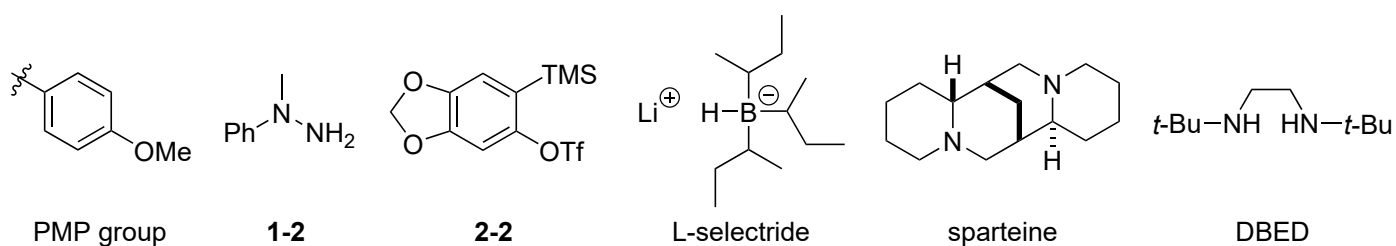
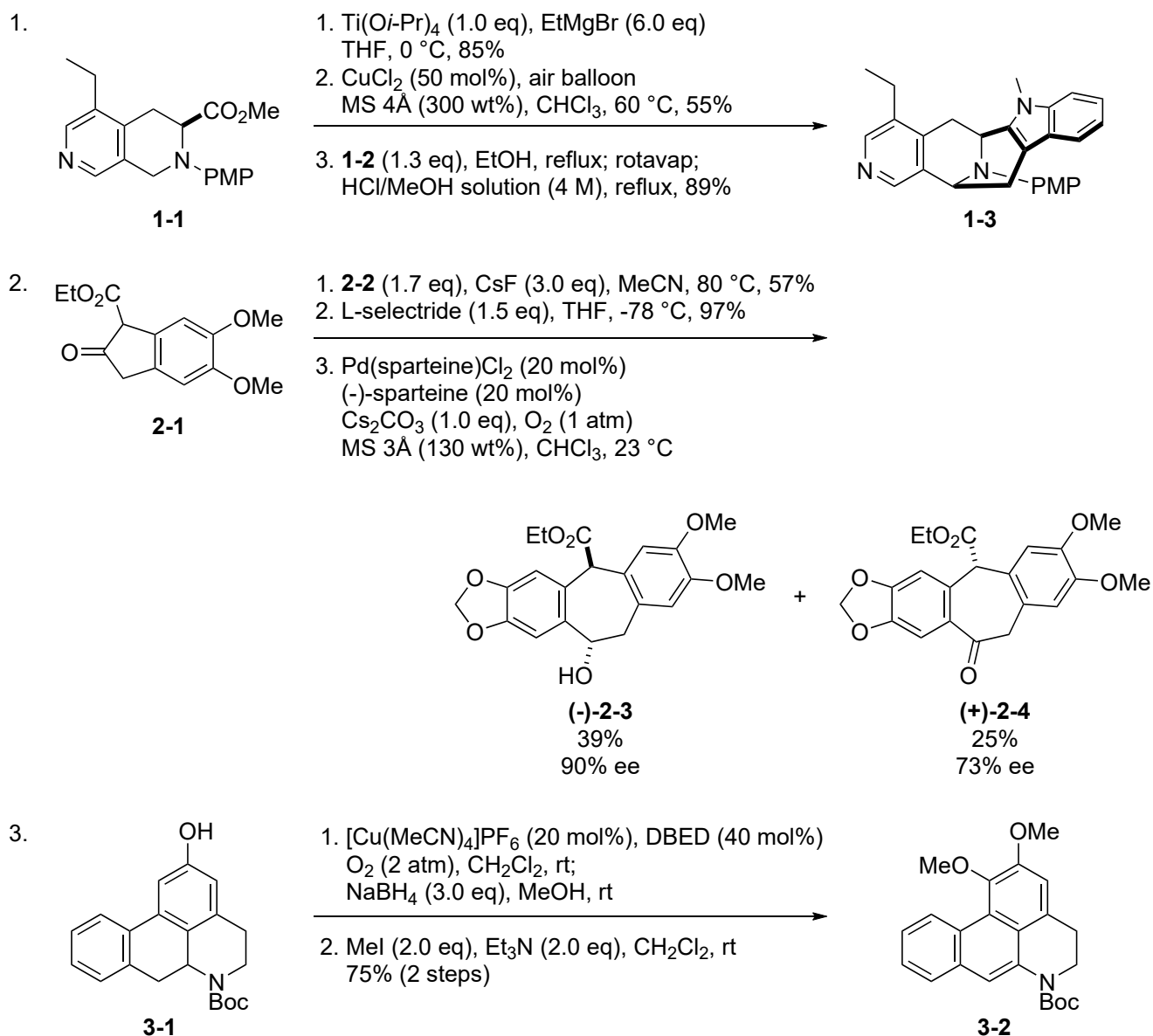


Please explain the reaction mechanisms.



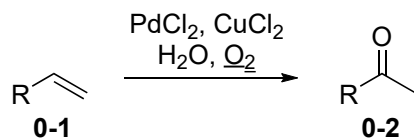
Topic: Application of aerobic oxidation to total synthesis

**Brief Introduction**

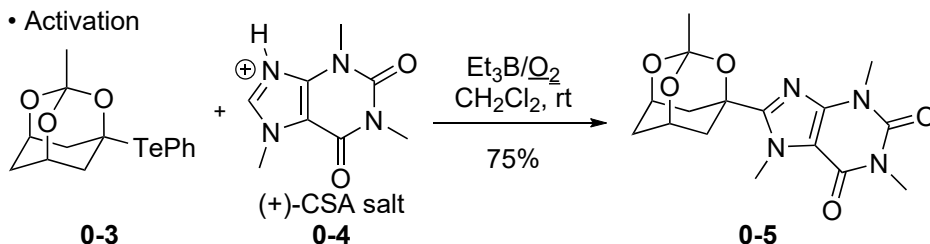
Roles of O<sub>2</sub>

I. Oxidation of metal reagent (Q1, Q2)

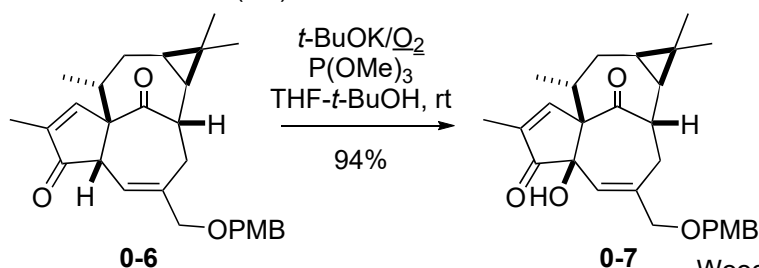
• Wacker oxidation



• Activation

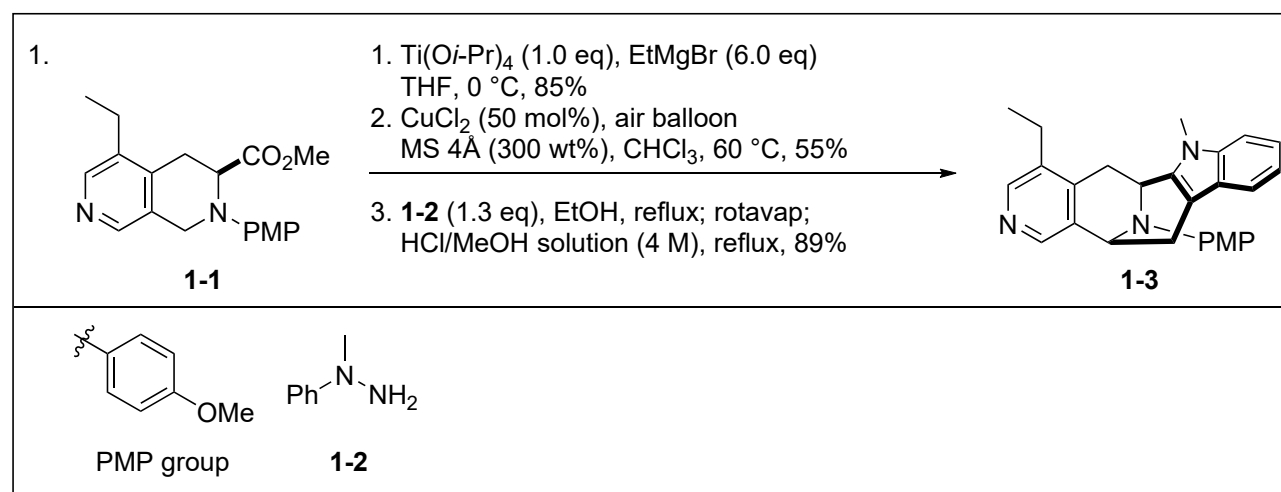
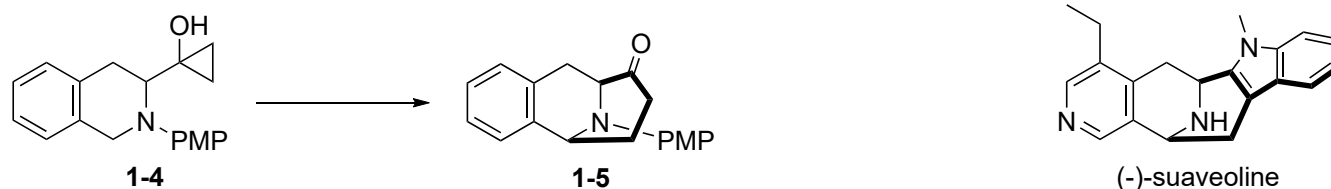


II. Source of O atom (Q3)



Wood, J. L. *et al.* *J. Am. Chem. Soc.* **2004**, *126*, 16300.

