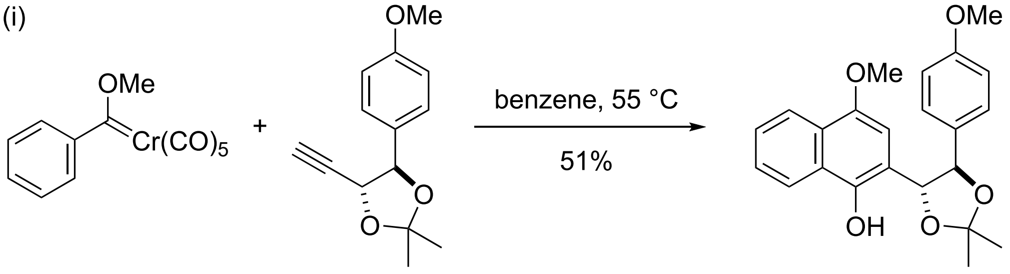
Problem session (6)

2020.5.23 Daiki Kuwana

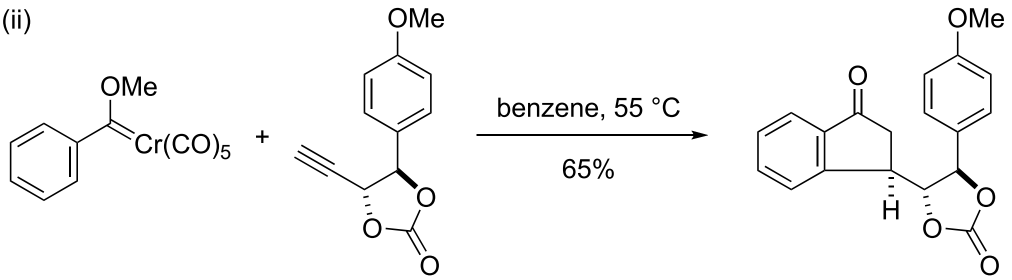
I. Please explain the reaction mechanisms and regioselectivities.
II. (Problem 1) Please explain the difference of major products between (i) and (ii).

1. (i)



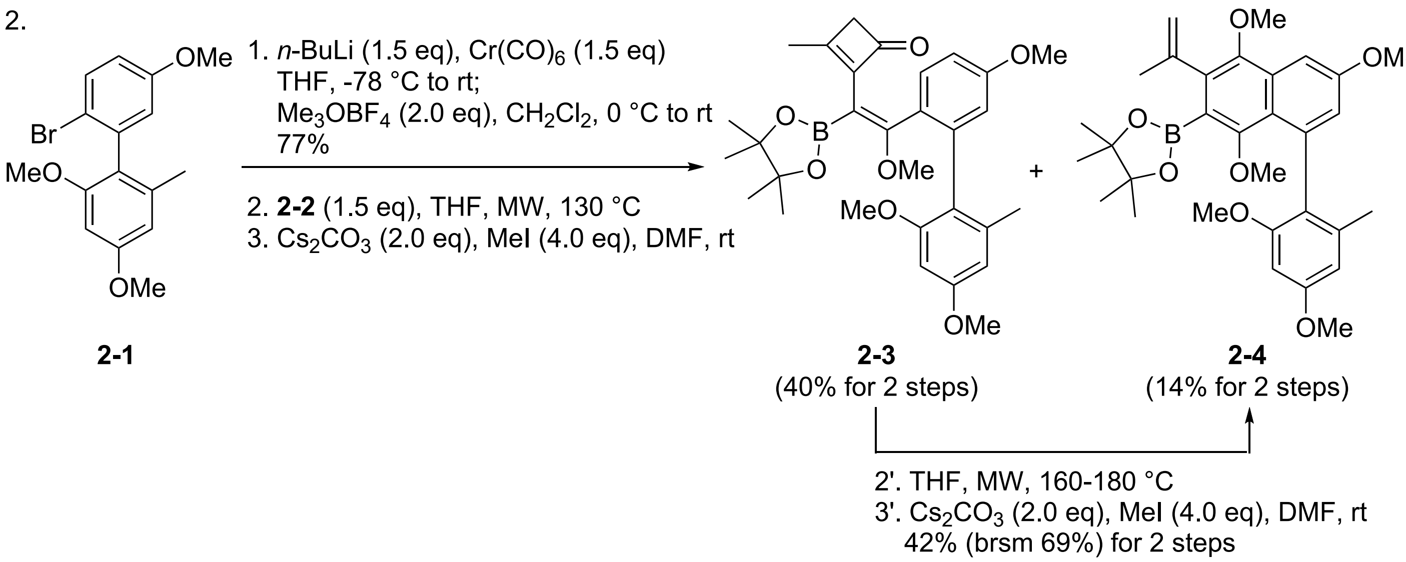
1-1 **1-2** (0.95 eq) **1-3**

(ii)

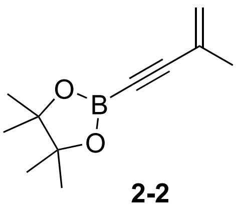


1-1 **1-4** (0.95 eq) **1-5**

2.



2-1 **2-3** (40% for 2 steps) **2-4** (14% for 2 steps)



2-2

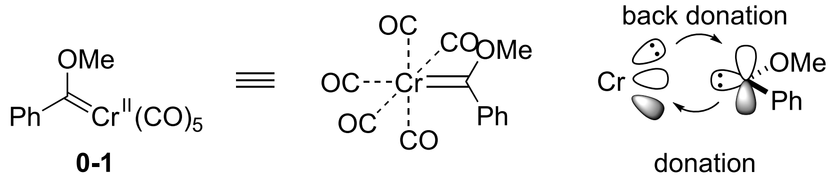
Problem session (6)

2020.5.23 Daiki Kuwana

Topic: Dötz (Wulff-Dötz) reaction

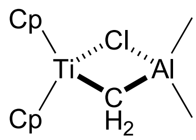
Brief Introduction

1. Fischer carbene complex



middle and late transition metals (W, Fe, Co etc.)
ligand with good π-acceptor properties (CO etc.)
π-donating substituents (OR, NR_2, Ph etc.)

cf. Schrock carbene complex

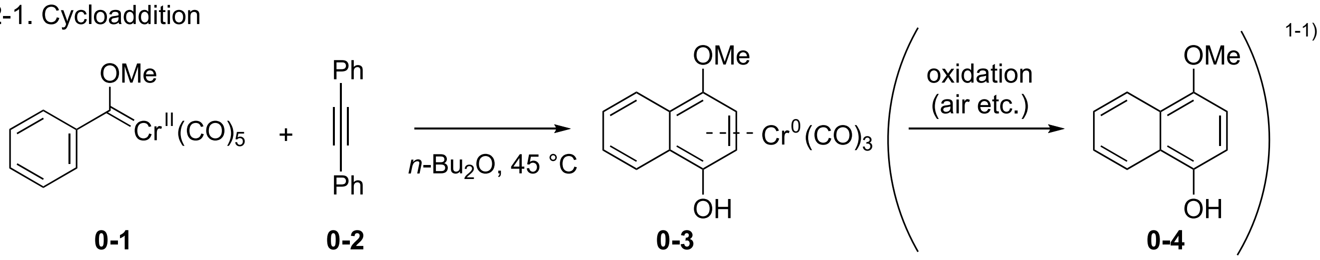


Tebbe reagent

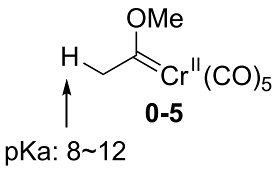
early transition metals (Ti, Ta etc.)
no π-accepting ligand
no π-donating substituents

2. Reaction from Fischer carbene complex

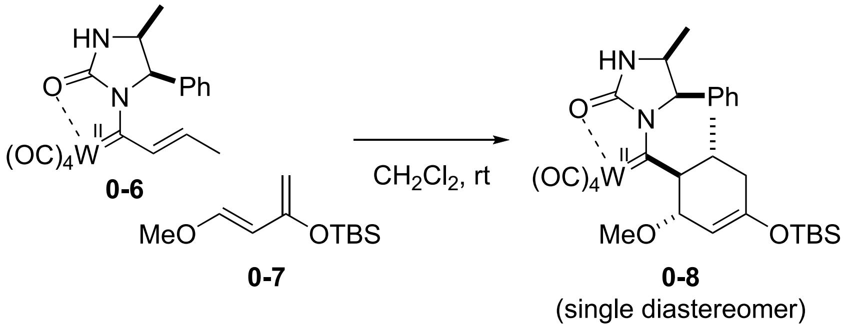
2-1. Cycloaddition



2-2. Deprotonation



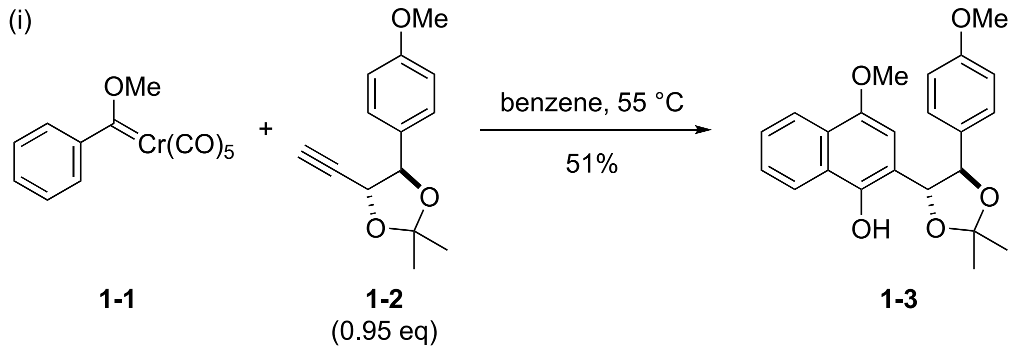
2-3. Aid for stereoselectivity in Diels-Alder reaction[1-2)]



