# Literature Report 6

# Eight-Step Total Synthesis of Phalarine

**Reporter:** **Zi-Biao Zhao**
**Checker:** **Xiao-Yong Zhai**
**Date:** **2019-5-27**

Li, L.; Yuan, K.; Jia, Q.; Jia, Y.*
*Angew. Chem. Int. Ed.* **2019**, *58,* 6074.

# CV of Prof. Yanxing Jia

## *Background:*

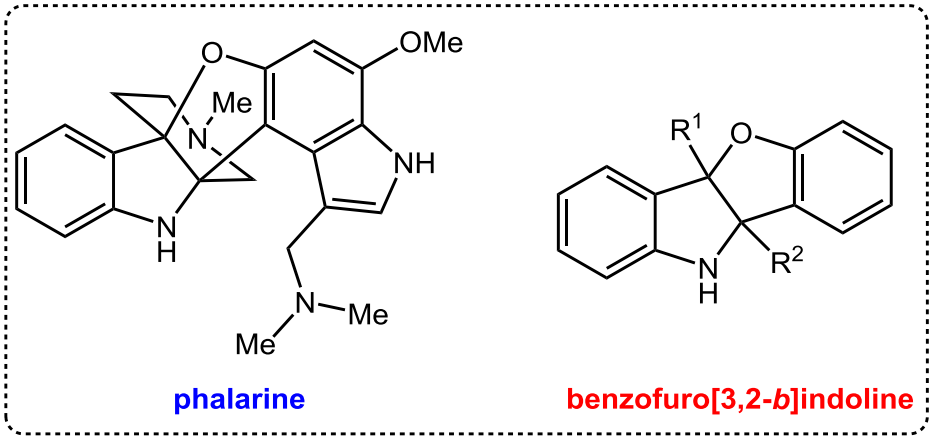
- **1993-1997** B.S., Lanzhou University
- **1997-2002** Ph.D., Lanzhou University (Tu, Y.-Q)
- **2002-2007** Postdoc., French National Research Center
- **2007-2011** Associate Professor, Peking University
- **2011-Now** Professor, Peking University

## *Research:*

- Total synthesis and biomimetic synthesis of natural products.
- Drug synthesis and structure-activity relationship.
- New methods and strategies for organic synthesis.

# Contents

# Introduction



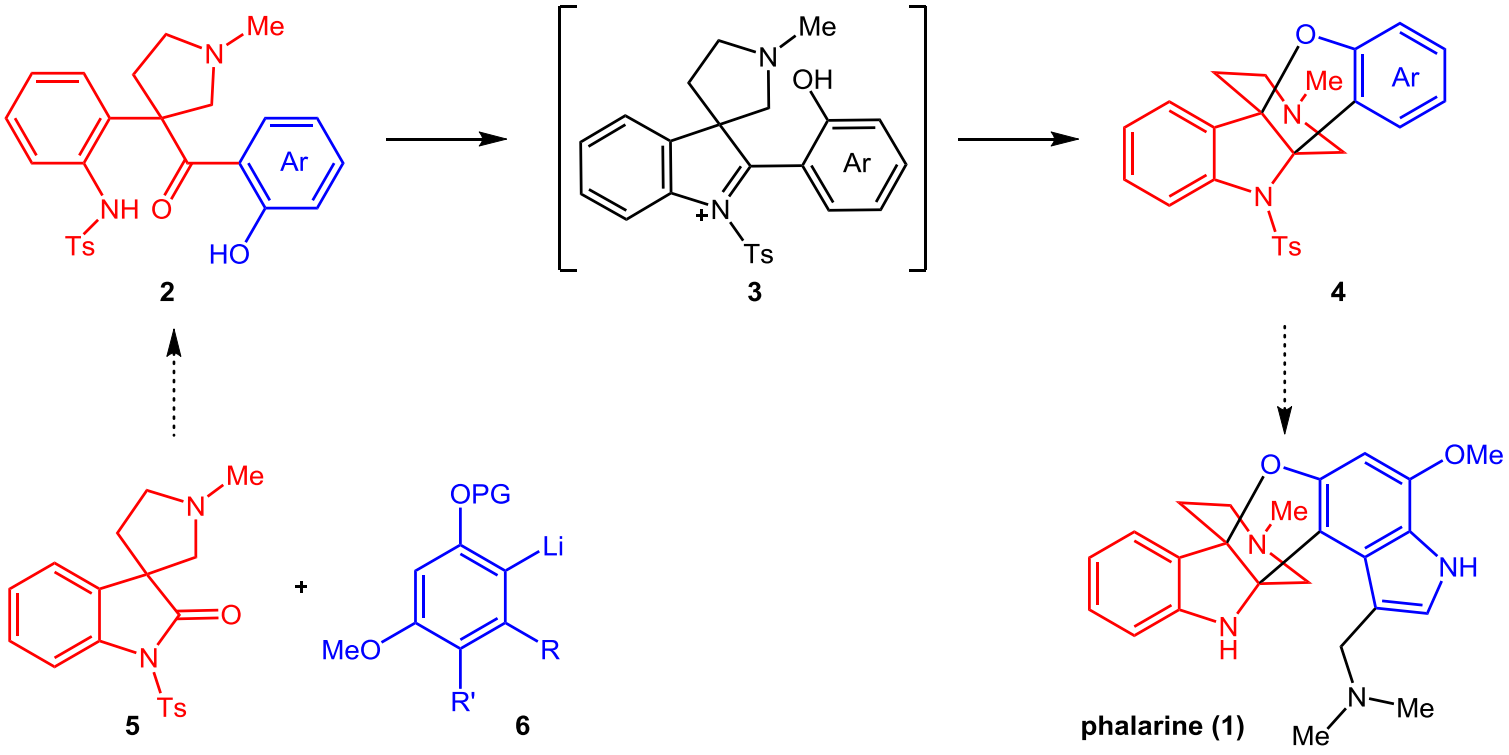

**phalarine** **benzofuro[3,2-*b*]indoline**

(Phalaris coerulescens)

- Phalarine was isolated from Phalaris coerulescens by Colegate in 1999.
- Phalarine possesses an benzofuro[3,2-*b*]indoline moiety, which has not been found in any other natural product .
- The toxicity effect of this new alkaloid is yet to be established.

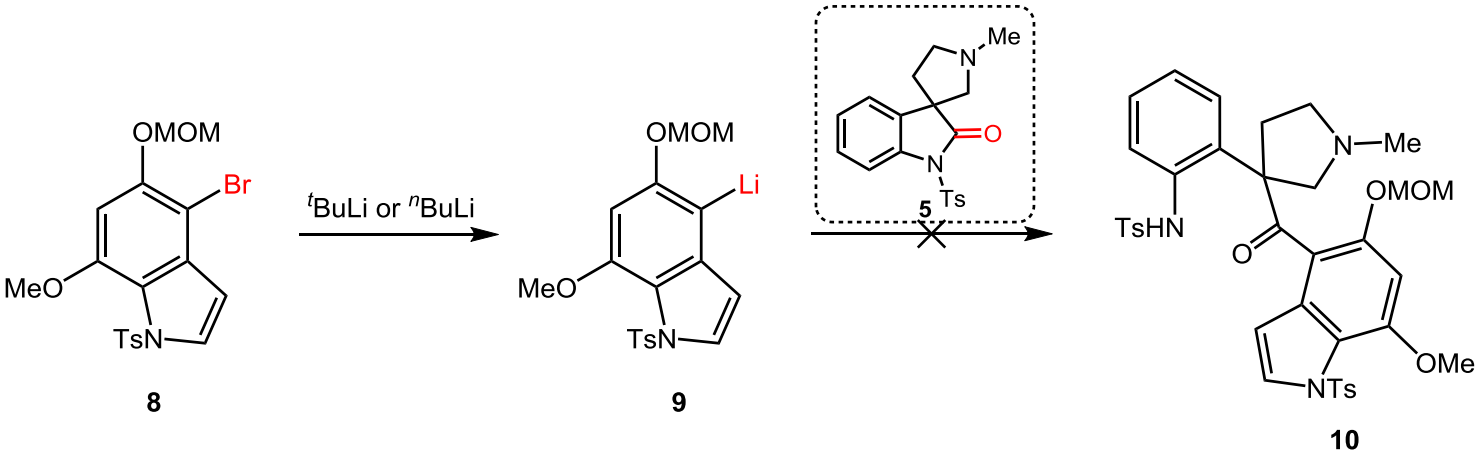
Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153.