1. Cu-catalyzed oxidative cyclization: Total synthesis of (-)-suaveoline

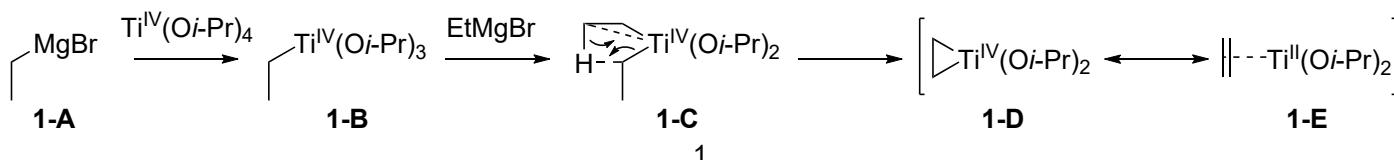


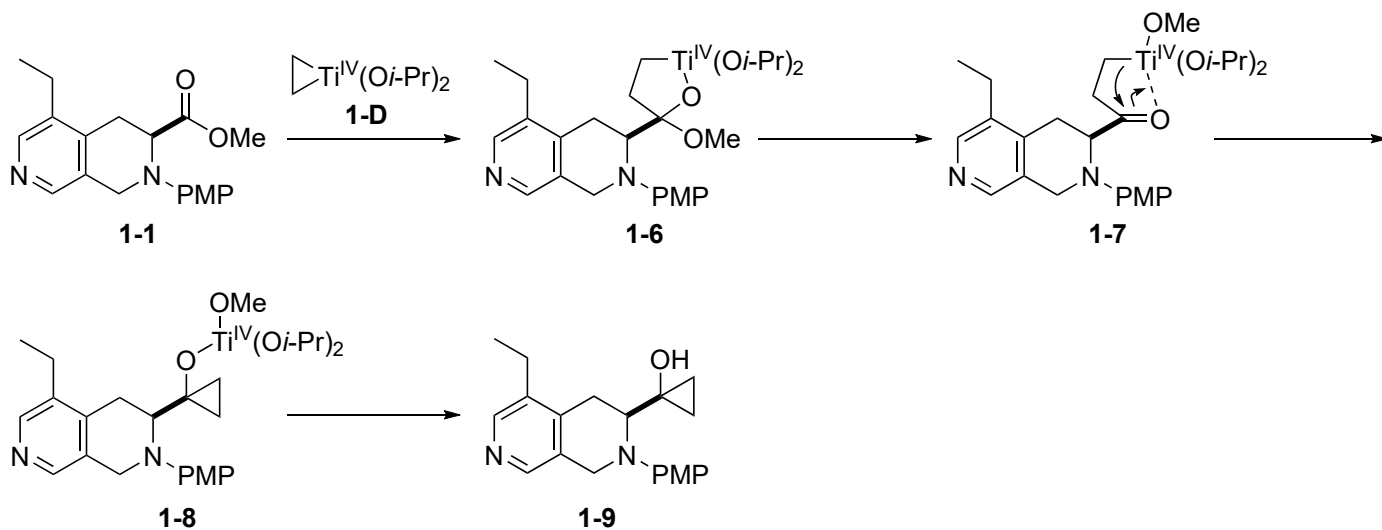
Zhang, M. *et al.* *Angew. Chem. Int. Ed.* **2019**, *58*, 6420.

**Answer**

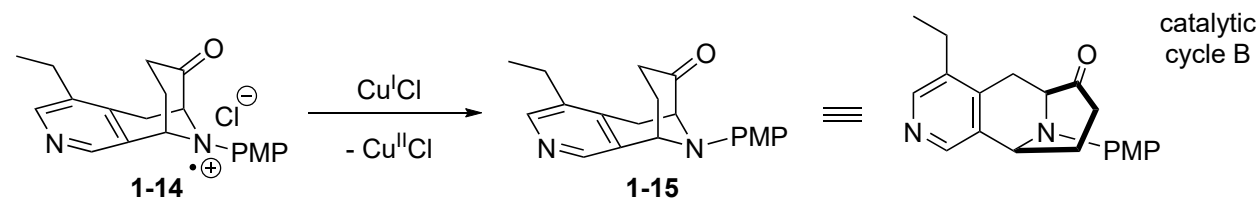
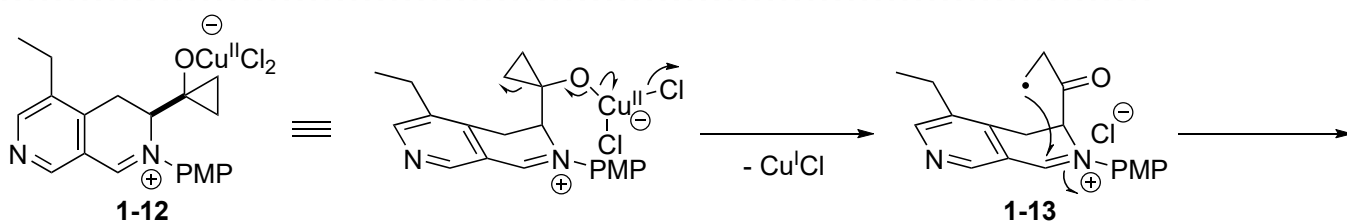
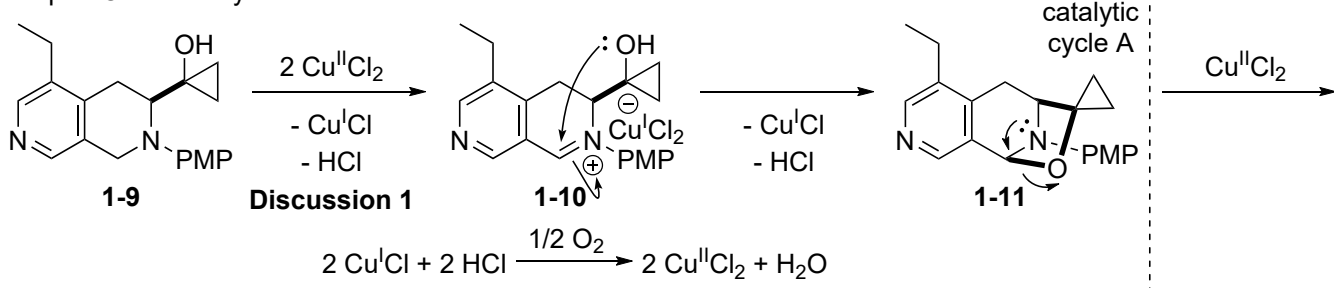
Step 1: Kulinkovich reaction

