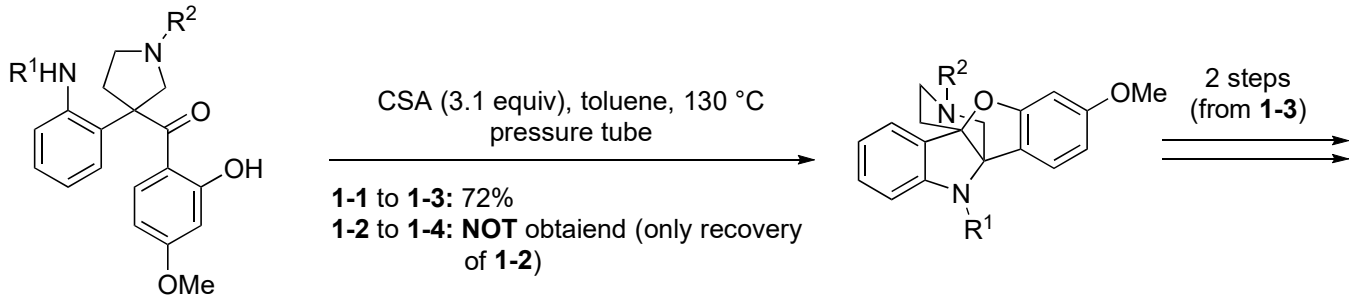
Problem Session (5)

2024.5.2 Junichi Taguchi

Topic: Sulfur in organic synthesis

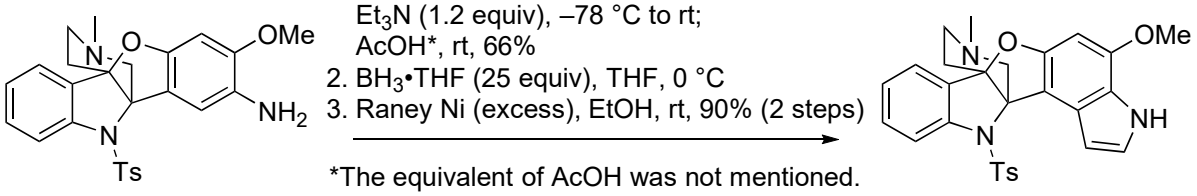
1 (1) Please explain the reaction mechanism.
(2) Even when starting with chiral **1-1**, the resulting product will be racemate **1-3**. Please explain the possible reason.
(3) When **1-2** was used for the first step, the desired **1-4** was not obtained. Please explain the possible reason.



(racemate)

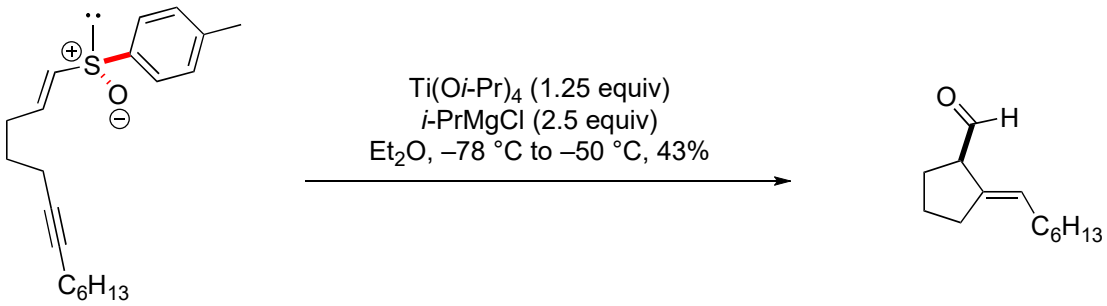
1-1: R^1= Ts, R^2= Me
1-2: R^1= H, R^2= CO_2Me

1-3: R^1= Ts, R^2= Me
1-4: R^1= H, R^2= CO_2Me

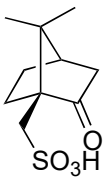


1-5 **1-6**

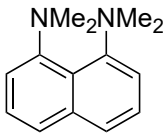
2 Please explain the reaction mechanism.



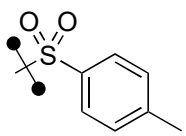
2-1 **2-2**



CSA



proton sponge



Ts

Problem Session -Answer- (5)

2024.5.2 Junichi Taguchi

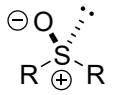
topic: Sulfur (+IV) in organic synthesis

main review: Kaiser, D.; Klose, I.; Neuhaus, J.; Maulide, N. *Chem. Rev.* **2019**, *119*, 8701.

Brief introduction:

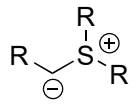
Organosulfur compounds have historically played a crucial role in organic chemistry, contributing to the development of novel chemical structures and architectures. Particularly, those containing a sulfur (+IV) center have been the focus of numerous investigations for over a century.

Sulfur (+IV) compounds -Four major groups-



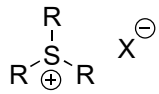
Sulfoxides
(Problem 2)

Carbon–carbon (C–C) and carbon–heteroatom (C–X) bond formation in the α-position of the sulfoxide starting materials, often through sigmatropic rearrangements



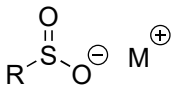
Sulfur ylides
(Problem 1)

Application as one-carbon synthons via various types of reactions, which have led to the development of a numerous number of novel protocols for the formation of heterocycles



Sulfonium salts
(Problem 1)

Application to three-membered ring formations, cross-coupling reactions, and radical/ionic reactions via C-S bond cleavage



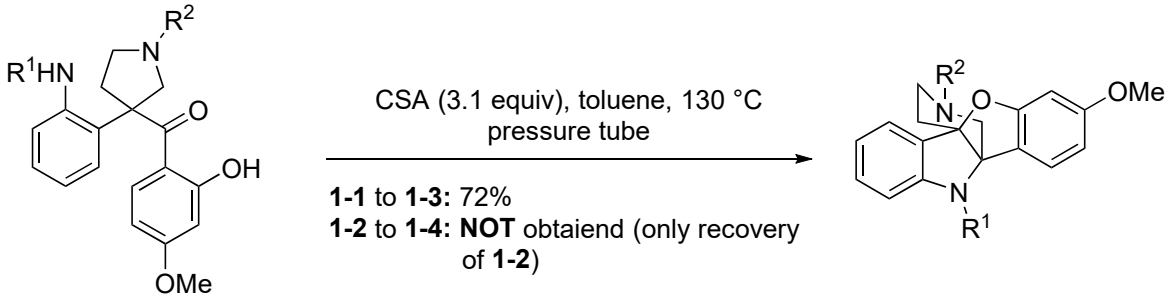
Sulfinate salts

highly useful building blocks for the construction of sulfonyl-group containing molecules and for the construction of various C–C and C–X bonds via SO_2 extrusion

1 Theme: Application of sulfur ylides (Total synthesis of phalarine by the Danishefsky group)

a) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444. b) Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448. c) Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506.