# Original Strategy Toward Phalarine

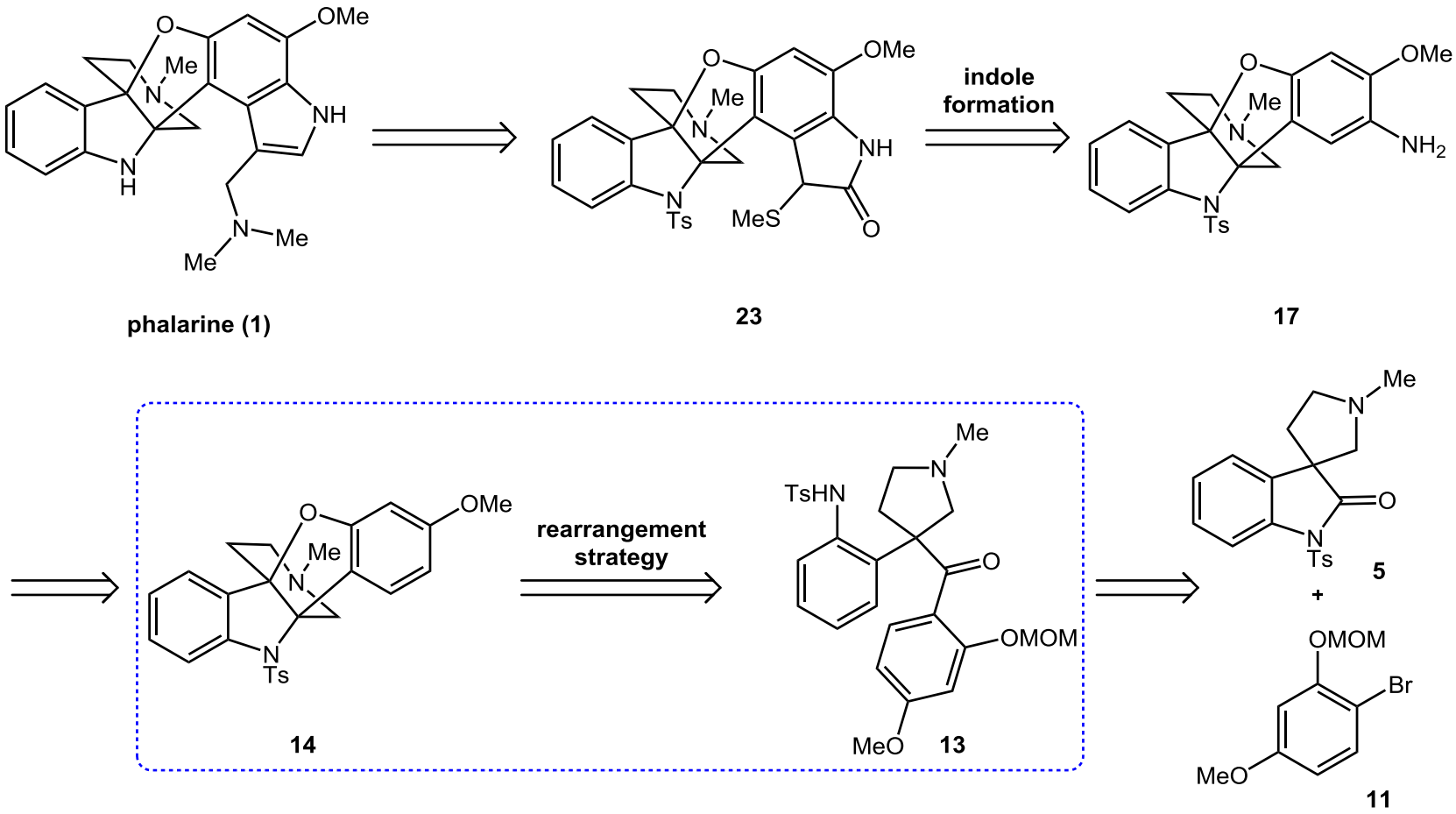



Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46, 1448.*

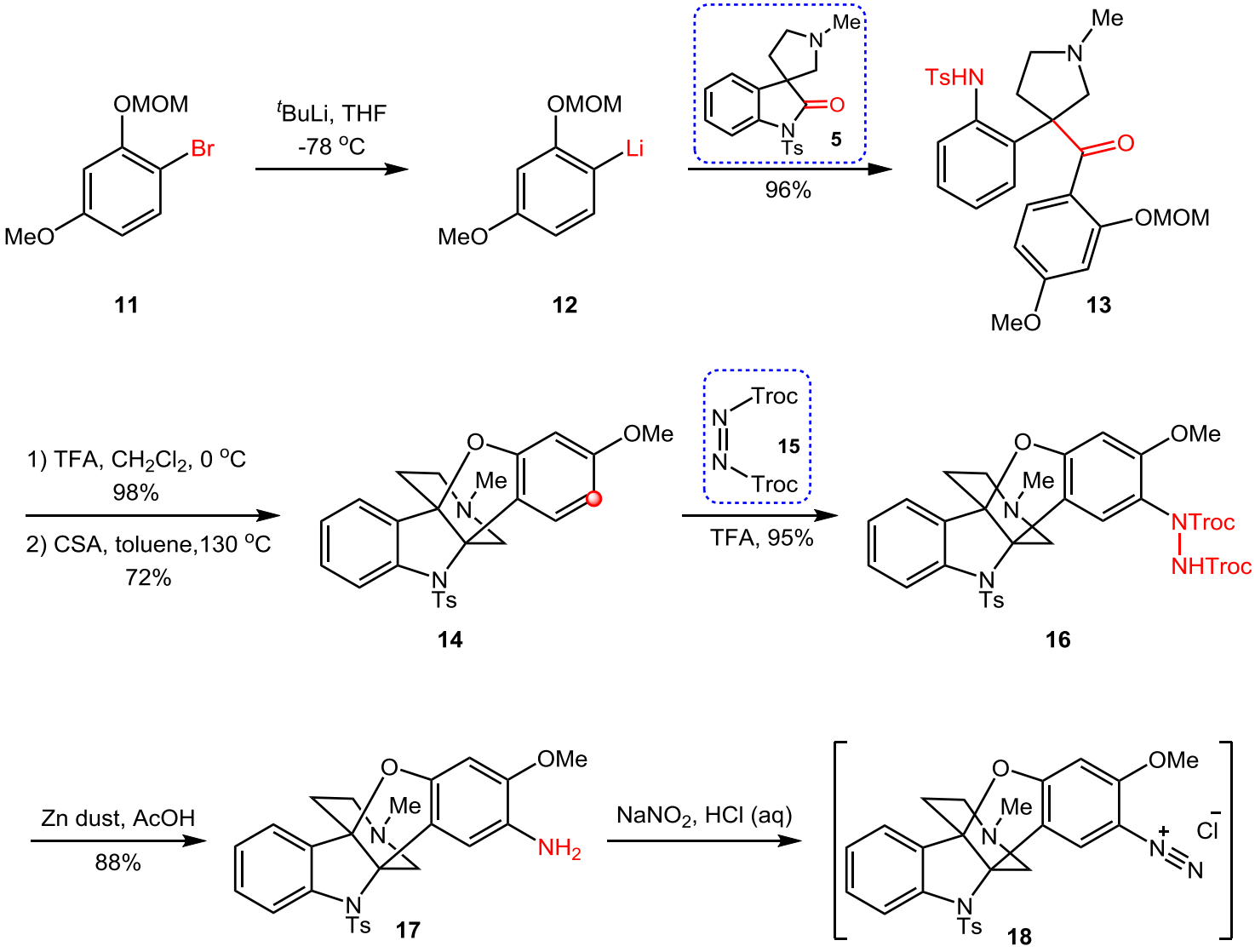
# Preliminary Synthesis



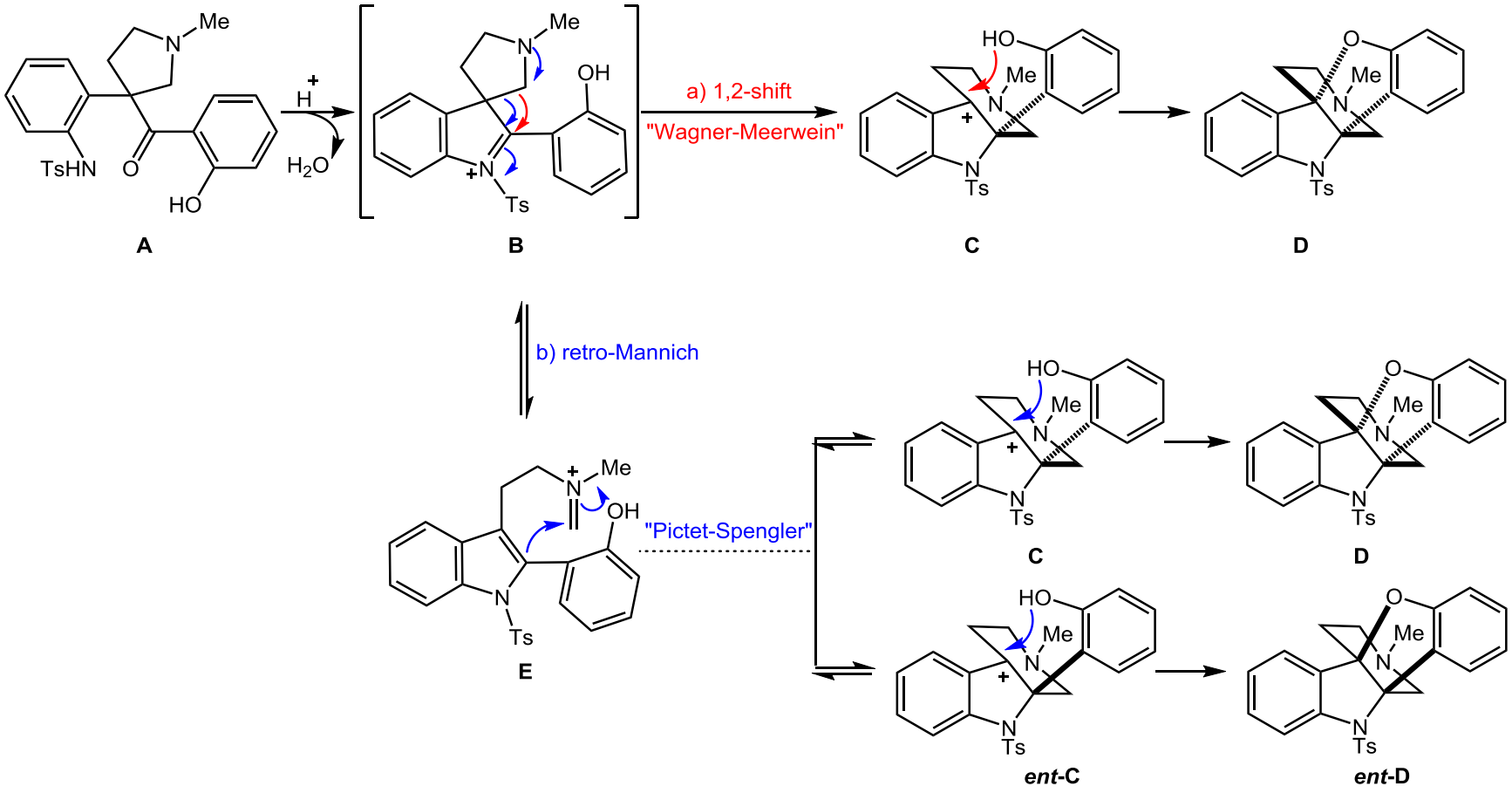
# Retrosynthetic Analysis



# Total Synthesis of Phalarine

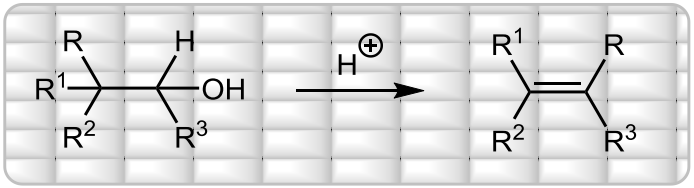


