

Literature Report VII

Rapid Access to 2,2-Disubstituted Indolines via Dearomative Indolic-Claisen Rearrangement: Concise, Enantioselective Total Synthesis of (+)-Hinckdentine A

Reporter: Tong Niu

Checker: Bao-Qian Zhao

Baidilov, D.; Elkin, P. K.; Athe, S.; Rawal, V. H. *J. Am. Chem. Soc.* 2023, 145, 14831

● 2023.09.11 ●

CV of Prof. Viresh H. Rawal

Research:

- ❑ Discovering new ways to make complex molecules
 - ❑ Development of effective catalysts for enantioselective reactions
-



Education & Professional Experience:

- ❑ **1980** B.S., University of Connecticut
- ❑ **1986** Ph.D., University of Pennsylvania
- ❑ **1986-1988** Postdoc., Columbia University
- ❑ **1988-1994** Assistant Professor, OSU
- ❑ **1994-1995** Associate Professor, OSU
- ❑ **1995-** Professor, The University of Chicago

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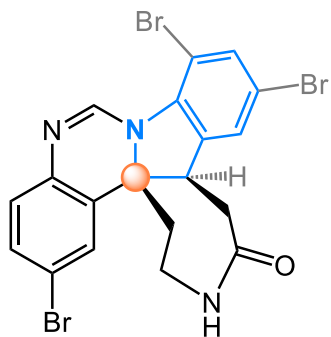
2 Dearomative Indolic-Claisen Rearrangement

3 Enantioselective Total Synthesis of (+)-Hinckdentine A

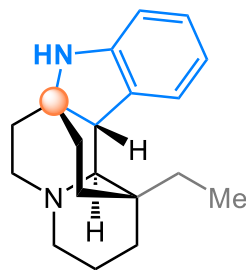
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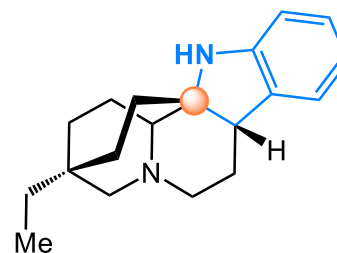
Indoline Alkaloids Possesing Disubstitution at C2-Position



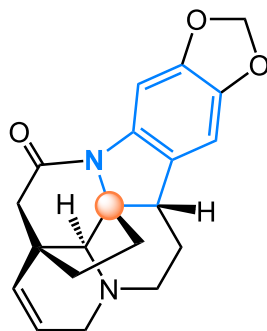
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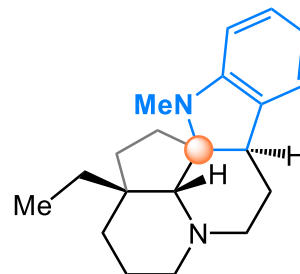
Melonine (1983, 2a)
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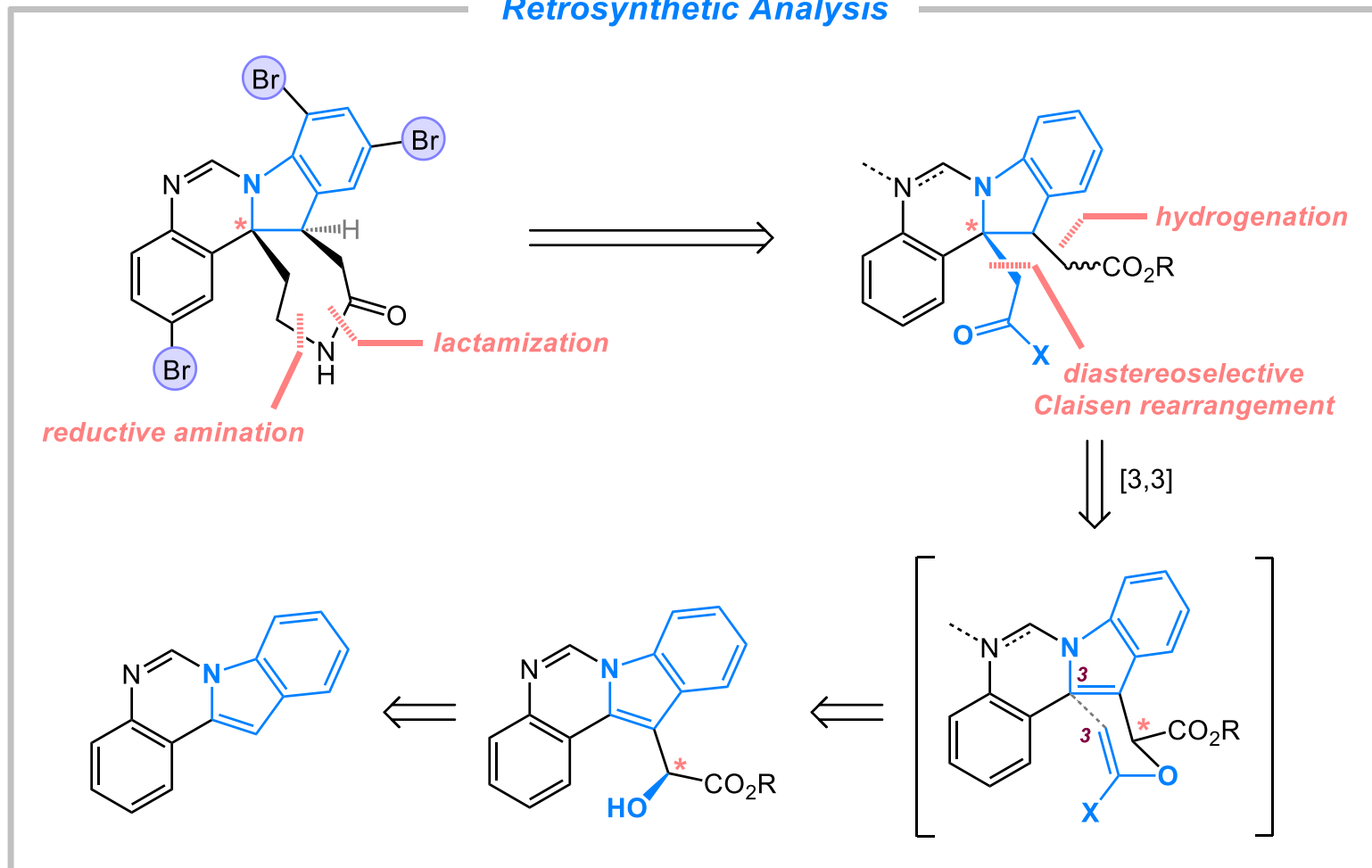
Vallesamidine (4)

Disubstitution at C3 & Fully Substituted Indoline—Well Developed
2,2-Disubstituted Indolines—Less Developed

Wang, X.; Wang, Y.; Li, X.; Yu, Z.; Song, C.; Du, Y. *RSC Med. Chem.* **2021**, 12, 1650

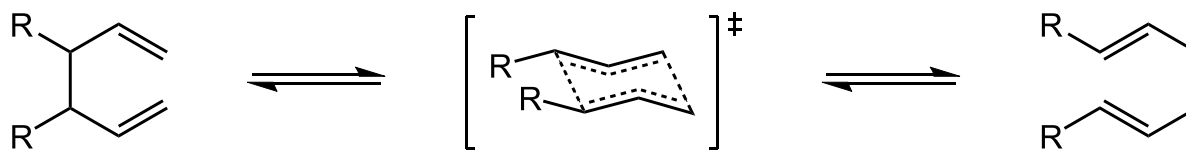
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Retrosynthetic Analysis