160409\_PS\_Shunichiroah\_KATOH

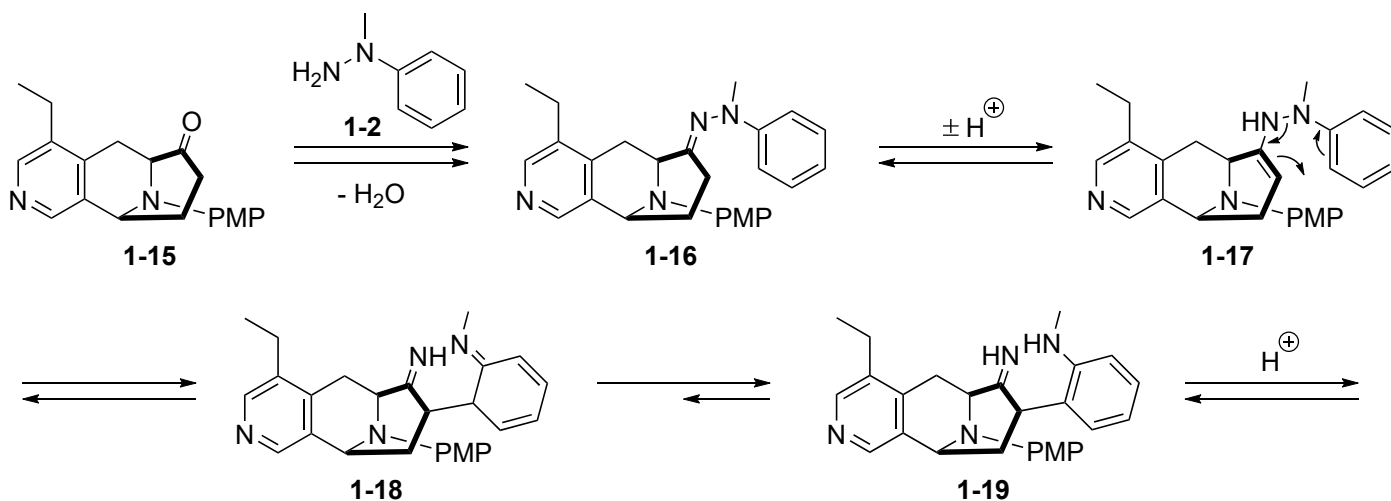


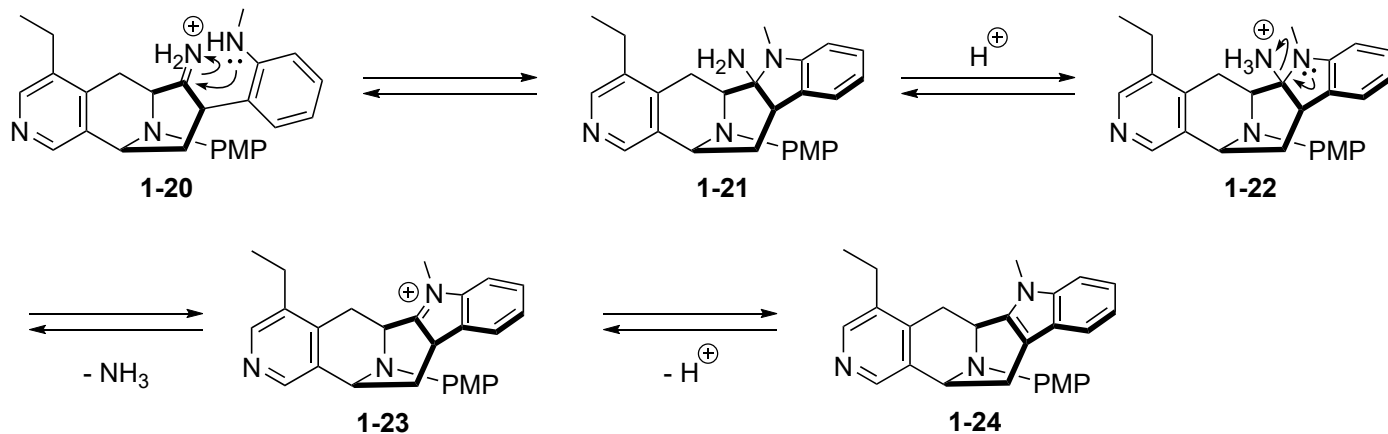


Step 2: Oxidative cyclization



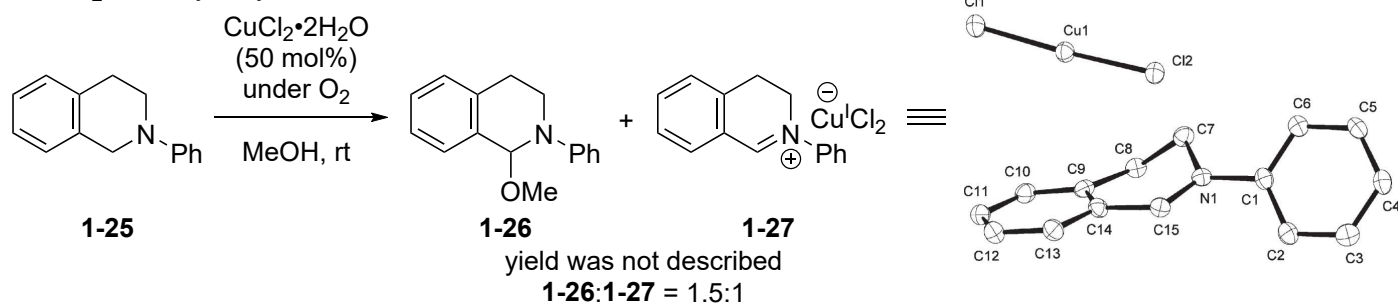
Step 3: Fischer indole synthesis





## Discussion

### 1. 2. O<sub>2</sub> in catalytic cycle A

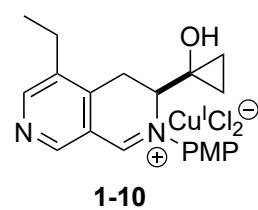
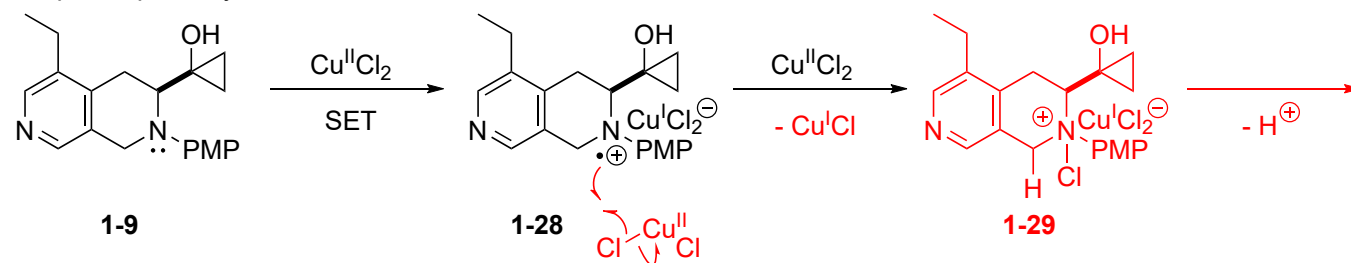


Klussmann, M. *et al.* *J. Am. Chem. Soc.* **2011**, *133*, 8106.

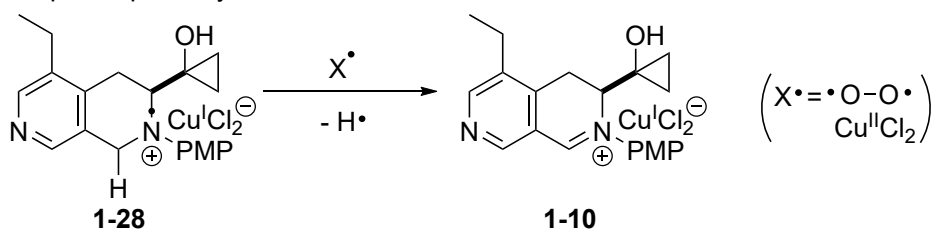
1-27 was immediately formed even in the absence of O<sub>2</sub>.

∴ Major role of O<sub>2</sub> is thought to be reoxidize Cu<sup>I</sup> to Cu<sup>II</sup>.

