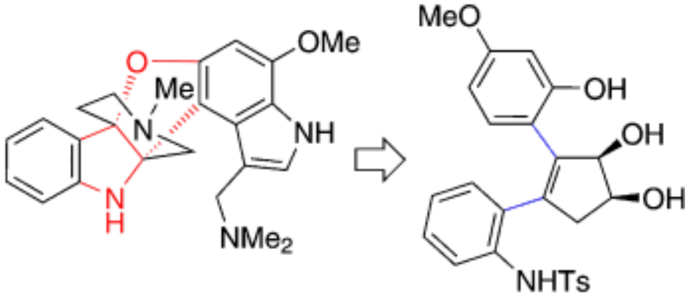
Formal Syntheses of (-)- and (+)-Phalarine

A Journey Start from Oxidative Coupling
Ends at Oxidative Coupling



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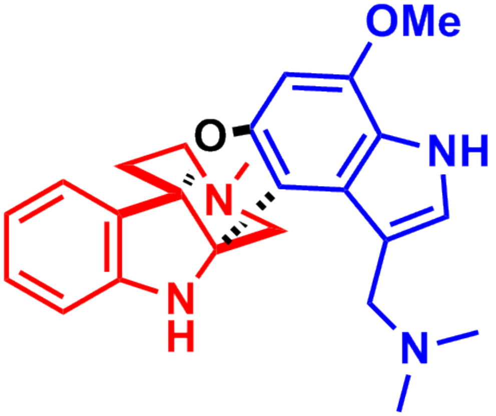
Current Literature
Jie Xu
01.29.11

Ding, H.; Chen, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 676 – 679

Isolation



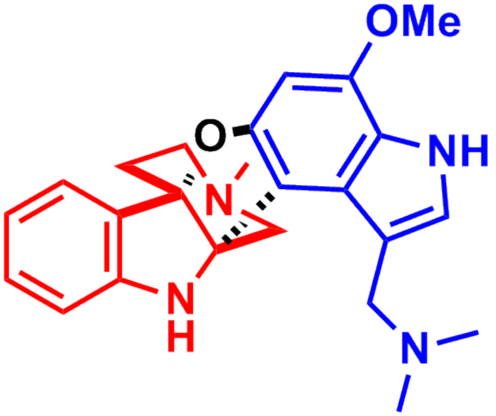
Phalarine

Phalaris Coerulescens
(Blue Canary Grass)

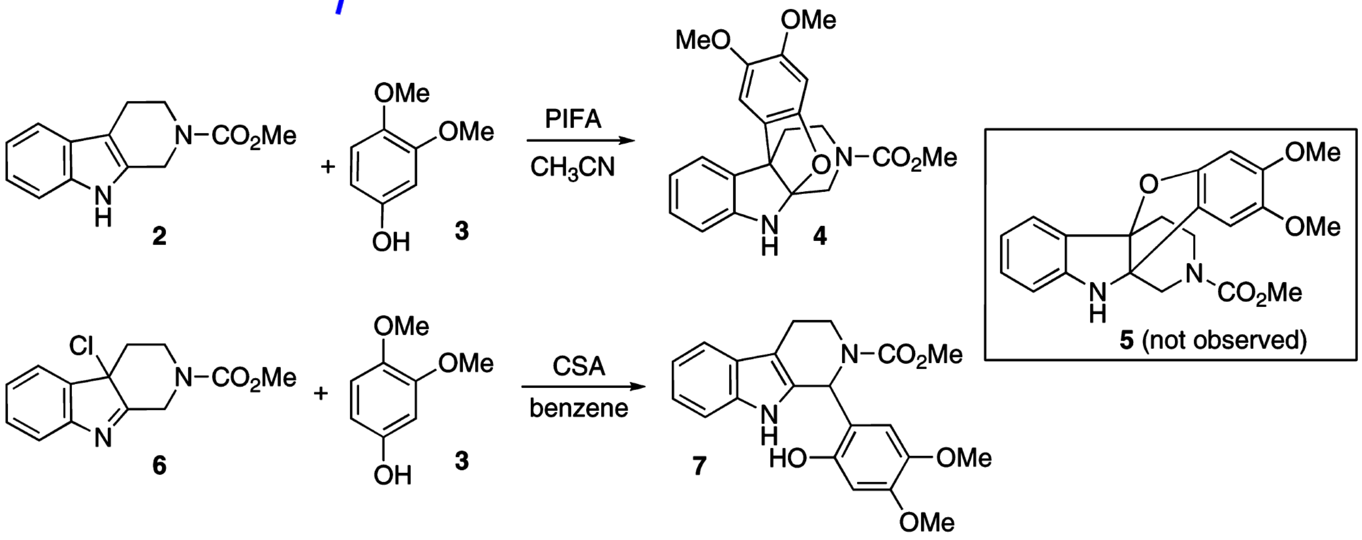
- ***In an agronomy-centered investigation directed at the suitability of Phalaris coerulescens for introduction into Australia, Colegate and co-workers isolated a furanobisindole alkaloid.***
- ***Structure confirmed by MS and NMR (not supported by system degradation).***
- ***No promising biological activity has been asserted.***

Colegate, S. M. *et al. Phytochemistry* **1999**, *51*, 153 – 157.

