

Literature Report I

Total Synthesis of (+)- and (\pm)-Hosieine A

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Checker: Xiao-Yong Zhai
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Wood, J. L. *et al. Angew. Chem. Int. Ed.* **2018**, 130, 7790-7793.

CV of John Louis Wood

Education and Employment:

- **1980–1985** B.S., University of Colorado, Boulder
- **1985–1991** Ph.D., University of Pennsylvania
- **1991–1993** Postdoctor, Harvard University
- **1993–1997** Assistant Professor, Yale University
- **1997–1998** Associate Professor, Yale University
- **1998–2006** Professor, Yale University
- **2006–2013** Professor, Colorado State University
- **2013–** Distinguished Professor, Baylor University



Research Interests:

- Total synthesis of natural products
-

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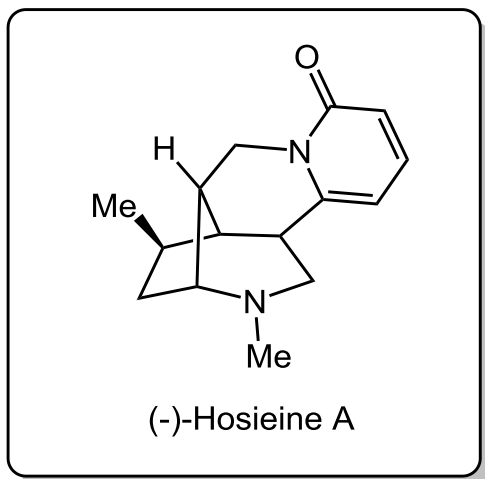
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Introduction



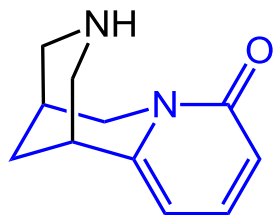
Ormosia hosiei Hemsl & E. H. Wilson
(红豆树)

- It was isolated from the roots of *Ormosia hosiei* Hemsl & E. H. Wilson;
- It has potential application value in the treatment of schizophrenia and Alzheimer's disease;
- The first asymmetric synthesis of (-)-hosieine A was completed by Hong and co-workers.

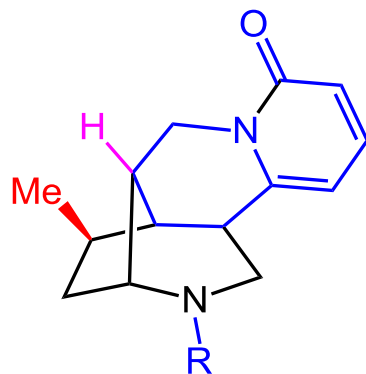
Massiot, G. *et al. Phytochemistry* **2014**, *107*, 97-101
Hong, R. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 10940-10943

Introduction

A class of cytisine-like lupin alkaloids

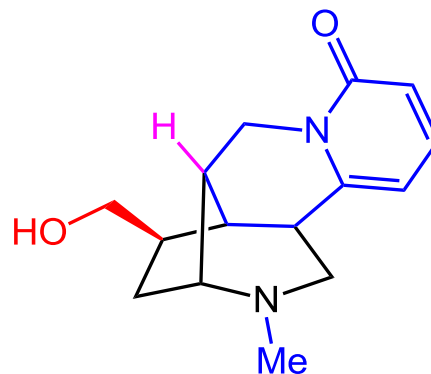


(-)-Cytisine (1)

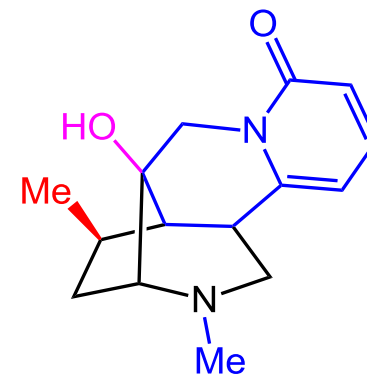


R = Me, (-)-Hosieine A (2)

R = H, (-)-Hosieine C (4)

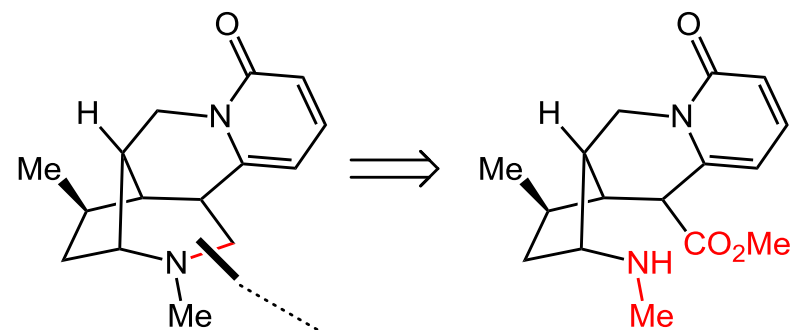


(-)-Hosieine B (3)



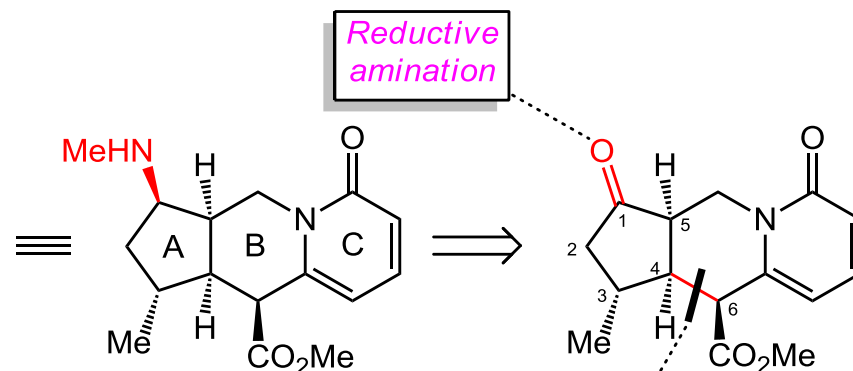
(-)-Hosieine D (5)

Retrosynthetic analysis



(-)-Hosieine A [(-)-2]

