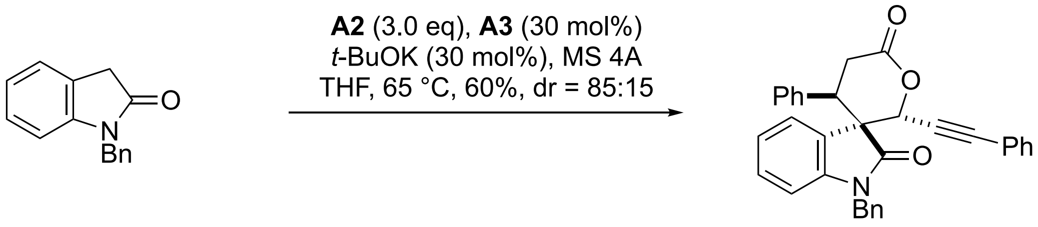
Problem Session (2)

2025/05/16 Haruka Aritaki

Topic: Synthesis of Spirooxindoles

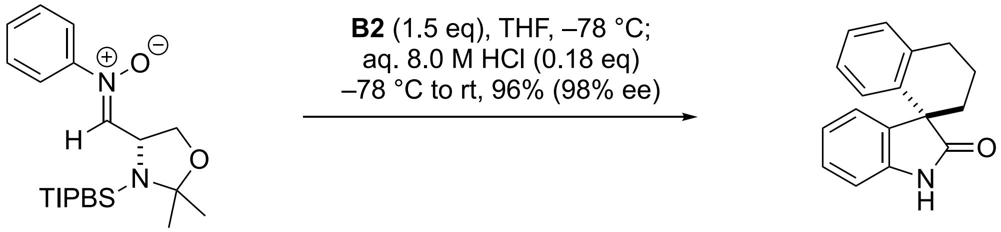
Please explain the mechanisms for the reactions in schemes **A**–**C**.

A



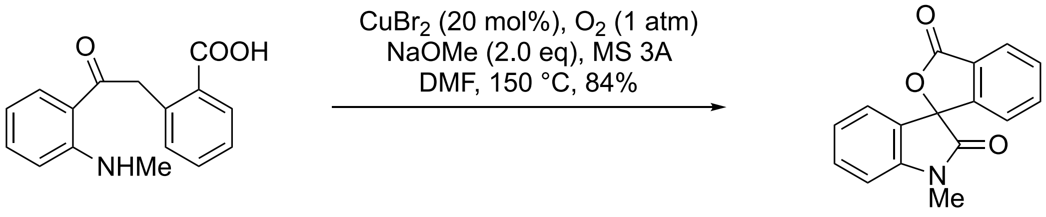
A1 **A4**

B

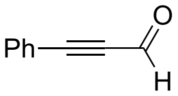


B1 **B3**

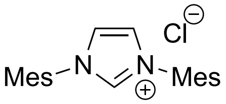
C



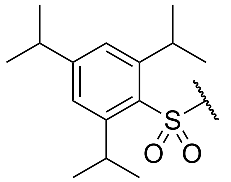
C1 **C2**



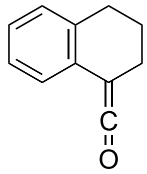
A2



A3



TIPBS = 2,4,6-triisopropylbenzenesulfonyl



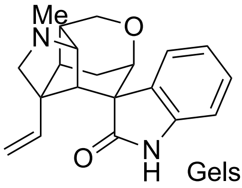
B2

Problem Session (2) -Answer-

2025/05/16 Haruka Aritaki

Introduction

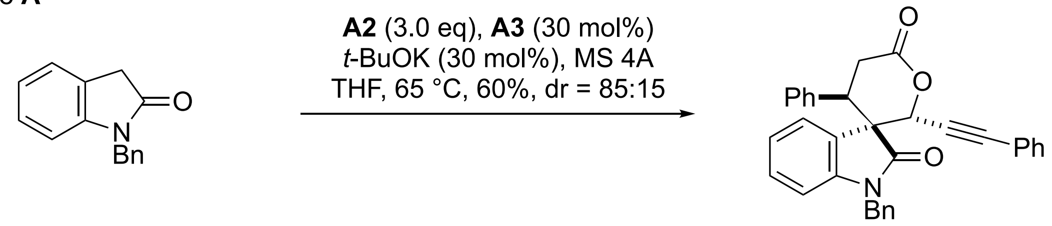
Spirooxindole is a structural motif central to a variety of both natural products (such as gelsemine) and pharmaceutically relevant materials. Therefore, I chose synthesis of spirooxindoles as the theme for today's Problem Session.