Biosynthesis

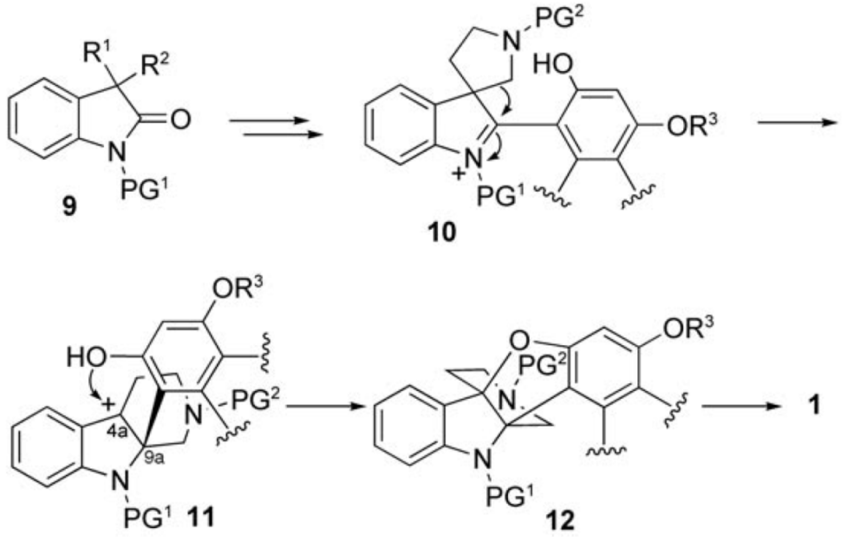


- ***Initial electrophilic attack at C_3***
- ***Oxidized form gives structure isomer due to an imine to bis-enamine transformation followed by an S_N2' attack.***



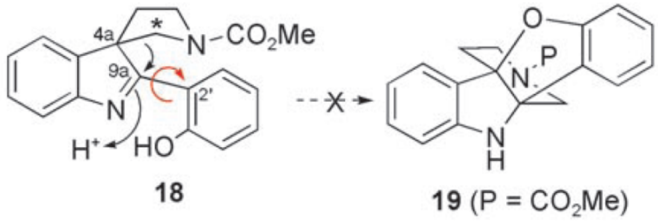
Chan, C.; Li, C.; Zhang, F.; Danishefsky, S. J.; *Tetrahedron Lett.* **2006**, *47*, 4839 – 4841.

Ring Expansion Strategy



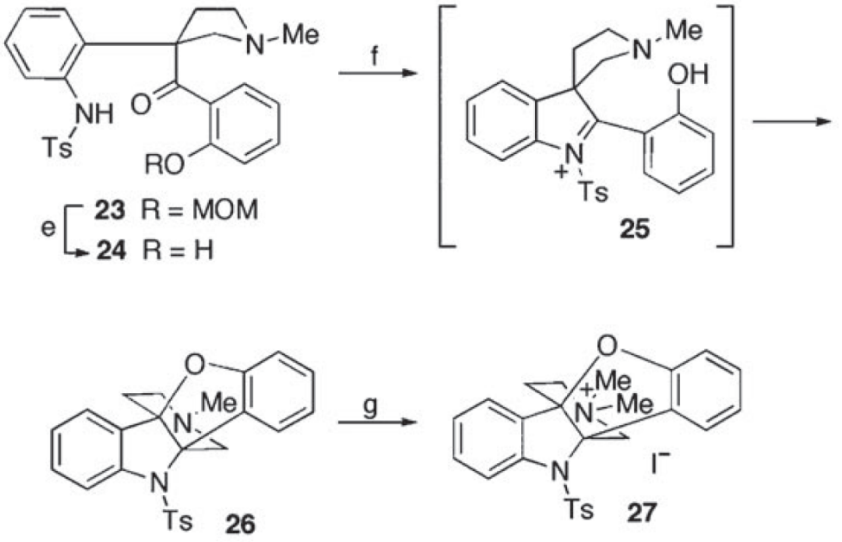
- Be constructed on-site by ring expansion of an **azaspiroindolenine** structure
- The rearrangement step would create a **positive** charge at the C_3, thereby setting the stage for the critical **O-C** bond formation

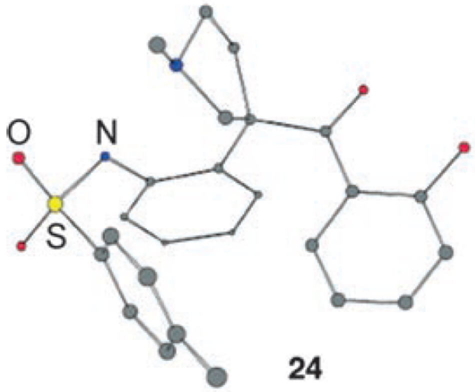
- Migratory aptitude of the **urethane-bound** methylene carbon atom could be rather low.
- **H-bonding** between the phenolic function and the nitrogen atom could restrict the free rotation.



Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444 – 1447.

