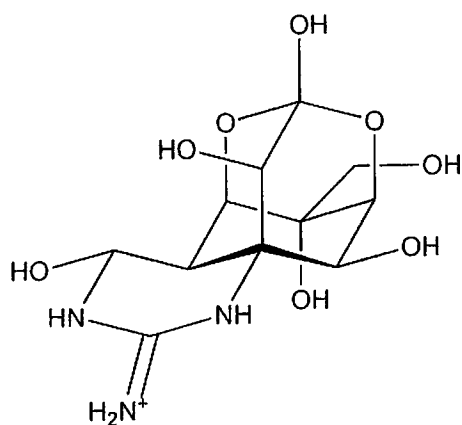


Total Synthesis of Tetrodotoxin

~Testament to the power of C-H amination~



(-)-Tetrodotoxin (1)

Total synthesis:

racemic

Kishi, Y. et al. *J. Am. Chem. Soc.* **1972**, *94*, 9217.

J. Am. Chem. Soc. **1972**, *94*, 9219.

Yoshimura, J. et al. *J. Org. Chem.* **2005**, *70*, 7496

chiral

Isobe, M. et al. *J. Am. Chem. Soc.* **2003**, *75*, 251.

Isobe, M. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 4782.

J. Du bois et al. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

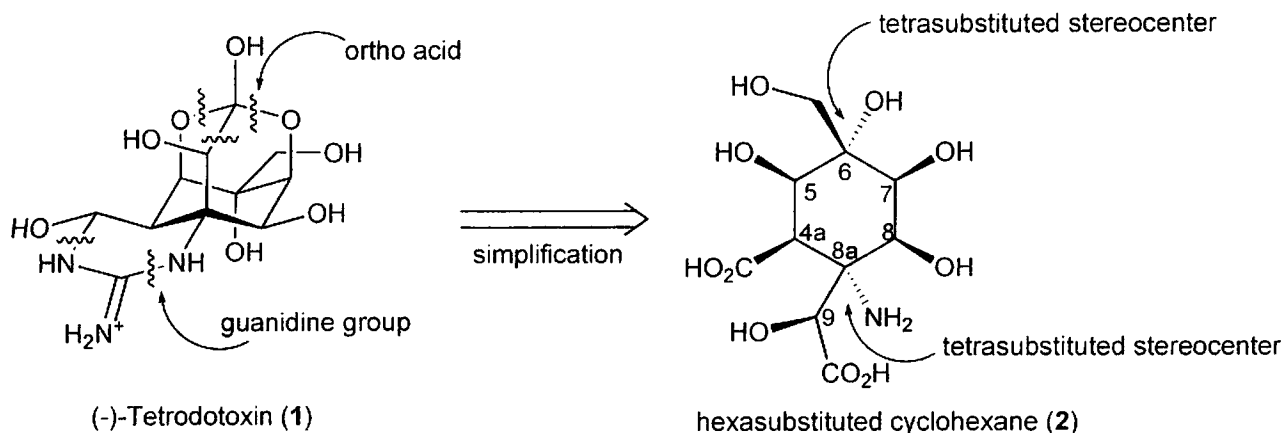
bioactivity: selective blocker of voltage-gated Na⁺ ion channels

CONTENTS

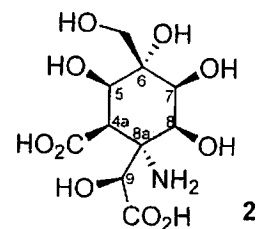
1. Strategy of Total Synthesis
2. C-H Amination Reaction
3. Total Synthesis of Tetrodotoxin

