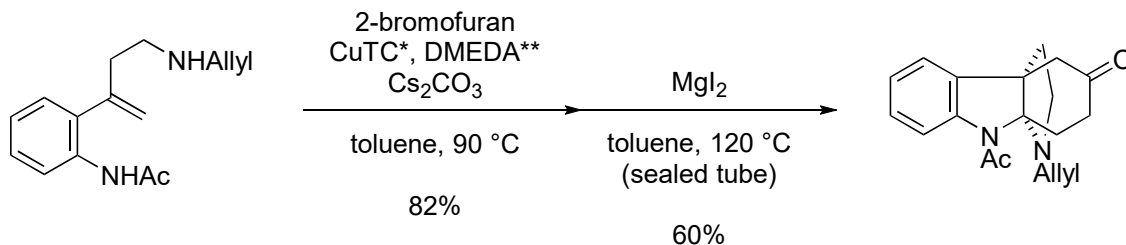


Inoue Group - Group Meeting Problems

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Provide a reasonable mechanism for these reactions.

1

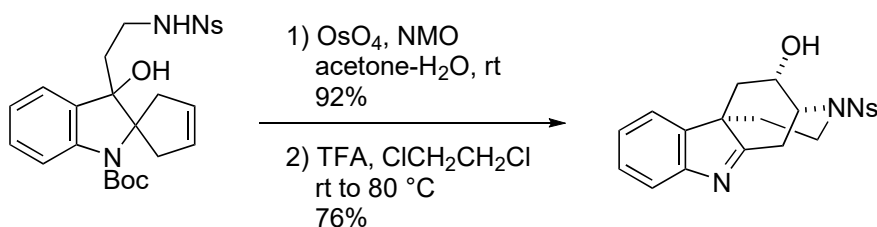


* CuTC = copper(I) thiophene-2-carboxylate

** DMEDA = *N,N'*-dimethylethylenediamine

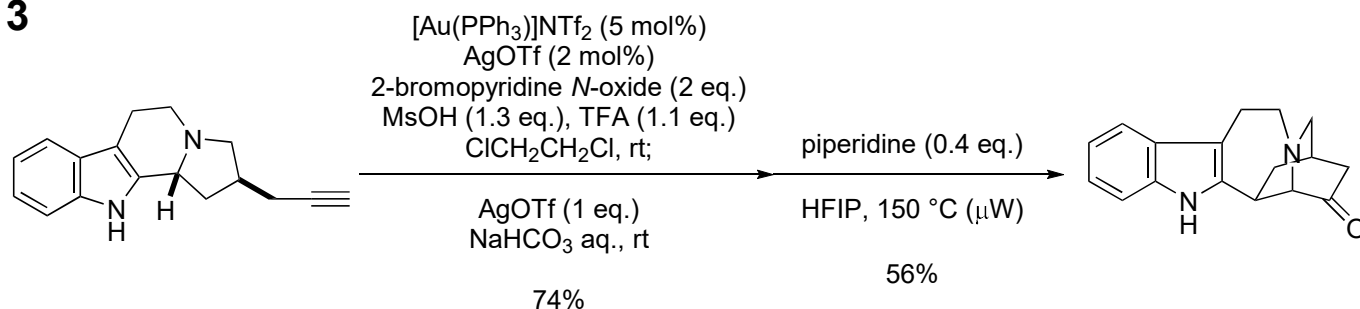
C. A. Leverett, G. Li, S. France and A. Padwa, *J. Org. Chem.*, ASAP (2016)
(doi: 10.1021/acs.joc.6b00771)

2

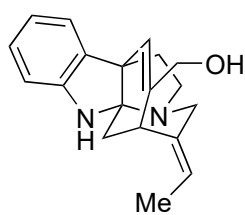


G. Li, X. Xie and L. Zu, *Angew. Chem. Int. Ed.*, Early View (2016)
(doi: 10.1002/anie.201604770)

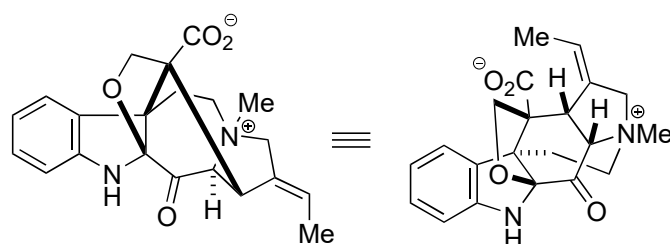
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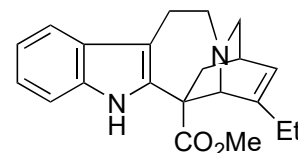
Y. Zhang, Y. Xue, H. Yuan and T. Luo, *Chem. Sci.*, Advance Article (2016)
(doi: 10.1039/c6sc00932h)



