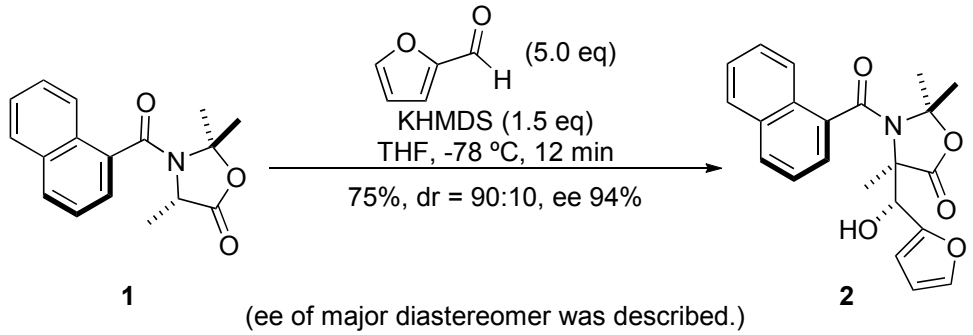
Problem Session (4)

2015/8/1 Atsushi Hayata

Please provide the reaction mechanisms and stereoselectivities.

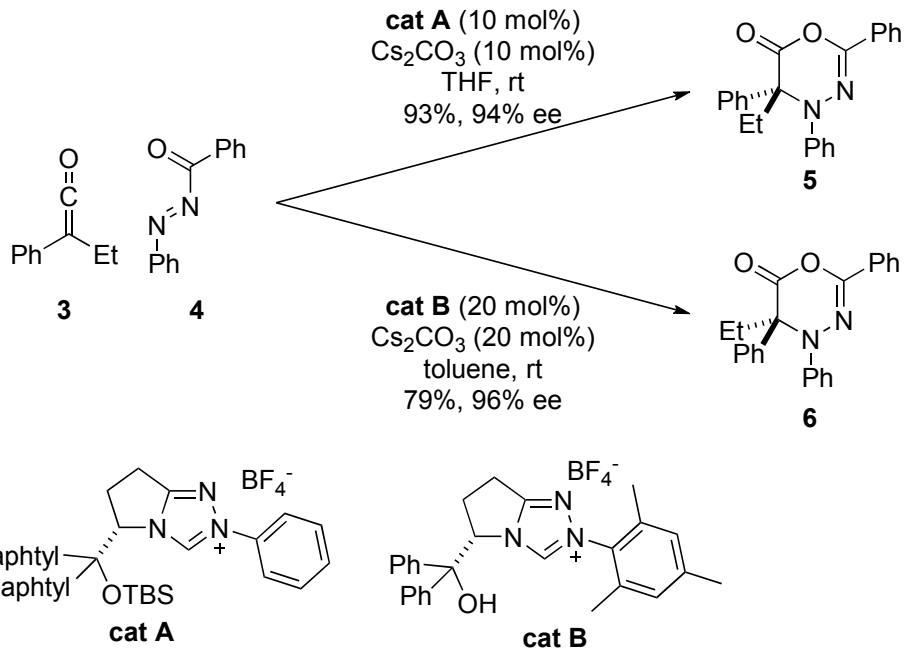
1



1 **2**

(ee of major diastereomer was described.)