1. Construction of phalarine skeleton



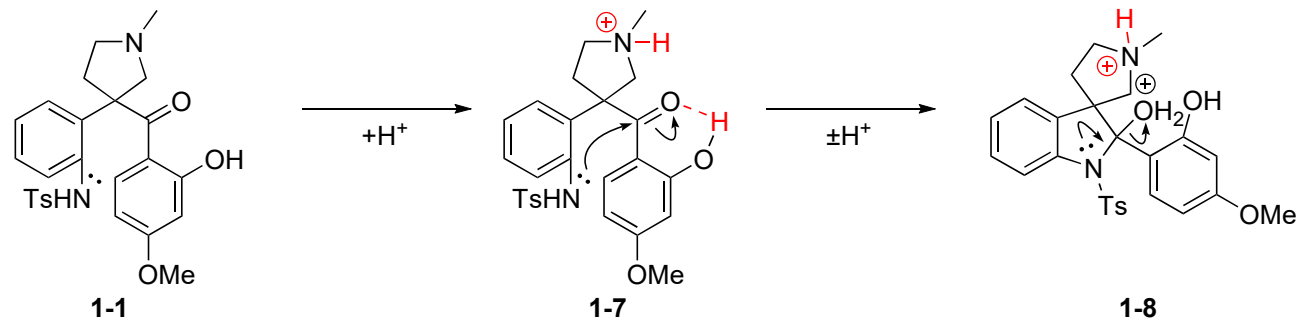
1-1 to **1-3:** 72%
1-2 to **1-4:** **NOT** obtaiend (only recovery of **1-2**)

(racemate)

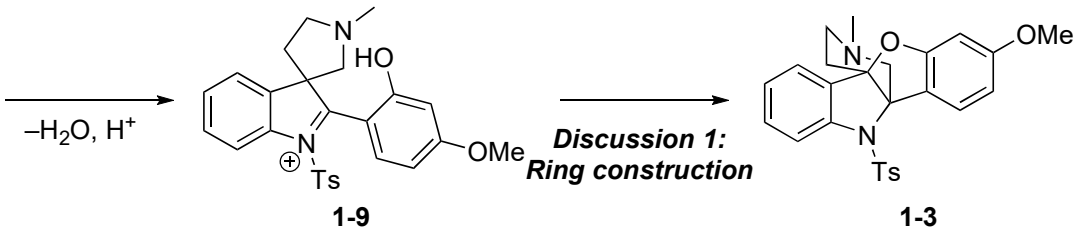
1-1: R^1= Ts, R^2= Me
1-2: R^1= H, R^2= CO_2Me

1-3: R^1= Ts, R^2= Me
1-4: R^1= H, R^2= CO_2Me

Reaction mechanism (**1-1** to **1-3**):



1-1 **1-7** **1-8**



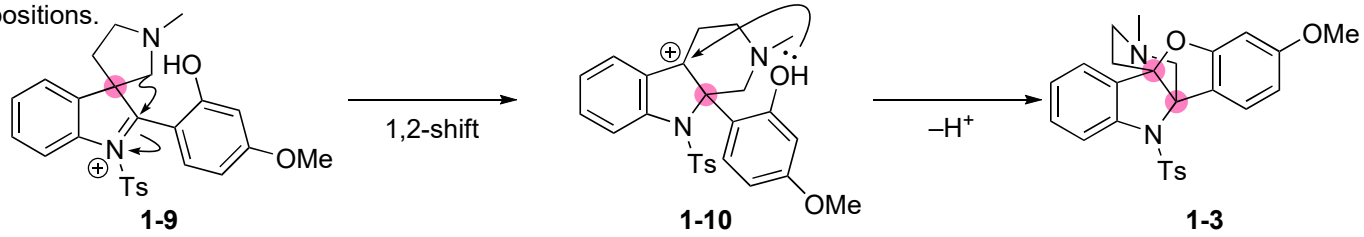
1-9 **1-3**

Discussion 1: Ring construction

1. Possible mechanistic pathways

1-1. Wagner-Meerwein-type rearrangement

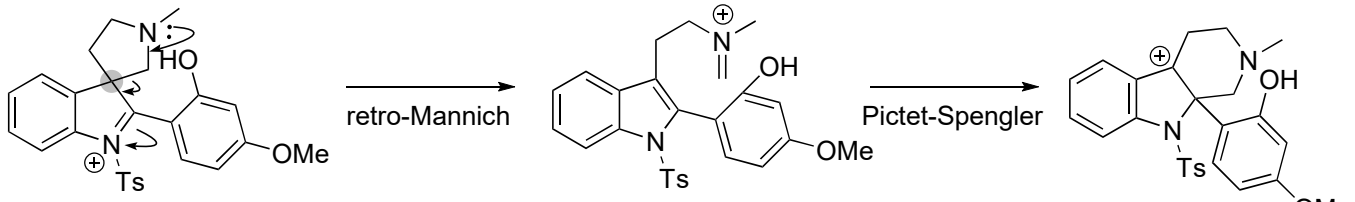
If **1-3** is exclusively formed through this rearrangement, chirality transfer would occur between the highlighted positions.



1-9 **1-10** **1-3**

1-2. Retro-Mannich and Pictet-Spengler sequence

Once the retro-Mannich reaction occurs, the highlighted chirality would disappear.



