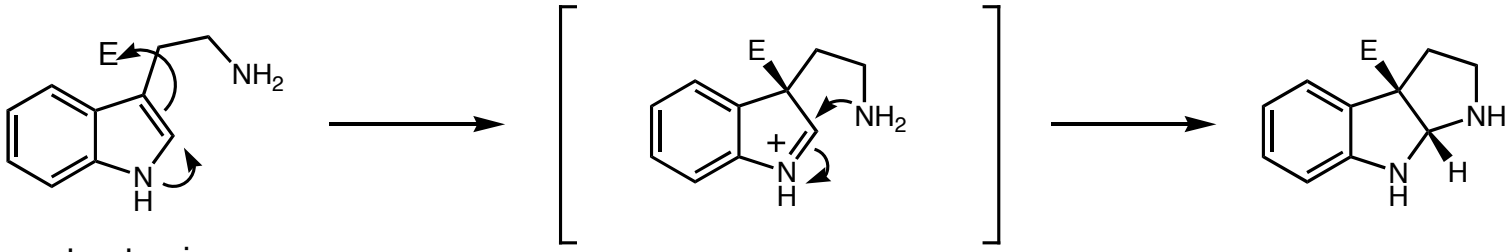
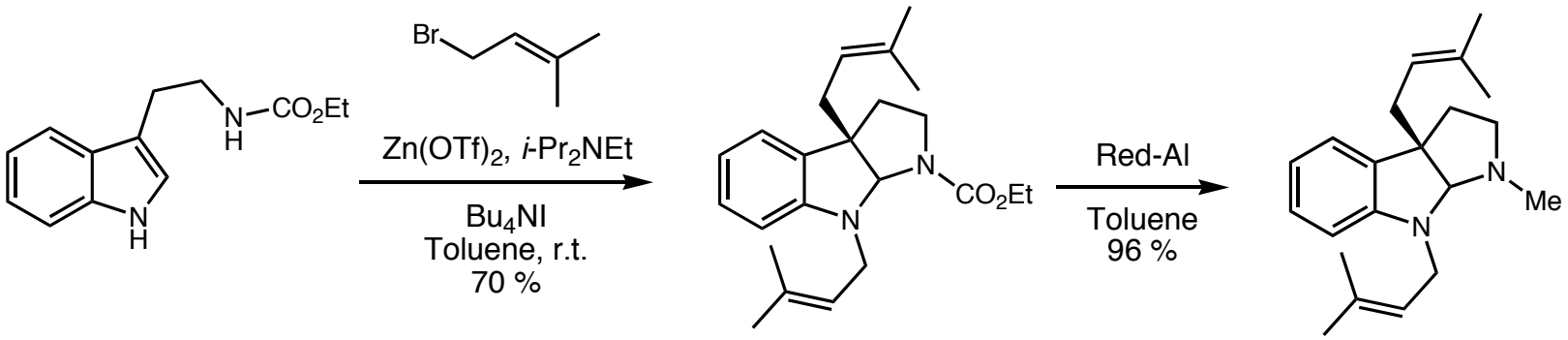


■ Alkylative cyclization allows rapid access to racemic flustramines



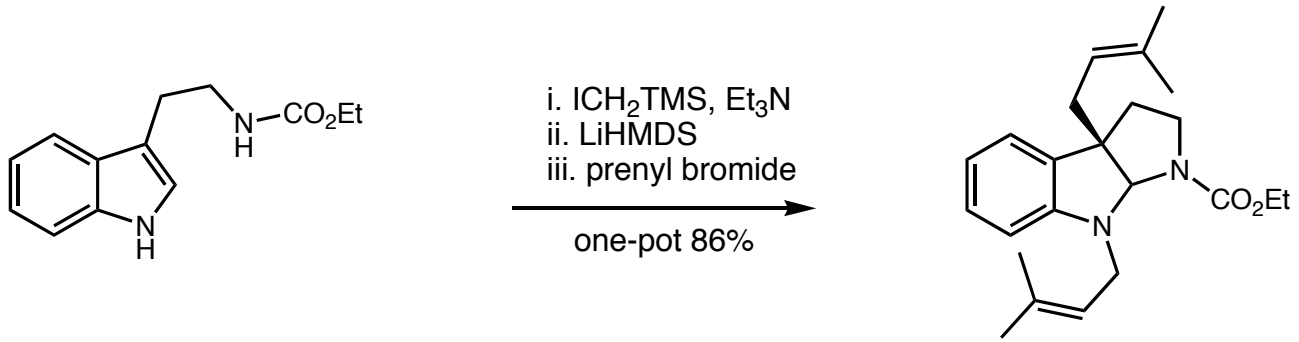
(±) debromoflustramine B

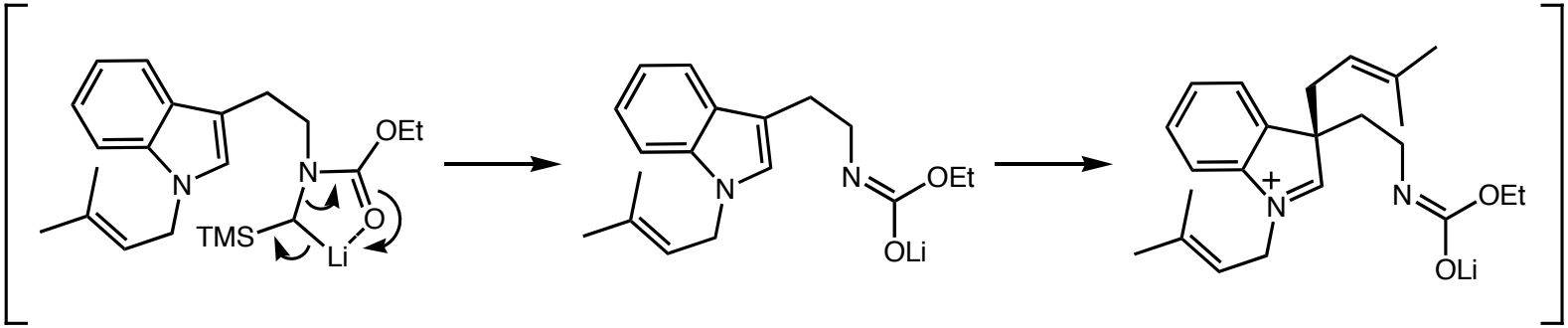
Tan, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801.

Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Menéndez used a similar strategy to access the flustramine core



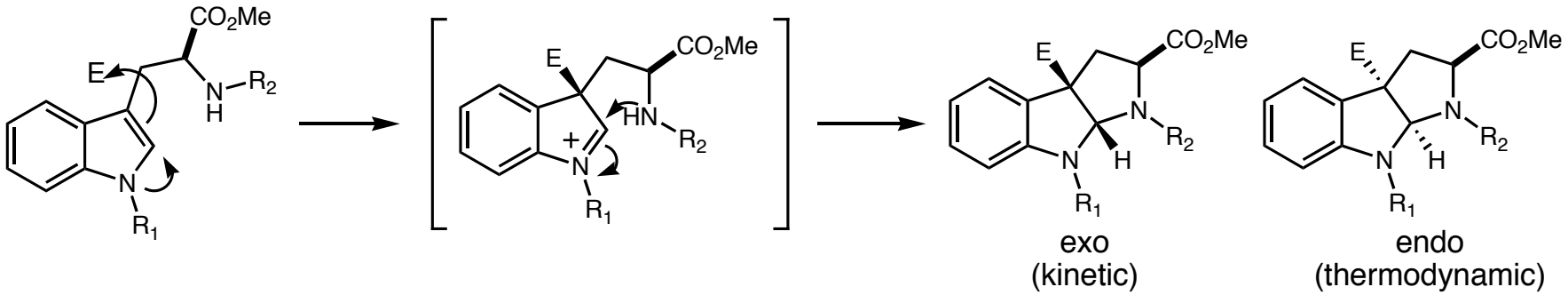


López-Alvarado, P.; Caballero, E.; Avendaño, C.; Menéndez, C. J. *Org. Lett.* **2006**, *8*, 4303.

Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Tryptophan derivitaves give rise to possible diastereomers



exo (kinetic)

endo (thermodynamic)

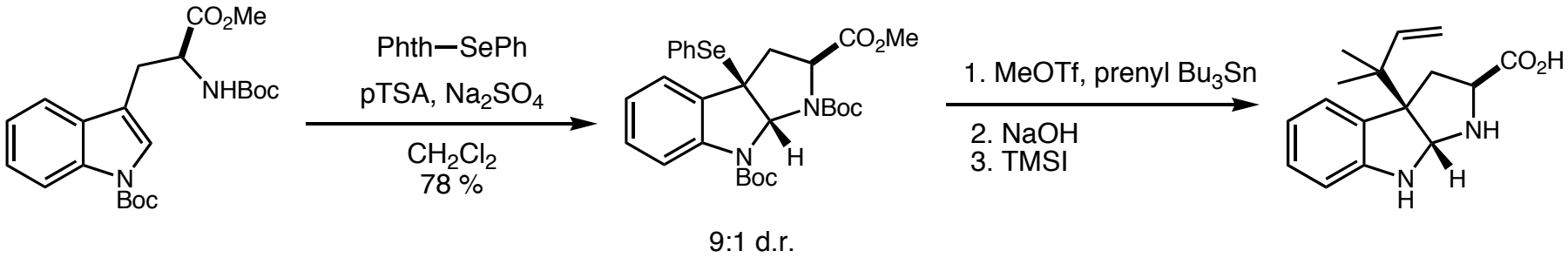
Combined Yield (%)	electrophile	R_1	R_2	endo:exo
85	H	H	CO_2Me	9:1
65	PhthSePh	Boc	Boc	1:9
76	PhthSePh	CO_2Bn	CO_2Me	1:12
83	PhthSePh	CO_2Me	CO_2Me	1:11
40	PhthSePh	SO_2Ph	CO_2Me	<2:98
31	PhthSePh	SO_2PMP	CO_2Me	<2:98
0	PhthSePh	H	CO_2Me	--

Crich, D.; Huang, X. *J. Org. Chem.* **1999**, *64*, 7218.

Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Application in Danishefsky's synthesis of amauromine and acetylardeemin



9:1 d.r.

Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.

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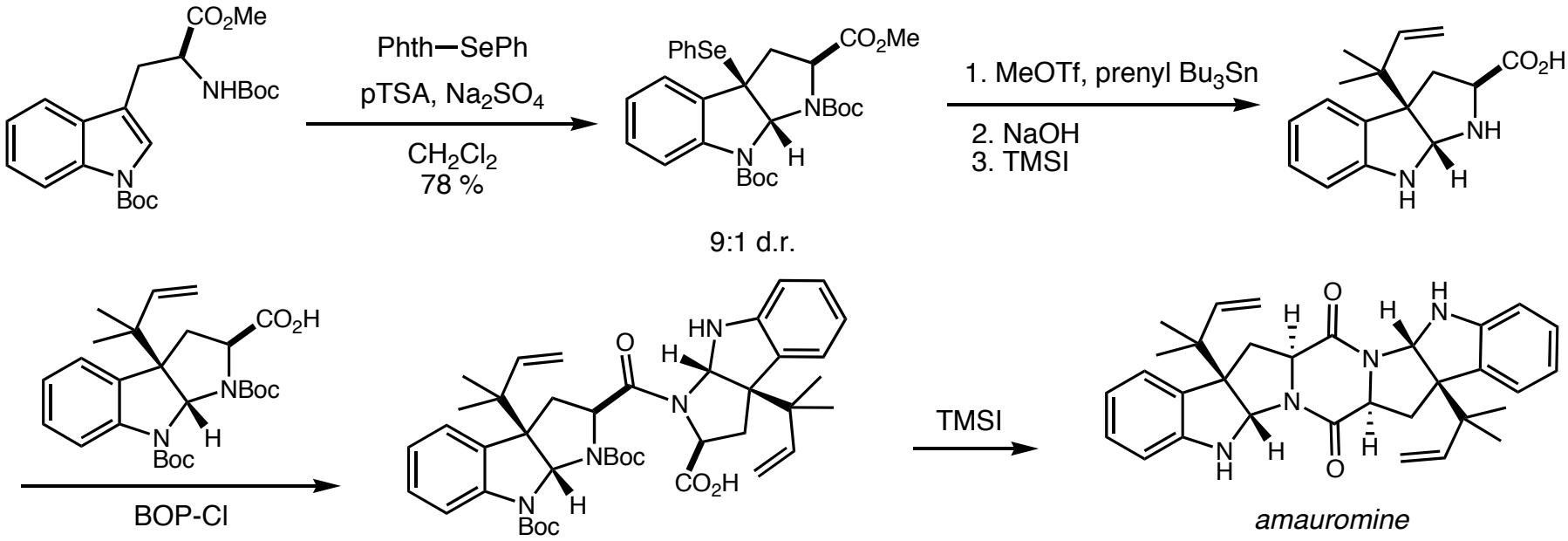

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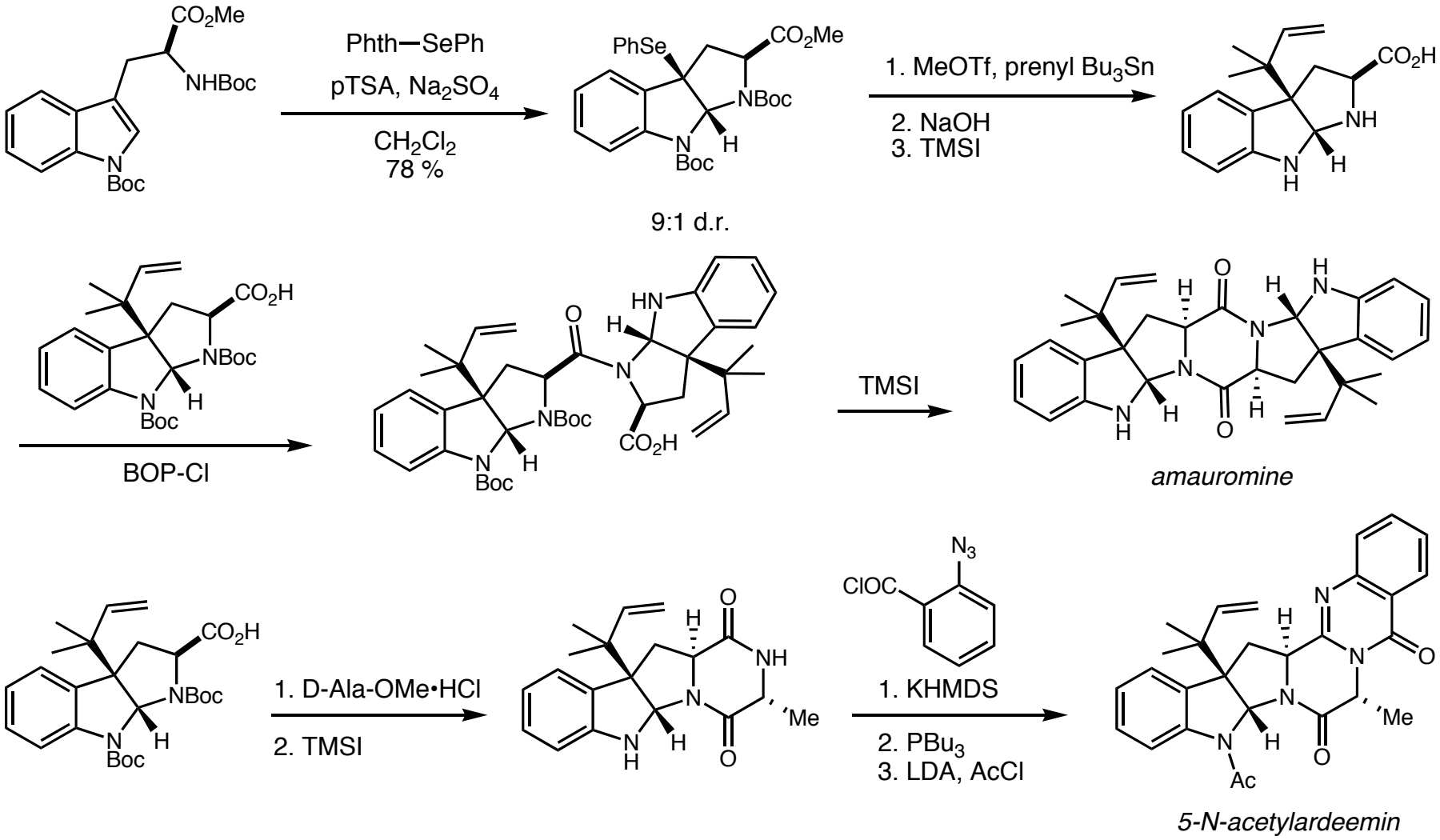