1. Strategy of Total Synthesis

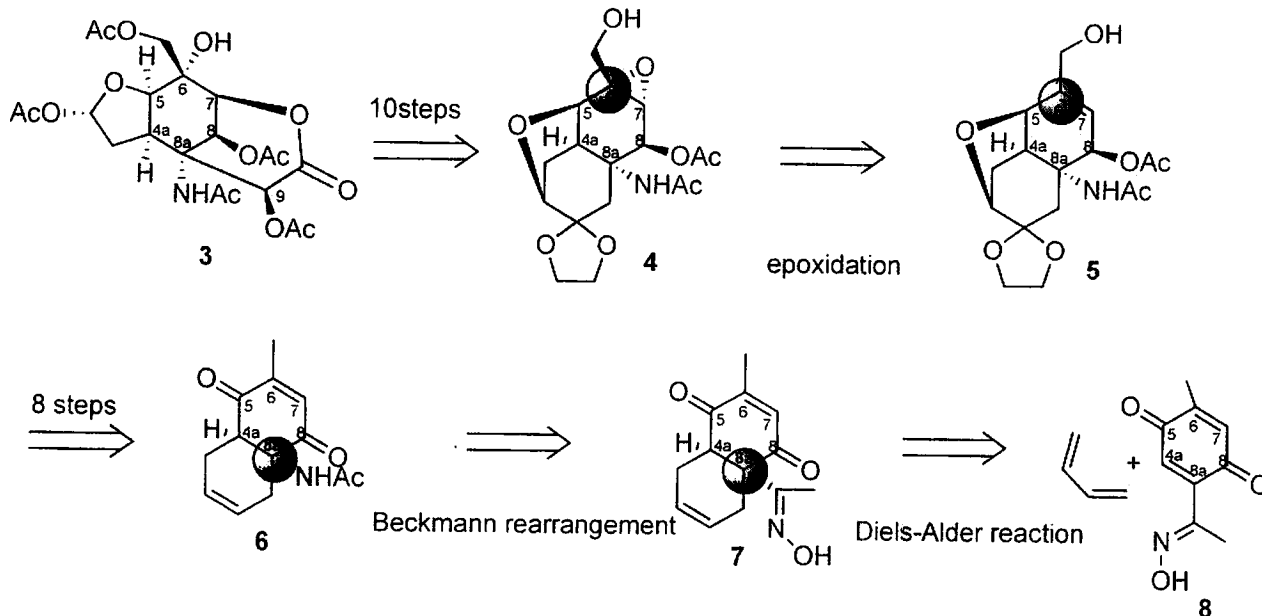
(1) Structural features



(2) Strategic features ~How to construct tetrasubstituted stereocenters~



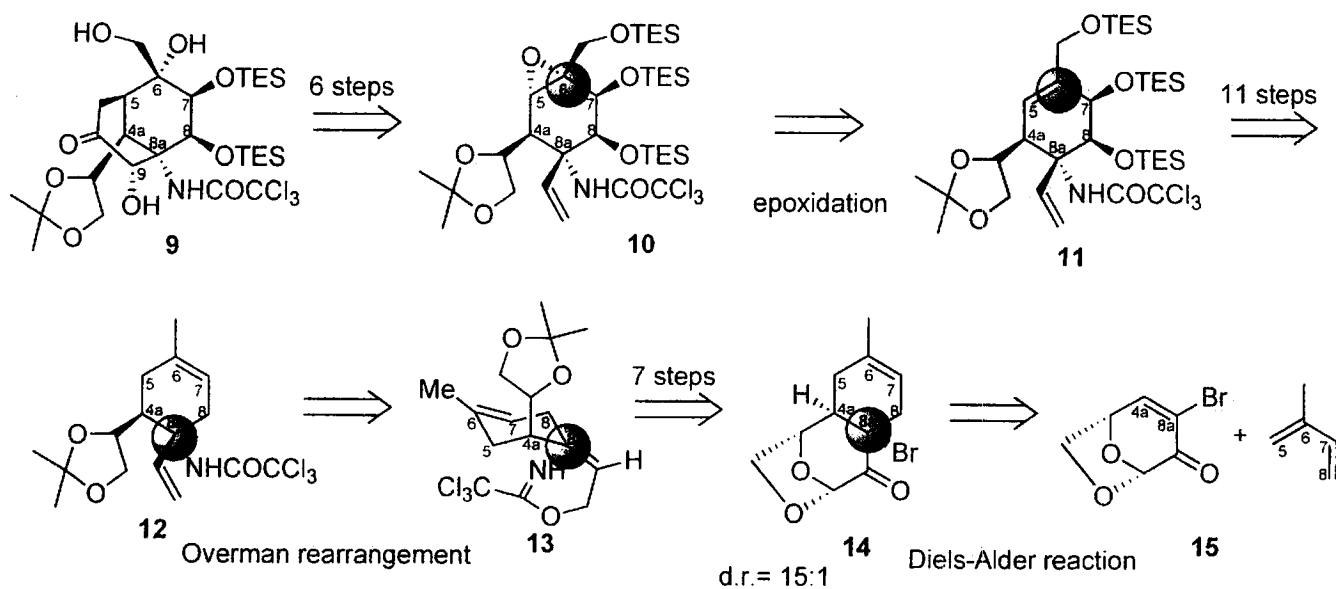
Kishi's synthesis



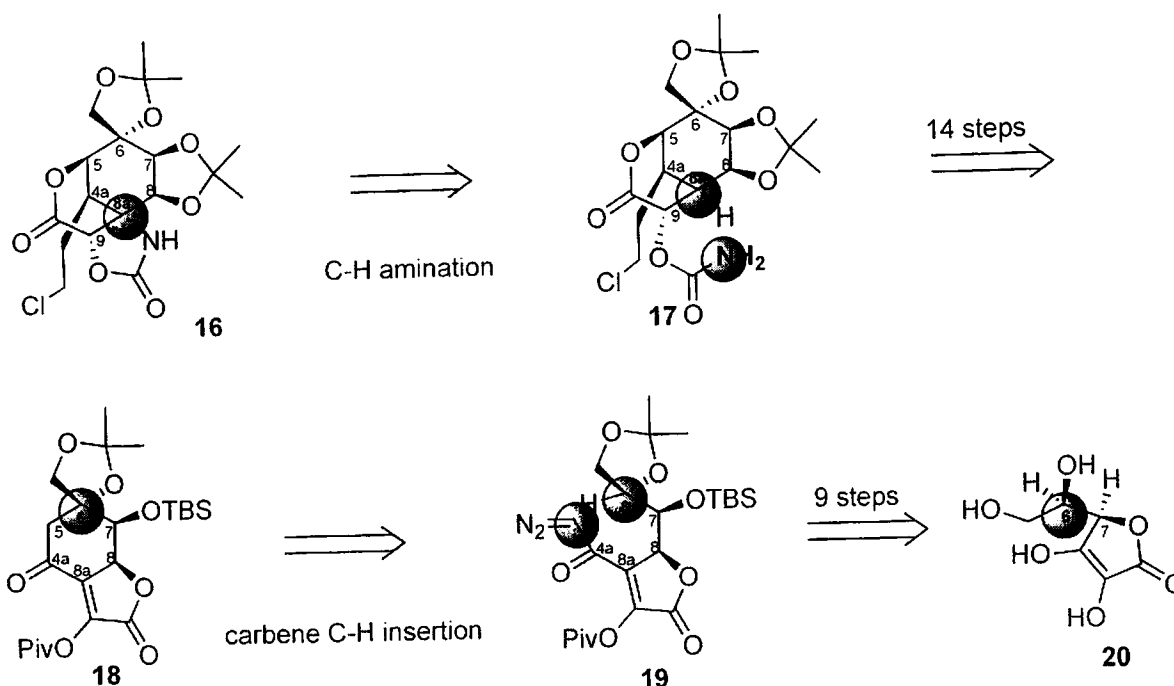
To achieve asymmetric synthesis...

