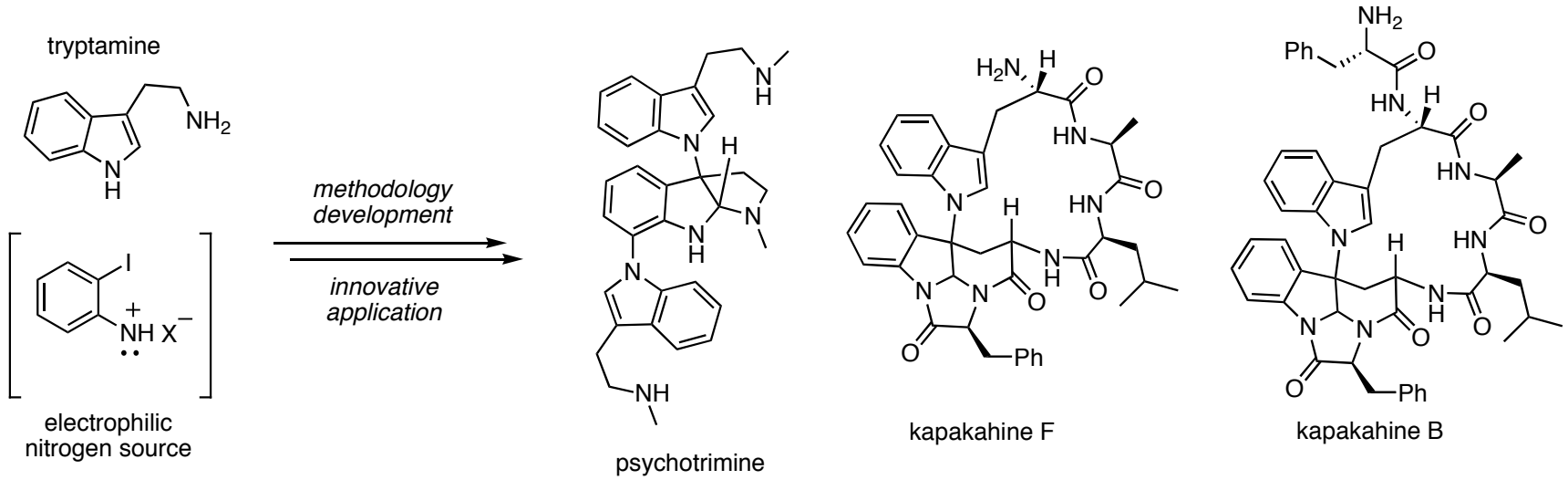
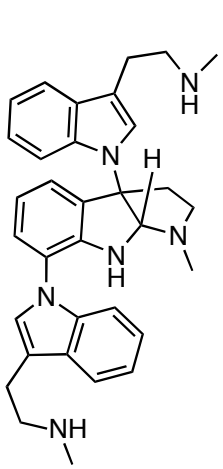
# Scalable Total Syntheses of *N*-Linked Tryptamine Dimers by Direct Indole-Aniline Coupling: Psychotrimine and Kapakahines B and F



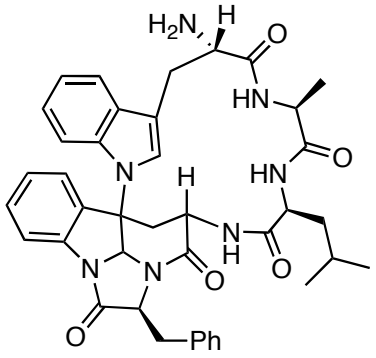

Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S.
*J. Am. Chem. Soc.*, **2010**, *132*, 7119–7137

John Maciejewski
*Wipf Group - Current Literature*
22 May 2010

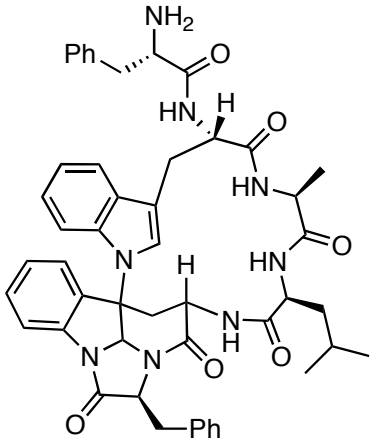
# Isolation of Targets



psychotrimine



kapakahine F



kapakahine B

## Psychotrimine

Isolated from leaves of *Psychotria rostrata* in 2004 (Takayama)
Shown to possess activity against colon and lung cancers

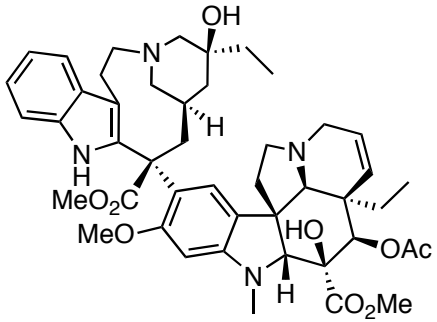
## Kapakahines

Kapakahine B: 0.3 mg isolated from sponge *Cribrochalina olemda* in 1995 (Scheuer)
Kapakahine F: 0.8 mg isolated from *C. olemda* in 2003 (Scheuer)
Exhibit promising anti-leukemia activity

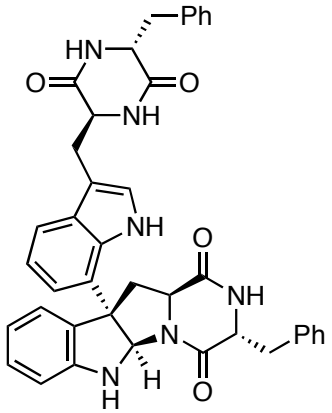

Takayama, H. *Org. Lett.* **2004**, 6, 2945
Scheuer, P. J. *J. Am. Chem. Soc.,* **1995**, *117*, 8271
Scheuer, P. J. *Org. Lett.* **2003**, 5 1387
Synthesis of kapakahine B and F, see Baran, P. *J. Am. Chem. Soc.,* **2009**, *131*, 6360
Synthesis of psychotrimine, see Baran, P. *J. Am. Chem. Soc.,* **2009**, *130*, 10886