Gelsemine

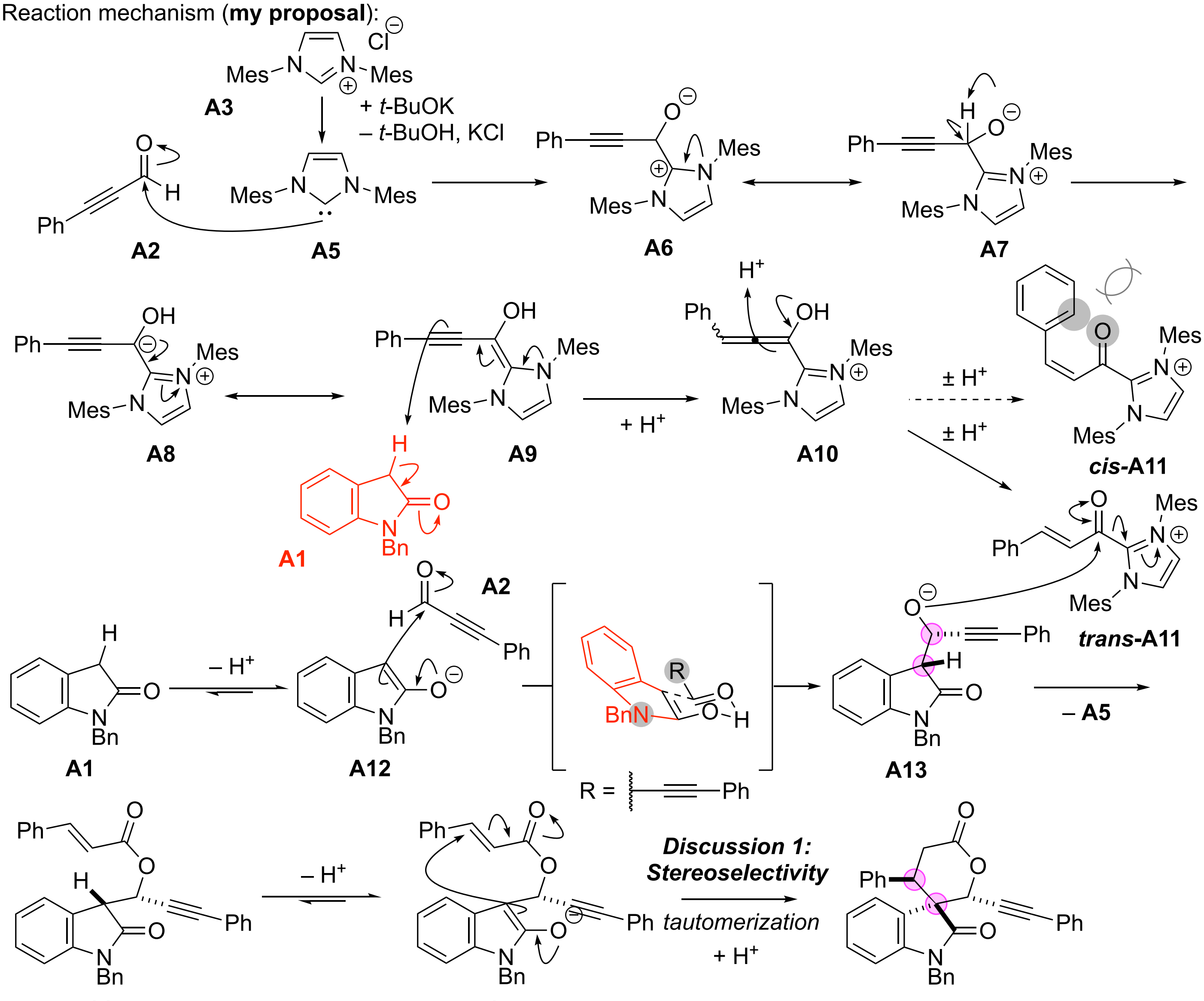
(Gelsemine has been featured as a topic in our seminar.
Please refer to 160227_Yuki_Fujimoto)

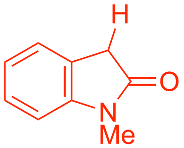
Scheme **A**[1]



A1 **A4**

Reaction mechanism (**my proposal**):



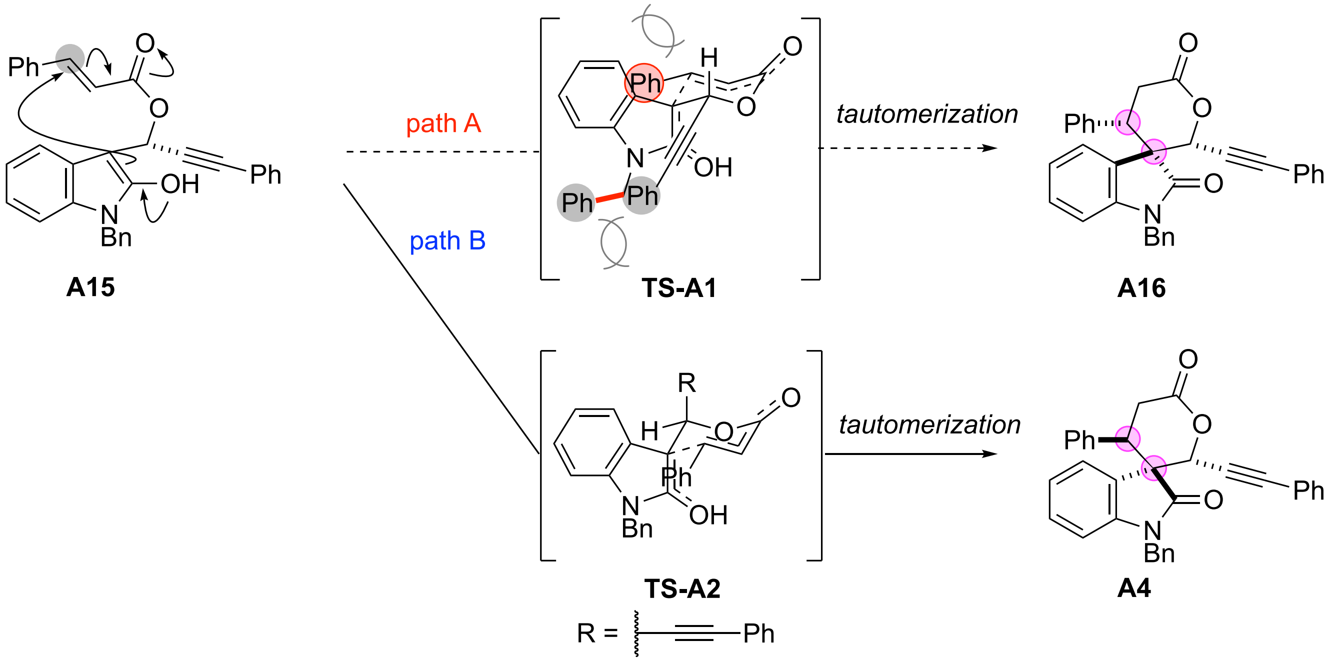
	pKa (in DMSO solution)
t-BuOH	29.4[6]
	18.5[7]

– What shuttle proton in this reaction?