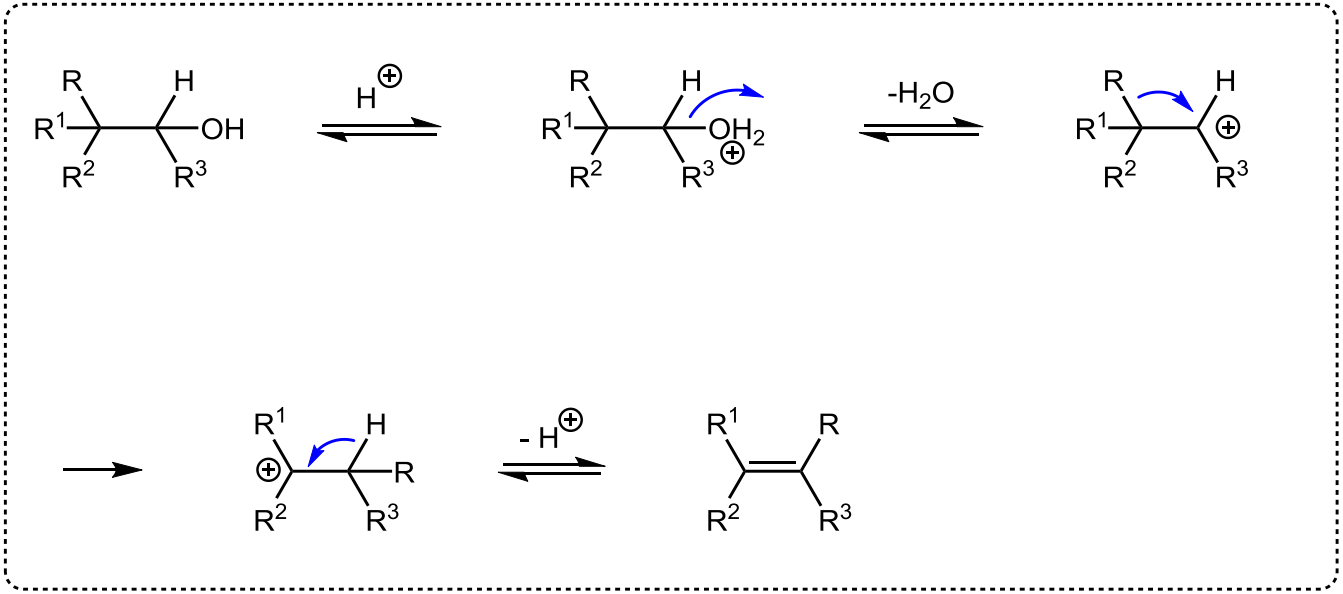
# Possible Mechanistic Pathways of the Rearrangement




Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46, 1444.*

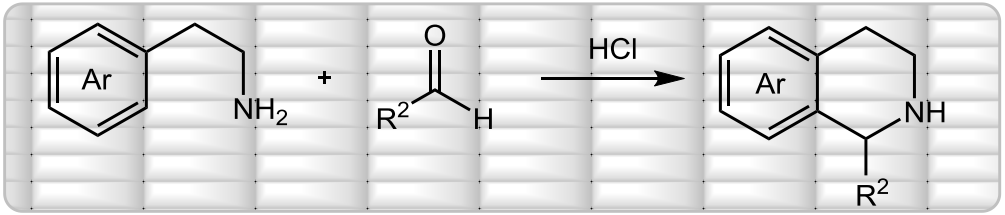
# Wagner-Meerwein Rearrangement

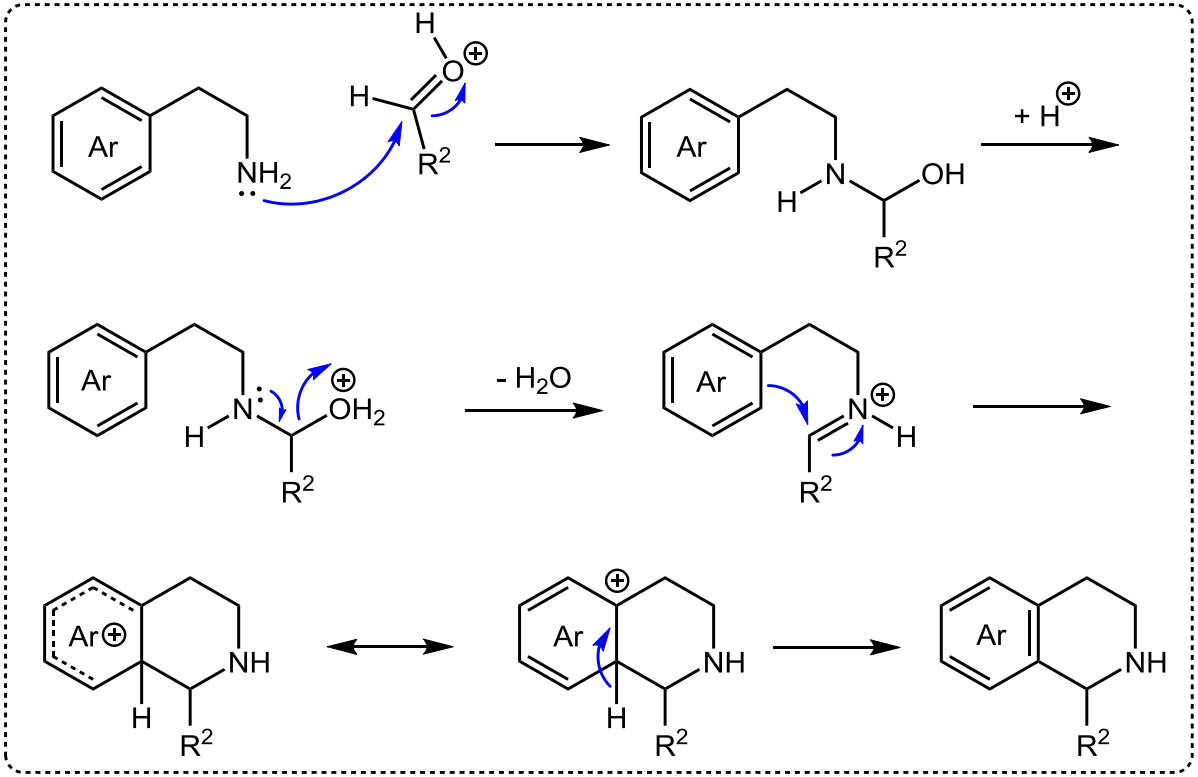



Wagner, G. *J. Russ. Phys. Chem. Soc*. **1899**, *31*, 690.