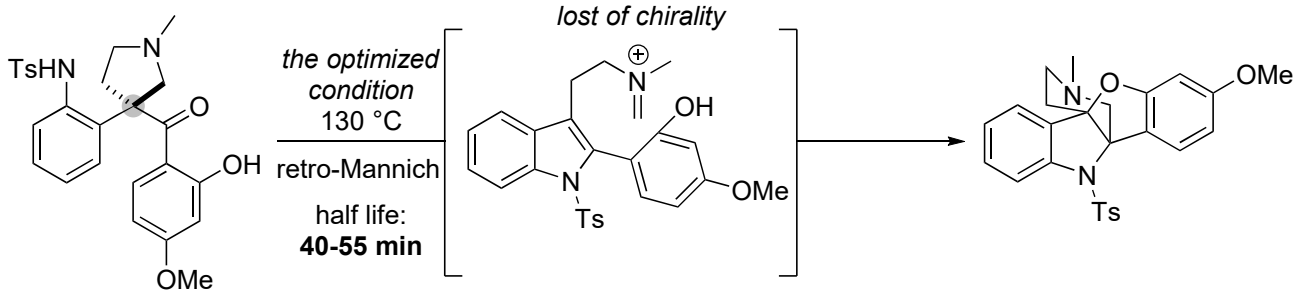
1-9 **1-11** **1-10**

2. Mechanistic insights

2-1. Racemization under the reaction condition

▸Enantiopure **(+)-1-1** was treated with CSA following the optimized condition, resulting in the formation of **1-3** **as the racemate**. Even when the reaction was interrupted at a very early stage, **1-3** was still generated as the racemate.

→ The ring construction is thought to proceed via intermediate **1-11**.



(+)-1-1 **1-11** **1-3** (racemate)

▸Even when enantiopure **1-3** was subjected to the condition for the ring construction, the racemization ocurred. However, the rate was far too low to account for the conversion enantiopure **(+)-1-1** to racemic **1-3**.

→ The formation of racemic **1-3** did not arise from racemization of the substantially enentiopure product.

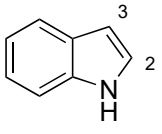
1-3 (enantiopure) —*the optimized condition,* 130 °C→ **1-3** (racemate)

half life: **136 min**

Considering these results, the retro-Mannich reaction would proceed immediately under the condition.

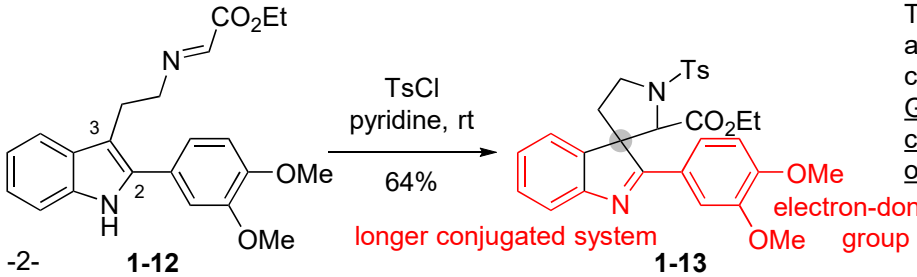
2-2. Pictet-Spengler reaction from C2 or C3 (See also 210410_Yusuke_Imamura)

Because of the inherent nucleophilicity of indoles, especially at a C3 position due to enamine-like reactivity, dearomatization reactions often proceed by addition of electrophiles at a C3 position. However, this reactivity sometimes changes depending on the steric environment of substrates.



indole

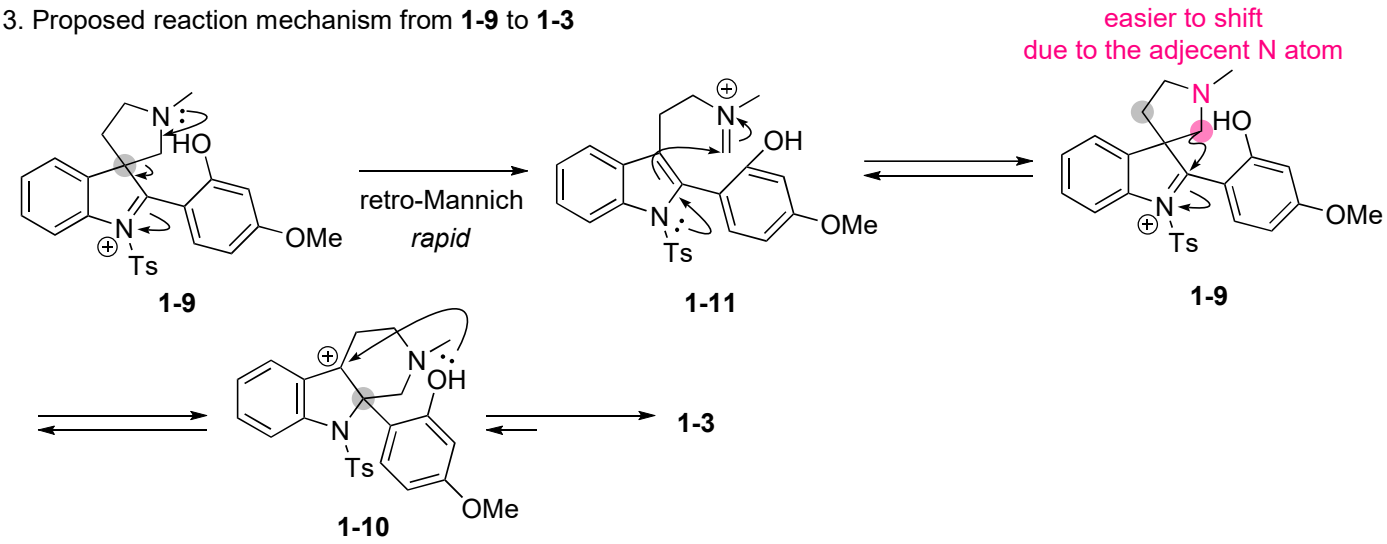
In the case of total synthesis of strychinine by the Woodward group[ref.1]



-2- **1-12** **1-13**

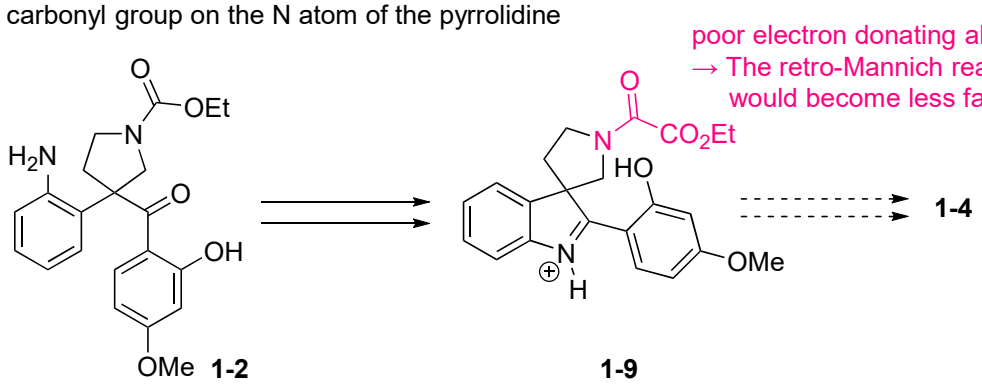
The authors placed the veratryl group at the C2 position in order to block condensations at that center. Given the similar structure, comparable reactivity would likely occur in the case of **1-11**.