Such as asymmetric Diels-Alder reaction or asymmetric Heck reaction are needed to construct chiral 4° carboncenter.

Isobe's synthesis (2nd generation) 39 steps



Du Bois's synthesis 32 steps



Advantages of C-H insertion strategy

Easier acquisition of chiral tetrasubstituted carbon precursors:

- Stereochemistry of tetrasubstituted carboncenter 8a is originated in the hydrogenation from convex face!!
- Stereochemistry of tetrasubstituted carboncenter 6 is originated in chiral 2° alcohol of natural product.

Complete selectivity: Carbene C-H insertion and C-H amination proceed exclusively retention.

Affording highly substituted 6 membered ring easily compared with Diels-Alder reaction:

- Shorter steps?

Can be used in late stage:

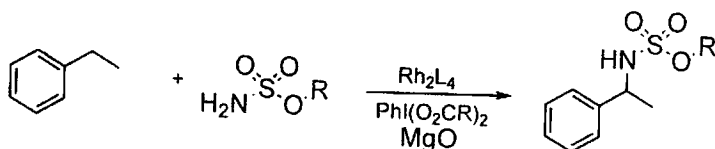
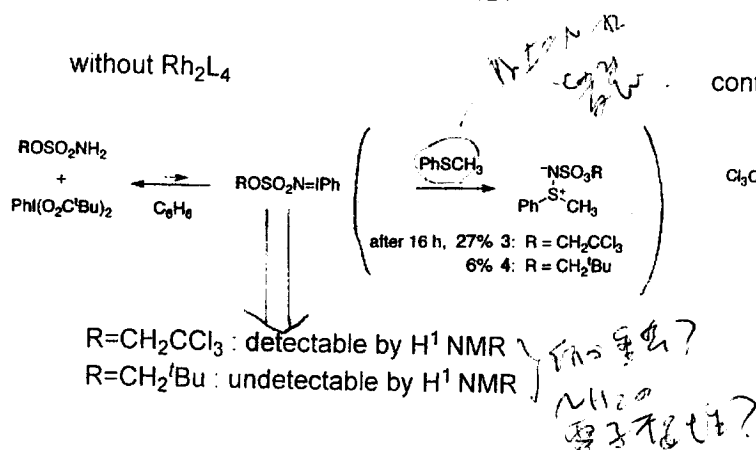
- Reliable intramolecular reaction.
- Mild condition.

2. C-H Amination Reaction

Angew. Chem. Int. Ed. 2001, 40, 598.
J. Am. Chem. Soc. 2007, 129, 562.

2-1 Mechanism

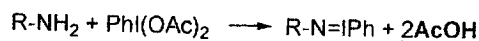
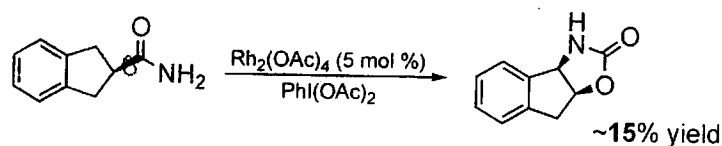
(1) Reaction example

(2) How does the oxidant (PhI(O₂CR)₂) work?

CONTENTS

1. Reaction example
2. How does the oxidant work?
3. Role of MgO
4. Concerted or radical?
5. Rh-nitrene association in the T.S.
6. Hammett analysis
7. Summary
8. Relation with carbene C-H insertion

(3) Role of MgO

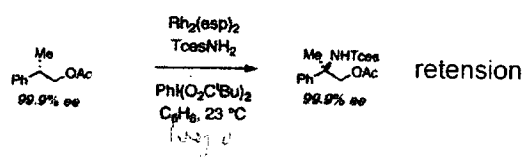


reduce the catalytic activity of Rh₂(OAc)₄

+2.3 equiv of MgO: 86% yield

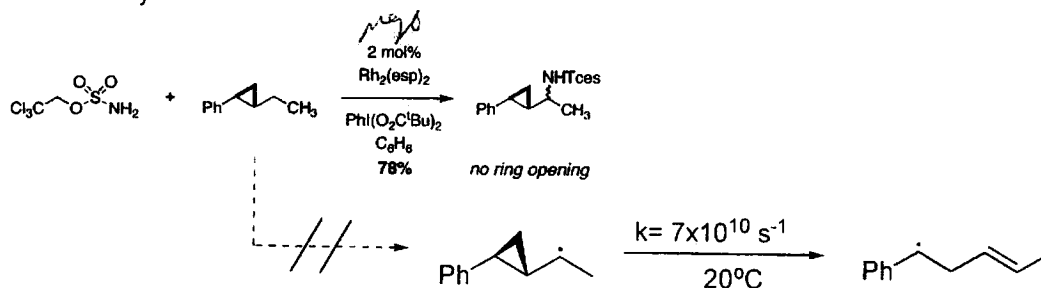
(4) Concerted or radical?

-chiral substrate



concerted mechanism is implied.