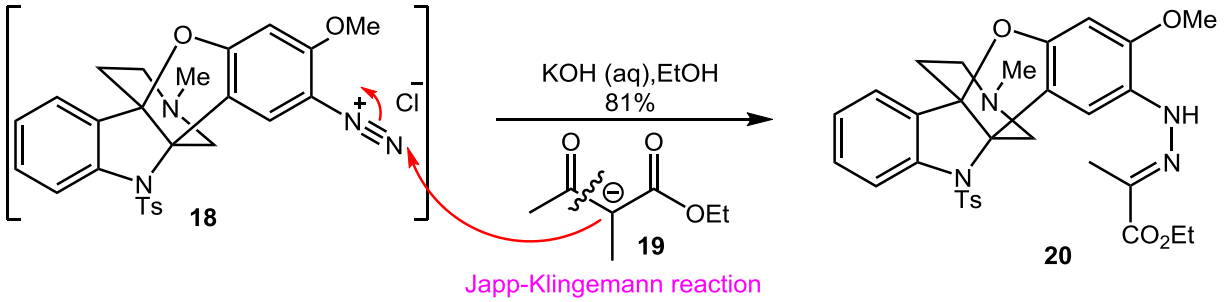
# Pictet-Spengler Reaction

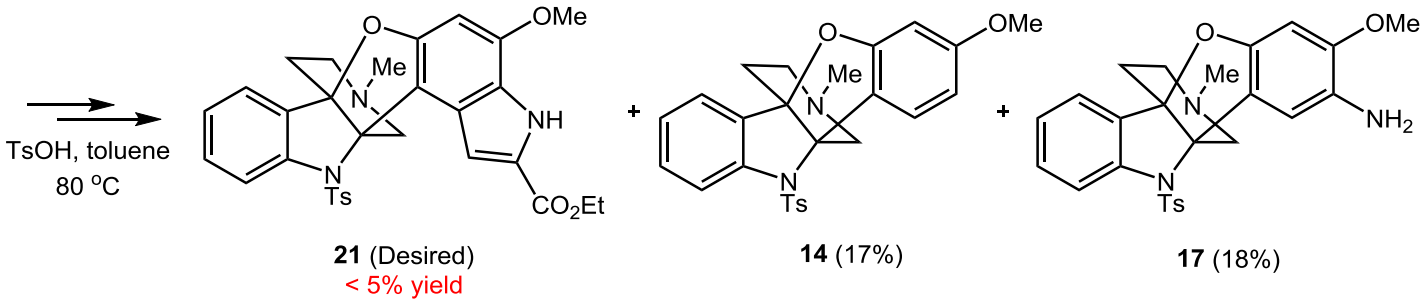


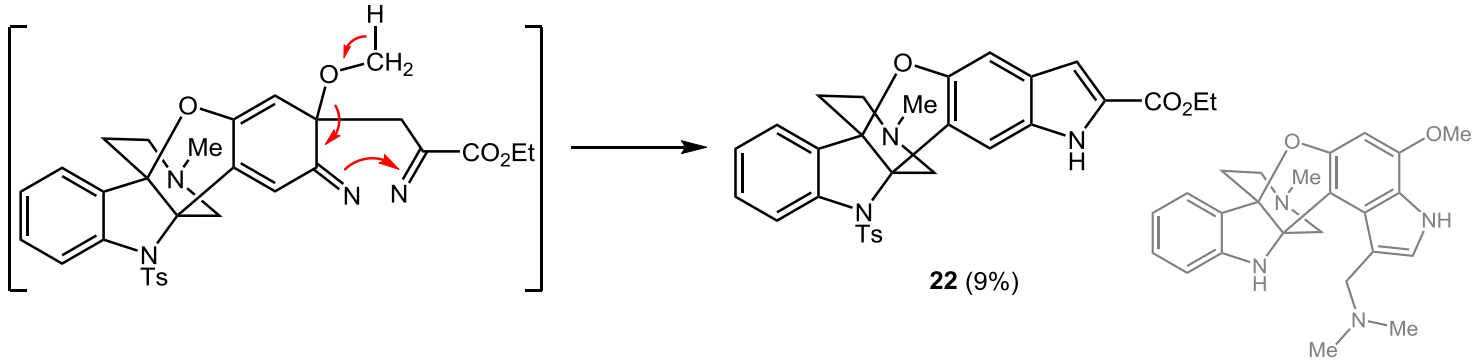




Pictet, A.; Spengler, T. *Ber*. **1911**, *44*, 2030.

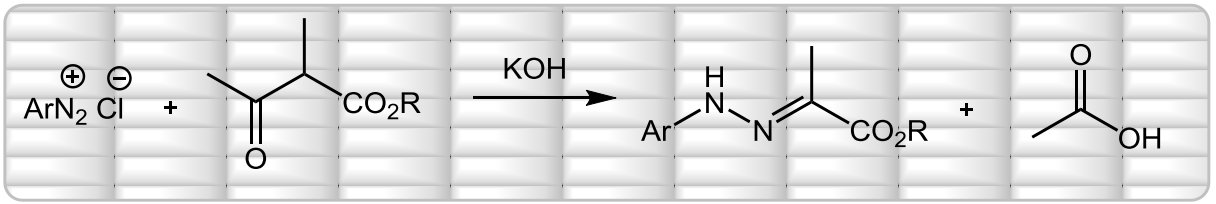
# Total Synthesis of Phalarine

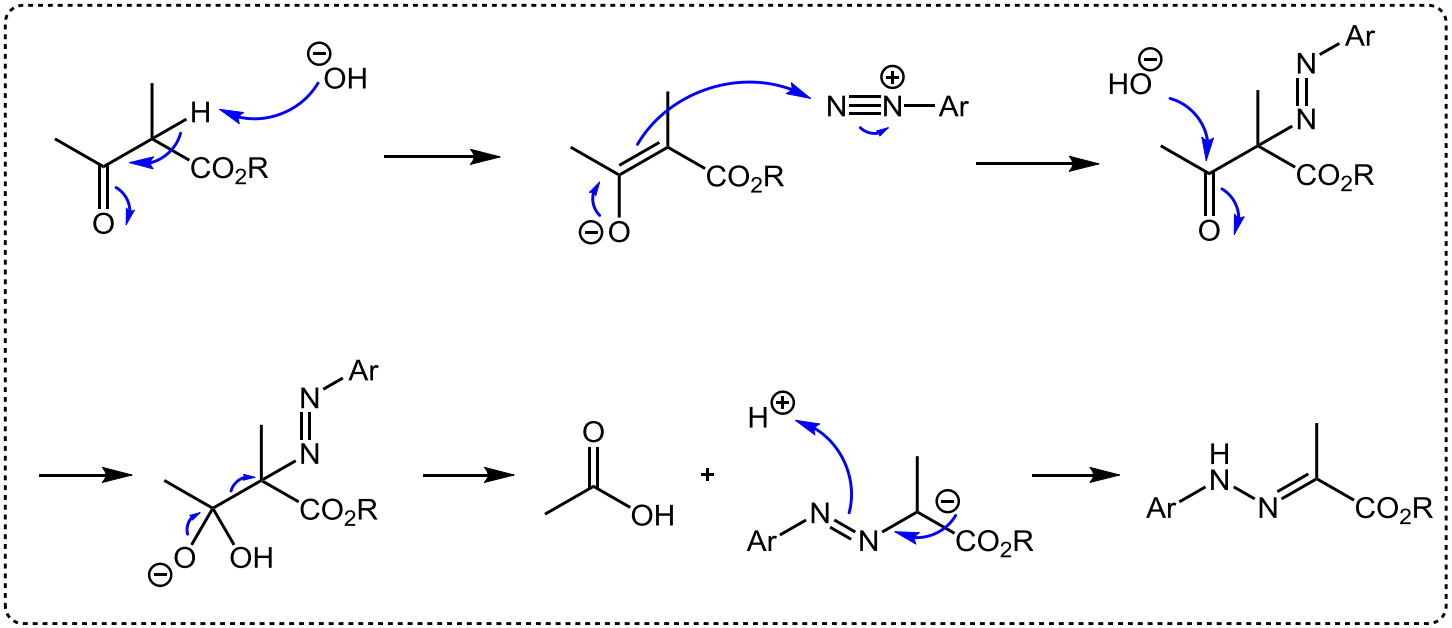


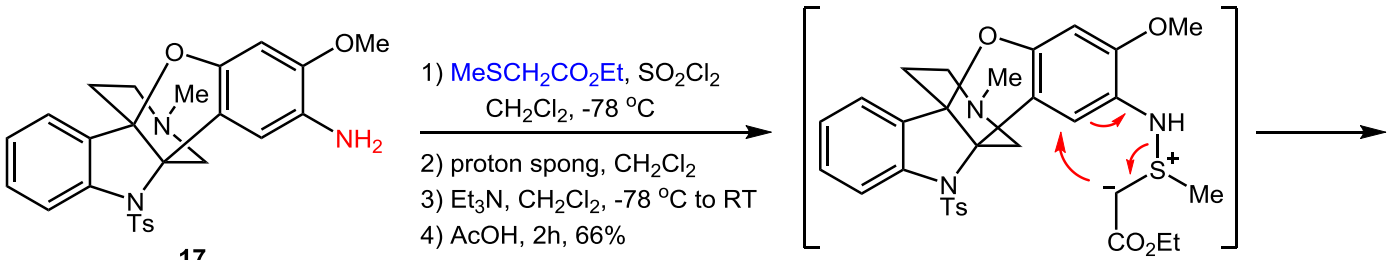
# Japp-Klingemann Reaction

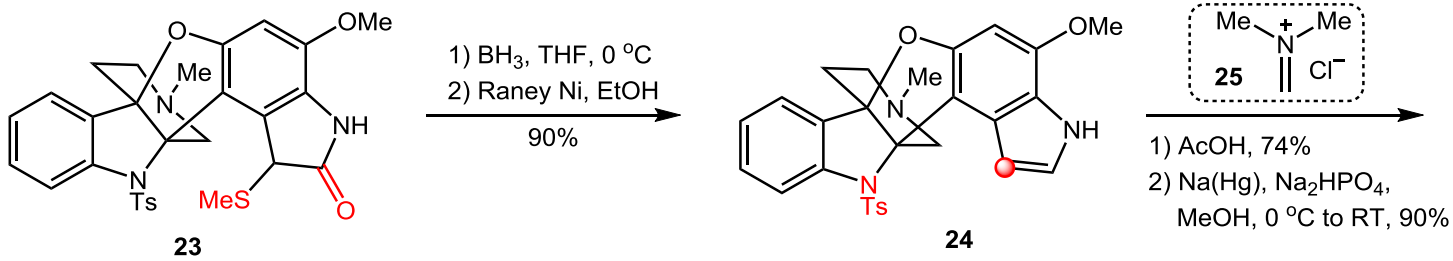


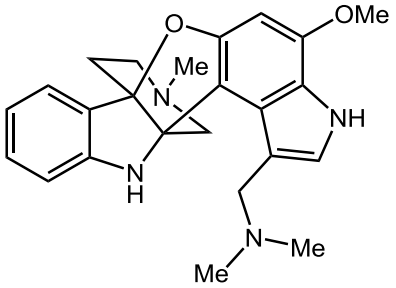




Japp, F. R.; Klingermann, F. *Ber.* **1887**, *20, 2942*.