3. Proposed reaction mechanism from **1-9** to **1-3**



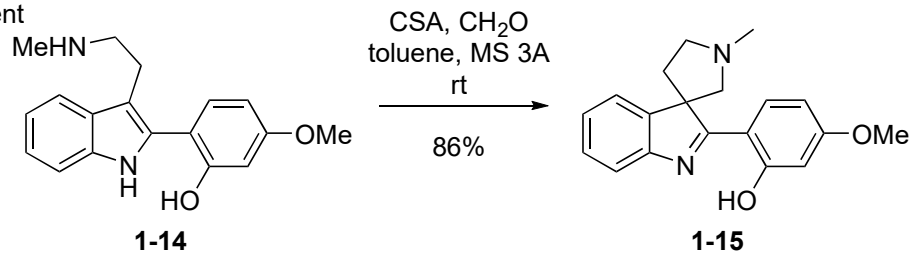
4. Failed conversion from **1-2** to **1-4**

4-1. Ethoxy carbonyl group on the N atom of the pyrrolidine



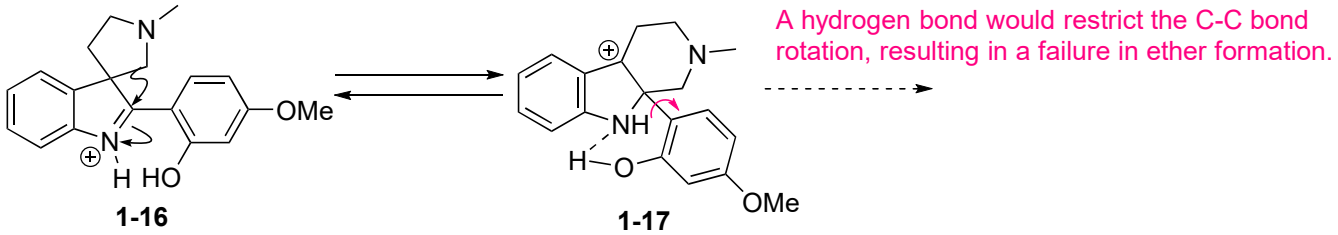
4-2. No tosyl group on the N atom of the indole

▸Control experiment



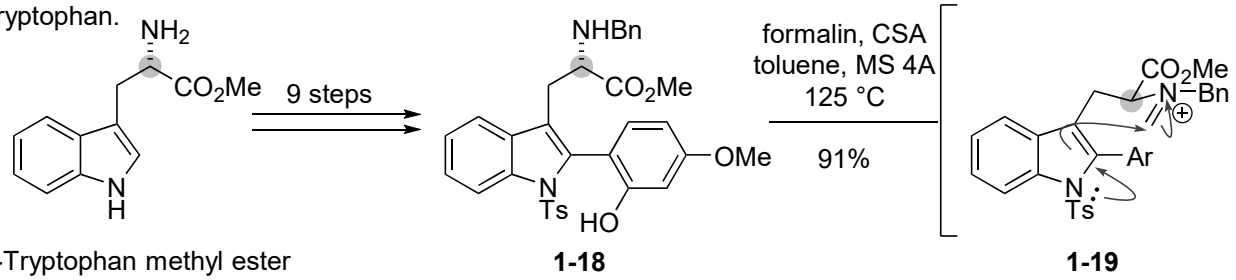
Without a tosyl group on the N atom of the indole, only generation of **1-15** occurred. This result suggests two potential roles for a tosyl group.

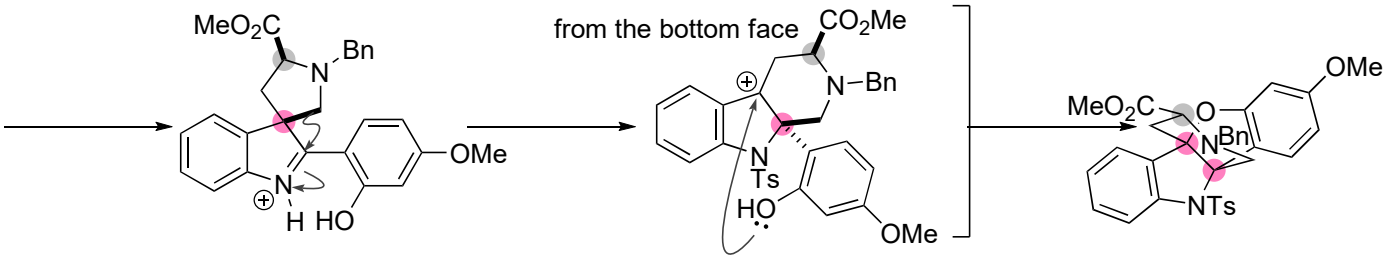
1. It would enhance the rearrangement by its electron-withdrawing ability.
2. It may prevent the formation of a hydrogen bond between the phenol-OH and indole-NH.



5. Improved synthetic route to enantiopure phalarine

The Danishefsky group accomplished the total synthesis of enantiopure phalarine via a chirality transfer from L-Tryptophan.





1-20 **1-21** **1-22**
(single diastereomer, enantiopure)