# Bond Connectivity in Indole-based Natural Products

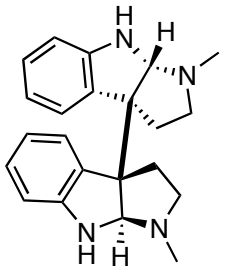
*C-C linkages*



vinblastine

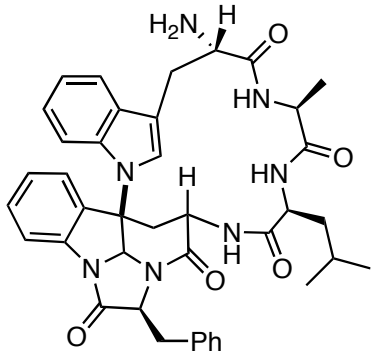


asperazine

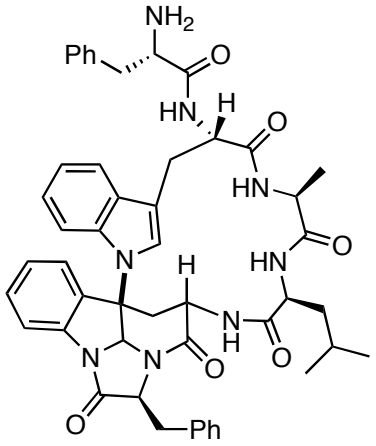


chimonanthine

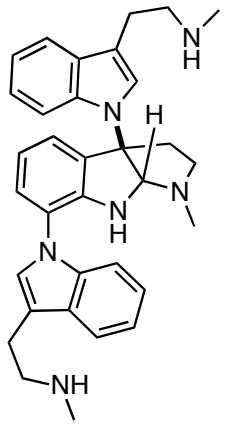
*N-C linkages*



kapakahine F

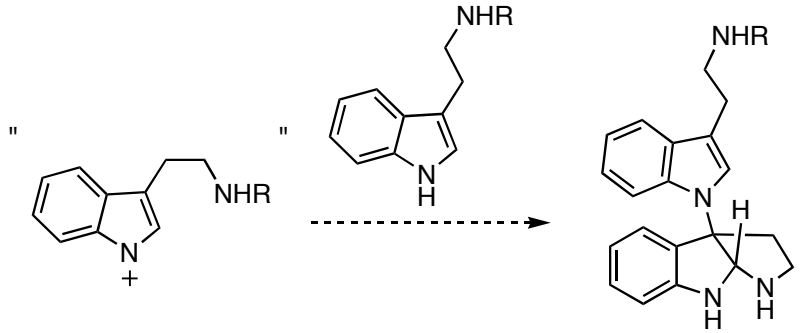


kapakahine B

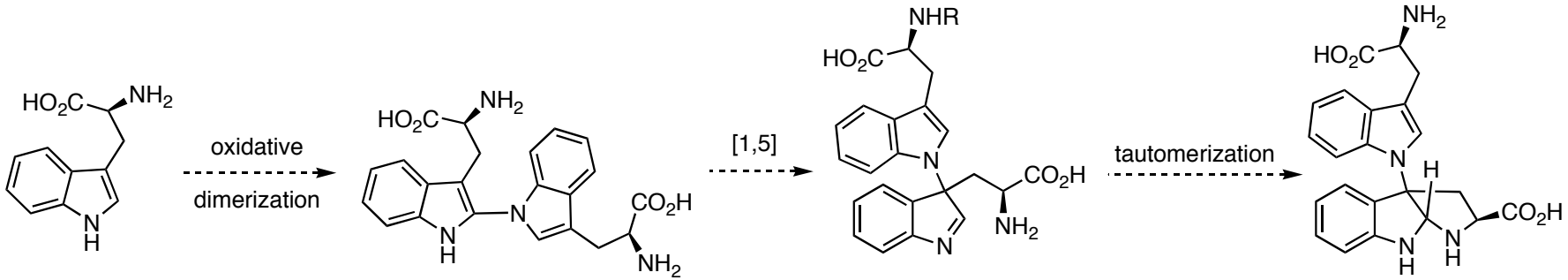


psychotrimine

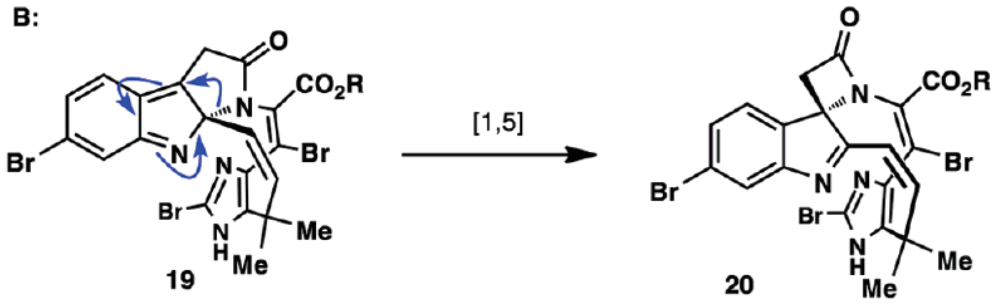
# Proposed Biosynthetic Routes to the N1-C3 Bond