Minfiensine



Calophylline A



Catharanthine

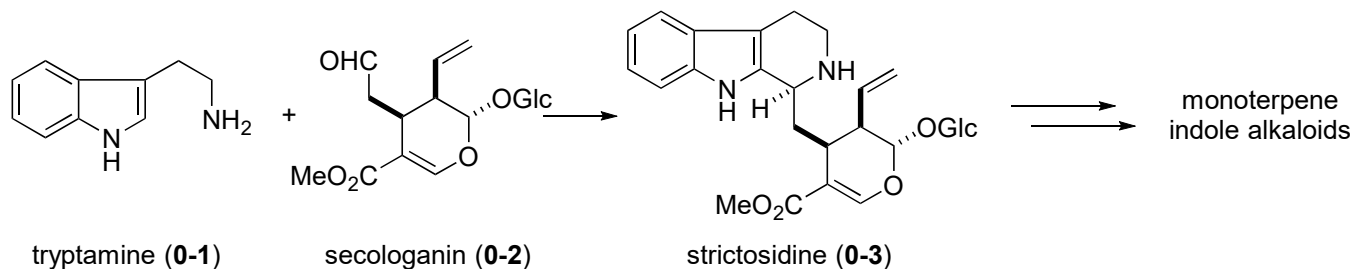
Inoue Group - Group Meeting Problems

D3 E. Yoshida

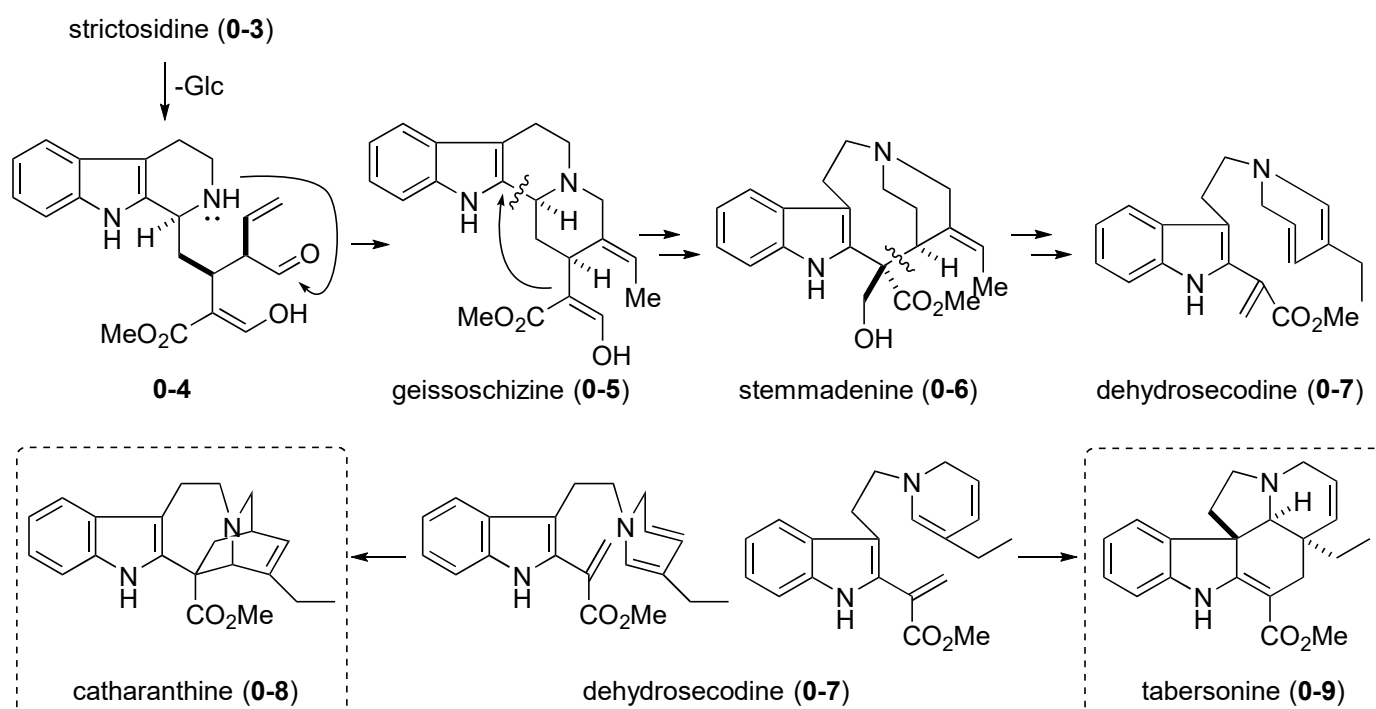
6/25/2016

0. Monoterpene indole alkaloid

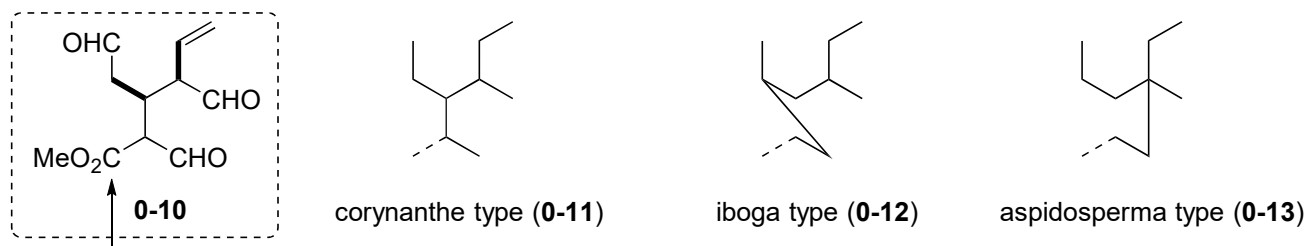
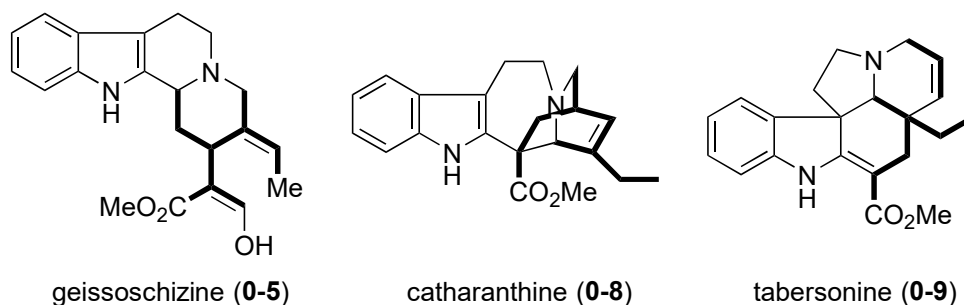
0-1. Outline of biosynthesis



0-2. Skeletally rearranged derivatives

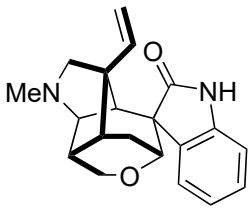


0-3. Classification by carbon structures



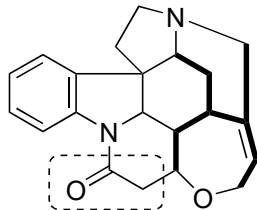
This carbon is sometimes removed by decarboxylation.