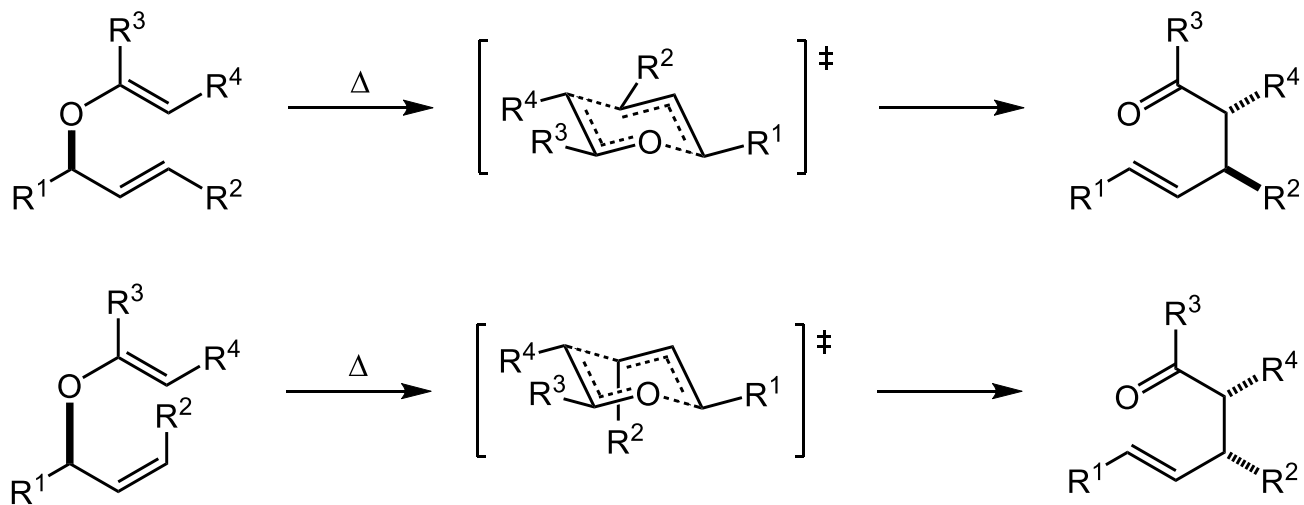


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Cope Rearrangement

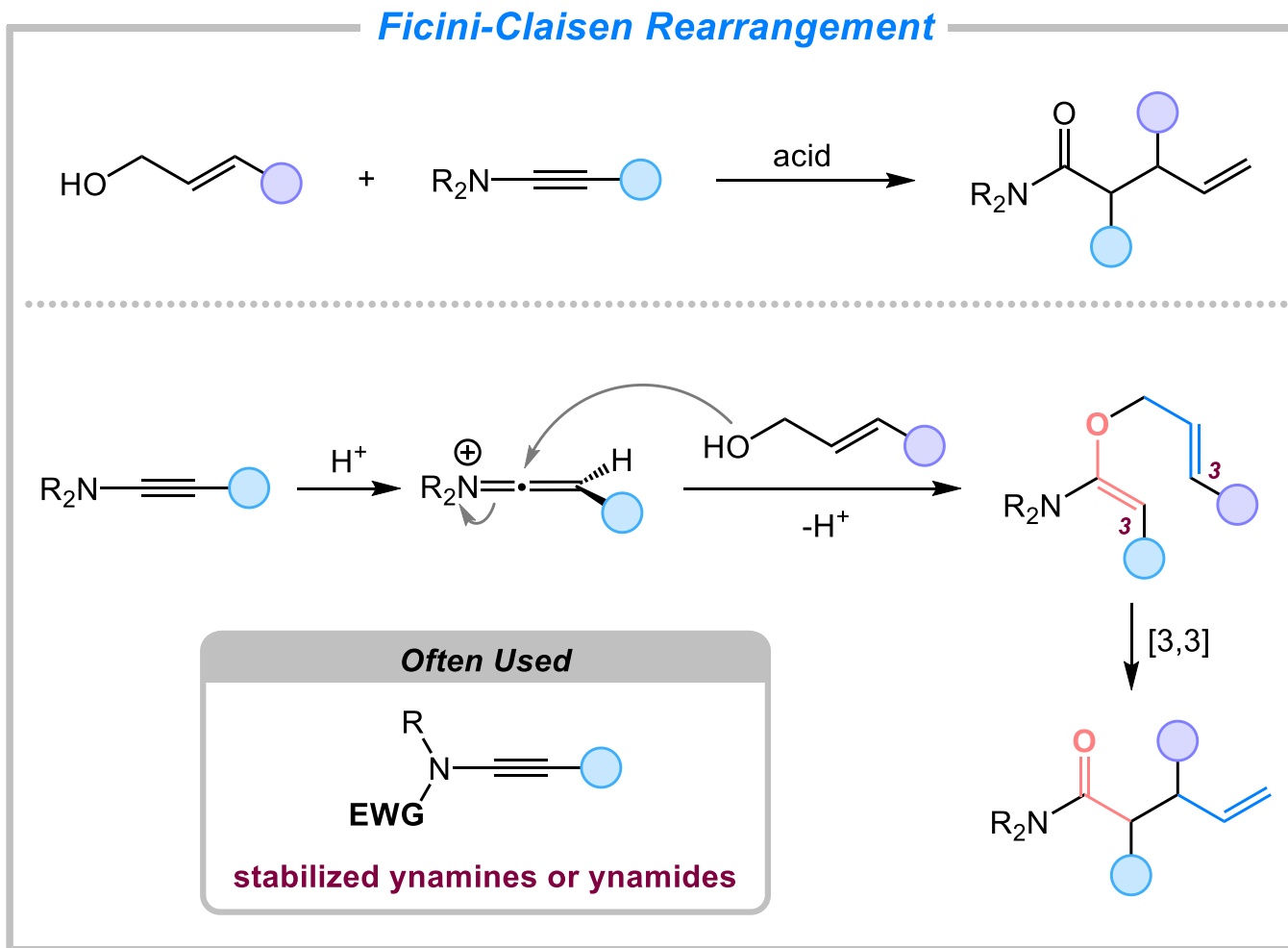


Claisen Rearrangement



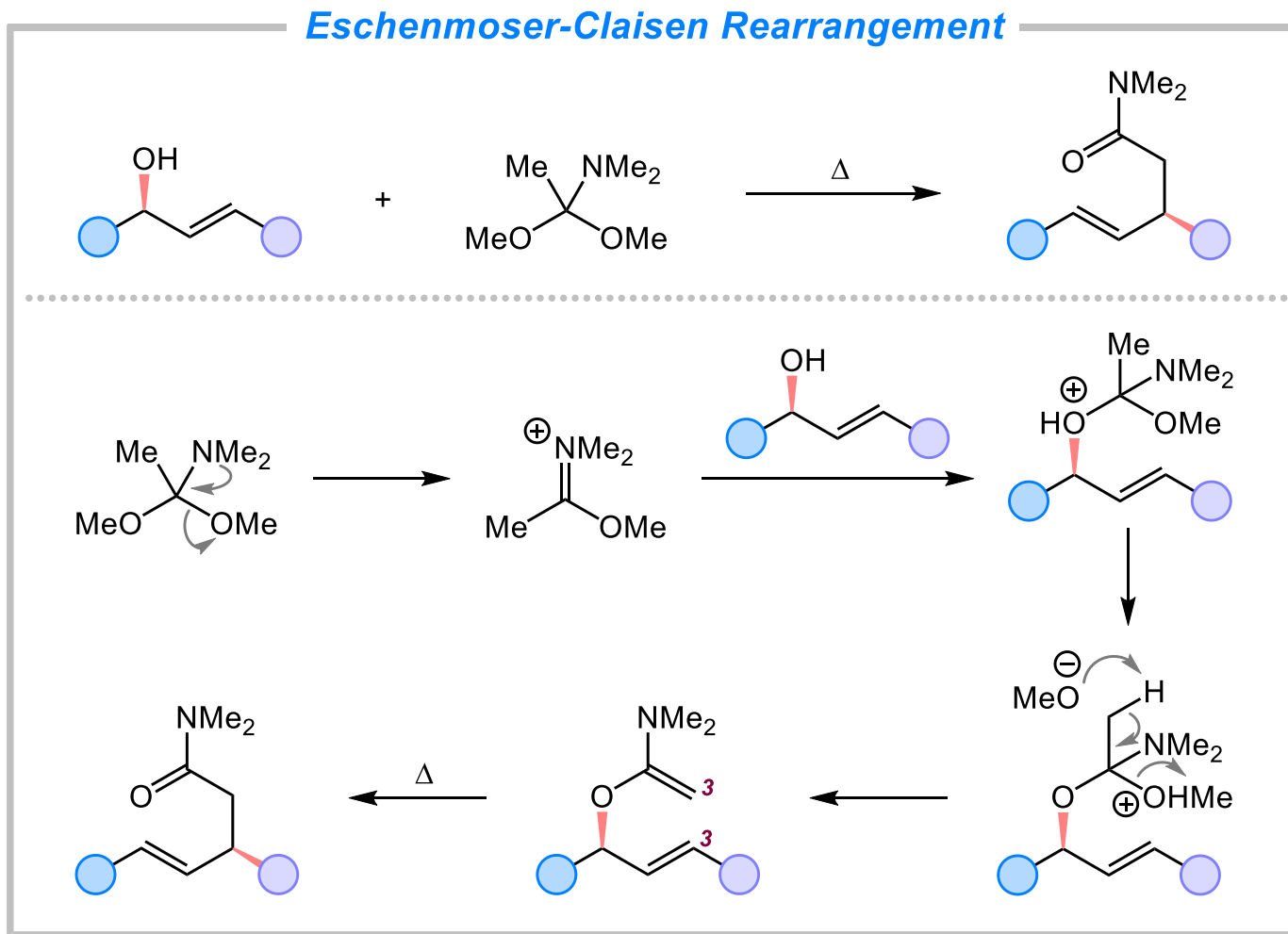
From Name Reaction

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Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zifcick, C. A. *Org. Lett.* **2002**, 4, 1383