*radical or cationic-based oxidative dimerization*



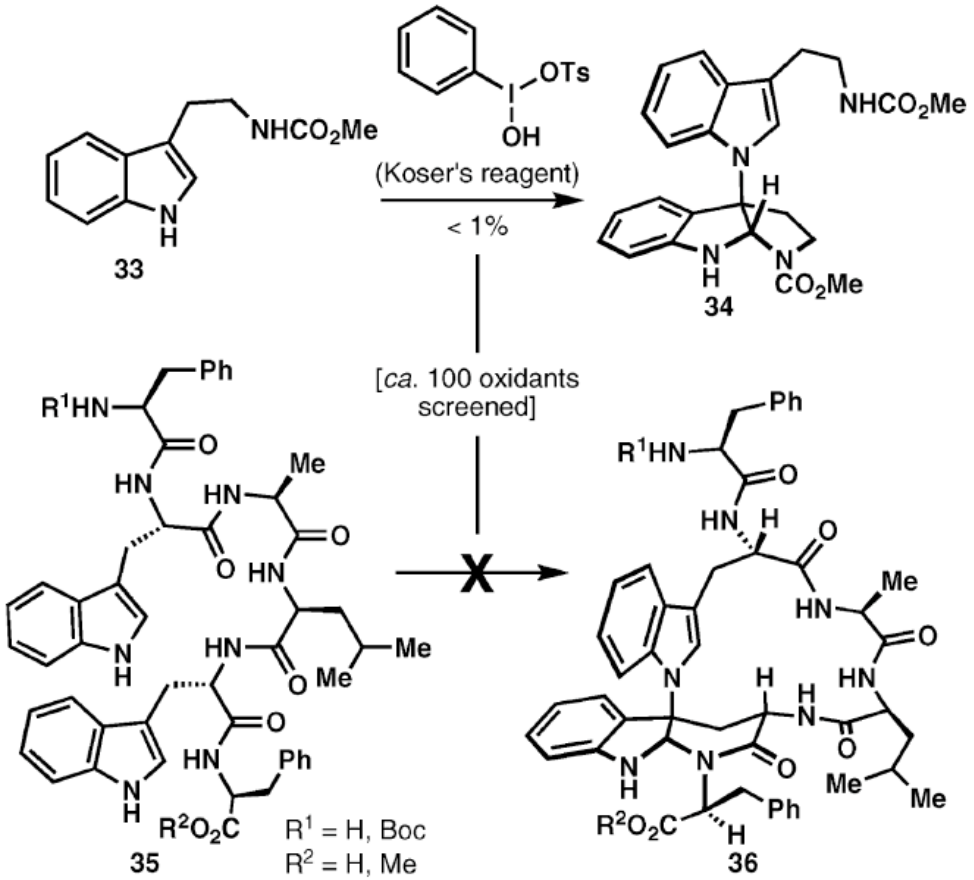

*oxidative dimerization of tryptophan*




*As applied by Baran and Shenvi in the total synthesis of chartelline C*

For [1,5] rearrangement, see: *J. Am. Chem. Soc.,* **2006**, *128*, 14028

# Direct Oxidative Dimerization

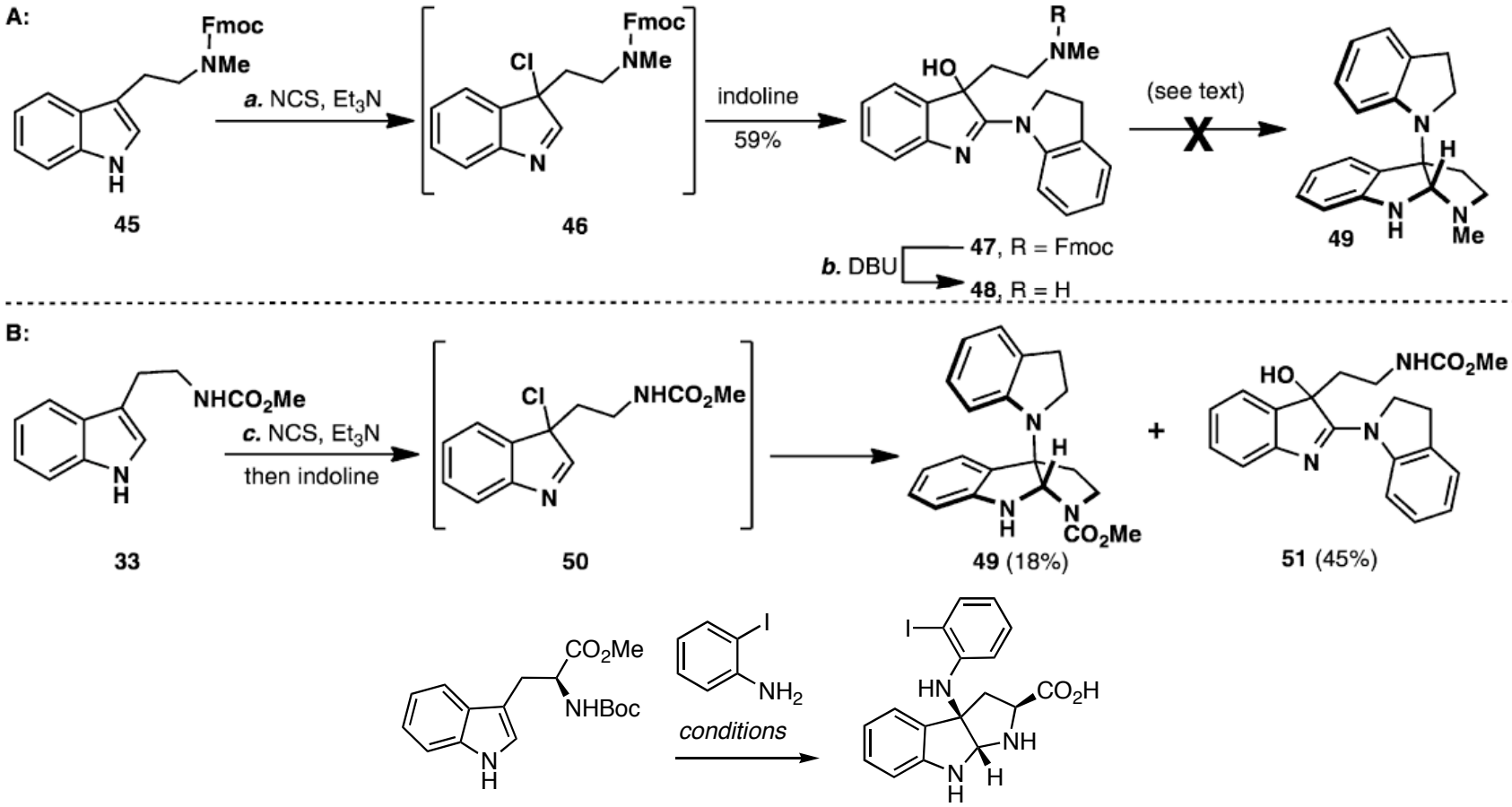



*Extensive screening of oxidants did not afford the desired N1-C3 linkage*

*Koser's reagent afforded trace amounts of the desired dimer*

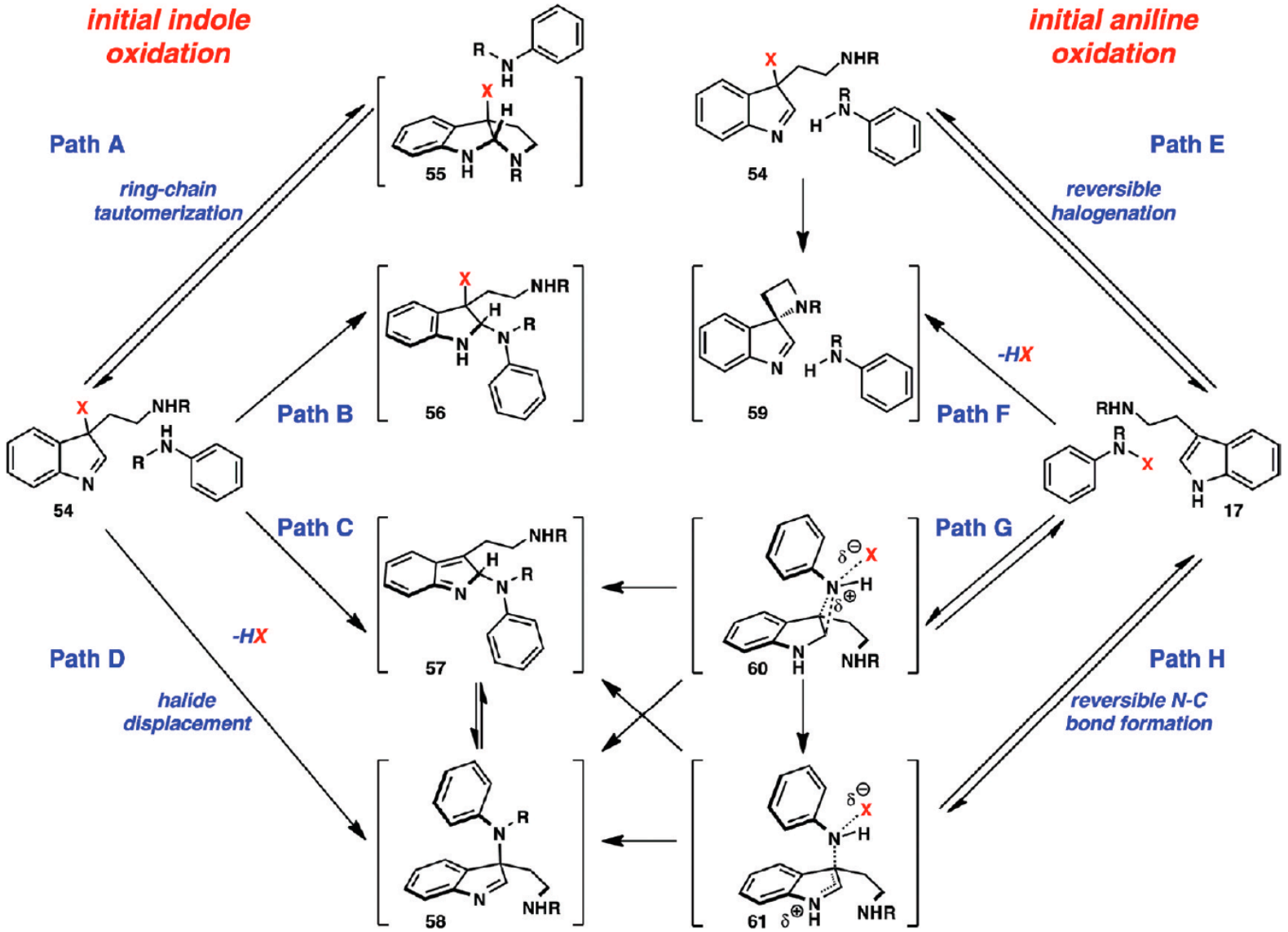
*Attempts at oxidative coupling of **35** to arrive at **36** were not fruitful*

# Screening for the Indole Cation Equivalent

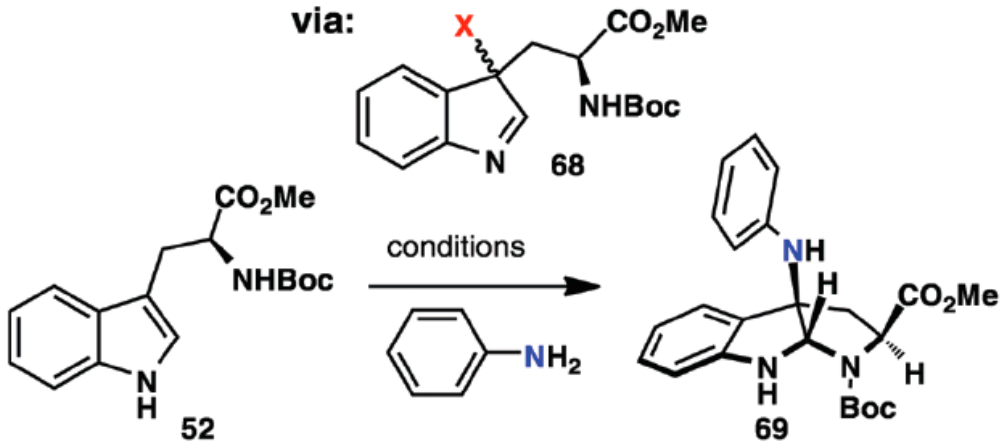



Instead of employing tryptamine dimerization, *o*-iodoaniline was screened as the nitrogen donor
NIS was the optimal reagent for conversion, isolated yield, diastereoselectivity, and scalability
Low temperature and the absence of any amine base were critical