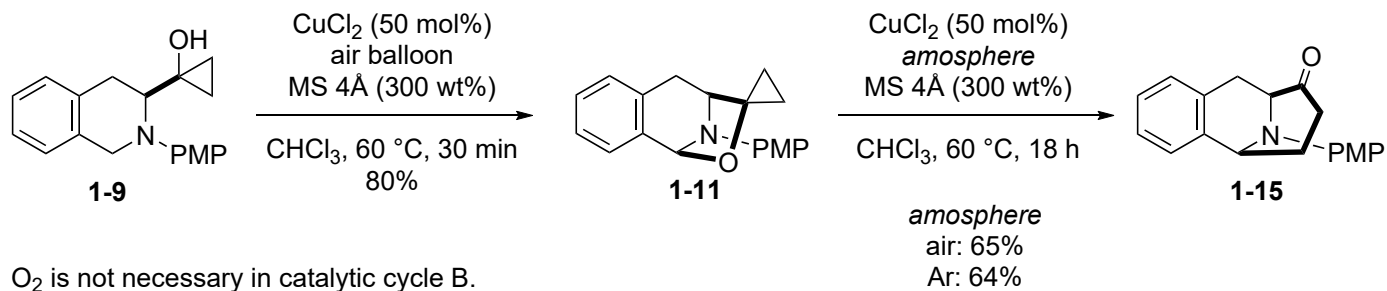
### Proposed pathway 1



### Proposed pathway 2

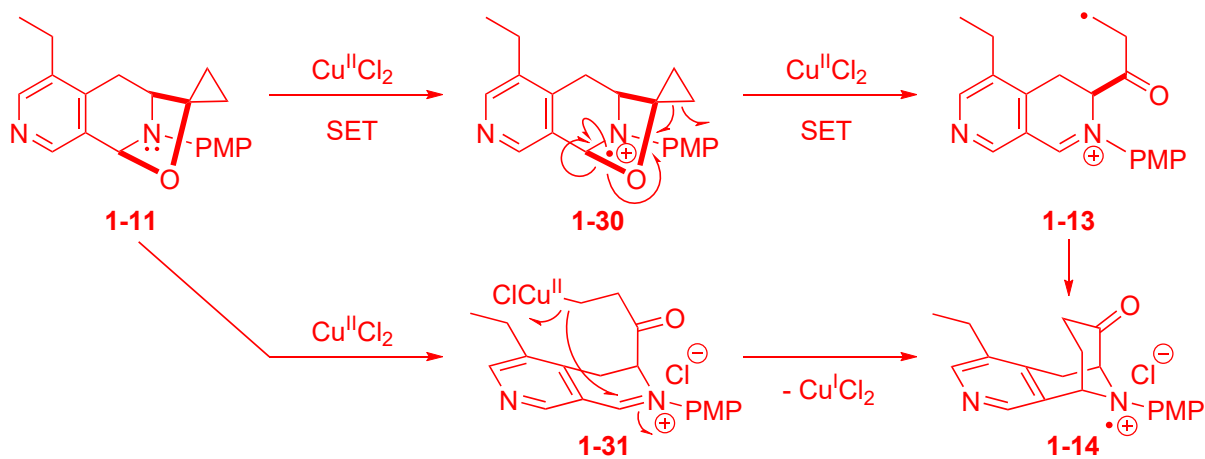


## 2. O<sub>2</sub> in catalytic cycle B

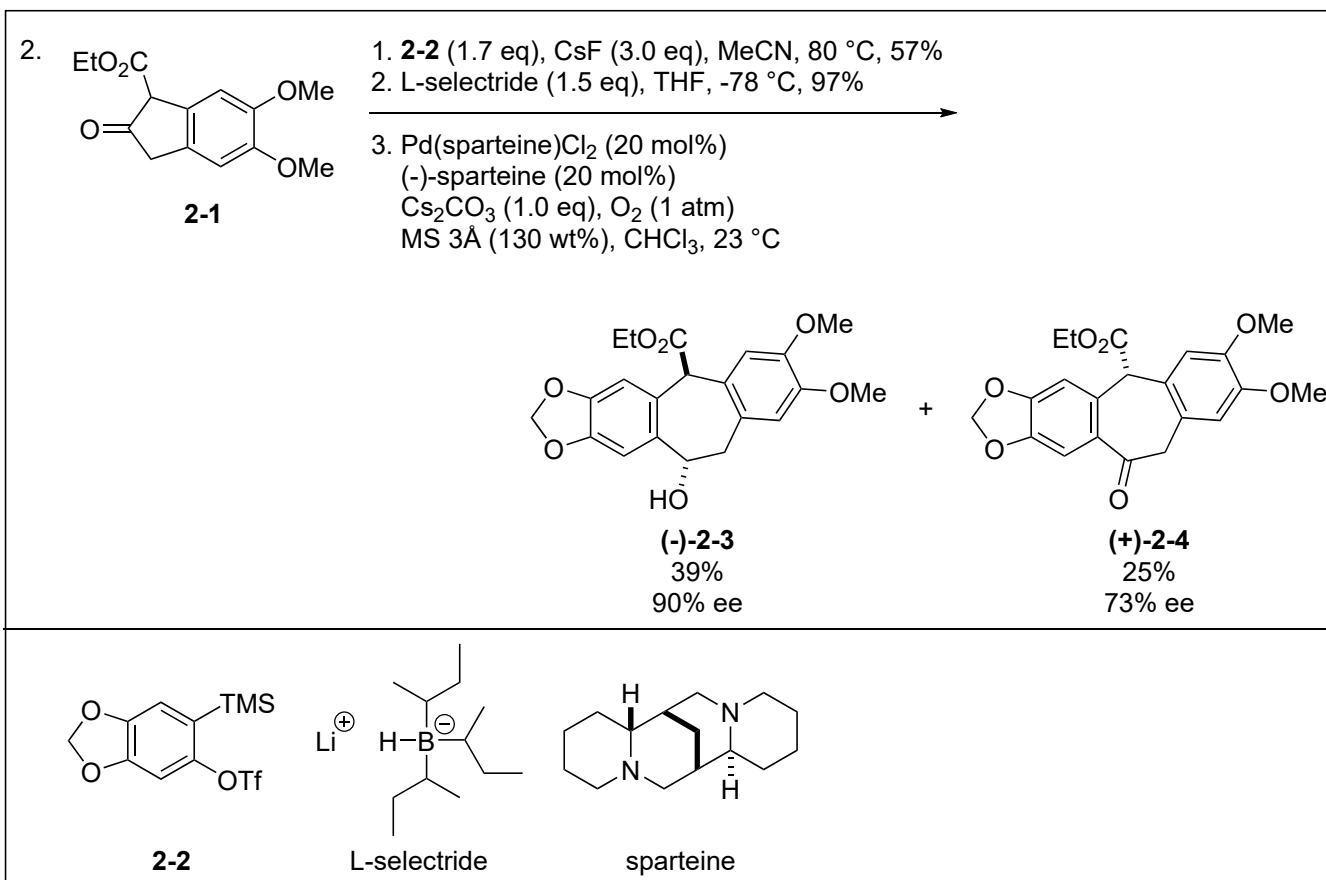
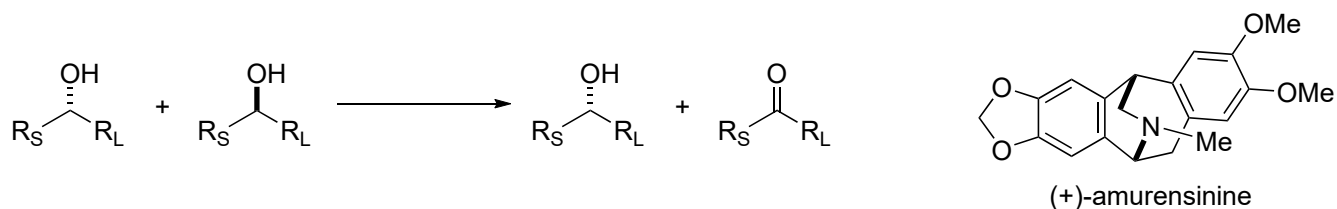


O<sub>2</sub> is not necessary in catalytic cycle B.

## 3. Another reaction pathway from 1-11 to 1-14



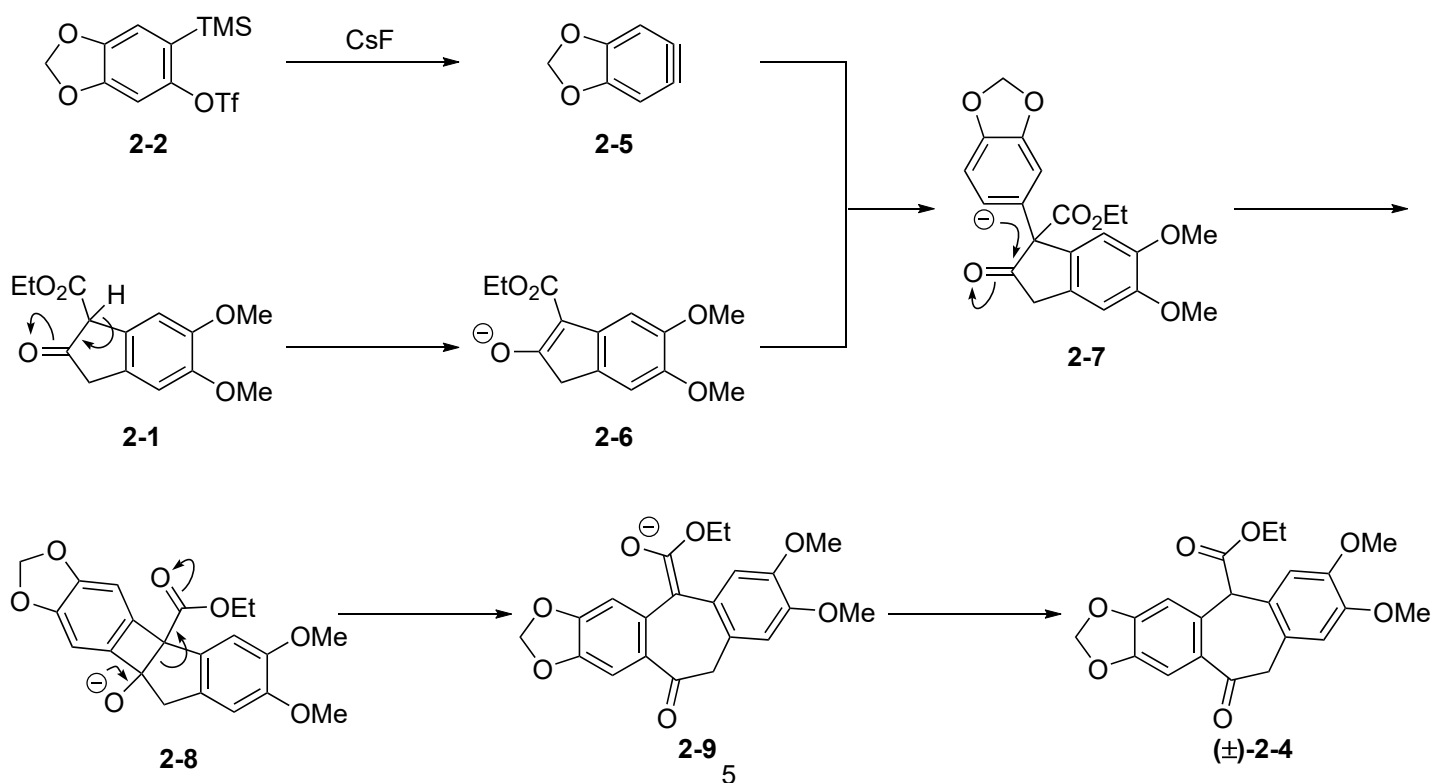
2. Pd-catalyzed enantioselective oxidation: Asymmetric synthesis of (+)-amurensinine