– **A1** would have more acidic proton than *t*-BuOH, so **A1** would shuttle proton in this reaction.

The authors proposed a different reaction mechanism from the one presented in the answer. Their proposed reaction mechanism will be discussed in ***Discussion 2***.

***Discussion 1*: Stereoselectivity**

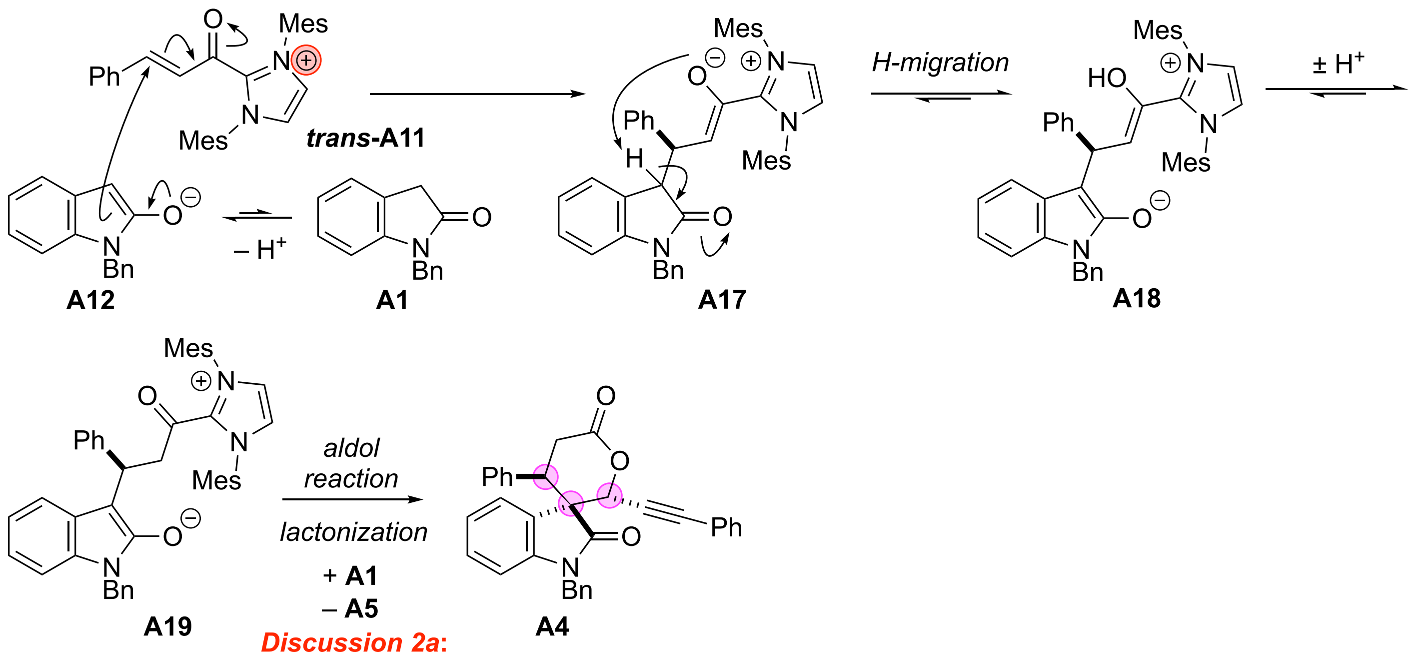


In this reaction, two products can be assumed (**A4**, **A16**). Which product is formed depends on whether the carbon atom highlighted in gray is positioned on the front side (path A) or the back side (path B) relative to the indole.

In **TS-A1**, there should be steric repulsion between the alkyne and the indole. Additionally, to avoid steric repulsion with the red-highlighted Ph group, it is assumed that the Ph group of N-Bn adopts a conformation facing the front side. In this orientation, steric repulsion is also expected between the two Ph groups highlighted in gray. Due to these two steric interactions, **TS-A1** would be a less favorable conformation compared to **TS-A2**, and the reaction is therefore considered to proceed via path B.

***Discussion 2*: Reaction mechanism (authors' proposal)**

Proposed mechanism (***trans*-A11** to **A4**):