# Mechanistic Considerations



# Rationalization of Diastereoselectivity

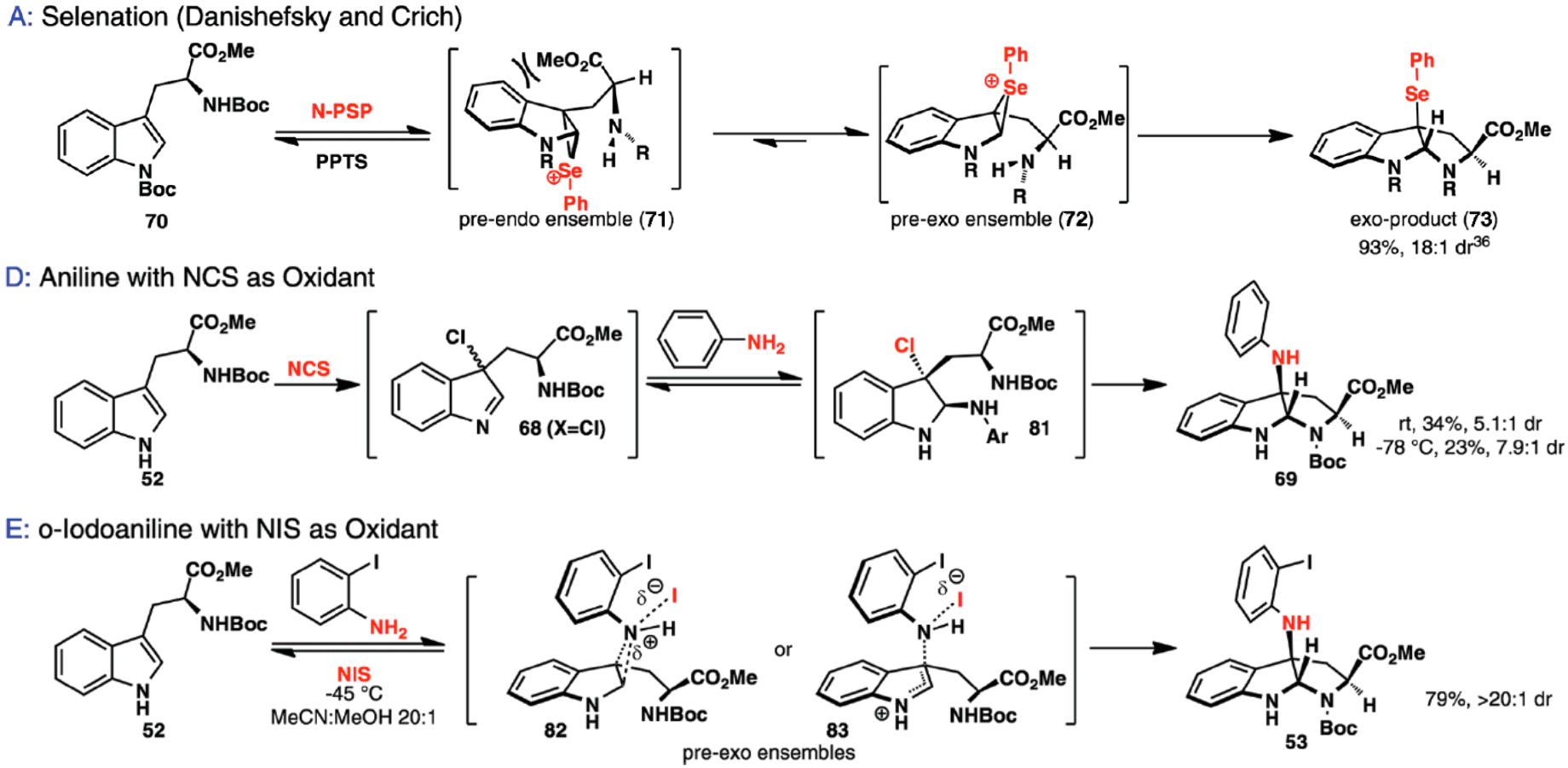



| Entry | Conditions[a] | dr (**68**)[b] | (%)[c] | dr (**69**)[b] |
|---|---|---|---|---|
| 1 | NCS, –78 °C; then aniline, rt | 1.4:1 | 23 | 7.9:1 |
| 2 | NCS, rt; then aniline, rt | 1.0:1 | 34 | 5.1:1 |
| 3 | aniline; then NCS, –78 °C | — | 11 | 7.4:1 |
| 4 | aniline; then NCS, rt | — | 10 | 7.6:1 |
| 5 | NBS, rt; then aniline, rt | 1.0:1 | 13 | 10.4:1 |
| 6 | NIS, rt; then aniline, rt | — | 0 | — |

[a] Aniline (2.0 equiv), $Et_3N$ (1.5 equiv), NXS (1.2 equiv), DCM. [b] Determined by crude $^1H$ NMR. [c] Isolated yield of **69**.

Order of addition, as well as the oxidant used effect the diastereoselectivity of the reaction
Suggests the halogen may be involved in the stereochemistry-determining step or effect the reaction rate

# Rationalization of *exo* Diastereoselectivity




Danishefsky, S. J. *J. Am. Chem. Soc.,* **1999**, *121*, 11953
Crich, J *J. Org. Chem.* **1999**, *64*, 7218

# Probing the Nature of the Electrophilic Aniline

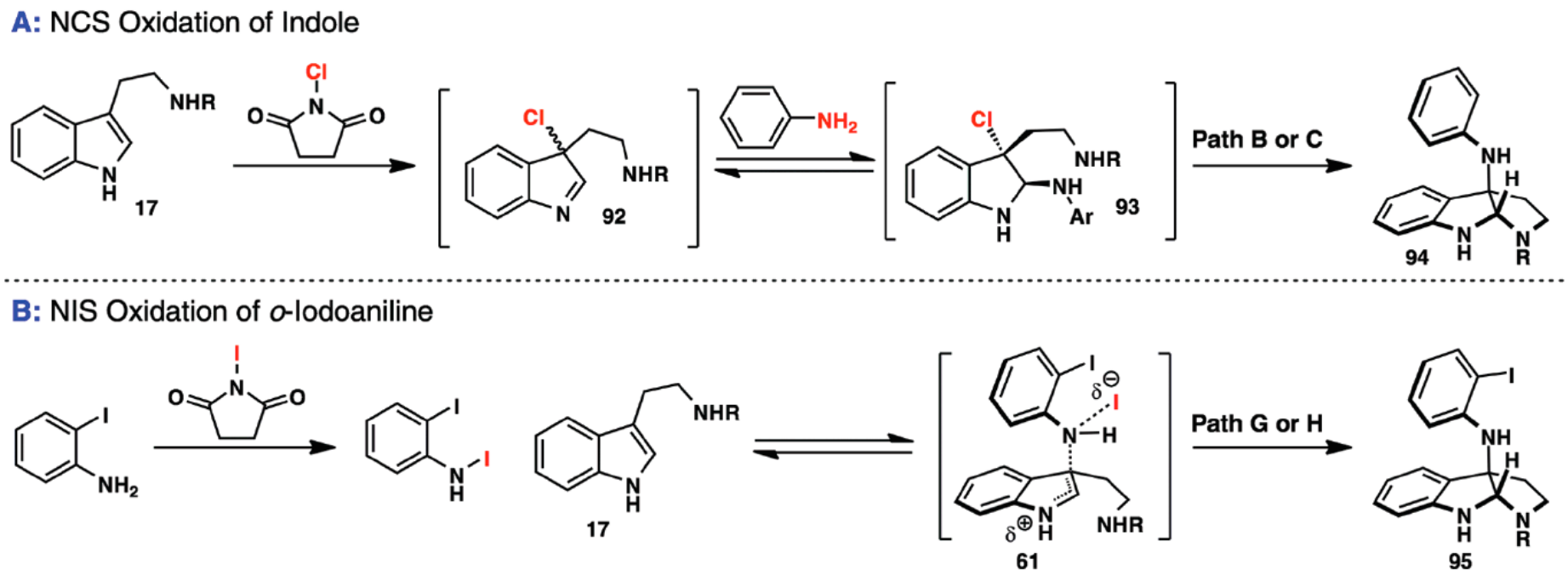
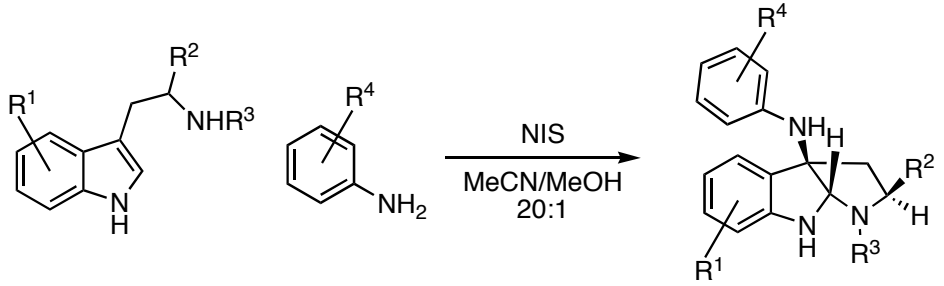
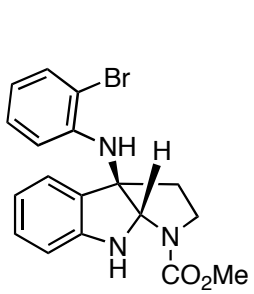