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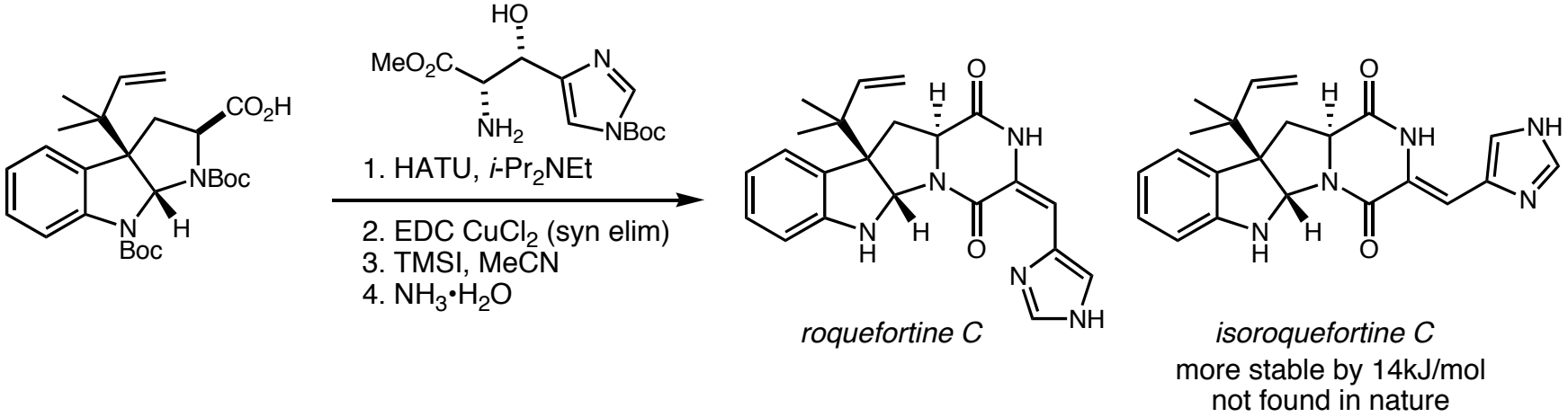
Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ The Joullié group synthesis of roquefortine C uses the same strategy as Danishefsky



more stable by 14kJ/mol
not found in nature

Shangguan, N.; Hehre, W. J.; Ohlinger, W. S.; Beavers, M. P. Joullié, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 6281.

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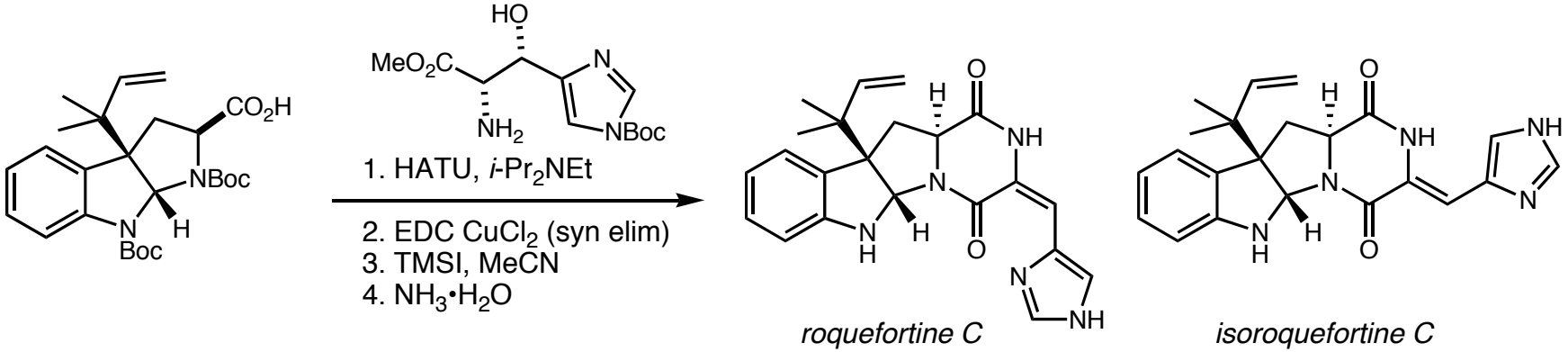

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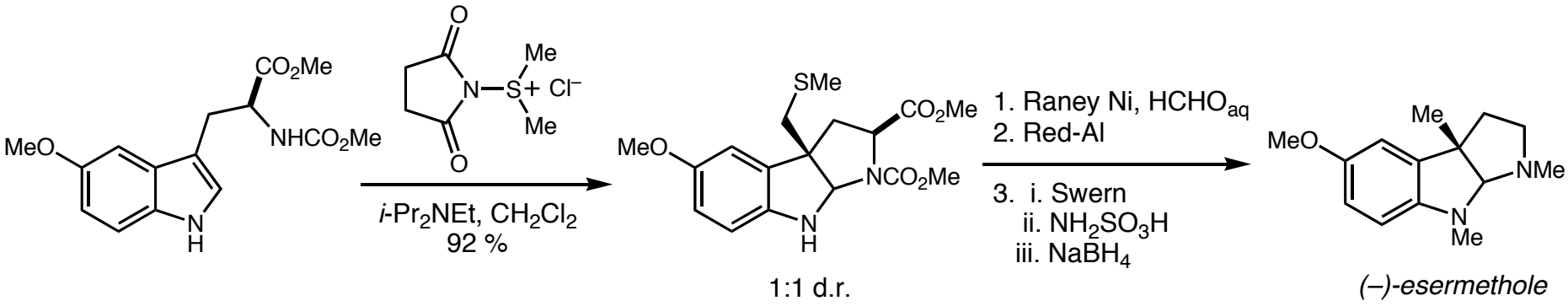
■ Other electrophiles are also competent for pyrroloindoline formation

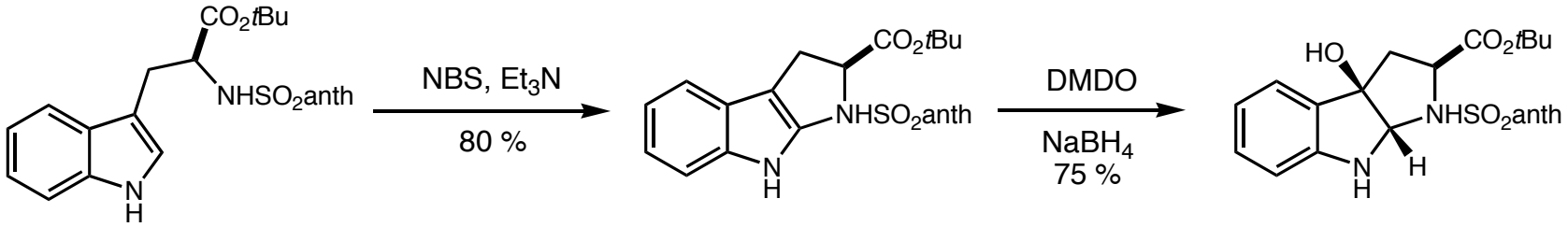


Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675.

Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Danishefsky used a slight variation to construct the Himastatin core



Kamanecka, T. M.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2993 and 2995.

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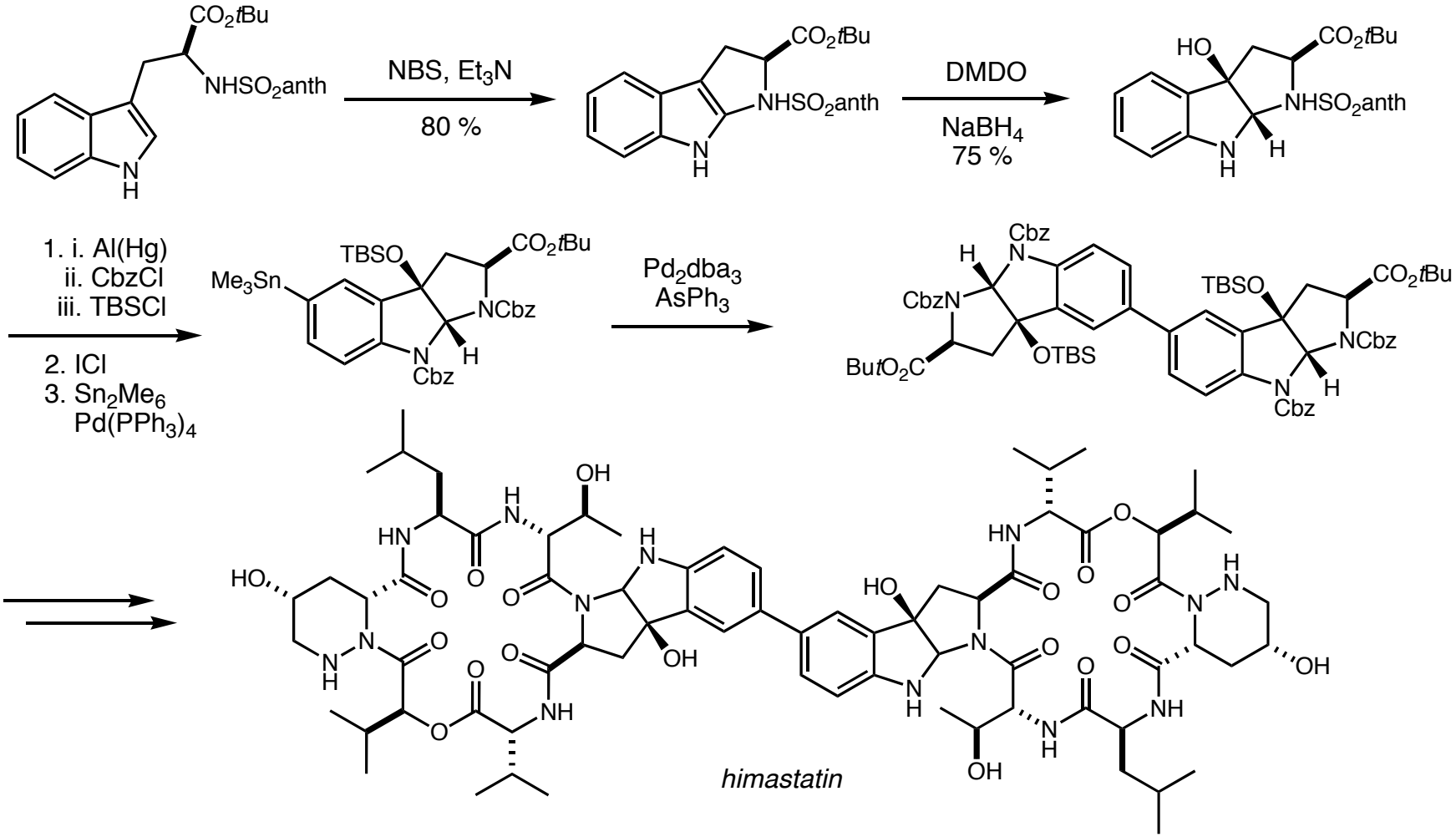

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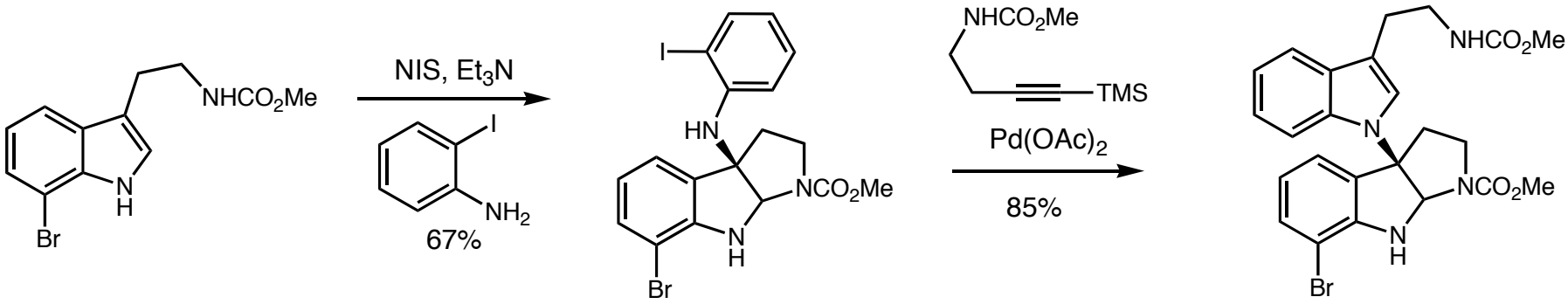
Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Electophilic sources of nitrogen have also been shown to work efficiently



Also works with tryptophan derivatives (45%)

Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

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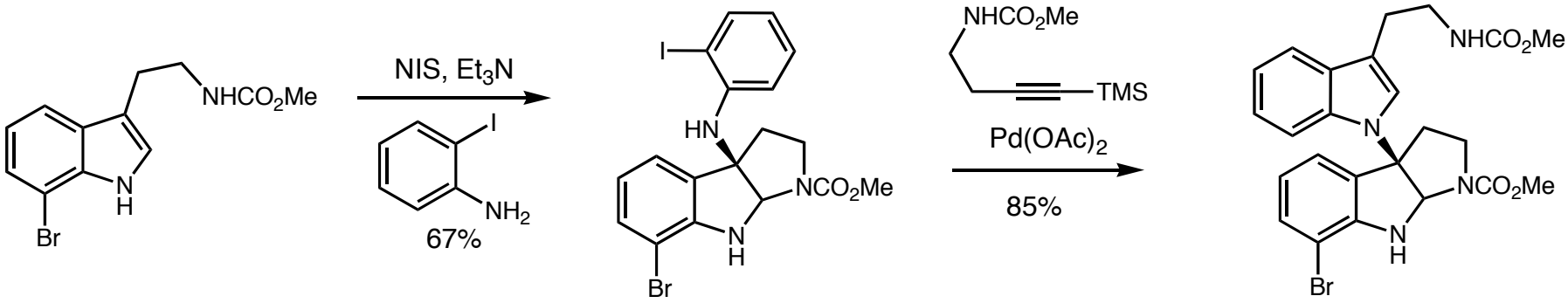