0-4. Selected examples of monoterpene indole alkaloids



Gelsemine (0-14)

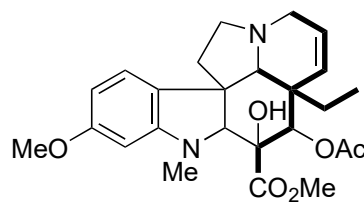
corynanthe type (C10)



from acetyl-CoA

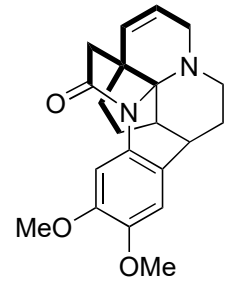
Strychnine (0-15)

corynanthe type (C9)



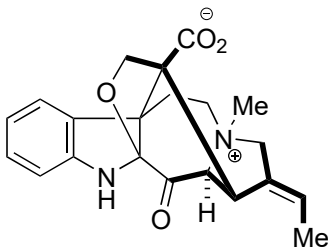
Vindoline (0-16)

aspidoasperma type (C10)



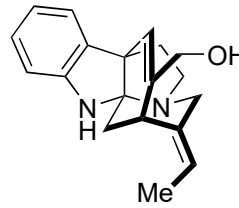
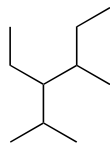
Isoschizogamine (0-17)

aspidoasperma type (C9)



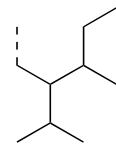
Calophylline A (0-18)

corynanthe type (C10)



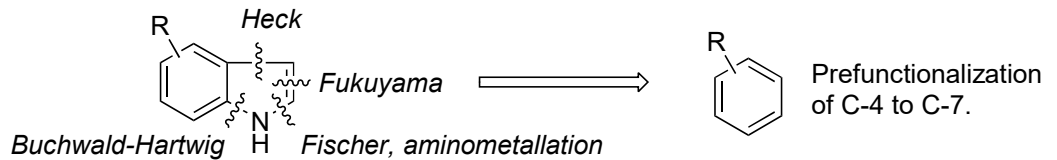
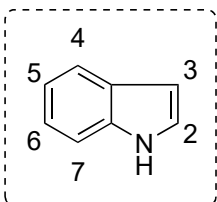
Minfiensine (0-19)

corynanthe type? (C9)



0-5. Characteristics of indole chemistry

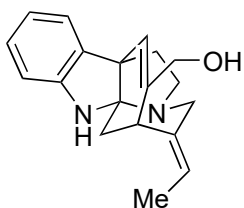
- C-3 and C-2 are easy to functionalize.
- C-3 is 10^{13} times more reactive to electrophiles than benzene.
- C-2 is easily functionalized by lithiation.
- Indole synthesis is needed especially when C-4 to C-7 are functionalized.



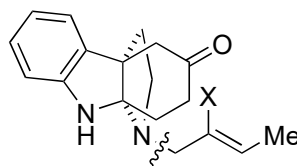
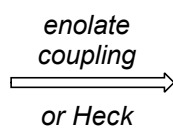
- The asymmetric construction of C-3 quaternary center is a major synthetic challenge.
- Indoles are easily oxidized due to the electron richness. However, a protecting group of N-1 is very limited. Only Boc and ArSO_2 are useful.

1. Total synthesis of (\pm)-Minfiensine

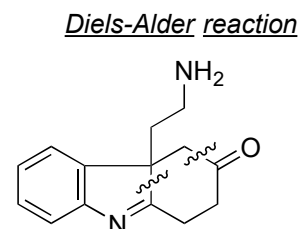
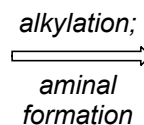
1-1. Retrosynthesis



Minfiensine (1-1)



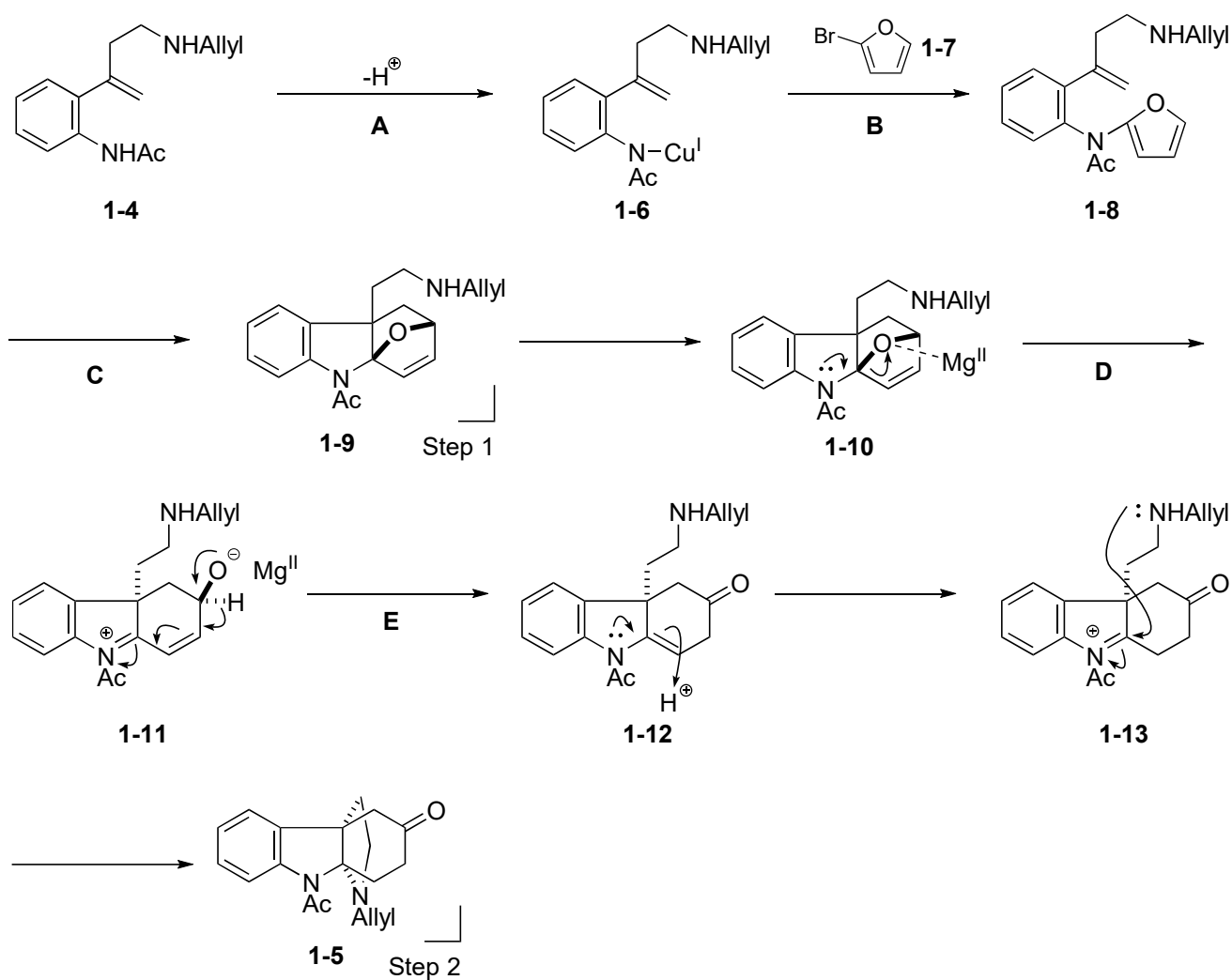
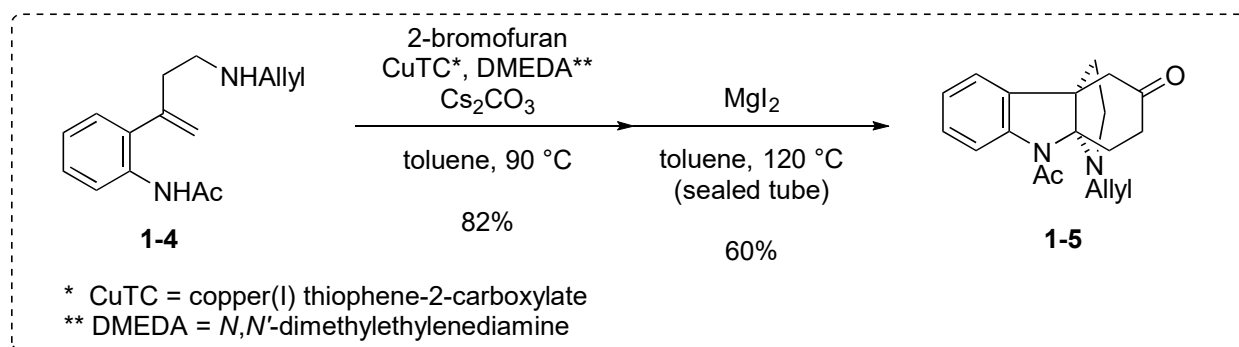
1-2