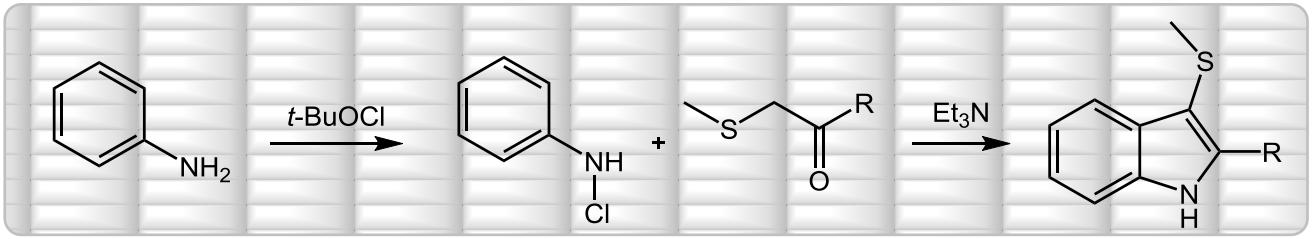
# Total Synthesis of Phalarine

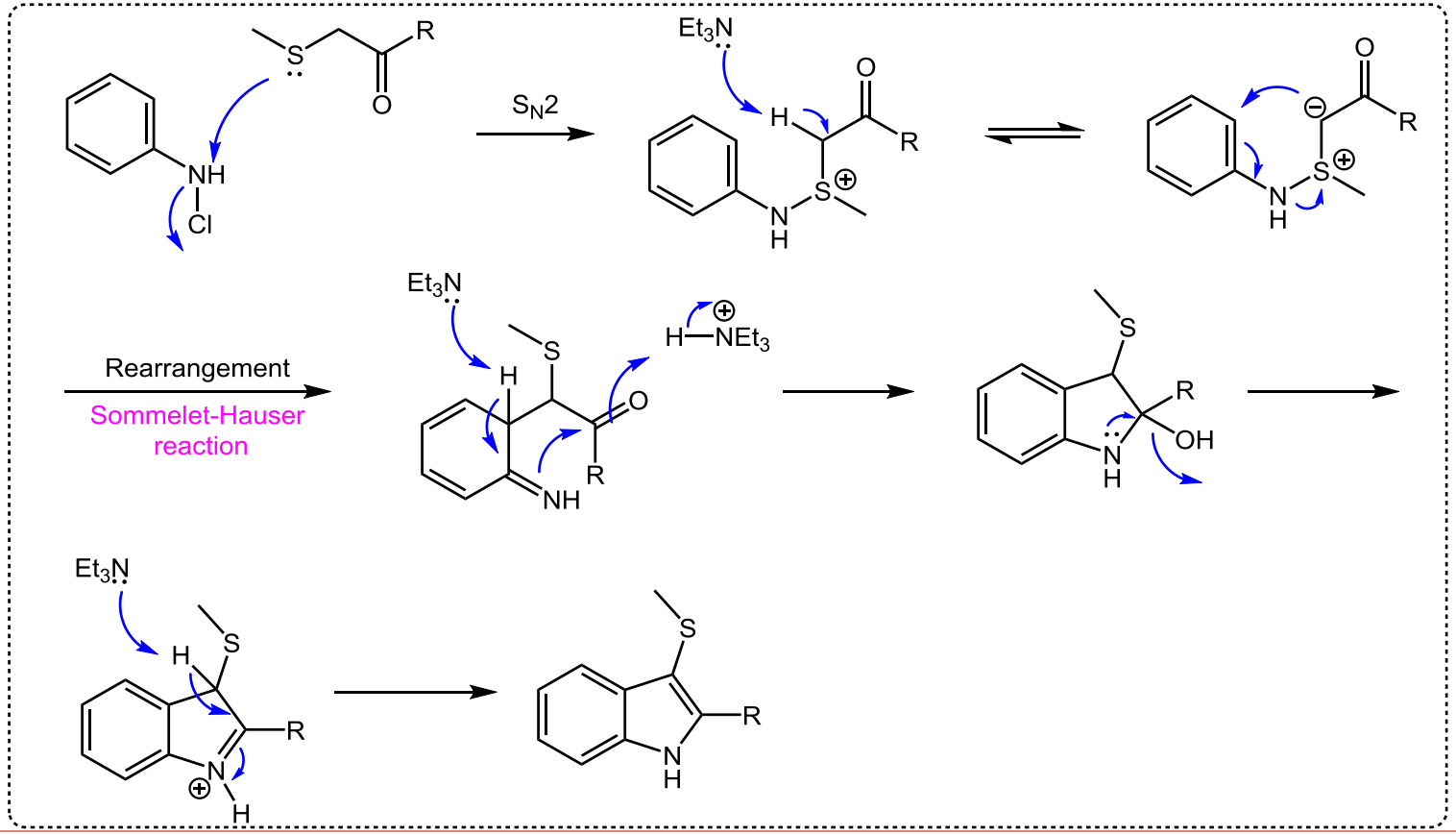


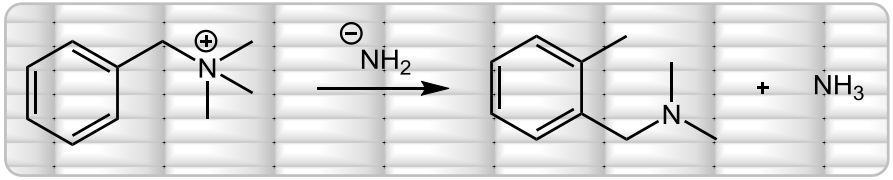



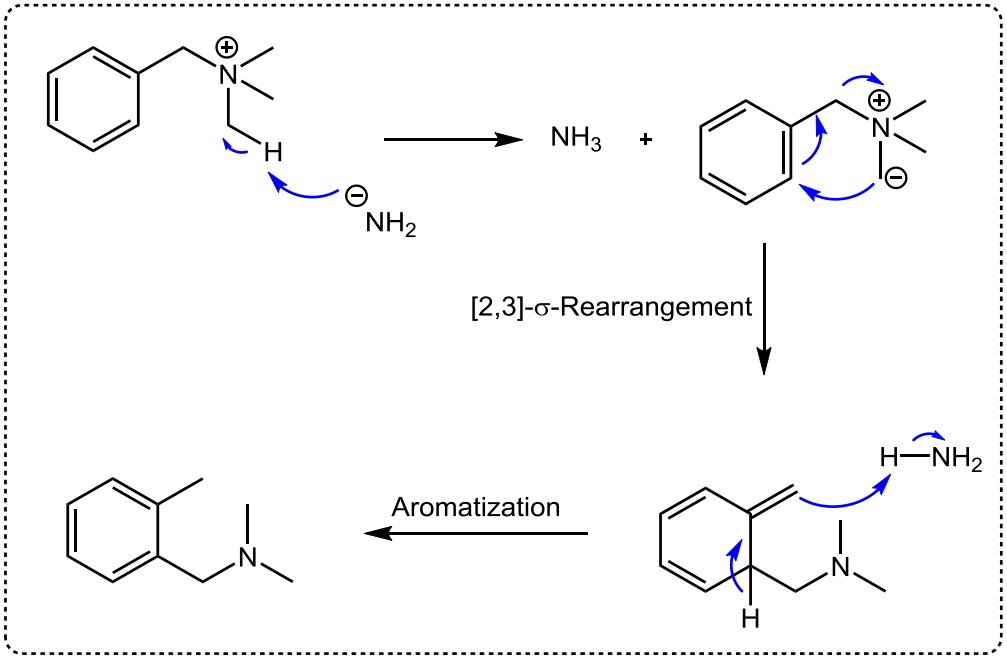
# Gassman Indole Synthesis



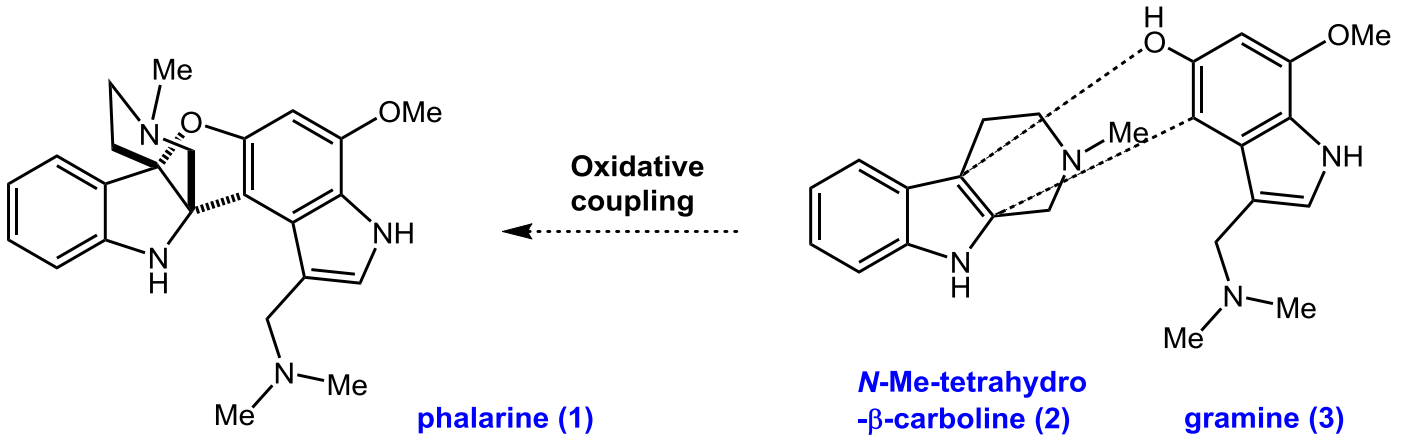
# Sommelet-Hauser Rearrangement




Sommelet, M. *Compt. Rend*. **1937**, *205*, 56.

