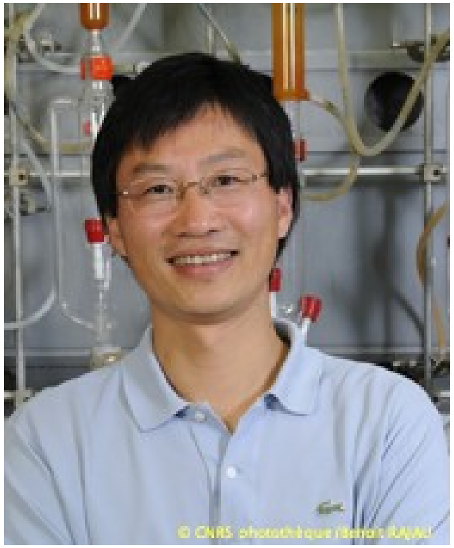
Literature Report

Palladium-Catalyzed Enantio-selective Desymmetrizing Aza-Wacker Reaction

Reporter: Mu-Wang Chen
Checker: Fan-Jie Meng
Date: 2018-06-04

Bao, X.; Wang, Q.; **Zhu, J.**
Angew. Chem. Int. Ed., **2018**, *57,* 1995.

CV of Jieping Zhu



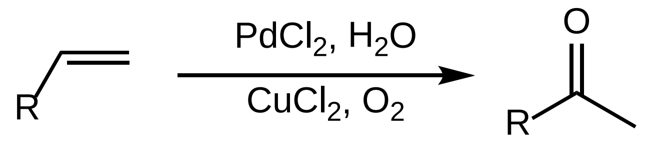
- 1980-1984 B.Sc., Hanzhou Normal University
- 1984-1987 M. Sc., Lanzhou University
- 1987-1991 Ph.D., University Paris XI, France
- 1991–1992 Post-doct., Texas A & M University, USA
- 1992–2010 Director of Research, ICSN, CNRS, France
- 2010–now Professor, EPFL-SB-ISIC-LSPN, Switzerland

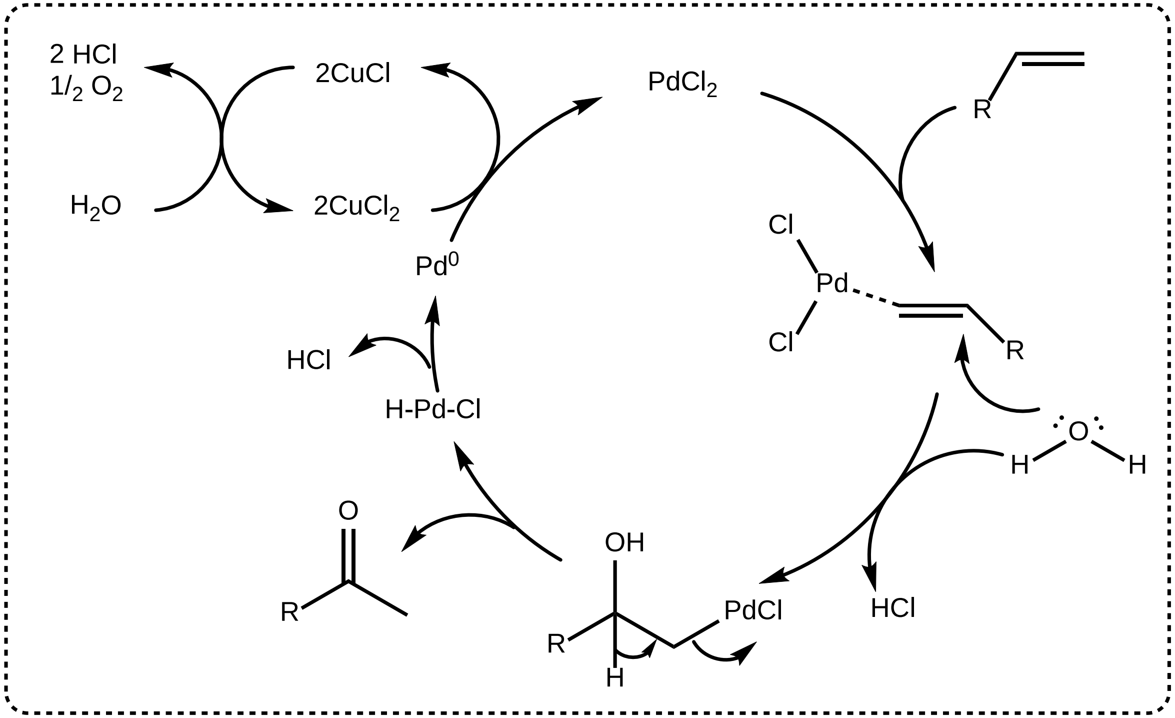
Research:

- Total synthesis of natural products
- Multicomponent reactions
- Metal-catalyzed domino process
- Catalytic enantioselective transformations

Contents

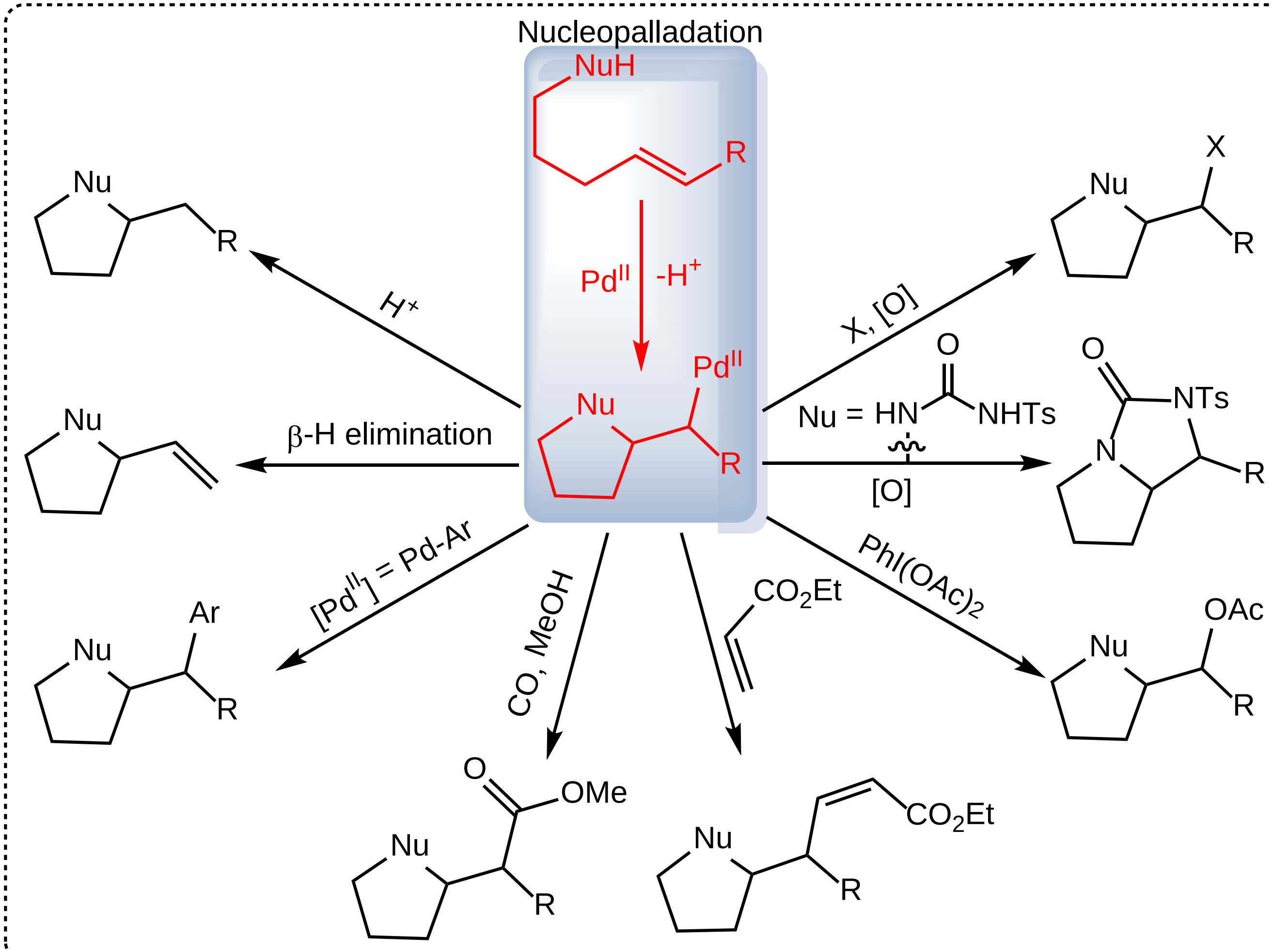
Introduction: Wacker Reaction





From Wikipedia

Introduction: Wacker Reaction

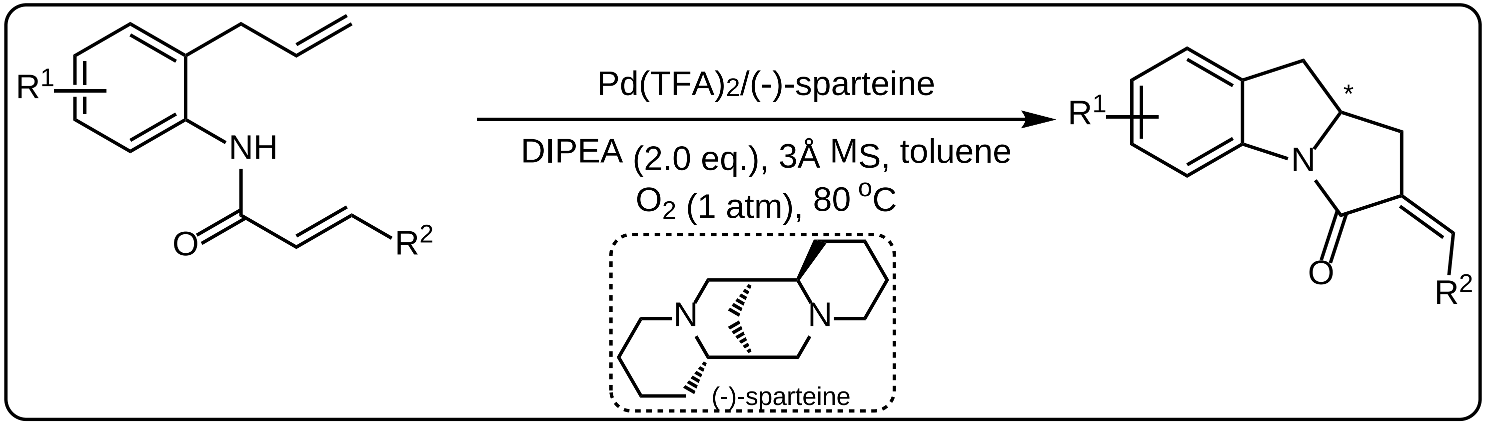


McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

Introduction: Aza-Wacker Reaction

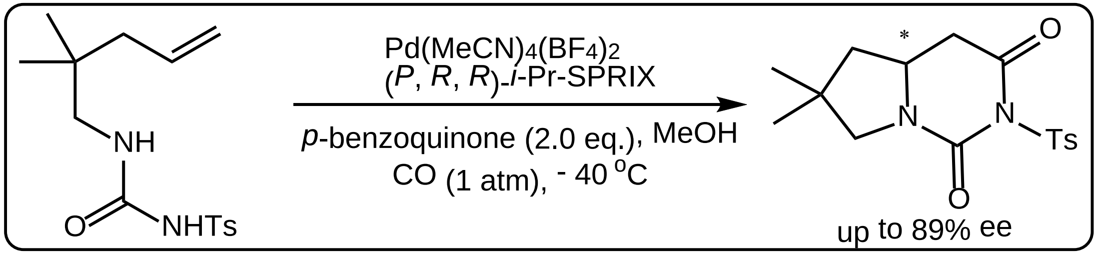
Enantioselective intramolecular aza-Wacker-type reaction:

