PGM-Catalyzed Cyclization Reactions for the Synthesis of Ergot Alkaloids

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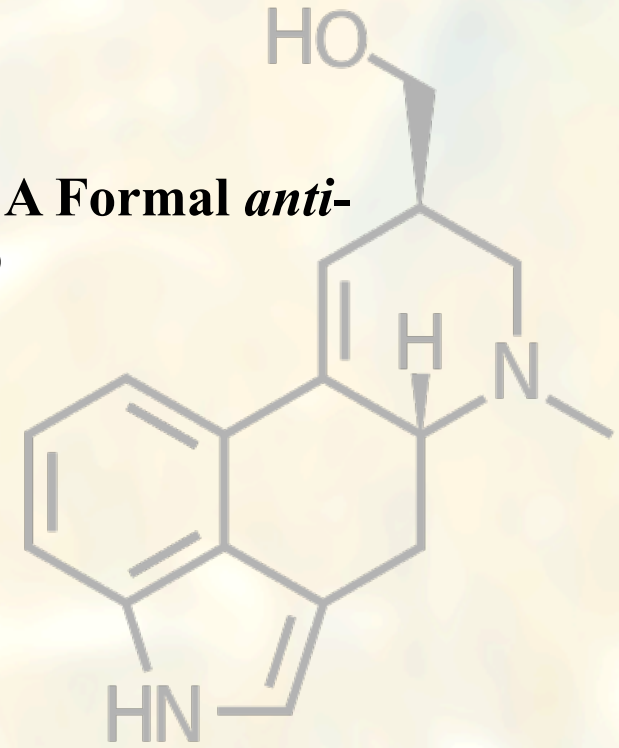
Wipf Group

Current Literature 11/18/17

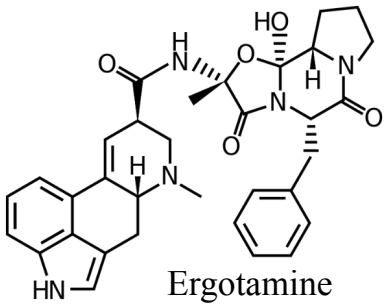
Overview

- Lysergol and the Ergot Alkaloids
- PGM Highlights in Total Syntheses
- **Enantioselective Total Synthesis of (+)-Lysergol: A Formal *anti*-Carbopalladation/Heck Cascade as the Key Step**
  - Org. Letters (2017)
  - Werz Group - Technische Universität Braunschweig

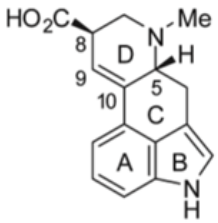


Lysergol Derivatives

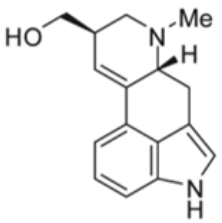
- *Claviceps purpurea*
- Ergot / Indole Alkaloids
- 5-HT1R Agonists (Serotonin)
- Fused-Indole and C5/C8 Stereocenters
- Plenty of Total Syntheses
  - Woodward (1956)
  - Highlight PGM (Pt-Group Metals)