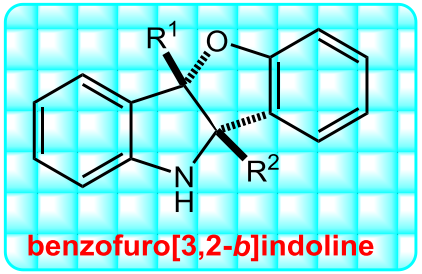
# Structure and Biogenetic Synthesis of Phalarine



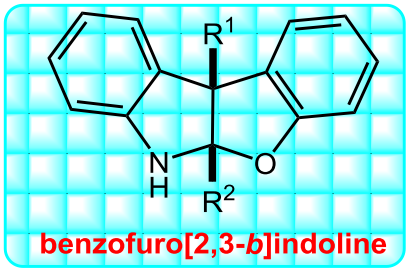

phalarine (1)

*N*-Me-tetrahydro -β-carboline (2)

gramine (3)




benzofuro[3,2-*b*]indoline




benzofuro[2,3-*b*]indoline

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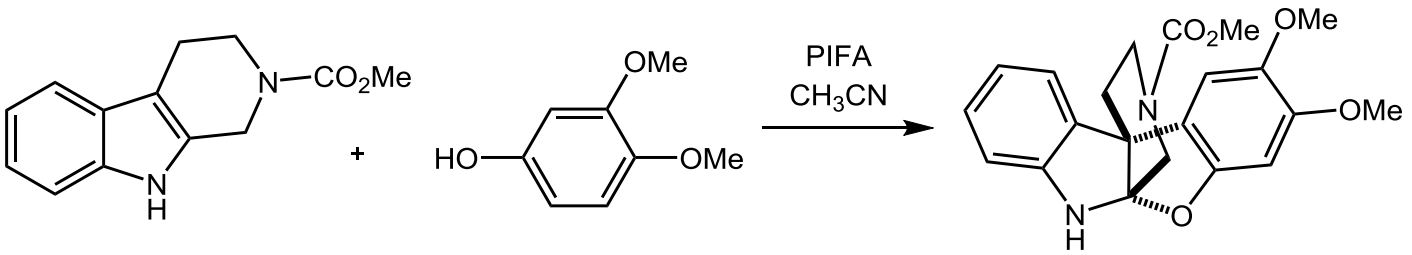
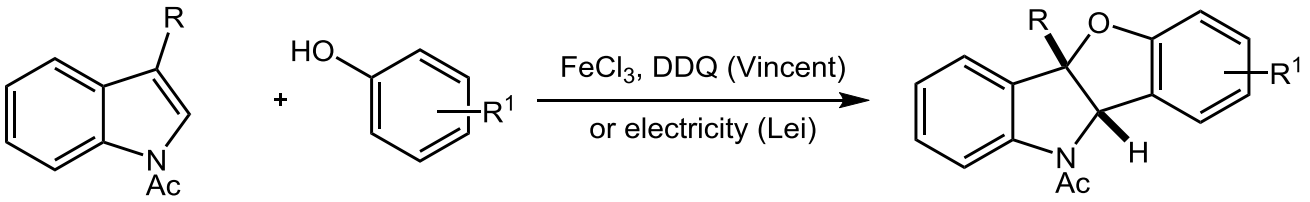
# Previous Work

**a) Danishefsky's initial attempts toward the synthesis of phalarine**




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

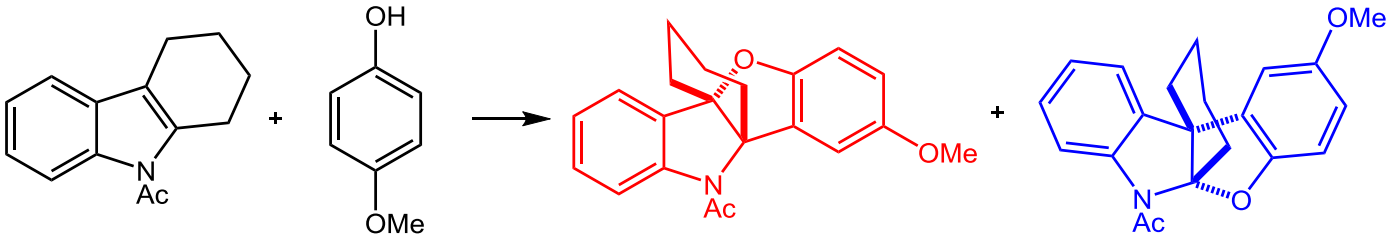
**b) Vincent and Lei's synthesis of benzofuro[3,2-*b*]indoles**




Lei, A. *et al. Nat. Commun*. **2017**, *8*, 775.
Vincent, G. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 11881.

# Previous Work

**c) Vincent and Lei's oxidative coupling of phenol with 2,3-disubstitued indole**

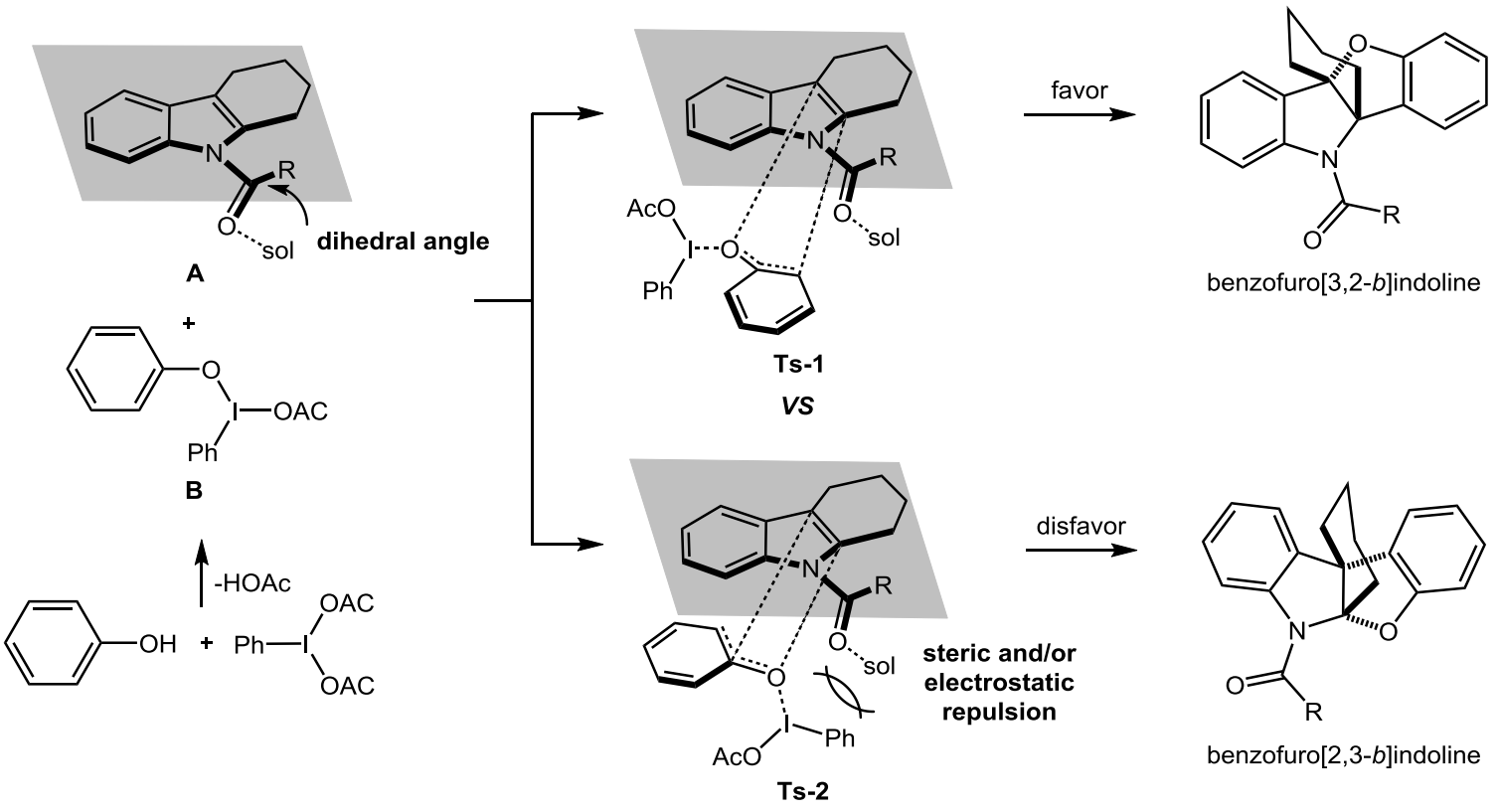



**A** **B**

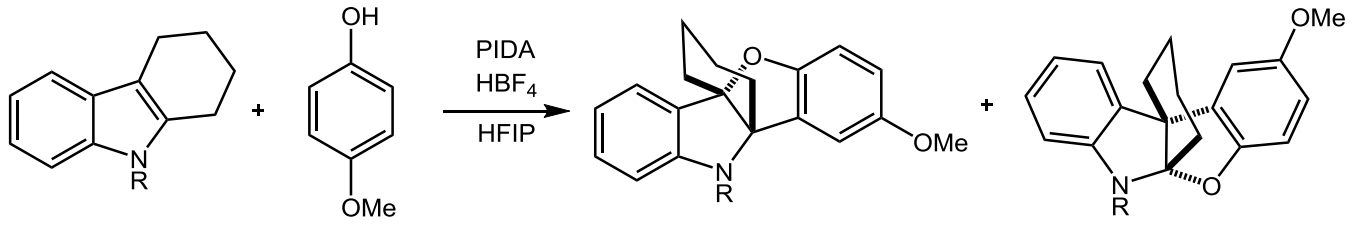
**Vincent**: $FeCl_3$, DDQ; **A**: 4%, **B**: 27%
**Lei**: electricity, ZnCl2; **A**: 25%, **B**: 70%


Lei, A. *et al. Nat. Commun*. **2017**, *8*, 775.
Vincent, G. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 11881.