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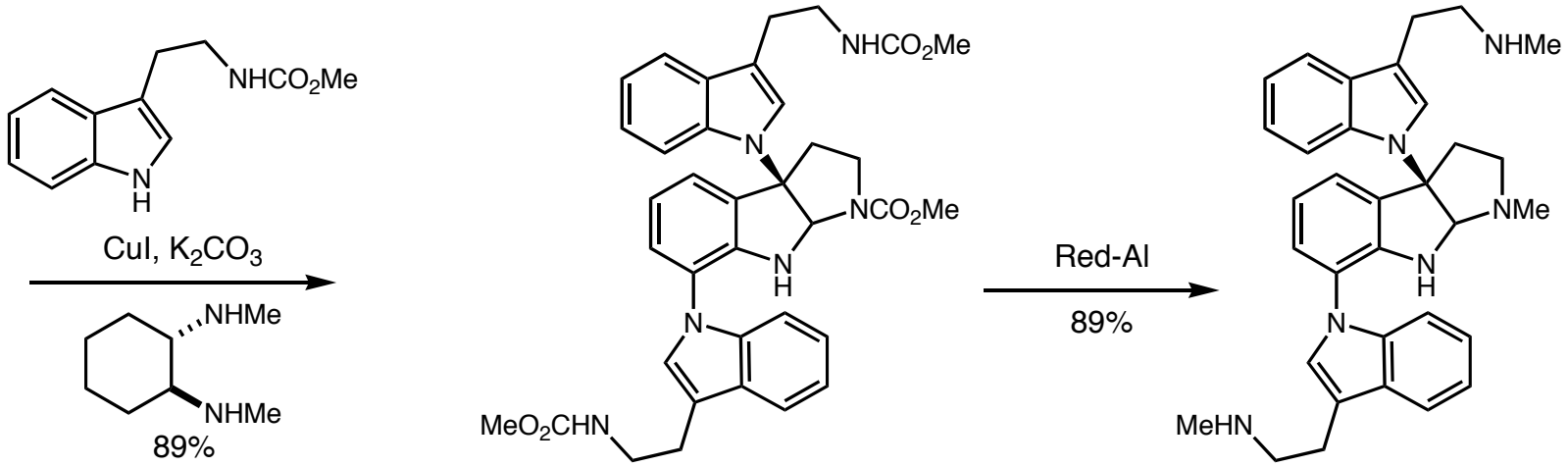

(±)-psychotrimine

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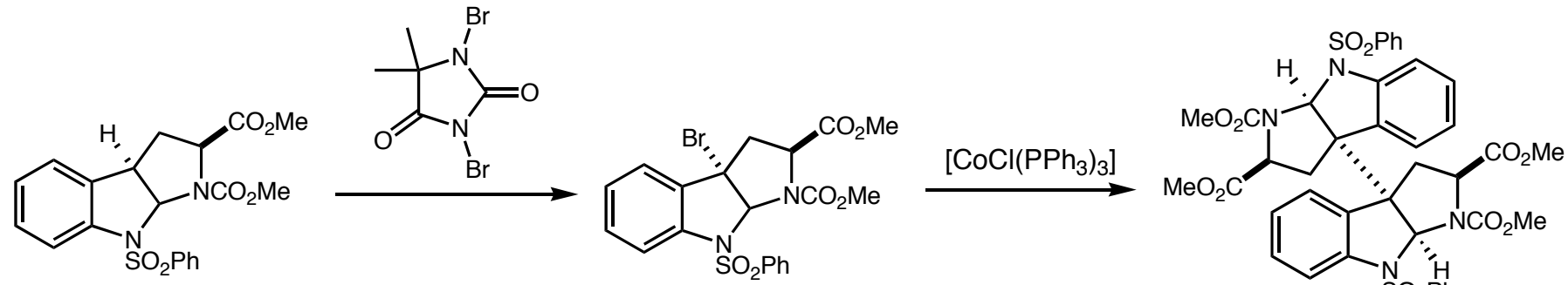
Synthetic Approaches to Pyrroloindoline Natural Products

Biomimetic Approach

■ Dimerization of benzylic radicals allows access to dimeric structures



cyclized with H_3PO_4

4 steps to *(+)-chimonanthine*

Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

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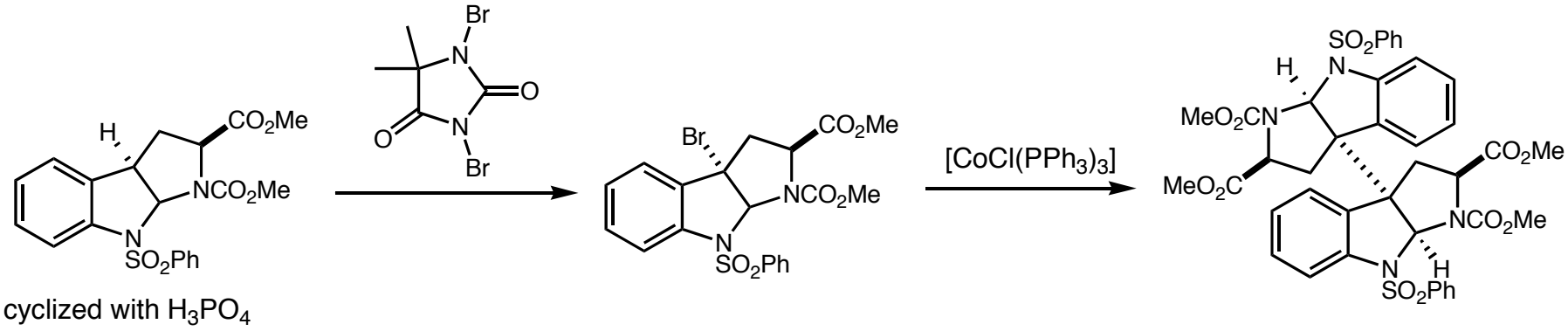

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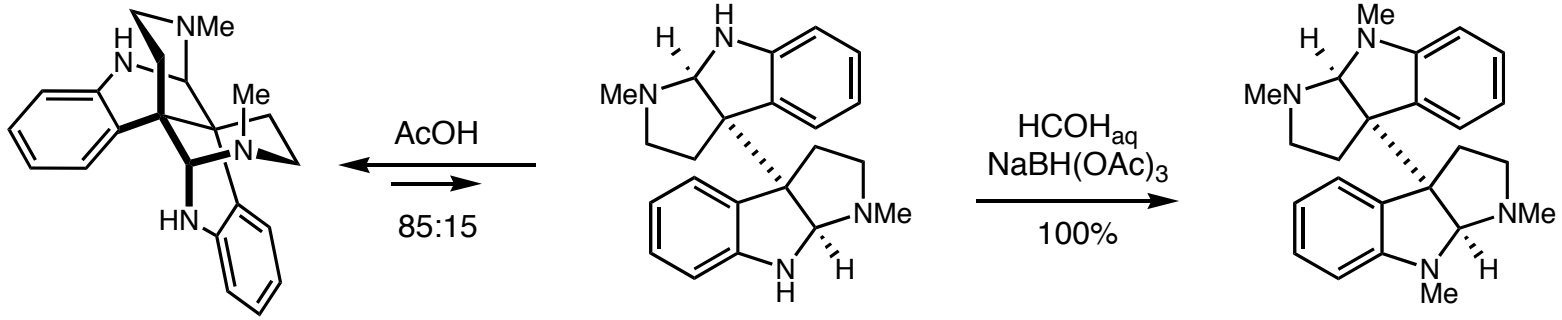

(–)-calycanthine

(+)-chimonanthine

(+)-folicanthine

Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

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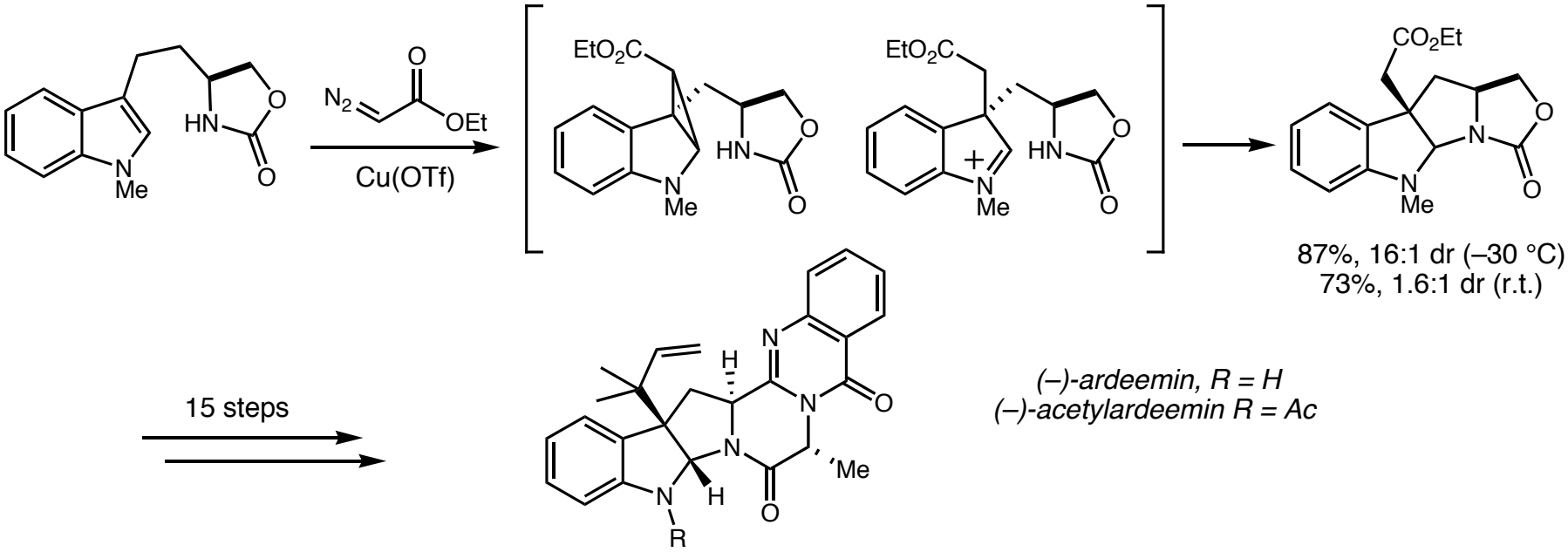
Biomimetic Approach

■ Tryptophan derivatives will react with carbenes to give the pyrroloindoline core upon cyclization



He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298.
Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618.

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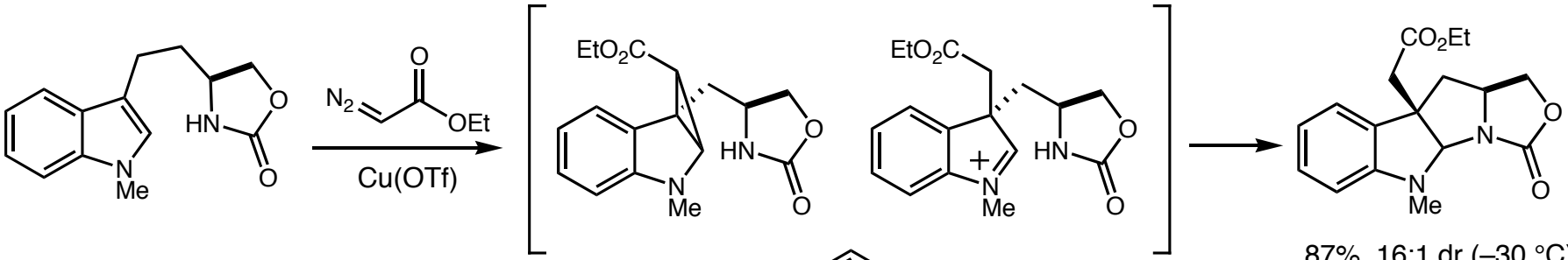
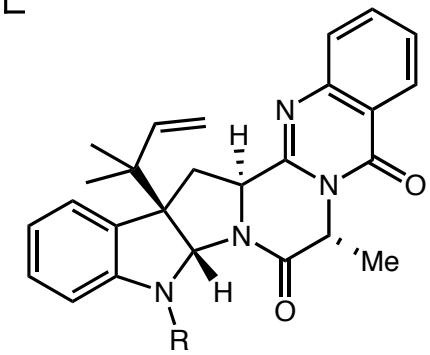
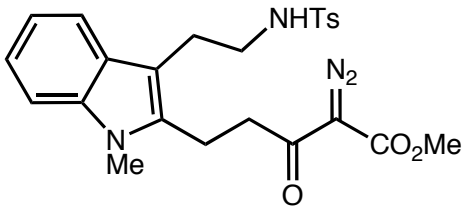


15 steps



(–)-ardeemin, R = H
(–)-acetylardeemin R = Ac

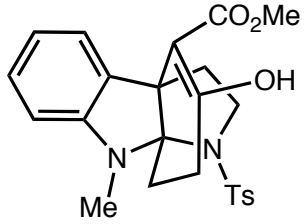
■ Qin uses a tethered carbene to access the fully substituted C-3 of Minfiensine



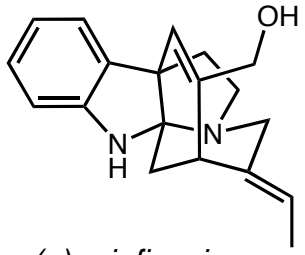
(10 steps)

CuOTf

81%



9 steps



(±)-minfiensine

He, B.; Song, H.; Du, Y.; Qin, Y. *J. Org. Chem.* **2009**, *74*, 298.
Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618.