1-3

The ethylidene unit dramatically narrows the retrosynthesis as is often the case with corynanthe alkaloids.

1-2. Reaction mechanism

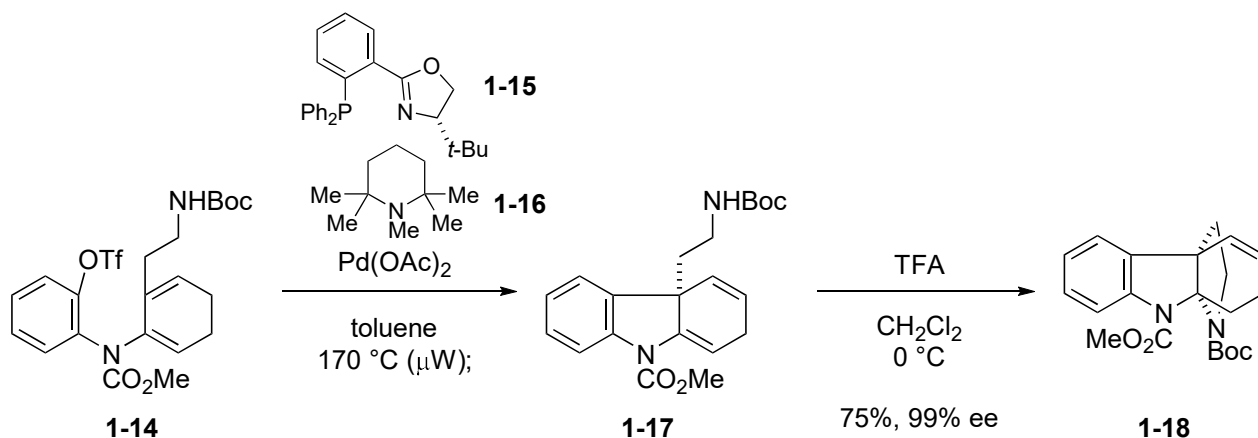


Buchwald-Hartwig coupling and Diels-Alder reaction. **A**: Formation of copper(I) amidate. **B**: Formal oxidative addition and reductive elimination.* **C**: Diels-Alder reaction. **D**: Lewis-acid promotes the cleavage of the strained C-O bond. **E**: 1,2-hydride shift.

* The mechanism is still being discussed. see: S. L. Buchwald *et al.*, *J. Am. Chem. Soc.*, **131**, 78 (2009)

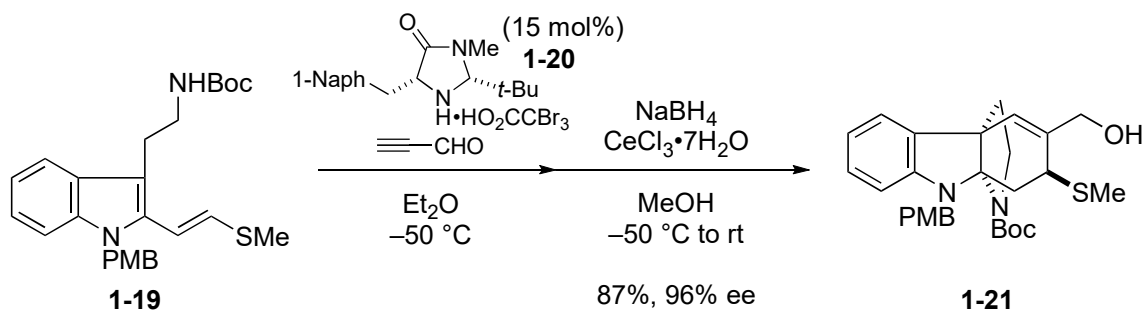
1-3. Asymmetric total syntheses

• Asymmetric Heck Reaction



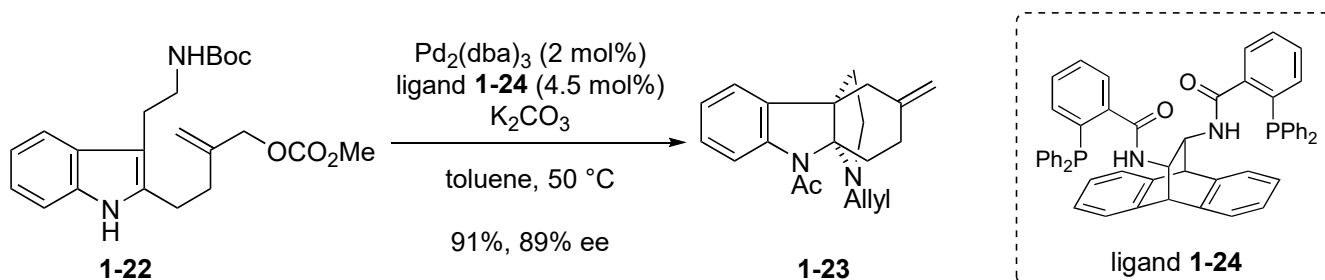
A. B. Dounay, L. E. Overman and A. D. Wroblewski, *J. Am. Chem. Soc.*, **127**, 10186 (2005)