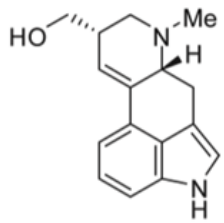
Ergotamine



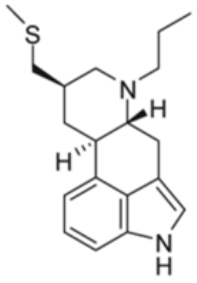
Lysergic Acid



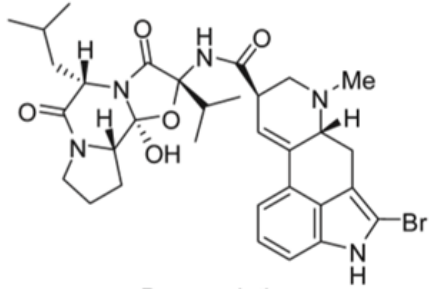
Lysergol



Isolysergol

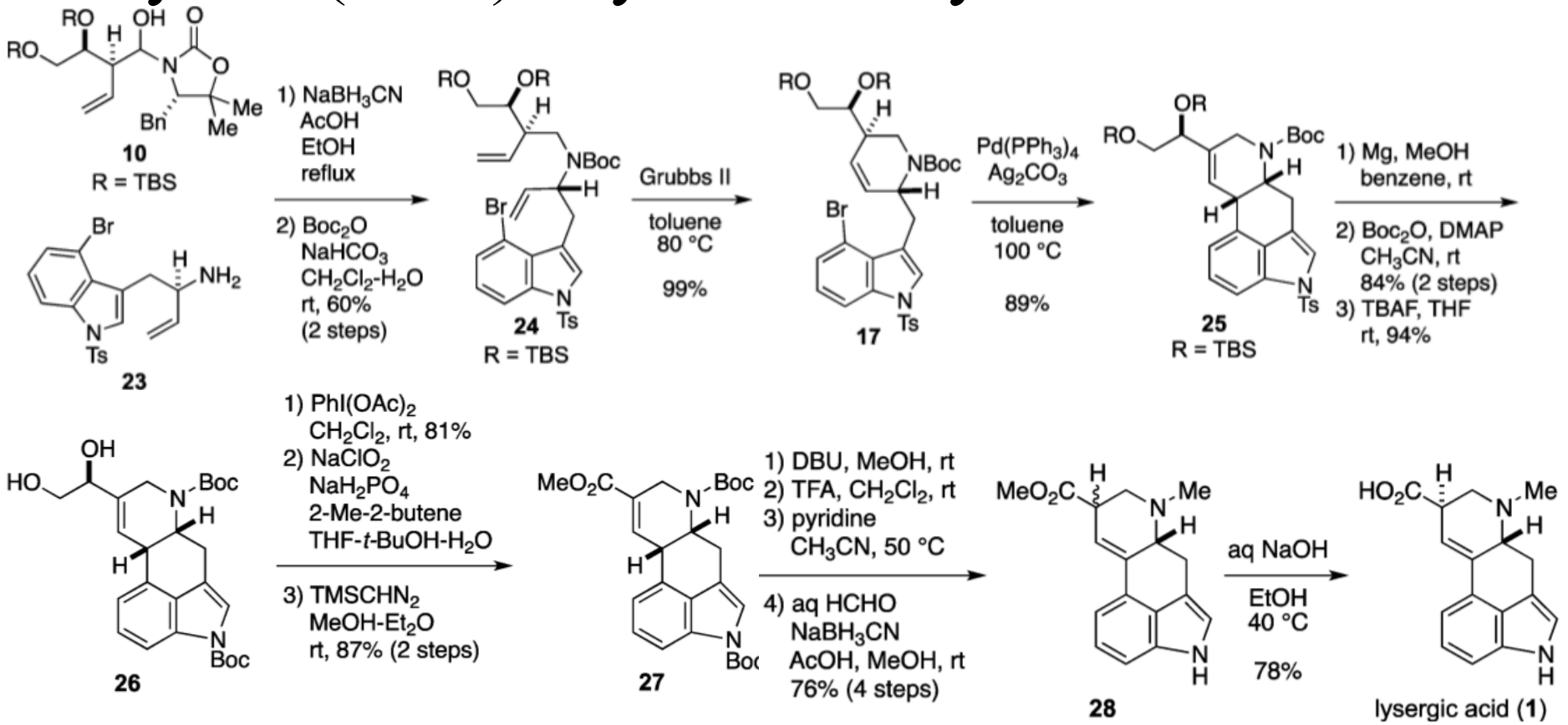


Pergolide