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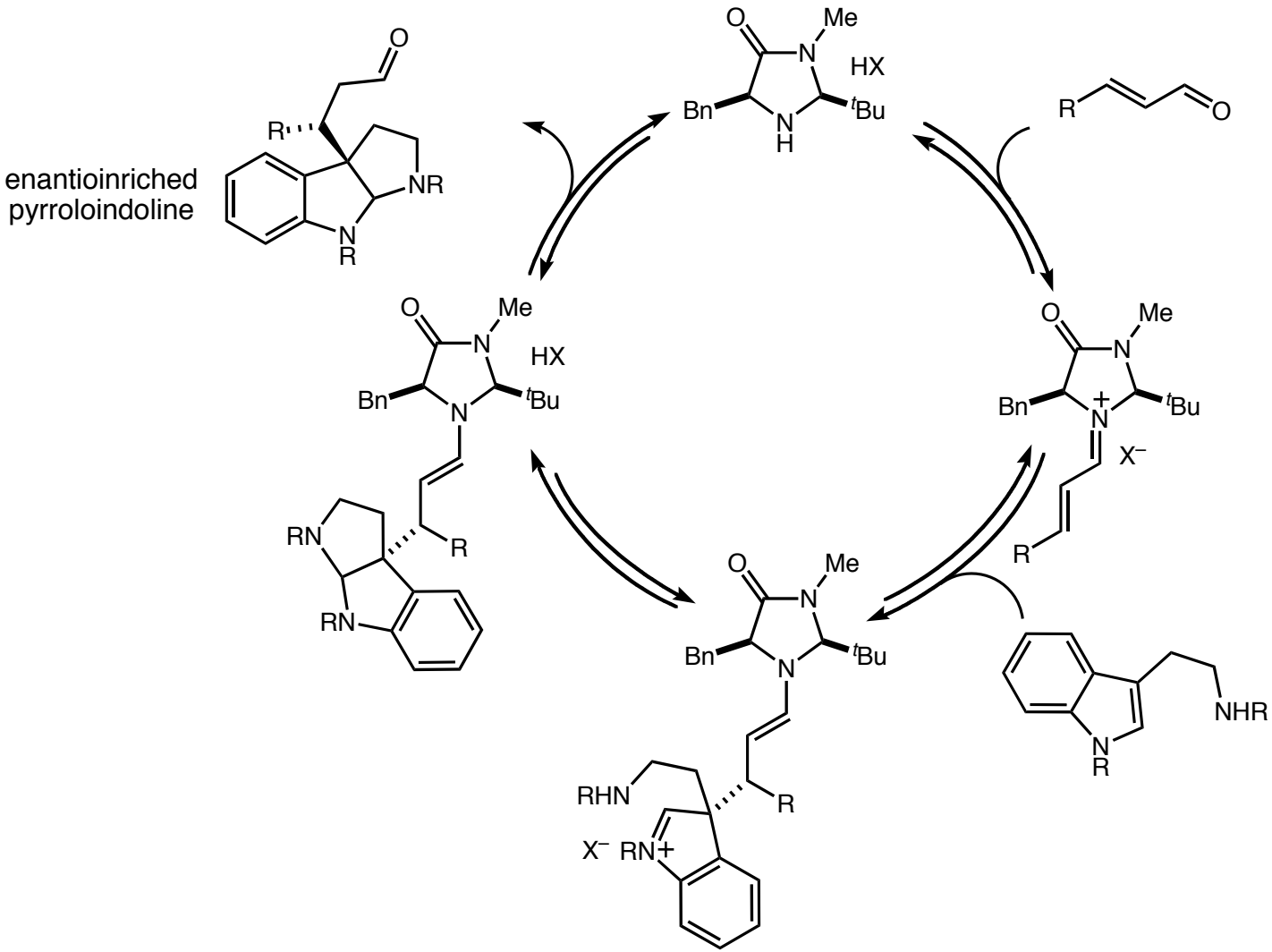
Biomimetic Approach

■ Catalytic asymmetric approach to the flustramines by the MacMillan group



Austin, J. F.; Kim, S-G.; Sinz, C. J.; Xiao, W-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482.

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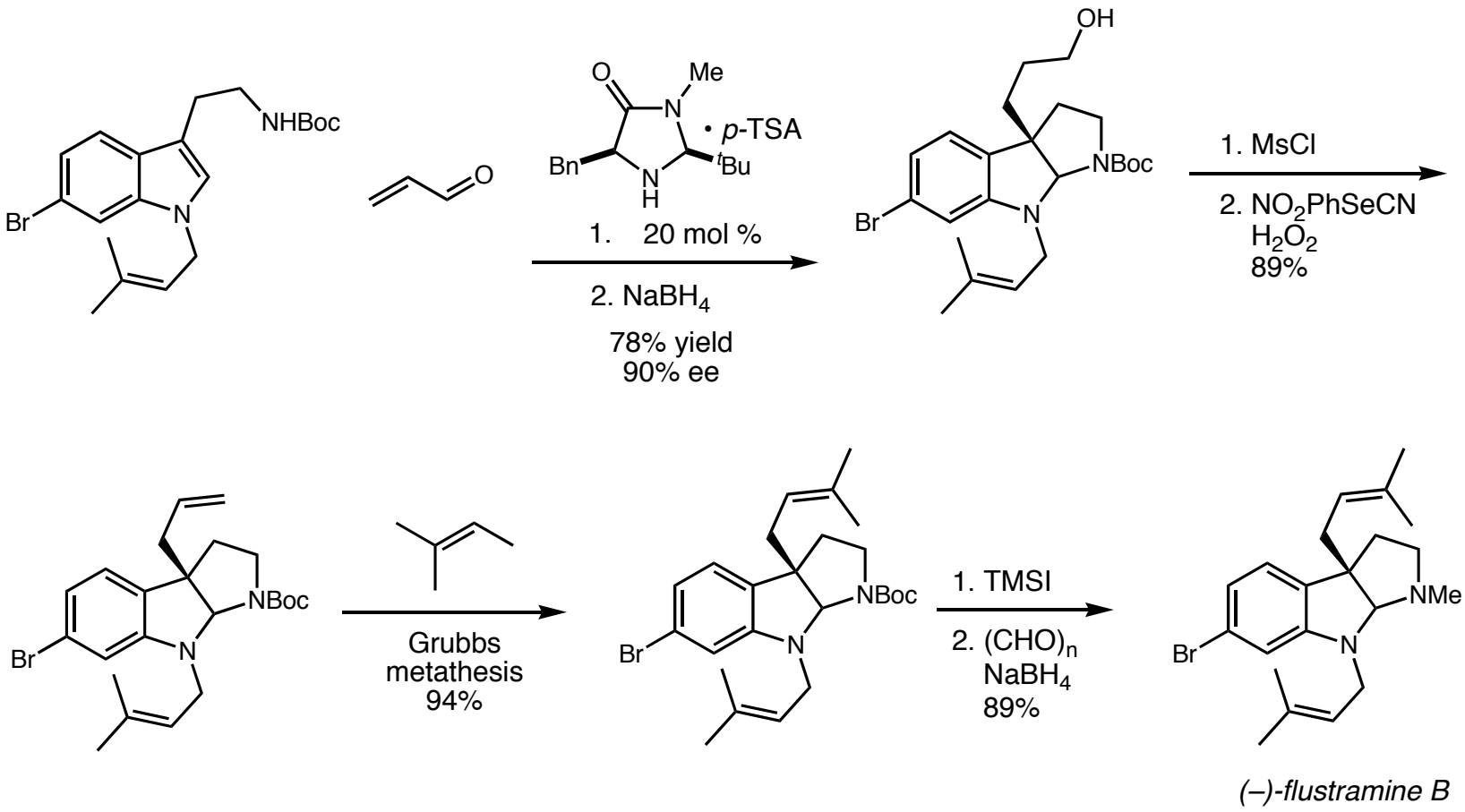

(–)-flustramine B

Austin, J. F.; Kim, S-G.; Sinz, C. J.; Xiao, W-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482.

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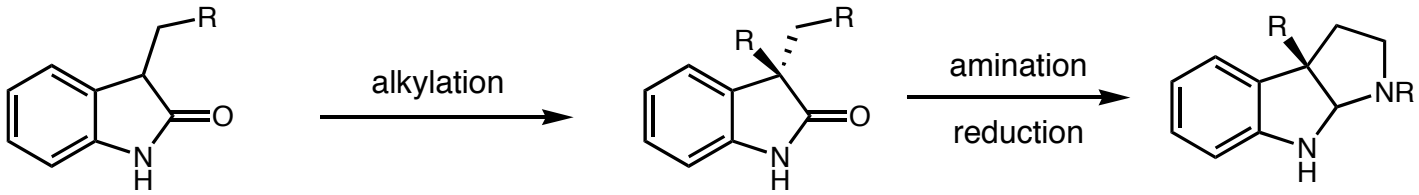
The 2-Oxoindole Approach

■ The pyrroloindoline core can also readily be attained through a suitable 2-oxoindole



generic 2-oxoindole

Julian, P. L.; Pikl. J.; Boggess. D. *J. Am. Chem. Soc.* **1934**, *56*, 1797.

■ Similarities to biomimetic approach but different oxidation state utilized

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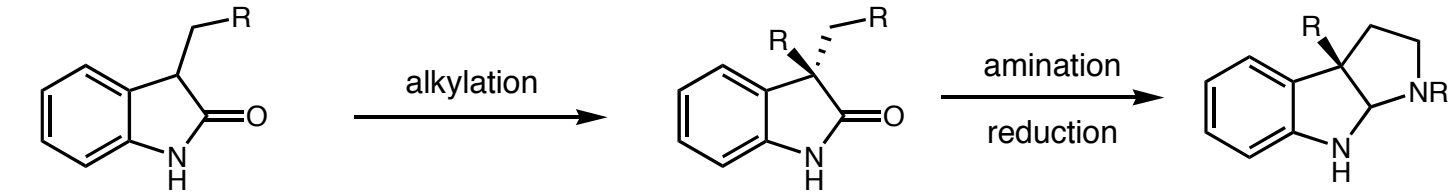
The 2-Oxoindole Approach

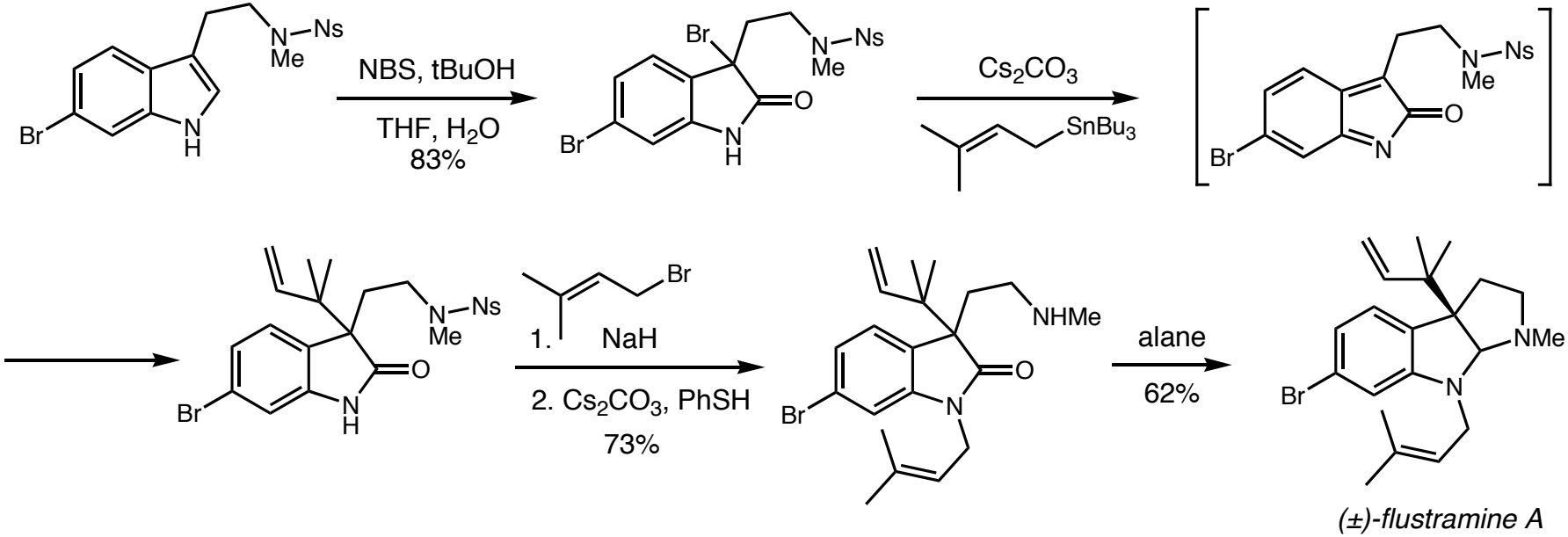
■ The pyrroloindoline core can also readily be attained through a suitable 2-oxoindole



generic 2-oxoindole

Julian, P. L.; Pikl. J.; Boggess. D. *J. Am. Chem. Soc.* **1934**, *56*, 1797.

■ Similarities to biomimetic approach but different oxidation state utilized



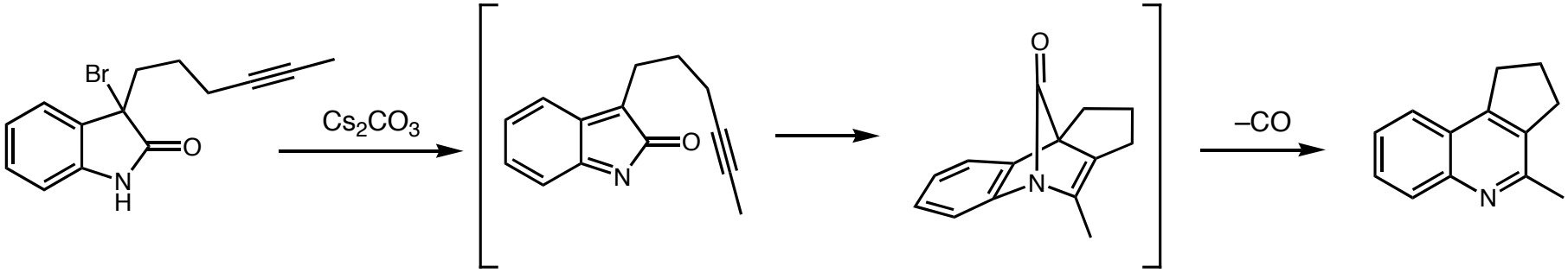
(±)-flustramine A

Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Evidence for the indole-2-one intermediate



Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

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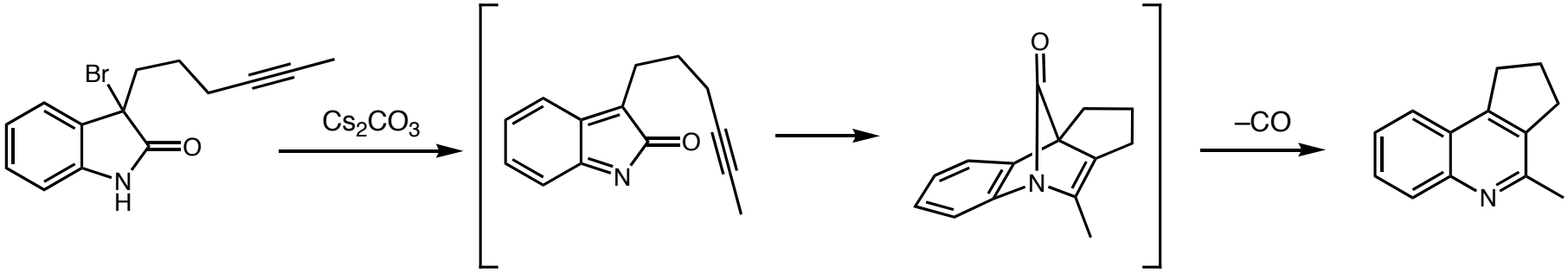
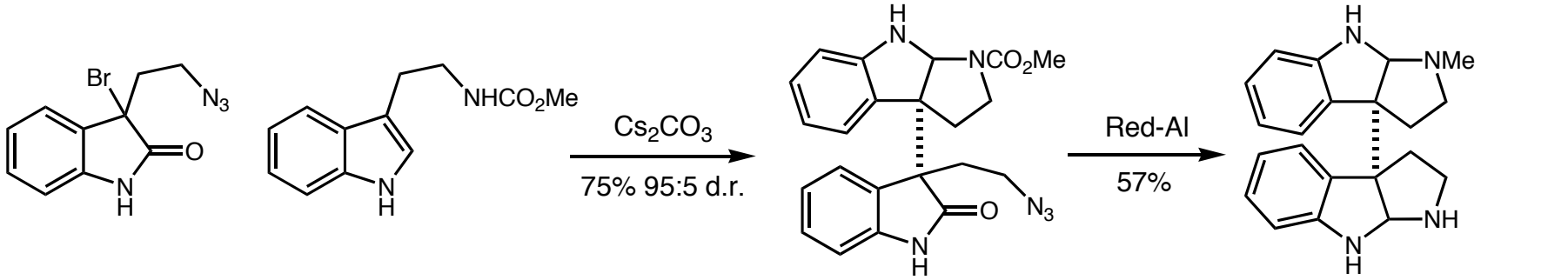
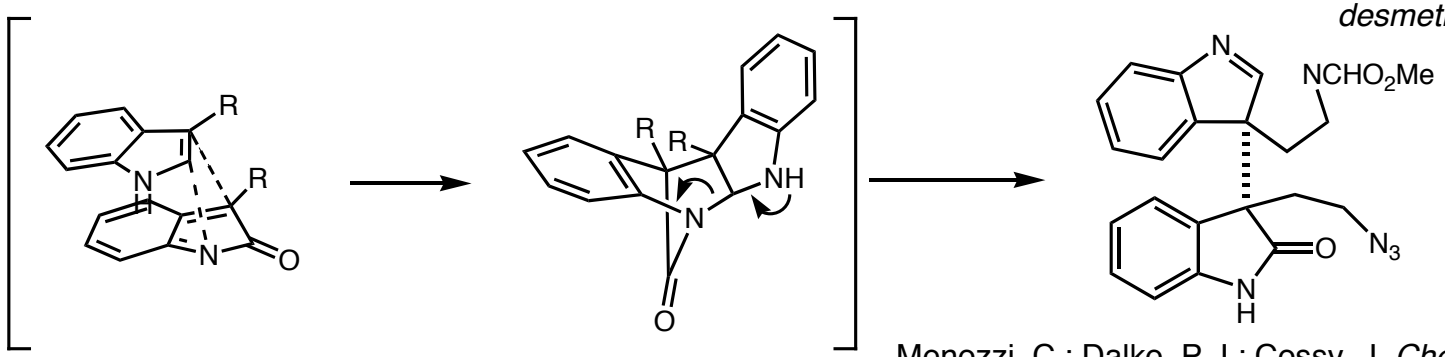


Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677.