• Organocatalytic Diels-Alder reaction



S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **131**, 13606 (2009)

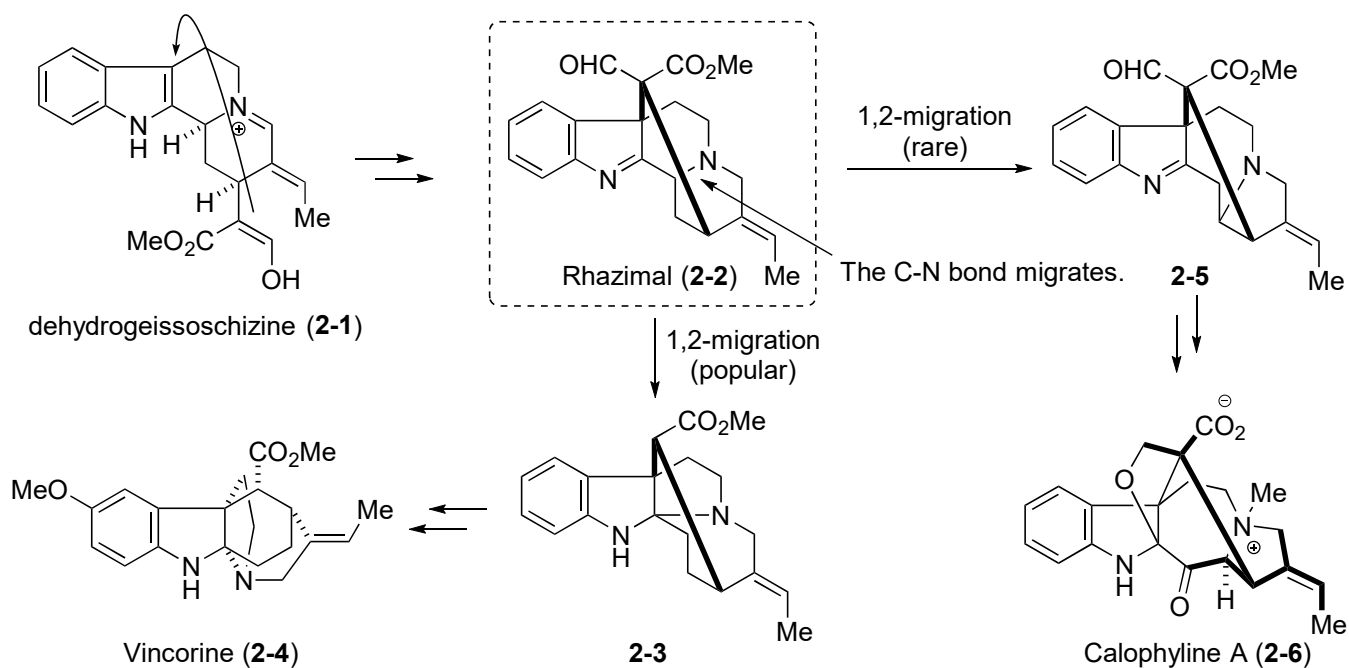
• Asymmetric Tsuji-Trost reaction



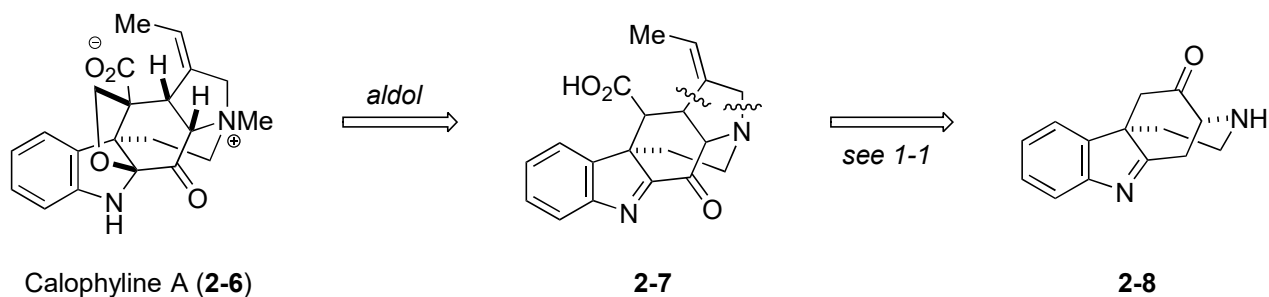
Z.-X. Zhang, S.-C. Chen and L. Jiao, *Angew. Chem. Int. Ed.*, Early View (2016)
 (doi: 10.1002/anie.201602771)