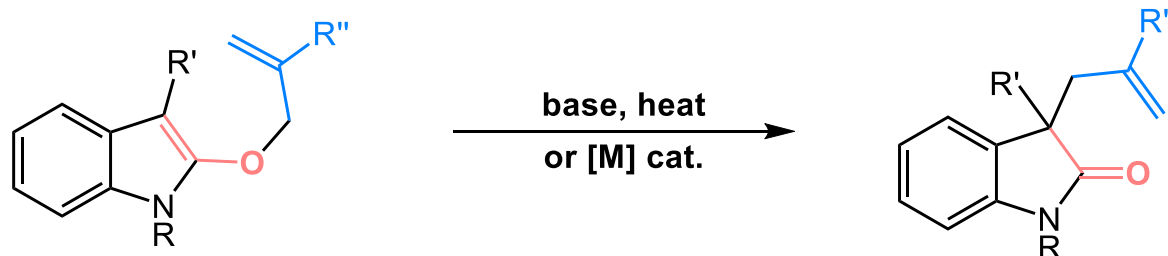
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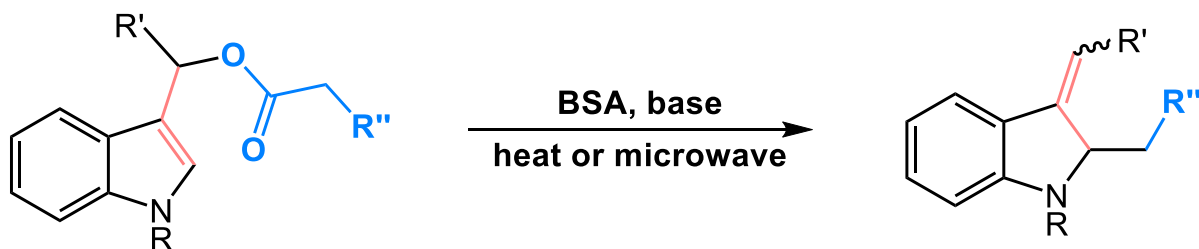
Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, 47, 2425

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Precedents for Dearomative Indolic Claisen Rearrangement



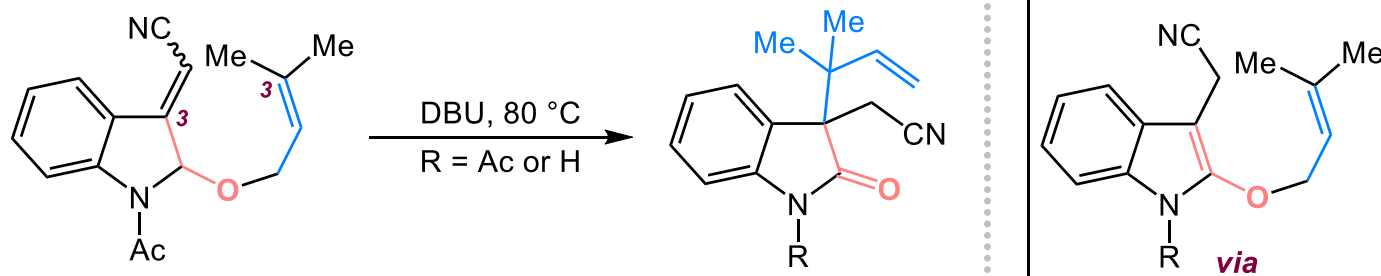
◆ Formation of the carbonyl group provides strong driving force



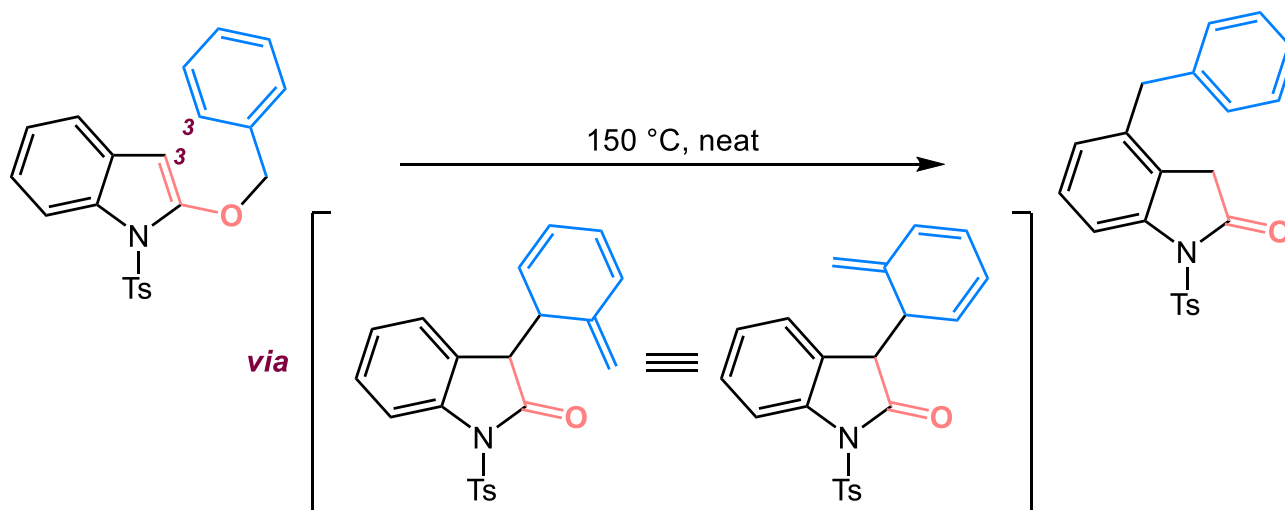
◆ Few report about indolines with a fully substituted C2 position

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Dearomative Claisen Rearrangement of Indoles



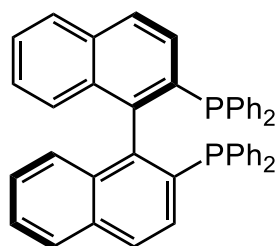
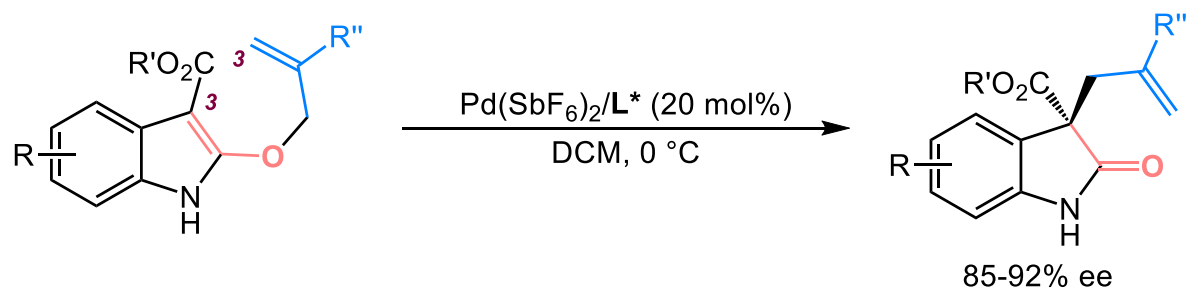
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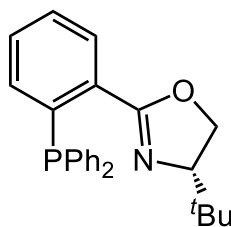
Kawasaki, T.; Ogawa, A.; Sakamoto, M. *J. Org. Chem* **2005**, *70*, 2957
Abe, T.; Kosaka, Y.; Asano, M.; Harasawa, N.; Yamada, K. *Org. Lett.* **2019**, *21*, 826

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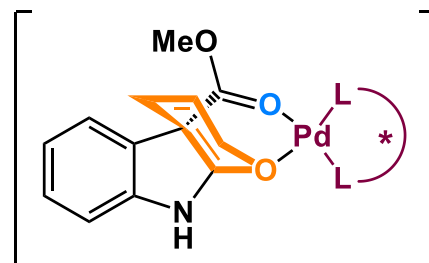
Catalytic Enantioselective Dearomative Claisen Rearrangement



or



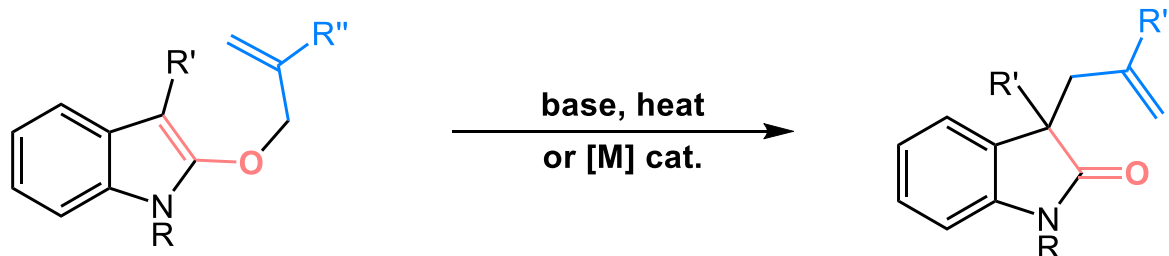
via



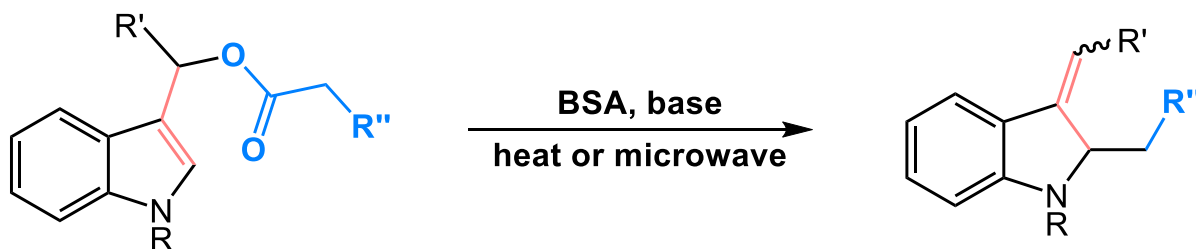
Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162