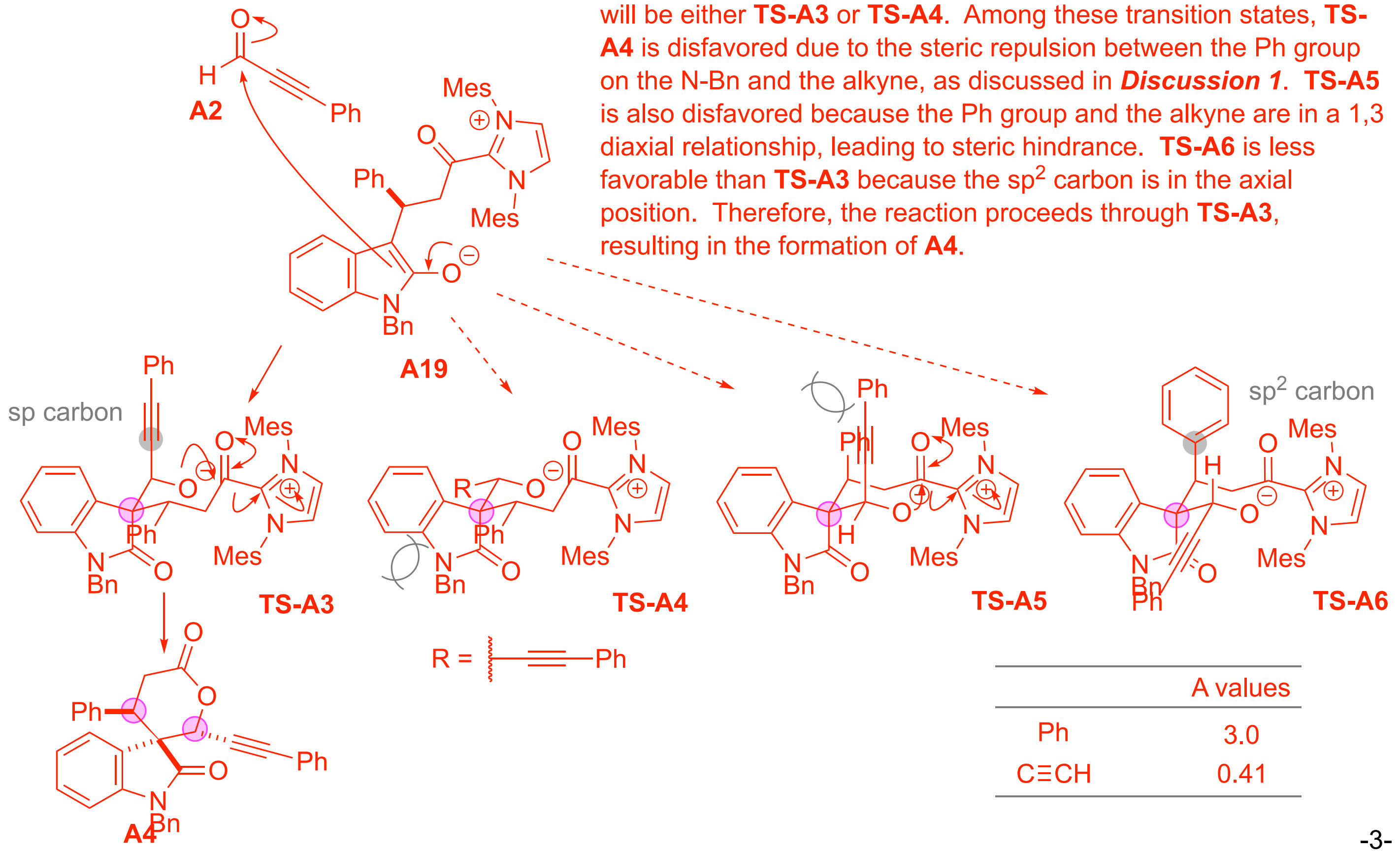


Discussion 2a*: *stereoselectivity

In this reaction mechanism, the fact that the cation on the intermediate is not quenched is considered to contribute to the high reactivity of ***trans*-A11** to **A19**. In other words, the reaction between ***trans*-A11** and **A12** is kinetically more favorable than the reaction between aldehyde **A2** and **A12**. Therefore, the reaction mechanism proposed by the authors, in which ***trans*-A11** reacts with **A12**, is considered the plausible mechanism.

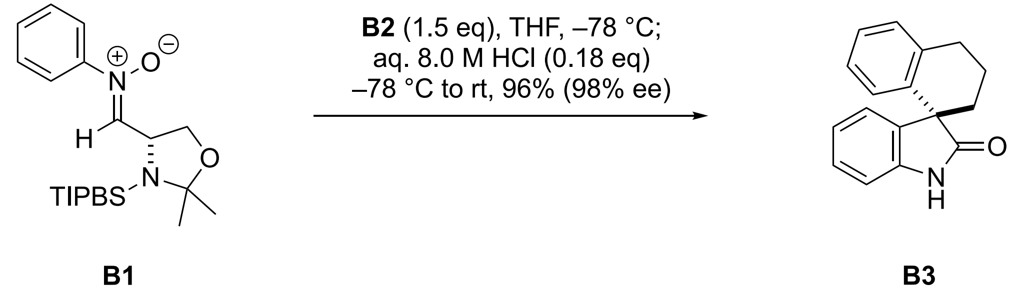
***Discussion 2a*: stereoselectivity**

When aldehyde **A2** approaches **A19** from the front side, the transition state of the following lactonization will be either **TS-A5** or **TS-A6**. When it approaches from the back side, the transition state will be either **TS-A3** or **TS-A4**. Among these transition states, **TS-A4** is disfavored due to the steric repulsion between the Ph group on the N-Bn and the alkyne, as discussed in ***Discussion 1***. **TS-A5** is also disfavored because the Ph group and the alkyne are in a 1,3 diaxial relationship, leading to steric hindrance. **TS-A6** is less favorable than **TS-A3** because the sp^2 carbon is in the axial position. Therefore, the reaction proceeds through **TS-A3**, resulting in the formation of **A4**.