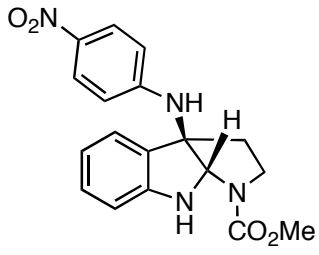

Figure A: aniline addition may occur through addition at C2 followed by migration
Figure B: phenylnitrenium and iodide pair react reversibly with tryptamine;
explains high diastereoselectivity as well as the dependence on the NXS oxidant (X=Cl, Br, or I)

# Comparing the Influence of Substituted Anilines

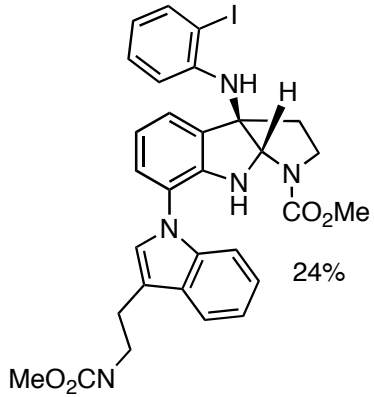


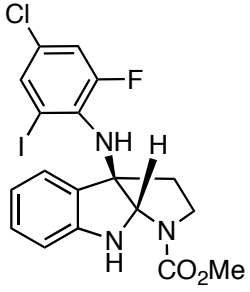

68%



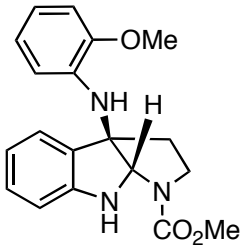

74%




24%




43%

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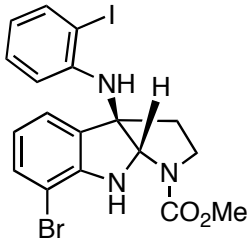
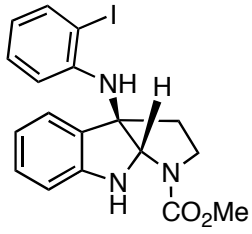
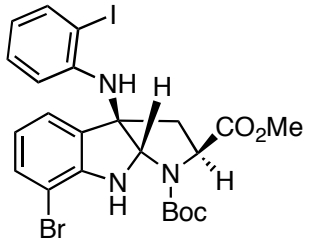


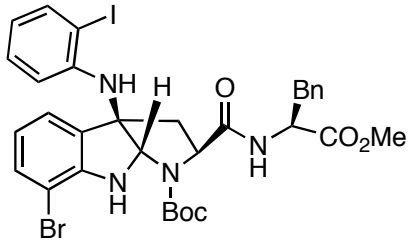

67%




63%



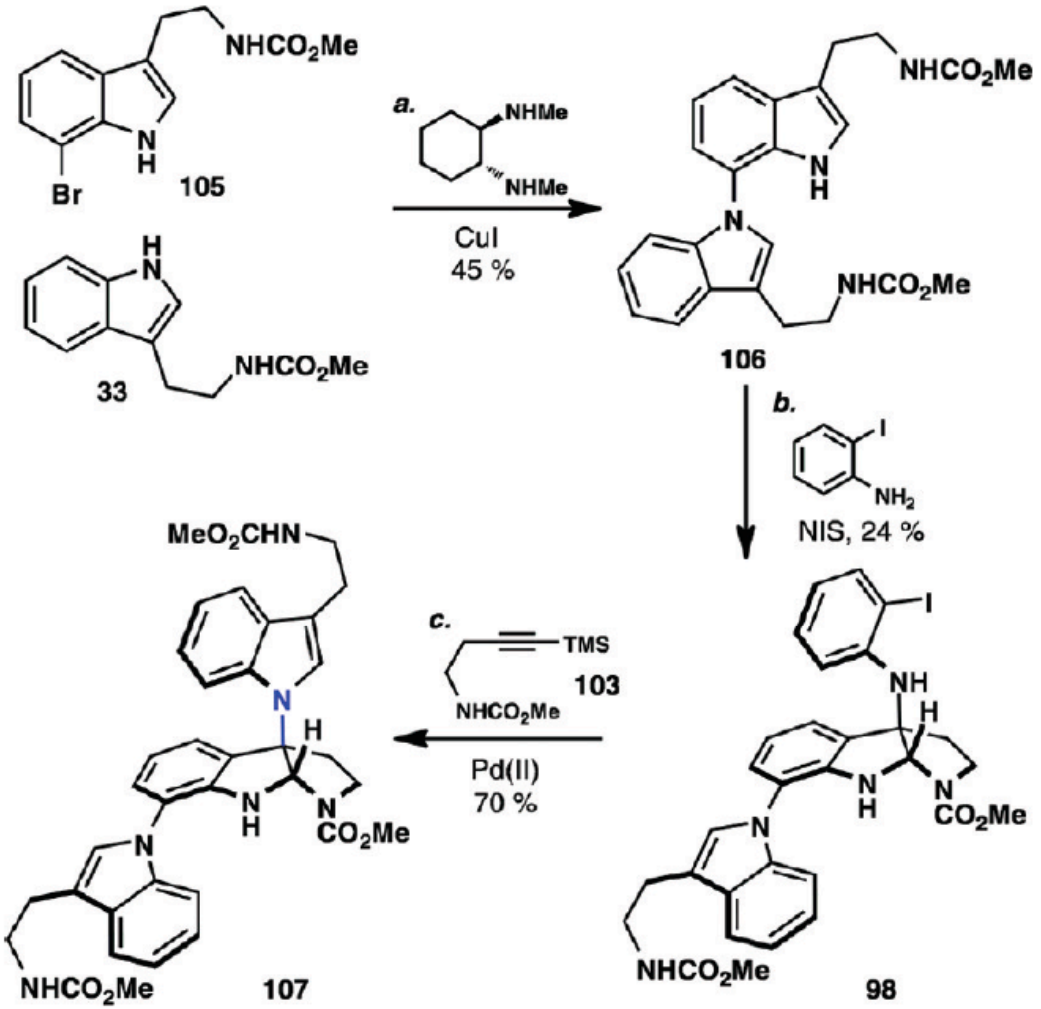

79%




78%

Electron-deficient aniline substrates perform better in reaction than electron-rich
Supports the presence of an electrophilic phenylnitrenium ion