■ Dalko invokes the same intermediate in the synthesis of *meso*-chimonanthine



desmethyl-meso-chemonanthine

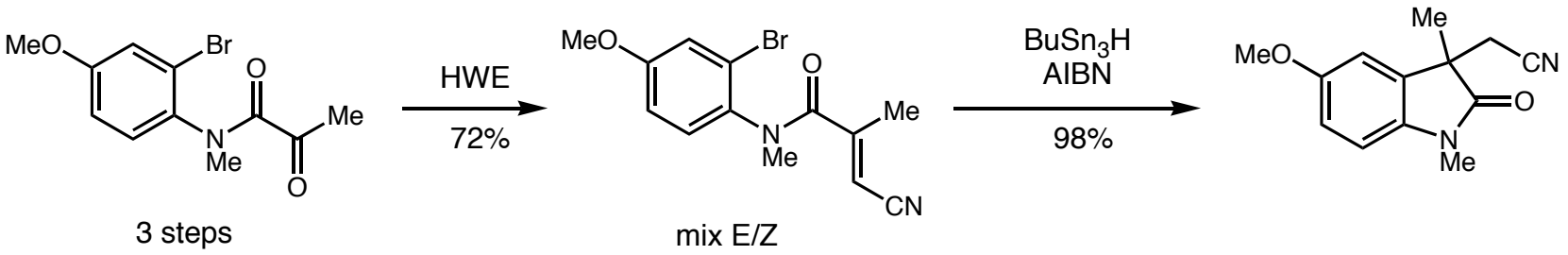


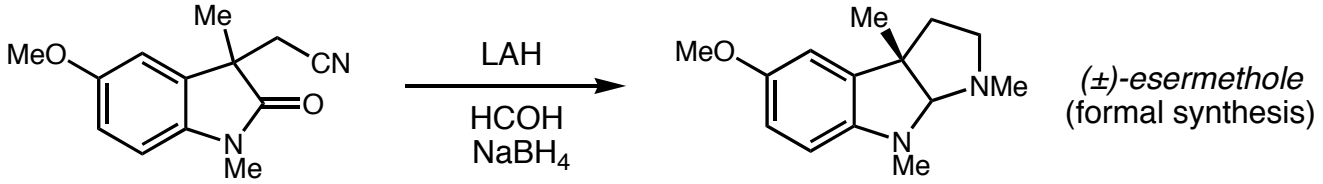
Menozzi, C.; Dalko, P. I.; Cossy, J. *Chem. Commun.* **2006**, 4638.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Radical cyclization to provide the oxoindole by Ishibashi





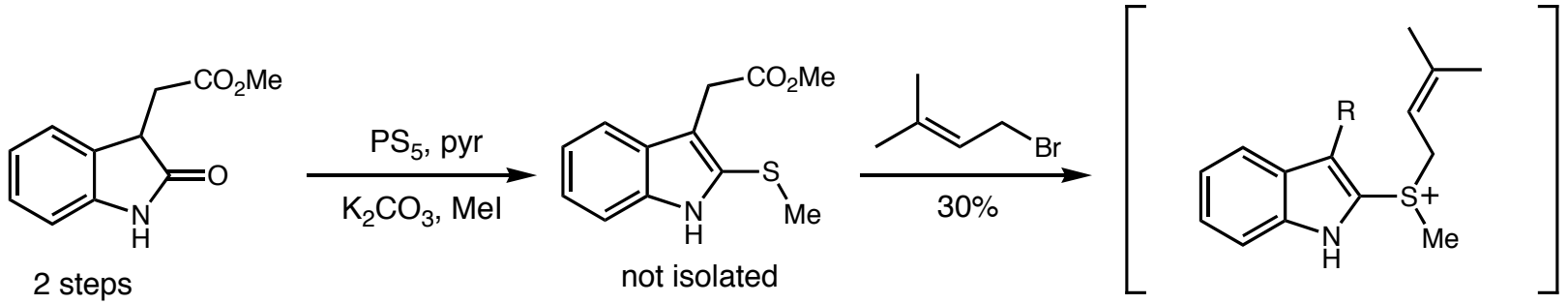
(±)-esermethole
(formal synthesis)

Ishibashi, H.; Kobayashi, T.; Machida, N.; Tamura, O. *Tetrahedron* **2000**, *56*, 1469.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Fujisawa pharmaceuticals thio-Claisen route to flustramine C core



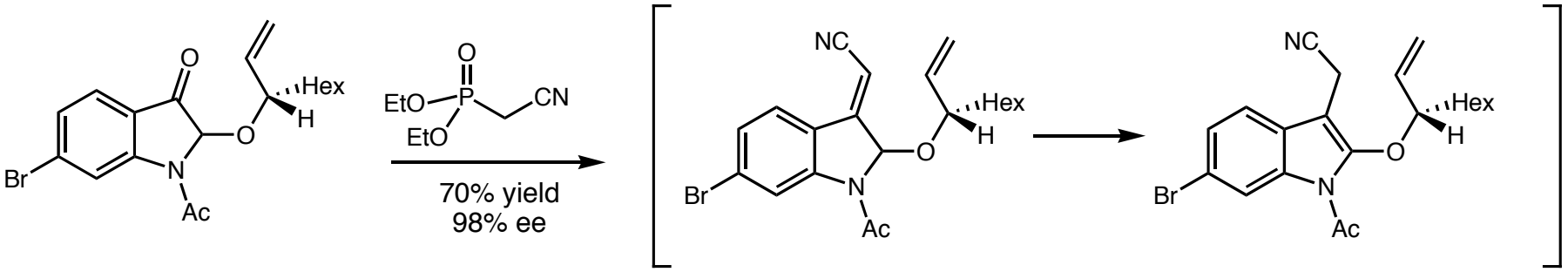
(±)-debromo-8,8a-dihydroflustramine C

Takase, S.; Uchida, I.; Tanaka, H.; Aoki, H. *Tetrahedron* **1986**, *42*, 5879.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Domino olefination/isomerization/Claisen rearrangement sequence to flustramines A and B



Synthetic Approaches to Pyrroloindoline Natural Products

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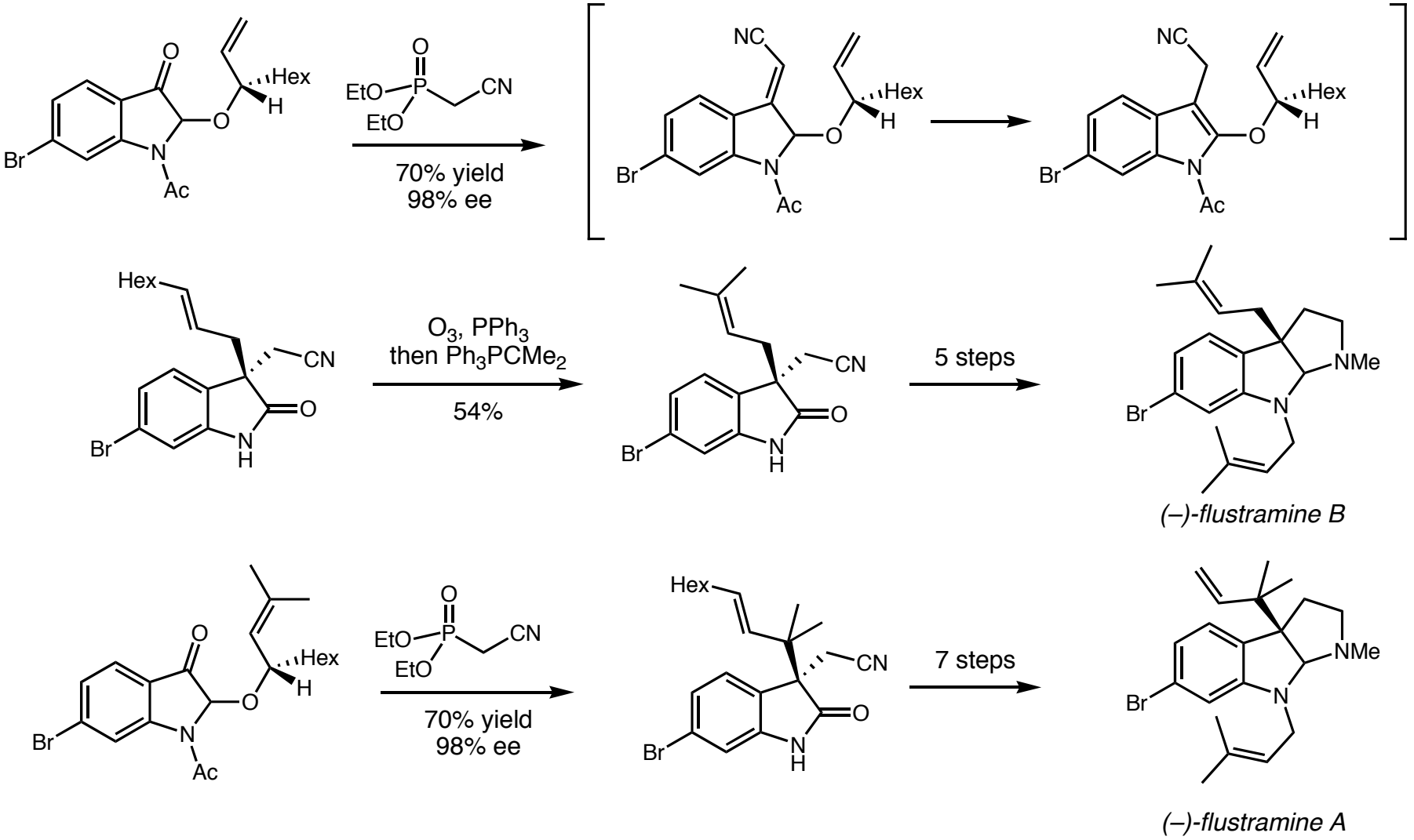


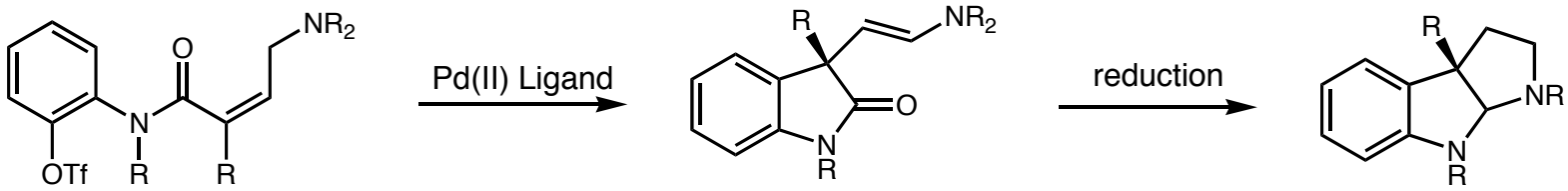
Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Overman uses two basic strategies to access the pyrroloindoline core

Strategy 1:
Intramolecular Heck reaction



Synthetic Approaches to Pyrroloindoline Natural Products

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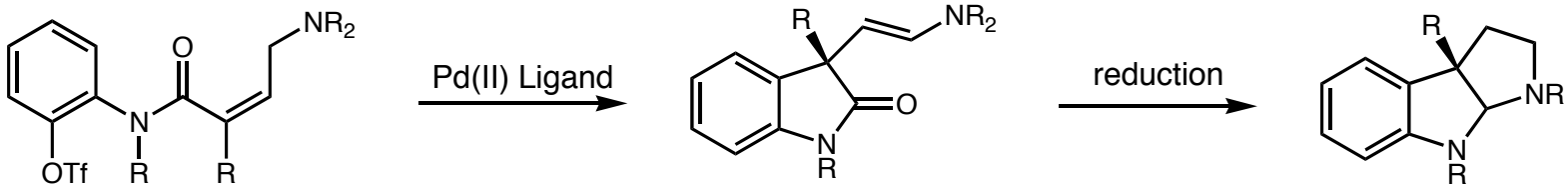
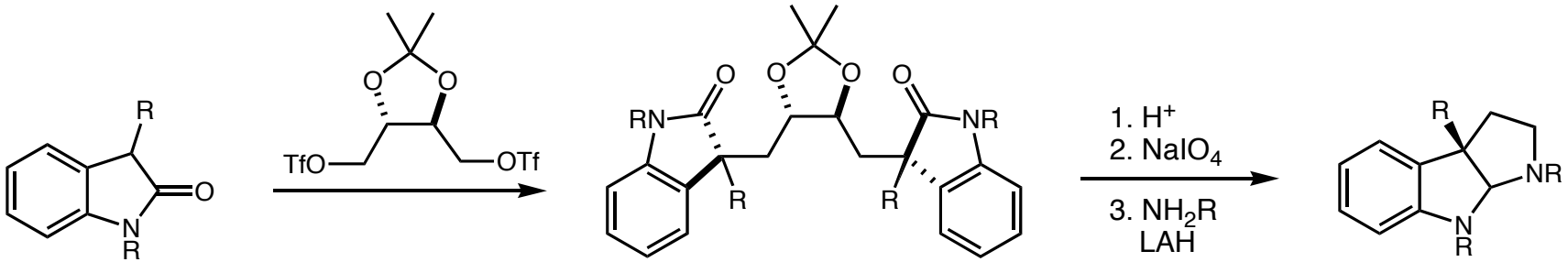


Strategy 2:
oxoindole alkylation



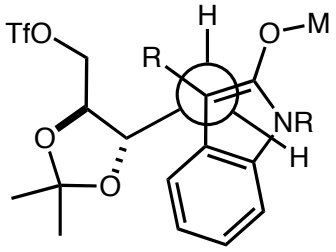
d.r. depends on
R groups, base, additives
solvent and temp