Lactamization
reduction

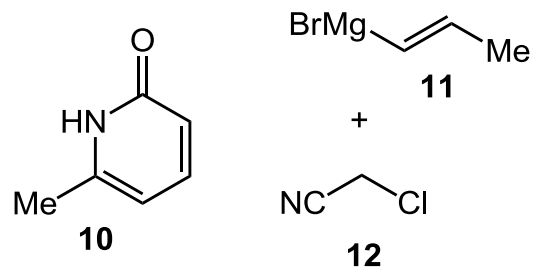


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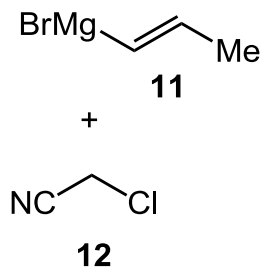
Reductive
amination

Michael
cyclization

7

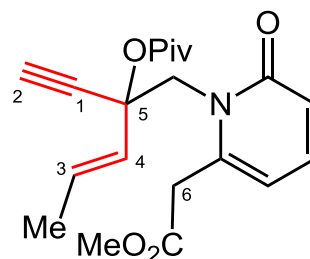


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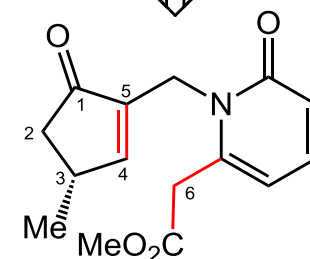
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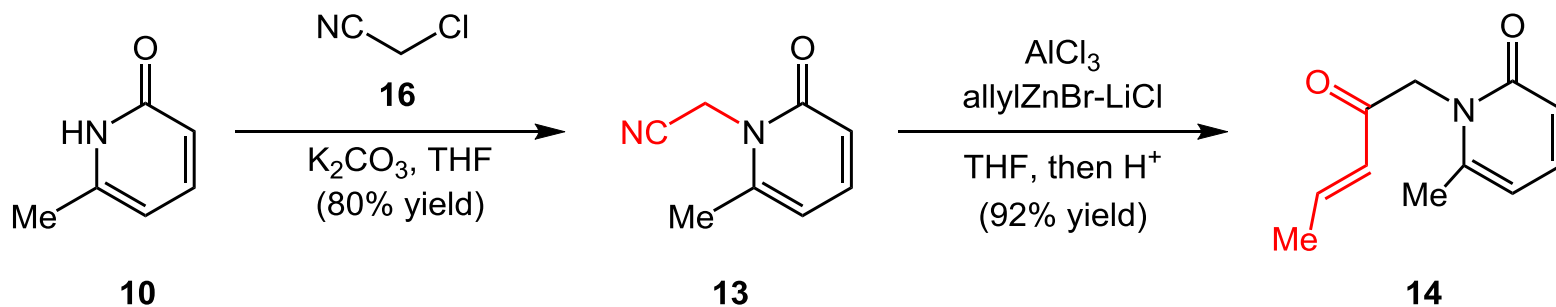
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Rautenstrauch
reaction

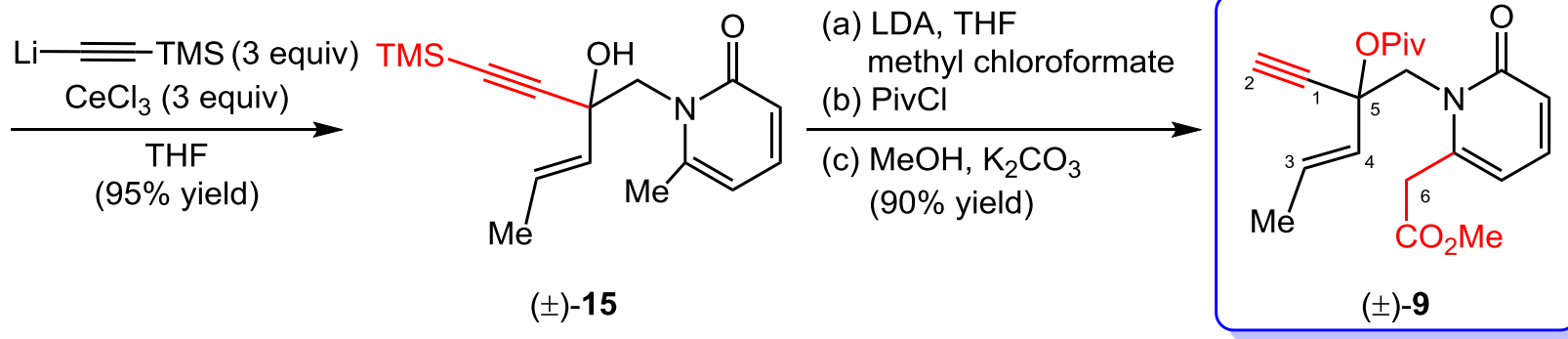


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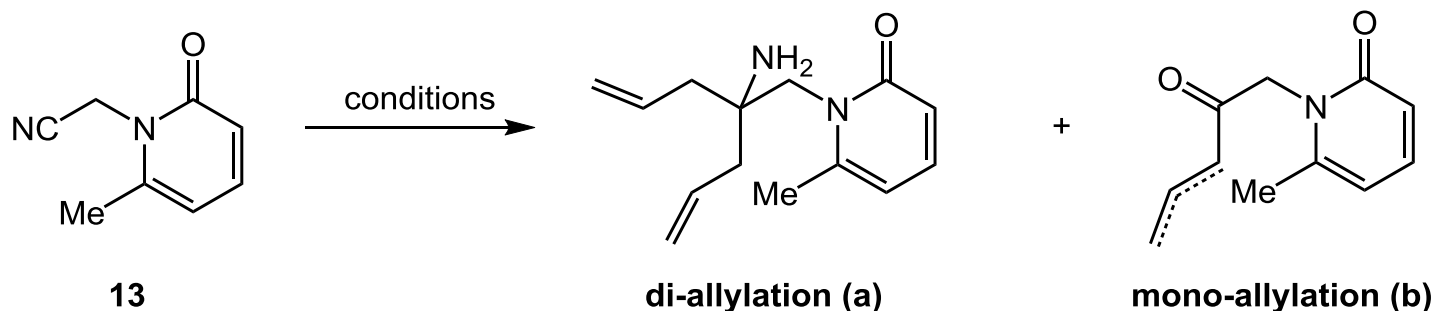
The synthesis of (\pm)-9