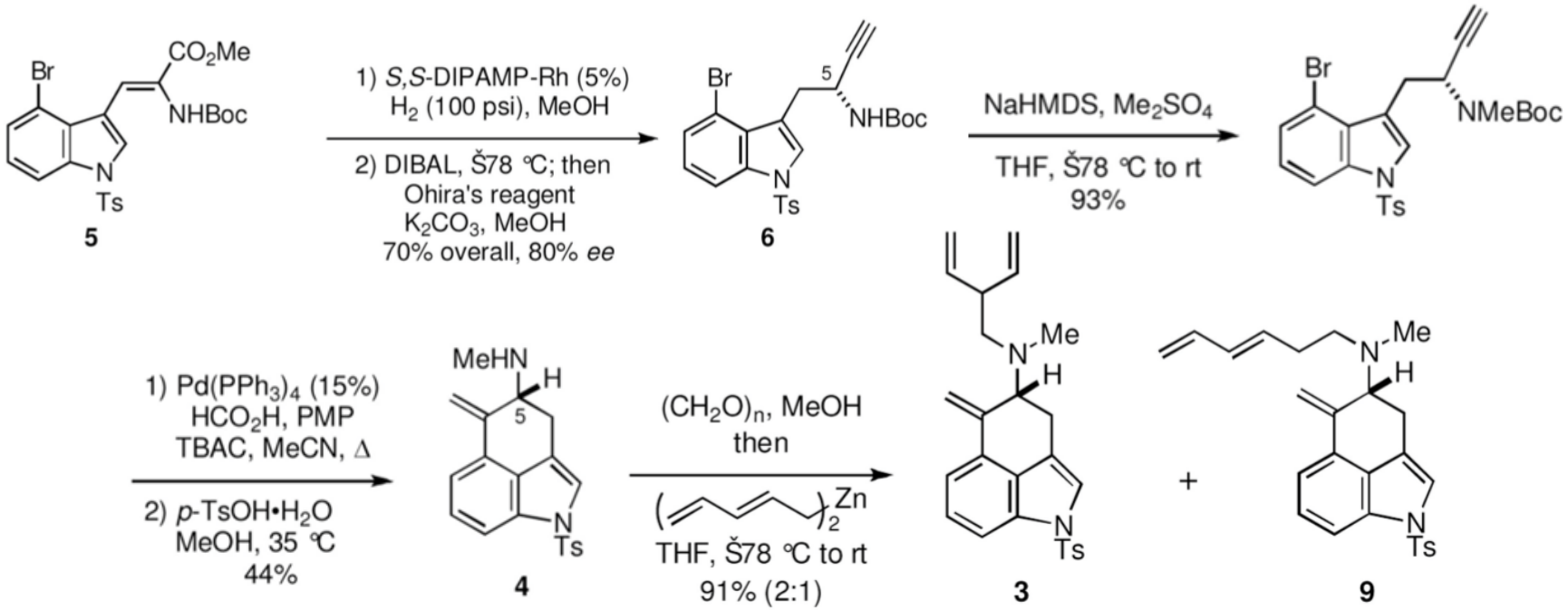


Bromocriptine

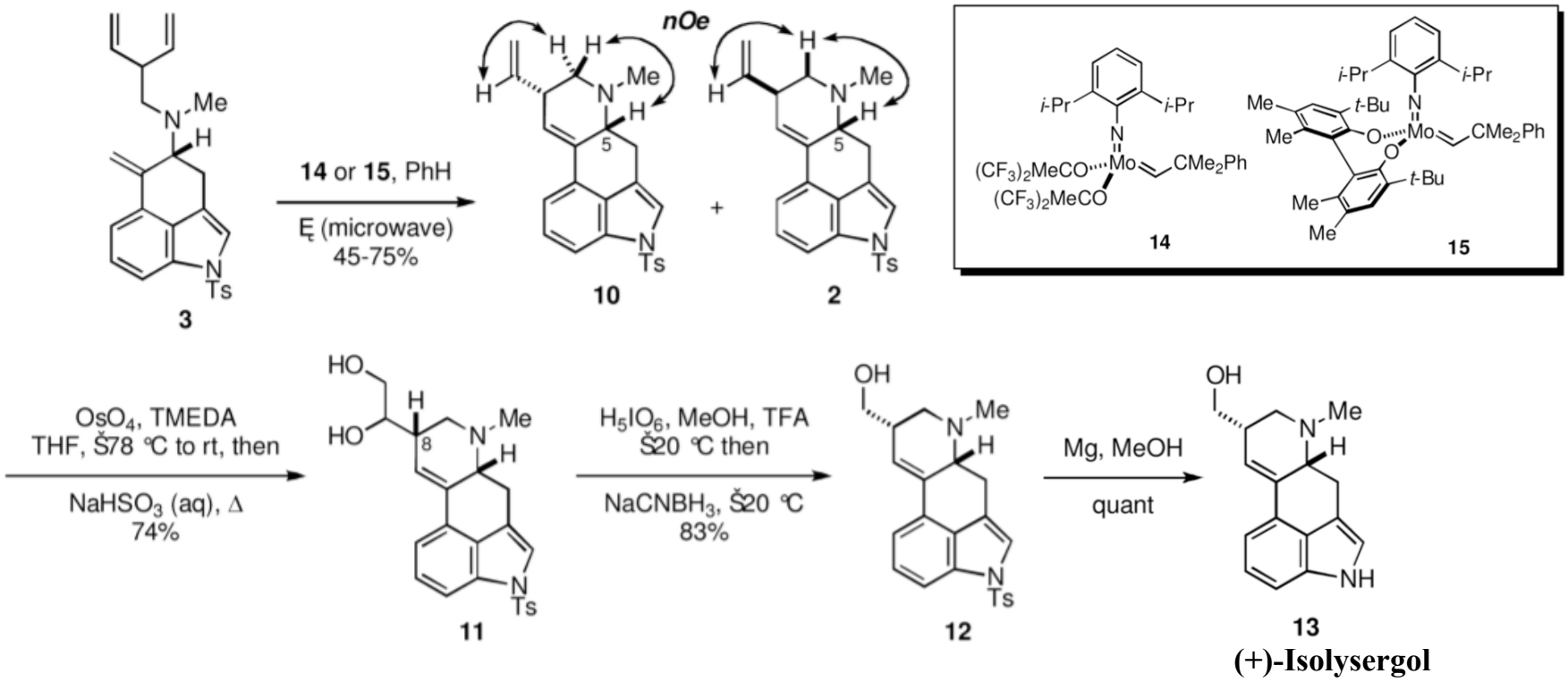
Fukayama (2009) Asymmetric Synthesis



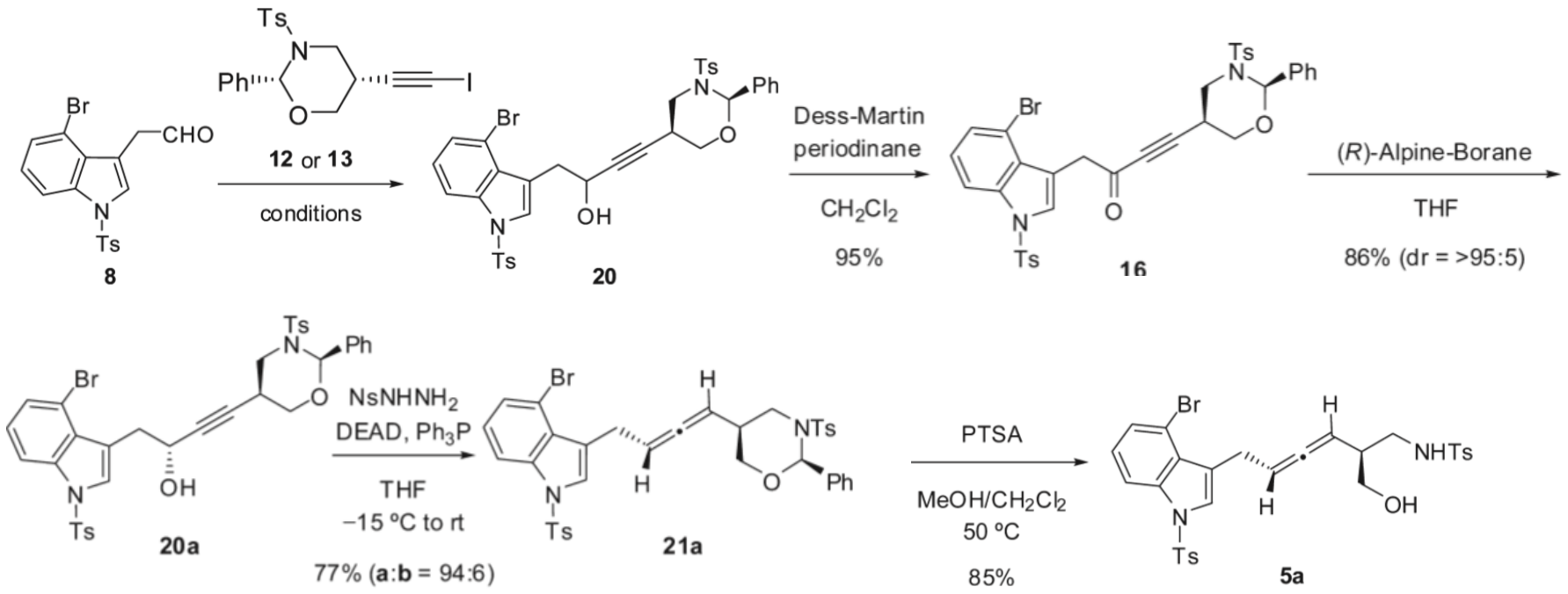
Martin (2012) Enantioselective