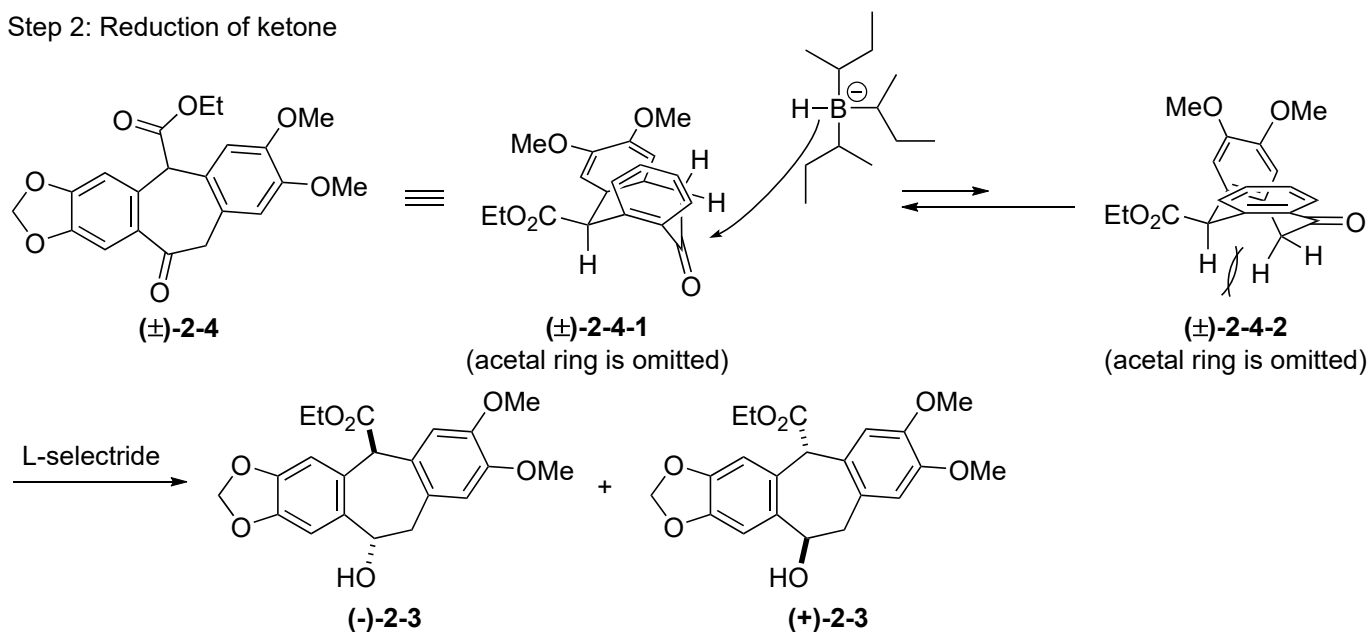
Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2008**, *130*, 13745.