Ring Expansion Strategy





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- ***Conditions***

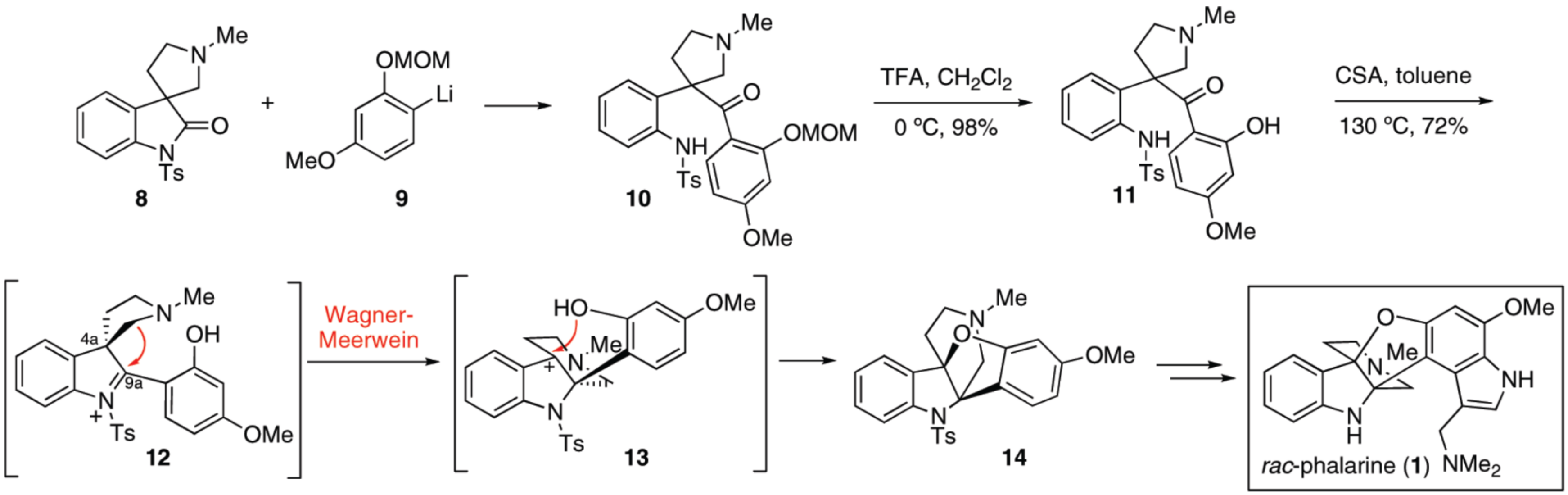
  e) TFA, CH_2Cl_2, 0 ^oC to RT, 95%;

  f) CSA, $PhCH_3$, 150 ^oC, 52%;

  g) MeI, benzene, 60% conv.

Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444 – 1447.

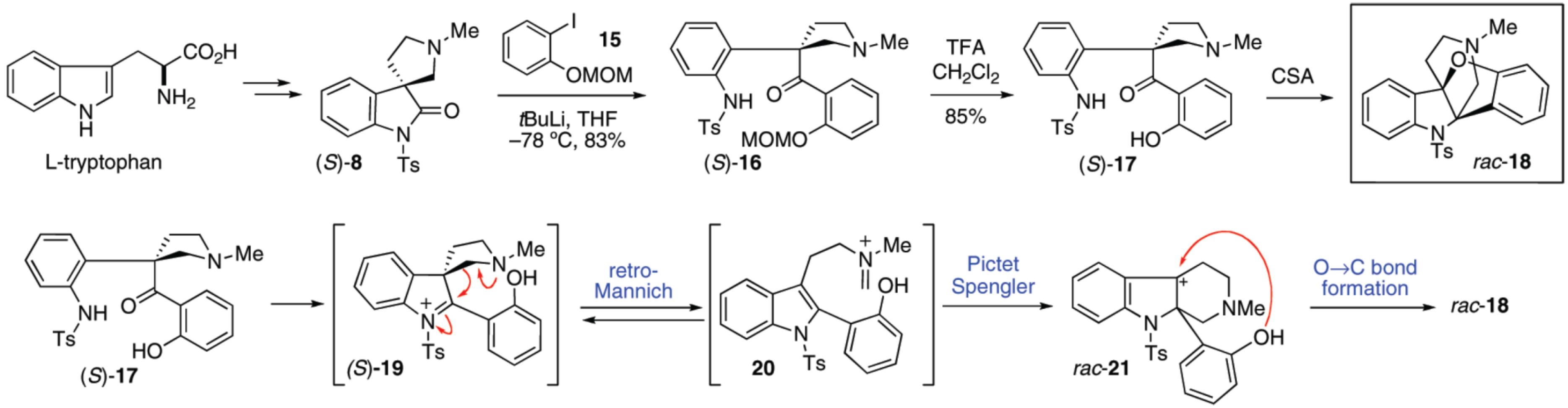
Danishefsky's Racemic Total Synthesis



- ***Rearrangement of azaspiroindolenine to the precursor to phalarine.***
- ***Gassman oxindole synthesis while Fischer indolization fails.***

Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448 – 1450.