Martin (2012) Enantioselective Metathesis



Ohno (2011) Enantioselective Cascade



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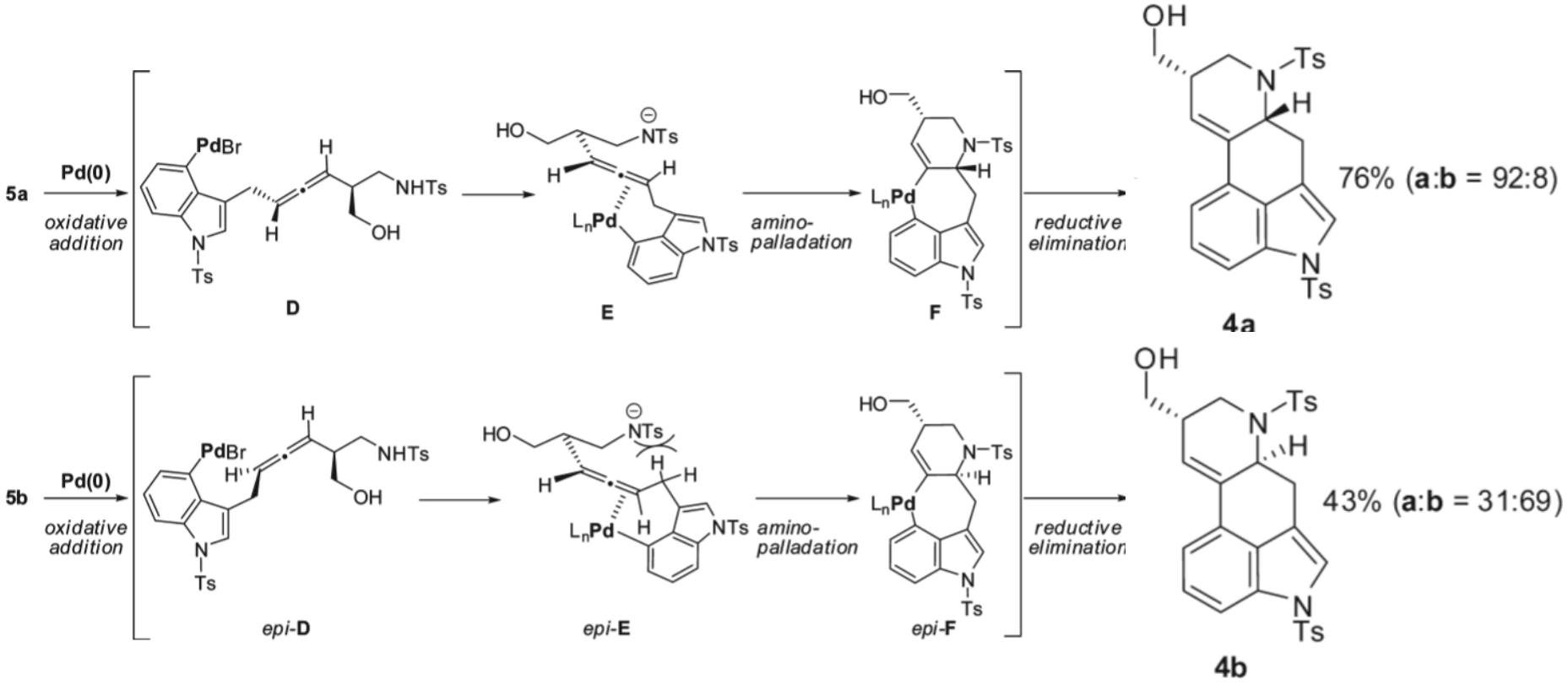
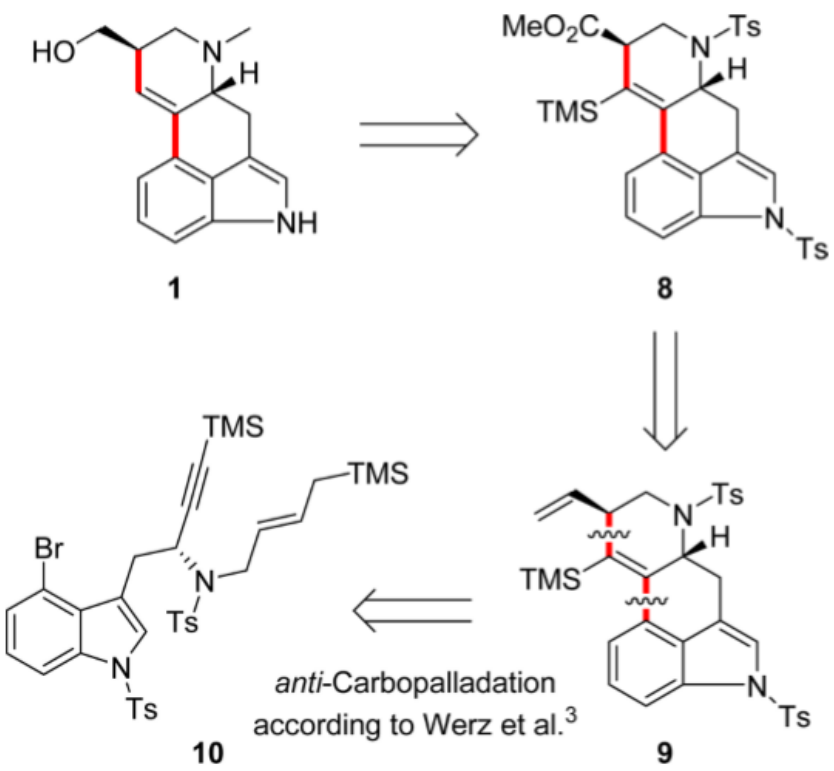