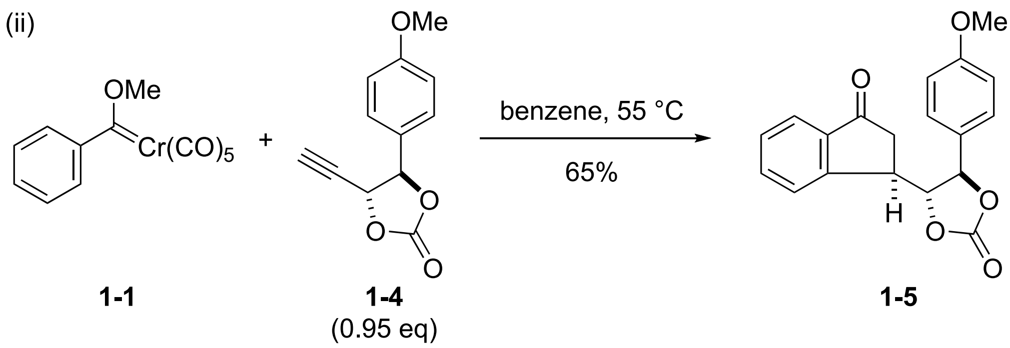
Answer

1. Cyclopentannulation [1-3)]

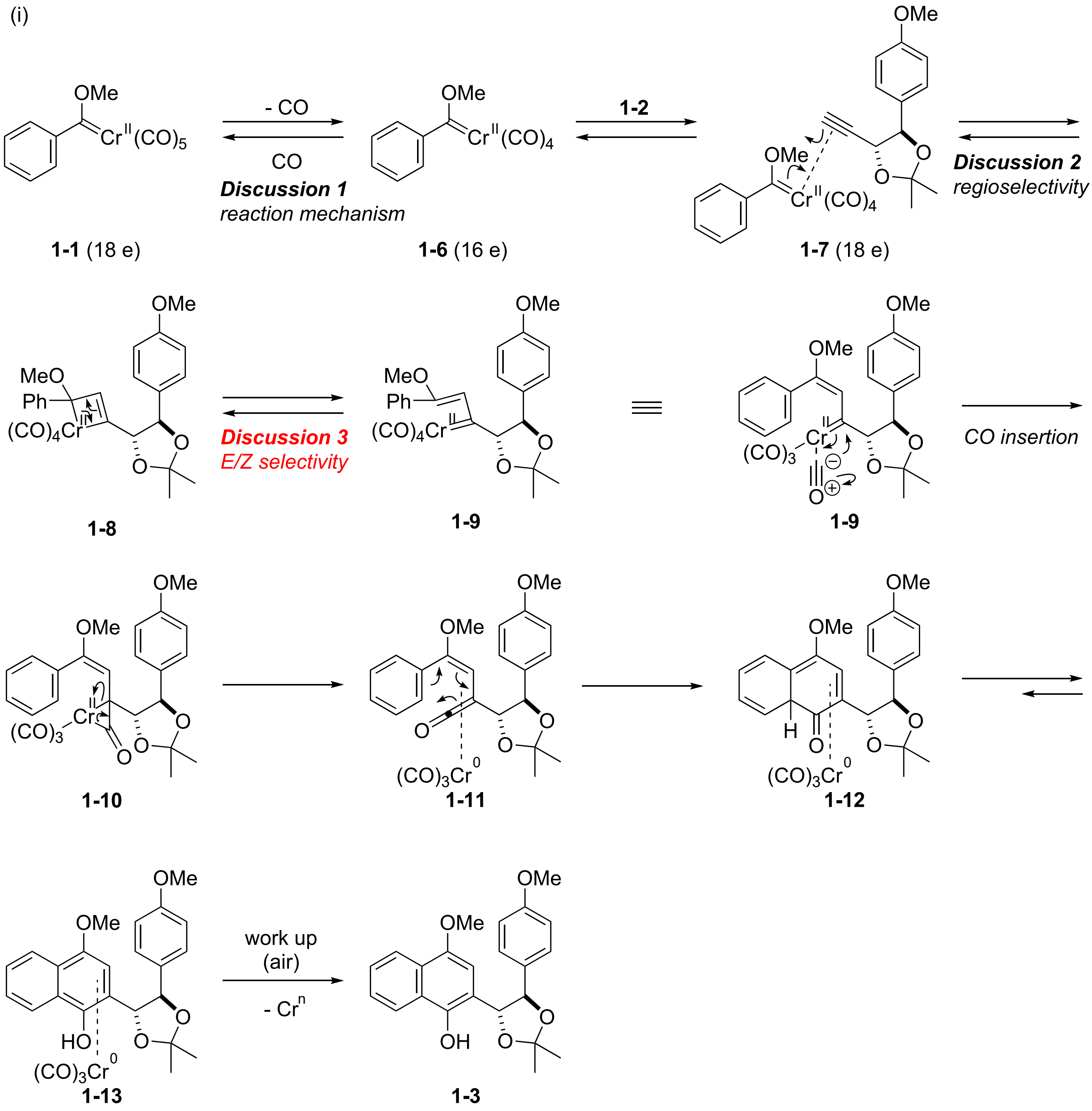
1. (i)



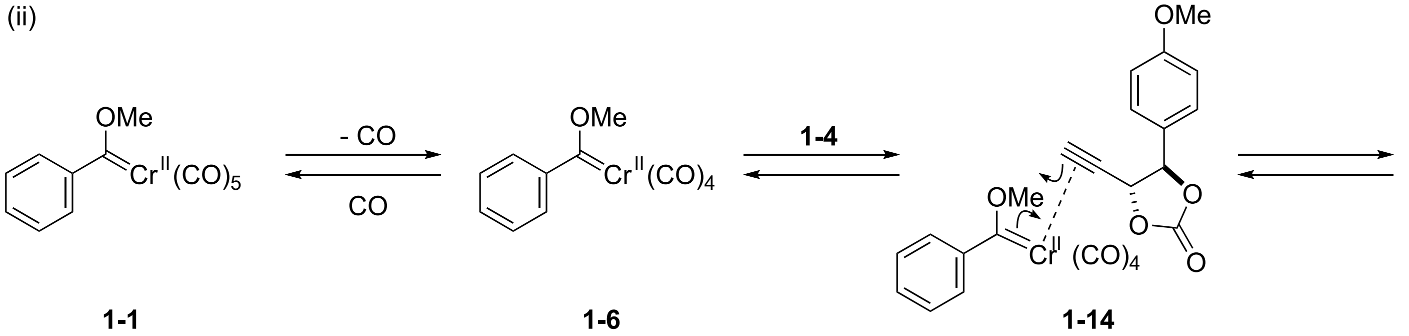
(ii)