Organozinc allylation reaction

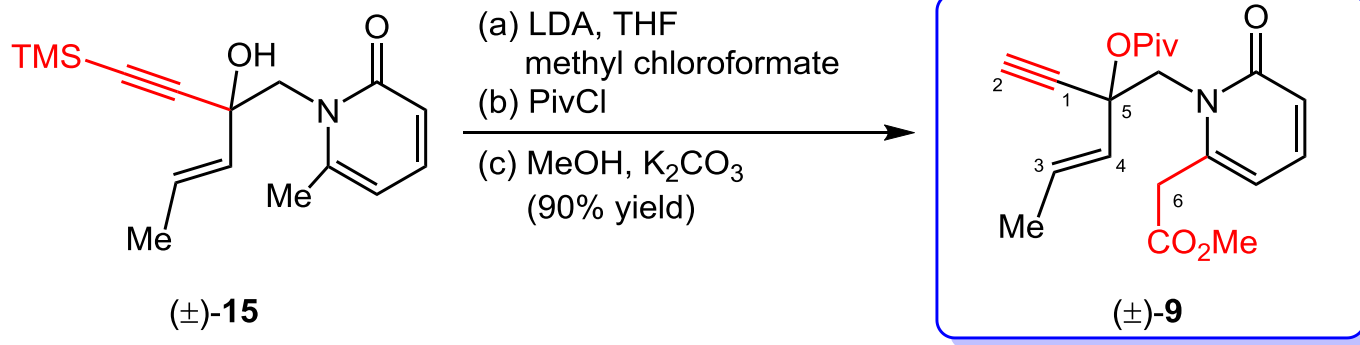
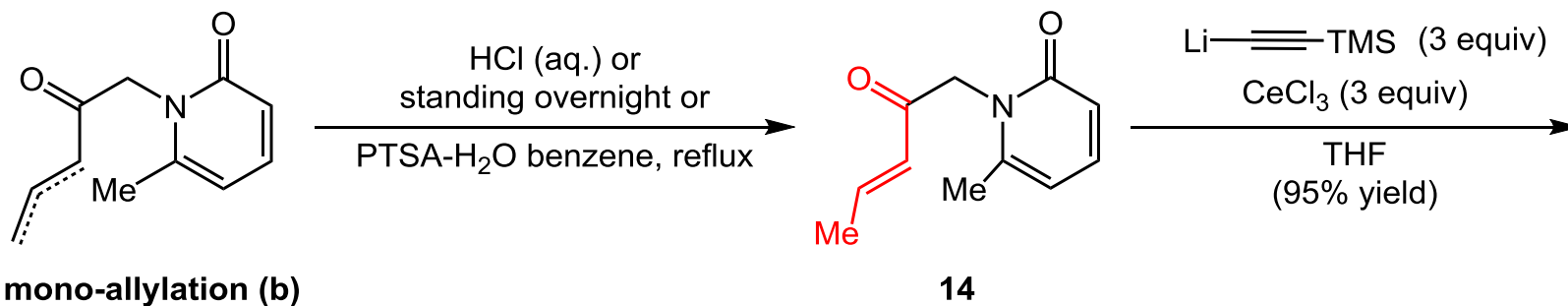