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Precedents for Dearomative Indolic Claisen Rearrangement



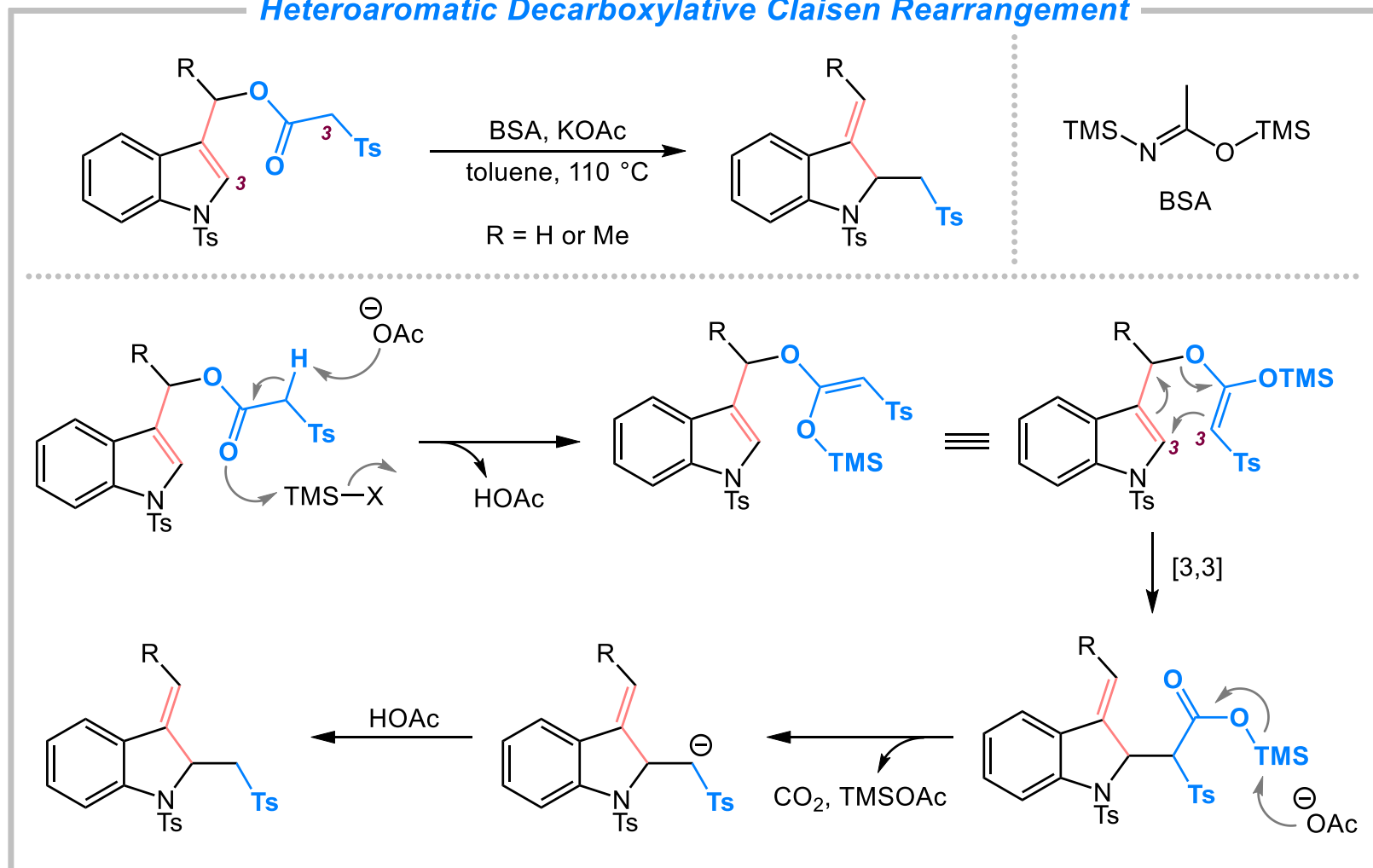
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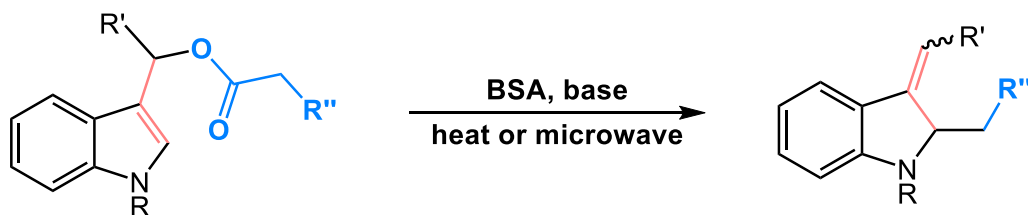
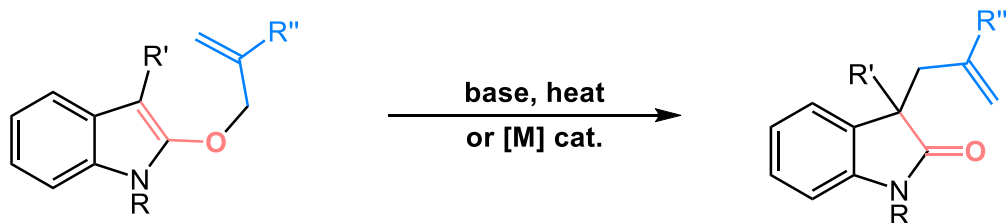
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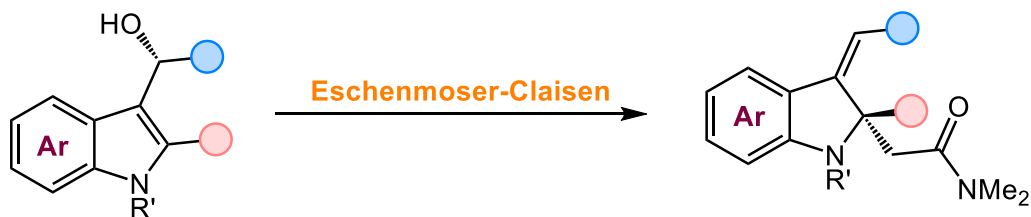
Craig, D.; King, N. P.; Kley, J. T.; Mountford, D. M. *Synthesis* **2005**, 2005, 3279