# Reverse the Regioselectivity



# Screening of Protecting Groups

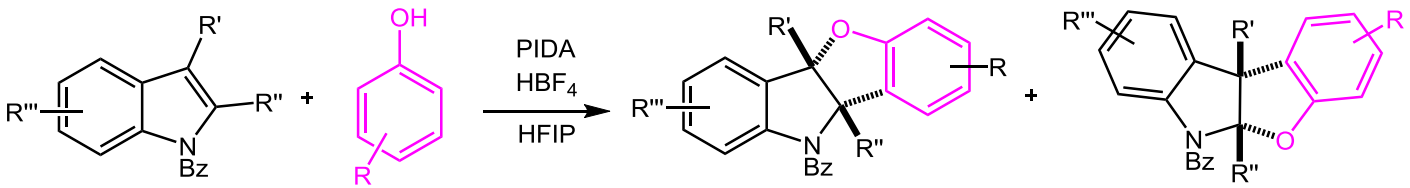



7 8a 9 10

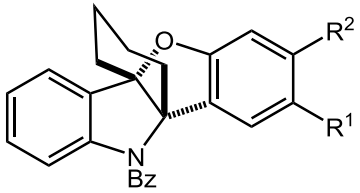
| Entry | Compound | R | Yield (%)[b] | Ratio of **9**:**10** |
|---|---|---|---|---|
| 1 | **7a** | Ac | 97 | 1:6.5 |
| 2 | **7b** | $Cl_3CCO$ | 0 | - |
| 3 | **7c** | Bz | 98 | 1:0.9 |
| 4 | **7d** | Piv | 53 | 1:0.8 |
| 5 | **7e** | acryloyl | 82 | 1:1 |
| 6 | **7f** | Ts | 69 | 1:3.1 |
| 7 | **7g** | Cbz | 45 | 0:1 |
| 8 | **7h** | *p*-Br-Bz | 86 | 1:0.9 |
| 9 | **7i** | *p*-$NO_2$-Bz | 87 | 1:0.9 |
| 10 | **7j** | *p*-MeO-Bz | 95 | 1:1 |
| 11 | **7k** | *o*-Me-Bz | 86 | 1:1.1 |
| 12 | **7l** | 1-naphthoyl | 97 | 1:0.9 |
| 13 | **7m** | 2-naphthoyl | 97 | 1:0.9 |

[a] Reaction conditions: **7** (0.1 mmol), **8a** (0.15 mmol), PIDA (0.15 mmol), $HBF_4$ (0.02 mmol), HFIP (1 mL), RT, 1 min. [b] Yield of isolated product is given.

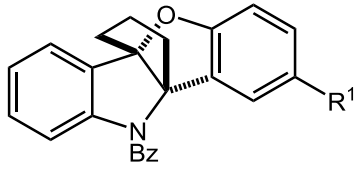
# Substrate Scope of Oxidative Coupling



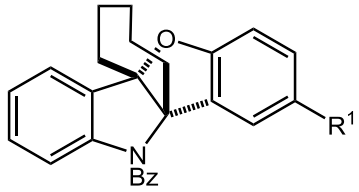

**7c, 11-18** **8a** **9** **10**



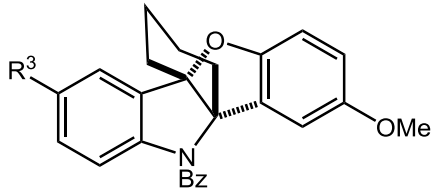

$R^1$ = OMe, $R^2$ = H, **9c**: 52%, **10c**: 46%
$R^1$ = OMe, $R^2$ = Br, **9n**: 40%, **10n**: 13%
$R^1$ = OMe, $R^2$ = F, **9o**: 36%, **10o**: 22%
$R^1$ = OPh, $R^2$ = H, **9p**: 47%, **10p**: n.d.
$R^1$ = H, $R^2$ = H, **9q**: 25%, **10q**: n.d.
$R^1$ = NHTs, $R^2$ = H, **9r**: 87%, **10r**: 8%.
$R^1$ = NHBoc, $R^2$ = H, **9s**: 65%, **10s**: 29%.
$R^1$ = NHAc, $R^2$ = H, **9t**: 83%, **10t**: 13%.
$R^1$ = NHAc, $R^2$ = Cl, **9u**: 64%, **10u**: 17%.
$R^1$ = NHAc, $R^2$ = F, **9v**: 64%, **10v**: 17%.
$R^1$ = $NHCOCF_3$, $R^2$ = H, **9w**: 50%, **10w**: n.d.



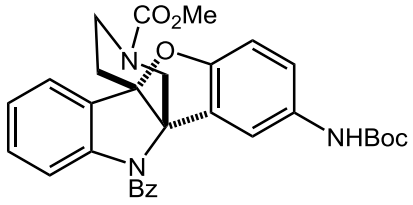

$R^1$ = NHTs, **9x**: 47%, **10x**: 8%.
$R^1$ = NHBoc, **9y**: 54%, **10y**: 40%
$R^1$ = NHAc, **9z**: 50%, **10z**: 42%..




$R^1$ = NHAc, **9aa**: 59%, **10aa**: 36%
$R^1$ = NHTs, **9ab**: 49%, **10ab**: 24%.

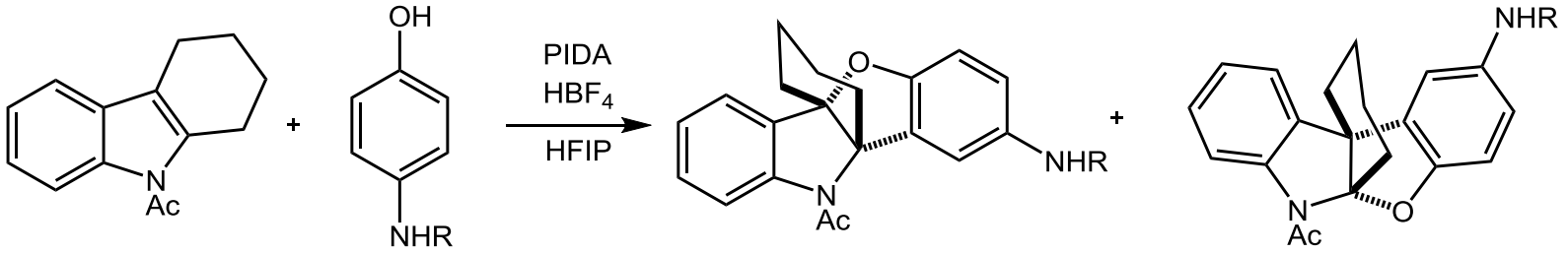



$R^3$ = Cl, **9ac**: 35%, **10ac**: 53%.
$R^3$ = OMe, **9ad**: 12%, **10ad**: 58%.