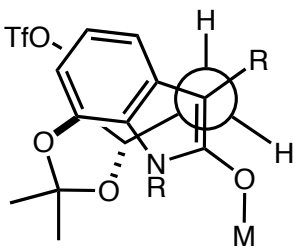
Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

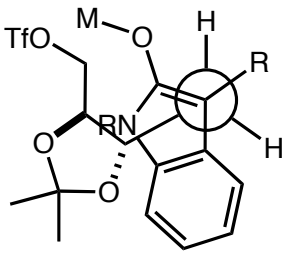
■ Possible alkylation transition states proposed by Overman

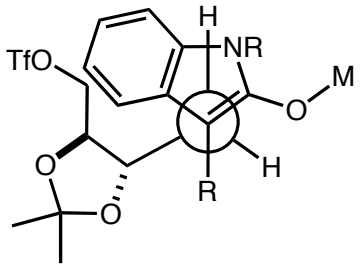
Si face alkylation **favored**

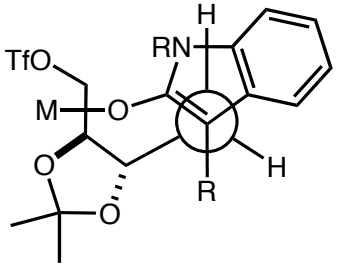


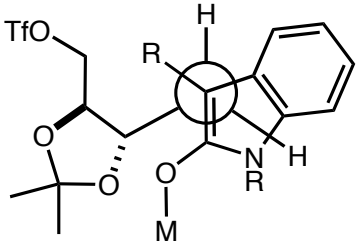


Re face alkylation

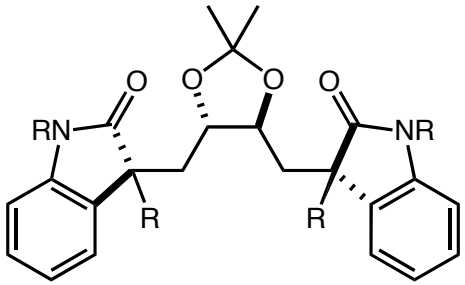




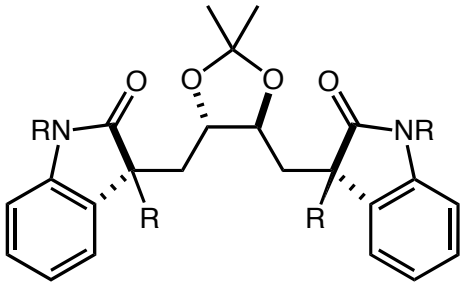




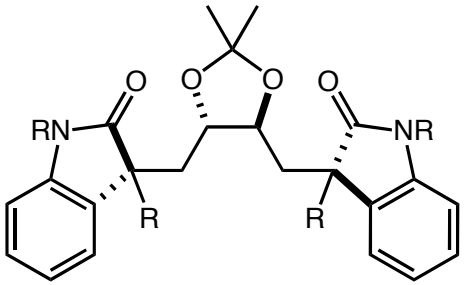
Open transition states using Li or K enolates with THF/DMPU



major C_2



C_1



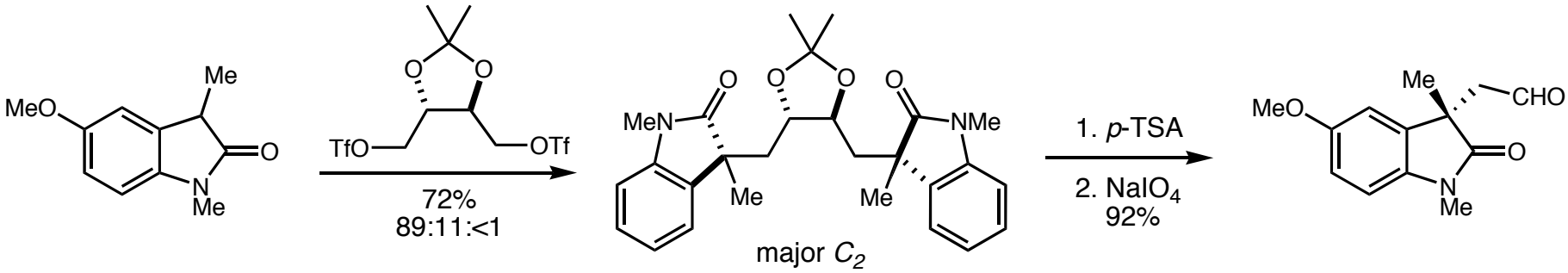
minor C_2

Huang, A.; Kodanko, J. J.; Overman, L. E.*J. Am. Chem. Soc.* **2004**, *126*, 14043.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Bisalkylation strategy in the synthesis of (–)-phenserine



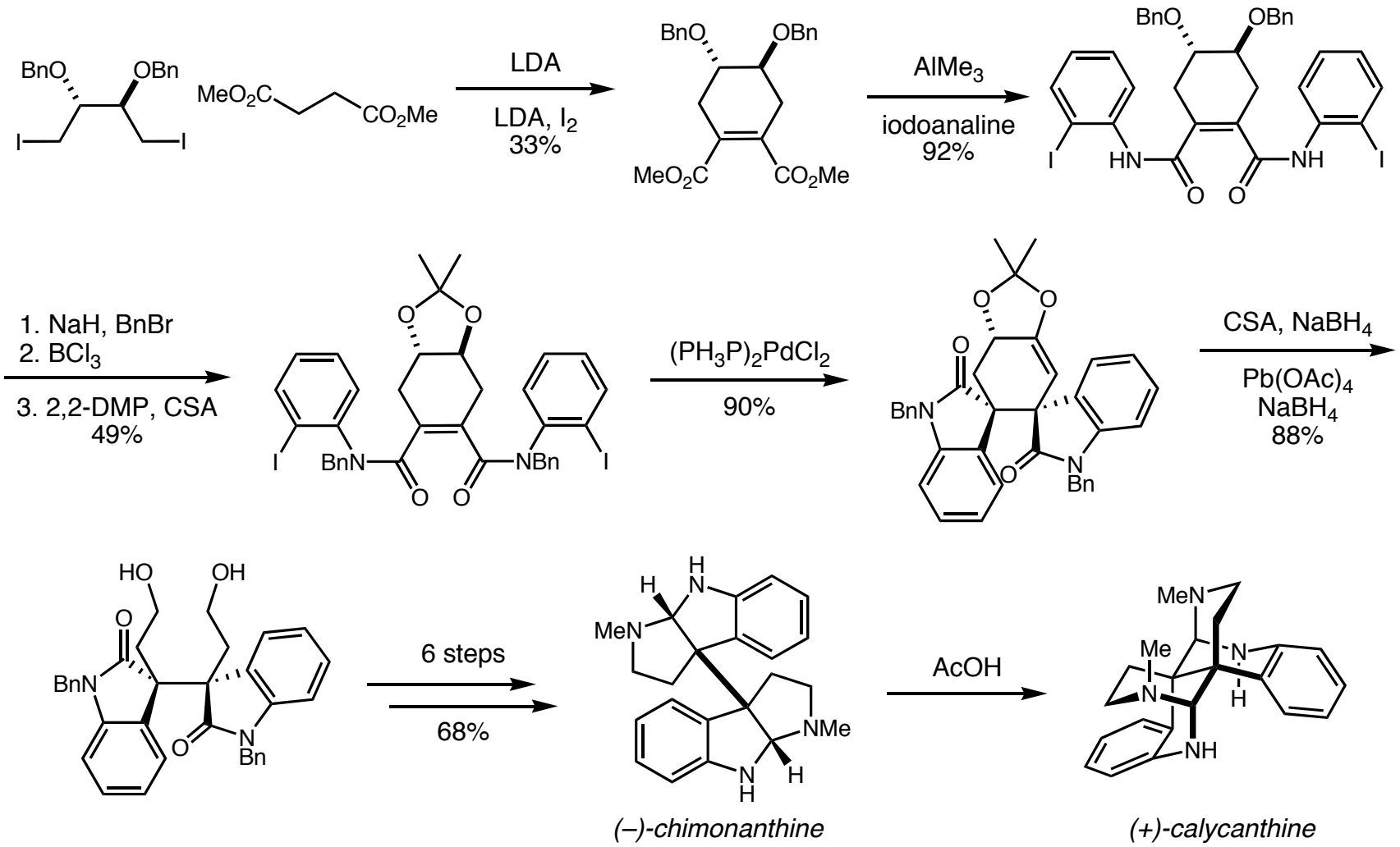
(–)-phenserine

Huang, A.; Kodanko, J. J.; Overman, L. E.*J. Am. Chem. Soc.* **2004**, *126*, 14043.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Heck cascade to chimonanthine



(–)-chimonanthine

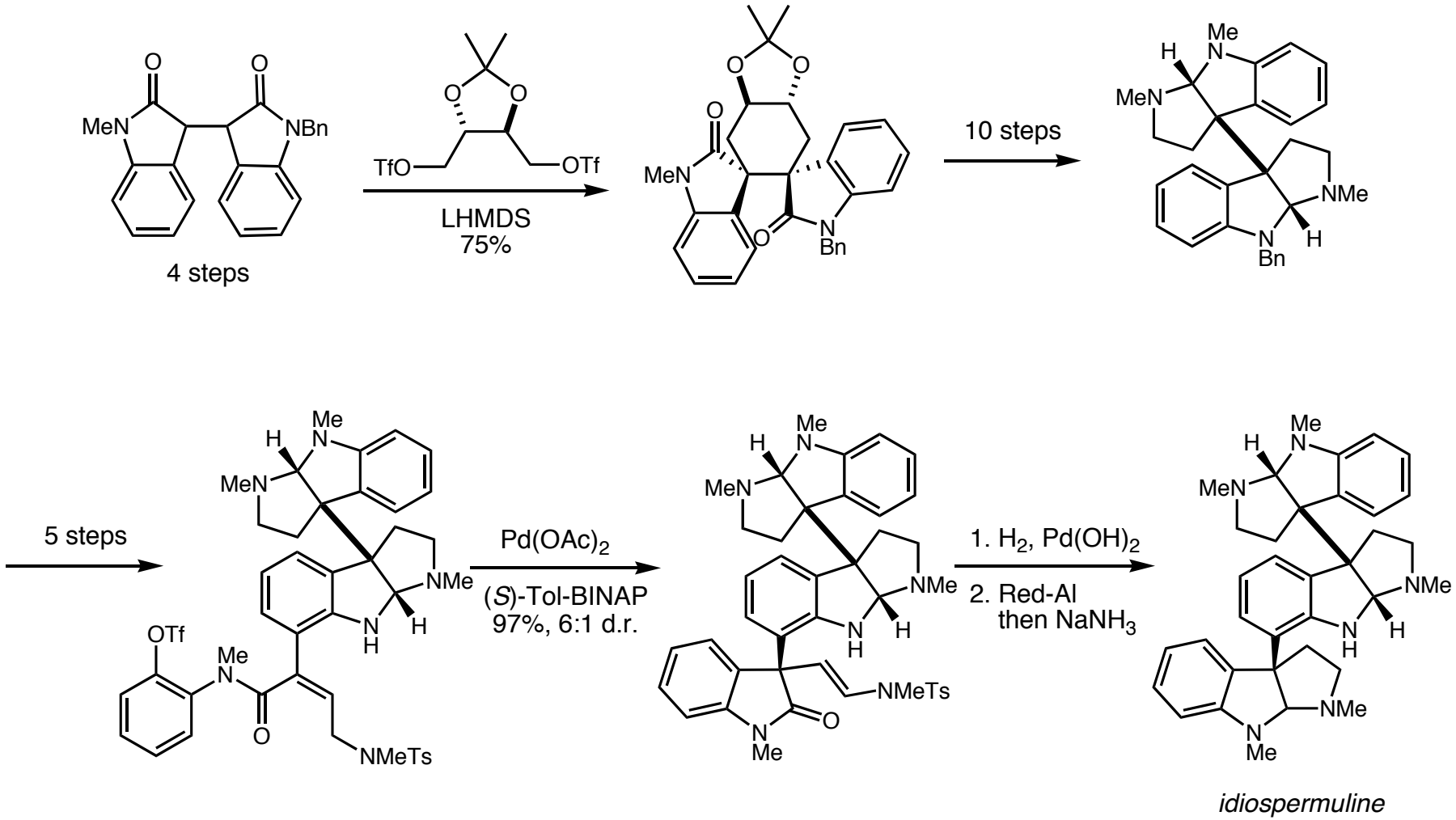
(+)-calycanthine

Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Combination of alkylation and Heck reaction in Overman synthesis of idiospermuline

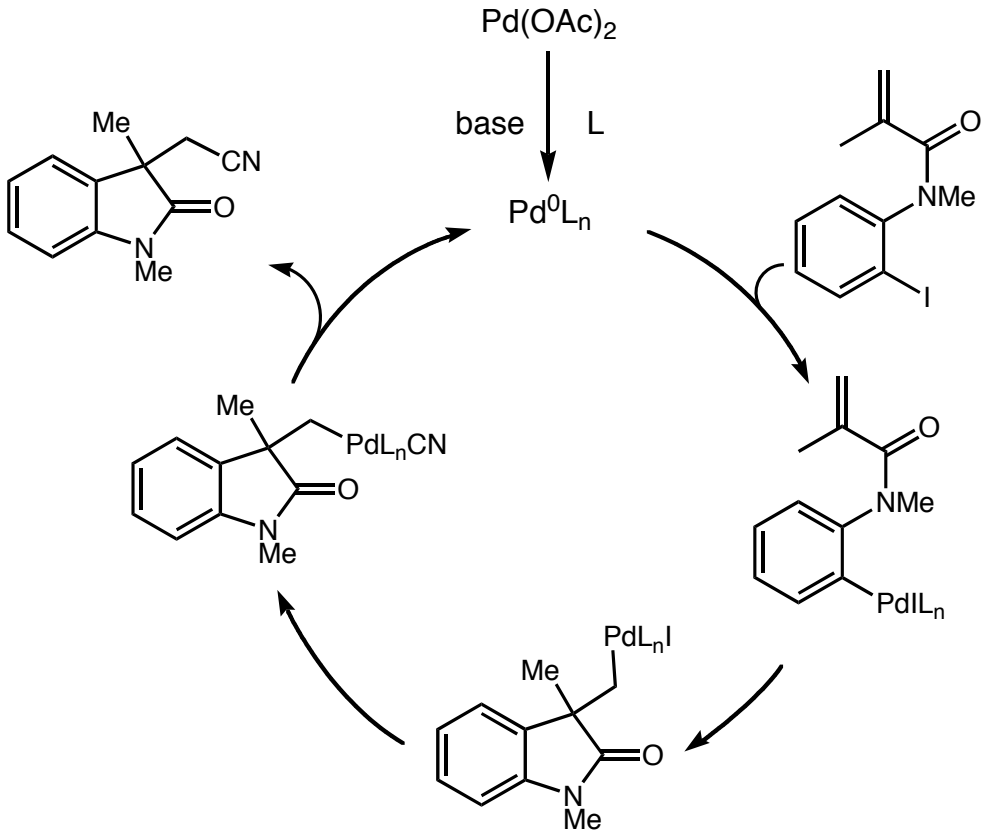


Overman, L. E.; Peterson, E. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2525.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Zhu uses a domino Heck-cyanation sequence to obtain the oxoindole



Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.