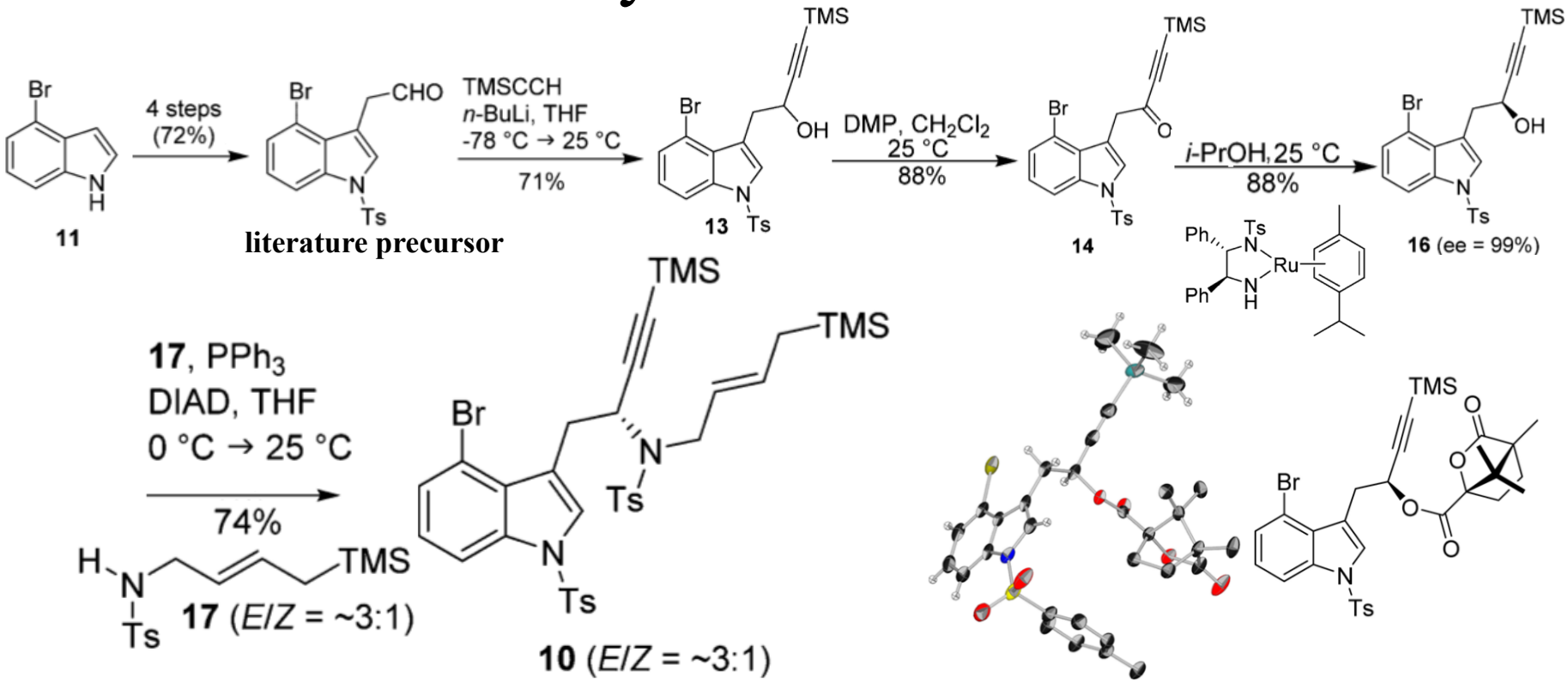


Milde (2017) - Synopsis

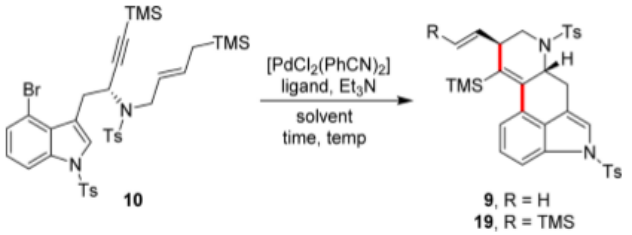
- 12 Steps from Literature Precursor
- 13% Overall Yield
- Enantioselective
- Key step: Tandem *Anti*-Carbopallidation/ Heck Cascade