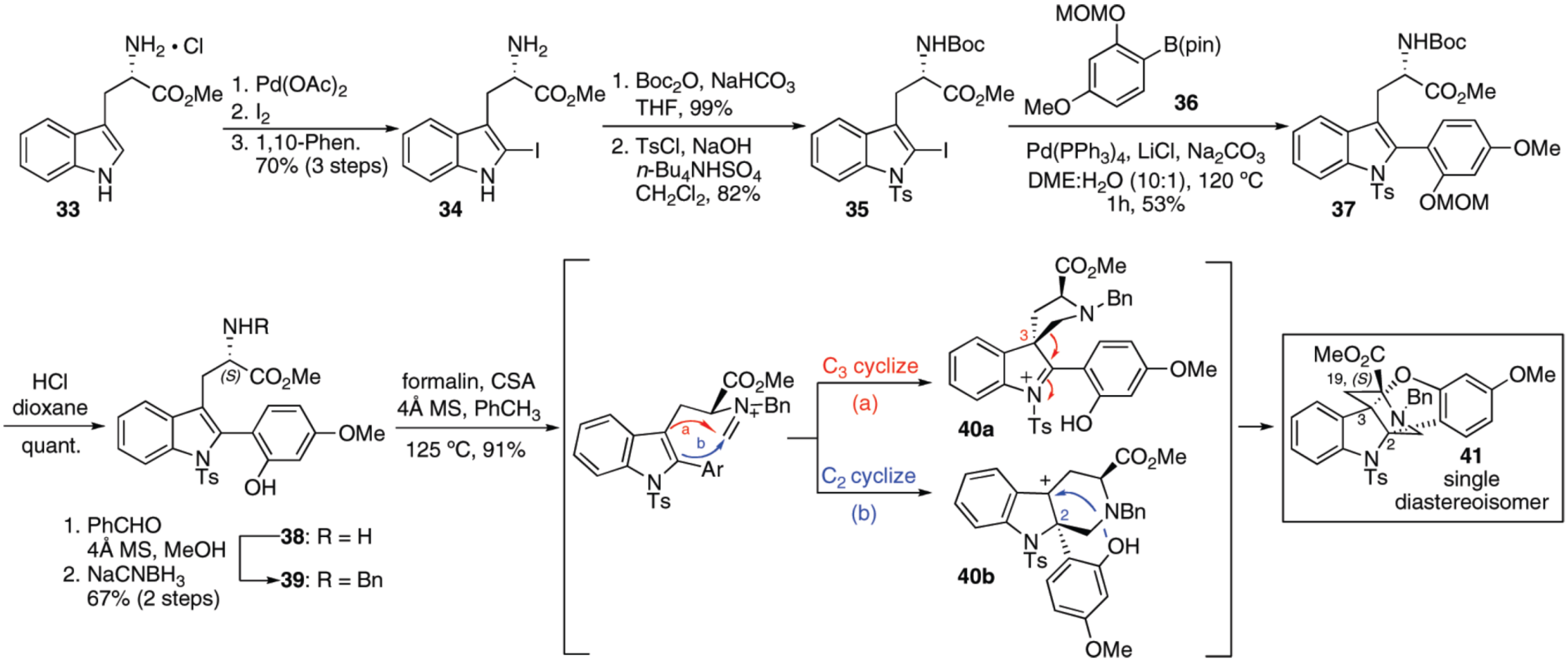
Racemic Product



- ***The formation of racemic 18 did not arise from racemization of the substantially enantiopure product.***
- ***Retro-Mannich cleavage sequence accounts for the racemization.***

Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448 – 1450.

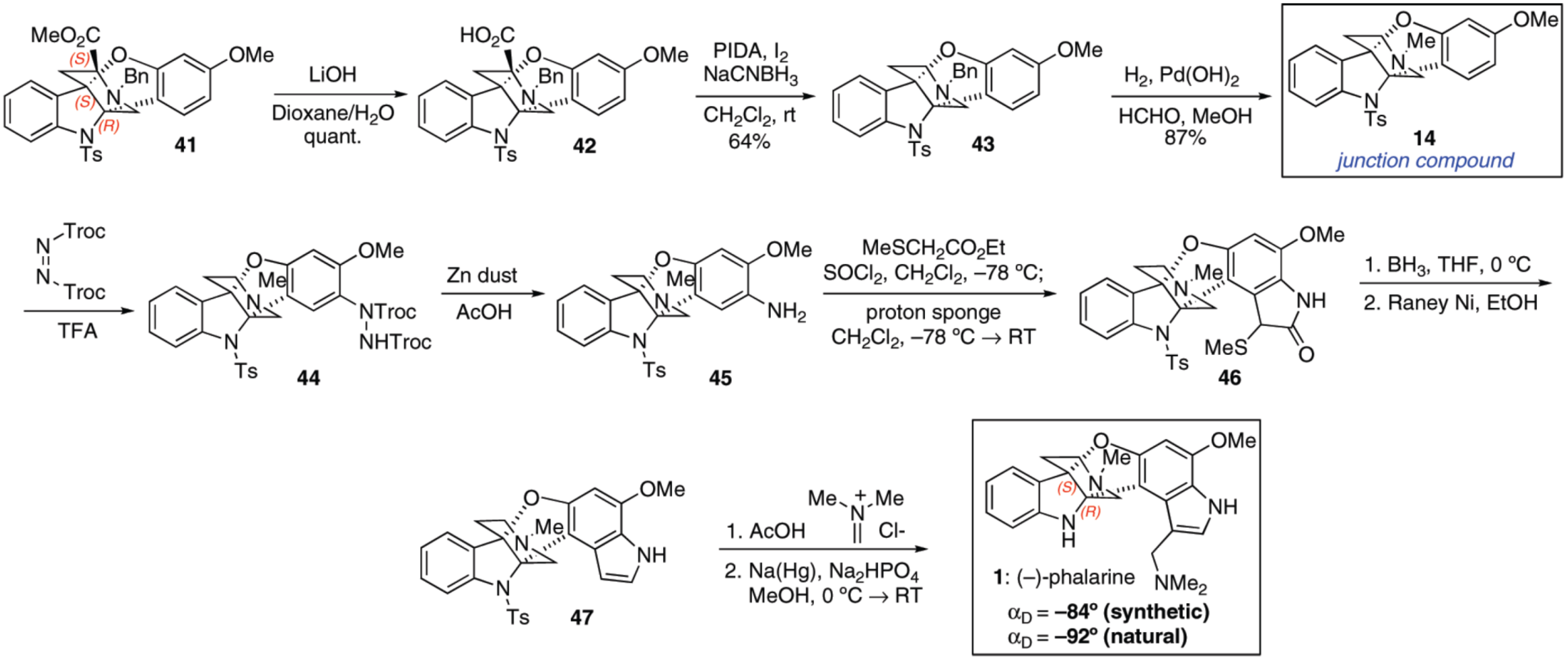
Traceless Transfer of Chirality



- ***The chirality inherent in L-tryptophan was transferred to Phalarine in a traceless fashion***

Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506

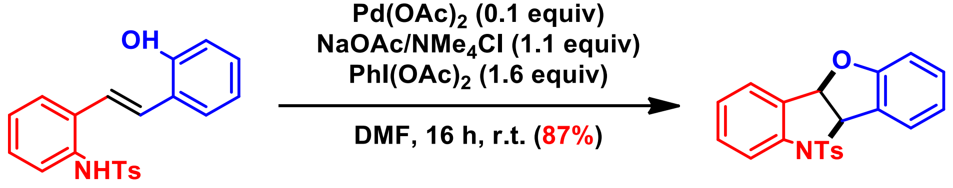
Completion of Enantiopure Synthesis

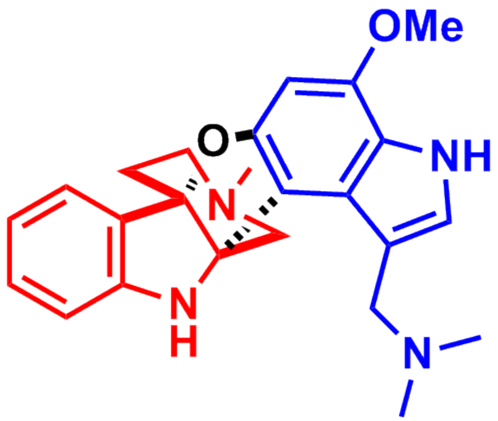


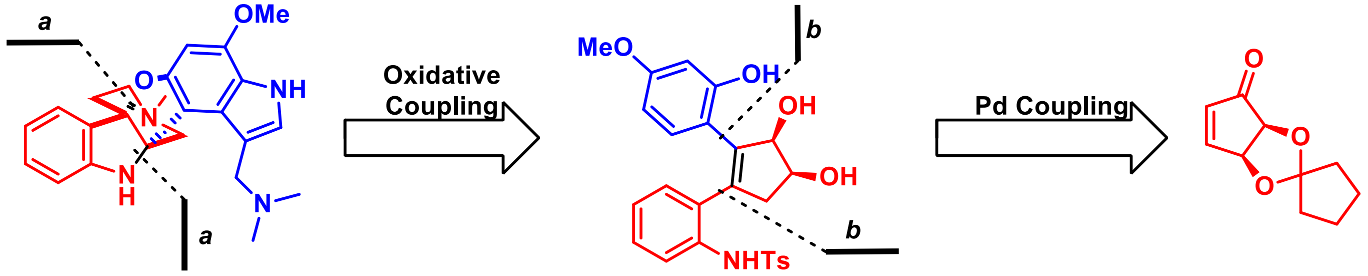
- ***The absolute configuration was confirmed by X-ray analysis of compound 14.***

Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2010**, *132*, 8506

Oxidative Coupling Strategy

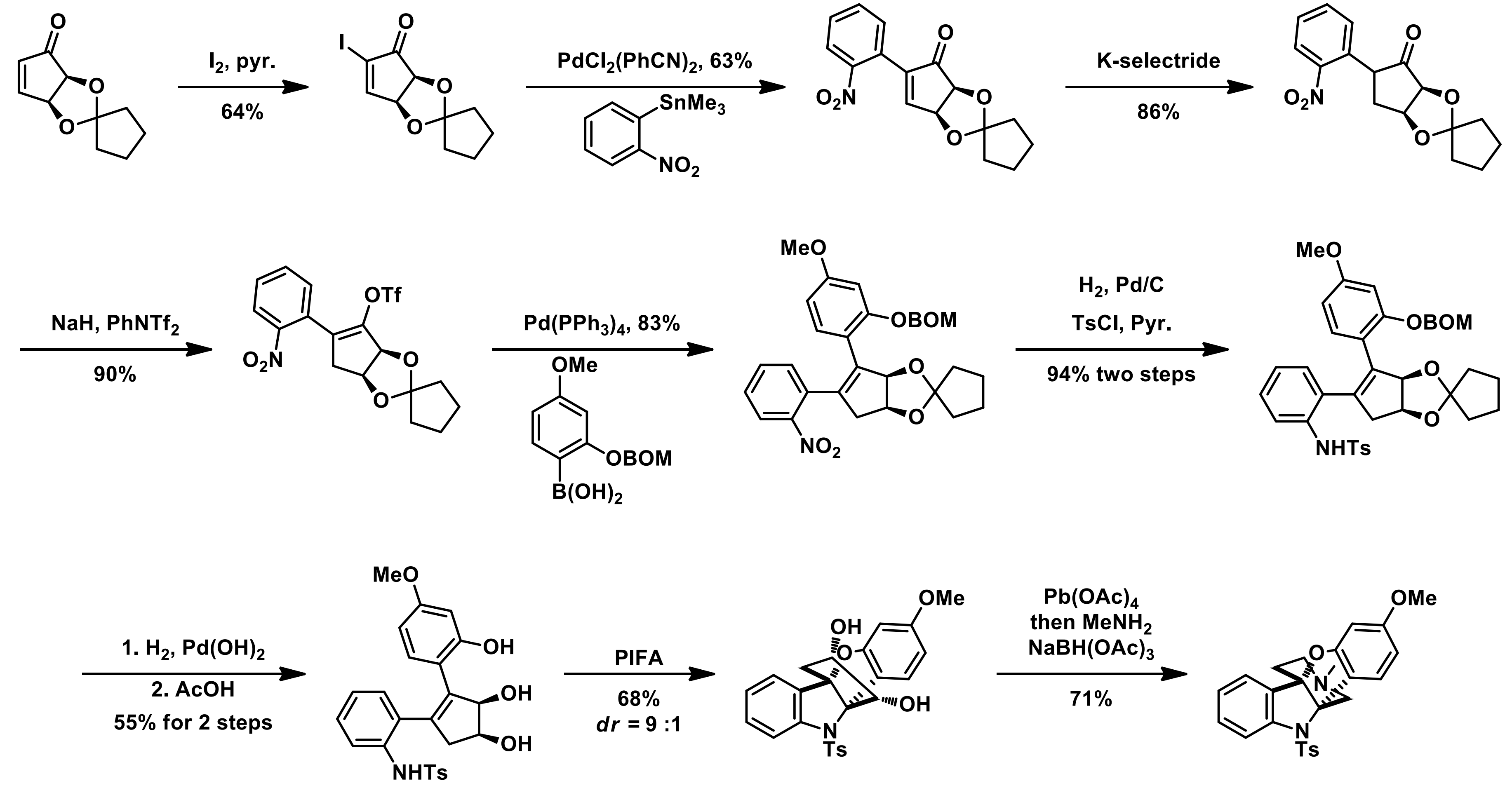






Muniz K. *J. Am. Chem. Soc.* **2007**, *149*, 1454.
Ding, H.; Chen, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 676 – 679.

Formal Synthesis



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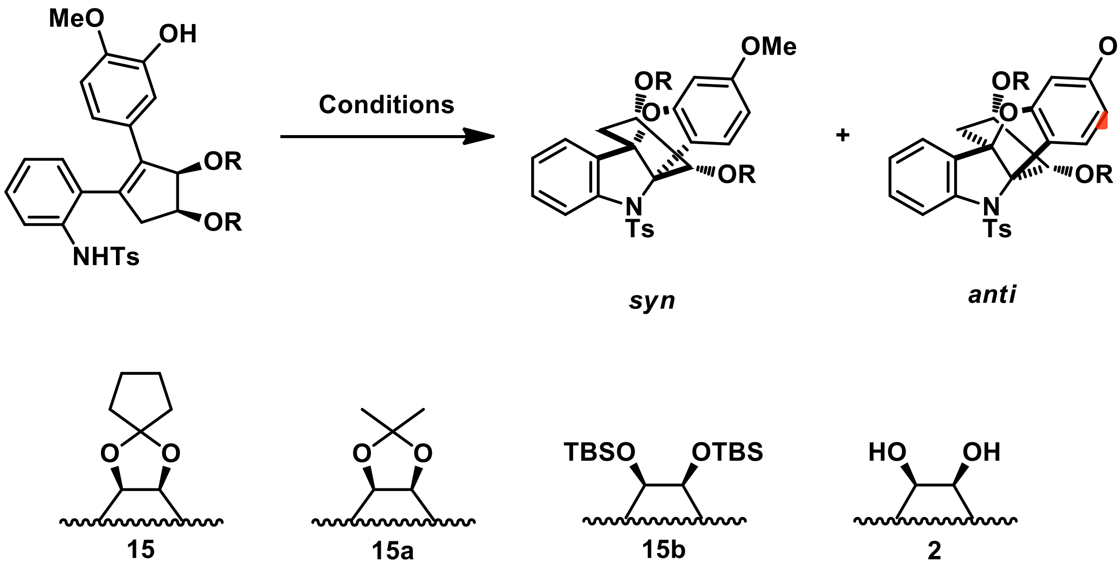
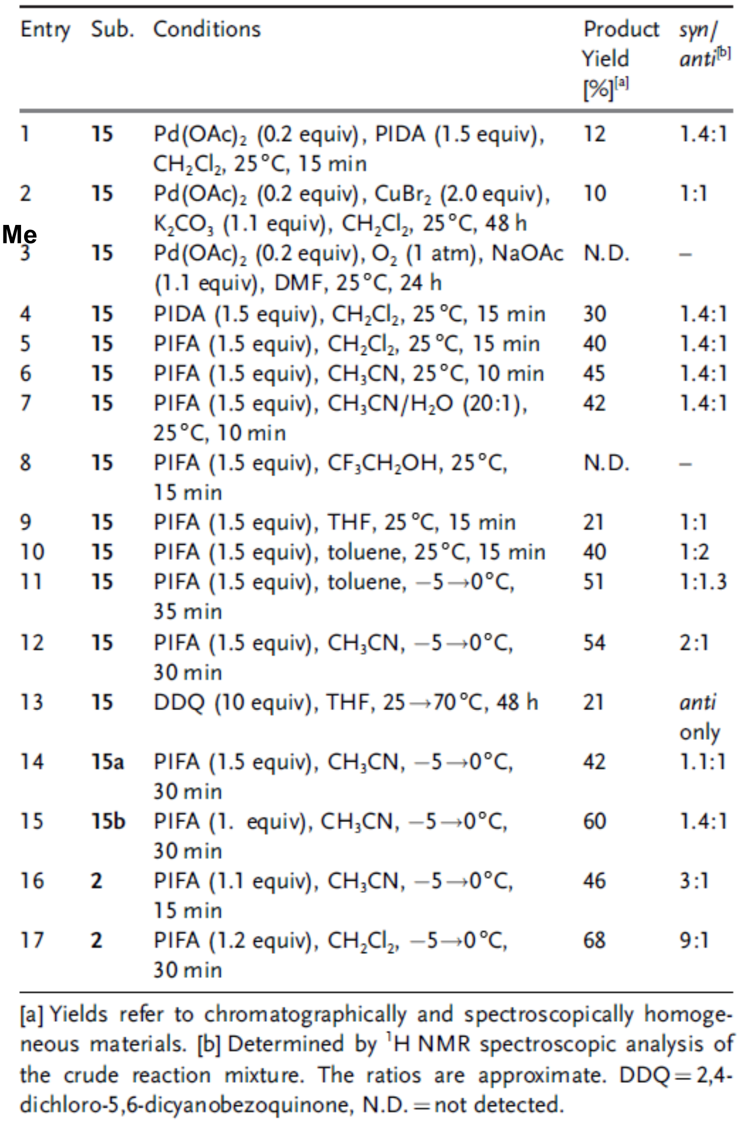
Catalyst Screening