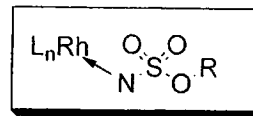
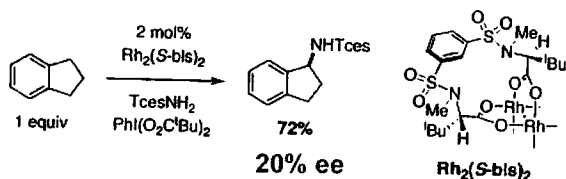
-radical clock study



If a C-H abstraction / radical rebound mechanism was operative, the lifetime of the putative radical would have to be exceedingly short (ca. 200 fs = 2 × 10⁻¹³ s).

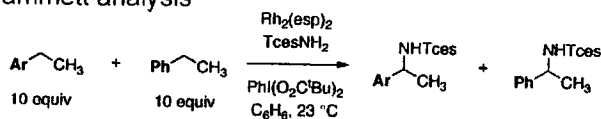
(5) Rh-nitrene association in the C-N bond forming event

-Optically active dinuclear catalyst was employed.

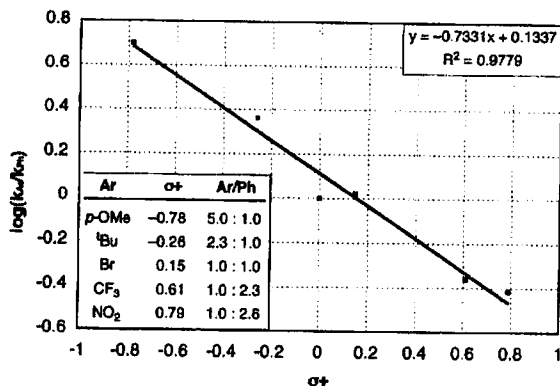


This result gives strong circumstantial support for a **metal-bound nitrene (nitrenoid) as the active oxidant** in the reaction.

(6) Hammett analysis



$$\rho = -0.73 < 0$$



→ preference for oxidation of electron-rich arene substrates

→ cationic charge in the transition state at the oxidizing carbon center

corresponding to the reactivity

Intramolecular reaction:
 α -etheral $\sim 3^\circ >$ benzylic \geq allylic $> 2^\circ \gg 1^\circ$

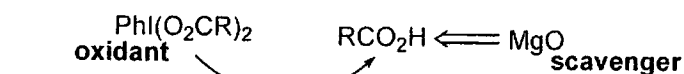
Intermolecular reaction:
 $3^\circ >$ α -etheral \geq benzylic $> 2^\circ \gg 1^\circ$

c.f. ρ -values

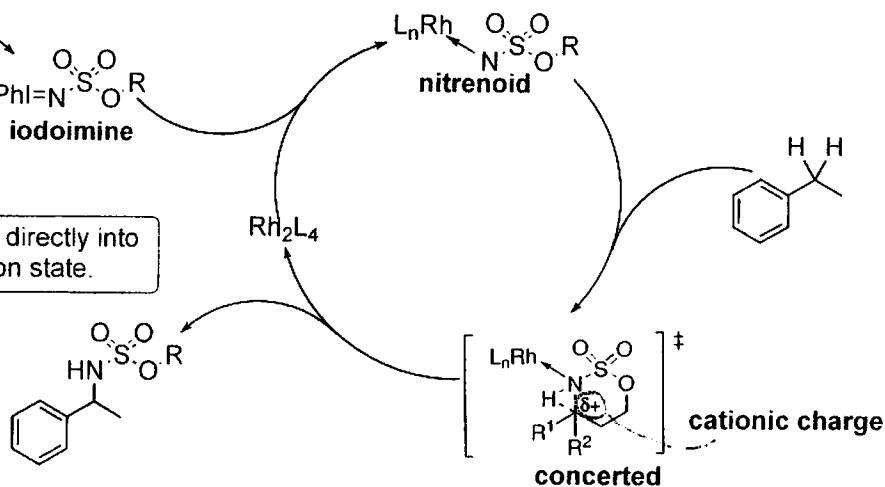
intramolecular C-H amination : -0.55
 intramolecular carbene C-H insertion : -0.78
 intermolecular carbene C-H insertion : -1.27

⇒ similar

(7) Summary (speculation)

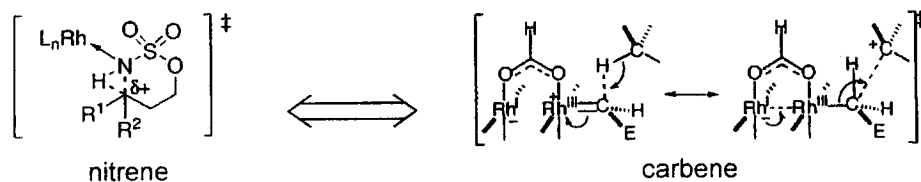


Rh-nitrene intermediate that inserts directly into the C-H bond via concerted transition state.



(8) Relation with carbene C-H insertion

This speculated mechanism and intimate certain parallels between Rh-catalyzed nitrene and carbene C-H functionalization.



Why does the dirhodium complex promote C-H amination ?

~Speculation using calculated carbene C-H insertion data~

E. Nakamura et al. *J. Am. Chem. Soc.* 2002, 124, 7181.

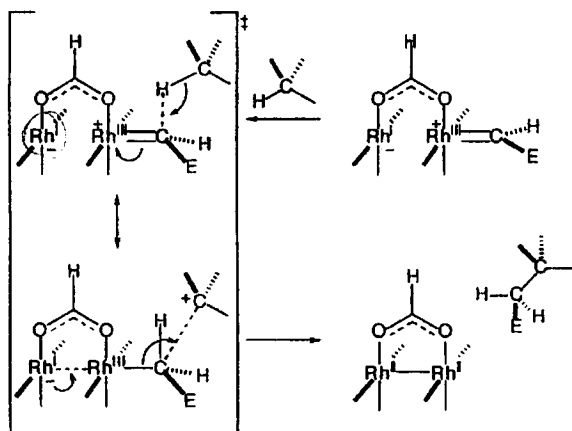


fig.1 Carbene C-H insertion mechanism

Does dirhodium nitrene complex possess similar features ??