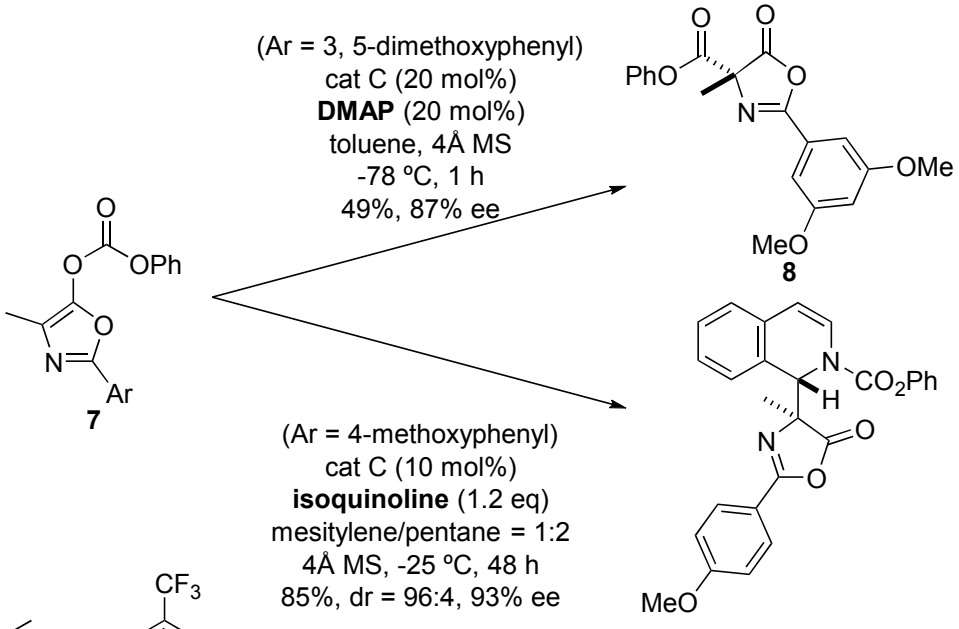
2



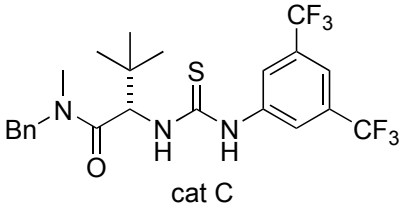
3 **4** **5** **6**

cat A **cat B**

3



7 **8** **9**



cat C

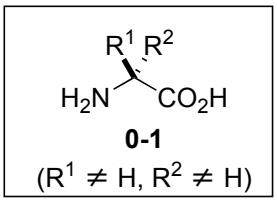
(ee of major diastereomer was described.)

Problem Session (4) -Answer-

2015/8/1 Atsushi Hayata

0 Introduction

α,α-disubstituted amino acids

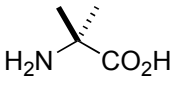


0-1

($R^1 \neq H$, $R^2 \neq H$)

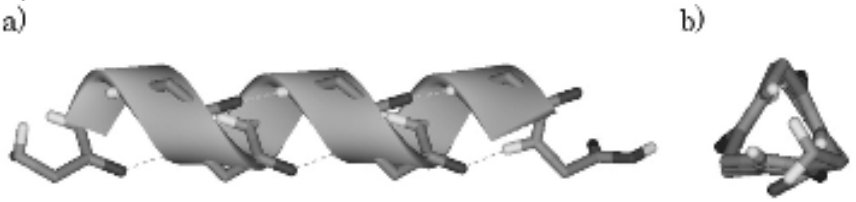
amino acid
(1) increase of chemical stability
(2) increase of hydrophobicity
(3) restriction of conformational freedom of the side chains
peptide
(1) restriction of conformational freedom of the secondary structure
(2) increase of metabolic stability

Aib (dimethylglycine)