**Answer**

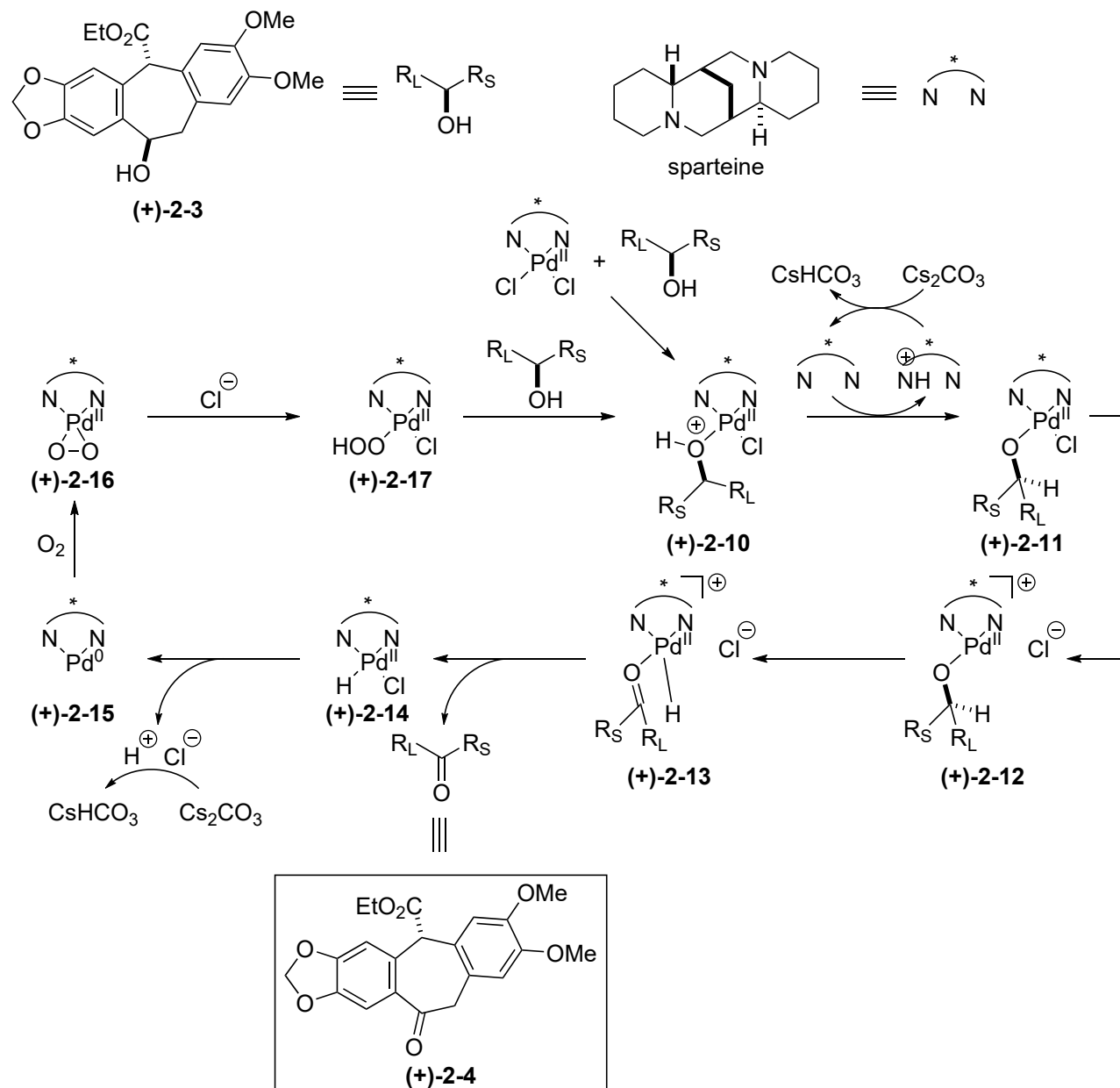
Step 1: Ring expansion using benzyne



Step 2: Reduction of ketone

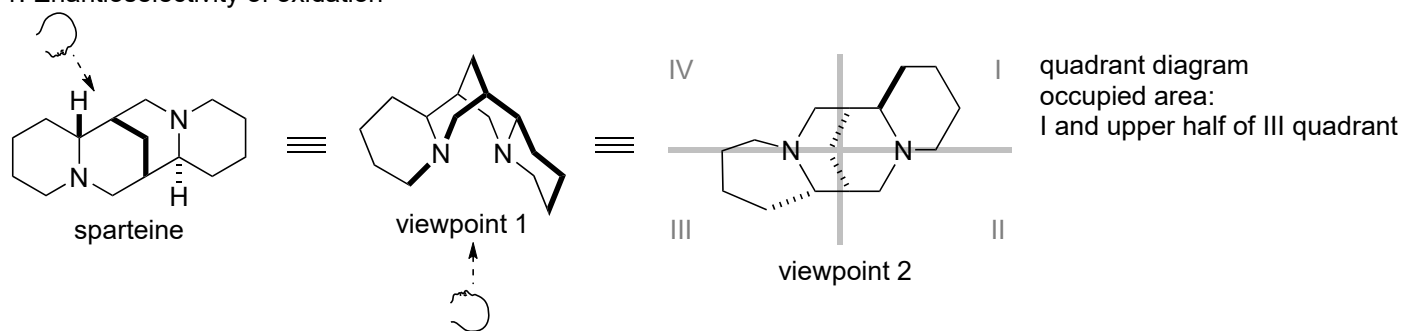


Step 3: Kinetic resolution

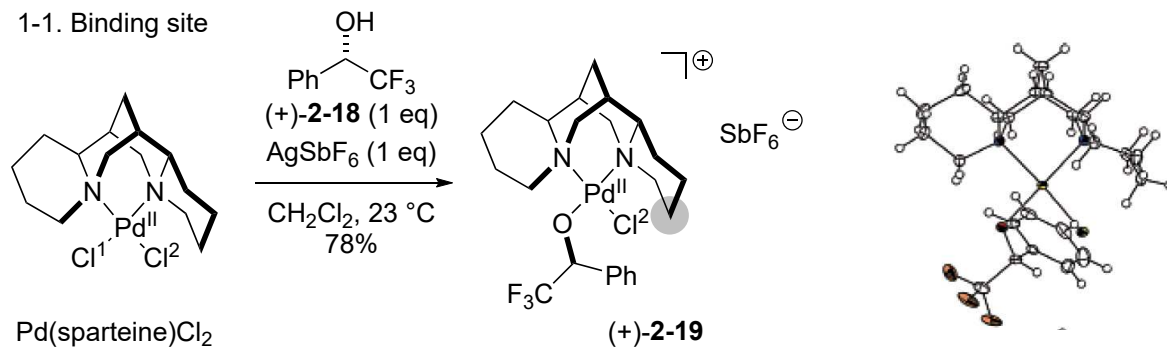


## Discussion

### 1. Enantioselectivity of oxidation

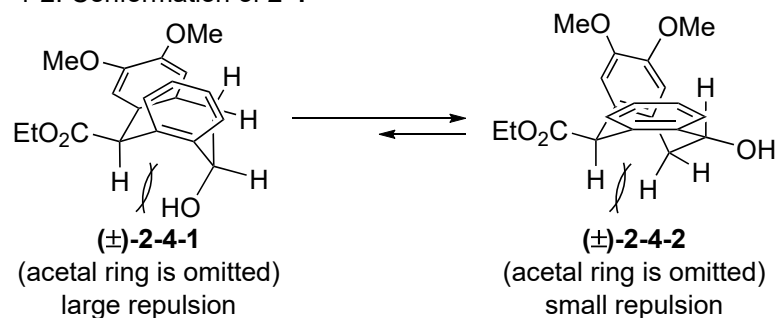


#### 1-1. Binding site

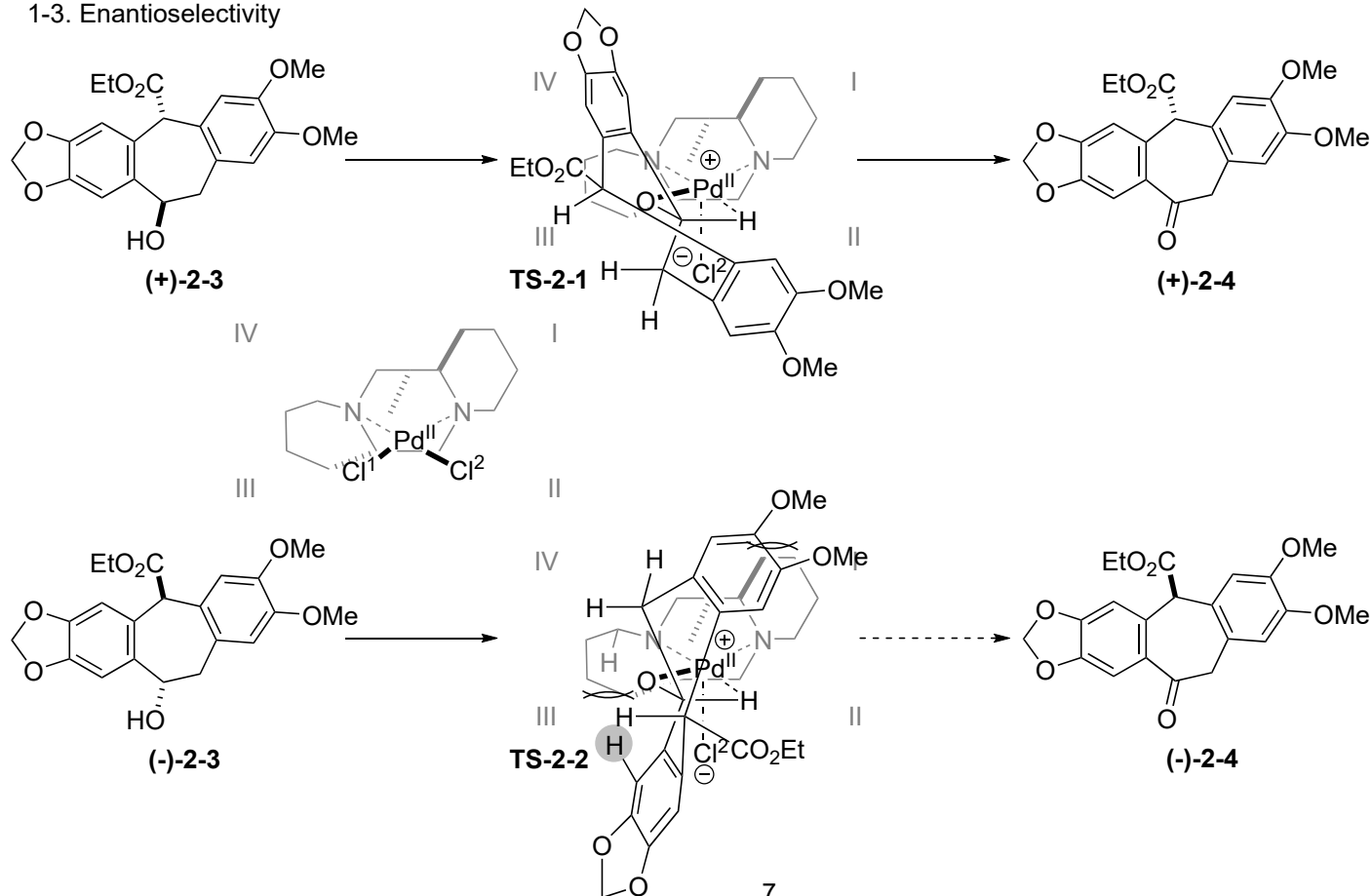


Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4482.

#### 1-2. Conformation of **2-4**

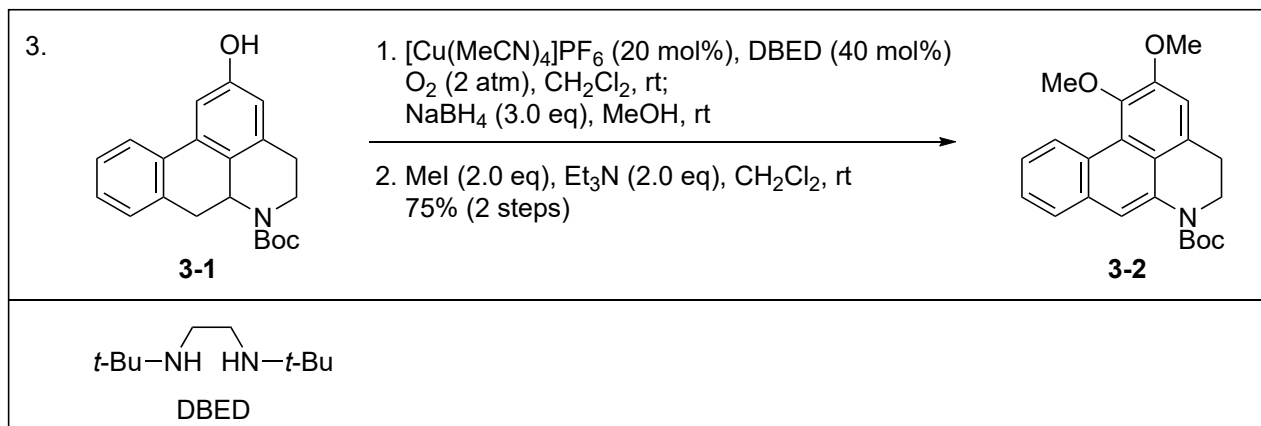
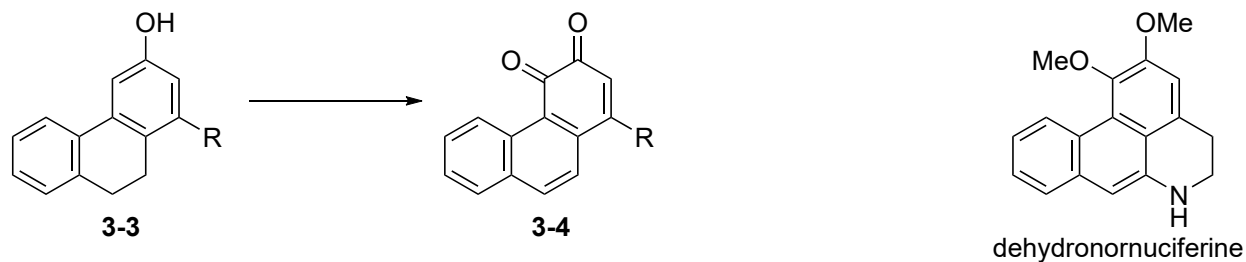