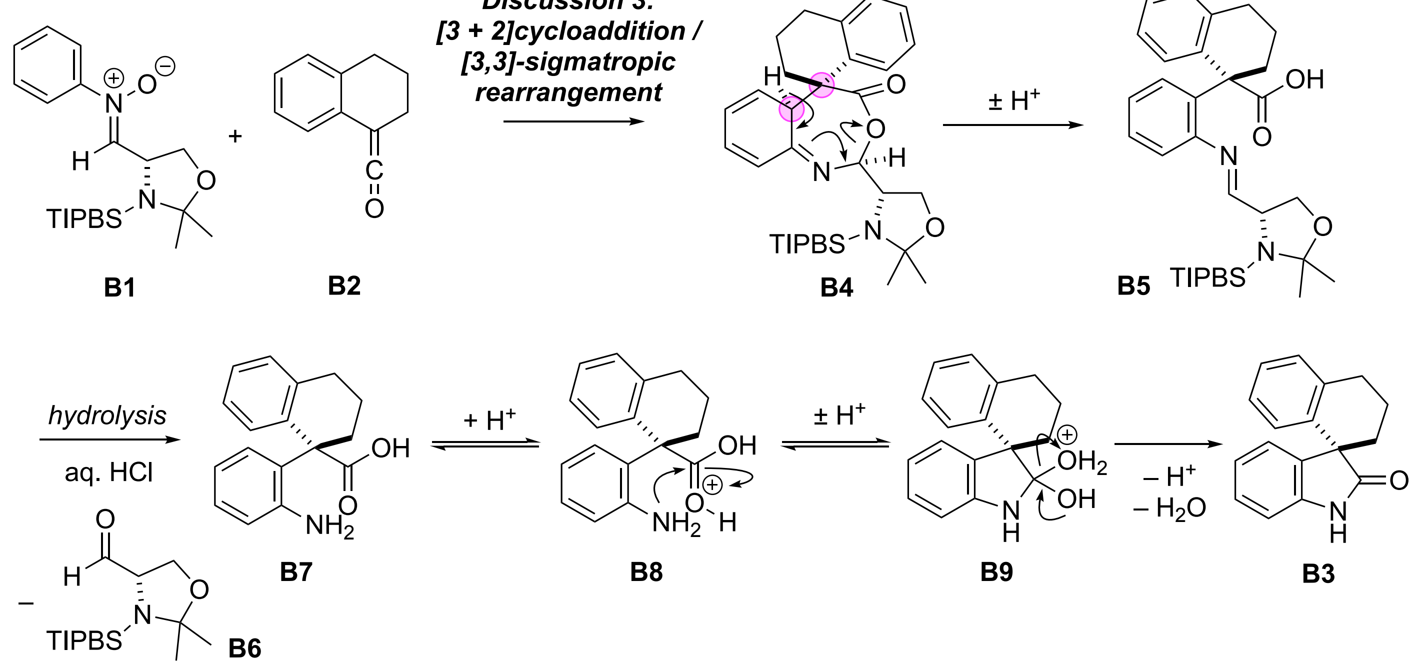


	A values
Ph	3.0
C≡CH	0.41

Scheme **B**[2]



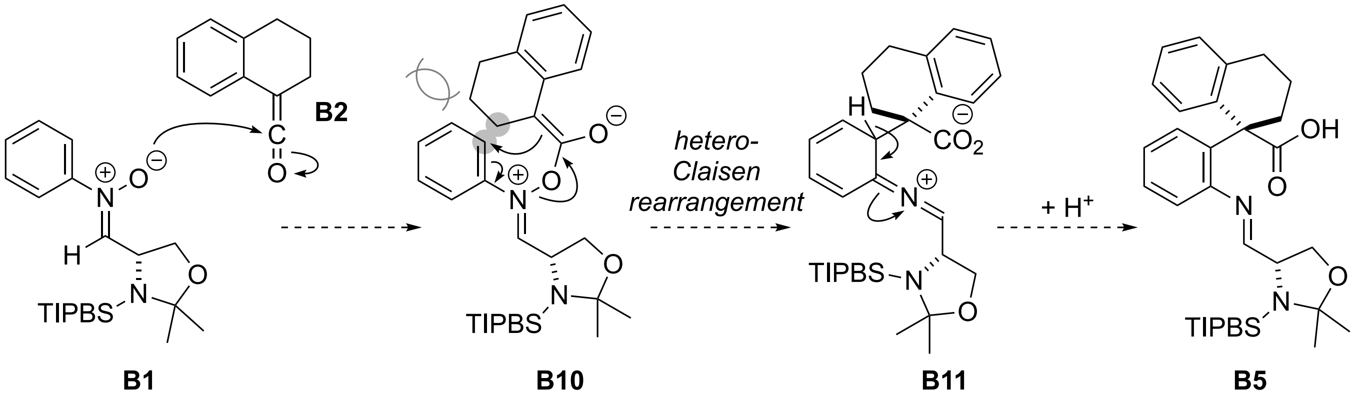
Reaction mechanism:



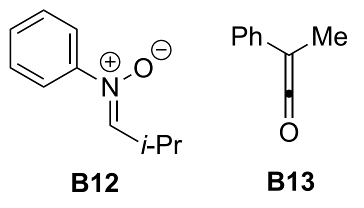
Discussion 3: **[3 + 2]cycloaddition / [3,3]-sigmatropic rearrangement**

3.1. Another possible mechanism (nucleophilic addition → hetero-Claisen rearrangement, **B1** to **B5**)

Reaction mechanism:

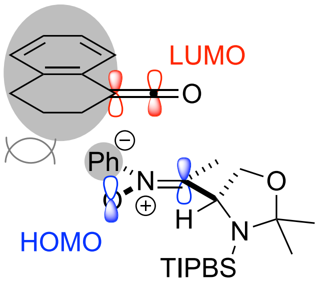


In this reaction mechanism, during the hetero-Claisen rearrangement, there exists a large steric repulsion between the carbon atoms highlighted in gray. Therefore, I thought the reaction would not proceed. In fact, the study reported that, for similar substrates (**B12** and **B13**), attempts to locate the TS for this step by constraining the forming C-C and the breaking N-O bonds at various partial bond distances in the gas phase and in solution yielded highly unstable TSs with a free energy of at least 44.1 kcal/mol relative to the separated reactants[3].