Organozinc allylation reaction

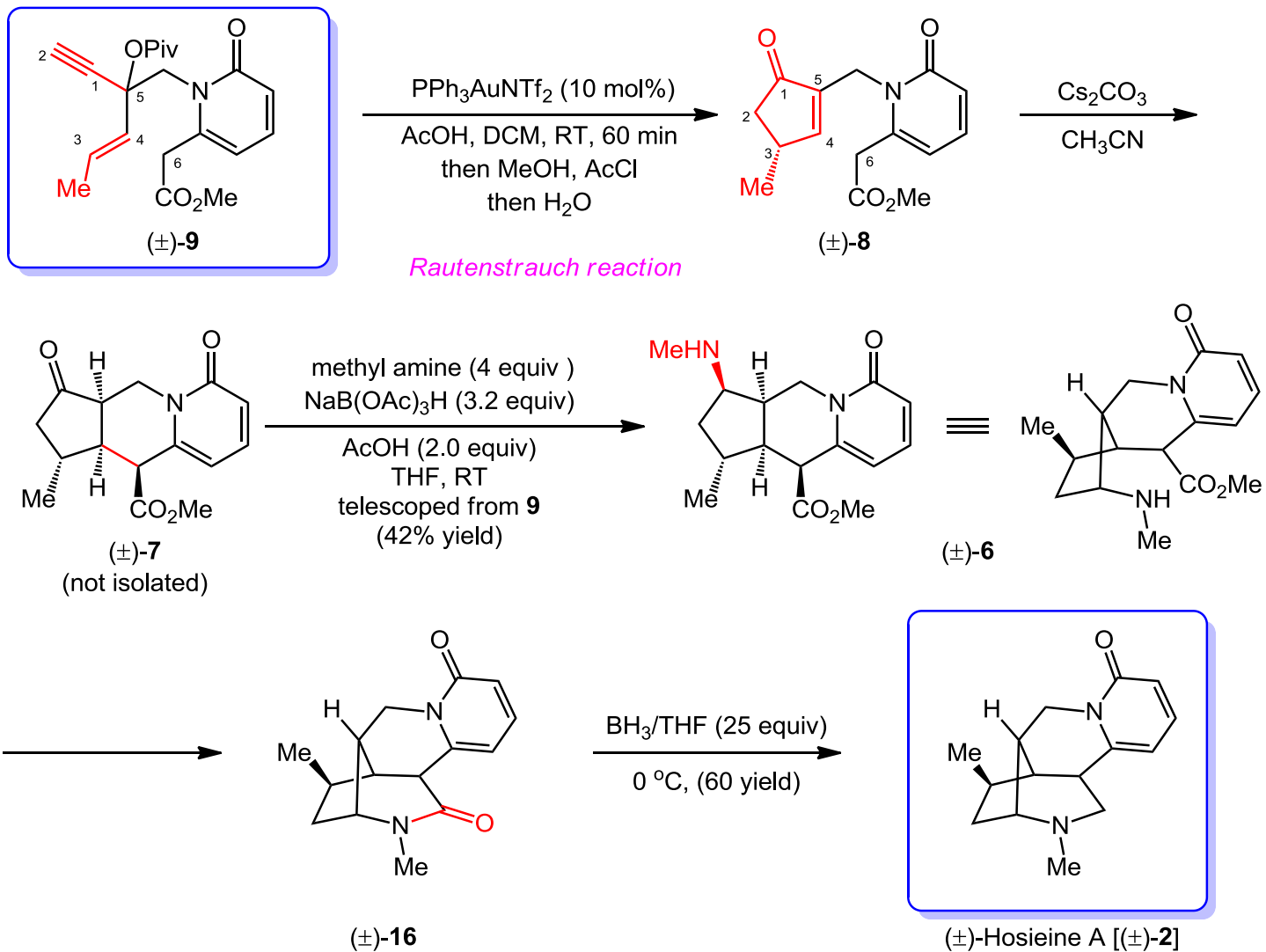


entry	conditions	product (yield)	ratio (mono : di)
1	MgBr, -78 °C to 60 °C	-	-
2	MgBr, CuBr (20 mol%), -78 °C to 60 °C	-	-
3	MgBr, -78 °C, 30 min then HCl (aq.)	50-60%	1 : 1
4	MgBr, -78 °C, 2 h then HCl (aq.)	50-60%	1 : 1
5	TMS, BCl ₃ , rt, 16 h then HCl (aq.)	15%	mono only
6	Br, Zn, AlCl ₃ , 30 min then HCl (aq.)	98%	2 : 1
7	ZnBr-LiCl, AlCl ₃ , 30 min then HCl (aq.)	92%	>20 : 1

The synthesis of (\pm)-9

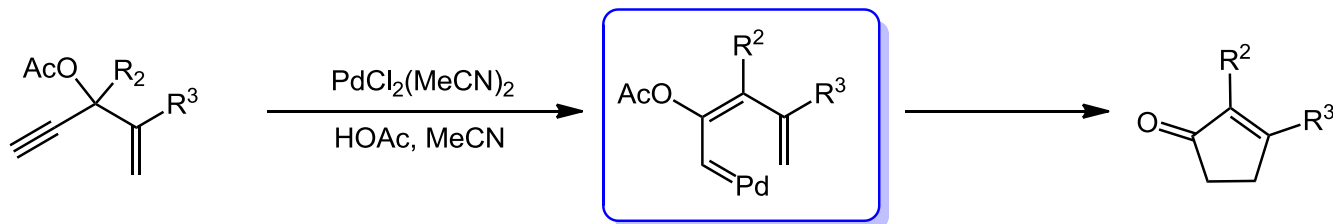


The synthesis of (±)-Hosieine A [(±)-2]



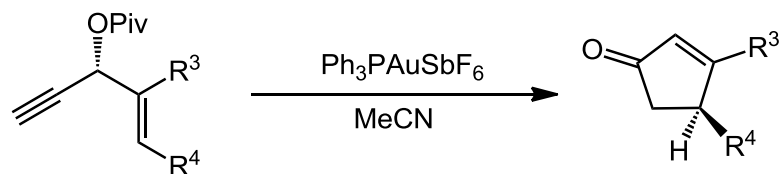
Rautenstrauch reaction

a) Rautenstrauch's work



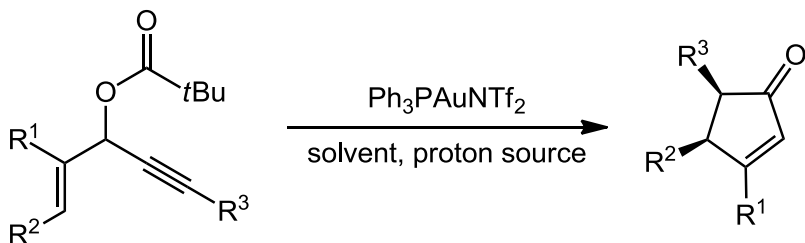
Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950-952.

b) Toste's work



Toste, D. *et al. J. Am. Chem. Soc.* **2005**, *127*, 5802-5803.

c) Lautens's work

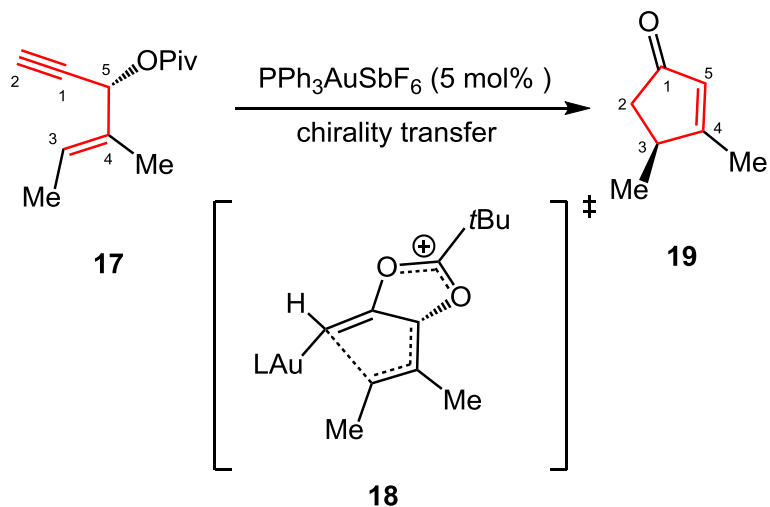


solvent: CH₂Cl₂, CDCl₃, DCE, toluene
proton sources: H₂O, AcOH, HCl

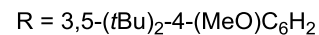
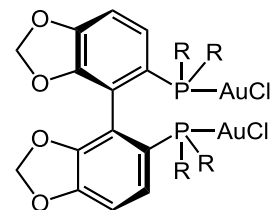
Lautens, M. *et al. Org. Lett.* **2016**, *18*, 5058-5061.