# Initial Route to Psychotrimine

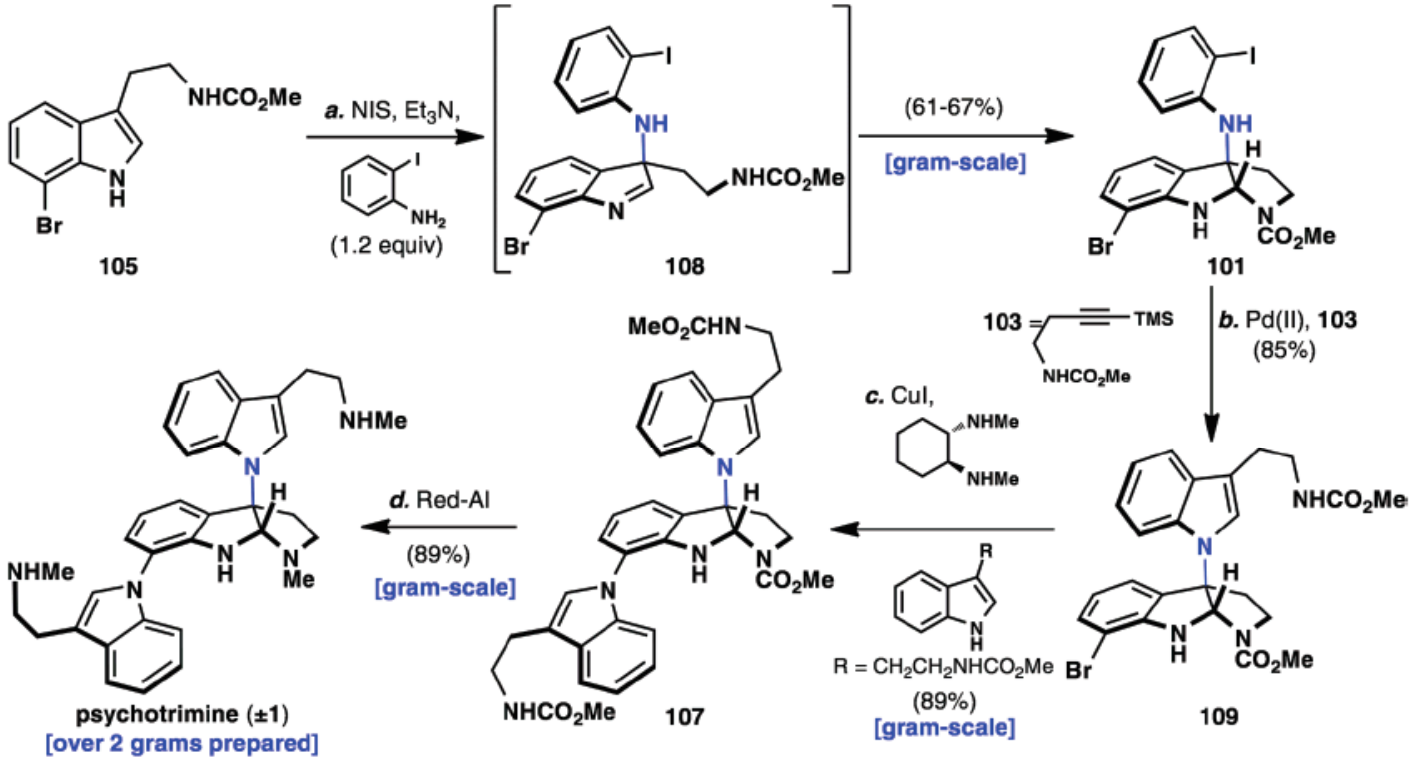



[a] Reagents and conditions: (a) **33** (3.0 equiv), CuI (0.30 equiv), (±)-*trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (0.60 equiv), $K_2CO_3$ (7.0 equiv), 1,4-dioxane, 101 °C, 20 h, 45%; (b) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.5 equiv), MeCN/MeOH (20:1), −45 °C, 1 h, 24%; (c) **103** (7 equiv), $Pd(OAc)_2$ (0.3 equiv), $K_2CO_3$ (3.5 equiv), LiCl (1.0 equiv), DMF, 90 °C, 0.5 h, 70%.

Buchwald-Goldberg-Ullmann coupling followed by indole-aniline oxidative coupling afforded **98** in lower than expected yield

Larock indolization was employed to afford **107**

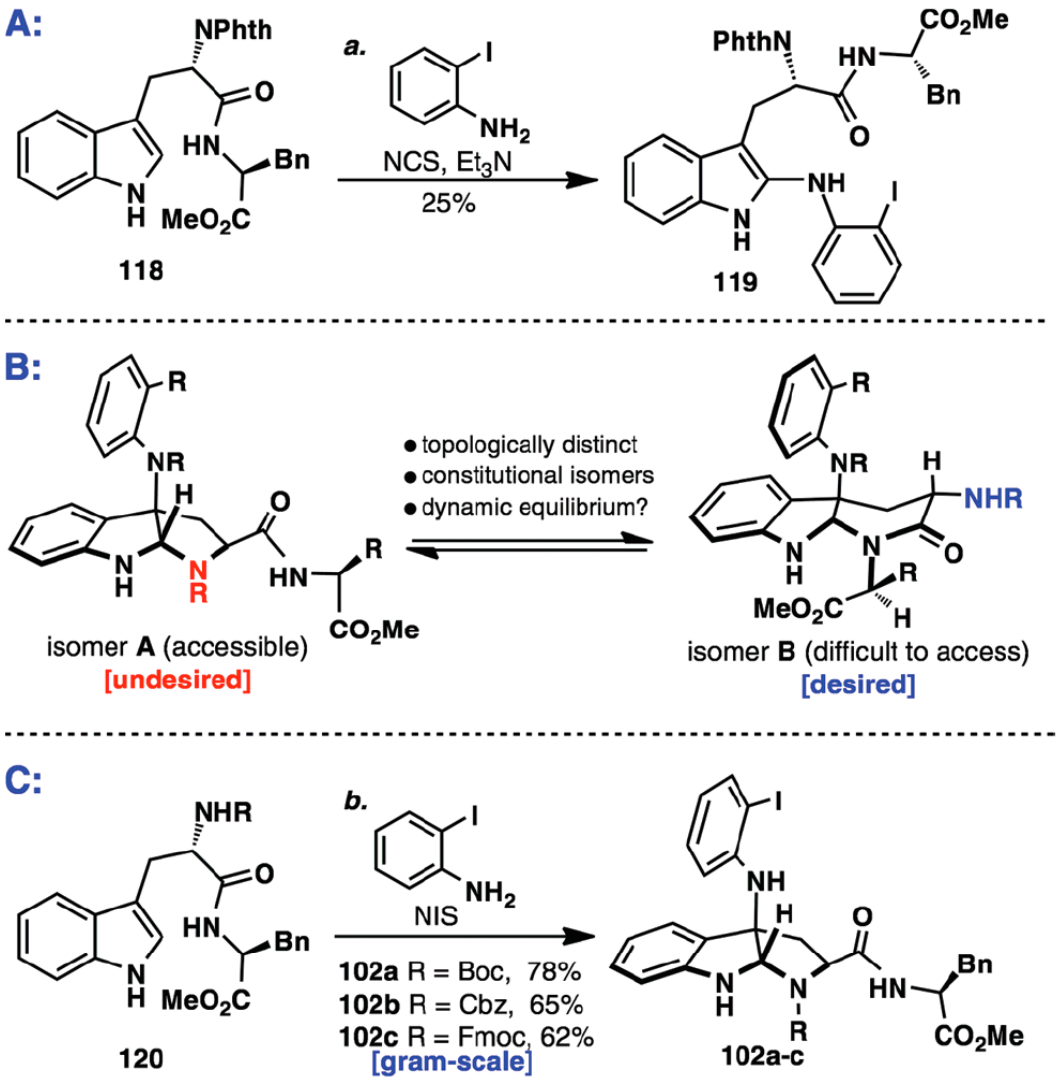
# Gram-scale Preparation of Psychotrimine




[a] Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (3.0 equiv), $Et_3N$ (1.2 equiv), MeCN, −45 → 23 °C, 1 h, 61−67%, 25−30% **105**; (b) $Pd(OAc)_2$ (0.21 equiv), $Na_2CO_3$ (2.6 equiv), LiCl (0.9 equiv), **103** (2.7 equiv), DMF, 102 °C, 20 min, 85%; (c) CuI (0.32 equiv), (±)-*trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (0.60 equiv), $K_2CO_3$ (7.0 equiv), **33** (3.0 equiv), 1,4-dioxane, 101 °C, 9 h, 89%; (d) sodium bis(2-methoxyethoxy)aluminum hydride (22 equiv), toluene, 110 °C, 30 min, 89%.