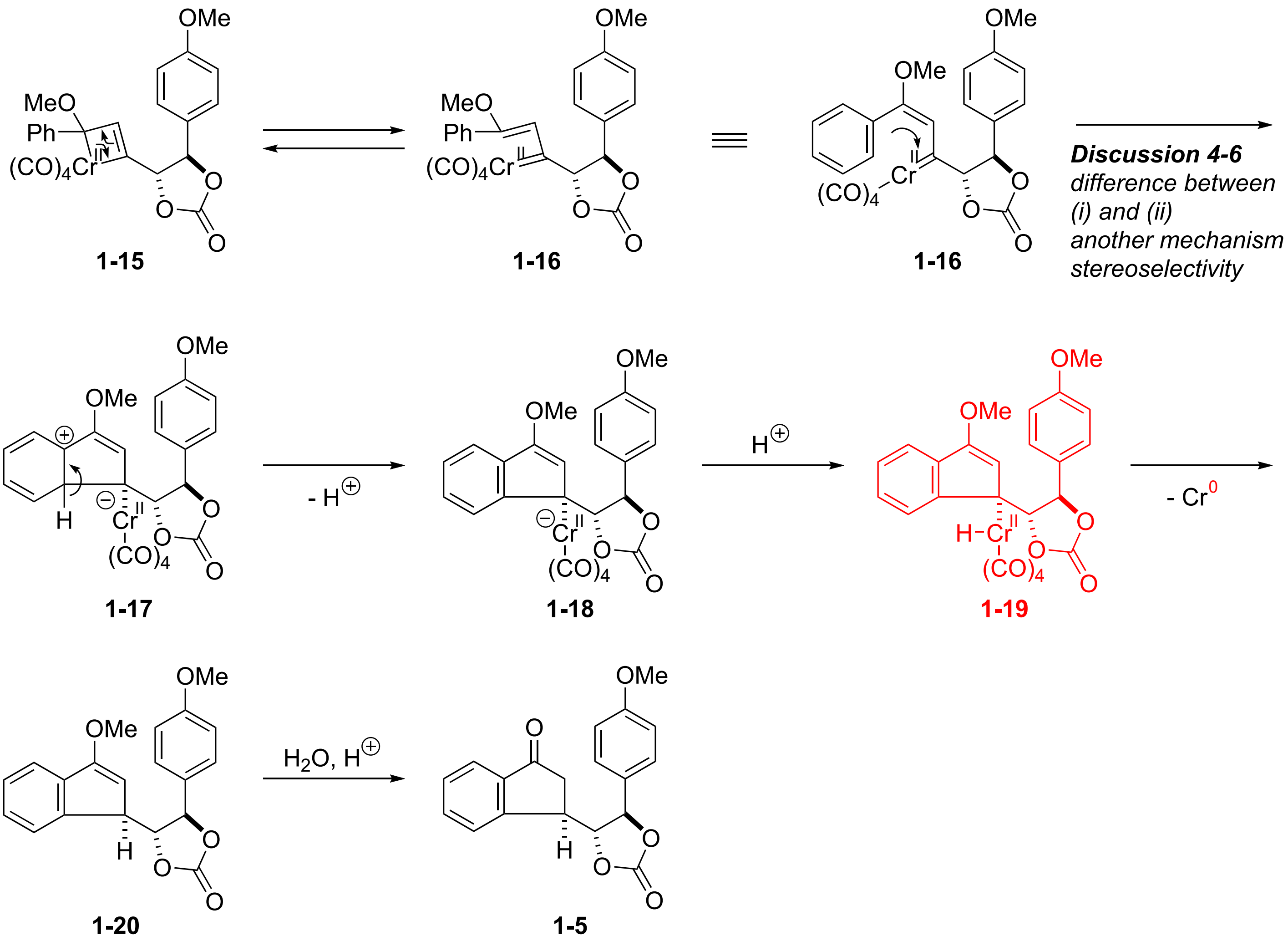


(i)


OMe
Cr^{II}(CO)$_5$
- CO
CO
Discussion 1
reaction mechanism
Cr^{II}(CO)$_4$
1-2
Discussion 2
regioselectivity
1-1 (18 e)
1-6 (16 e)
1-7 (18 e)
MeO
Ph
(CO)$_4$Cr
Discussion 3
E/Z selectivity
1-8
1-9
(CO)$_3$
Cr
CO insertion
1-9
1-10
(CO)$_3$Cr^0
1-11
H
1-12
HO
1-13
work up
(air)
- Cr^n
OH
1-3

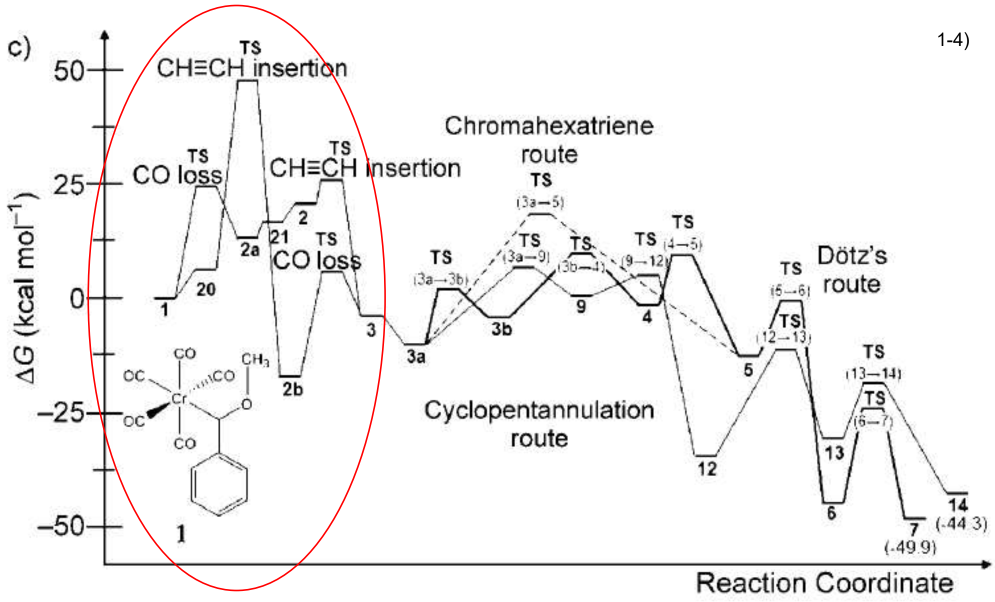
(ii)

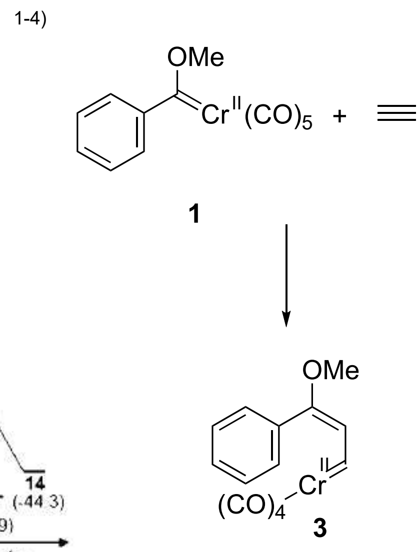

OMe
Cr^{II}(CO)$_5$
- CO
CO
Cr^{II}(CO)$_4$
1-4
1-1
1-6
1-14



Discussion

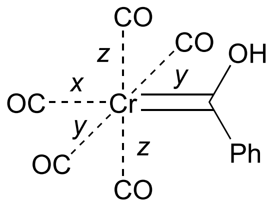
1. CO elimination and coordination of alkyne





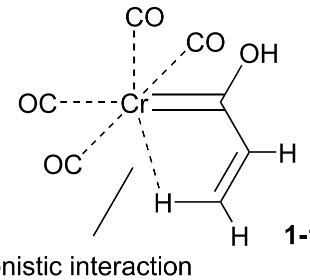
CO loss seems to occur before alkyne insertion.

· dissociation energy



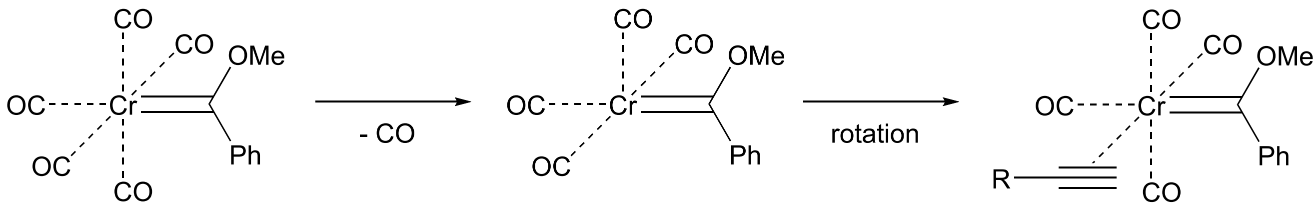
1-1'

calcd dissociation energy of CO
x: 198 kJ/mol
y: 154 kJ/mol
z: 156 kJ/mol
(generally x>y,z and y≥z)



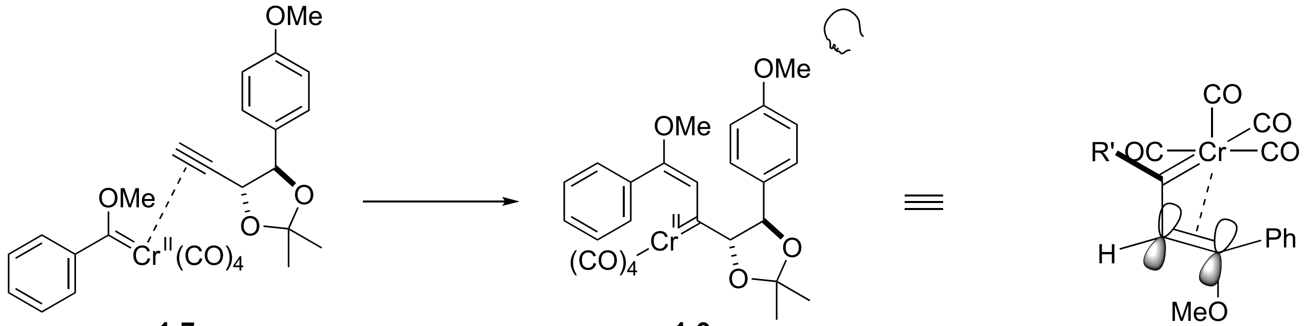
Dötz, K. H. *et al. J. Am. Chem. Soc.* **1996**, *118*, 10551.