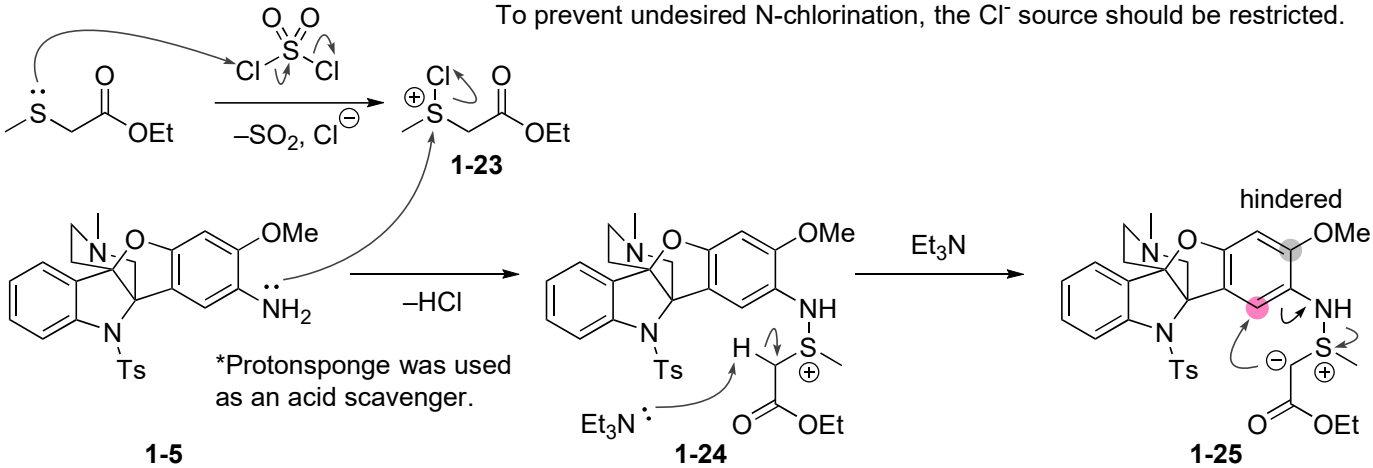
2. Modified Gassman oxindole synthesis

1. $MeSCH_2CO_2Et$ (1.2 equiv)
   SO_2Cl_2 (1.2 equiv), CH_2Cl_2, –78 °C;
   1-5 (1.0 equiv),
   proton sponge (1.2 equiv), –78 °C;
   Et_3N (1.2 equiv), –78 °C to rt;
   AcOH*, rt, 66%
2. BH_3•THF (25 equiv), THF, 0 °C
3. Raney Ni (excess), EtOH, rt, 90% (2 steps)

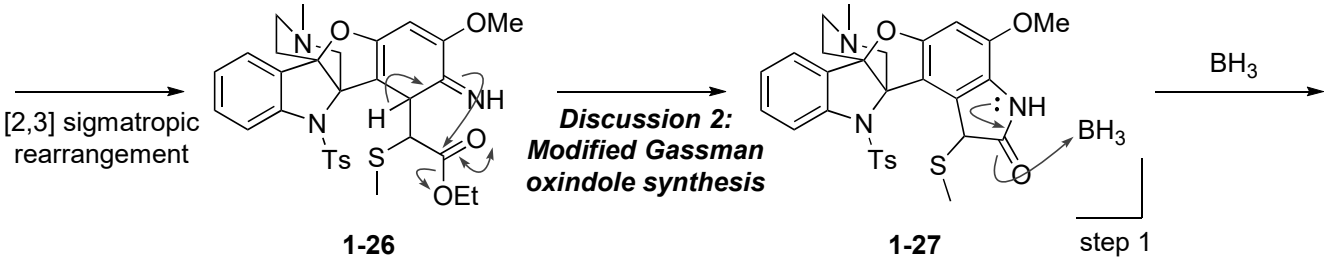
*The equivalent of AcOH was not mentioned.

1-5 **1-6**

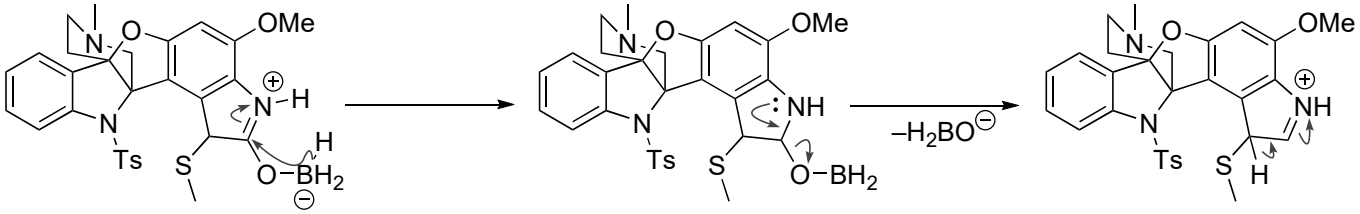
To prevent undesired N-chlorination, the Cl^- source should be restricted.



1-5 **1-24** **1-25**

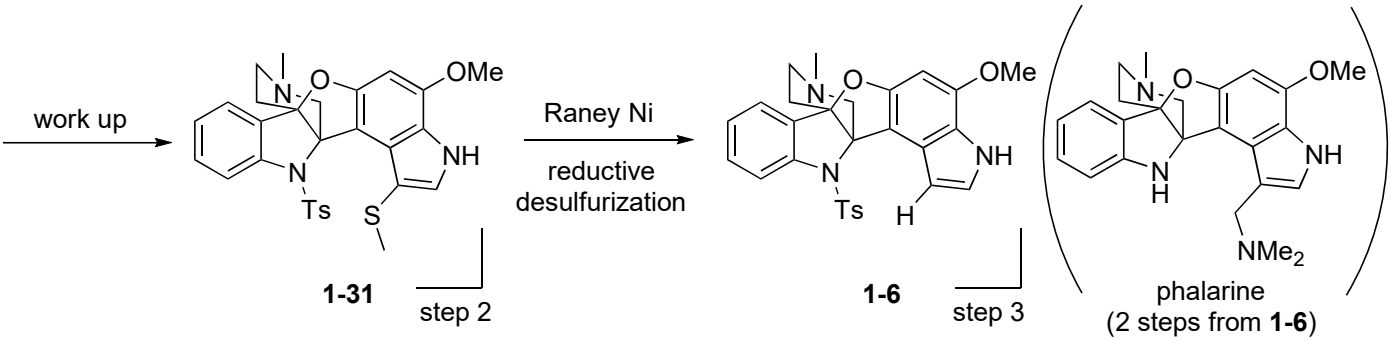


1-26 **1-27**



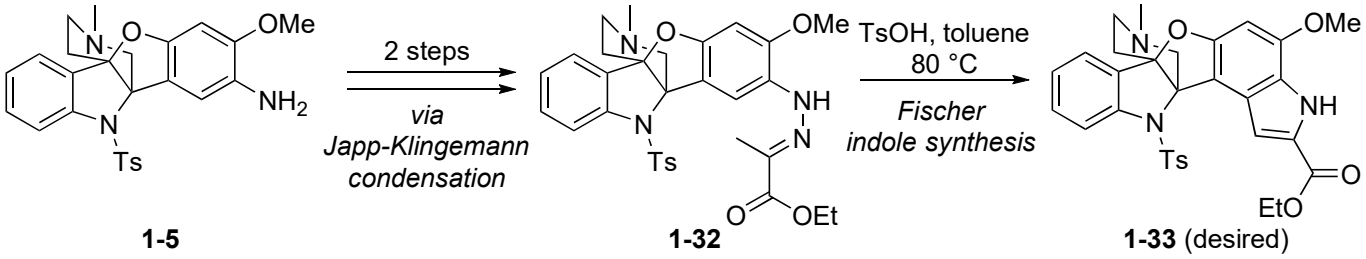
1-28 **1-29** **1-30**

*Other Lewis basic positions would also react with BH_3, requiring an excess amount of reductants. These reactions are omitted for clarity.