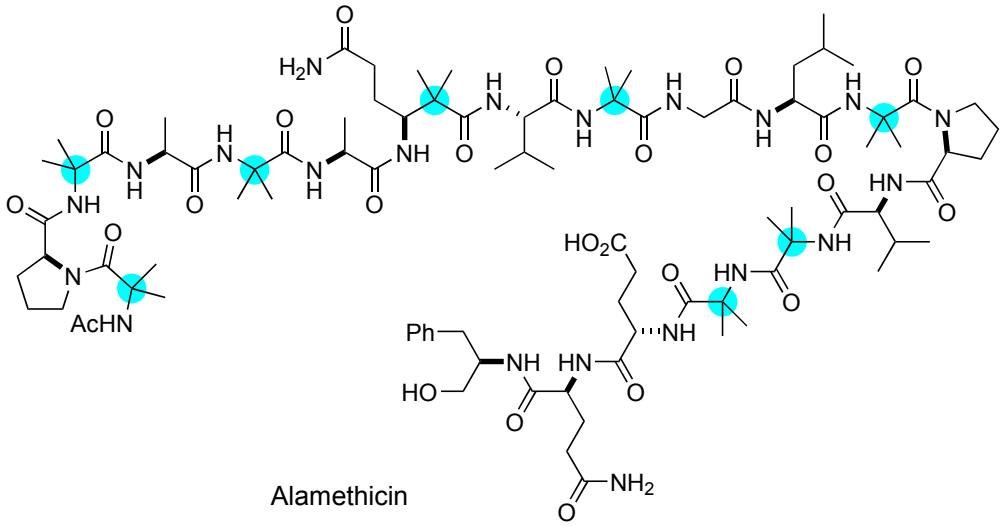
0-2

3_{10}-helix

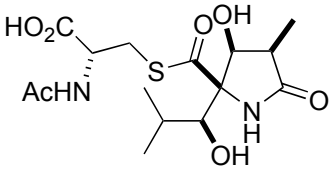


Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349.

natural products containing α,α-disubstituted amino acids



Alamethicin

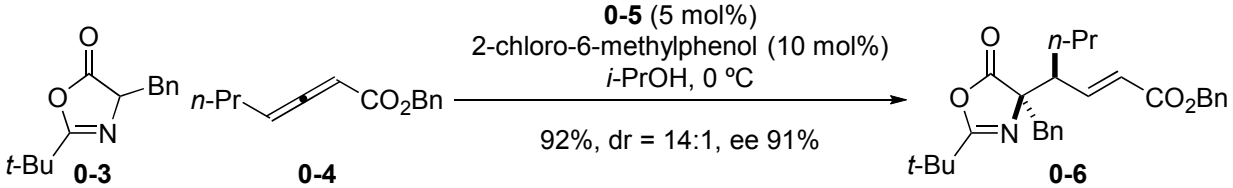


Lactacystin

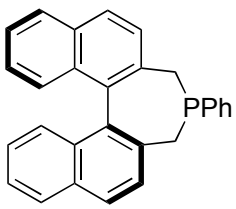
syntheses of α,α-disubstituted amino acids

review
Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1.
Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406.

asymmetric catalyst
1. metal complex (phosphine catalyst)



0-3 **0-4** **0-6**

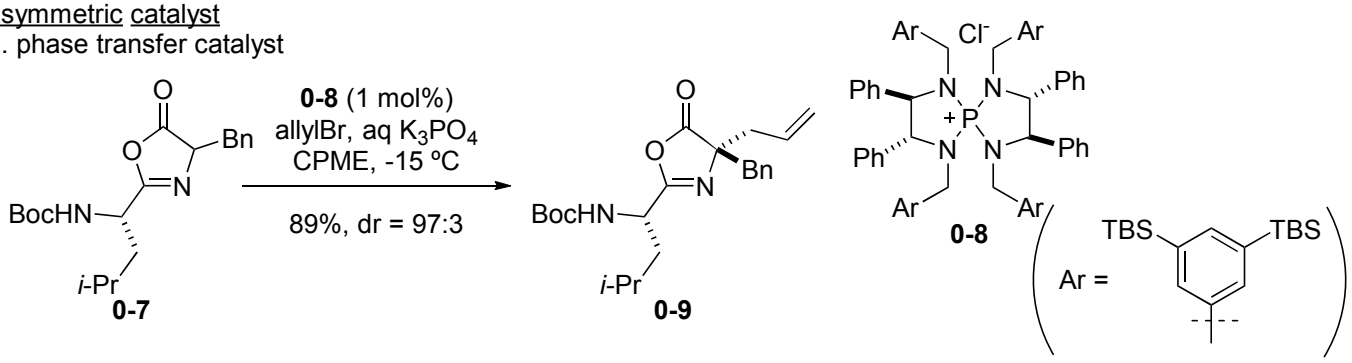


0-5

Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438.

asymmetric catalyst

2. phase transfer catalyst



Uraguchi, D.; Asai, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 733.