Indole-aniline oxidative coupling was performed first to afford **101**
Larock indole synthesis was used to efficiently prepare **109**
Buchwald-Goldberg-Ullmann coupling installed the final tryptamine moiety

# Kapakahines B and F




[a] Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-chlorosuccinimide (2.0 equiv), triethylamine (1.2 equiv), MeCN −45 → 4 °C, 2.5 h, 25%; (b) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.6 equiv for **102b**, 1.55 equiv for **102a**,**c**), MeCN, −45 → −35 °C, 2.5 h.

Oxidative coupling at C3 followed by [1,5] shift to afford **119**

Decreased nucleophilicity of amide relative to carbamate

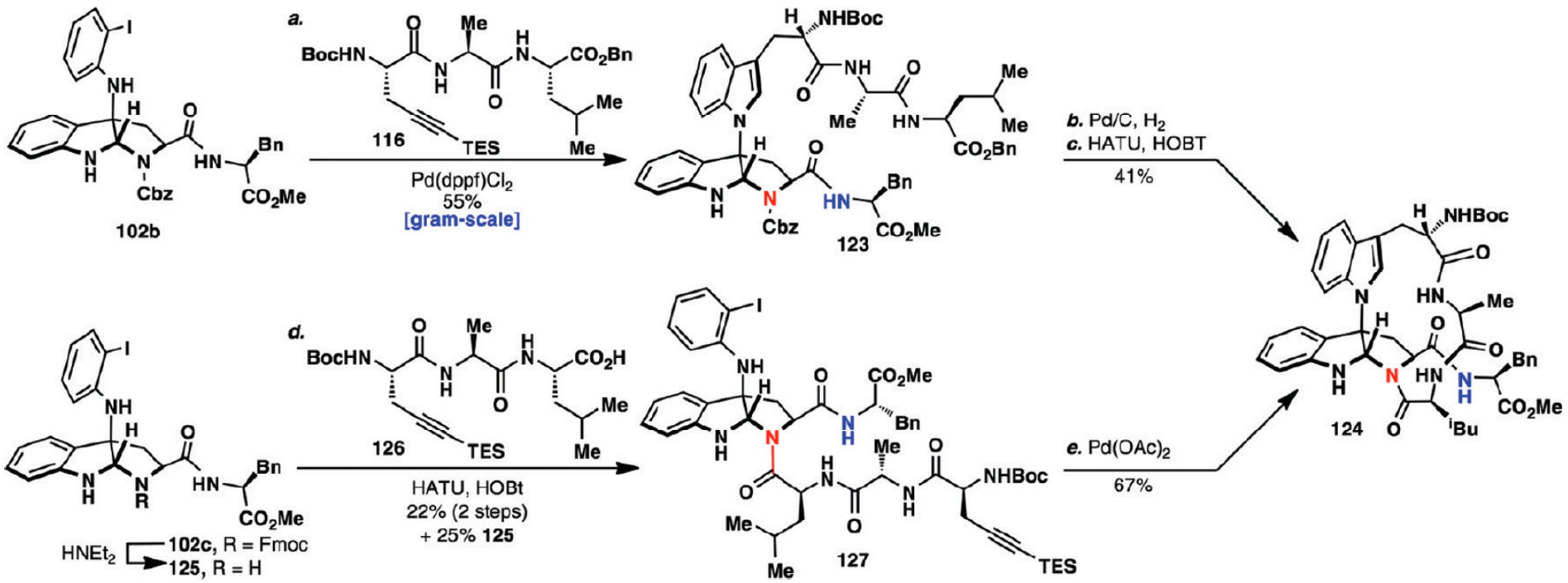
Pyrroloindoline core accessible

Possibility to equilibrate constitutional isomers

Indole-aniline oxidative coupling affords pyrroloindoline core in good yields

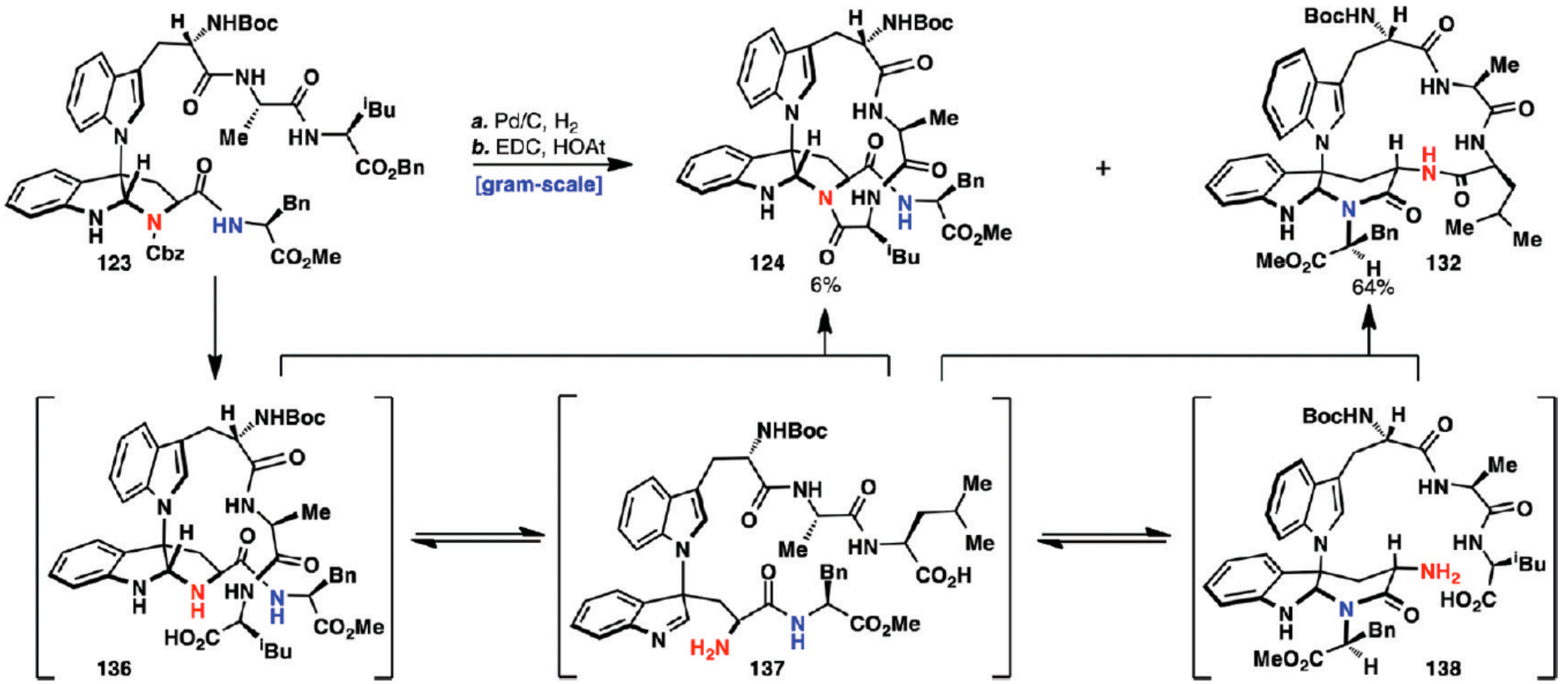
# Kapakahines B and F

***Scheme 14.*** Two Routes to the Pyrroloindoline-Containing Macrocycle **124**[a]




Larock indole synthesis affords **123**
Peptide coupling affords iodide **127**
Unable to isomerize **124** into the desired carboline scaffold