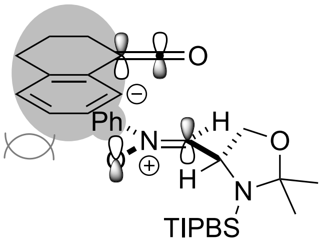


3.2. Which bond undergose the reaction: the C=C bond or the C=O bond?

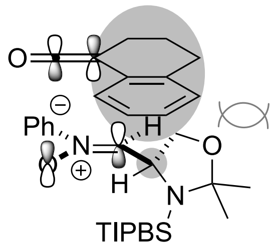
C=C bond:



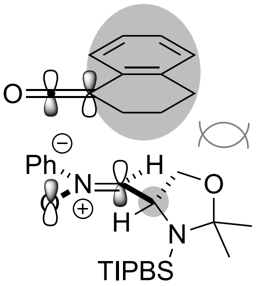
TS-B1



TS-B2

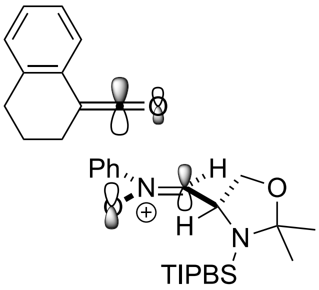


TS-B3

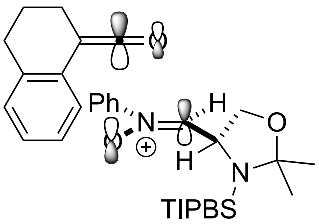


TS-B4

C=O bond:



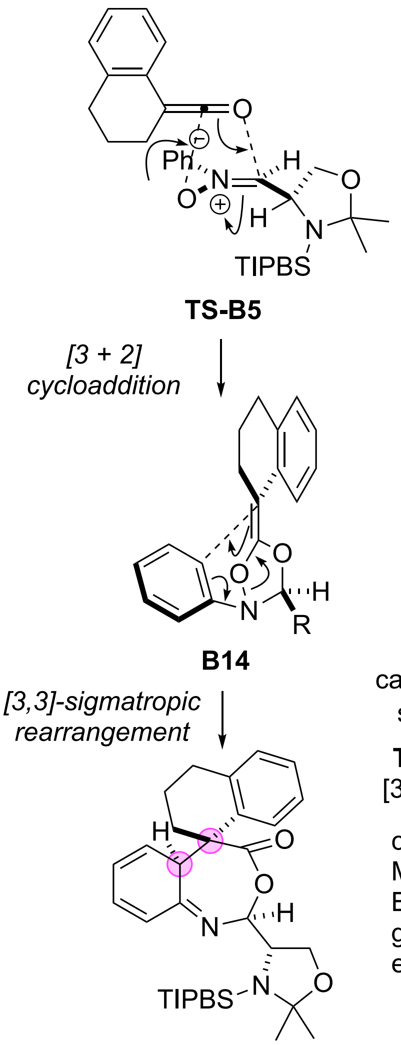
TS-B5



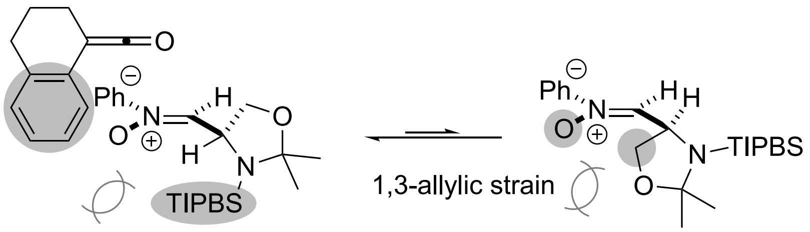
TS-B6

When the reaction occurs at the C=C bond of ketene, the substituent on the ketene is expected to approach the substituent on the nitrone more closely compared to the reaction at the C=O bond, leading to a large steric repulsion. Therefore, the reaction would proceed via **TS-B5** or **TS-B6**.

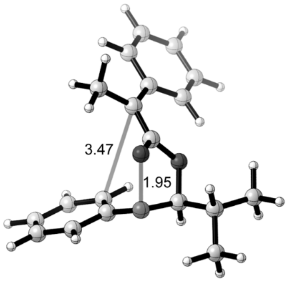
3.3. Stereoselectivity and reaction mechanism



B4



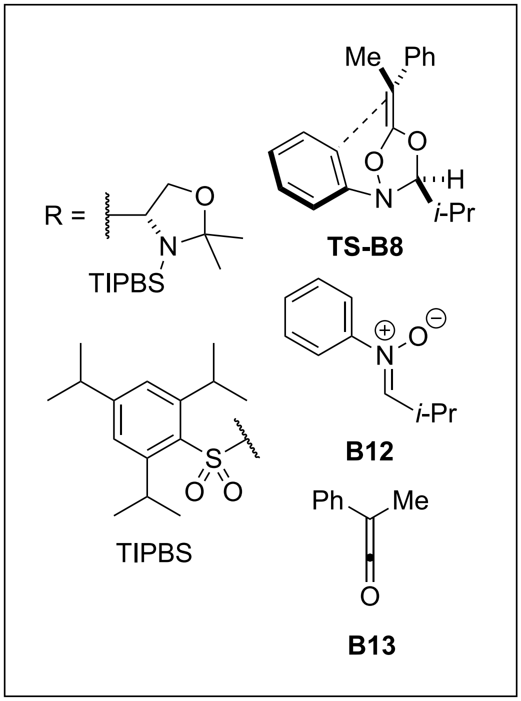
TS-B6 **TS-B7**



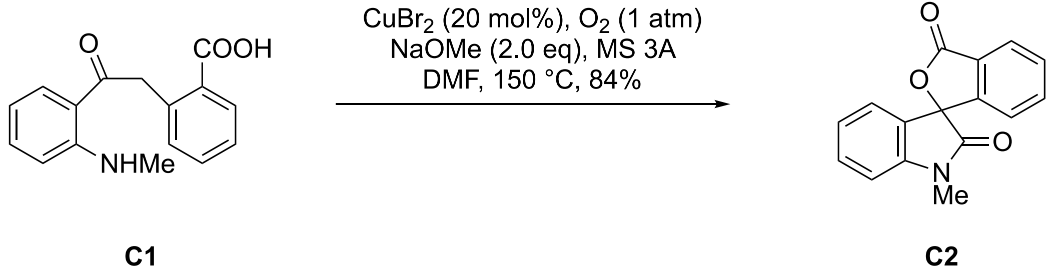
calculated structure of **TS-B8** with similar substrates (**B12**, **B13**)^3

TS-B8 is transition state during [3,3]-sigmatropic rearrangement.