#### 1-3. Enantioselectivity





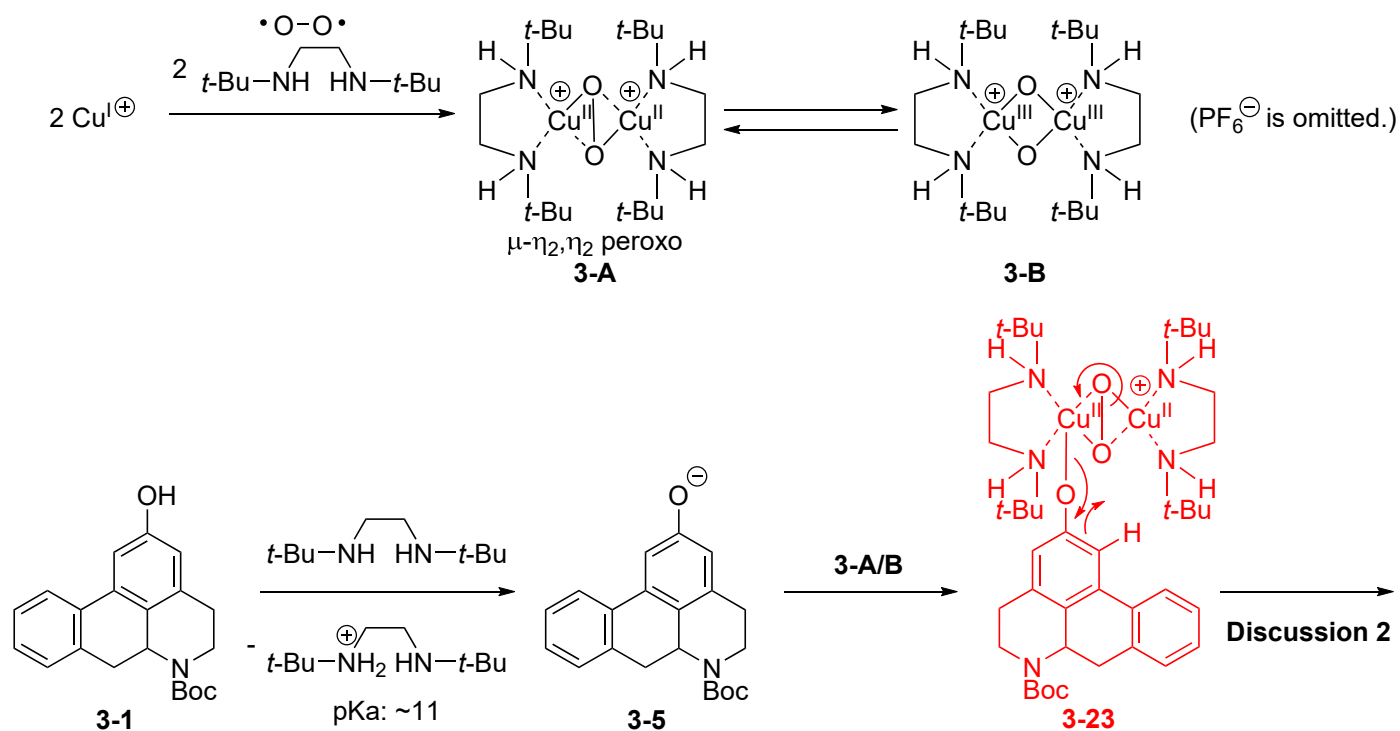
3. Selective dearomatization of phenol: Total synthesis of dehydronornuciferine



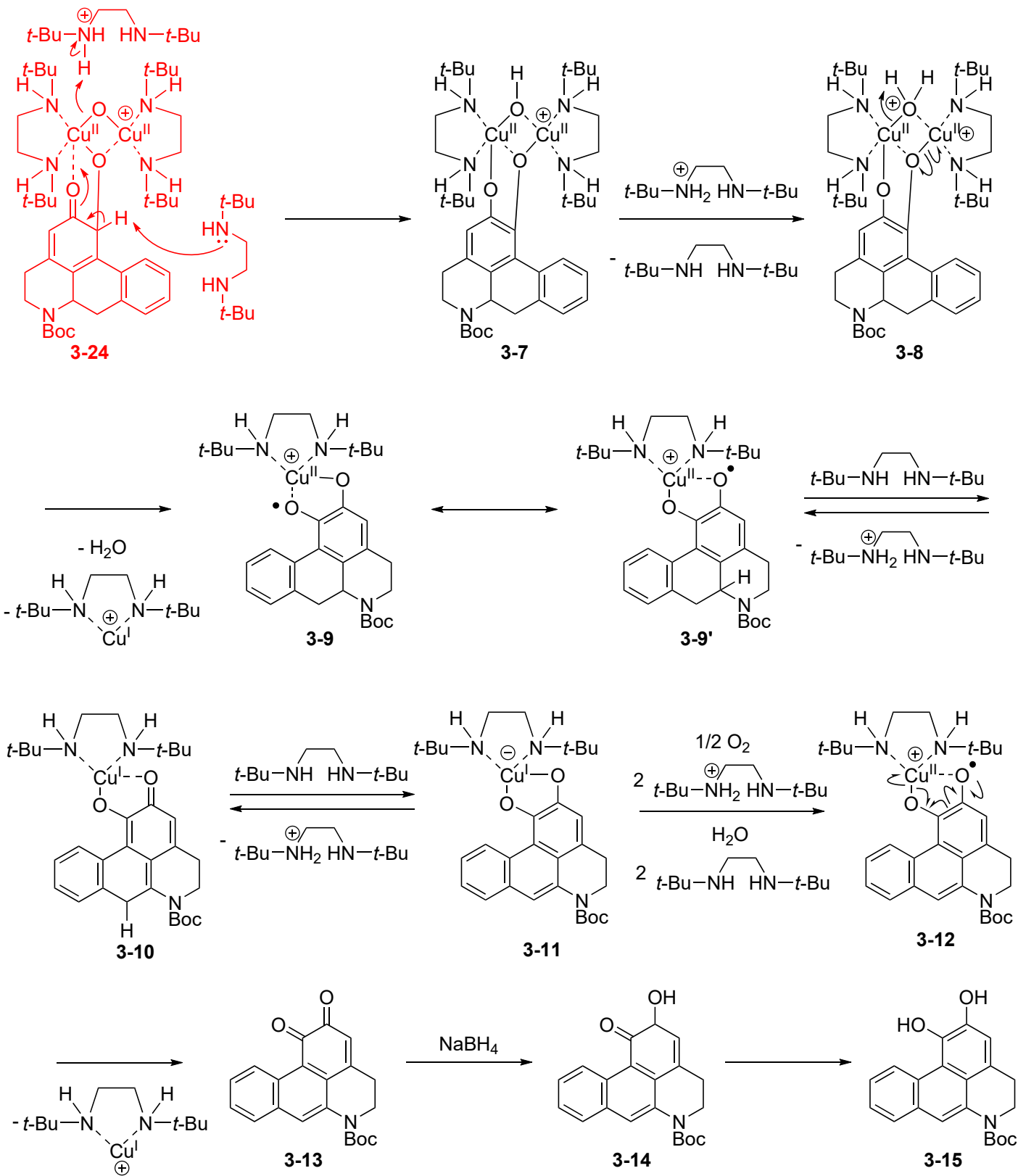
Esguerra, K. V. N.; Lumb, J. P. *Angew. Chem. Int. Ed.* **2018**, *57*, 1514.

**Answer**

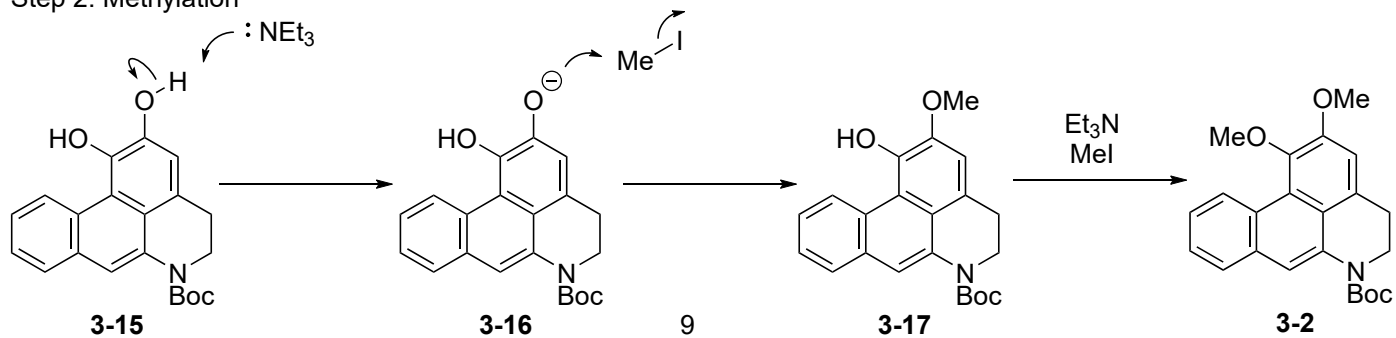
Step 1: Regioselective oxidation and rearomatization



Esguerra, K. V. N.; Lumb, J. P. *Synthesis* **2019**, *51*, 334.