· mechanism of coordination

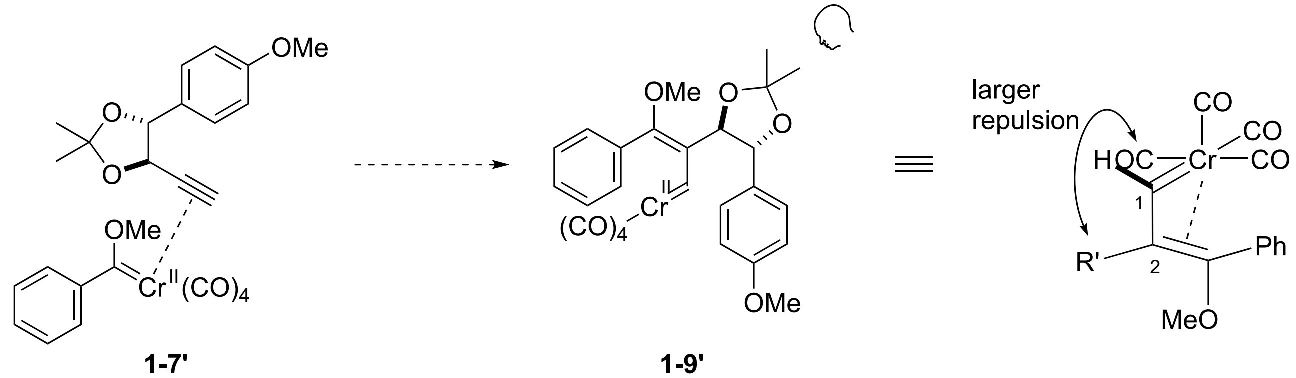


1-1 **1-6**

2. Regioselectivity



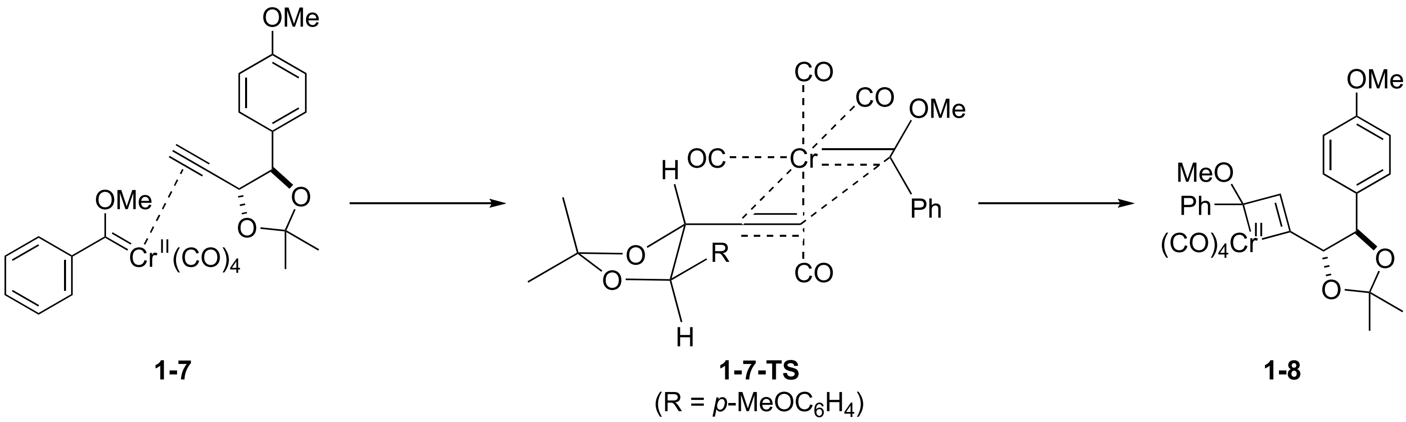
1-7 **1-9**

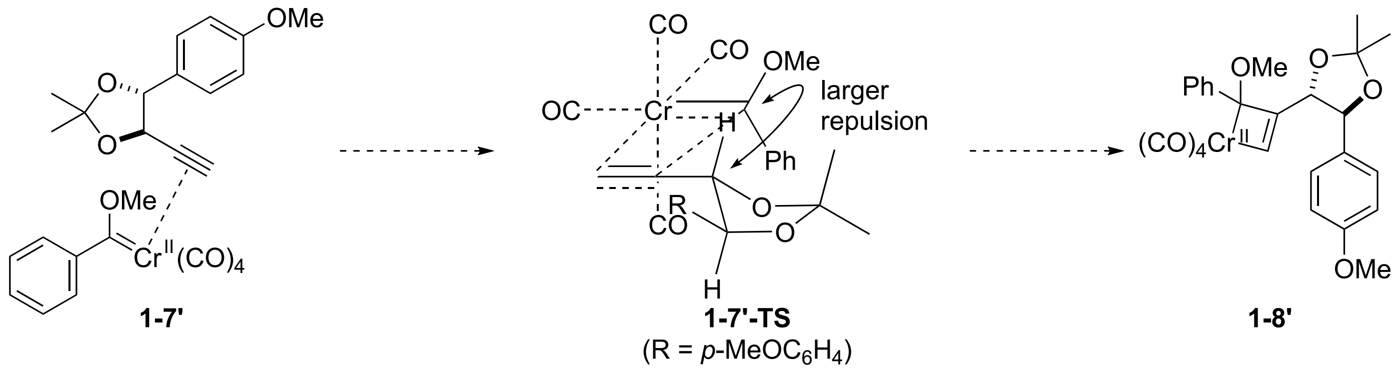


1-7' **1-9'**

"Extended Hückel calculations reveal that the substituent at the 2-position of this intermediate is at least 1 Å closer to its nearest CO ligand than the substituent on the 1-position." [1-5), 1-6)]

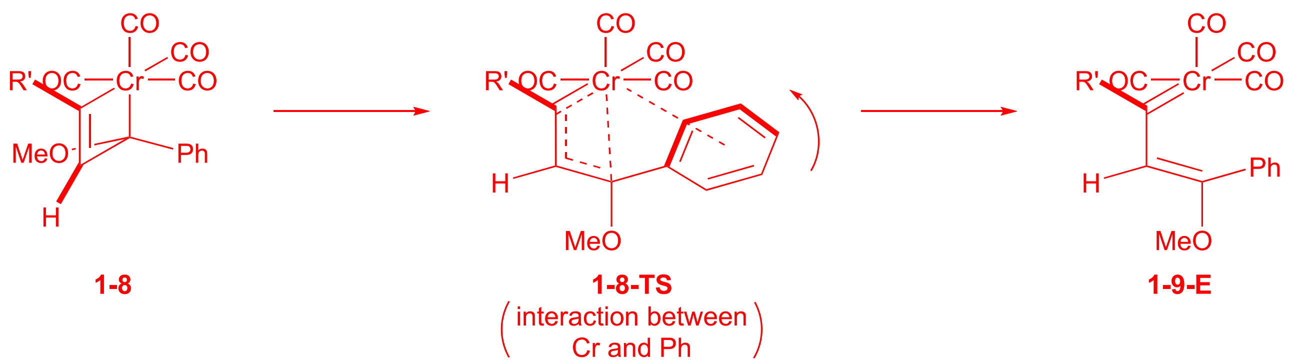
· another proposal



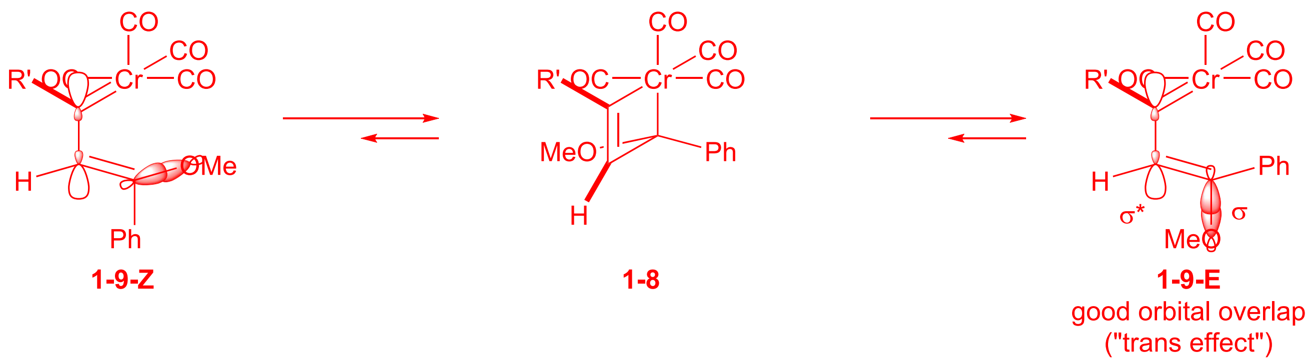


This way of thinking may not be applied to problem 2.