Dearomative Indolic-Claisen Rearrangement

Precedents for Dearomative Indolic Claisen Rearrangement

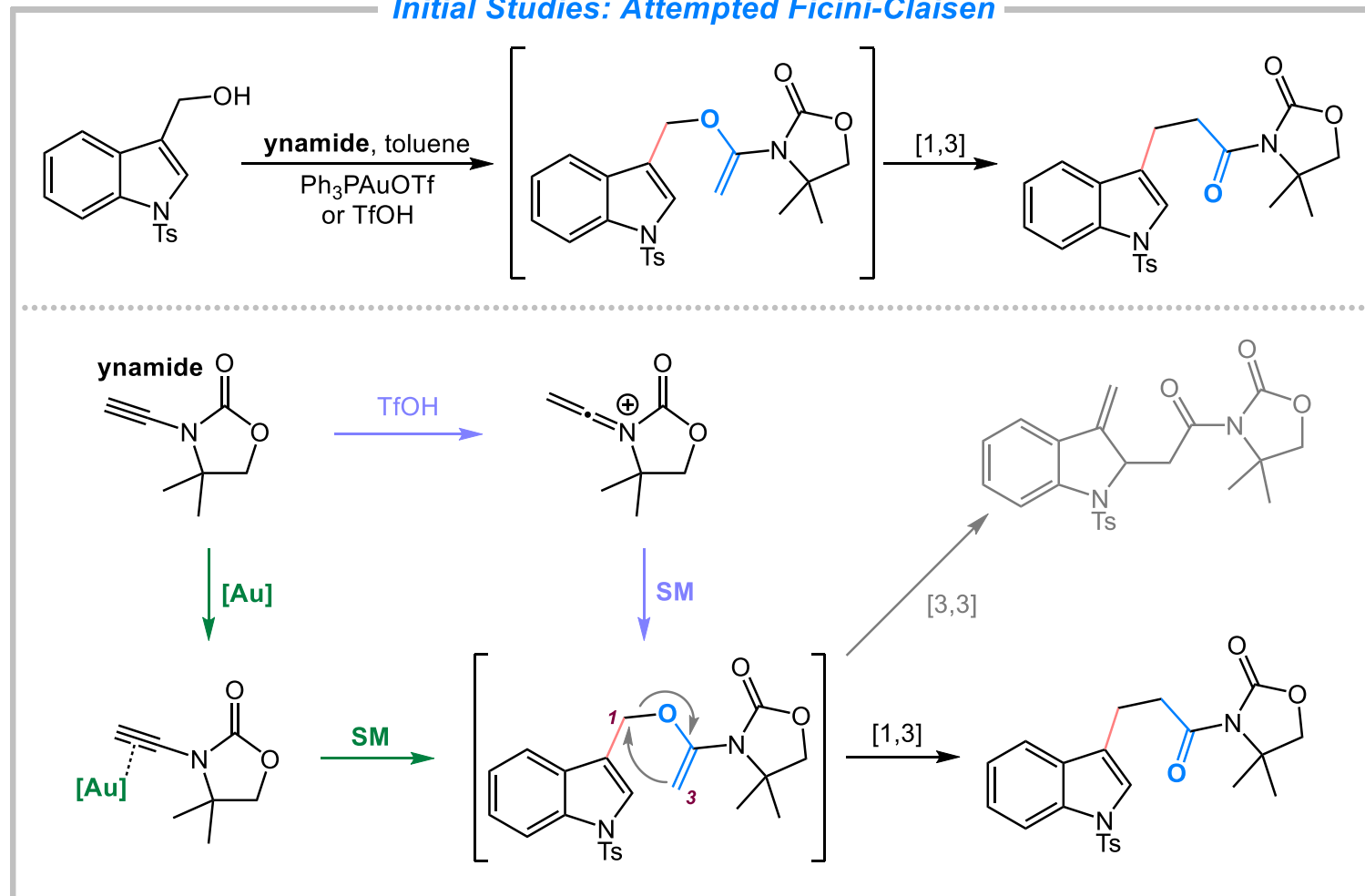


This Work: Dearomative Claisen towards 2,2-Disubstituted Indolines

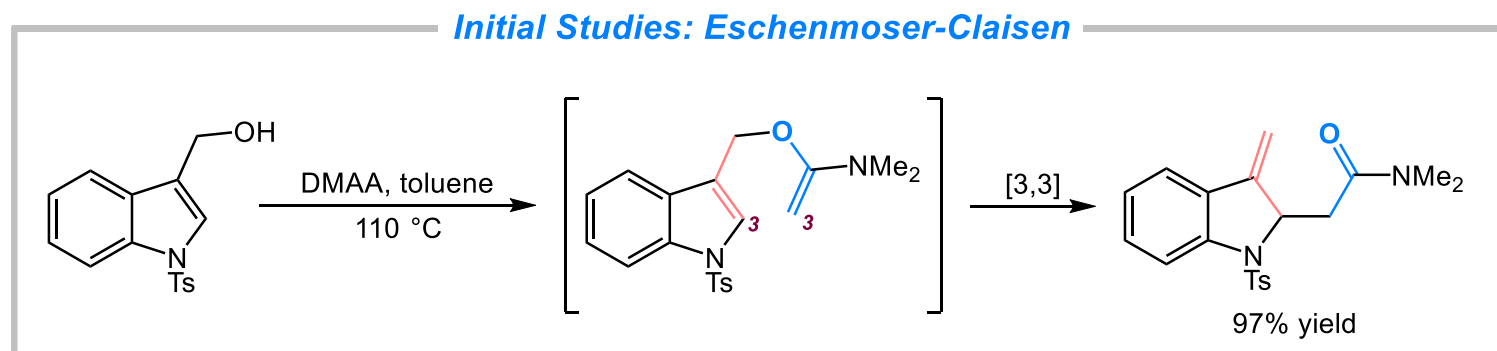


Dearomative Indolic-Claisen Rearrangement

Initial Studies: Attempted Ficini-Claisen

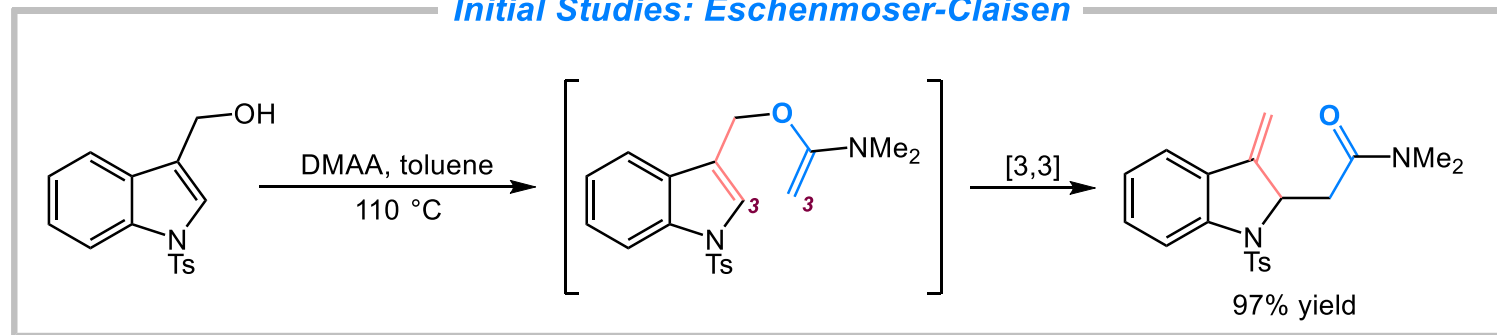


Dearomative Indolic-Claisen Rearrangement

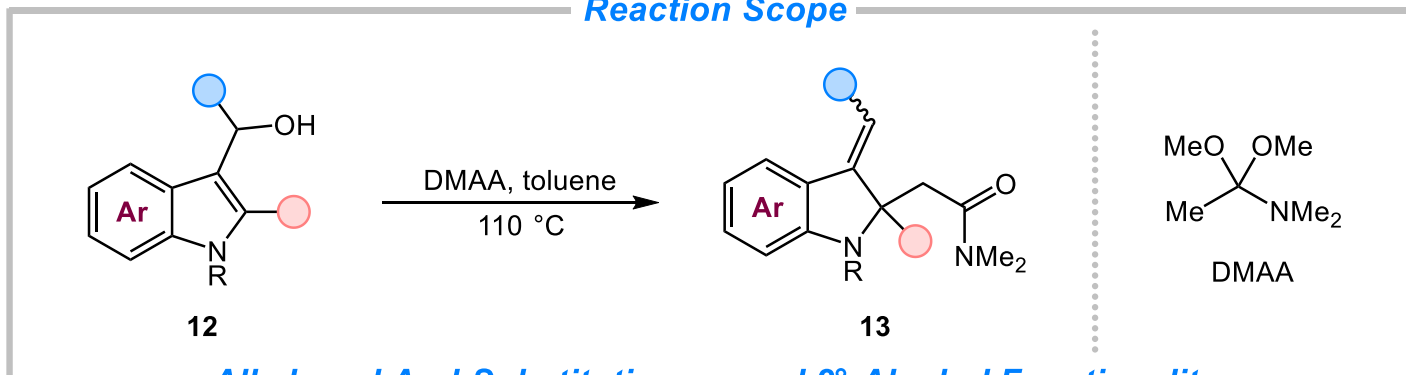