Asymmetric Rautenstrauch reaction

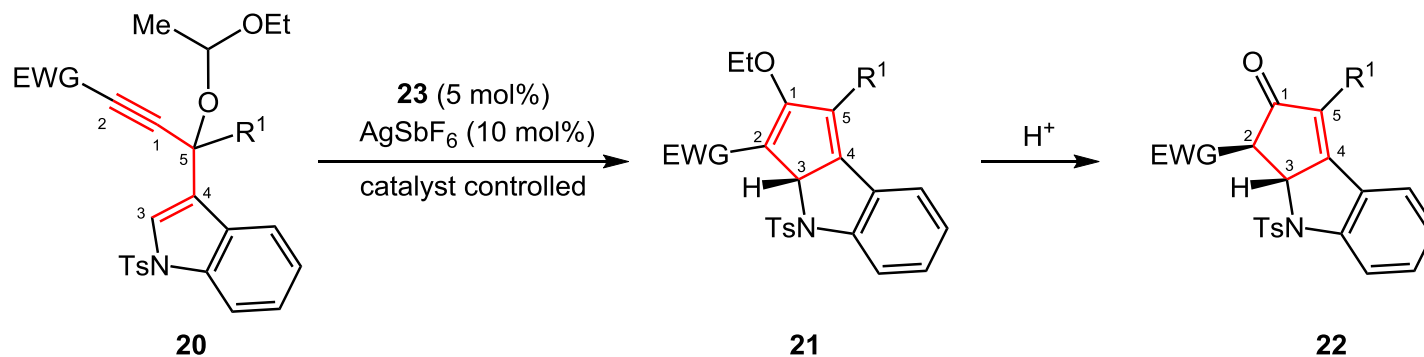
a) Chirality transfer



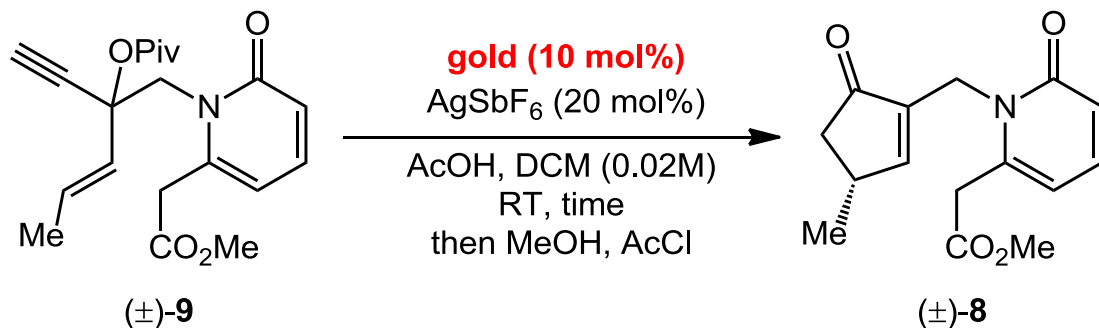
(S)-DTBM-Segphos(AuCl)₂ (**23**)



b) Catalyst controlled

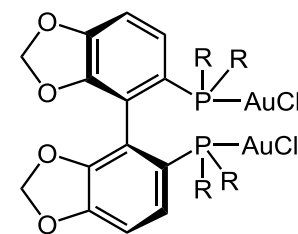


Different chiral gold catalysts



Entry	gold	additive	er
1	$\text{PPh}_3\text{AuNTf}_2$	-	-
2	I	4Å MS	75:25
3	I	-	75:25
4	II	-	70:30
5	III	-	85:15
6	IV	-	83:17
7	V	-	55:45

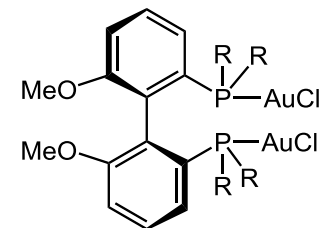
(S)-Segphos



$\text{R} = 3,5\text{-}(t\text{Bu})_2\text{-4-(MeO)C}_6\text{H}_2$ (**I**)

$\text{R} = 3,5\text{-(Me)}_2\text{-C}_6\text{H}_3$ (**II**)

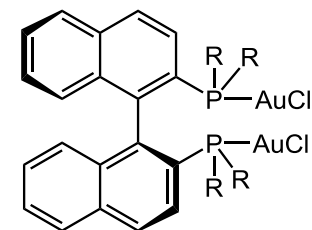
(S)-Biphep



$\text{R} = 3,5\text{-}(t\text{Bu})_2\text{-4-(MeO)C}_6\text{H}_2$ (**III**)

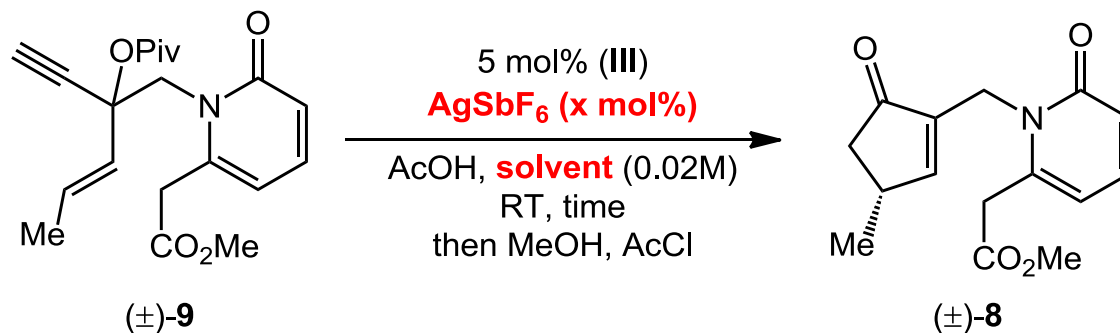
$\text{R} = 3,5\text{-}(t\text{Bu})_2\text{-C}_6\text{H}_3$ (**IV**)

(S)-Binap



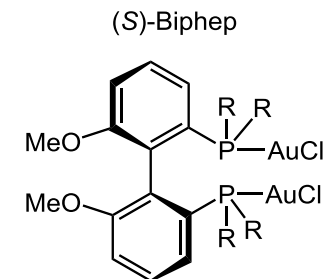
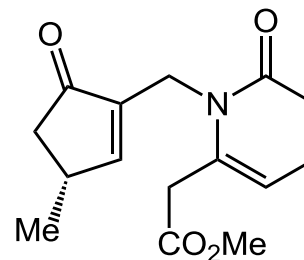
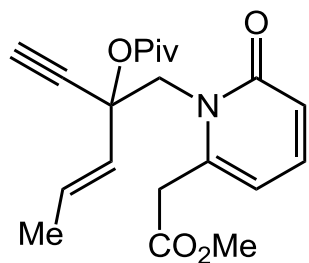
$\text{R} = 3,5\text{-(Me)}_2\text{-C}_6\text{H}_3$ (**V**)