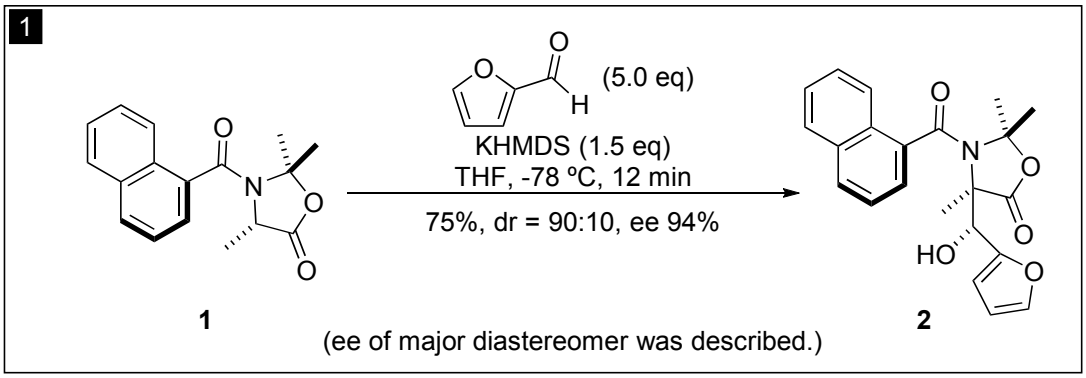
3. organic catalyst

N-heterocyclic carbenes -> problem 2
thiourea -> problem 3

without asymmetric catalyst

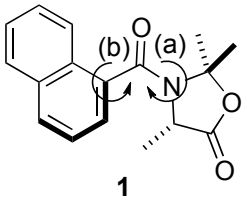
-> problem 1

1



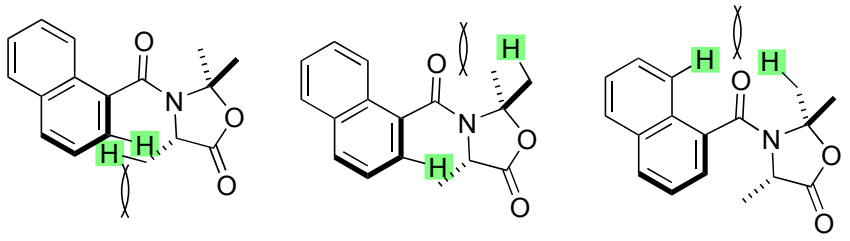
Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Lett.* **2014**, *16*, 788.

conformation of 1

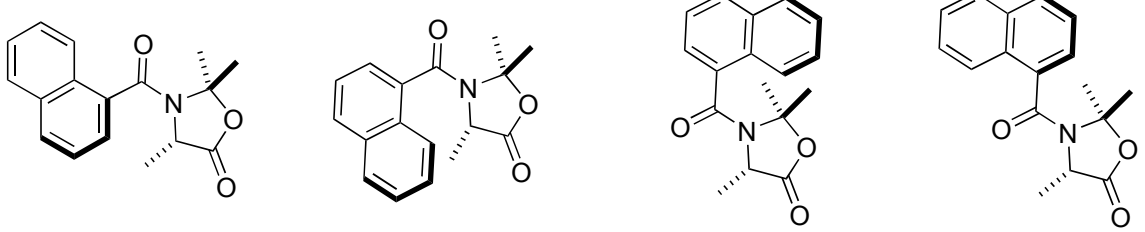


two rotaionable bonds
(a) N-CO rotation: *cis*/*trans* stereoisomers
(b) Ar-CO rotation: *M*/*P* stereoisomers

Bond rotations are constrained due to the steric repulsion between highlighted hydrogen atom.

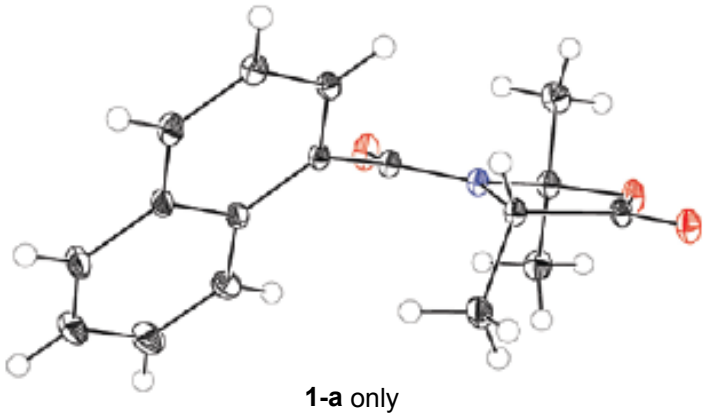


four conformations



1-a (*P*, *cis*) **1-b** (*M*, *cis*) **1-c** (*P*, *trans*) **1-d** (*M*, *trans*)