Dearomative Indolic-Claisen Rearrangement

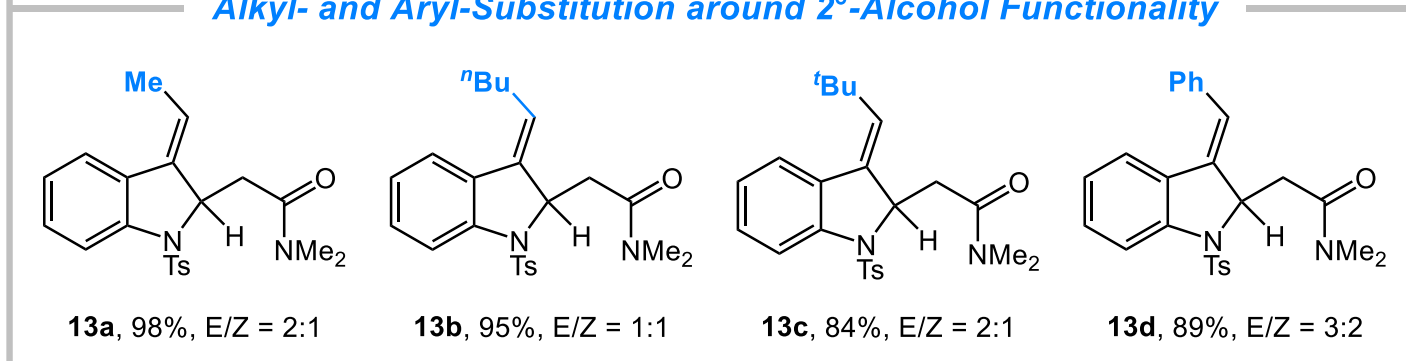
Initial Studies: Eschenmoser-Claisen



Reaction Scope

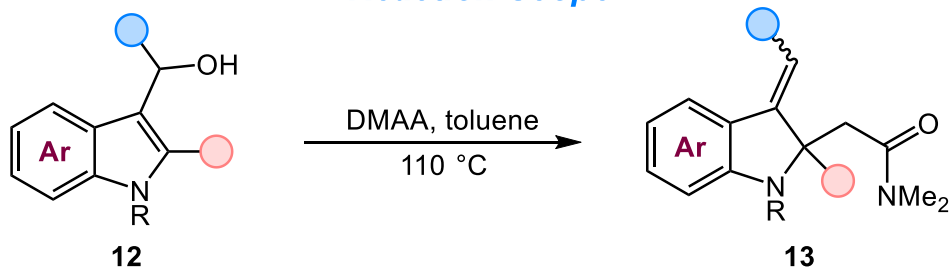


Alkyl- and Aryl-Substitution around 2°-Alcohol Functionality

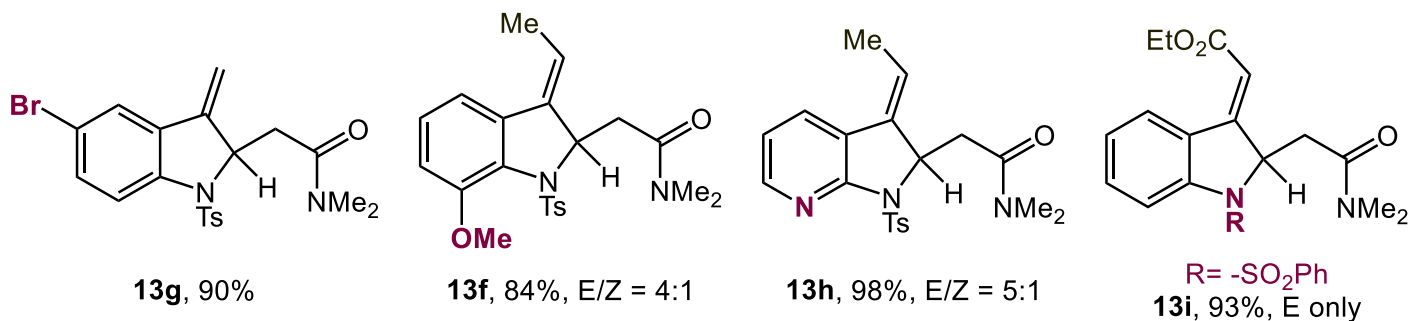


Dearomative Indolic-Claisen Rearrangement

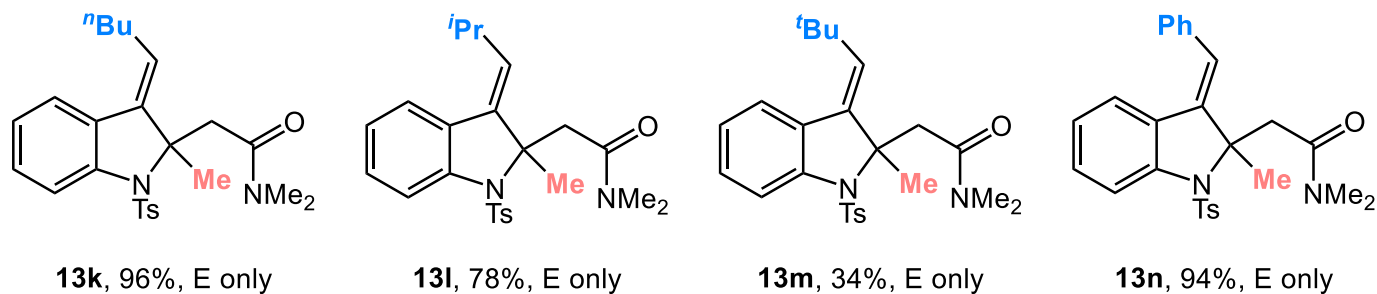
Reaction Scope



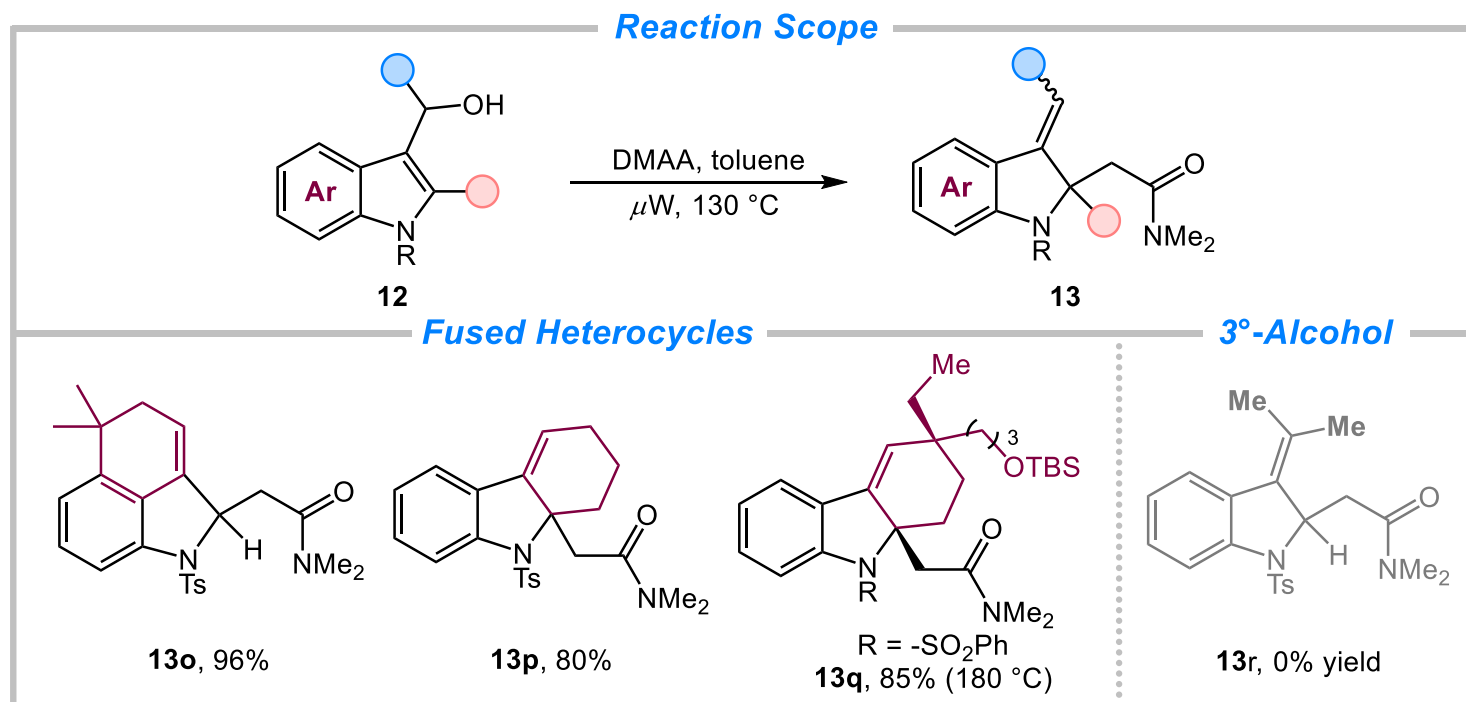
Indole Ring Perturbations