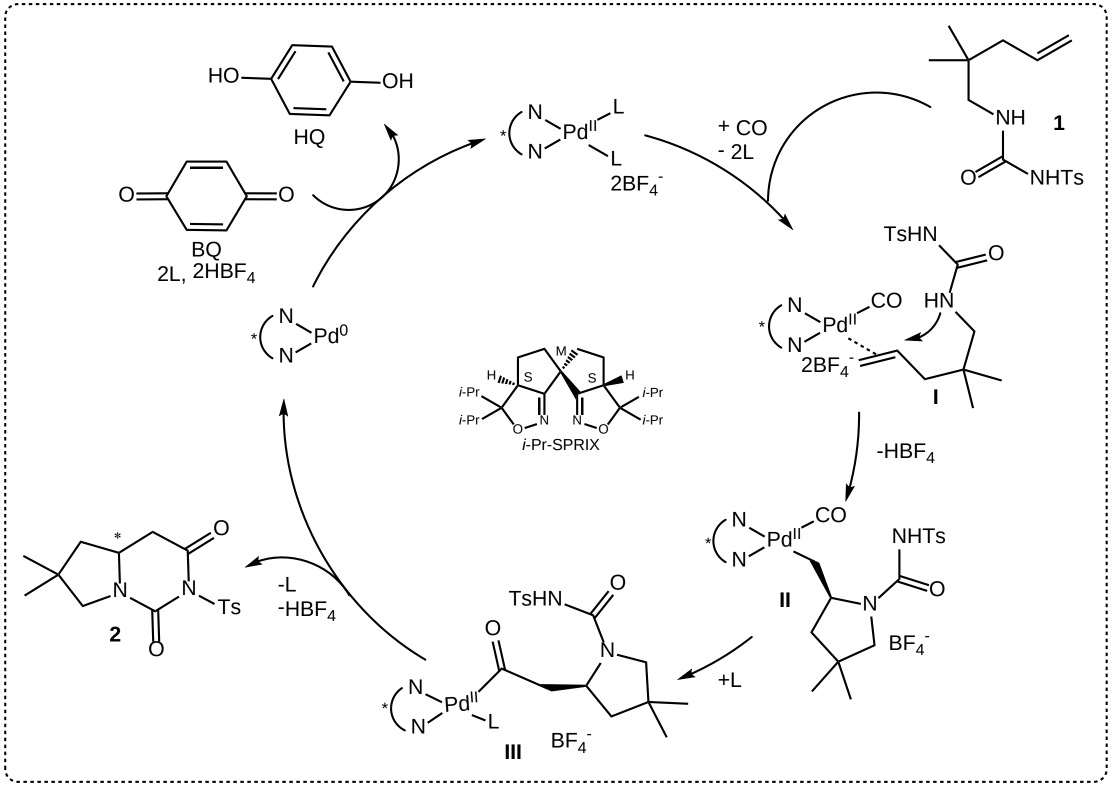
a) the **reversibility** of the aminopalladation step
b) the **competing** *syn*- and *anti*-aminopalladation processes
c) the **limited** choice of chiral ligands



Yang, D. et al. *J. Am. Chem. Soc.* **2006**, *128*, 3130.
Yang, D. et al. *Org. Lett.* **2009**, *11*, 5626.
Yang, D. et al. *Org. Lett.* **2017**, *19*, 316.

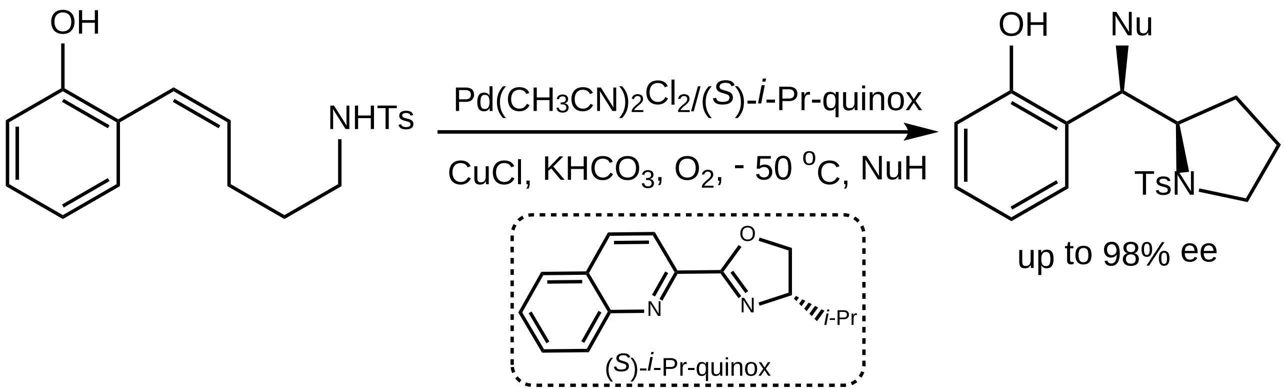
Introduction: Aza-Wacker Reaction



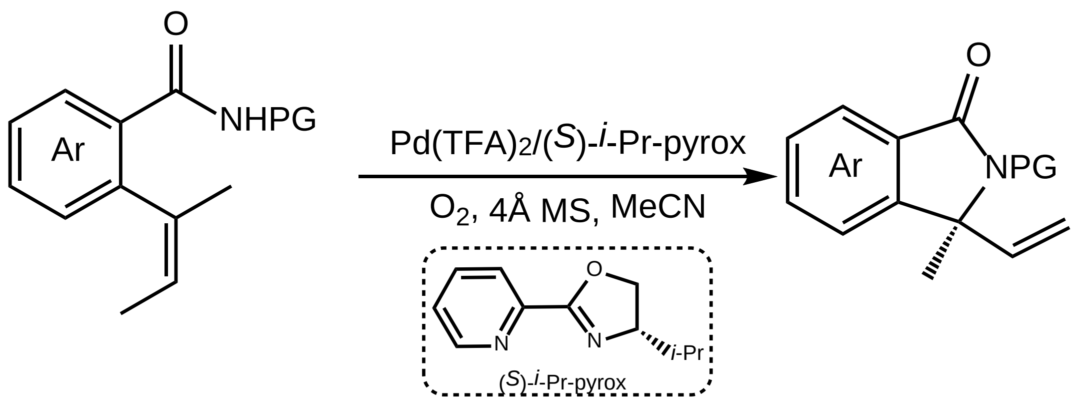


Sasai, H. et. al. *J. Org. Chem.* **2009**, *74,* 9274.

Introduction: Aza-Wacker Reaction

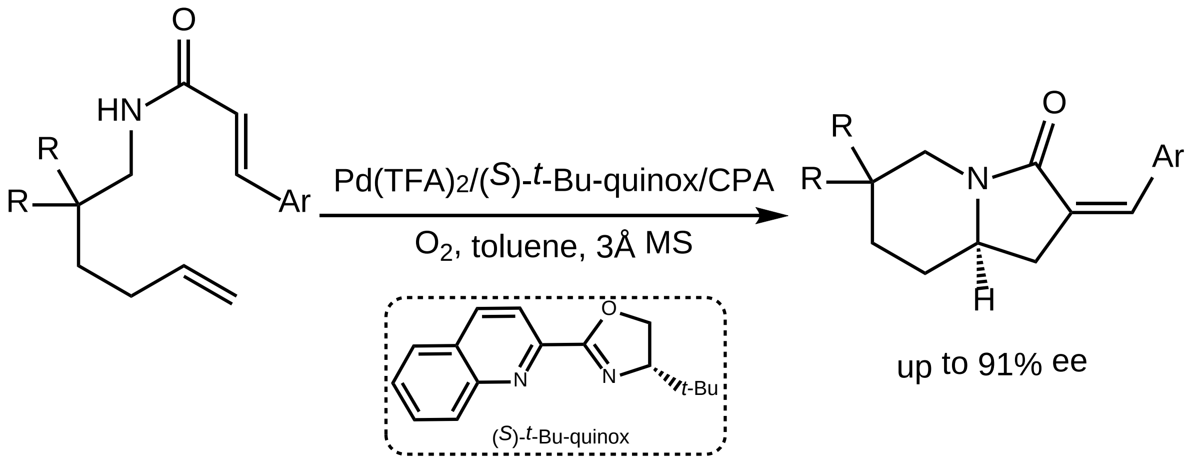


Sigman, M. S. et. al. *Org. Lett.* **2012**, *14*, 4074.

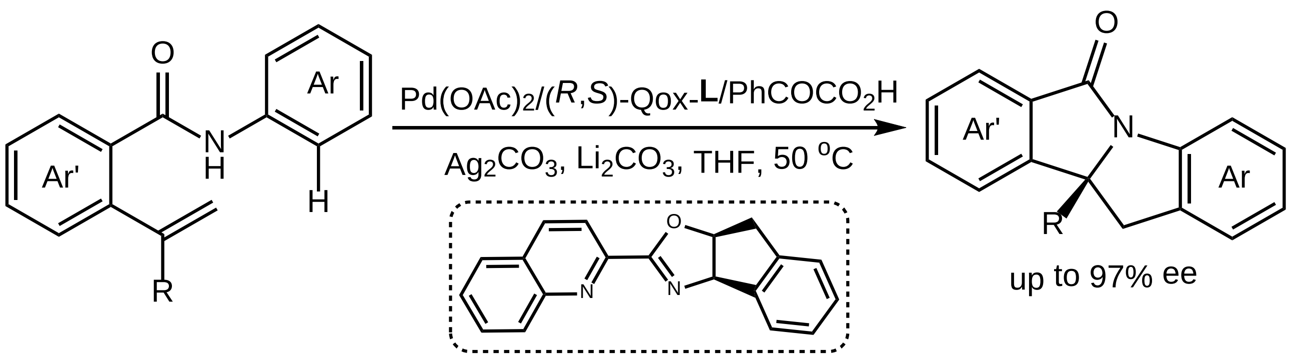


Zhang, W. et. al. *Angew. Chem. Int. Ed.* **2012**, *51*, 9141.

Introduction: Aza-Wacker Reaction

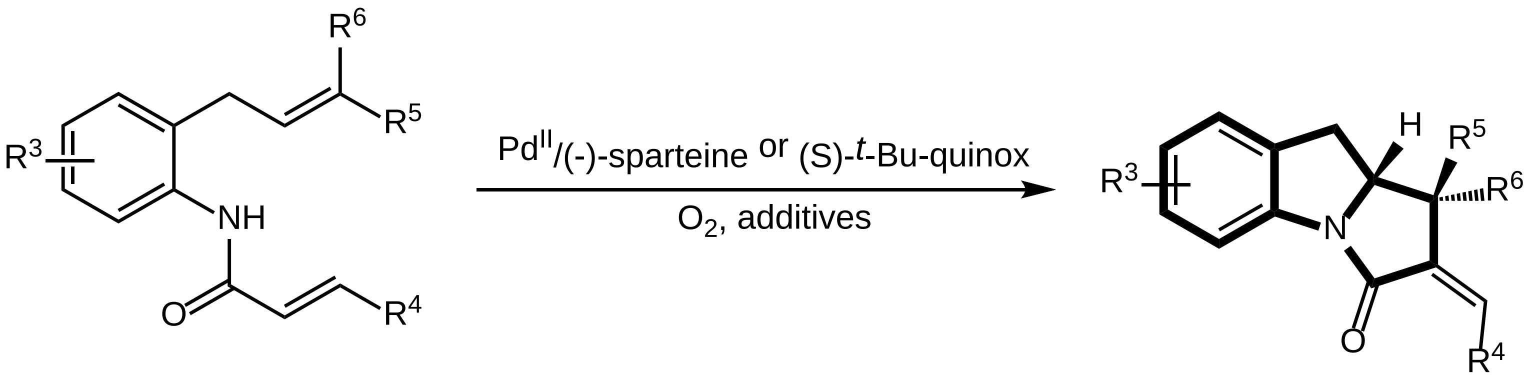


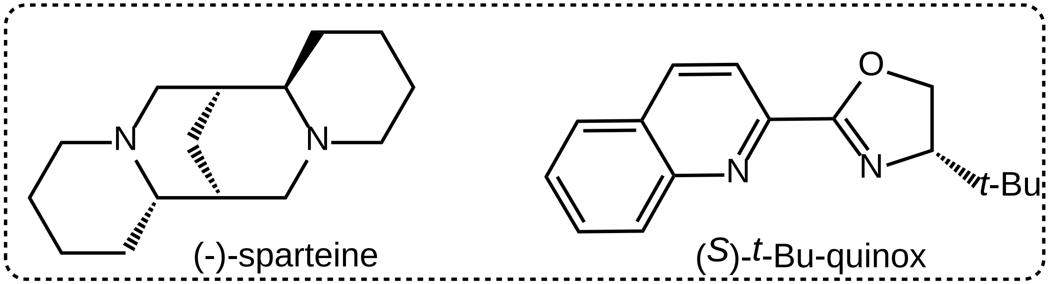
Gong, L.-Z. et. al. *Org. Chem. Front.* **2014**, *1, 473*.