Discussion 2: Modified Gassman oxindole synthesis

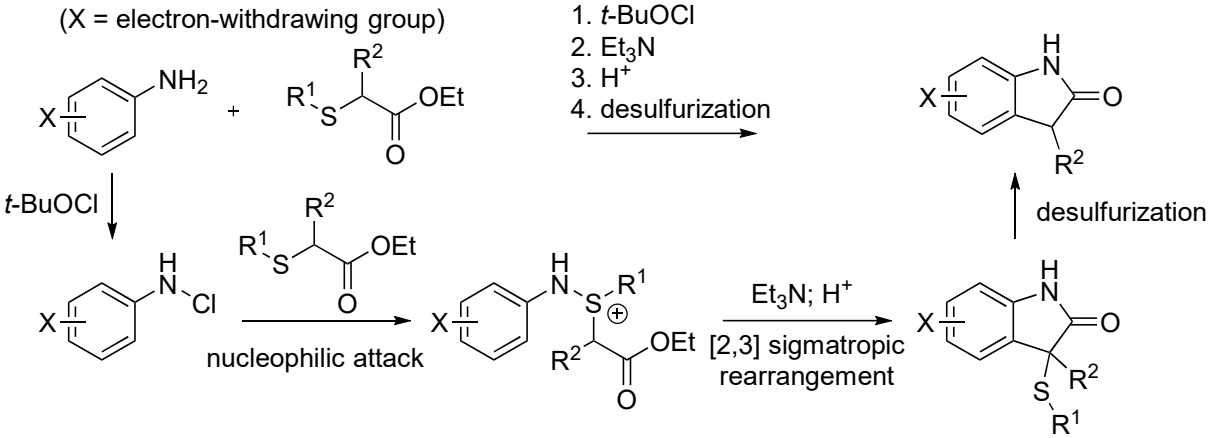
▸ Background -Initial attempt (Fischer indole synthesis)-



The unsuccessful synthesis of **1-33** forced the author to explore alternative methods for preparing an indole ring.

▸ Gassman oxindole synthesis

The Gassman oxindole synthesis is a multi-step process for synthesizing oxindoles containing an electron-withdrawing group.[ref.2]



For anilines with an electron-donating group, the reaction is less favorable due to the disfavored nucleophilic attack of a sulfur atom on the nitrogen atom.

In the case of the synthesis of phalarine, the aniline has an ortho-methoxy group. Therefore, the author applied a modified Gassman oxindole procedure involving a chlorosulfonium salt.[ref.3]

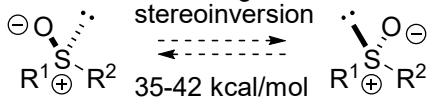
2 Theme: Applicaiton of chiral sulfoxides as "chiral aldehydes"
main paper: Narita, M.; Urabe, H.; Sato, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 3671.

Introduction:

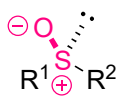
Chiral sulfoxides are one of the most efficient and versatile chiral condtrollers in C-C and C-X bond formations due to the three factors shown the below.

(1) **high optical stability** :

The thermal stereomutation of sulfoxides occurs at a significant rate only at about 200 °C.



(2) **efficiency as a carrier of the chiral information** :

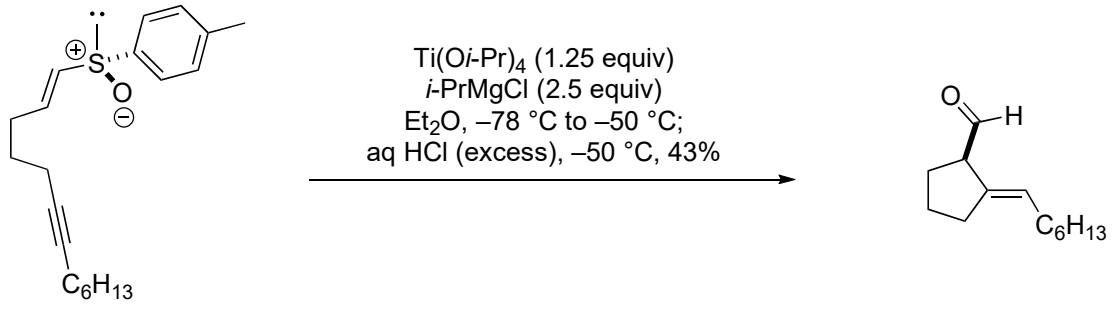


▸a lone pair of electorons, an oxygen atom, and two alkyl or aryl groups
→**well-defined chiral environment**
▸a polarized S-O bond
→efficient cooridination to Lewis acids and transition metals, leading to highly rigid and ordered transition-state geometries that permit effective transfer of the chiral information

(3) **accessibility in both enentiomeric forms**

A lot of methods to obtain chiral sulfoxides have been developed.

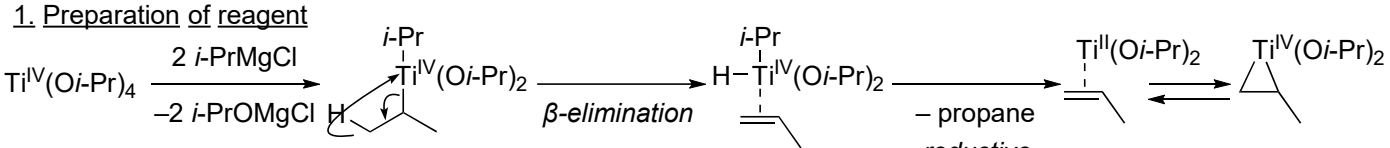
Please explain the reaction mechanism.