2. Total synthesis of (±)-Calophylline A

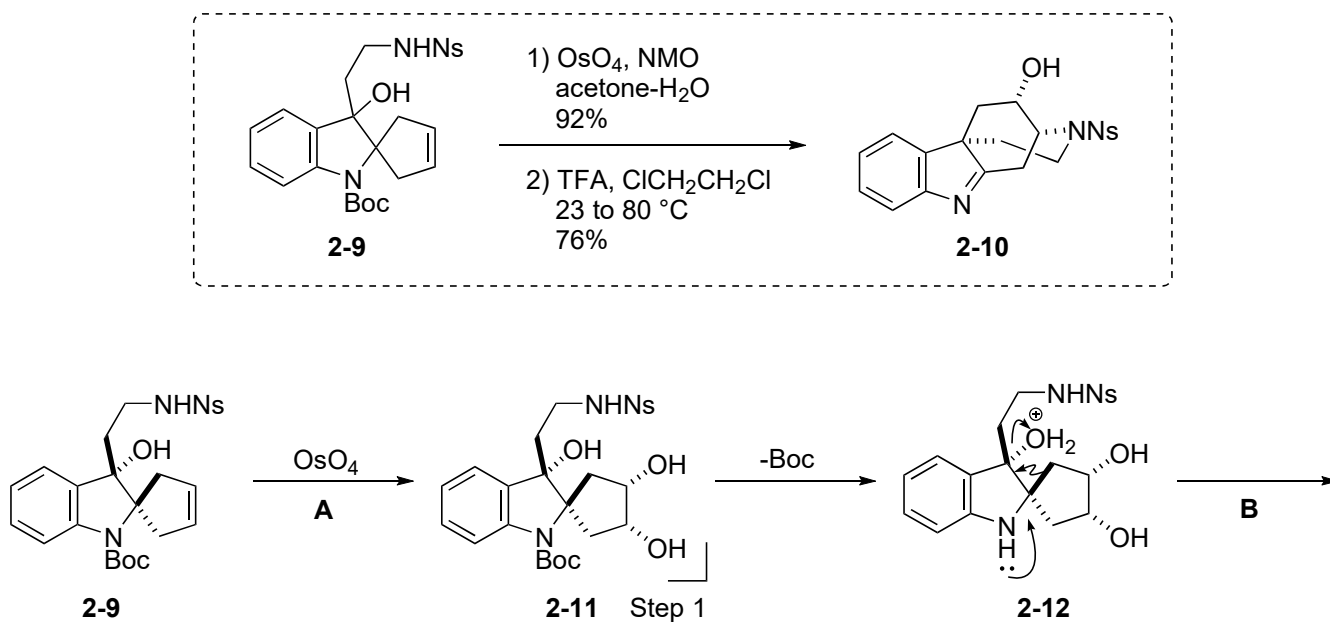
2-1. Related natural products

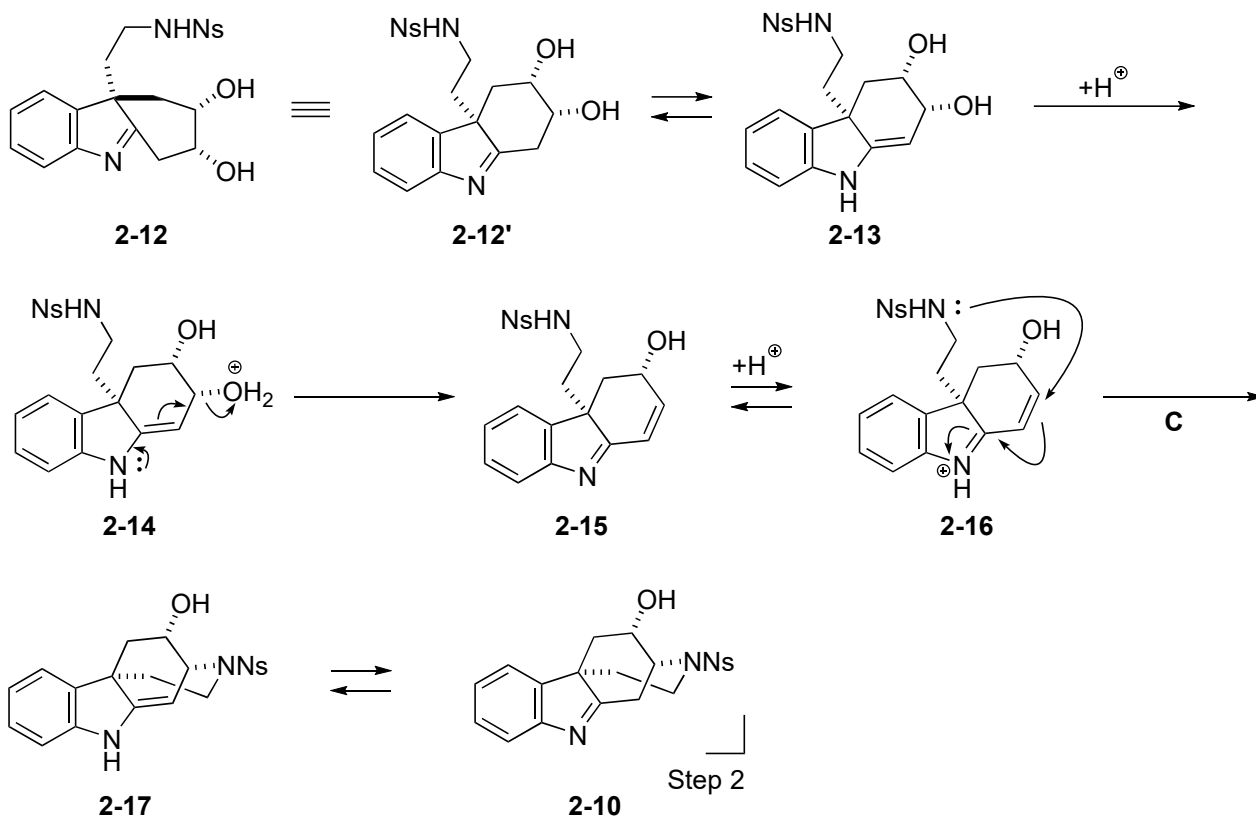


2-2. Retrosynthesis



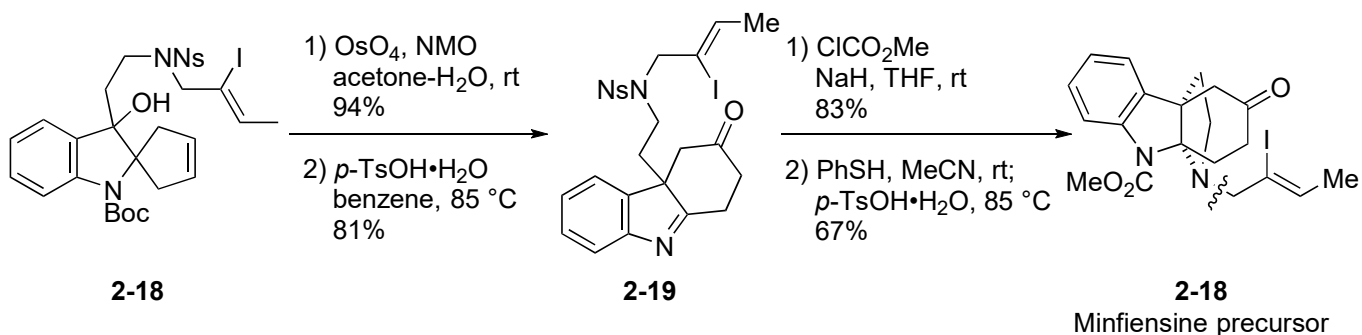
2-3. Reaction mechanism





Aza-pinacol rearrangement. **A**: The bulky Boc group or the directing hydroxy group are responsible to the complete facial selectivity of osmium-catalyzed dihydroxylation. **B**: Aza-pinacol rearrangement. **C**: Conjugate addition.