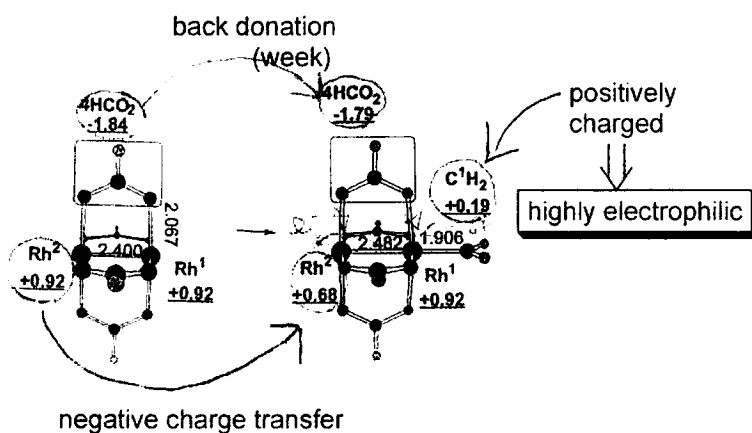
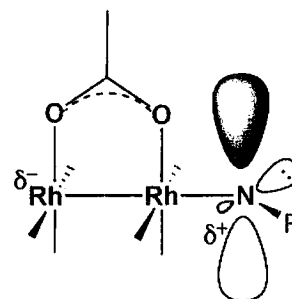


fig.2 Dirhodium carbene complex

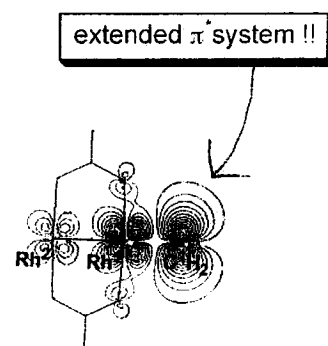
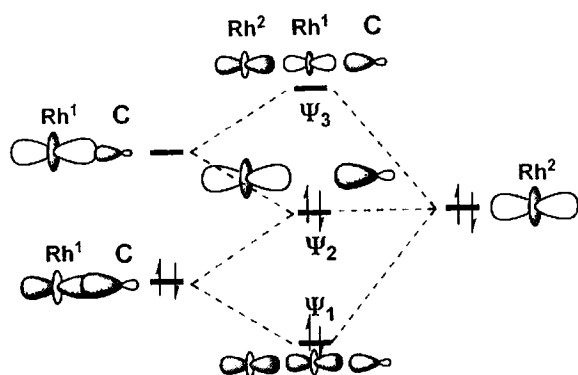


fig.3 LUMO of Rh-carbene complex

fig.4 Rh-Rh-C σ -system

Nonbonding $4d_{22}$ orbital interacts with $Rh^1-C \sigma/\sigma^*$ -orbitals, which weakens the $Rh^1-C \sigma$ -bond.

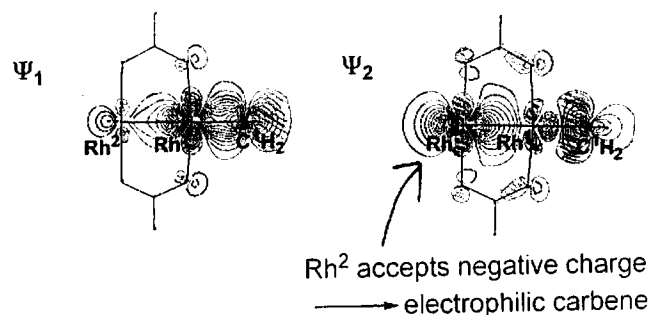
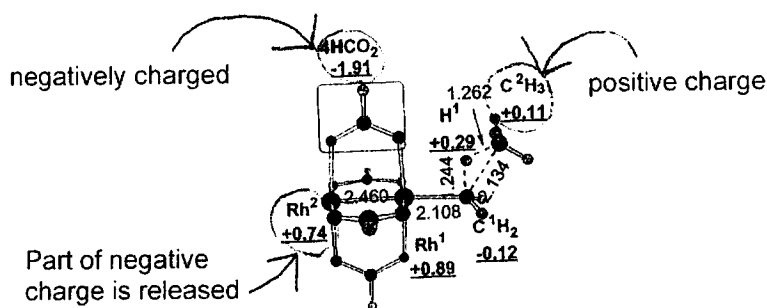
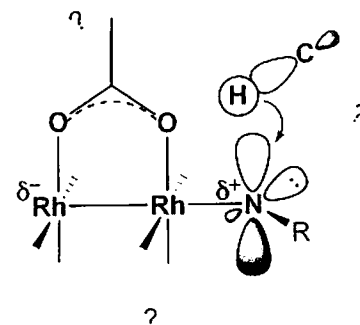
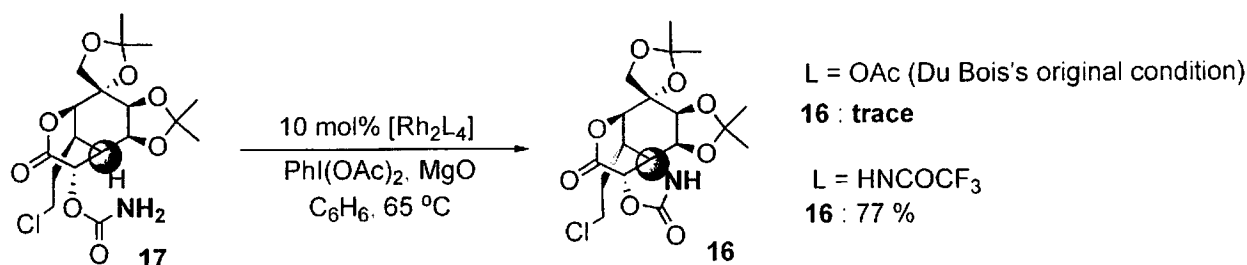
fig.5 Rh-Rh-C σ -system ; orbitals