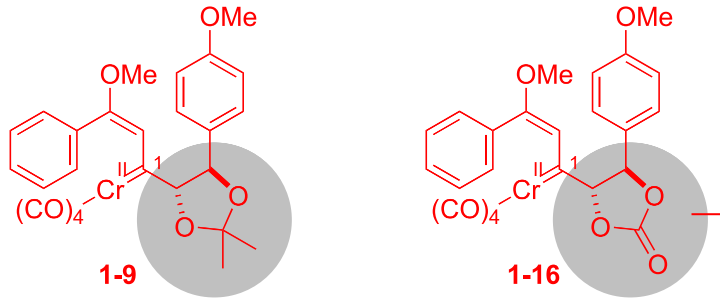
3. *E/Z* selectivity



proposal by Wulff [1-7)]

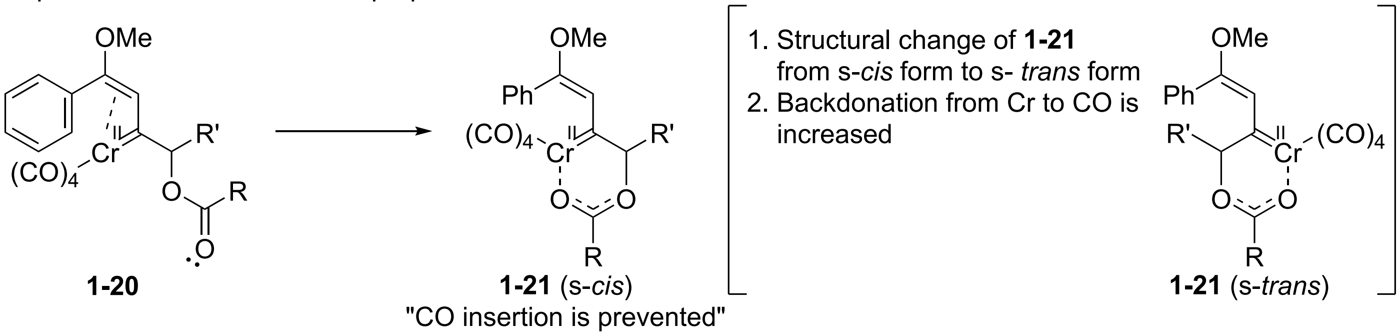


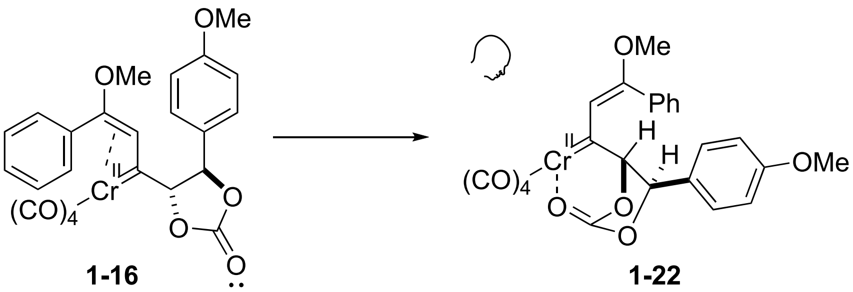
4. difference between (i) and (ii)



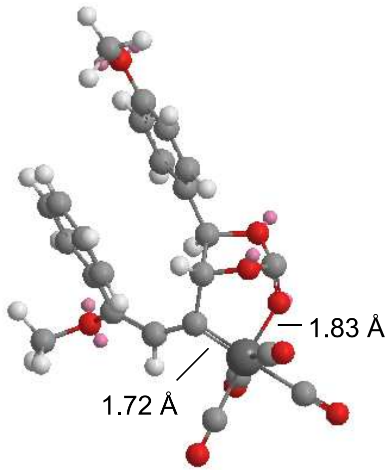
low electron density
→ C1 becomes more electrophilic