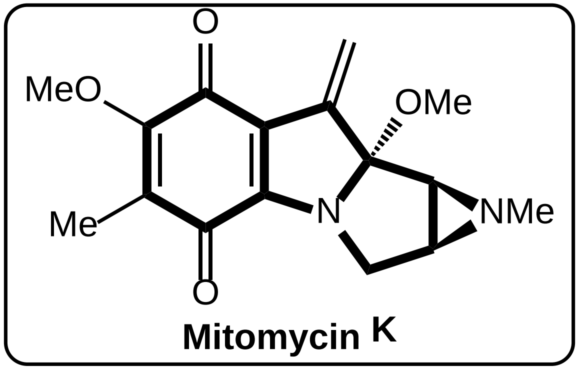


Liu, G. et. al. *Angew. Chem. Int. Ed.* **2017**, *56,* 5336.

Pd-Catalyzed Enantioselective Aza-Wacker Reaction

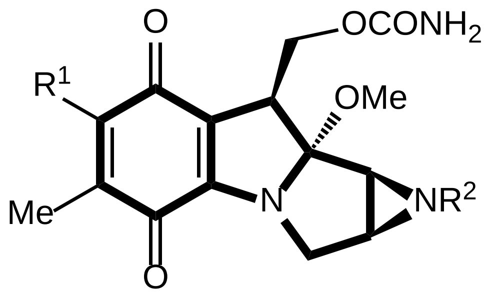






Yang, D. et. al. *Angew. Chem. Int. Ed.* **2017**, *56,* 5886.

Enantioselective Synthesis of (+)-Mitomycin K

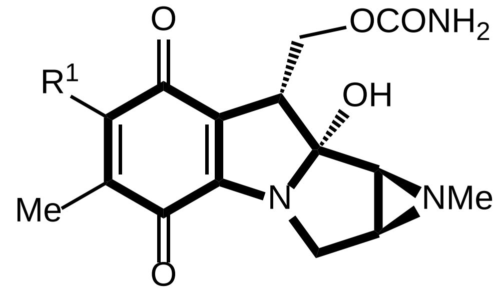


Mitomycin A R^1 = OMe, R^2 = H
Mitomycin C R^1 = NH_2, R^2 = H

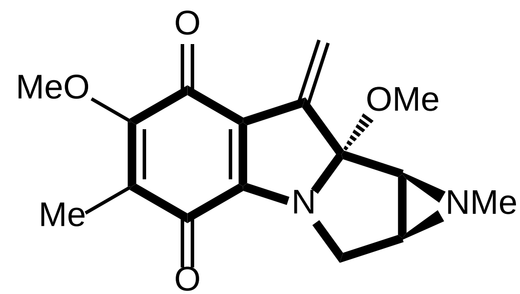
Kishi et al. **1977**;
Fukuyama et al. **1987** & **1989**