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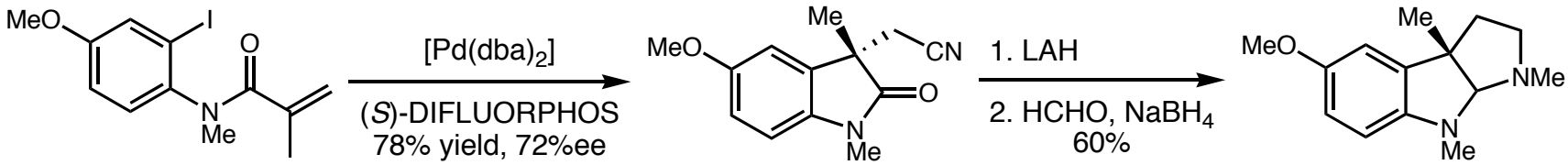

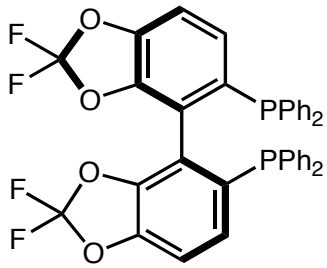

(*S*)-DIFLUORPHOS

Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.

Synthetic Approaches to Pyrroloindoline Natural Products

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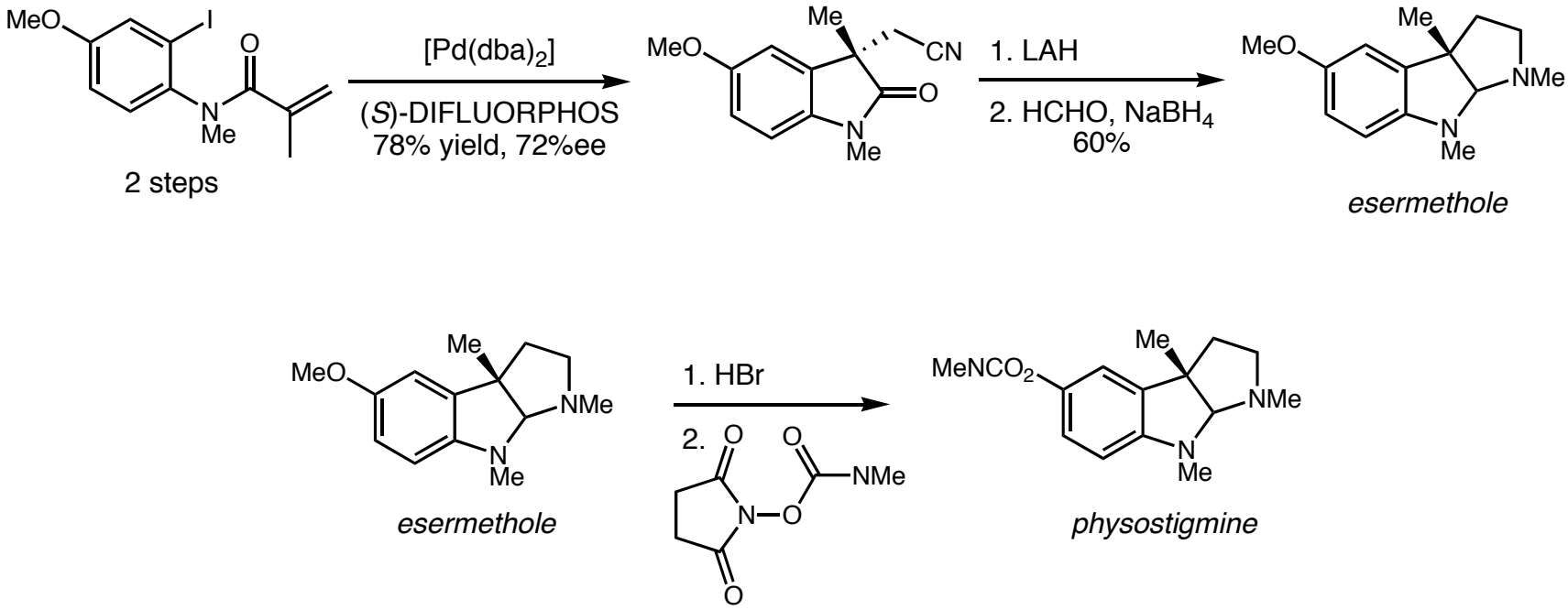
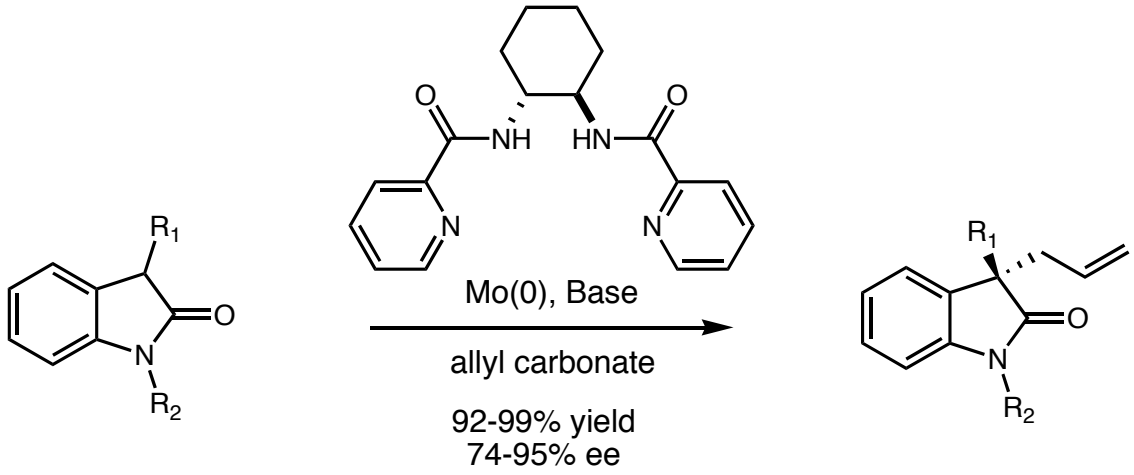


Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.

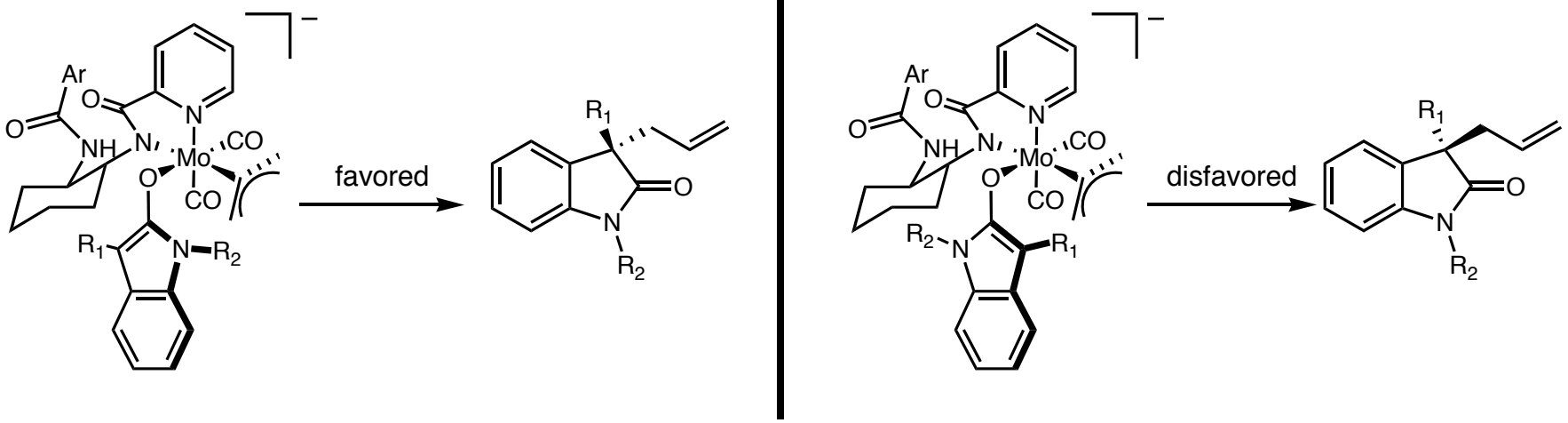
Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Trost asymmetric allylation in the synthesis of (–)-physostigmine



■ Proposed model for enantiodescrimination

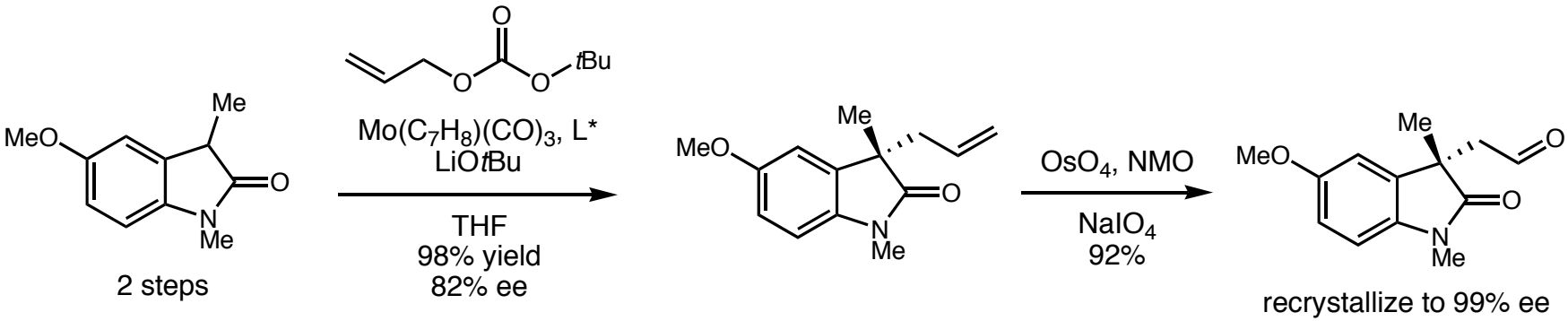


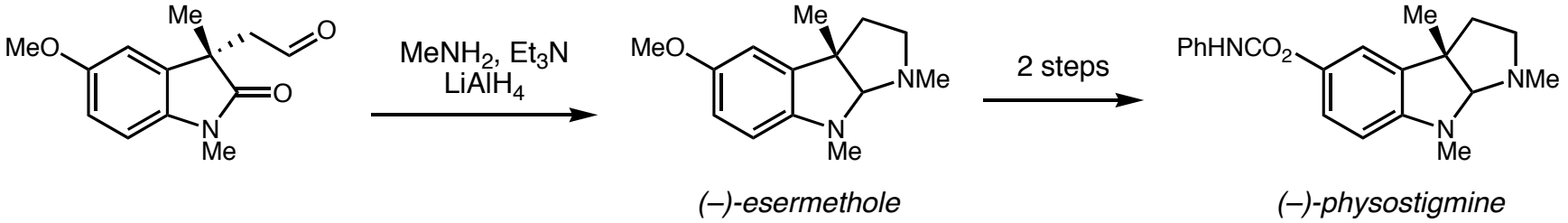
Trost. B. M. Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.

Synthetic Approaches to Pyrroloindoline Natural Products

The 2-Oxoindole Approach

■ Trost asymmetric allylation in the synthesis of (–)-esermethole and (–)-physostigmine



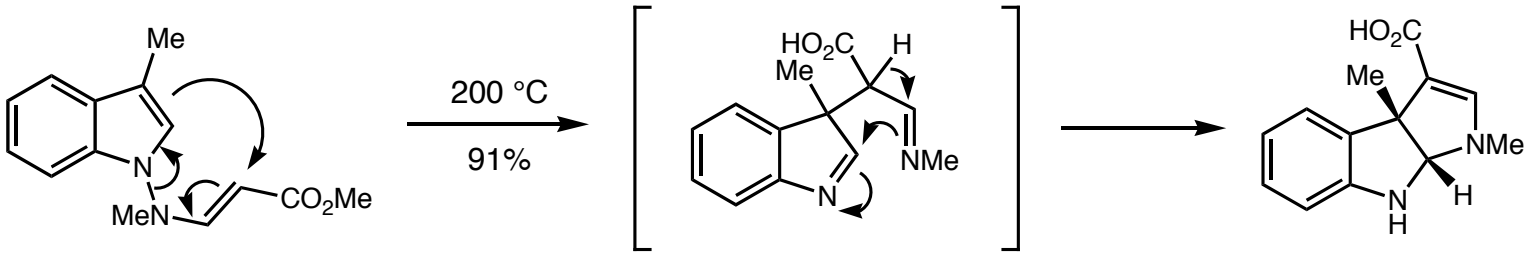


Trost. B. M. Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.

Synthetic Approaches to Pyrroloindoline Natural Products

Other Methods

■ Bis-enamine rearrangement to pyrroloindoline core of calabar alkaloids



Santos. P. F.; Srinivasan, N.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147.

Synthetic Approaches to Pyrroloindoline Natural Products

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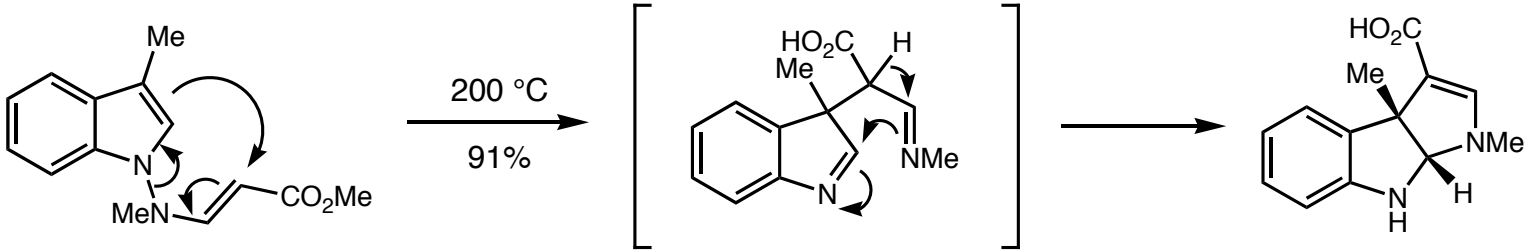
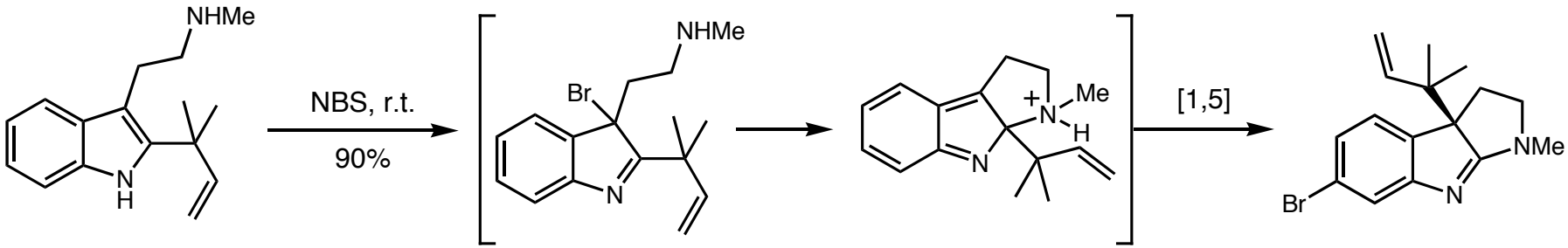


Santos. P. F.; Srinivasan, N.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147.