Cascade Precursor Synthesis

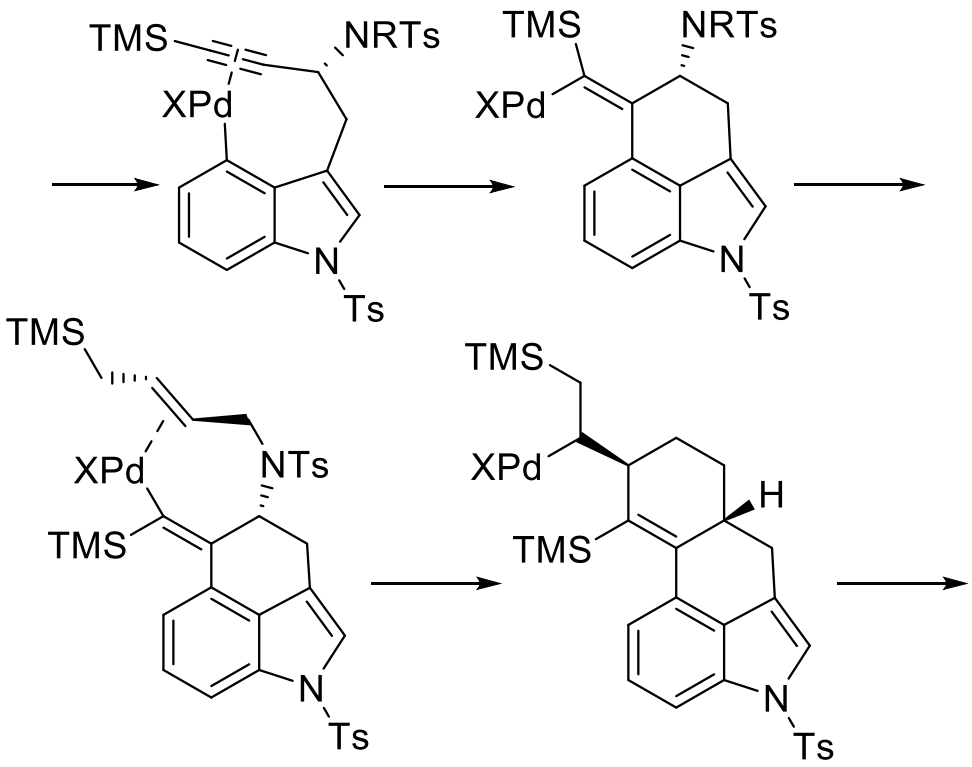


Anti-Carbopallidation/Heck Coupling

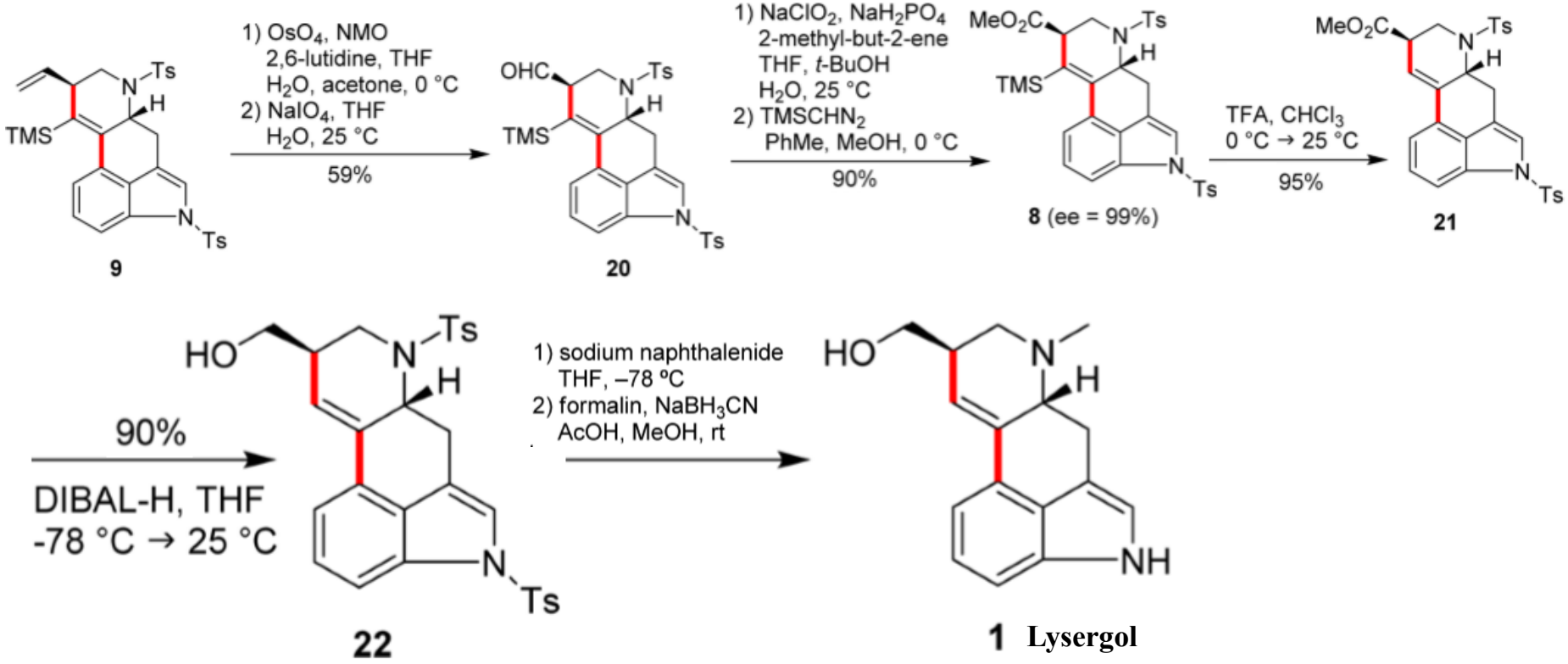


entry	ligand	solvent	temp (°C)	time (h)	yields (%)
1	[*t*-Bu$_3$PH][BF$_4$]	DMF	70	15.5	**9**, 29
					19, 37
2	[*t*-Bu$_3$PH][BF$_4$]	DMF	100	1.5	**9**, 41
					19, 34
3	XPhos	DMF	100	2.5	**9**, 59
					19, 13
4	BrettPhos	DMF	100	7.5	**9**, 56
					19, 13
5	XPhos	DMF	120	2.0	**9**, 68
					19, 17
6	XPhos	DMA	120	2.0	**9**, 80
					19, 17
7[b]	XPhos	DMF	120	decomposition	
8[c]	XPhos	DMF	120	many side reactions	
9	XPhos	DMA	140	2.0	**9**, 72
					19, 12