Different solvents and silver/gold ratios



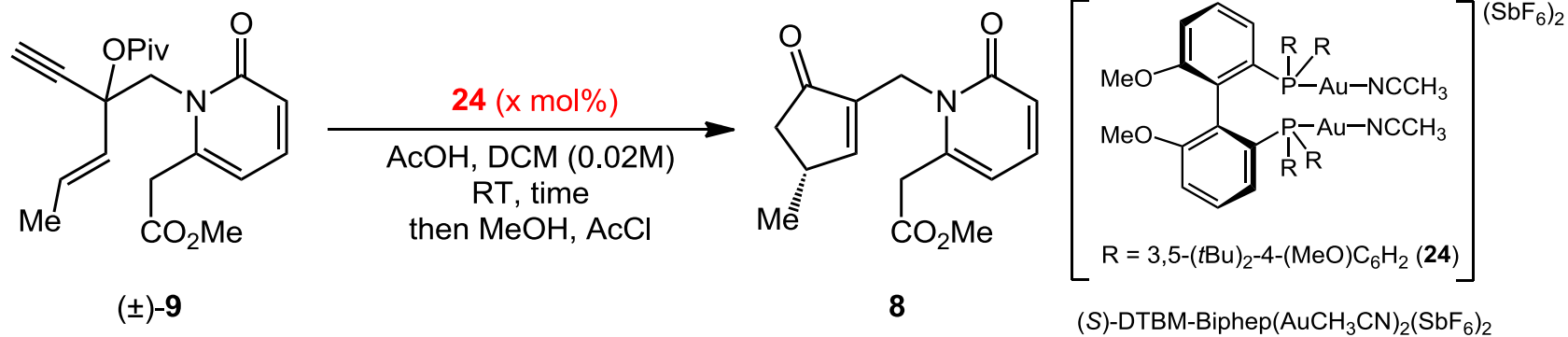
entry	AgSbF ₆ (x mol%)	solvent	er
1	10	Tol	-
2	10	DCM	87:13
3	10	MeNO ₂	73:27
5	10	DCE	80:20
7	10	CH ₃ CN	78:22
8	10	THF	68:32
9	5	DCM	77:23
10	50	DCM	Complex mixture

Different temperatures



entry	tempt. (°C)	time (conversion %)	er
1	25	60 min (100 %)	87:13
2	0	6 h (~40)	93:7
3	-20	6 h (trace)	-
4	-5	24 h (~66 %)	56:44
5	-5	72 h (100%)	60:40

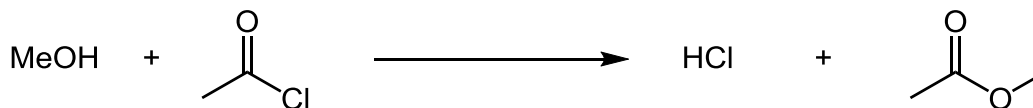
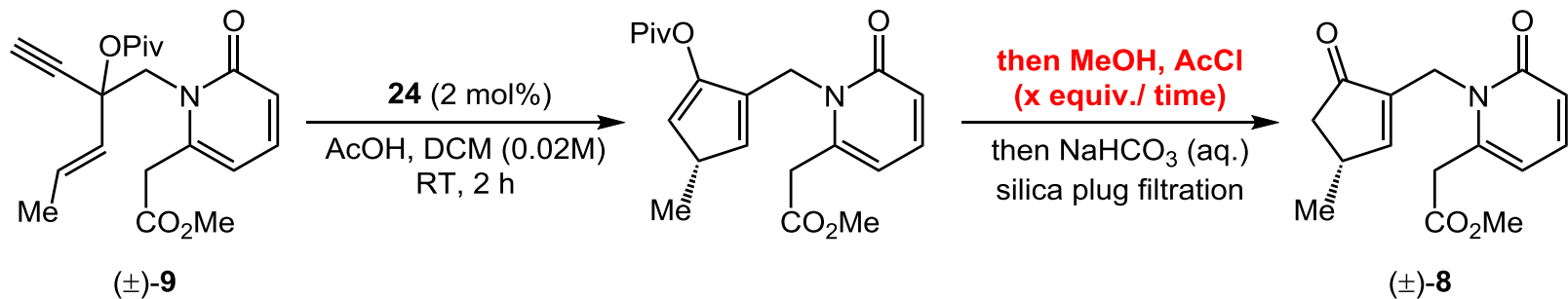
Catalyst loading and reaction times.



entry	x mol%	time (min)	er
1	50	30	77:23
2	5	90	88:12
3	2	120	92:8
4 ^a	2	120	11:89