Entry	Sub.	Conditions	Product Yield [%][a]	*syn*/*anti*[b]
1	**15**	Pd(OAc)$_2$ (0.2 equiv), PIDA (1.5 equiv), CH$_2$Cl$_2$, 25 °C, 15 min	12	1.4:1
2	**15**	Pd(OAc)$_2$ (0.2 equiv), CuBr$_2$ (2.0 equiv), K$_2$CO$_3$ (1.1 equiv), CH$_2$Cl$_2$, 25 °C, 48 h	10	1:1
3	**15**	Pd(OAc)$_2$ (0.2 equiv), O$_2$ (1 atm), NaOAc (1.1 equiv), DMF, 25 °C, 24 h	N.D.	–
4	**15**	PIDA (1.5 equiv), CH$_2$Cl$_2$, 25 °C, 15 min	30	1.4:1
5	**15**	PIFA (1.5 equiv), CH$_2$Cl$_2$, 25 °C, 15 min	40	1.4:1
6	**15**	PIFA (1.5 equiv), CH$_3$CN, 25 °C, 10 min	45	1.4:1
7	**15**	PIFA (1.5 equiv), CH$_3$CN/H$_2$O (20:1), 25 °C, 10 min	42	1.4:1
8	**15**	PIFA (1.5 equiv), CF$_3$CH$_2$OH, 25 °C, 15 min	N.D.	–
9	**15**	PIFA (1.5 equiv), THF, 25 °C, 15 min	21	1:1
10	**15**	PIFA (1.5 equiv), toluene, 25 °C, 15 min	40	1:2
11	**15**	PIFA (1.5 equiv), toluene, $-5 \rightarrow 0$ °C, 35 min	51	1:1.3
12	**15**	PIFA (1.5 equiv), CH$_3$CN, $-5 \rightarrow 0$ °C, 30 min	54	2:1
13	**15**	DDQ (10 equiv), THF, $25 \rightarrow 70$ °C, 48 h	21	*anti* only
14	**15a**	PIFA (1.5 equiv), CH$_3$CN, $-5 \rightarrow 0$ °C, 30 min	42	1.1:1
15	**15b**	PIFA (1. equiv), CH$_3$CN, $-5 \rightarrow 0$ °C, 30 min	60	1.4:1
16	**2**	PIFA (1.1 equiv), CH$_3$CN, $-5 \rightarrow 0$ °C, 15 min	46	3:1
17	**2**	PIFA (1.2 equiv), CH$_2$Cl$_2$, $-5 \rightarrow 0$ °C, 30 min	68	9:1

[a] Yields refer to chromatographically and spectroscopically homogeneous materials. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The ratios are approximate. DDQ = 2,4-dichloro-5,6-dicyanobezoquinone, N.D. = not detected.