explanation based on authors' proposal



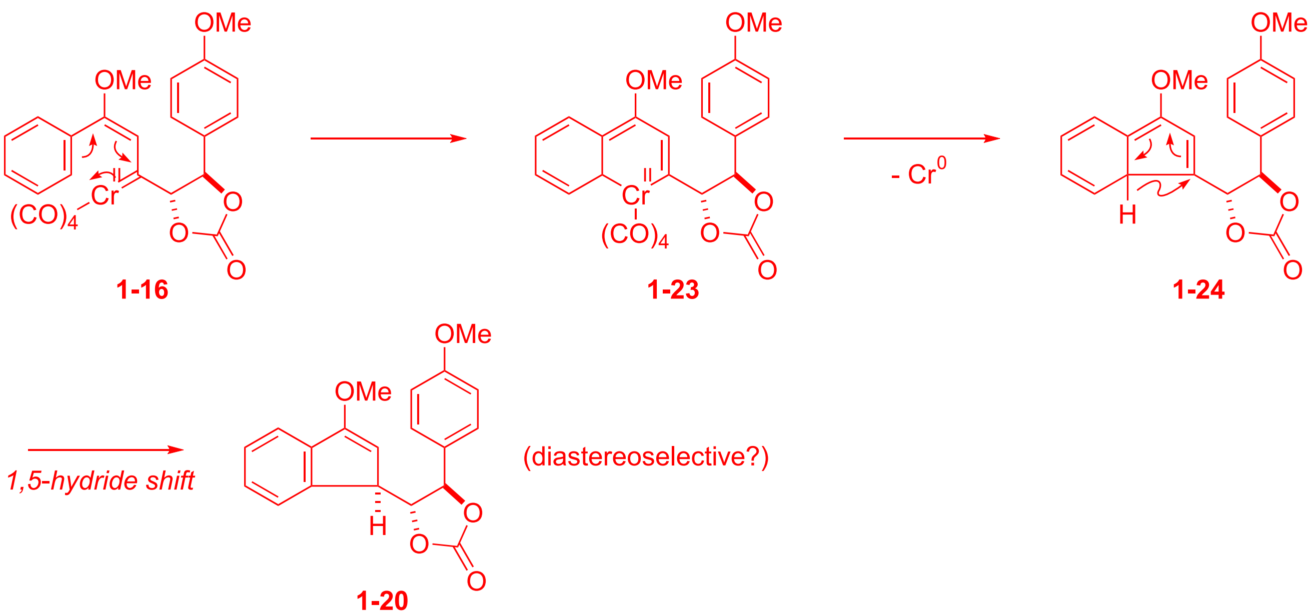


structure of **1-22** drawn using Chem 3D

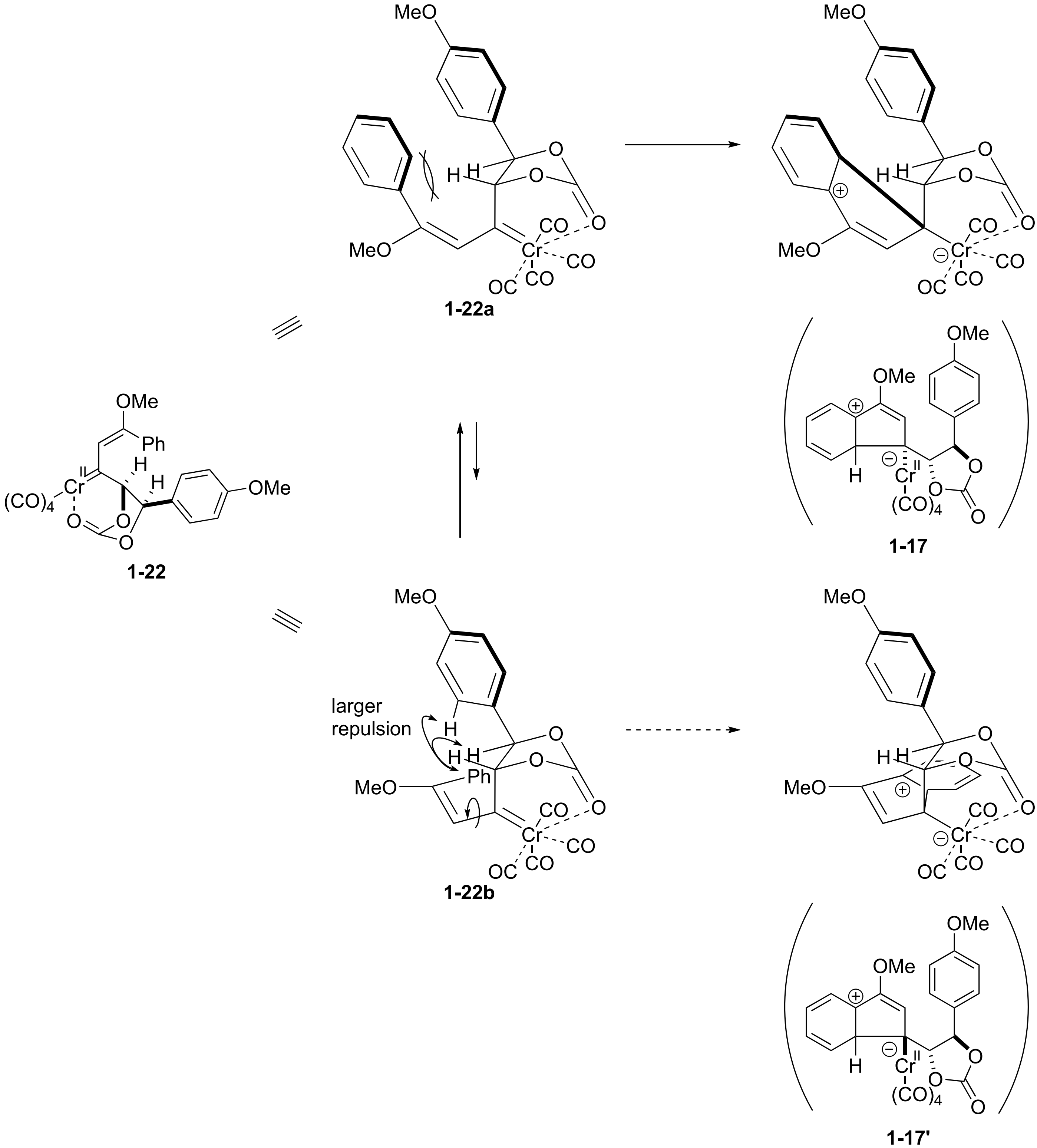


long bond distance →
strain energy may be decreased

5. another reaction mechanism



6. Stereoselectivity in (ii)



Reference

1-1) Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 64.

1-2) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D. Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438.

1-3) Fernandes, R. A.; Gholap, S. P.; Chavan, V. P.; Saiyed, A. S.; Bhattacharyya, T. *Org. Lett.* **2020**, 22*,* 3438*.*

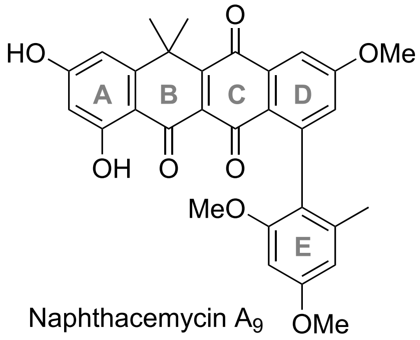
1-4) Jimenez-Halla, J. O. C.; Solà, M. *Chem. Eur. J.* **2009**, *15*, 12503.

1-5) Wulff, W. D. *et al.* *"Organic Reactions"* **2008**, *70*, chapter2. 121.

1-6) Hofmann, P.; Hãmmerle *Nouv. J. Chem.* **1991**, *15*, 769.

1-7) Waters, M. L.; Brandvold, T. A.; Isaacs, L.; Wulff, W. D. *Organometallics* **1998**, *17*, 4298.

2. Total synthesis of naphthacemycin A_9

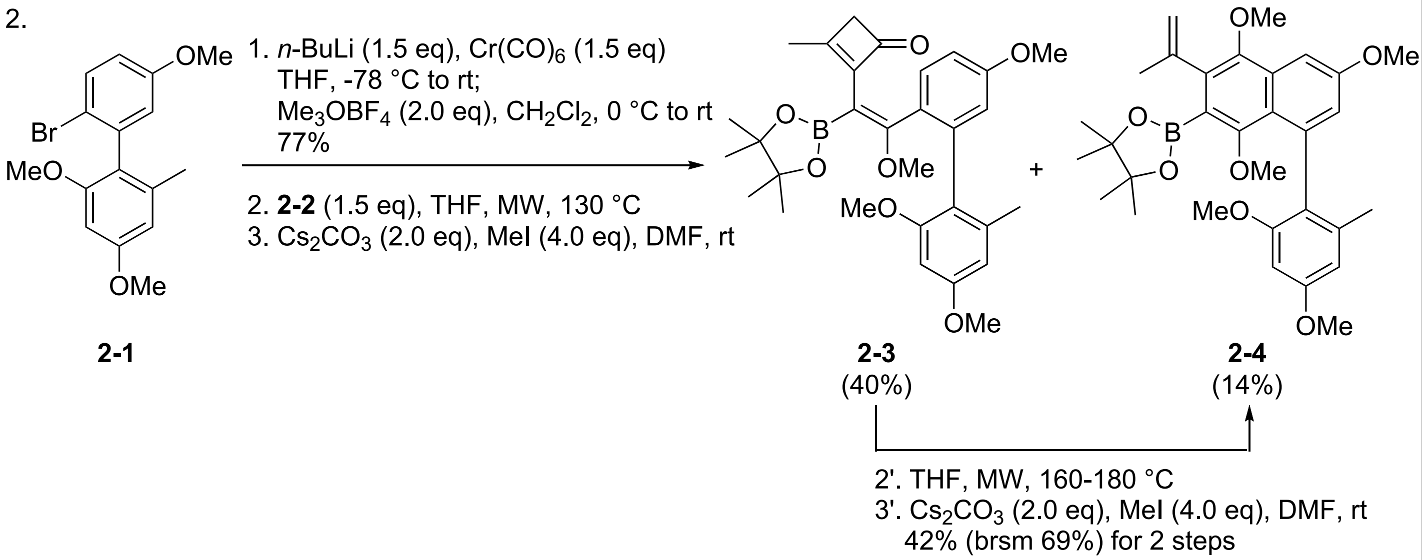


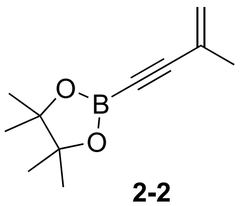
Naphthacemycin A_9

Isolation
Streptomyces sp. KB-3346-5 [2-1)]

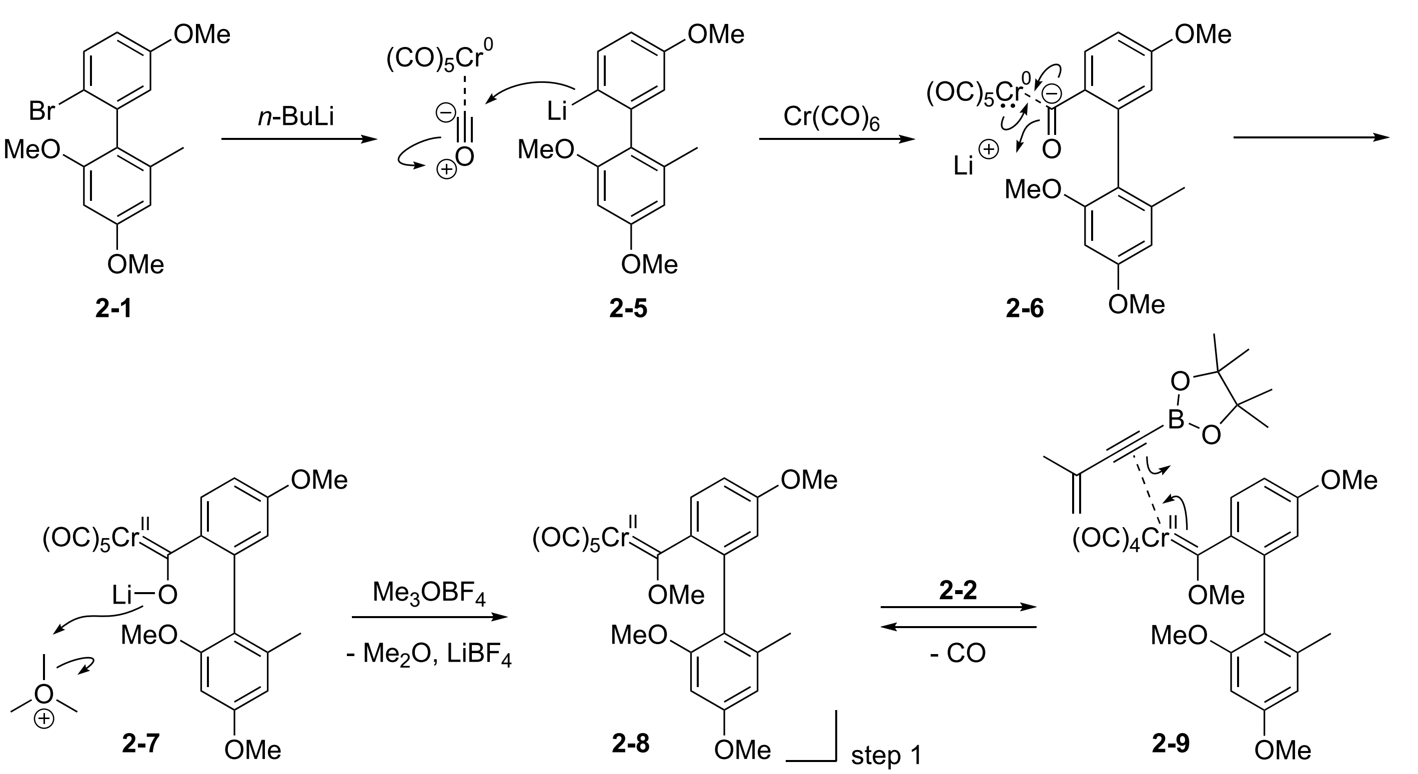
Bioactivity
circumventors of β-lactam resistence in MRSA
(naphthacemycin A_9 itself also has anti-MRSA activity) [2-2)]