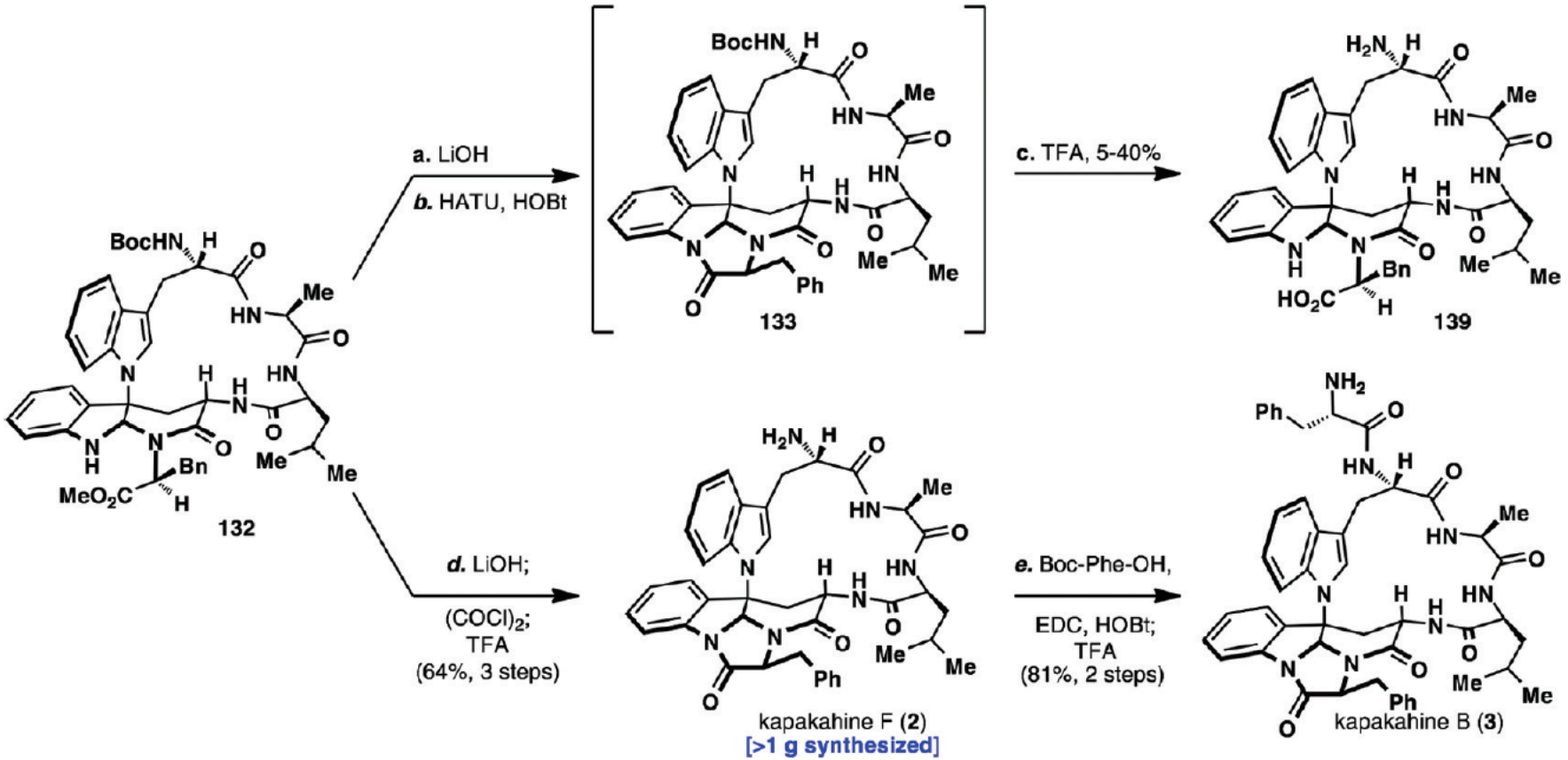
# Kapakahines B and F




[a] Reagents and conditions: (a) 10% Pd/C (0.20 equiv), $H_2$, MeOH, 1 h; (b) EDC (3.0 equiv), HOAt (6.0 equiv), DCM/DMF (20:1), 12 h, 70% (**124**:**132**, 1:11).

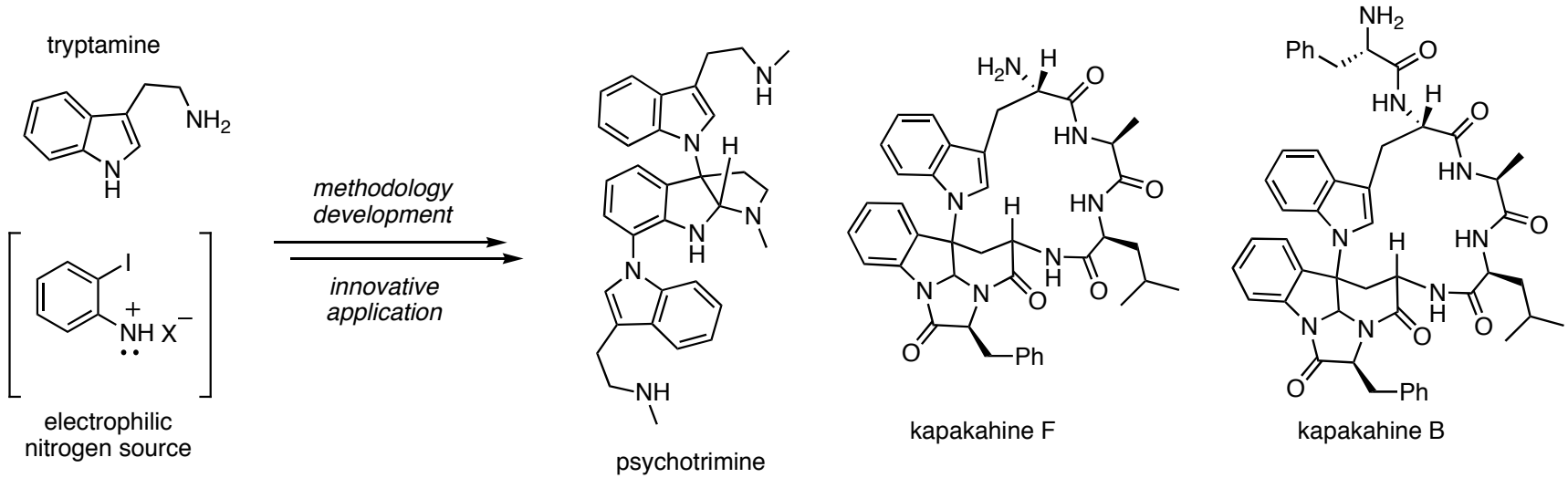
Removal of both the Cbz and benzyl groups allow equilibrium between **136** and **138**

# Kapakahines B and F




[a] Reagents and conditions: (a) LiOH, THF/$H_2O$/MeOH (40:2:1), 1 h; (b) HATU (4.0 equiv); (c) TFA/DCM (1:6), 0.5 h; (d) LiOH, THF/$H_2O$/MeOH (40:2:1), 1 h; $(COCl)_2$ (4.0 equiv), $Et_3N$ (1.0 equiv), DCM, 1 h; TFA/DCM (1:10), 1 h, 64% (three steps); (e) Boc-Phe-OH (1.2 equiv), EDC (2.0 equiv), HOBt (1.8 equiv), $Et_3N$ (3.0 equiv), DCM 1 h; TFA/DCM (1:10), 1 h, 81% (two steps).

# Conclusions




Biological data on synthetic natural products:

Kapakahines B and F did not possess significant cytotoxicity in the NCI 60-cell line

Kapakahine B had an $IC_{50}$ value of 11.7 μM for breast cancer cells (tested by BMS)

Psychotrimine showed broad biological activity between 1.3 and 40 μM in the NCI 60-cell line

*This methodology not only broadens our understanding of chemical reactivity, but allows access to complex molecules in quantities that would otherwise be unavailable from traditional isolation practices*