[a]Reaction conditions: **10** (1.0 equiv), [PdCl$_2$(PhCN)$_2$] (10 mol %), ligand (20 mol %), Et$_3$N (5.0 equiv), solvent (25 mM), temp, time. [b]*n*-Bu$_4$NOAc (5.0 equiv) was used instead of Et$_3$N. [c][Pd(OAc)$_2$] (10 mol %) was used instead of [PdCl$_2$(PhCN)$_2$].



Finishing the Synthesis



In Conclusion

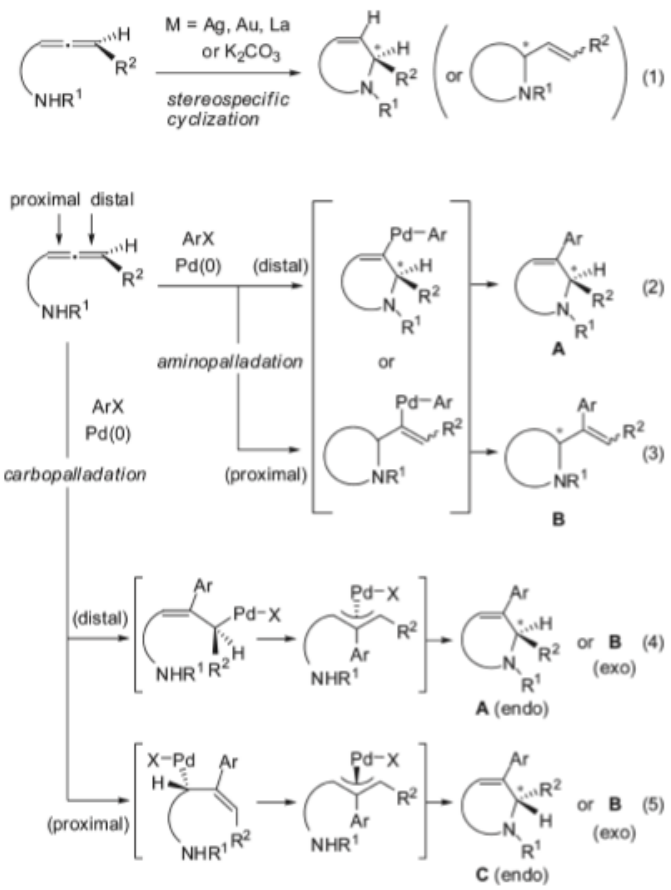
- Indole Alkaloids
- PGM Highlights in Total Synthesis
  - Back-to-back Metathesis/Heck Cyclizations (Fukayama, 2009)
  - Late-Stage Asymmetric Metathesis (Martin, 2012)
  - Aminopallidation (Ohno, 2011)
- Anti-Carbopallidation Heck Cascade (Milde, 2017)
- Questions?