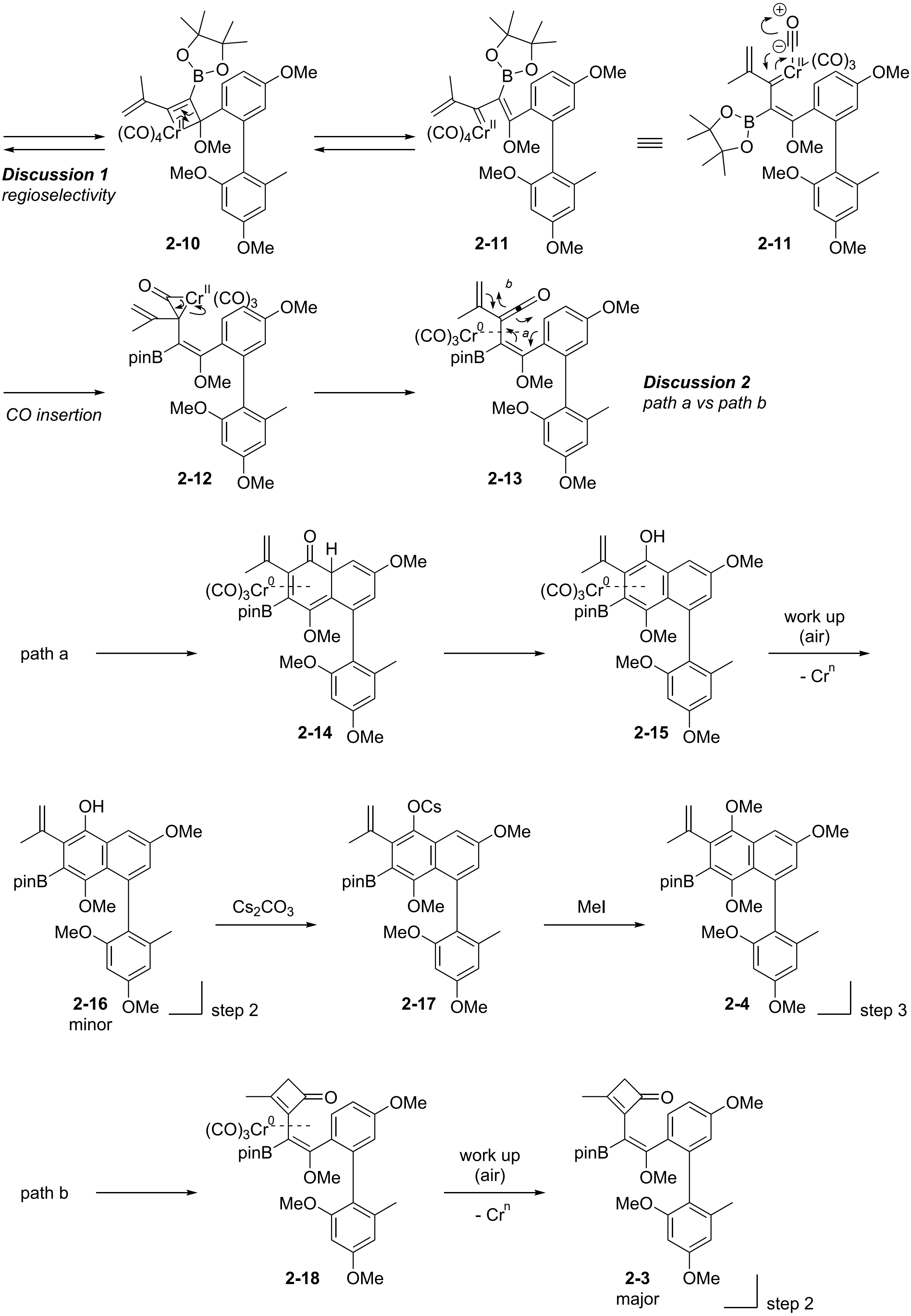
Total synthesis (racemic)
Omura (2017, Problem 2) [2-3)]; Shia (2018) [2-4)]; Kraus (2018) [2-5)]