Mitomycin F R^1 = OMe, R^2 = Me
Porfiromycin R^1 = NH_2, R^2 = Me

Kishi et al. **1977**

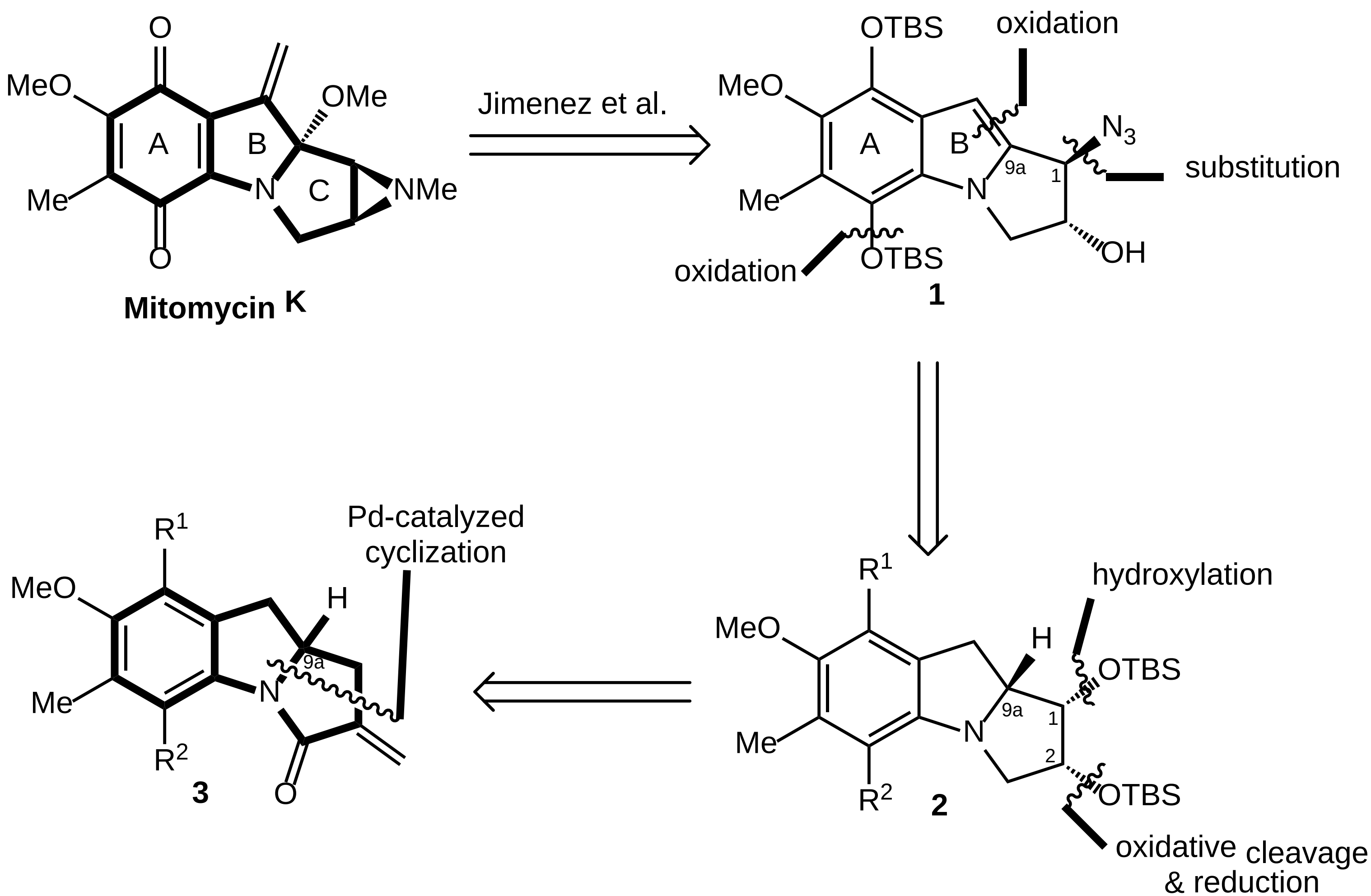


Mitomycin B
Kishi et al. **1977**

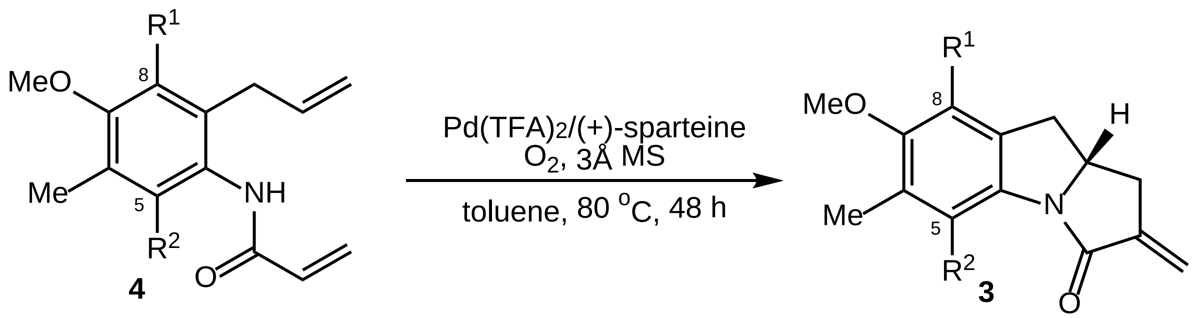


Mitomycin K
Danishefsky et al. **1992;**
Jimenez et al. **1996**

Retrosynthetic Analysis



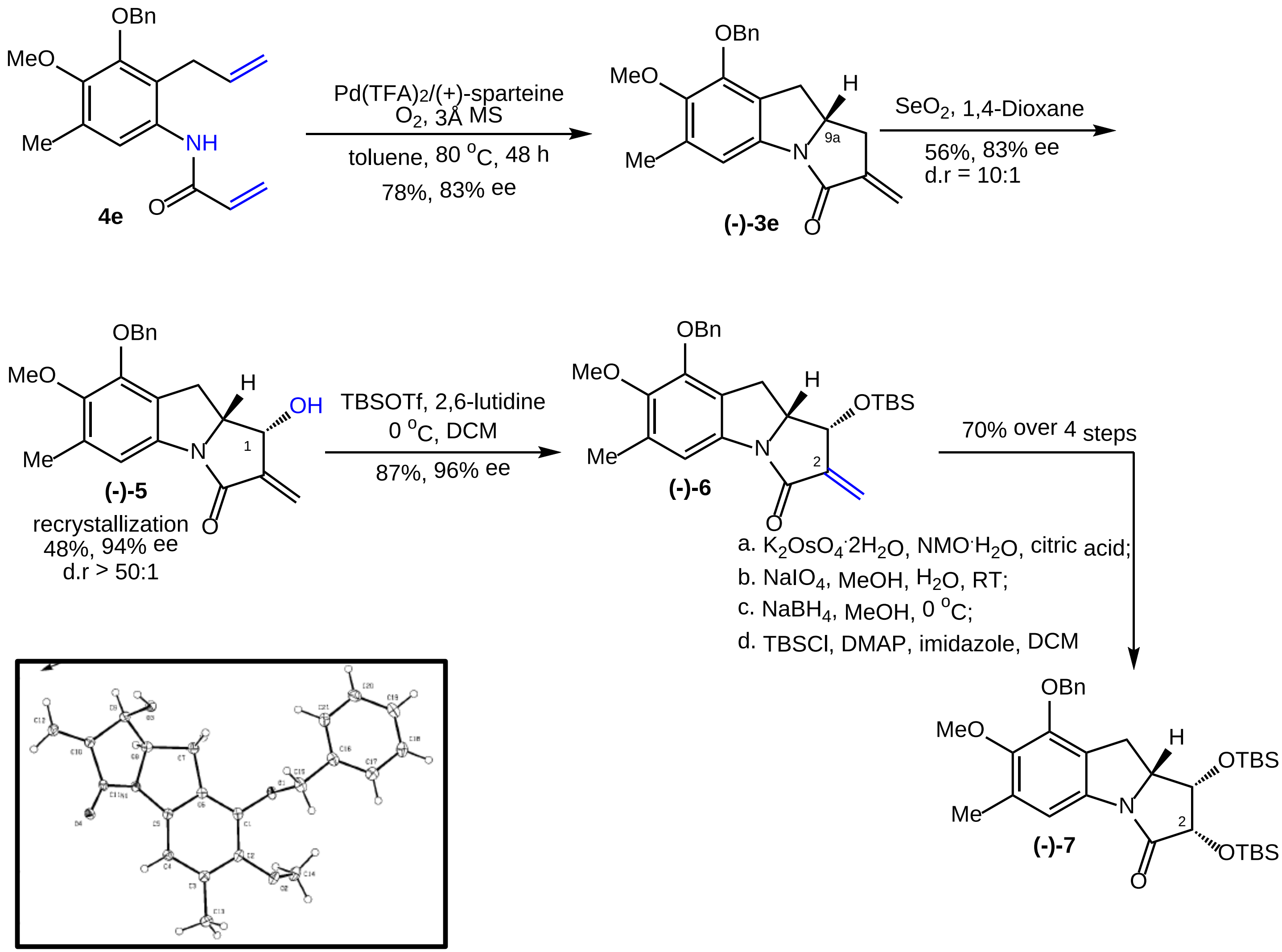
Optimizing Reaction Conditions



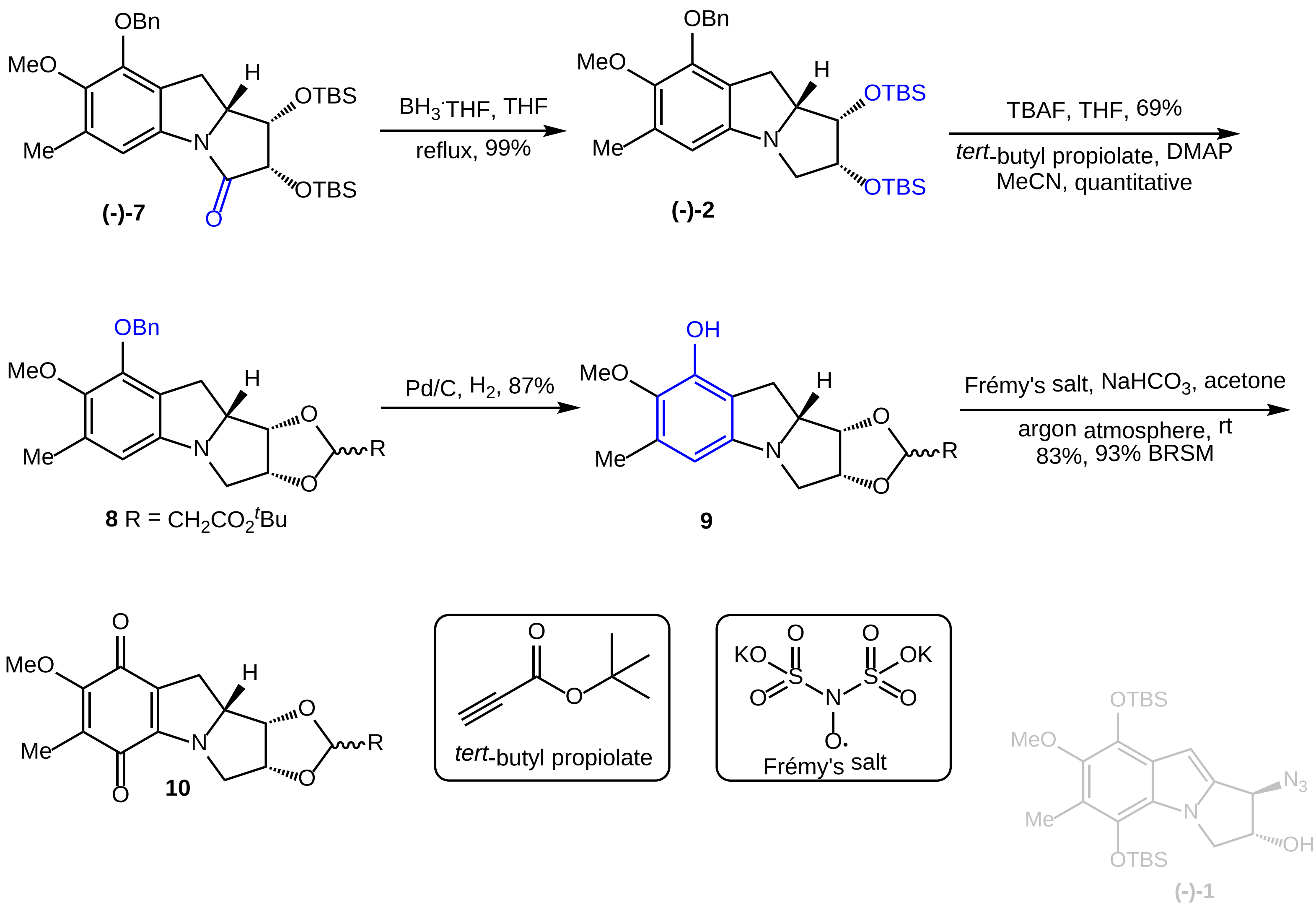
Compound	R^1	R^2	Yield (%) [b]	ee (%) [c]
4a	H	OBn	24	-23
4b	H	OMe	38	3
4c	OBn	OMe	30	28
4d	H	H	49	69
4e	OBn	H	47	83

[a] **4** (0.2 mmol), $Pd(TFA)_2$ (10 mol%), (+)-sparteine (40 mol%), 3Å MS (100 mg), O_2 (1 atm), toluene (1.0 mL), 80 °C, 48 h. [b] Yields of isolated products. [c] Determined by HPLC.

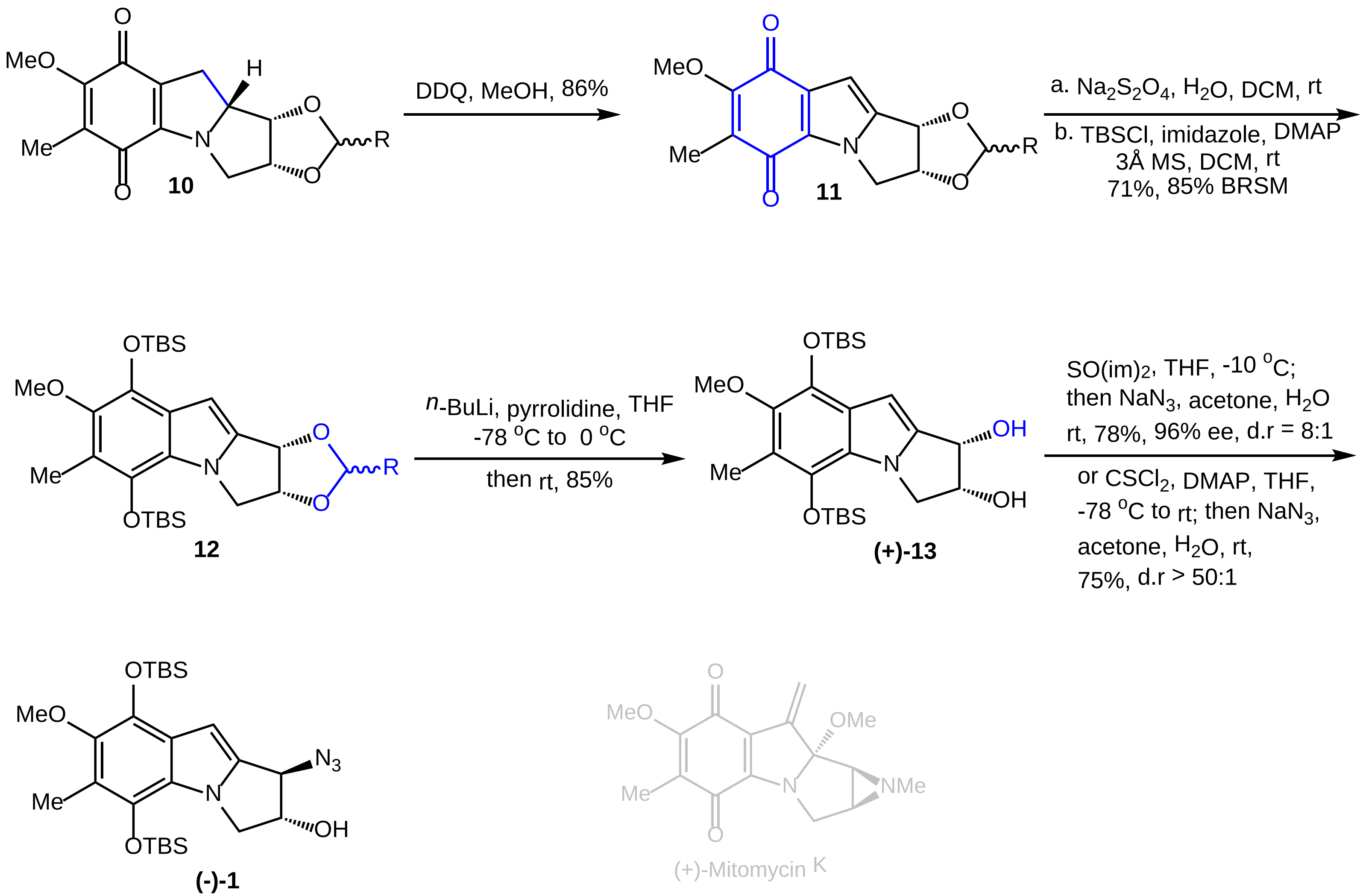
Enantioselective Synthesis of Amide (-)-7