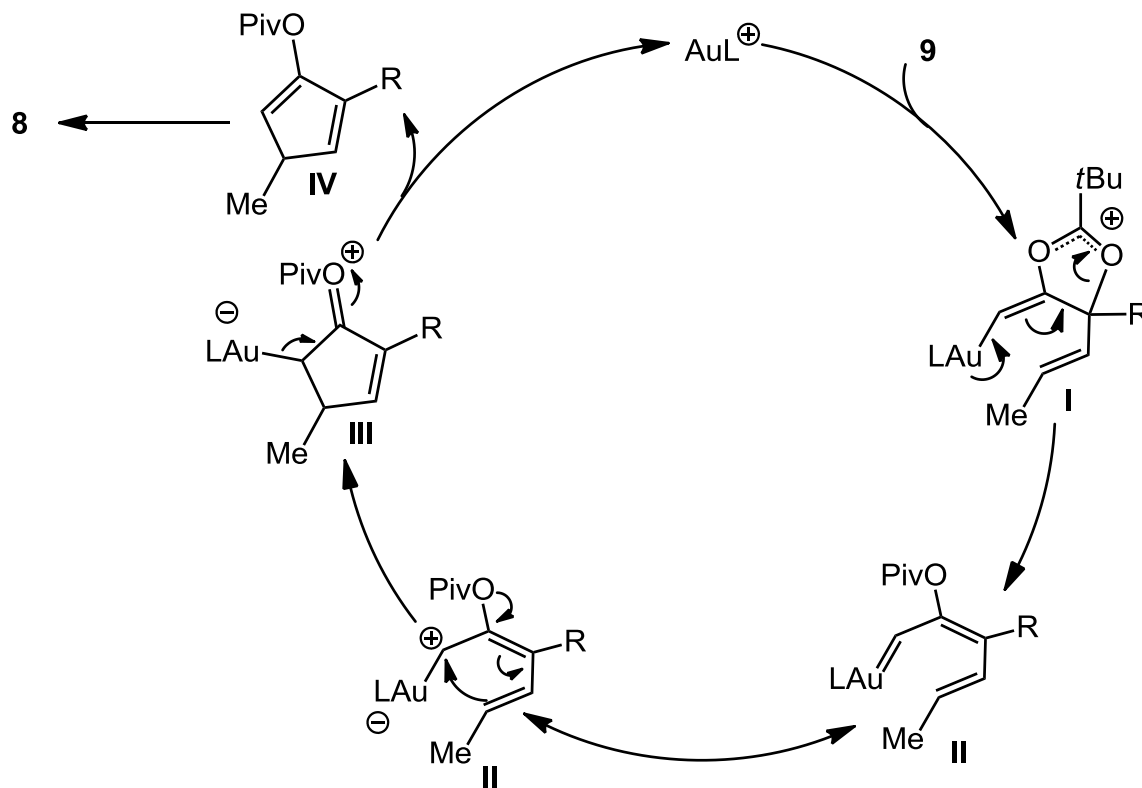
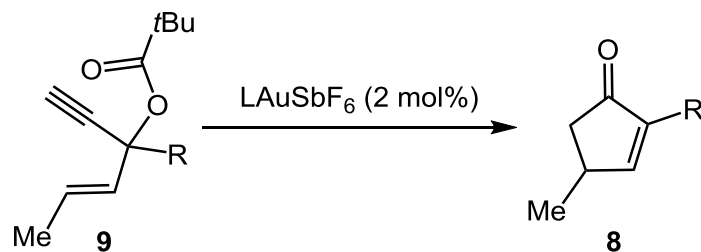
^a The reaction was performed with (*R*)-**24**.

Different work-up conditions

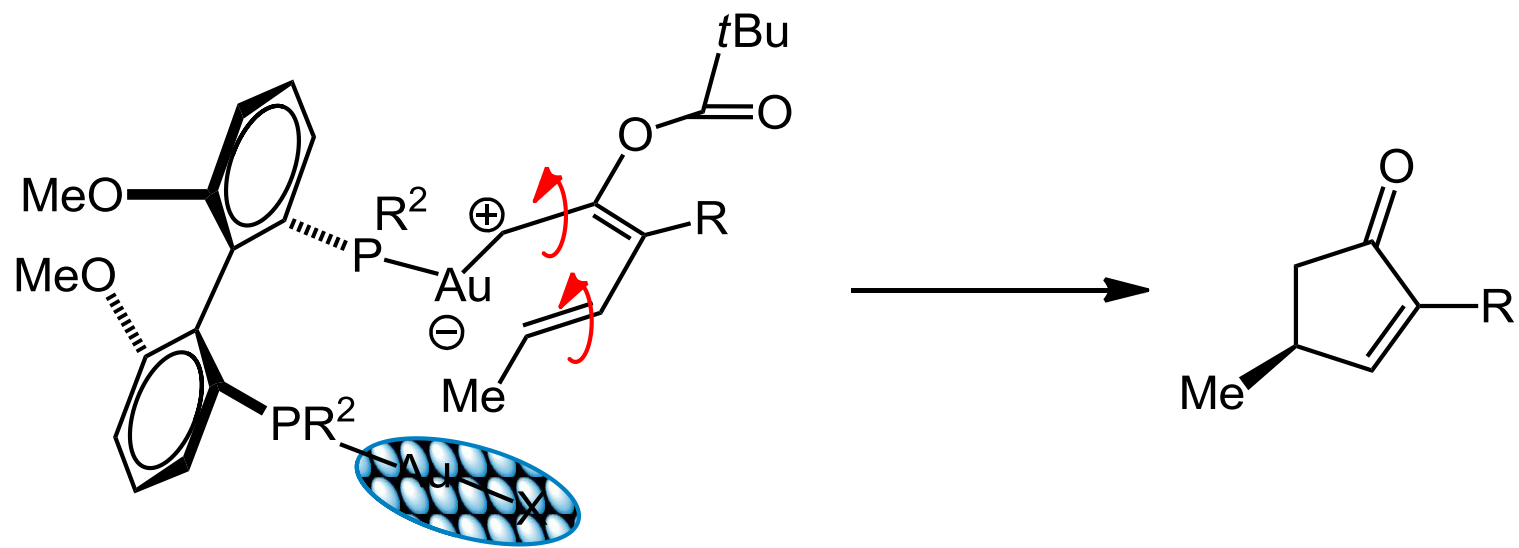


entry	x equiv	time (min)	er
1	2	5	low conversion
2	10	5	90:10
3	50	3	90:10
4	50	20	57:43