X-ray structure



1-a only

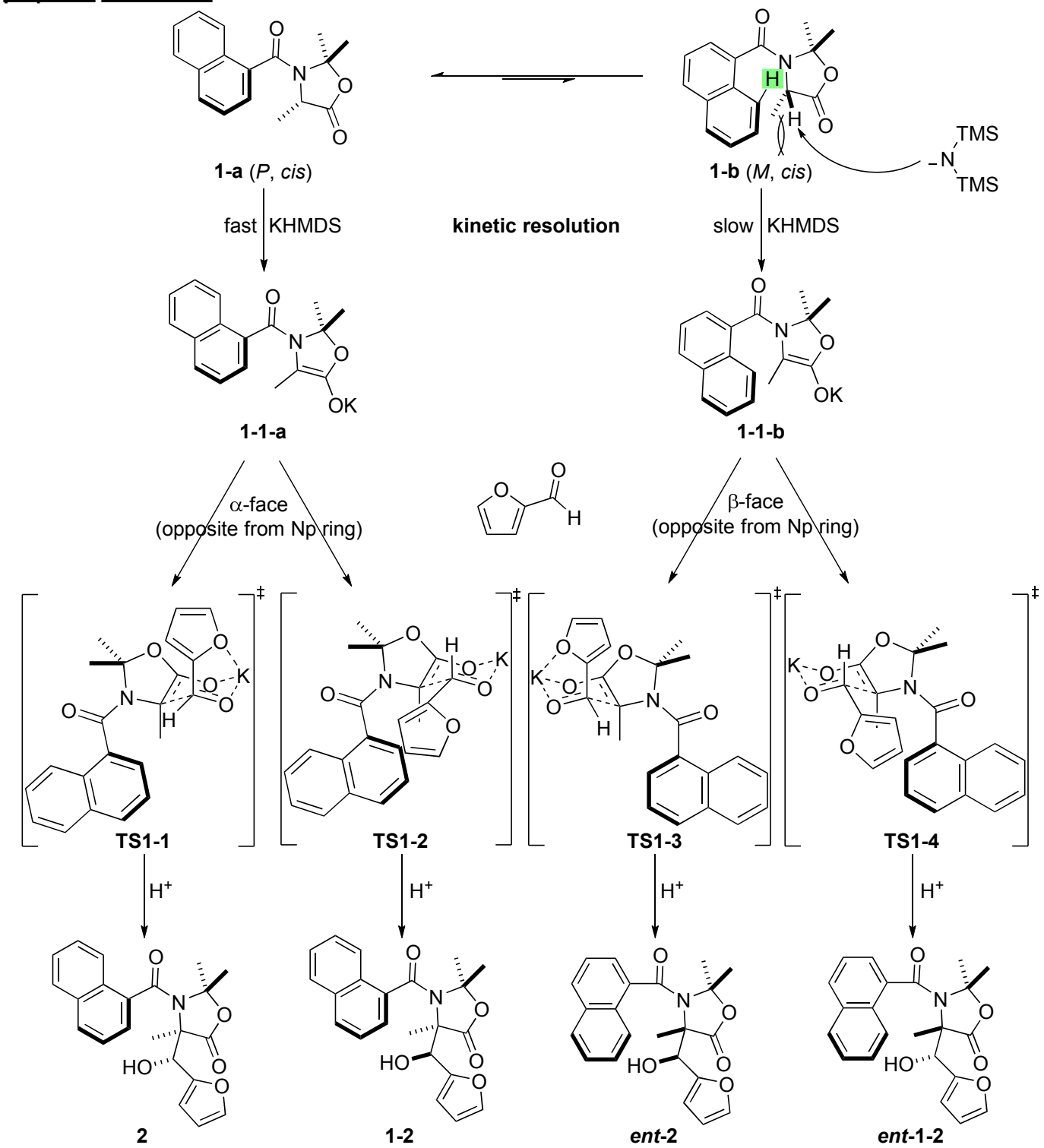
NMR analysis (THF-d_8, -78 ºC)