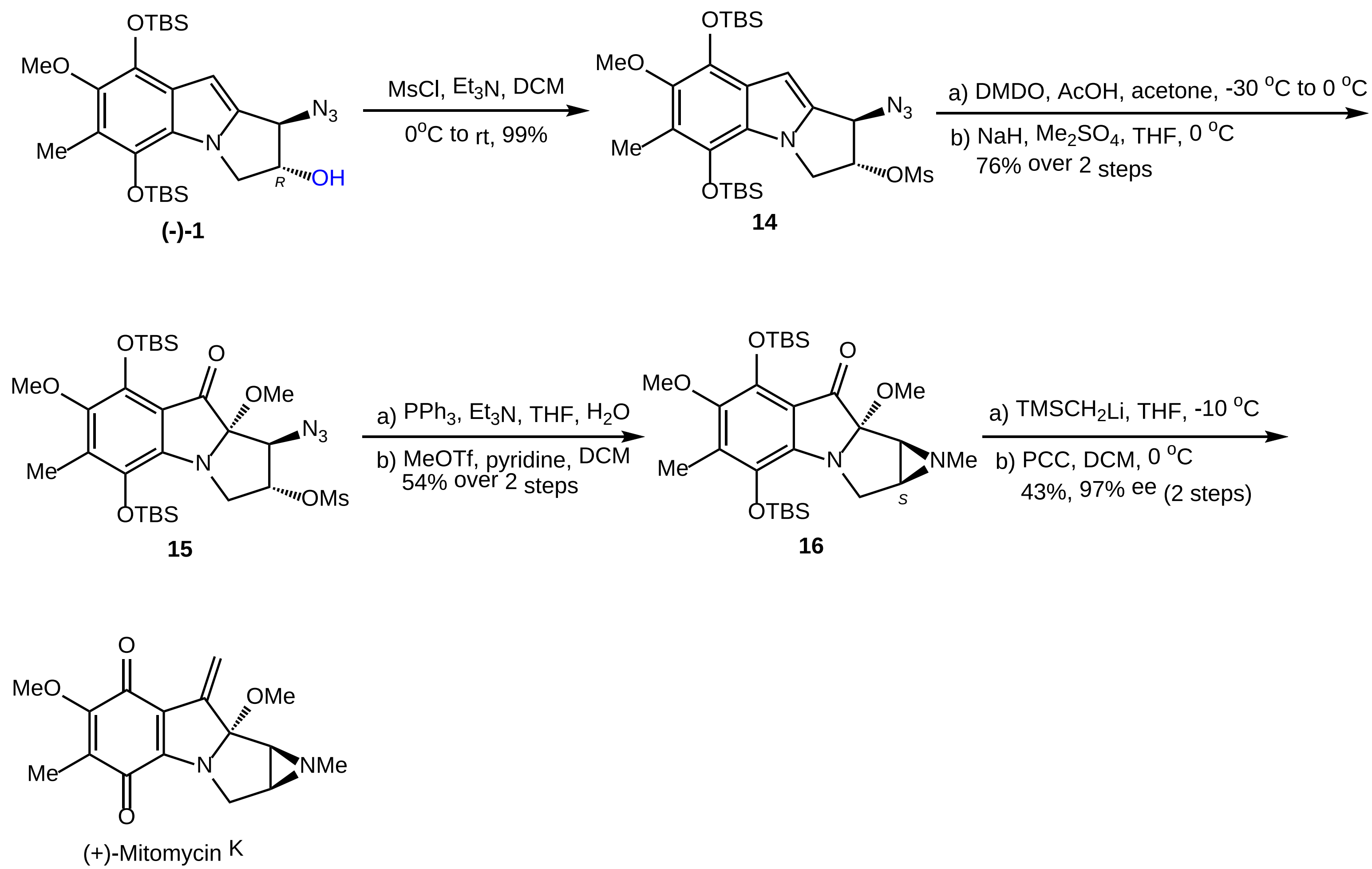
Enantioselective Synthesis of (-)-1



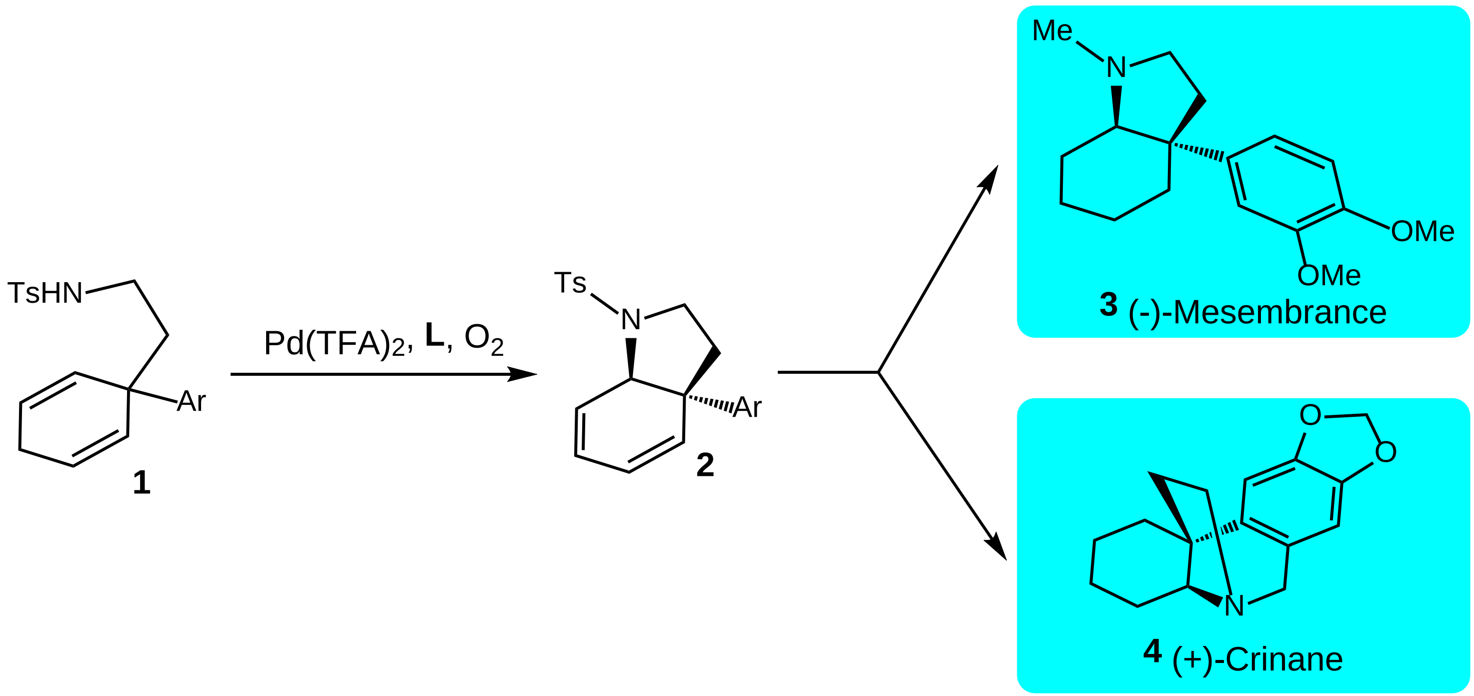
Enantioselective Synthesis of (-)-1



Enantioselective Synthesis of (+)-Mitomycin K

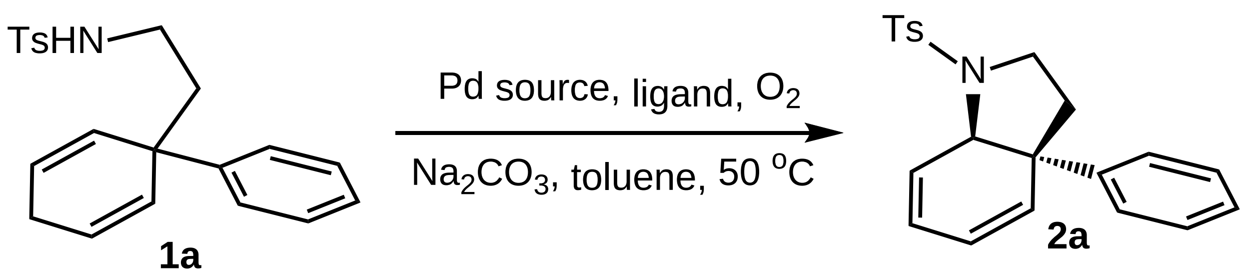


Pd-Catalyzed Enantioselective Aza-Wacker Reaction



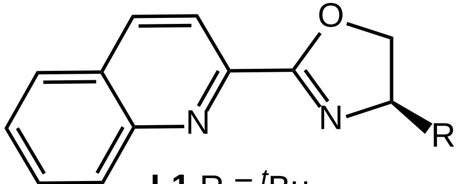
Zhu, J. et. al. *Angew. Chem. Int. Ed.* **2018**, *57,* 1995.

Optimization of the Reaction Conditions

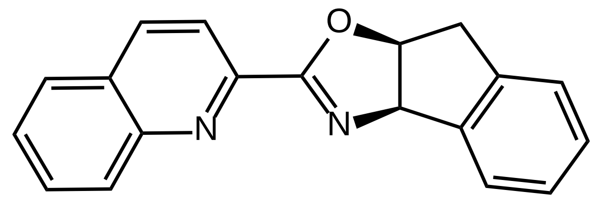


Entry	Pd salt	Ligand	Yield (%) [b]	ee (%) [c]
1[d]	$Pd(OAc)_2$	pyridine	65	-
2	$Pd(OAc)_2$	(-)-sparteine	8	-
3	$Pd(OAc)_2$	**L1**	27	9
4	$Pd(TFA)_2$	**L1**	trace	-20
5	$Pd(TFA)_2$	**L2**	9	3

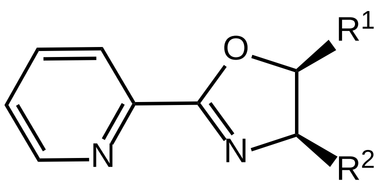
Structures of Quinox and Pyrox-type Ligand



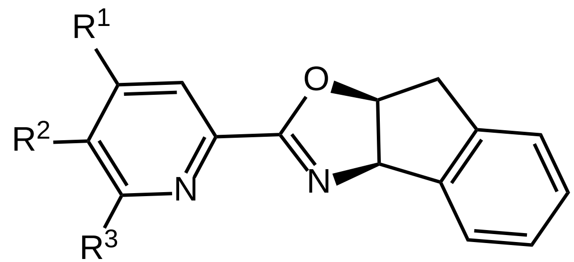
L1 R = ^{t}Bu
L2 R = ^{i}Pr
L3 R = Ph



L4



L5 R^1 = H, R^2 = ^{t}Bu
L6 R^1 = R^2 = Ph



L7 R^1 = R^2 = R^3 = H
L8 R^1 = OMe, R^2 = R^3 = H
L9 R^2 = CF_3, R^1 = R^3 = H
L10 R^1 = R^2 = H, R^3 = Me

Optimization of the Reaction Conditions

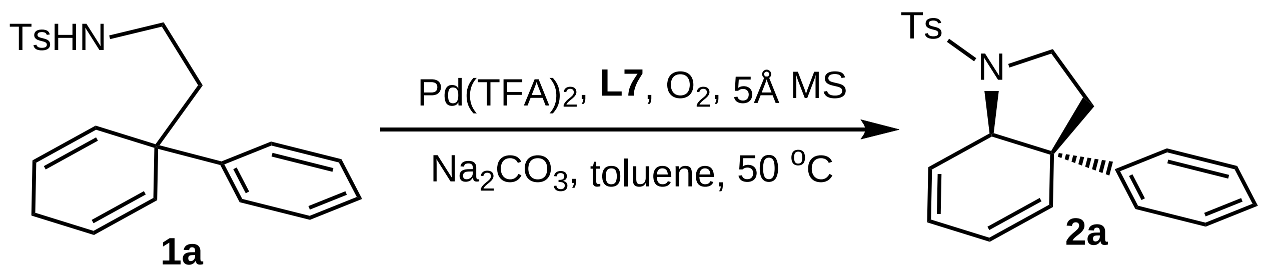
Entry	Pd salt	Ligand	Yield (%) [b]	ee (%) [c]
6	$Pd(TFA)_2$	**L3**	9	16
7	$Pd(TFA)_2$	**L4**	16	51
8	$Pd(TFA)_2$	**L5**	13	40
9	$Pd(TFA)_2$	**L6**	25	59
10	$Pd(TFA)_2$	**L7**	41	70
11	$Pd(TFA)_2$	**L8**	27	62
12	$Pd(TFA)_2$	**L9**	23	56

Optimization of the Reaction Conditions

Entry	Pd salt	Ligand	Additive	Yield (%) [b]	ee (%) [c]
13	$Pd(TFA)_2$	**L10**	-	18	52
14	$Pd(TFA)_2$	**L7**	3Å MS	23	70
15	$Pd(TFA)_2$	**L7**	4Å MS	24	75
16	$Pd(TFA)_2$	**L7**	5Å MS	22	81

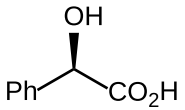
[a] **1a** (0.1 mmol), PdX_2 (0.01 mmol), ligand (0.02 mmol), Na_2CO_3 (0.2 mmol), O_2, and toluene (2.0 mL) at 50 °C. [b] Yields refer to those of the isolated products. [c] Determined by SFC analysis on a chiral stationary phase. [d] Performed at 80 °C.

Effects of the Chiral Acids on the Reaction Outcome

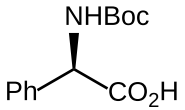


Entry	Acids [b]	Yield (%) [c]	ee (%) [d]
1	(*R*)-mandelic acid	trace	-
2	(*S*)-*N*-Boc-Phe	trace	-
3	(*R*)-CPA **1**	7	56
4	(*R*)-CPA **4**	trace	-
5	(*R*)-CPA **5**	9	16

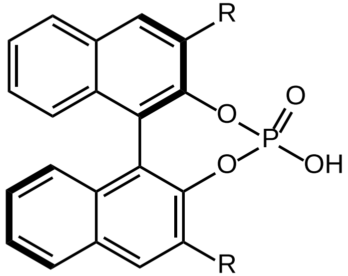
Structures of the Carboxylic Acids and Phosphoric Acids



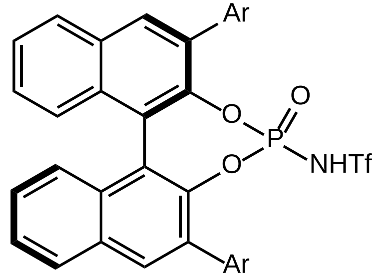
(*R*)-mandelic acid



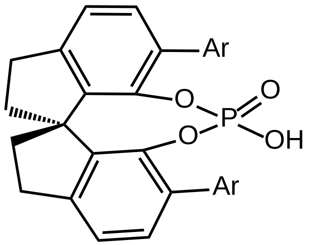
(*S*)-N-Boc-Phe



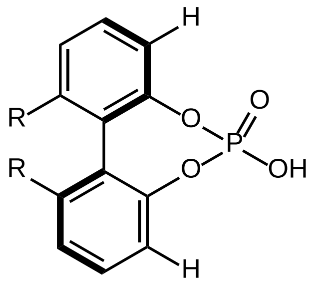
(*R*)-CPA **1** R = 2,4,6-Tris^{i}Pr-C_6H_2
(*R*)-CPA **2** R = Ph
(*R*)-CPA **3** R = H



(*R*)-CPA **4**
Ar = 2,4,6-Tris^{i}Pr-C_6H_2



(*R*)-CPA **5**
Ar = 2,4,6-Tris^{i}Pr-C_6H_2



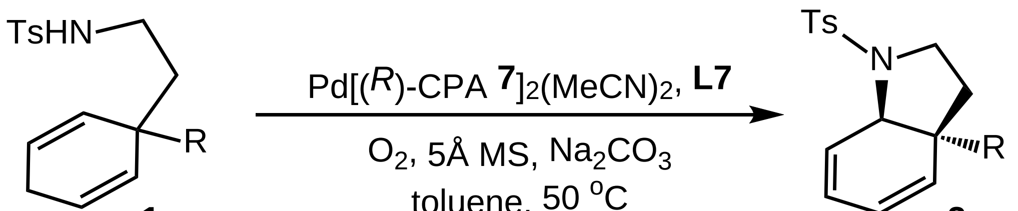
PA **6** R = H
(*R*)- CPA **7** R = Me

Effects of the Chiral Acids on the Reaction Outcome

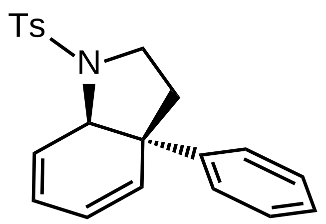
Entry	Acids [b]	Yield (%) [c]	ee (%) [d]
6	(*R*)-CPA **2**	33	84
7	(*R*)-CPA **3**	31	88
8	(*S*)-CPA **3**	23	80
9	PA **6**	48	84
10	Pd[(*R*)-CPA **3**]$_2$(MeCN)$_2$[e]	32	94
11	**Pd[(*R*)-CPA 7]$_2$(MeCN)$_2$[e]**	**63**	**93**
12	Pd[(*R*)-CPA **3**]$_2$(MeCN)$_2$[f]	10	3

[a] **1a** (0.1 mmol), Pd(TFA)$_2$ (0.01 mmol), **L7** (0.02 mmol), Na_2CO_3 (0.2 mmol), O_2, 5 Å M.S. (70.0 mg), and toluene (2.0 mL) at 50 °C. [b] Acid (0.02 mmol). [c] Yields refer to those of the isolated products. [d] Determined by SFC analysis on a chiral stationary phase. [e] Catalyst loading (0.01 mmol). [f] Without ligand.