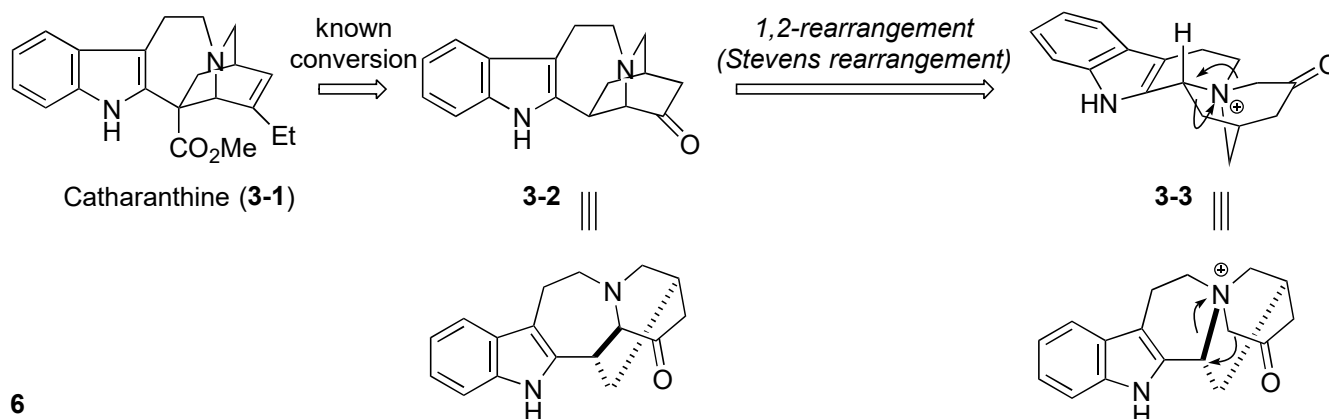
2-4. Another application



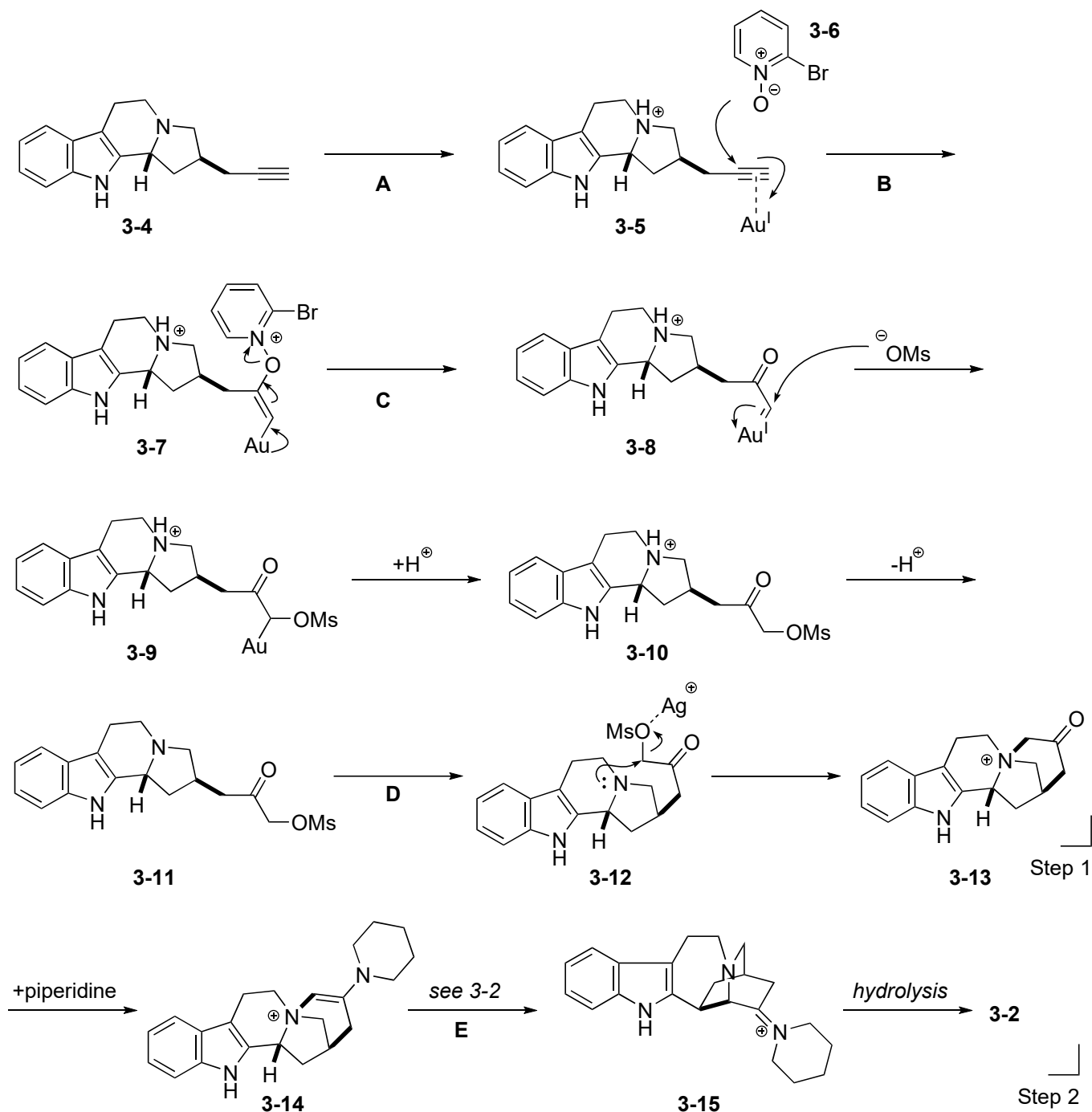
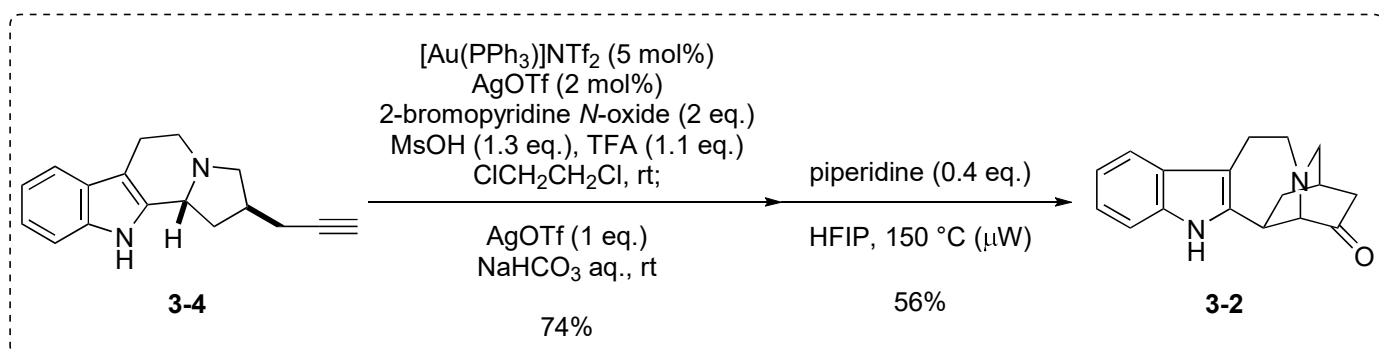
Y. Yu, G. Li, L. Jiang and L. Zu, *Angew. Chem. Int. Ed.*, **54**, 12627 (2015)