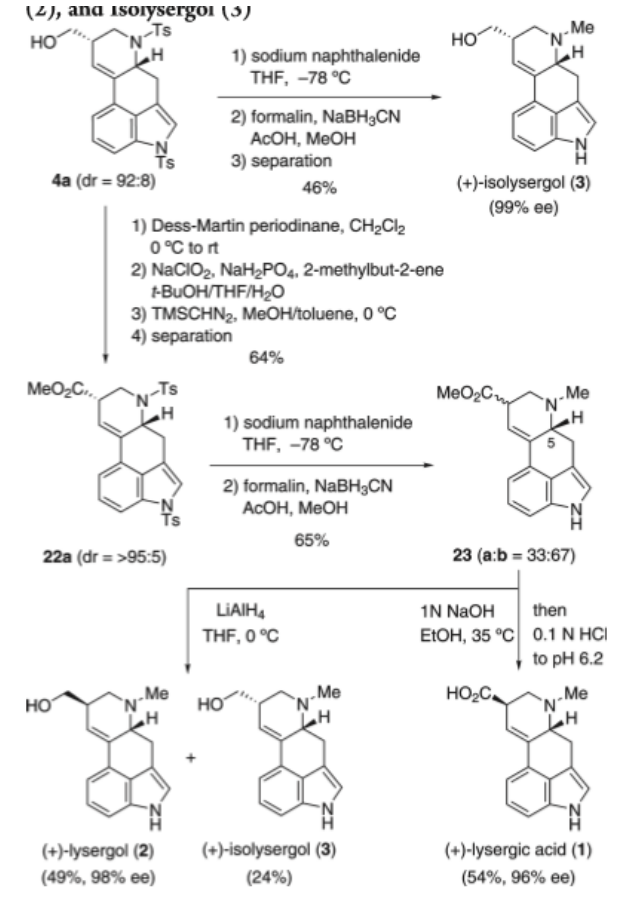
Citations

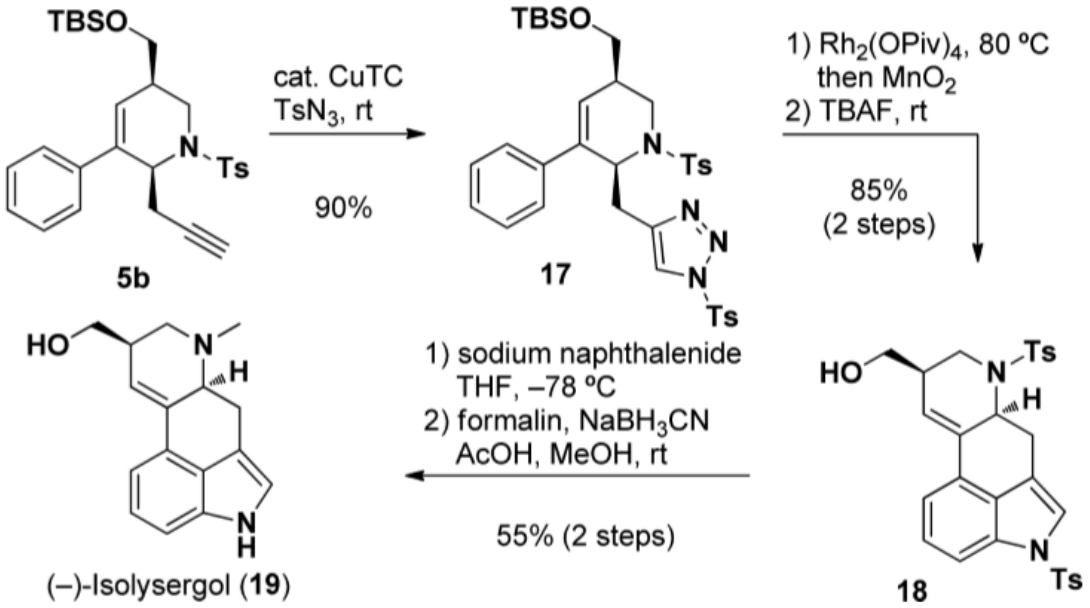
- Woodward
  - http://pubs.acs.org/doi/pdf/10.1021/ja01594a039
- Fukayama
  - http://pubs.acs.org/doi/pdf/10.1021/ol4019562
- Martin
  - http://europepmc.org/articles/PMC2879020
- Ohno
  - http://pubs.acs.org/doi/abs/10.1021/jo102388e
- Milde
  - http://pubs.acs.org/doi/pdf/10.1021/acs.orglett.7b00675

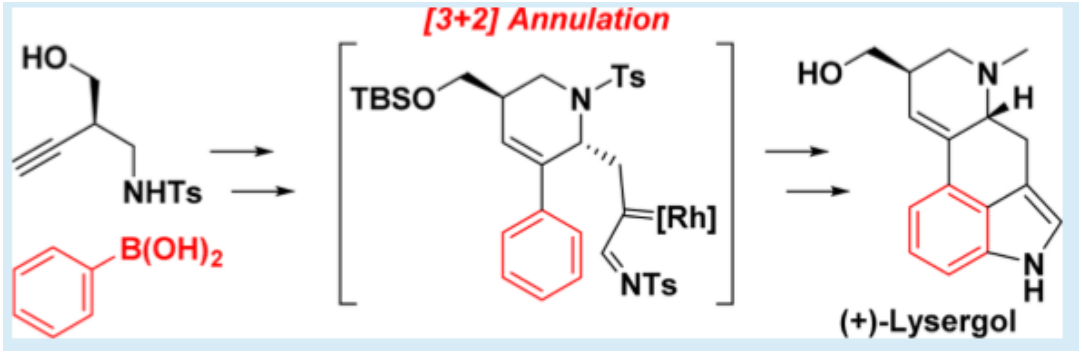
Ohno Synthesis

Scheme 2. Product Distribution of Transition-Metal-Mediated Cyclization of Allenes Bearing an Amino Group






TBSO
N
Ts
5b
cat. CuTC
TsN3, rt
90%
TBSO
N
Ts
N
N
N
Ts
17
1) Rh2(OPiv)4, 80 °C
then MnO2
2) TBAF, rt
85%
(2 steps)
HO
N
H
N
H
(–)-Isolysergol (19)
1) sodium naphthalenide
THF, –78 °C
2) formalin, NaBH3CN
AcOH, MeOH, rt
55% (2 steps)
HO
N
Ts
H
N
Ts
18


[3+2] Annulation
HO
NHTs
B(OH)2
TBSO
N
Ts
[Rh]
NTs
HO
N
H
N
H
(+)-Lysergol