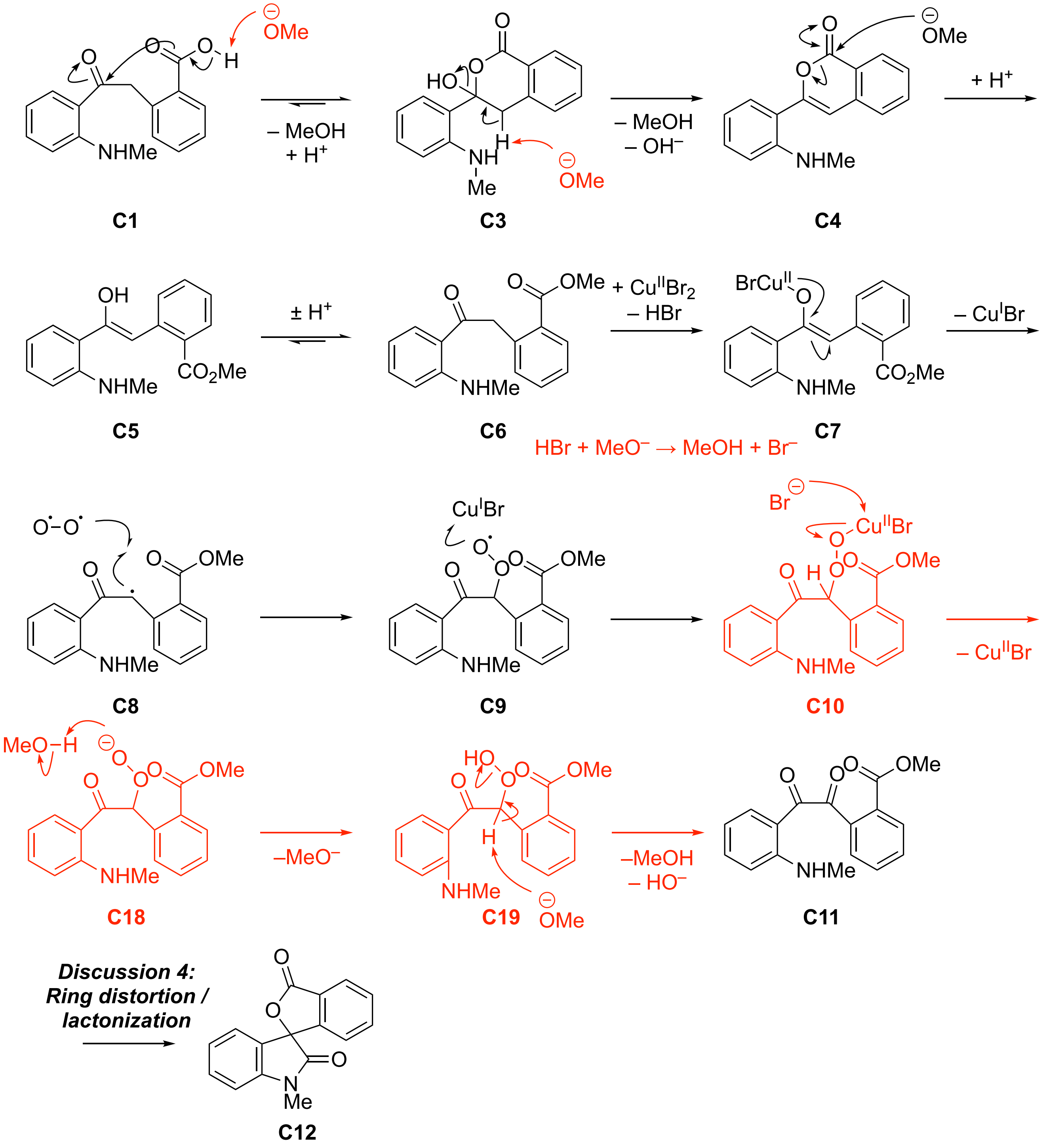
calculated at
M06-2X/6-311 + G-(d,p) (THF)//
B3LYP/6-31G(d)
gas-phase B3LYP/6-31G(d)
energies are given in brackets



Scheme **C**[4]