3. Formal synthesis of Catharanthine

3-1. Retrosynthesis



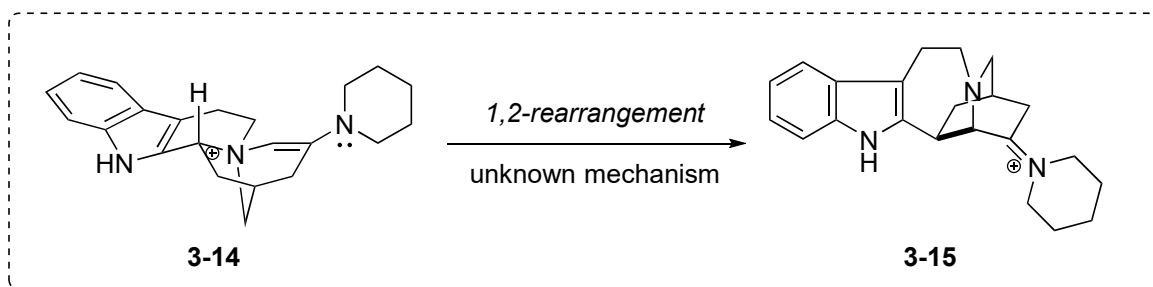
3-2. Reaction mechanism



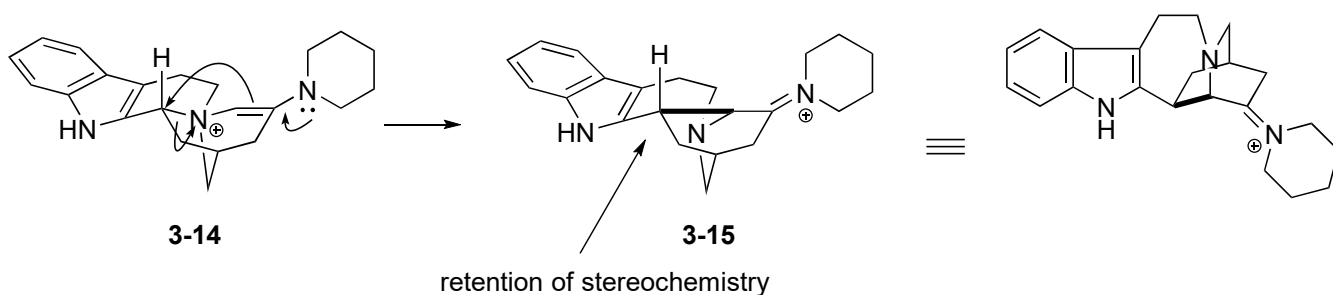
Stevens rearrangement. **A**: Protonation of amine under the acidic conditions. **B**: Nucleophilic attack to the more cationic site. **C**: Generation of gold(I) carben. **D**: Silver(I) activates the methanesulfonate.* **E**: Enamine-catalyzed Stevens rearrangement.

* The counteranion is not determined.

3-3. Discussion on 1,2-rearrangement



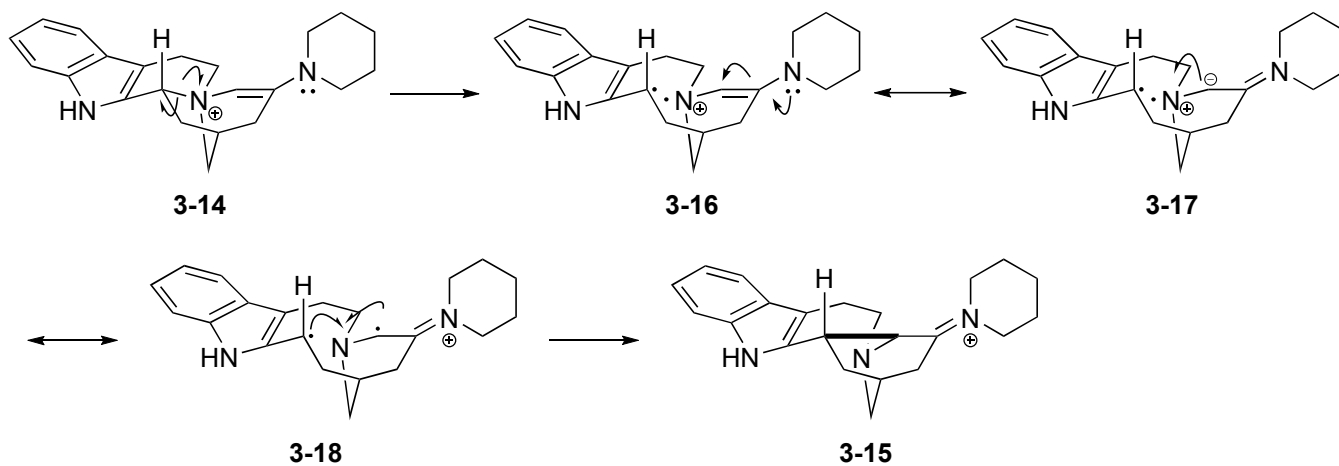
- Concerted pathway (theoretically denied)



1,2-carbanion rearrangement* is symmetrically forbidden.

* 2 pairs of $(4n+2)$ electrons participate in the reaction, and both of C-N σ -bond and enamine $6e^-$ are *supra*. So there are even number of $(4n+2)s$ electrons, and such reaction is denied by Woodward-Hoffmann rules.

- Biradical pathway (proposed by authors, standard mechanism of Stevens rearrangement)



- Cationic pathway (proposed by authors)