2-1 **2-2**

Reaction mechanism:

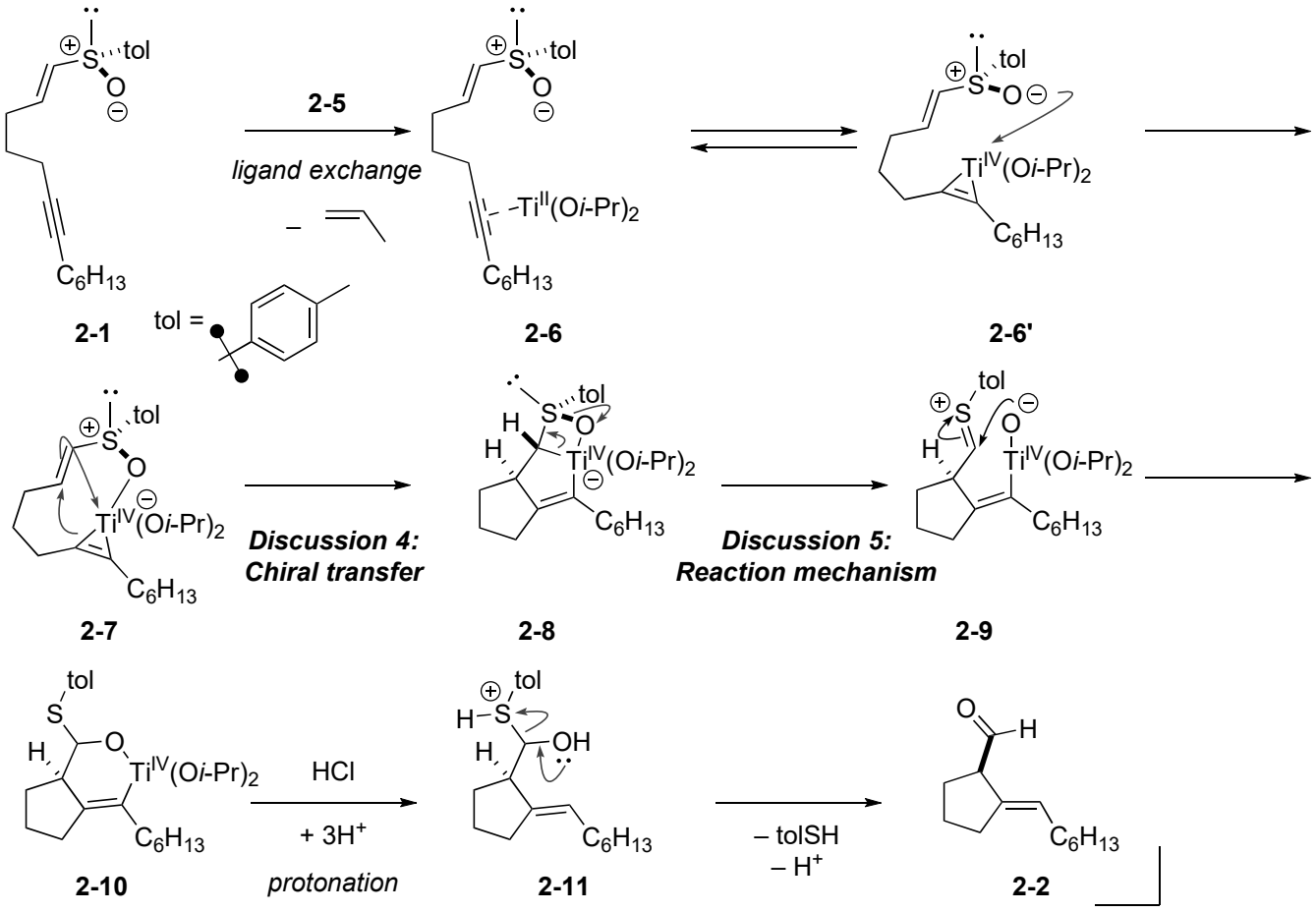
1. Preparation of reagent



Discussion 3: Preparation of Ti reagents

2-3 **2-4** **2-5** **2-5'**

2. Ti-mediated cyclization

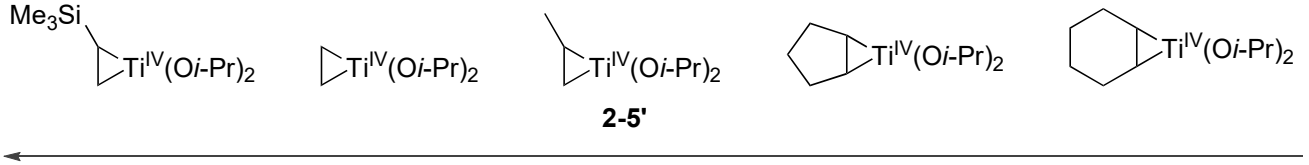


Discussion 3: Preparation of Ti reagents

The preparation of Ti^{IV} species closely follows the method originally reported by the Kulinkovich group[ref.5], with the main difference being the bulkiness of the Grignard reagent used (EtMgBr vs i-PrMgCl). Upon formation of Ti^{IV} reagents, i-PrMgCl produces a propylene, which is larger than the ethylene generated from EtMgBr, thus facilitating subsequent ligand exchange more effectively[ref.6].

Behavior of Ti reagents towards unsaturated comopunds depending on their structures[ref.7]