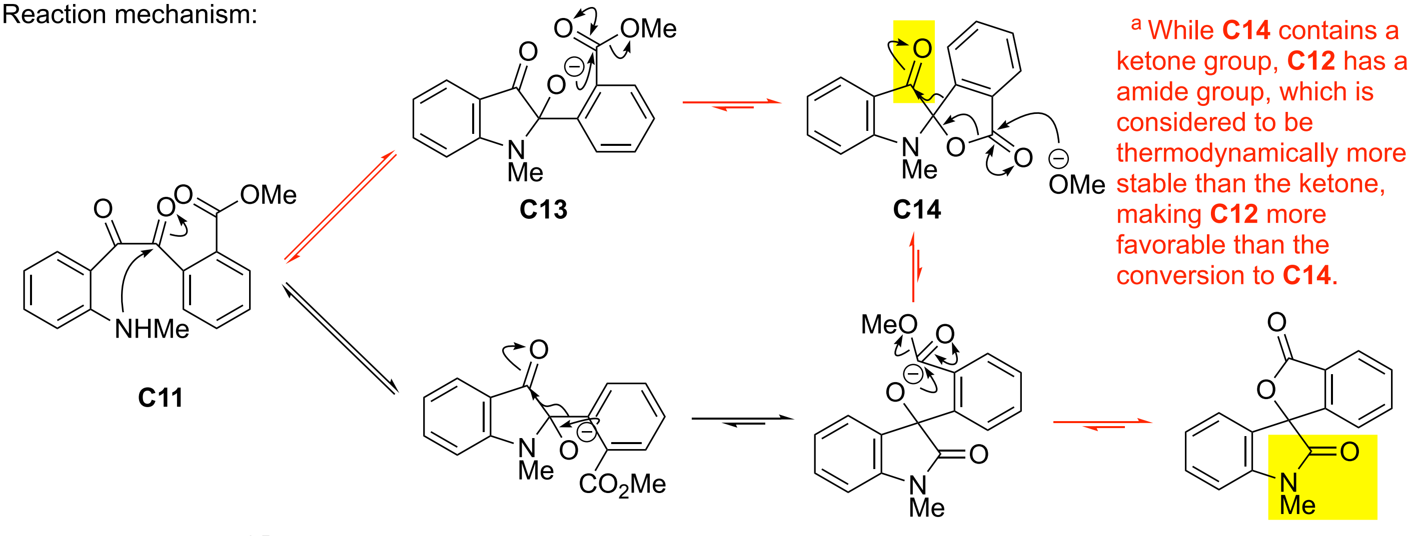


Reaction mechanism:



***Discussion 4*: Ring destortion / lactonization**

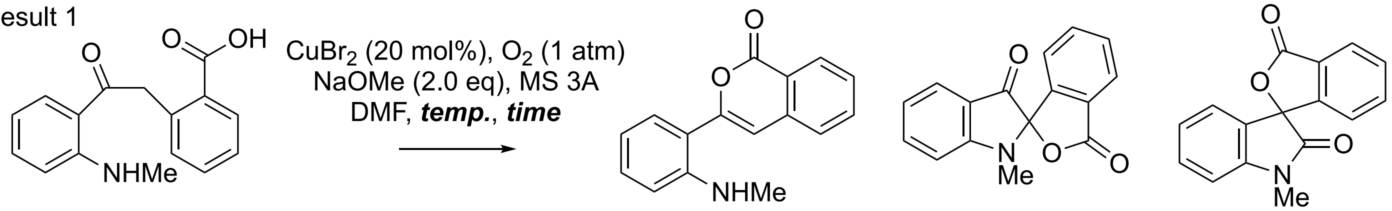
Reaction mechanism:



[a] While **C14** contains a ketone group, **C12** has an amide group, which is considered to be thermodynamically more stable than the ketone, making **C12** more favorable than the conversion to **C14**.

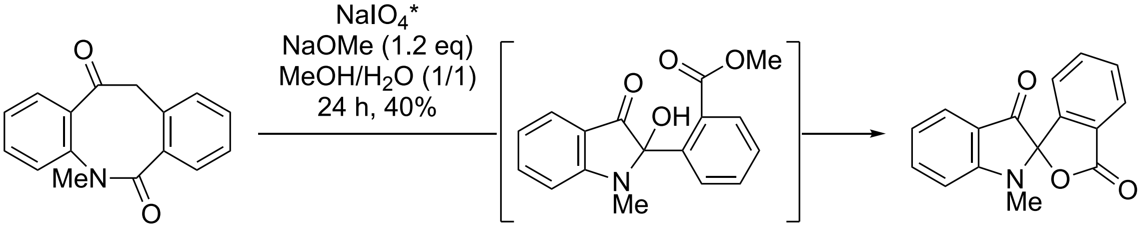
Experimental results[4,5]:

Result 1



entry	**C1**	***temp.***	***time***	**C4**	**C14**	**C12**
1		90 °C	28 h	10%	26%	30%
2		150 °C	4 h	8%	14%	38%
3		150 °C	8 h	0%	0%	79%

Result 2

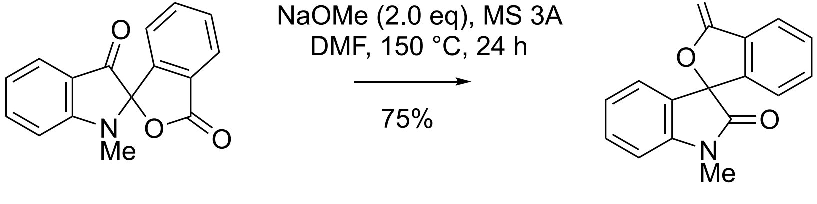


C16 **C17** (proposed intermediate) **C14**

*equivalent of NaIO$_4$ was not mentioned

****C16** and reagents were heated in boiling 50% aqueous methanol

Result 3



C14 **C12**

Based on results 1 and 3, it can be inferred that **C14** is a reaction intermediate that converges to **C12**, which is thermodynamically more favorable[a]. Based on result 2, the conversion from **C17** to **C14** is considered to be kinetically more favorable than the conversion to **C12**. Therefore, in the conversion from **C11** to **C12**, the pathway involving **C14** as a reaction intermediate is the most plausible.

References

1. Du, D.; Hu, Z.; Jin, J.; Lu, Y.; Tang, W.; Wang, B.; Lu, T. *Org. Lett.* **2012**, *14*, 1274–1277.
2. Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lebi, T.; Smith, A. D. *Org. Lett.* **2012**, *14*, 2762–2765.
3. Celebi-Olcum, N.; Lam, Y.-H.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. *Angew. Chem. Int. Ed.* **2011**, *50*, 11478–11482.
4. Zhang, C.; Liu, M.; Ding, M.; Xie, H.; Zhang, F. *Org. Lett.* **2017**, *19*, 3418–3421.
5. Letcher, R. M.; Kwok, N.-C.; Lo, W.-H.; Ng, K.-W. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1715–1719.
6. Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.