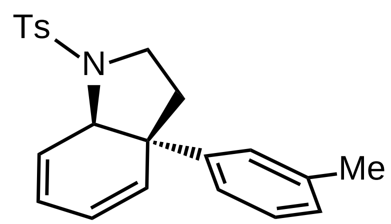
Scope of Desymmetrizing Aza-Wacker Reaction



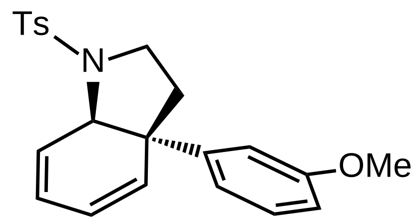
1a-r **2a-r**



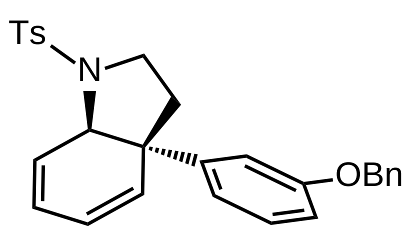
2a 63%, 93% ee



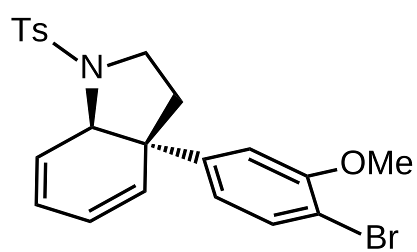
2b 65%, 92% ee



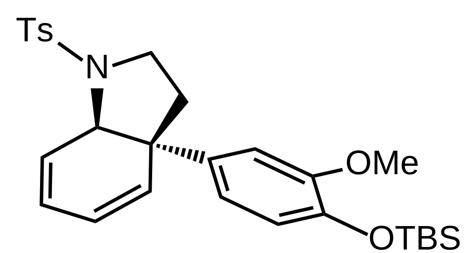
2c 65%, 93% ee



2d 56%, 95% ee

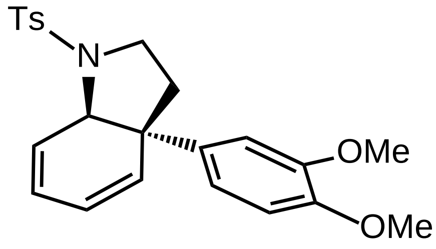


2e 51%, 82% ee

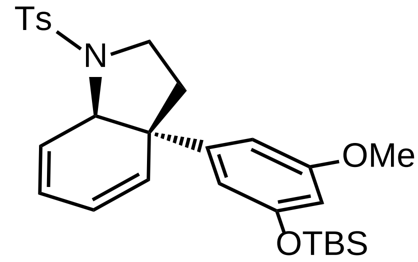


2f 61%, 90% ee

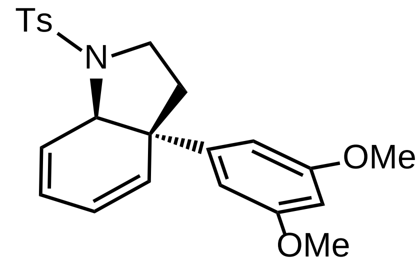
Scope of Desymmetrizing Aza-Wacker Reaction