- ***Works without palladium***
- ***Best with free diol substrate***

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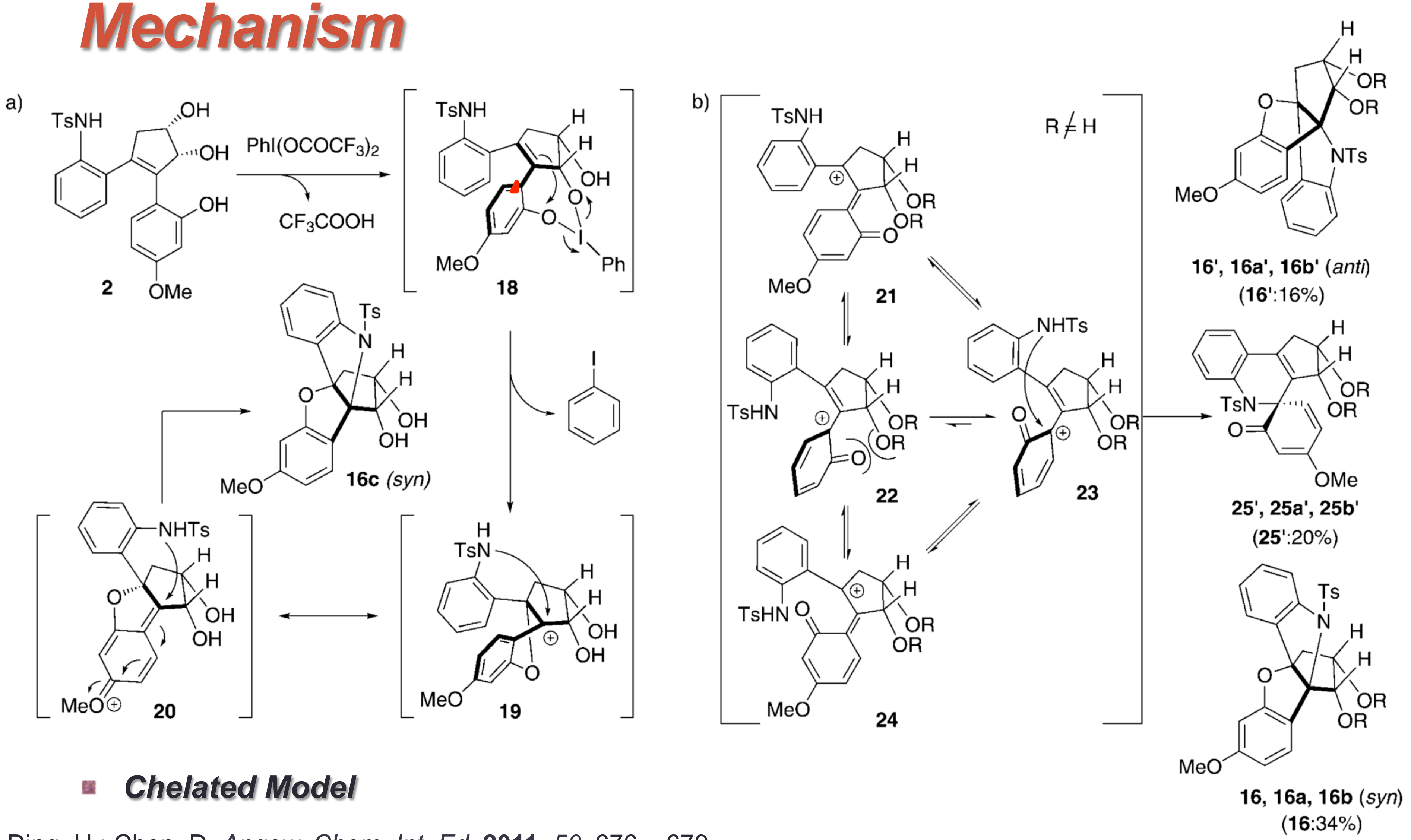
Mechanism



- ***Chelated Model***

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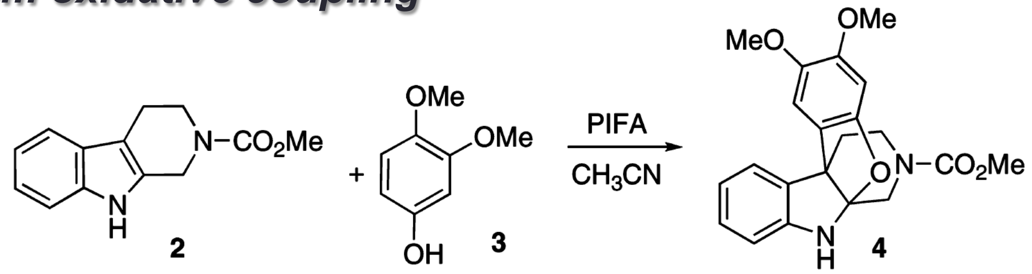
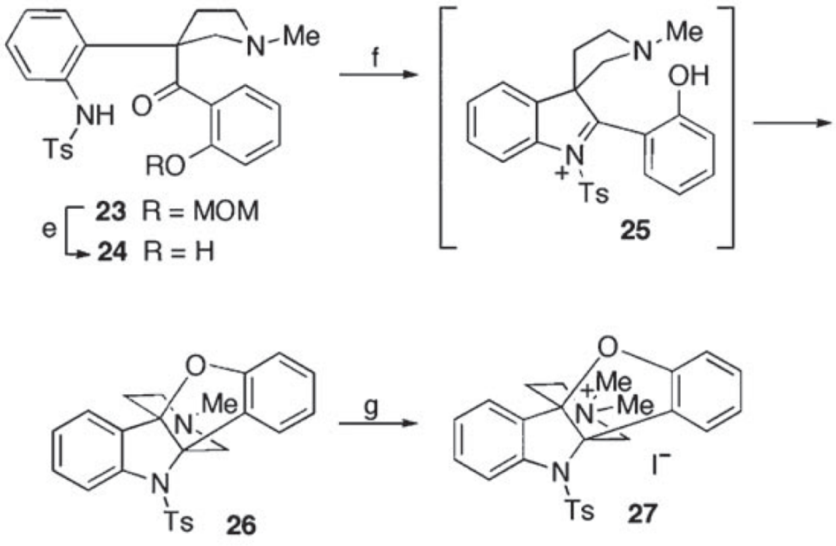
Summary

- ***A journey start from oxidative coupling***



- ***Rearrangement of azaspiroindolenine***



- ***Realization of oxidative coupling***