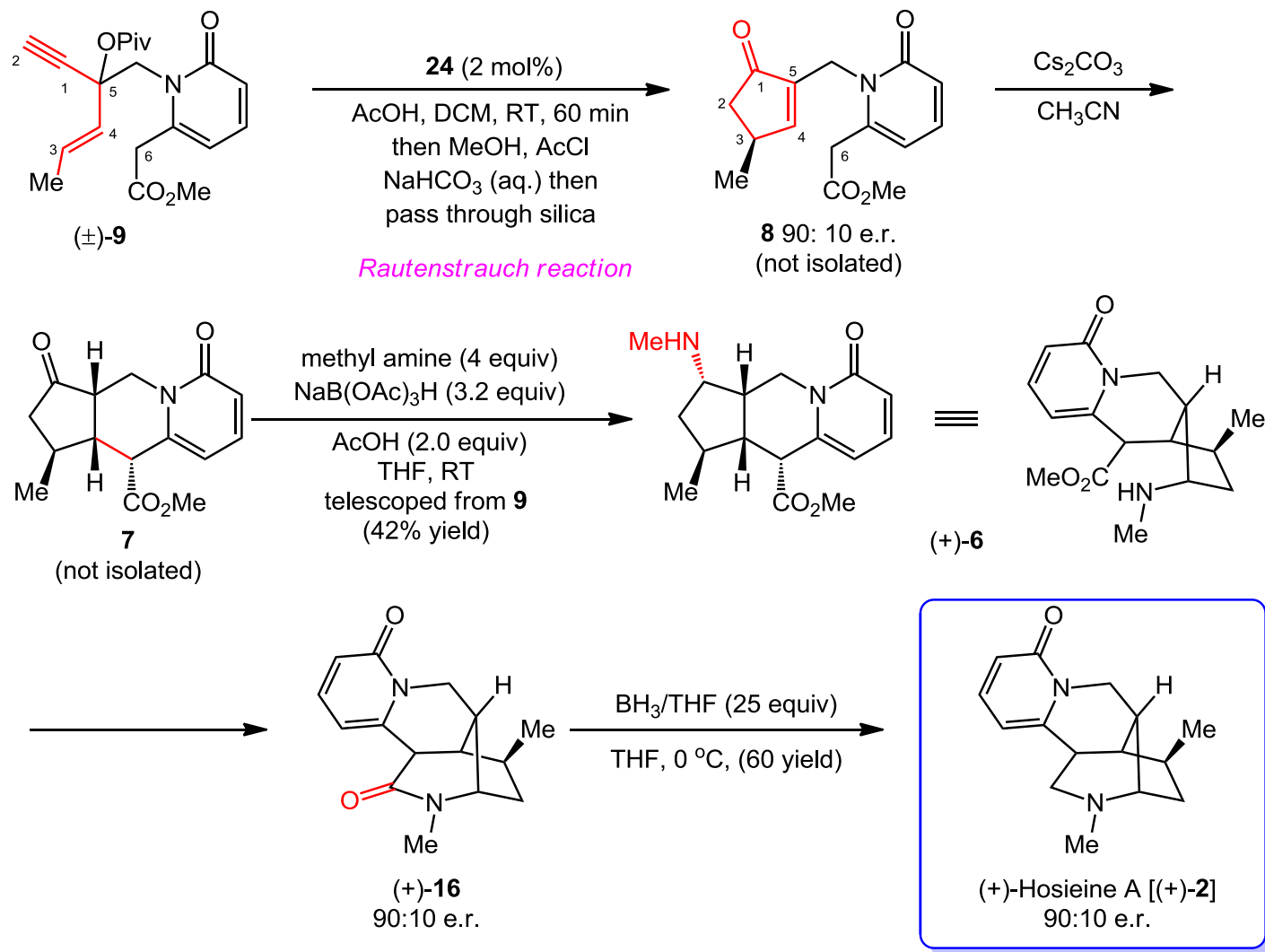
Mechanism for Rautenstrauch reaction



Explanation for stereochemistry

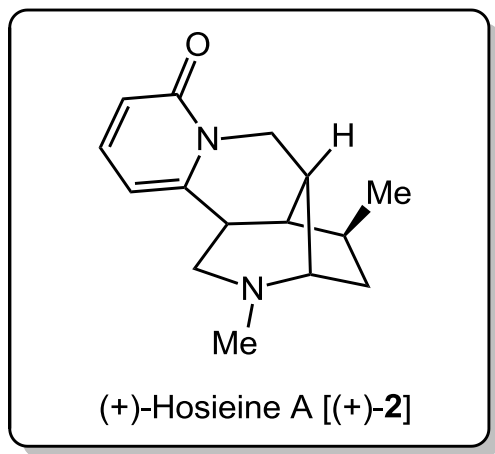


The synthesis of (+)-Hosieine A [(+)-2]

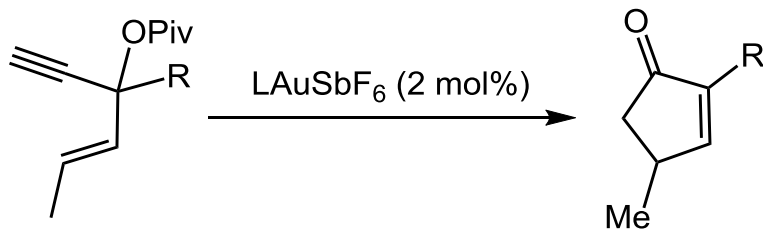


Summary

- Total Synthesis of (+)- and (+/-)-Hosieine A: 7 Steps, 16% Overall Yield;



- Gold-catalyzed Rautenstrauch Reaction was Developed.



The first paragraph

The synergism between complex-molecule synthesis and methods development continues to benefit both fields of research. The former often inspires the latter and the latter enables the development of improved strategies for the former. As part of our efforts to strategically deploy newly developed methods in complex syntheses we were drawn to a new class of cytosine-like lupin alkaloids, hosiaine A–D, which were isolated from the roots of *Ormosia hosi* Hemsl & E. H. Wilson (the fruit of which is a traditional Chinese medicine) by Massiot and co-workers.

The first paragraph

Among the four isolated congeners, hosieline A proved to be the most potent when assayed against the nicotinic acetylcholine receptor (nAChR) $\alpha_4\beta_5$, displaying activity that is significantly greater than nicotine itself. This potent activity, coupled with the limited natural abundance of **2** and the fact that nAChRs are of potential importance in developing treatments for schizophrenia and Alzheimer's disease, led us to begin considering potential strategies for a total synthesis. Herein we report efforts which have now culminated in the development of an efficient synthesis capable of delivering **2** in either racemic or enantioenriched forms.

The last paragraph

In conclusion, a formal synthesis of (-)-hosieline A and the total syntheses of (+)- and (+/-)-hosieline A have been completed and require only seven steps and proceed in an overall 16 % yield. During the course of this study, an unprecedented gold-catalyzed Rautenstrauch/Michael reaction sequence was developed and it expands the substrate scope of the initiating reaction, and exemplifies the power of this overall process in complex-molecule synthesis. Efforts to apply this strategy to production of novel nAChRs antagonists are underway and will be reported in due course.

***Thanks
for your attention***