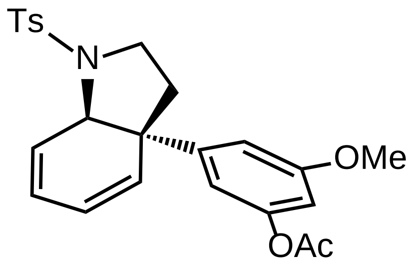
2g 57%, 89% ee



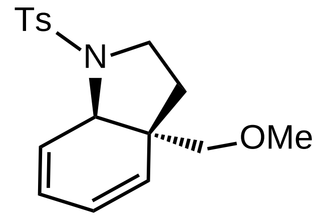
2h 61%, 90% ee



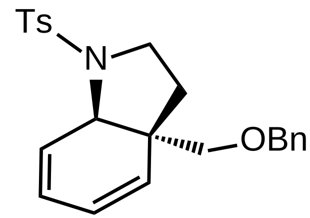
2i 60%, 92% ee



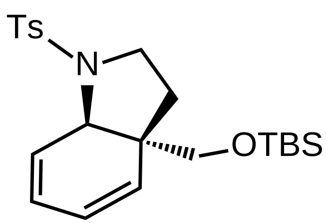
2j 71%, 90% ee



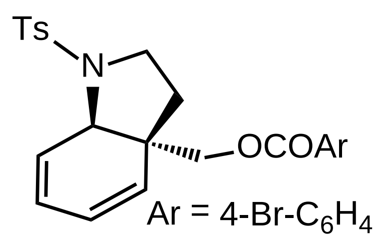
2k 49%, 82% ee



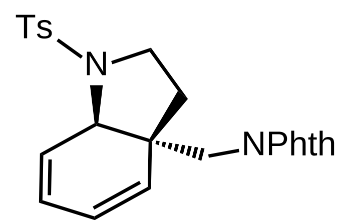
2l 63%, 81% ee



2m 55%, 84% ee

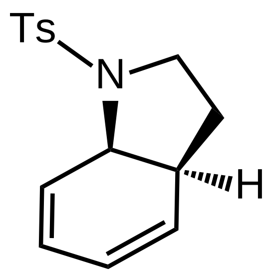


2n 55%, 90% ee

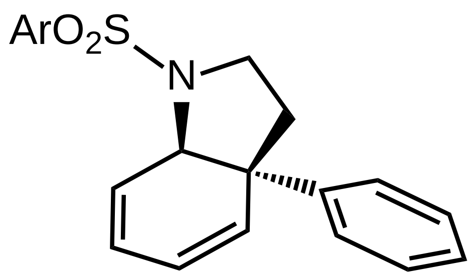


2n 62%, 91% ee

Scope of Desymmetrizing Aza-Wacker Reaction

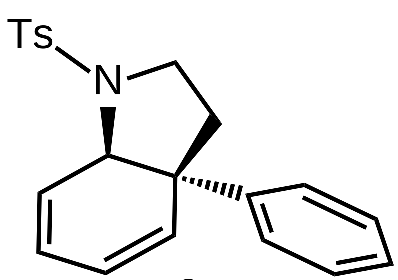


2p 44%, 92% ee

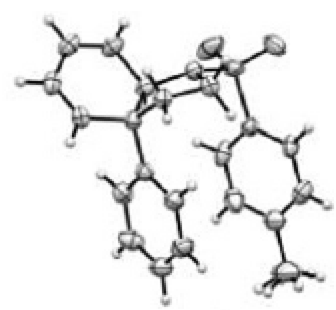


Ar = 4-$NO_2C_6H_4$

2q 61%, 93% ee

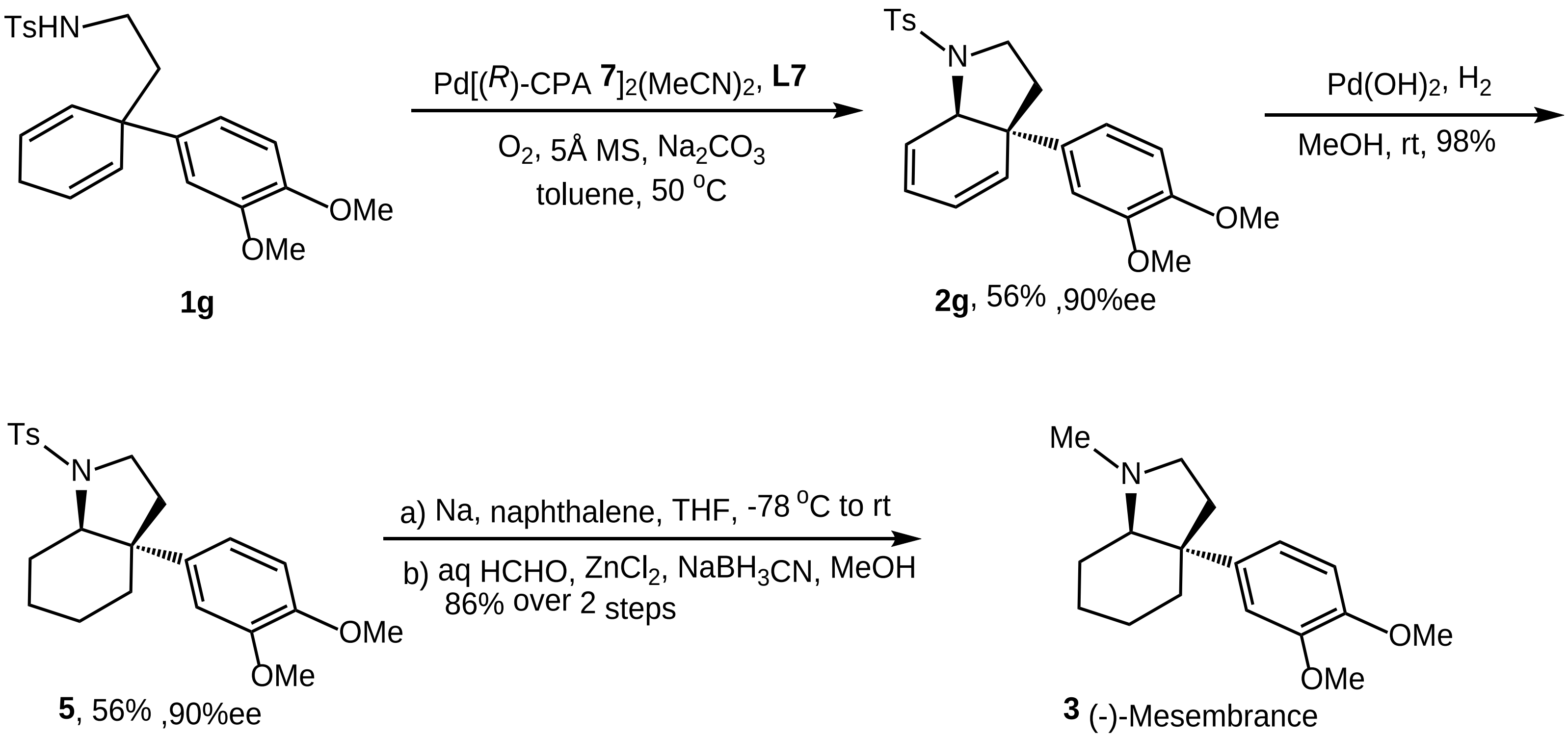


2a

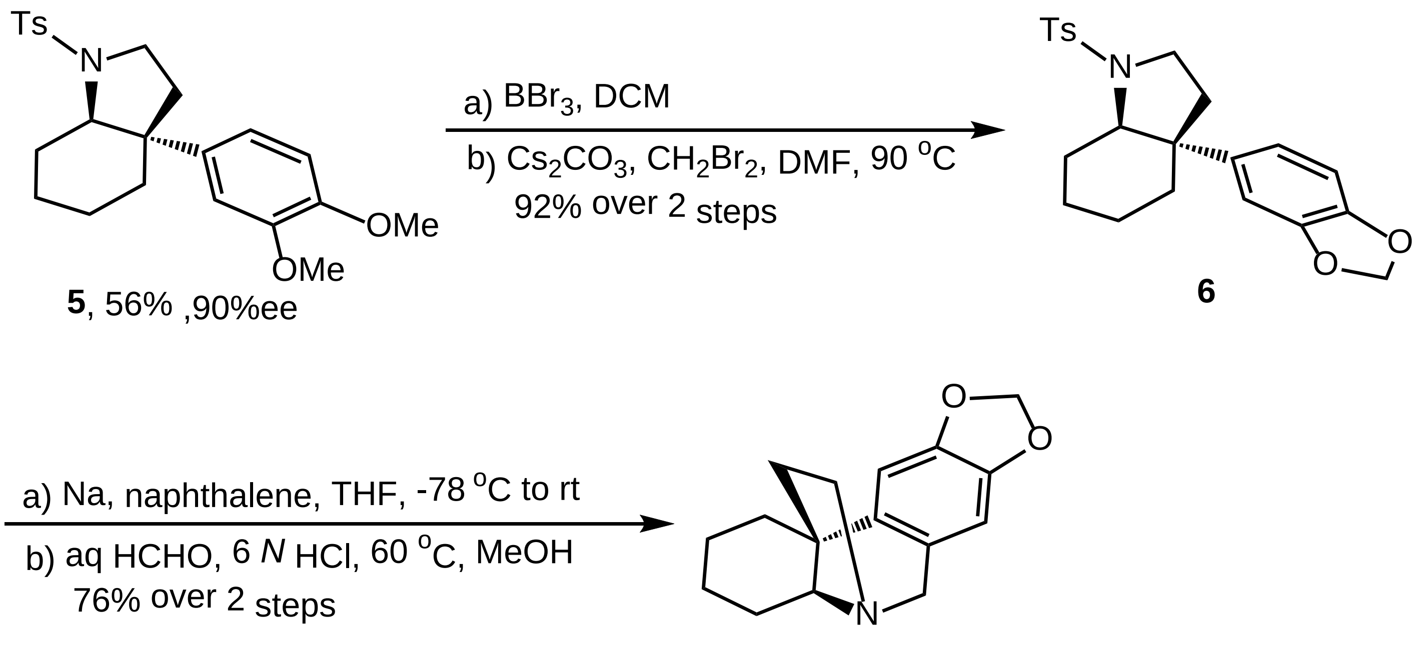


2a

Syntheses of (-)-Mesembrane



Syntheses of (+)-Crinane



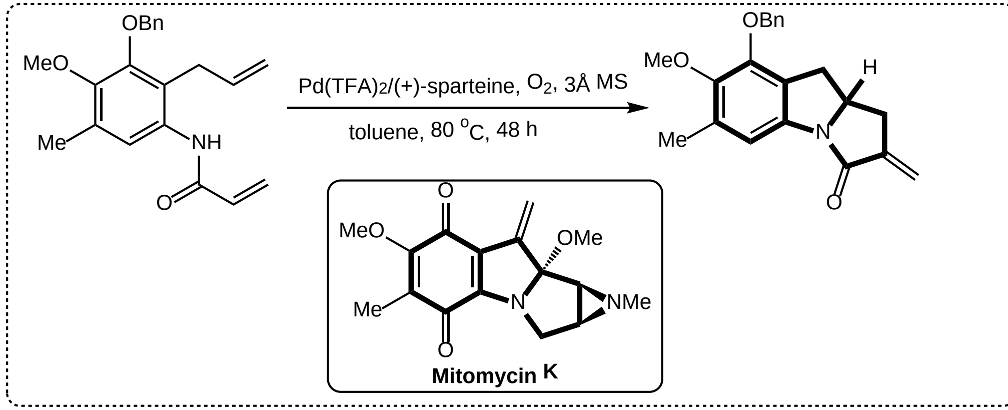
5, 56% ,90%ee

6

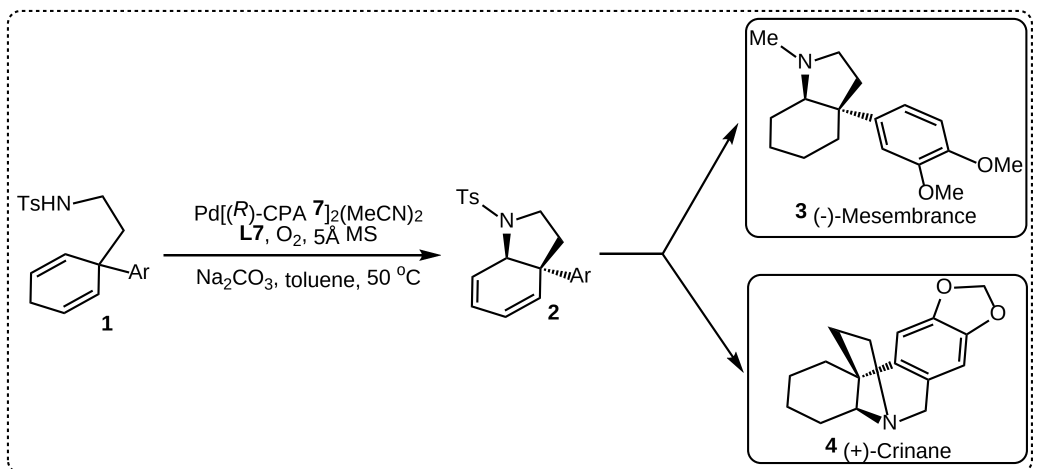
4 (+)-Crinane

Summary

Yang's work



Zhu's work



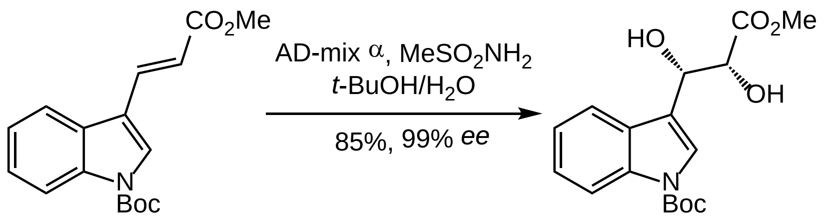
The First Paragraph

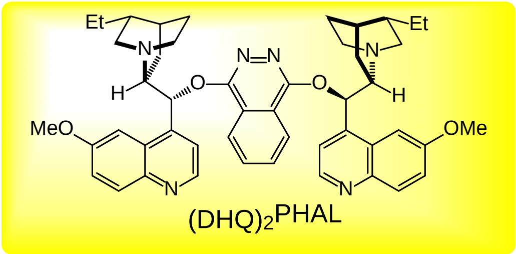
The palladium(II)-catalyzed Wacker reaction has found widespread application in the synthesis of natural products and designed bioactive compounds. The asymmetric Wacker-type cyclization involving a key stereocenter-generating oxypalladation step has also been successfully developed for the synthesis of chiral non-racemic oxaheterocycles. In contrast, the development of an oxidative enantioselective, intramolecular aza-Wacker-type reaction remained inherently more challenging and only few examples have been reported in the literature. Yang and co-workers reported, in 2006, the first examples of palladium(II)/(-)-sparteine-catalyzed oxidative domino cyclization of 2-allylacrylanilides. Other groups have subsequently reported different catalytic conditions for the oxidative enantioselective cyclization of either *N*-acyl or *N*-tosyl aminoalkene.

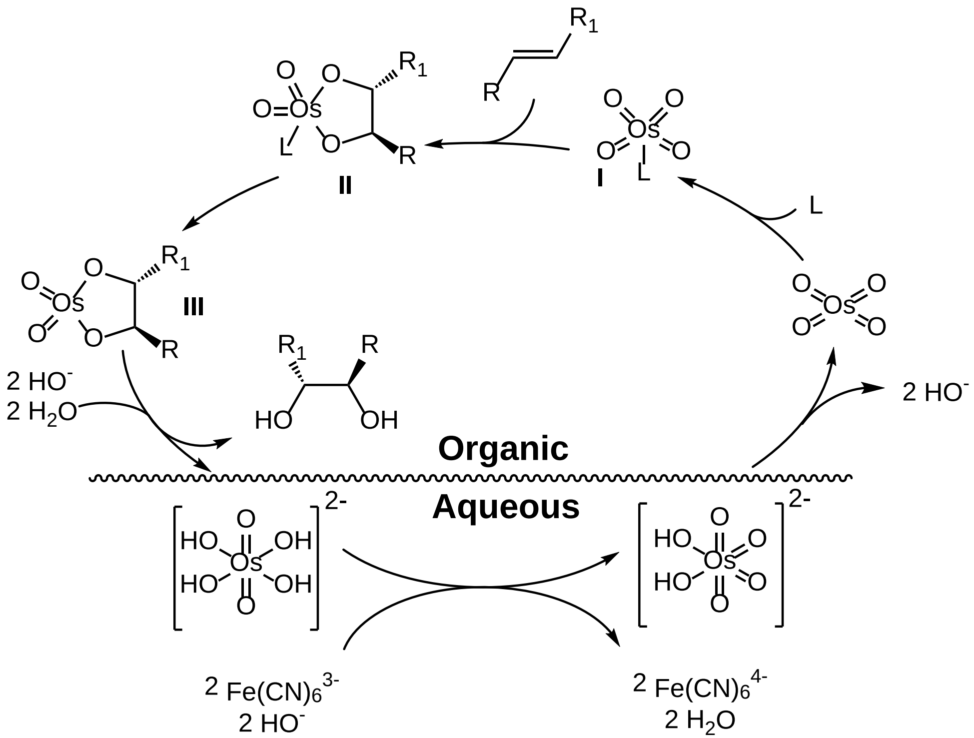
The Last Paragraph

In summary, we reported a catalytic enantioselective desymmetrizing aza-Wacker reaction. In the presence of a catalytic amount of newly developed chiral Pd(CPA)$_2$-(MeCN)$_2$ complex, a pyrox ligand and molecular oxygen, cyclization of functionalized prochiral 3,3-disubstituted cyclohexa-1,4-dienes afforded enantioenriched cis-3a-substituted tetrahydroindoles in good yields with excellent enantioselectivities. A cooperative effect between the chiral pyrox ligand and the phosphoric acid increased both the yield and the ee value of the product. Specifically, the pyrox ligand determined the sense of enantioselectivity, while the matched chiral phosphoric acid increased synergistically both the ee value and the yield of the product. Application of this reaction allowed us to develop a concise and divergent total synthesis of (-)-mesembrane and (+)-crinane.