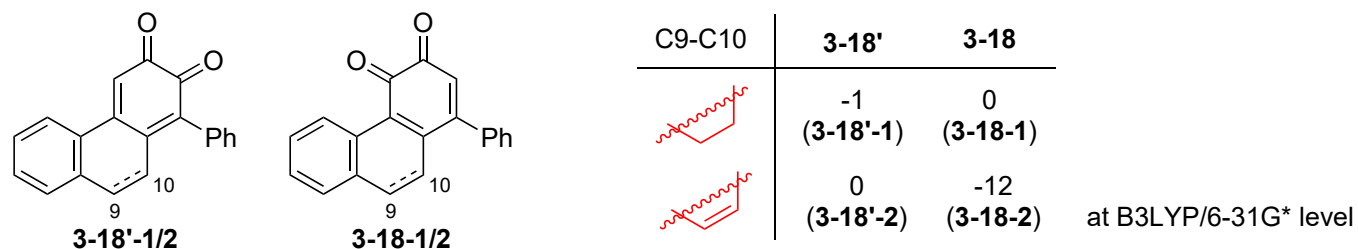
Step 2: Methylation



## Discussion

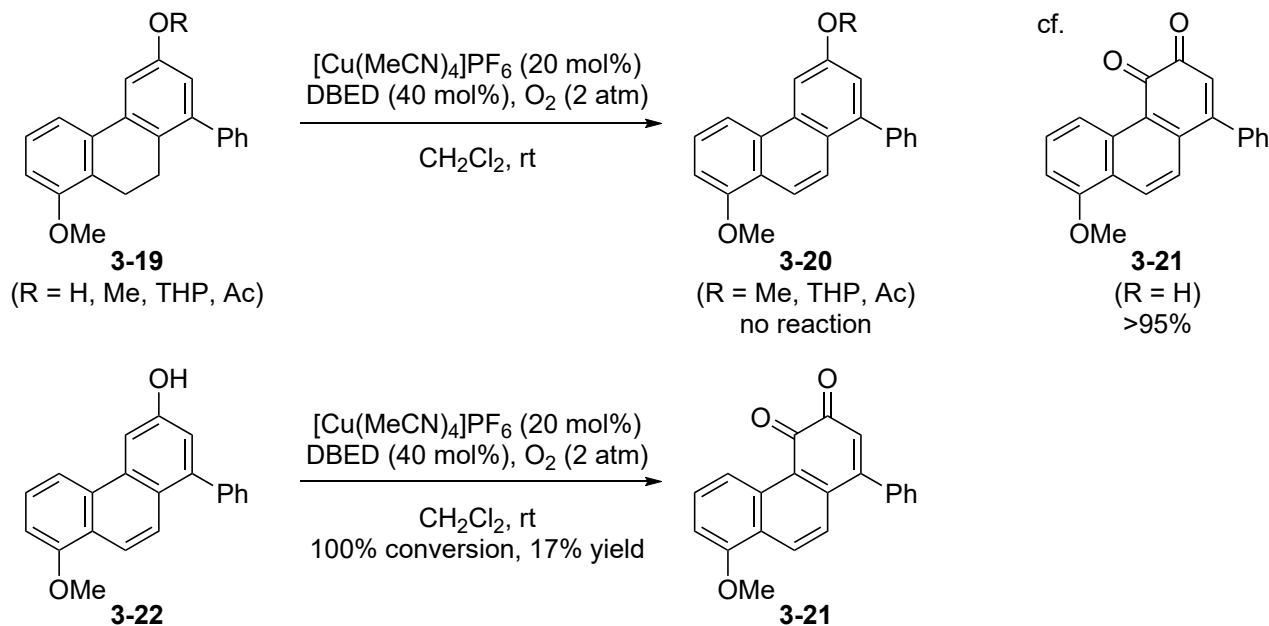
### 1. Phenol oxidation vs Benzylic C-H oxidation

#### 1-1. Computational analysis



The product becomes much more stable after benzylic C-H oxidation.

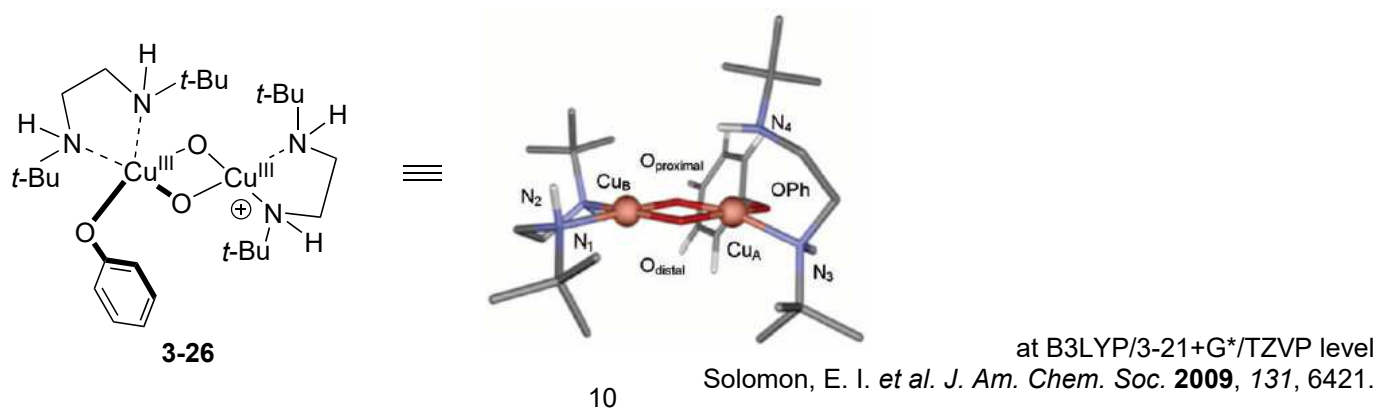
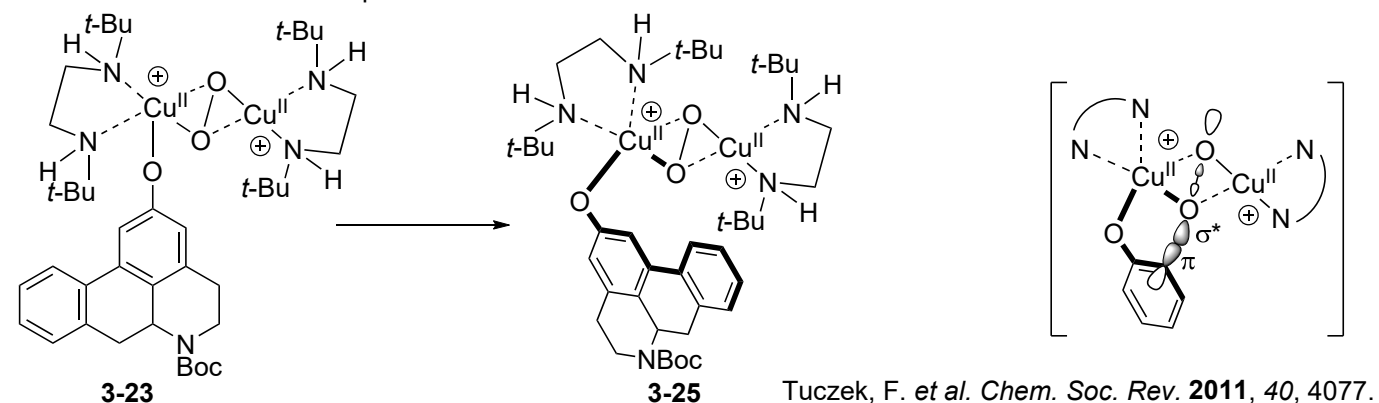
#### 1-2. Experimental results



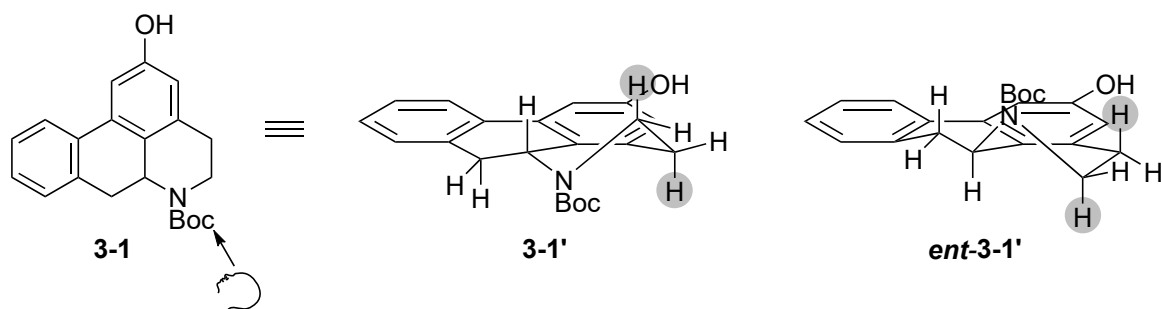
Dearomatization occurred first, then subsequently benzylic C-H oxidation proceeded.

## 2. Regioselectivity of dearomatization

### 2-1. Conformation of Cu complex



2-2. Conformation of **3-1**



3-3. Proposed TS structure and regioselectivity