Exclusive Formation of (E)-Olefin when R ≠ H

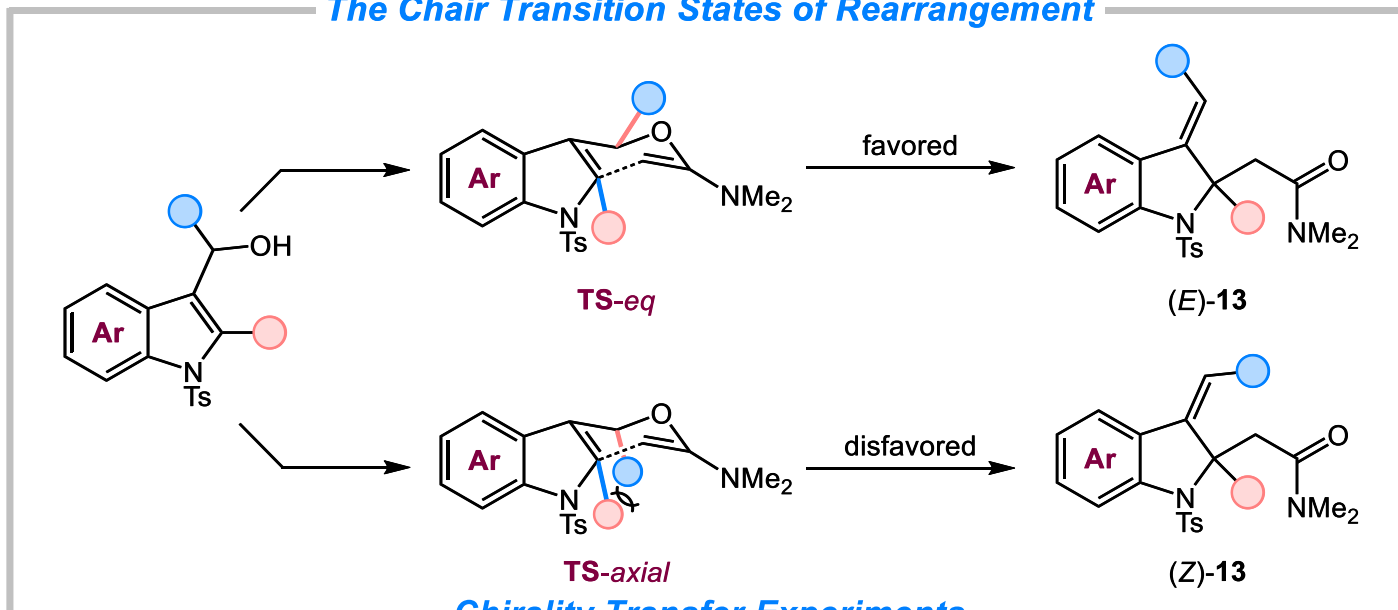


Dearomative Indolic-Claisen Rearrangement

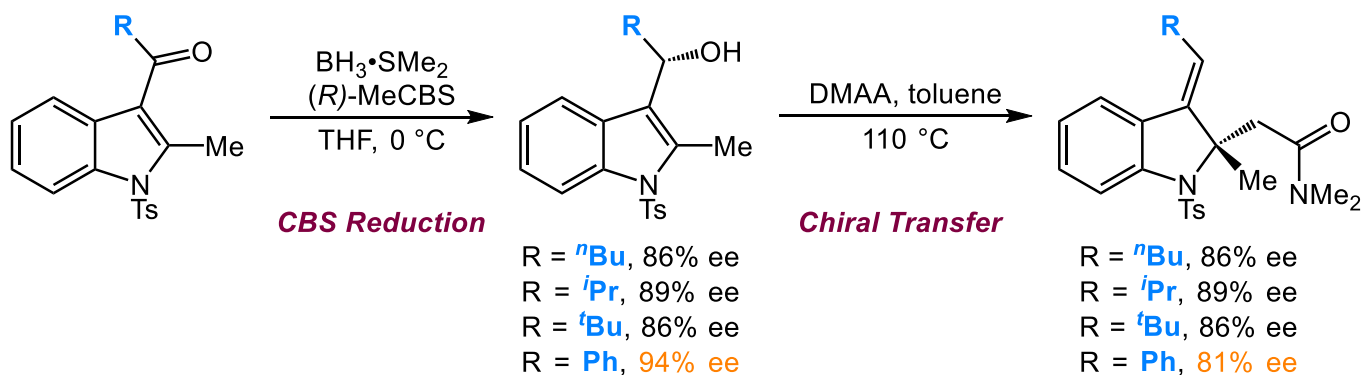


Dearomative Indolic-Claisen Rearrangement

The Chair Transition States of Rearrangement



Chirality Transfer Experiments

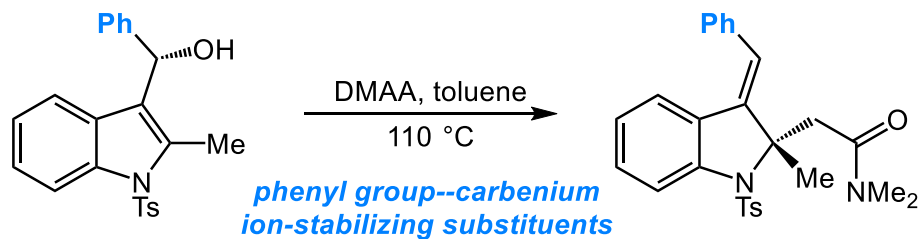


Dearomative Indolic-Claisen Rearrangement

Deterioration of Enantiomeric Purity

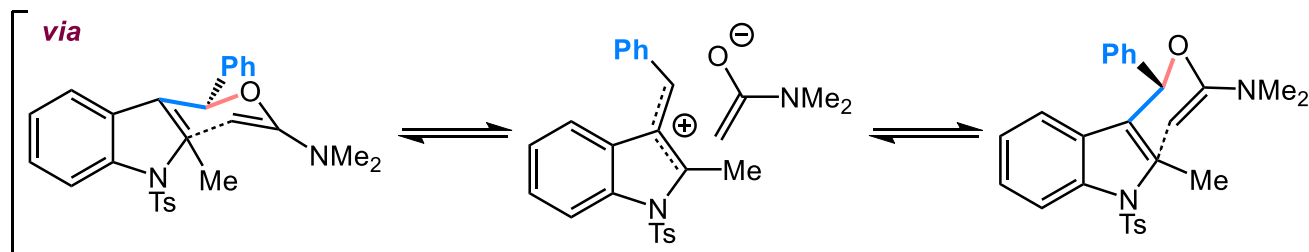
Stability of (S)-12n at rt:

$t_0 = 94\% ee$
 $t = 24 \text{ h}, 87\% ee$
 $t = 7 \text{ d}, 81\% ee$

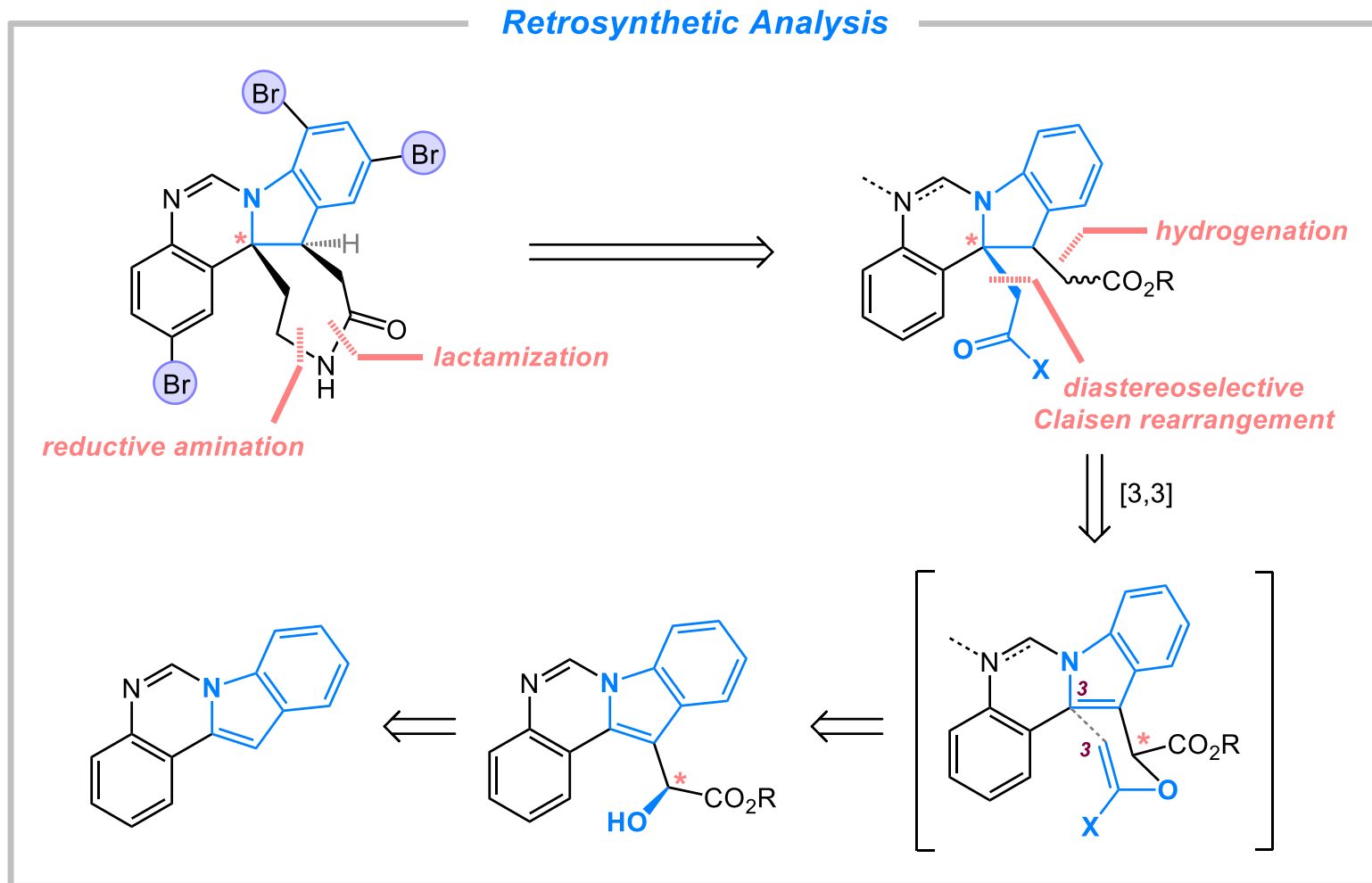


(S)-12n, 94% ee

(R)-13n, 81% ee

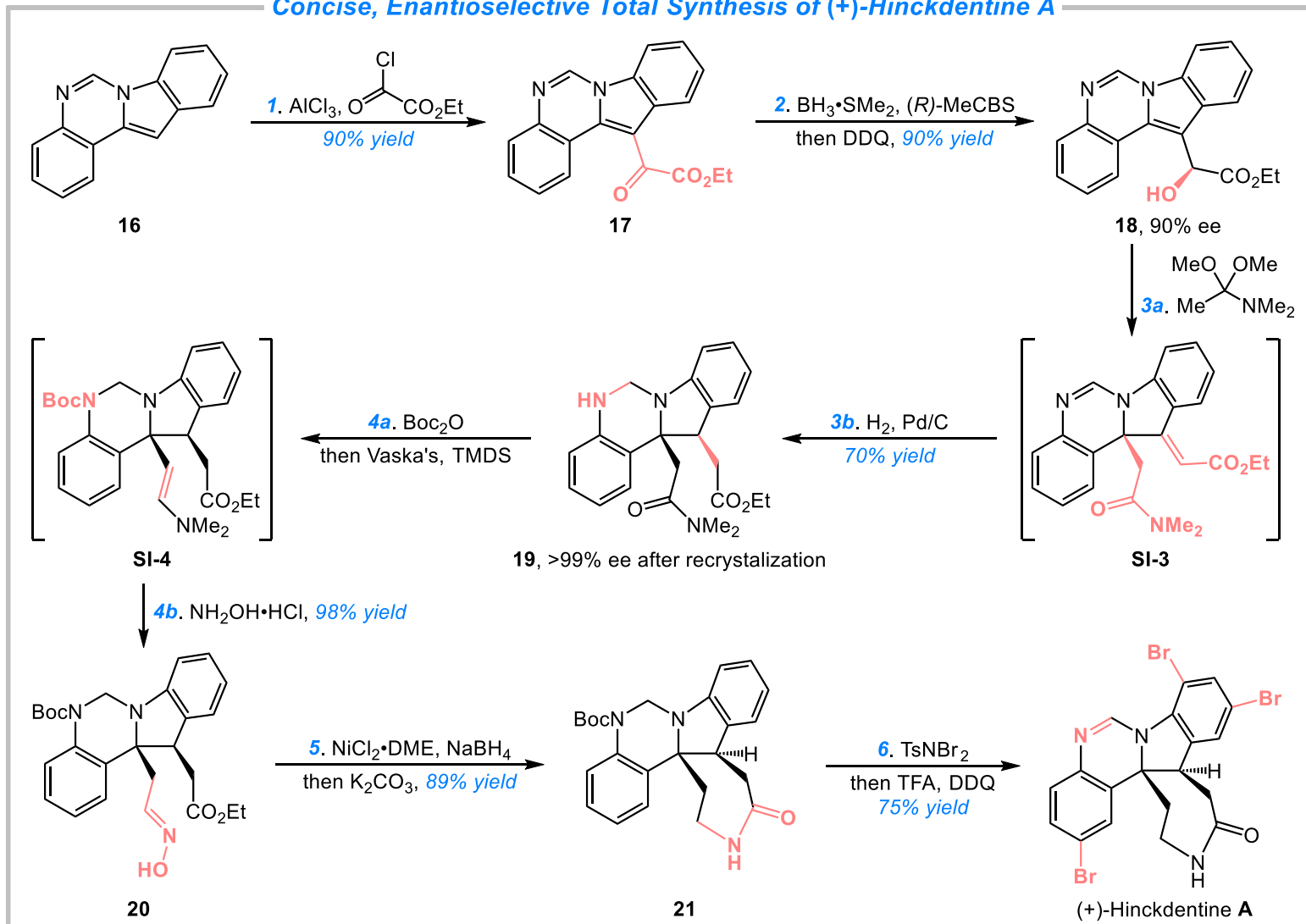


Enantioselective Total Synthesis of (+)-Hinckdentine A



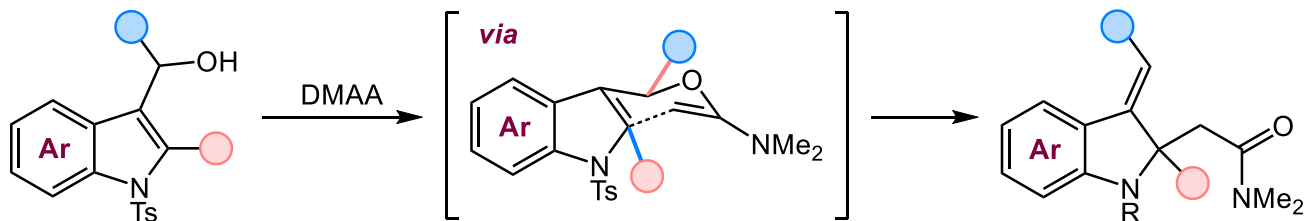
Enantioselective Total Synthesis of (+)-Hinckdentine A

Concise, Enantioselective Total Synthesis of (+)-Hinckdentine A

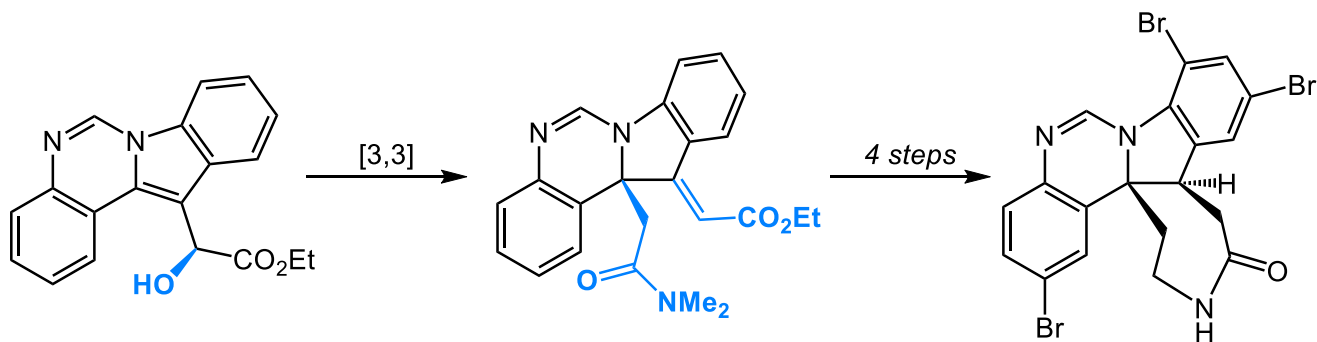


Summary

Methodology: Dearomative Claisen towards 2,2-Disubstituted Indolines



Application: Enantioselective Total Synthesis of (+)-Hinckdentine A



- ◆ High Chirality Transfer
- ◆ Diastereocontrolled Hydrogenation
- ◆ Chemoselective Amide-to-Oxime Conversion
- ◆ Regioselective Tribromination

Writing Strategies

□ The First Paragraph

Natural products
containing **2,2-disubstituted indoline**



Methods toward **2,2-disubstituted indoline**
was limited



The necessity to
develop **new approach**

- ✓ Our long-standing interest in alkaloids brought to our attention a subset of natural products that possess partial substitution at C3 and disubstitution at C2 of the indoline scaffold—for example, hinckdentine A, melonine, vallesamidine, and schizozygine.
- ✓ Whereas enormous effort has been expended on the synthesis of alkaloids bearing disubstitution at C3 or having fully substituted indoline skeletons, much less progress has been made toward a generic synthetic protocol to access thindoline motif of natural products such as those shown.
- ✓ A robust route to 2,2-disubstituted indolines, we envisioned, would offer rapid entry to these and other natural products.

Writing Strategies

□ The Last Paragraph

Summary
of this work



highlights of
the current method



Outlook
of this work

- ✓ To summarize, we have developed a powerful synthetic protocol for introducing a carbon fragment to the C2 position of indolines via the dearomative Meerwein-Eschenmoser-Claisen rearrangement of 3-indolyl alcohols.
- ✓ Other noteworthy steps in the synthesis include (1) diastereocontrolled hydrogenation of the alkene in the rearrangement product, (2) chemoselective amide-to-oxime conversion using Vaska's complex, and (3) regioselective tribromination of caprolactam **21**.
- ✓ The study of related dearomative Claisen rearrangements is expected to expand access to intricate frameworks found in natural products and complex molecules of biomedical interest.

Representative Examples

- ✓ The potent biological activities of indole alkaloids and the synthetic challenges posed by their **intricate** (*adj.* 错综复杂的, 难理解的) architectures have inspired numerous investigators and spurred a **plethora** (*n.* 过多) of advances in organic synthesis.
- ✓ The **paucity** (*n.* 缺乏) of such dearomative Claisen rearrangements, **coupled with** the presence of natural products possessing C2-disubstituted indolines as a key structural component, **inspired** us to investigate the [3,3] sigmatropic rearrangements of 3-indolyl alcohols **as a general route** to this challenging architectural motif.
- ✓ Through **judicious** (*adj.* 明智的, 判断正确的) screening of reaction parameters...

Acknowledgement

Thanks for your attentions!