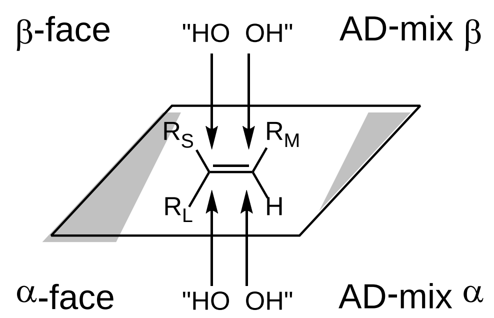
Sharpless Asymmetric Dihydroxylation







Empirical Model:

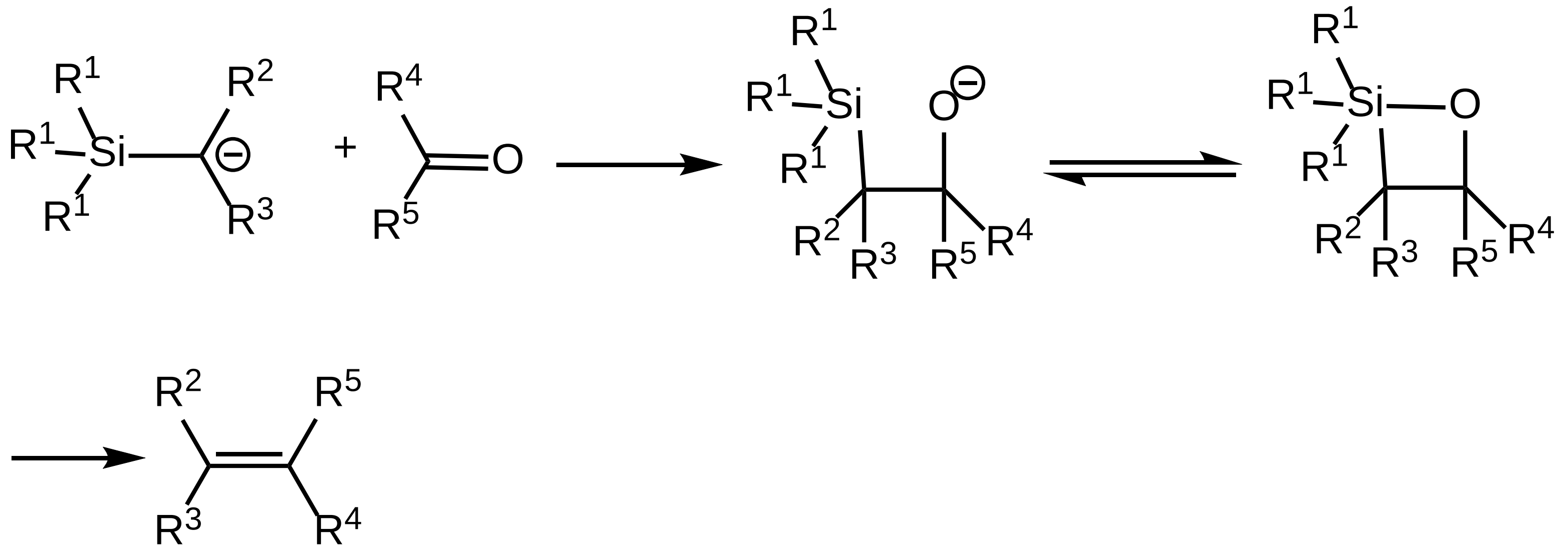


AD-mix α: (DHQ)$_2$PHAL + $K_2OsO_2(OH)_4$ + $K_3Fe(CN)_6$

AD-mix β: (DHQD)$_2$PHAL + $K_2OsO_2(OH)_4$ + $K_3Fe(CN)_6$

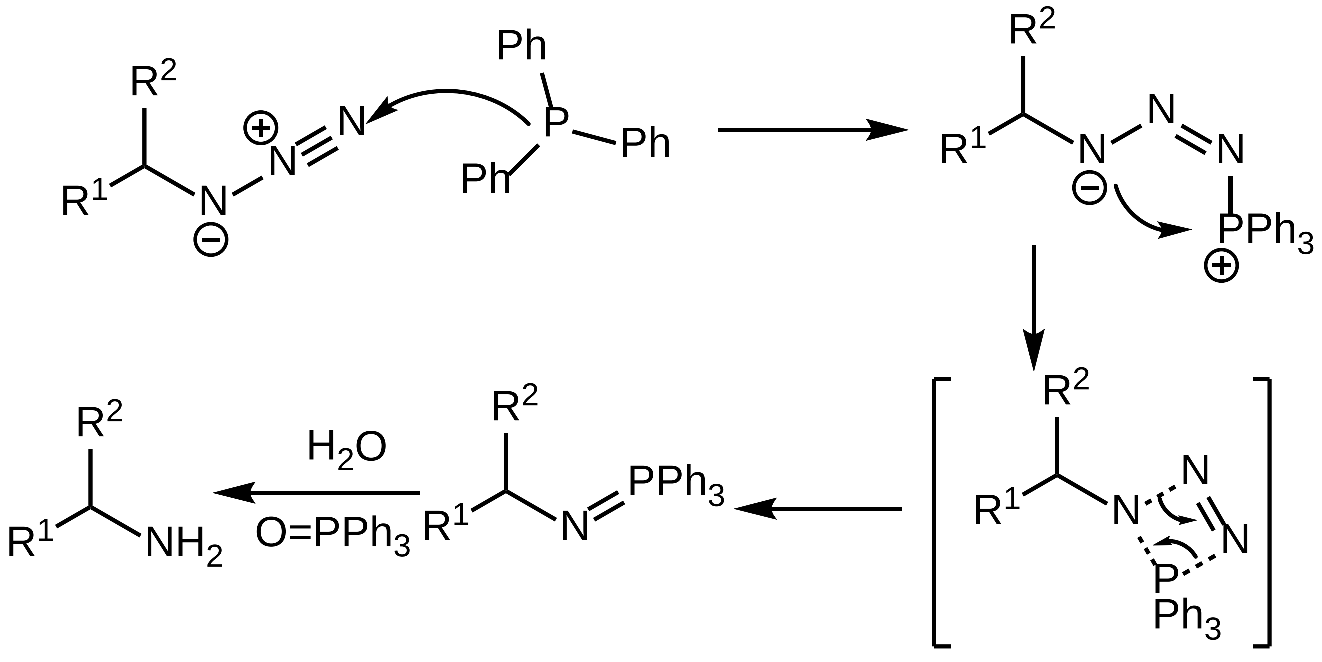
From Zhao Yang

Peterson olefination

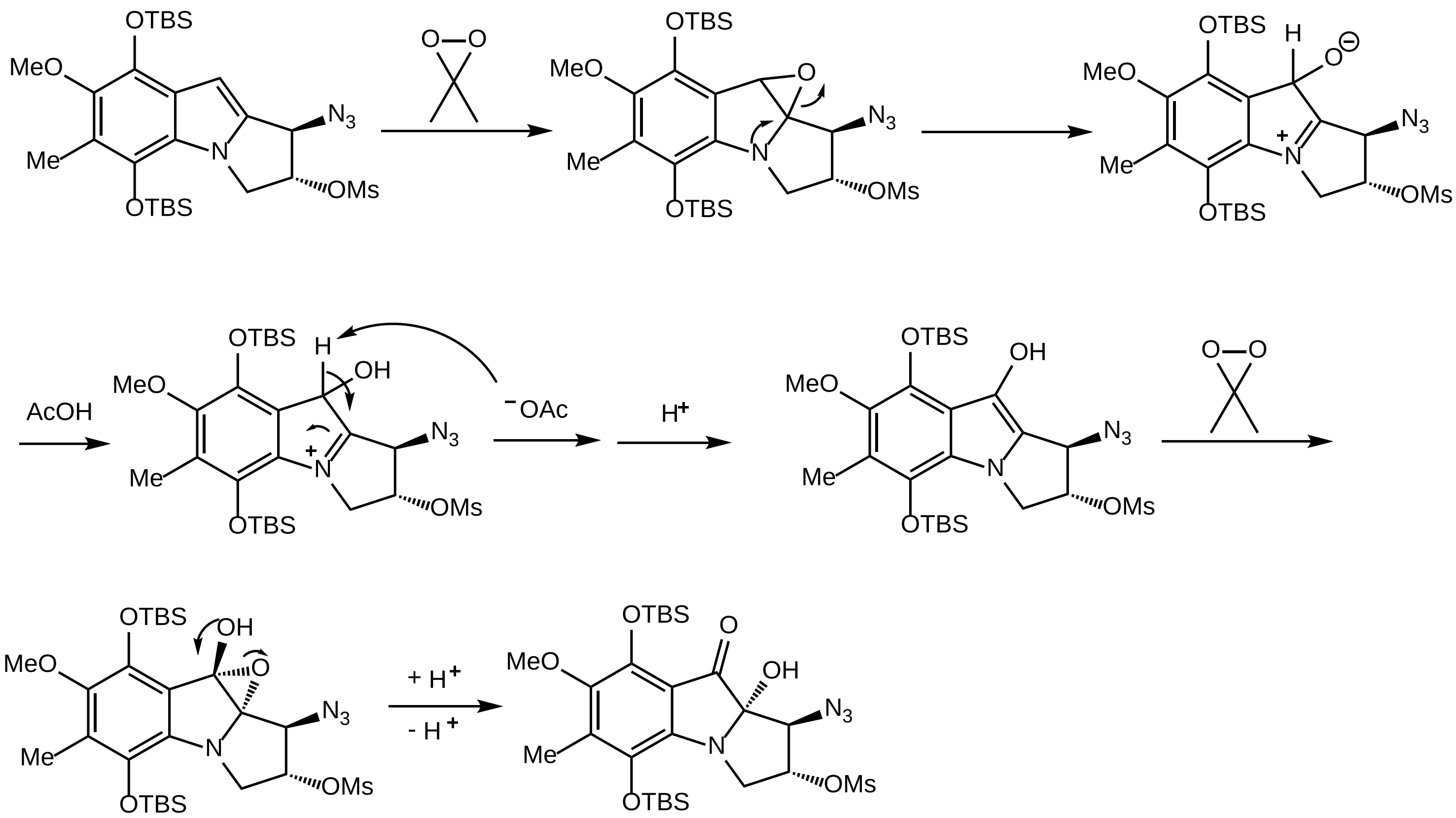


From Wikipedia

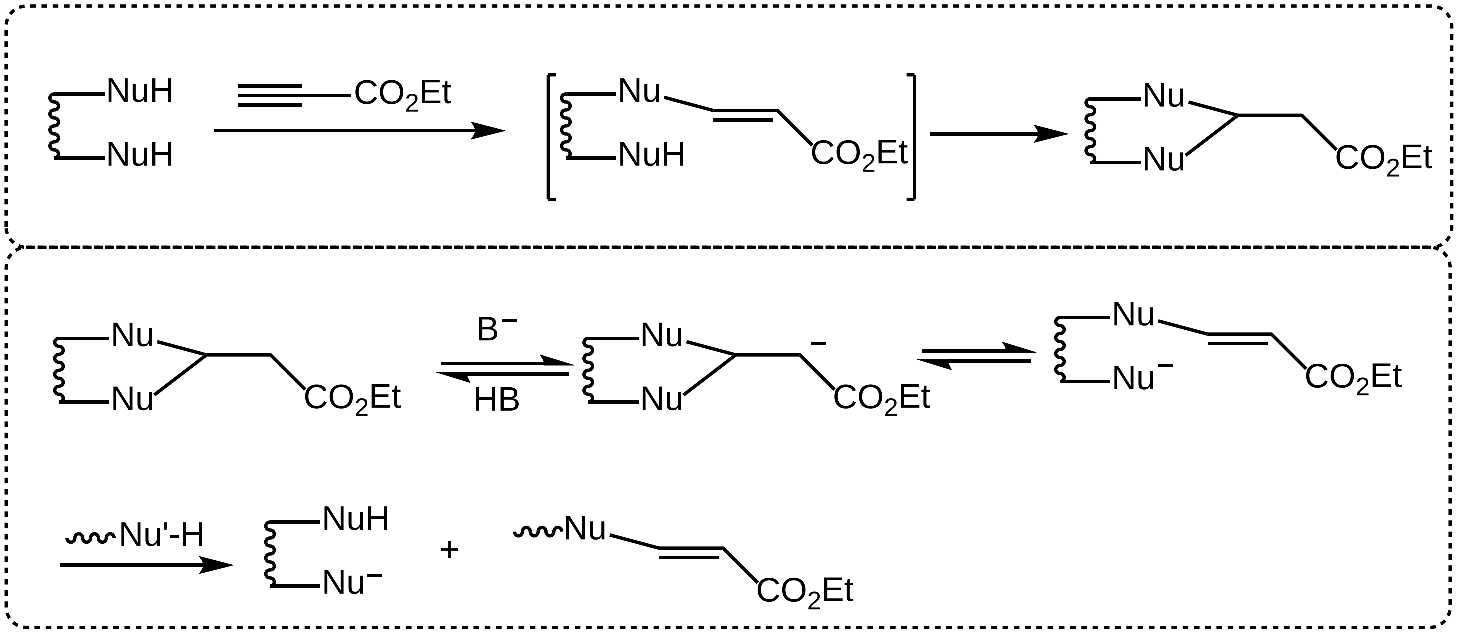
Staudinger reaction



From Wikipedia



Jimenez, L. S. et al. *Org. Lett.* **2003**, *5*, 785.



Vilarrasa, J. et al. *Org. Lett.* **2000**, *2*, 2809.