cis (**1-a** + **1-b**) / *trans* (**1-c** + **1-d**) = 100/2

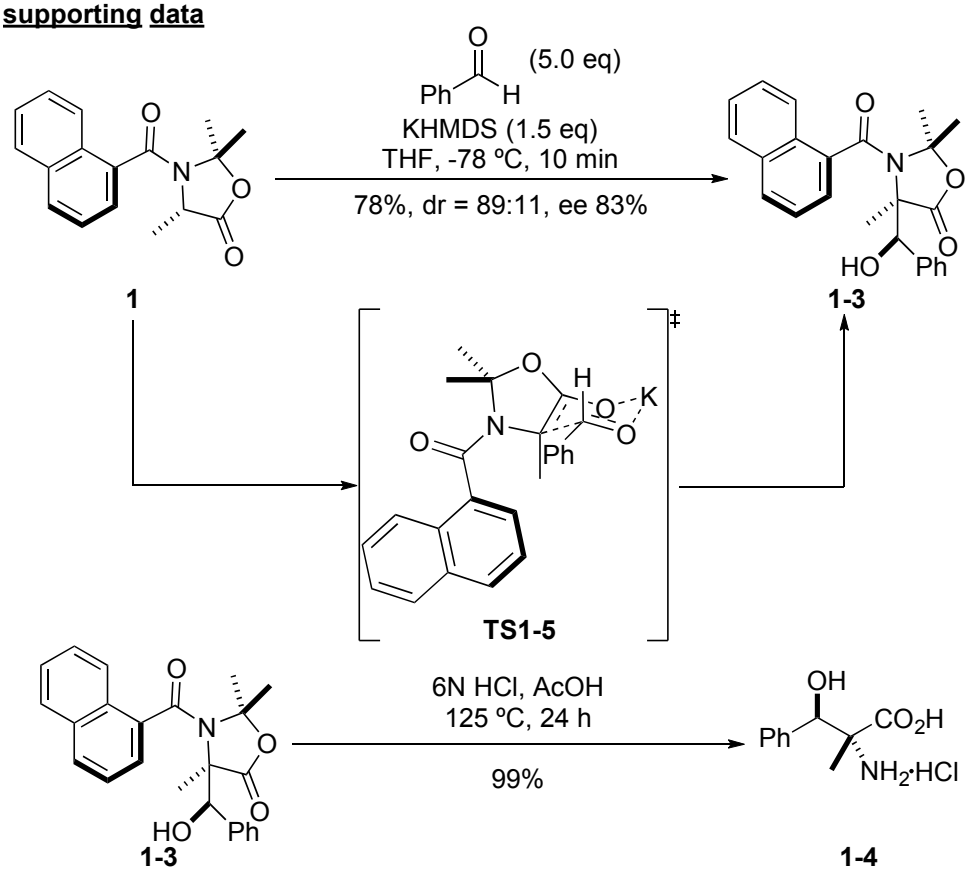
P, *cis* (**1-a**) / *M*, *cis* (**1-b**) = 100/29