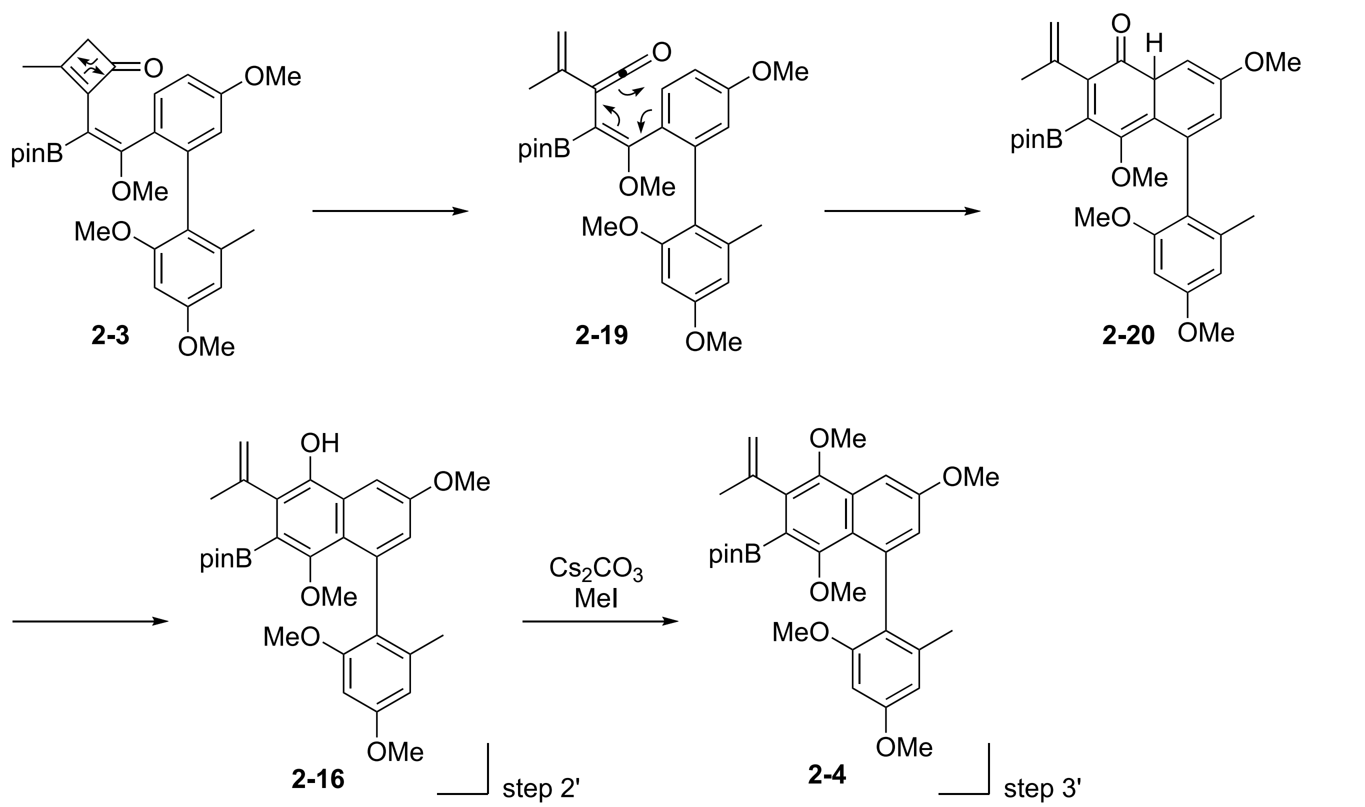


2-2



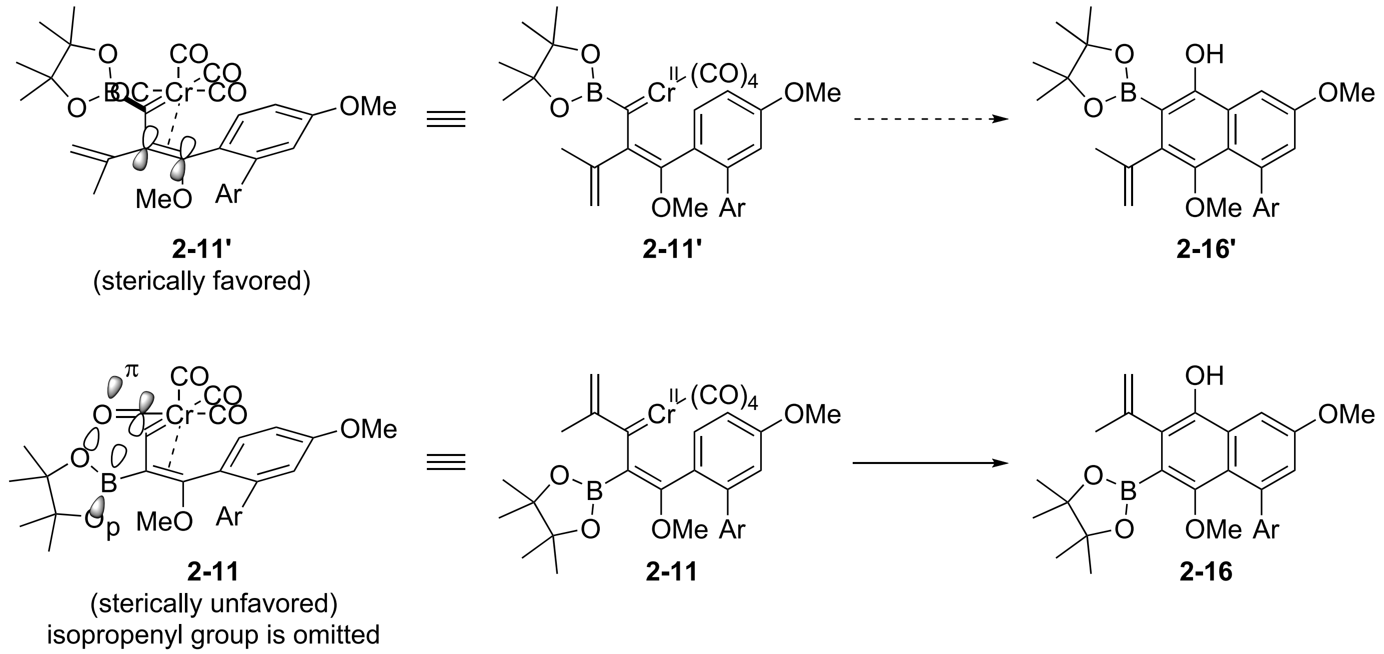


Discussion 1
regioselectivity
2-10
2-11
2-11
CO insertion
2-12
2-13
Discussion 2
path a vs path b
path a
2-14
2-15
work up
(air)
- Cr^n
2-16
minor
step 2
Cs2CO3
2-17
MeI
2-4
step 3
path b
2-18
work up
(air)
- Cr^n
2-3
major
step 2

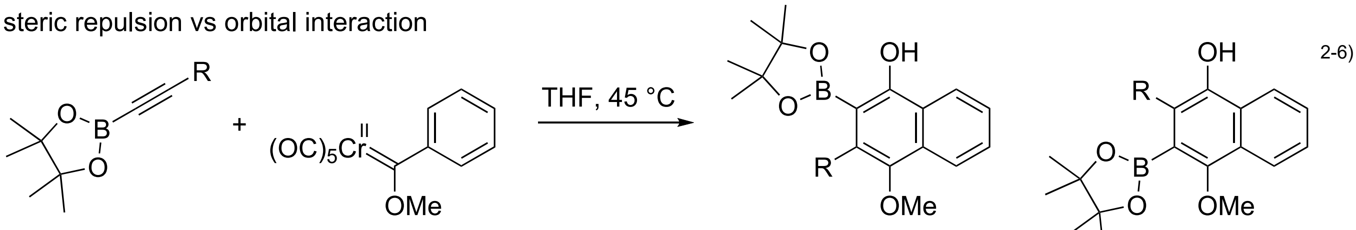


Discussion

1. regioselectivity



· steric repulsion vs orbital interaction

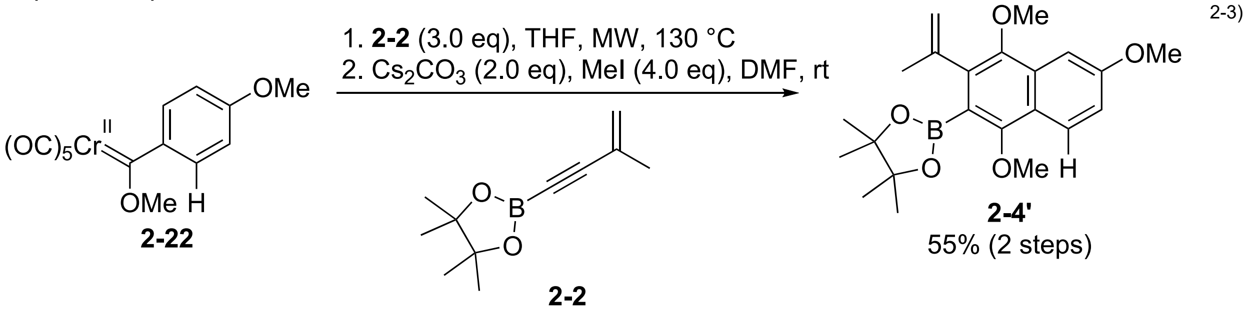


2-21 **2-22** **2-23'** (sterically favored) **2-23** (sterically unfavored)

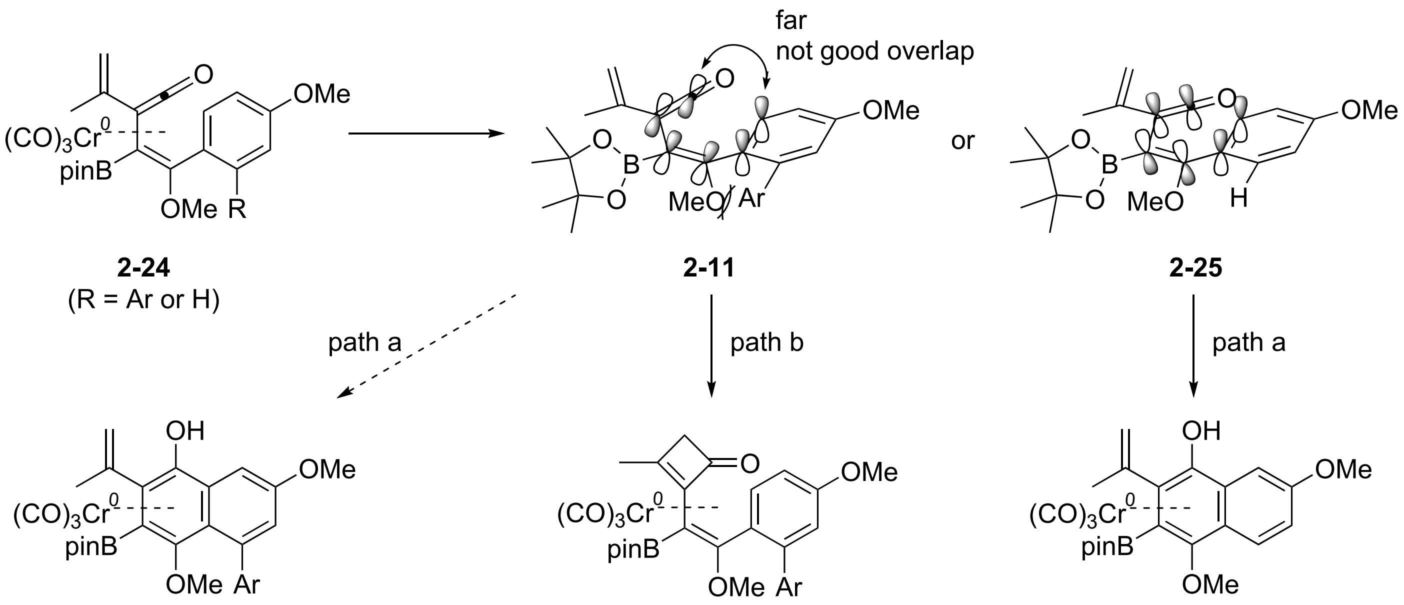
Table

entry	R	results
1	H (**2-21a**)	**2-23'a**: 50%
2	Me (**2-22b**)	**2-23b**: 53%
3	*n*-Bu (**2-22c**)	**2-23c**: 73%
4	Ph (**2-22d**)	**2-23d**: 64%

2. path a vs path b



2-22 **2-2** **2-4'** 55% (2 steps)



Reference

2-1) Fukumoto, A.; Kim, Y.-P.; Iwatsuki, M.; Hirose, T.; Sunazuka, T.; Hanaki, H.; Omura, S.; Shiomi, K. *J. Antibiotics* **2017**, *70*, 568.

2-2) Fukumoto, A.; Kim, Y.-P.; Matsumoto, A.; Takahashi, Y.; Suzuki, M.; Onodera, H.; Tomoda, H.; Matsui, H; Hanaki, H.; Iwatsuki, M.; Omura, S.; Shiomi, K. *J. Antibiotics* **2017**, *70*, 562.

2-3) Hirose, T.; Kojima, Y.; Matsui, H.; Hanaki, H.; Iwatsuki, M.; Shiomi, K.; Omura, S.; Sunazuka, T. *J. Antibiotics* **2017**, *70*, 574.

2-4) Huang, J.-K.; Lauderdale, T.-S. Y.; Lin, C.-C.; Shia, K.-S. *J. Org. Chem.* **2018**, *83*, 6508.

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2-6) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525.