more prone to undergo ligand exchange



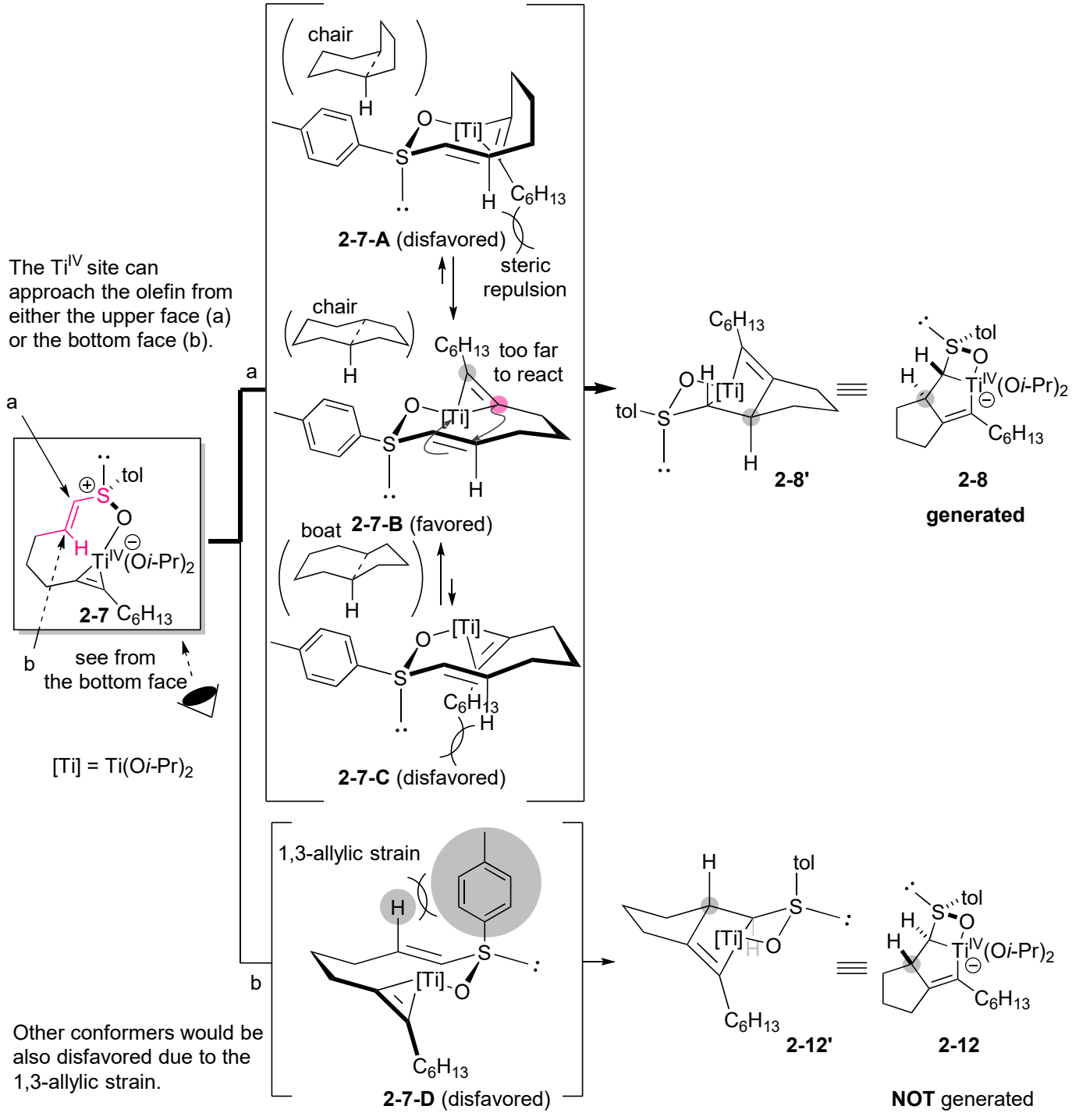
2-5'

more prone to undergo 1,2-insertion

Discussion 4: Chiral transfer in cyclization

The selectivity can be evaluated by examining the conformation of the 9-membered ring, treating it as a fused 5,6-ring system. The most stable conformation would require the following factors:

1. Less steric repulsion between the bulky C_6H_{13} moiety and other functionalities
2. Minimum 1,3-allylic strain

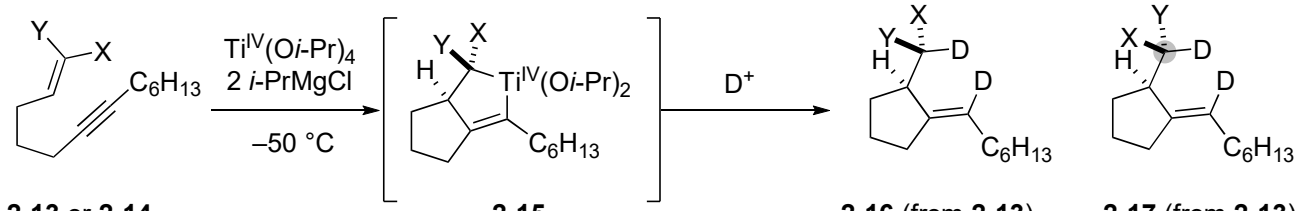


Discussion 5: Reaction mechanism of Ti^{IV}-mediated cyclization

▸ Presence of the carbon-titanium bond (deuteriolysis experiments)

1. Stereospecificity in the cyclization of sulfides[a]

racemization occurred during the reaction



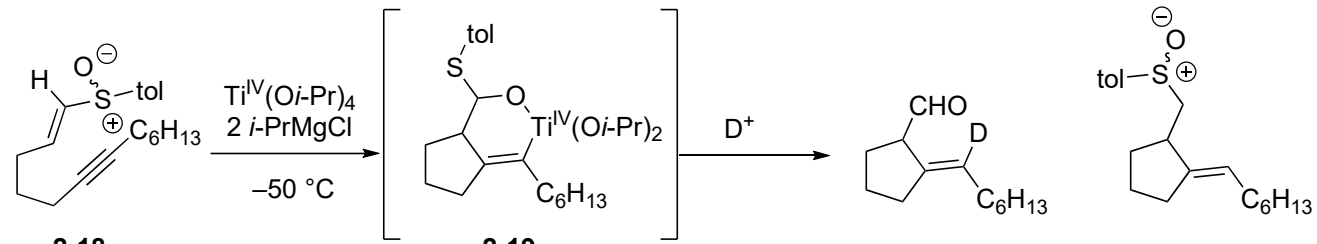
2-13 or **2-14** | **2-15** | **2-16** (from **2-13**) or **2-17** (from **2-14**) | **2-17** (from **2-13**) or **2-16** (from **2-14**)

Entry	Enyne X	Enyne Y	Enyne *E/Z*	Product Yield[b]	Product D[c,d]	Product Ratio[d]	Racemization
1: **2-13**	SMe	H	pure E	73%	97%	**2-16 : 2-17** = > 99 : < 1	**none**
2: **2-14**	H	SMe	8 : 92	76%	99%	**2-17 : 2-16** = 93 : 7	**none**

[a] The reaction temperatures were –50 °C for sulfides. [b] Combined yield of isomers. [c] Total deuterium incorporation at the carbon atom a to X and Y. [d] Determined by ^{1}H NMR spectroscopic analysis.

The geometric information of the starting material is preserved throughout the cyclization process.

2. Ti-mediated cyclization of the corresponding sulfoxide



2-18 | **2-19** | **2-20**: 74% (92% deuterated) | **2-21**: trace

These results indicate that **2-15** and **2-19** are possible intermidiates of the cyclization.

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