**9ae**: 25%, **10ae**: n.d.

# Reaction of 7a with *p*-NHAc-phenol and *p*-NHTs-phenol

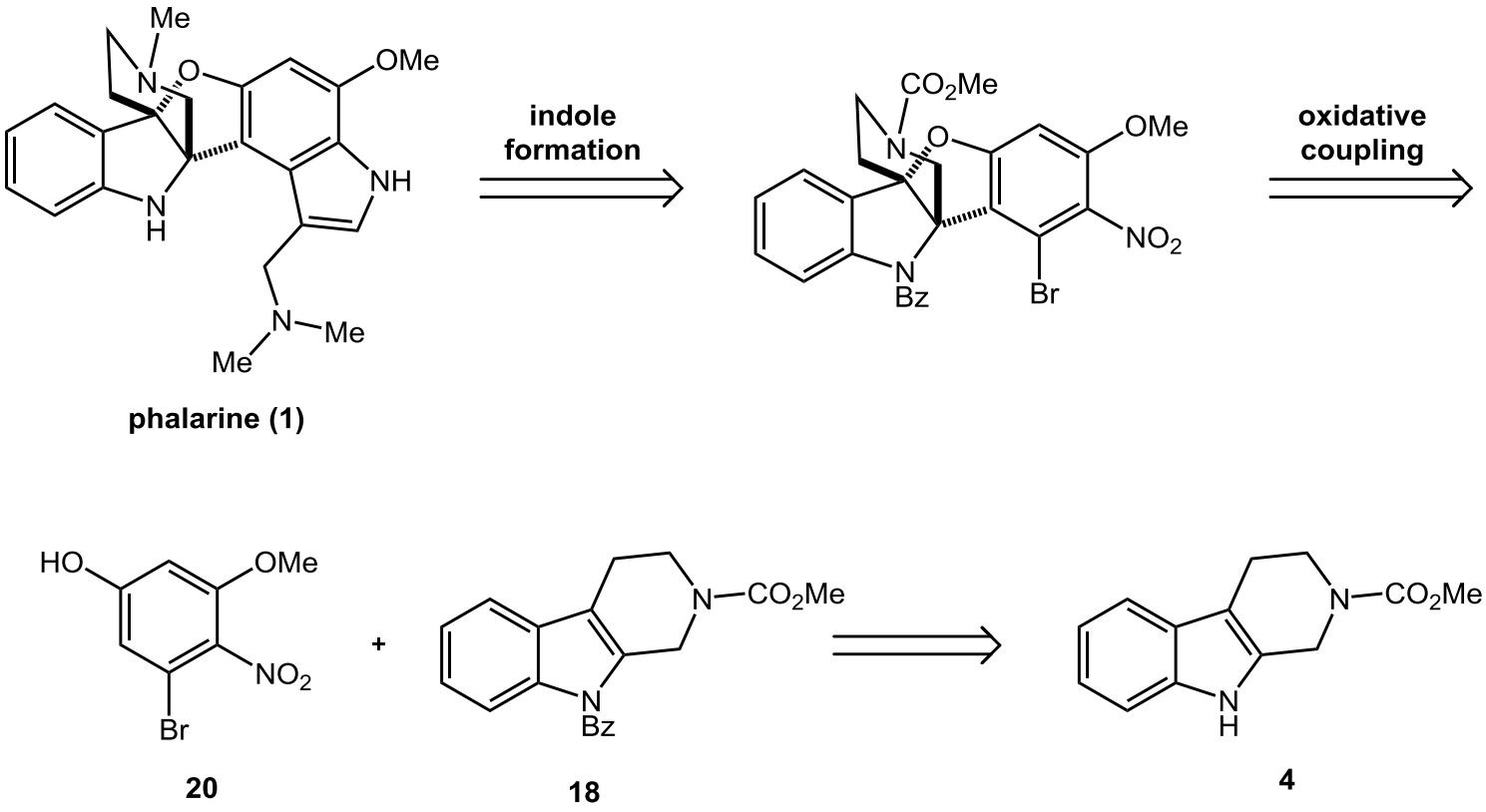



**7a** **8**

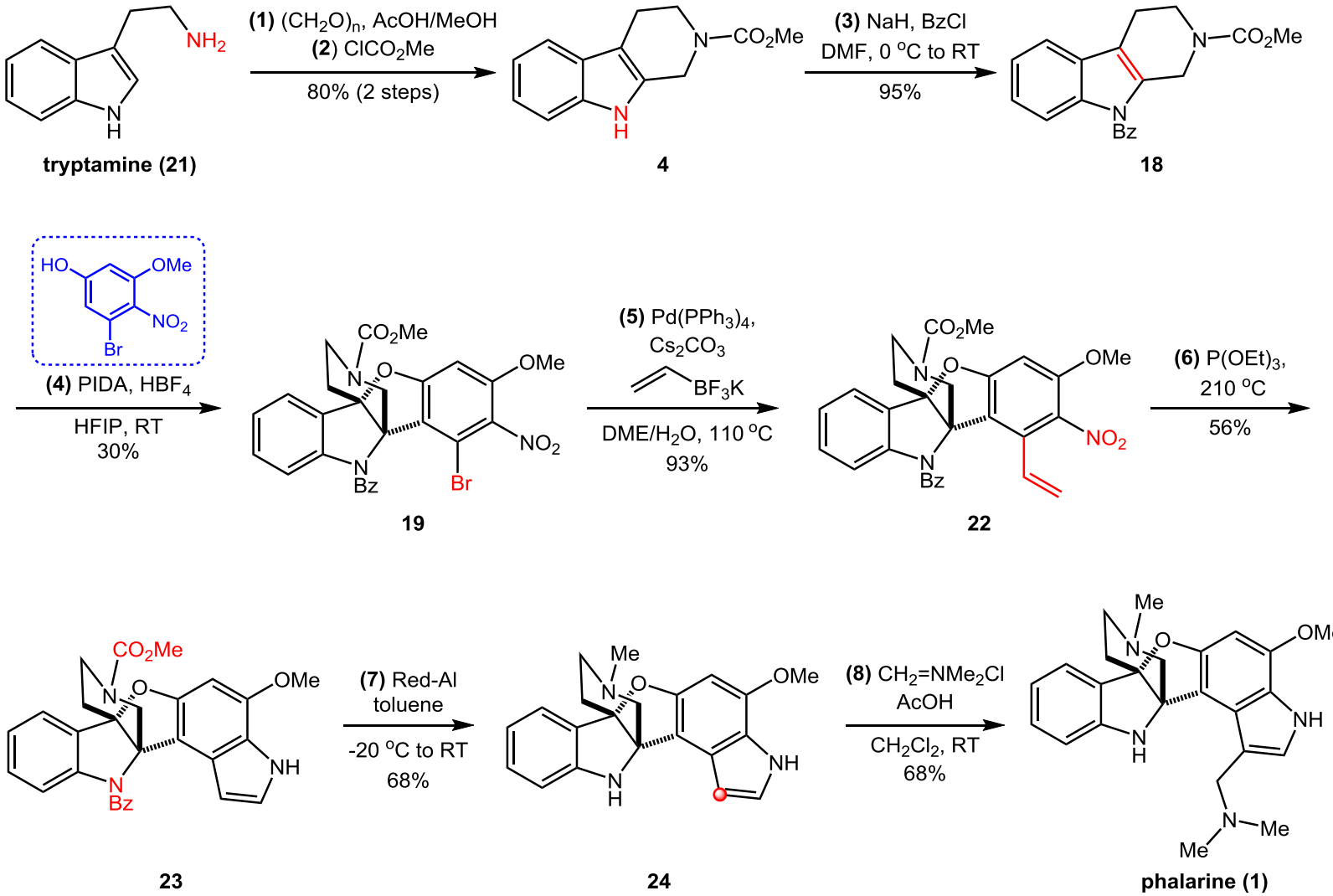
R = Ac, **9aj**: 9%
R = Ts, **9ak**: n.d.

R = Ac, **10aj**: 85%
R = Ts, **10ak**: 71%.

# Retrosynthetic Analysis



# Total Synthesis of Phalarine



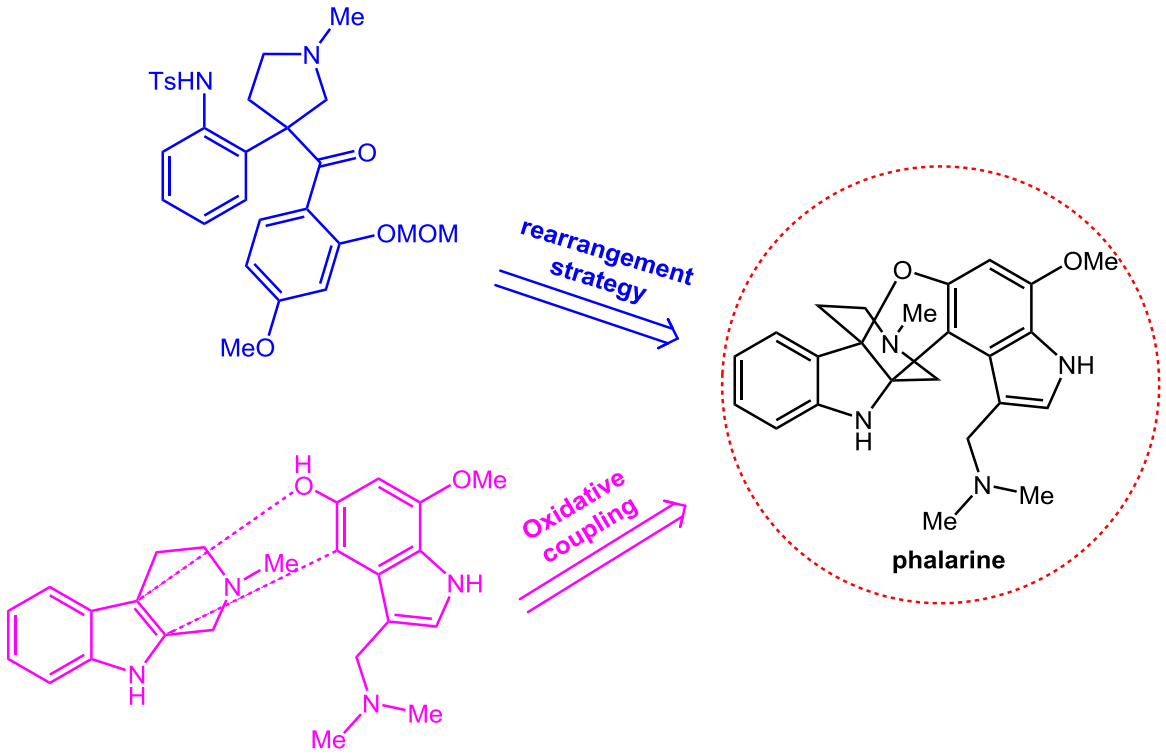
# Summary

**Danishefsky 's Work:**

- 11 steps and 22.4% overall yield
- Rearrangement strategy

**Jia' s Work:**

- 8 steps and 5.49% overall yield
- Oxidative coupling of indole and phenol



# The First Paragraph

During the course of an agronomic investigation of the suitability of introducing Phalaris coerulescens into Australia, Colegate and co-workers isolated and identified a novel furanobisindole alkaloid, named phalarine. Structurally, **1** possesses an unprecedented benzofuro[3,2-*b*]indoline moiety, which has not been found in any other natural product. However, its regioisomeric benzofuro[2,3-*b*]indoline moiety is found in natural products such as diazonamide A and azonazine. Biogenetically, **1** is postulated to arise from the direct oxidative coupling of *N*-Me-tetrahydro-β-carboline with 5-hydroxy-7-methoxygramine since **2** has been previously isolated from Phalaris coerulescens.

# The Last Paragraph

In summary, we have addressed the challenge of the regioselectivity of the direct oxidative coupling reaction between indoles and phenols to construct the benzofuro[3,2-*b*]indolines. The resulting method enabled us to accomplish the total synthesis of phalarine in only eight steps from commercially available tryptamine. This synthesis represents the shortest pathway for the total synthesis of phalarine to date.

# Acknowledgement

Thanks
for your attention