■ Dimethallyl rearrangement to flustramine C



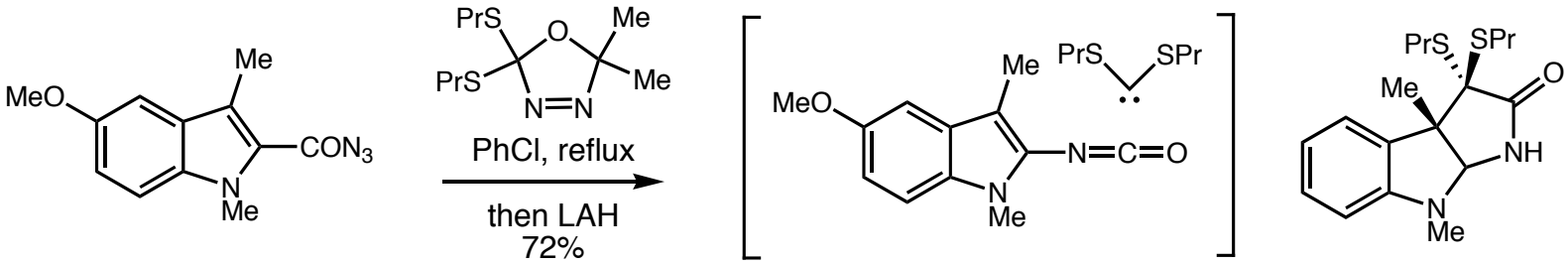
(±)-flustramine C

Lindel, T.; Bräuchle, L.; Golz, G.; Böhrer, P. *Org. Lett.* **2007**, *9*, 283.

Synthetic Approaches to Pyrroloindoline Natural Products

Other Methods

■ [4+1] cyclization of a bis(alkylthio)carbene and indole isocyanate



Rigby, J. H.; Sidique, S. *Org. Lett.* **2007**, *9*, 1219.

Synthetic Approaches to Pyrroloindoline Natural Products

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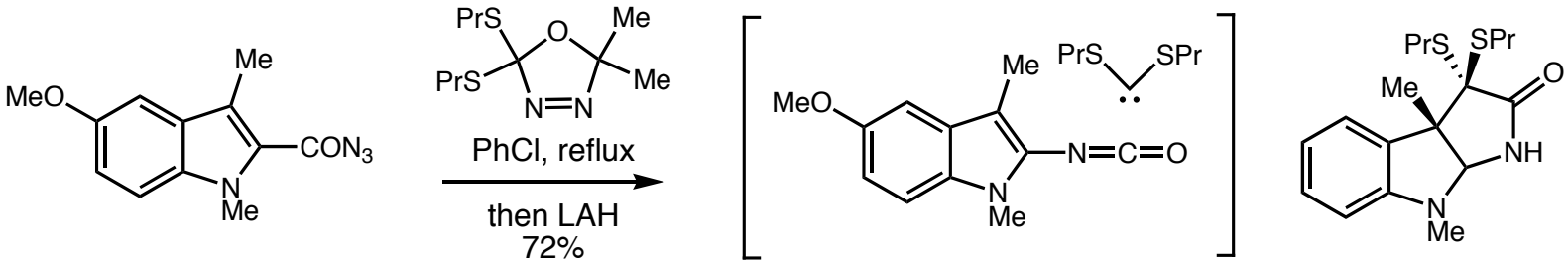
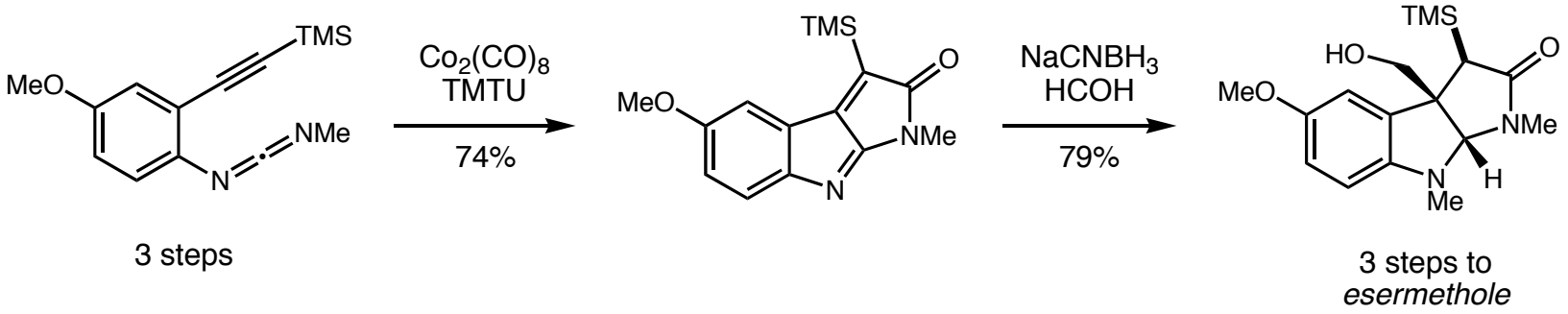


Rigby, J. H.; Sidique, S. *Org. Lett.* **2007**, *9*, 1219.

■ Aza-Pauson-Khand-type reaction of alkynecarbodiimides

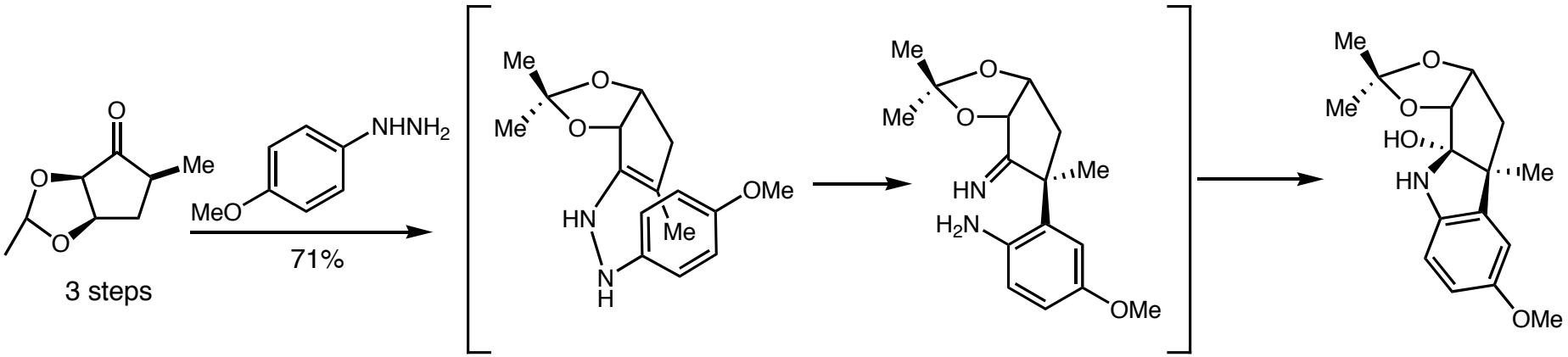


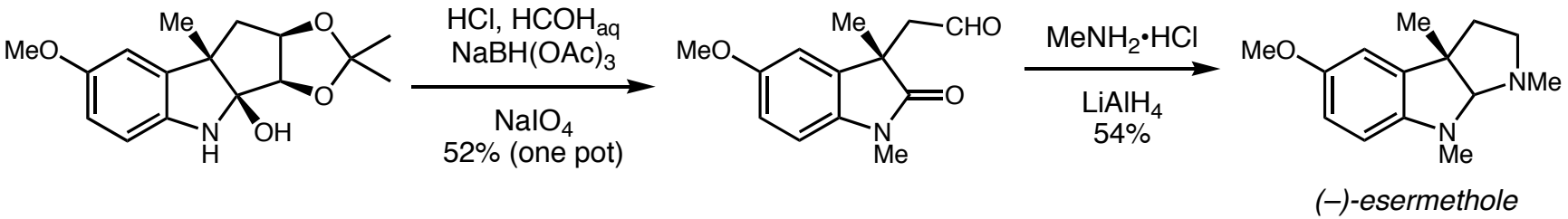
Aburano, D.; Yoshida, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 6878.

Synthetic Approaches to Pyrroloindoline Natural Products

Other Methods

■ Asymmetric synthesis of calabar alkaloids by Ogasawara





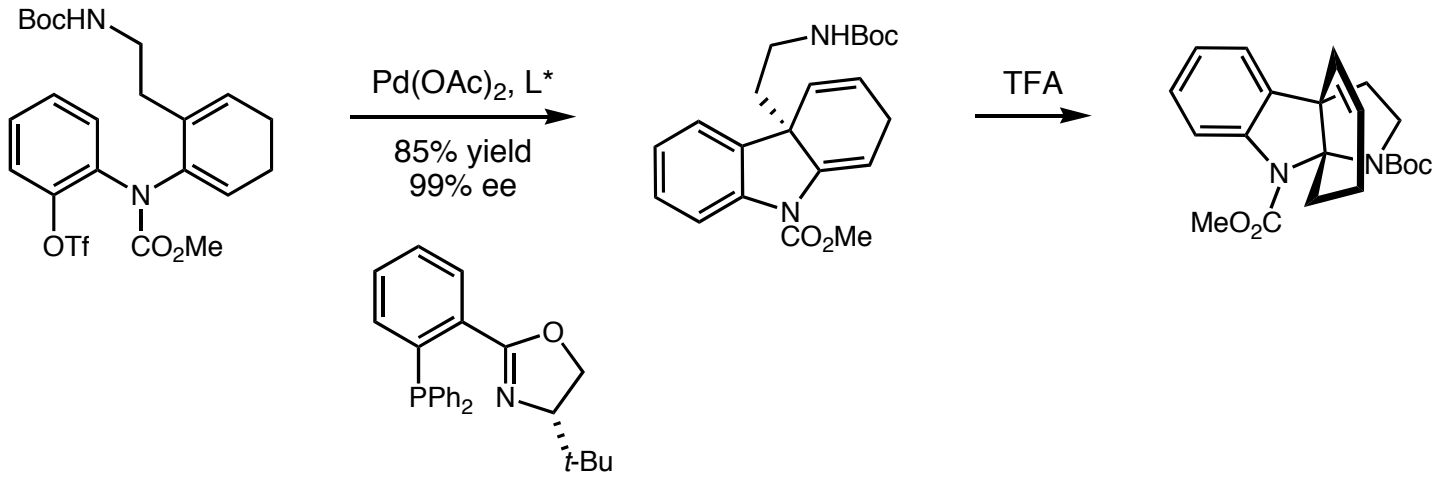
(–)-esermethole

Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Letters* **2001**, *42*, 1049.

Synthetic Approaches to Pyrroloindoline Natural Products

Other Methods

■ Overman synthesis of (+)-minfiensine

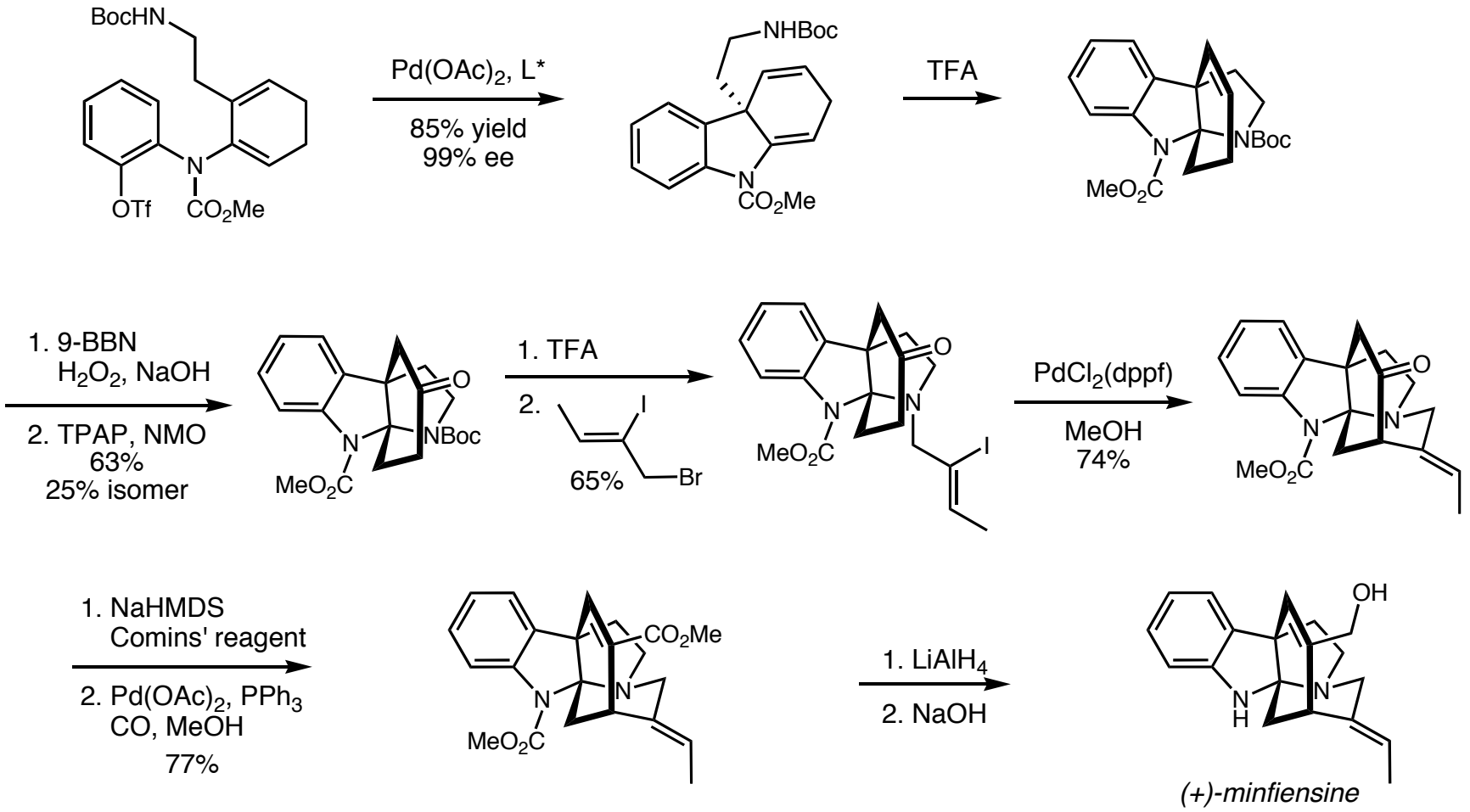


Dounay, A. B.; Humphreys, P. G.; Overman. L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.

Synthetic Approaches to Pyrroloindoline Natural Products

Other Methods

■ Overman synthesis of (+)-minfiensine



Dounay, A. B.; Humphreys, P. G.; Overman. L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.

Conclusions

- Each method has its strengths and weaknesses
- Biomimetic approach is rapid and tryptophan is an abundant source of chiral material
- Few enantioselective methods for pyrroloindoline construction have been developed
- Efficiently obtaining fully-substituted vicinal stereocenters of the pyrroloindoline core remains a challenge