fig.6 Transition state model



2-2 Scope ~Catalyst design~

In the case of tetrodotoxin...

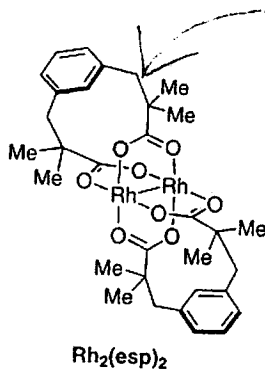


Likewise, in some cases, such as intermolecular reactions or reactions of unactivated C-H bond, Du Bois's original condition was not satisfactory. So, new catalyst systems were investigated...

-The dirhodium catalyst undergoes **structural changes** within minutes of initiating the reaction.

→ Bad effect ?

→ Robuster catalysts were examined, and $Rh_2(esp)_2$ was the most successful.

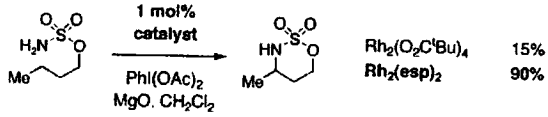


two carboxylates are connected

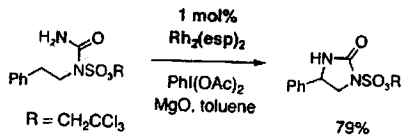
If carboxylate shifts were to occur, the chelate effect would disfavor complete ligand dissociation from Rh centers.

⇒ increased stability ⇒ **increased reactivity !!**

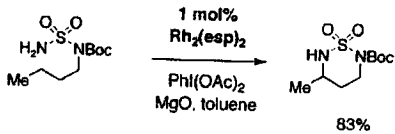
examples



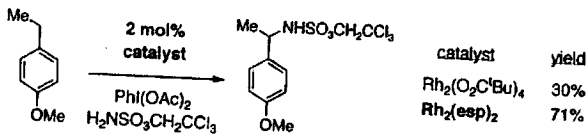
: unactivated 2° carbone



: $Rh_2(O_2C^tBu)_4$ afforded < 10%



: $Rh_2(O_2C^tBu)_4$ afforded < 15%

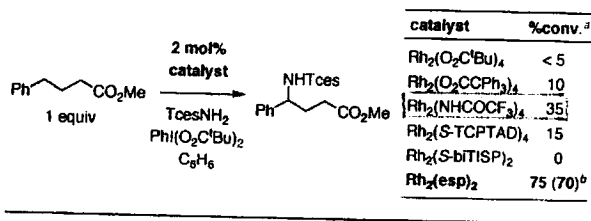


: intermolecular reaction

-Then, in the case of tetrodotoxin, why does $Rh_2(HNCOCF_3)_4$ exhibit good result ?

~Speculation~

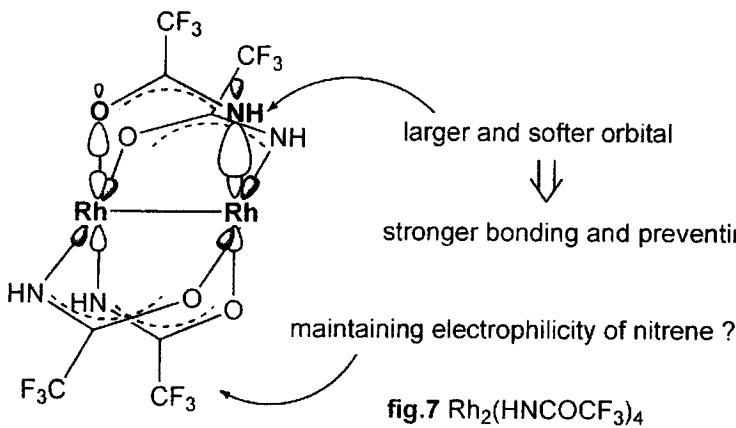
-In intermolecular reaction, $Rh_2(HNCOCF_3)_4$ afforded good result.



→ generally active catalyst ?

→ In the analogue of $Rh_2(esp)_2$ case, $Rh_2(HNCOCF_3)_4$ is stable ?

^a Product conversion estimated by integration of the ¹H NMR spectrum of the unpurified reaction mixture. ^b Isolated yield in parentheses.

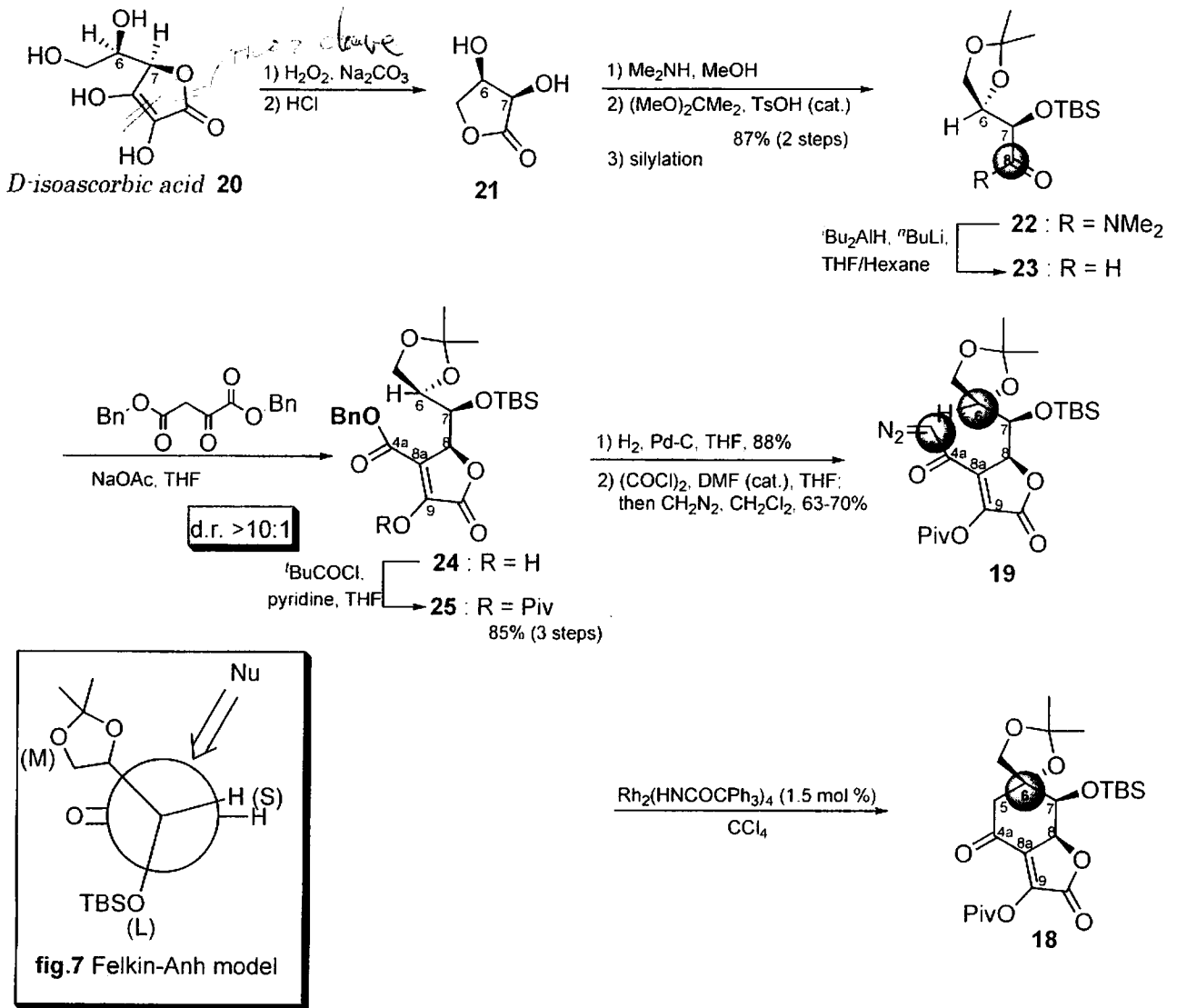
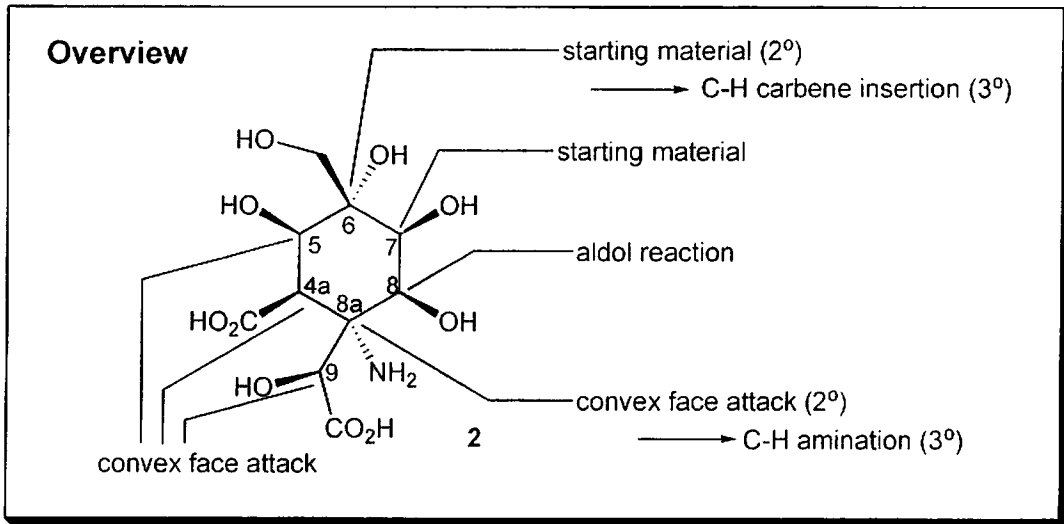


larger and softer orbital

stronger bonding and preventing from ligand dissociation ?

maintaining electrophilicity of nitrene ?

3. Total Synthesis of Tetrodotoxin



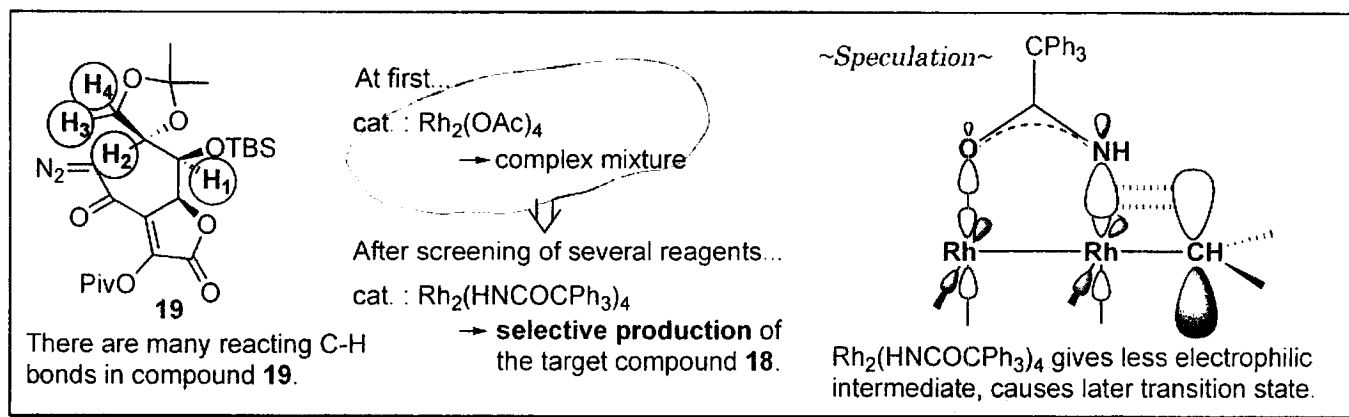
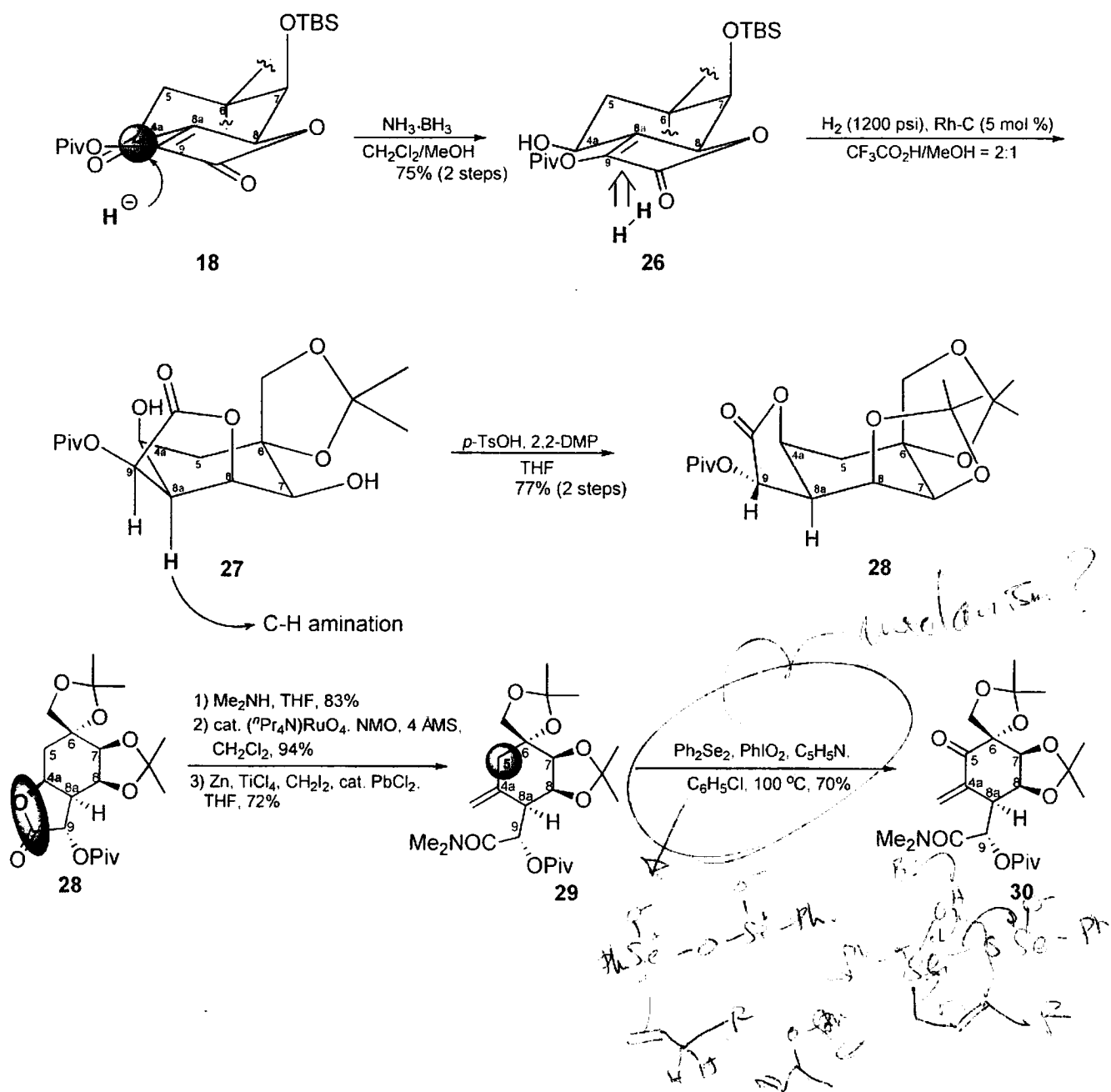


fig.8 Selectivity in C-H insertion

~Now that bicyclic framework is obtained...

~Construction of stereocenters by convex face attack~



Takai reaction (28 → 29; 3)