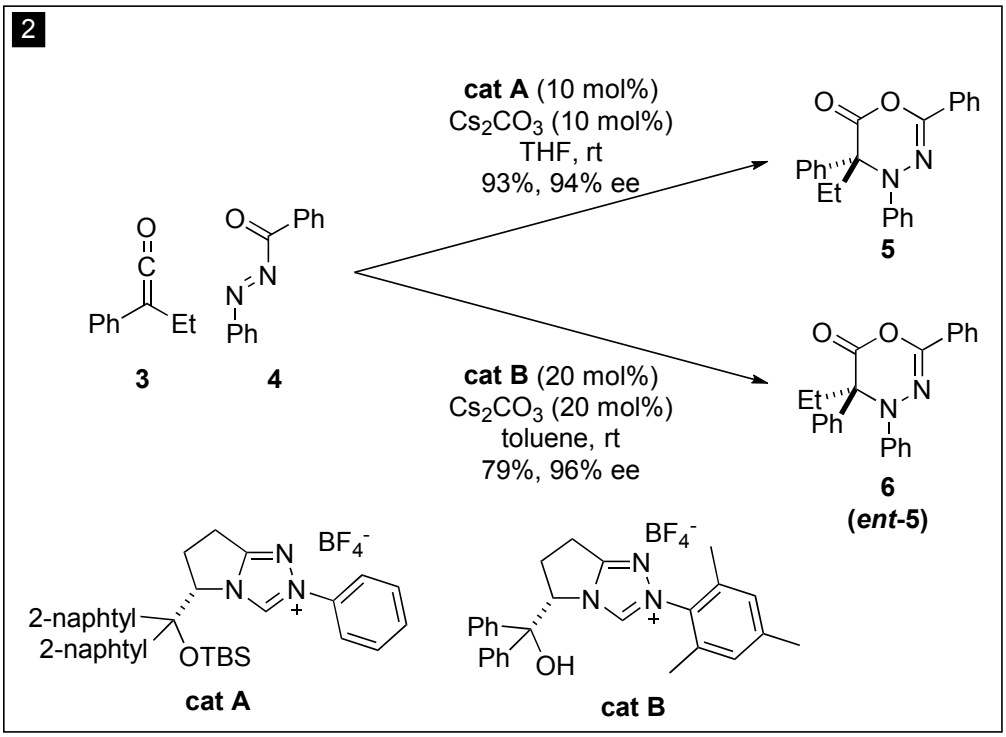
Branca, M.; Pena, S; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711.

proposed mechanism



supporting data

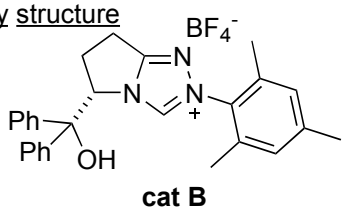


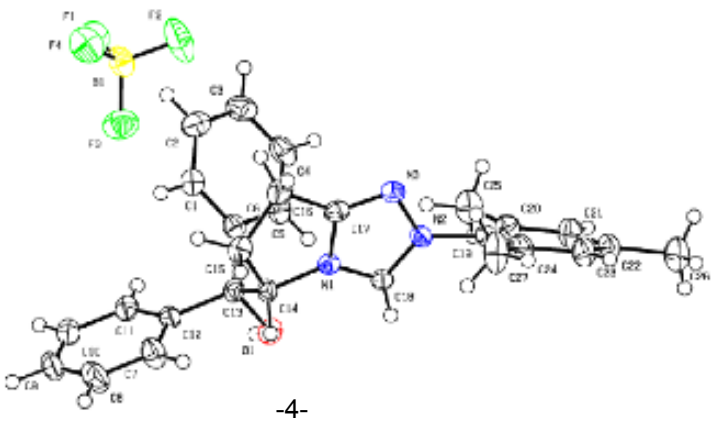


Huang, X-L.; He, L.; Shao, P-L.; Ye, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 192.
Zhang, Wenjing.; Zhu, Y.; Wei, D.; Li, Y.; Tang, M. *J. Org. Chem.* **2012**, *77*, 10729.

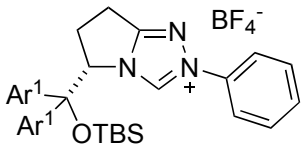
conformation of catalysts

X-ray structure



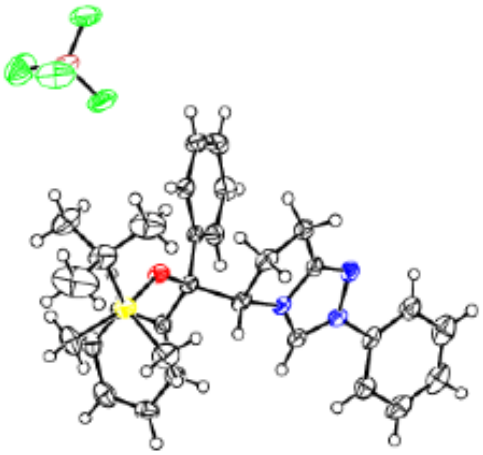


X-ray structure



cat 2-1: Ar^1 = Ph

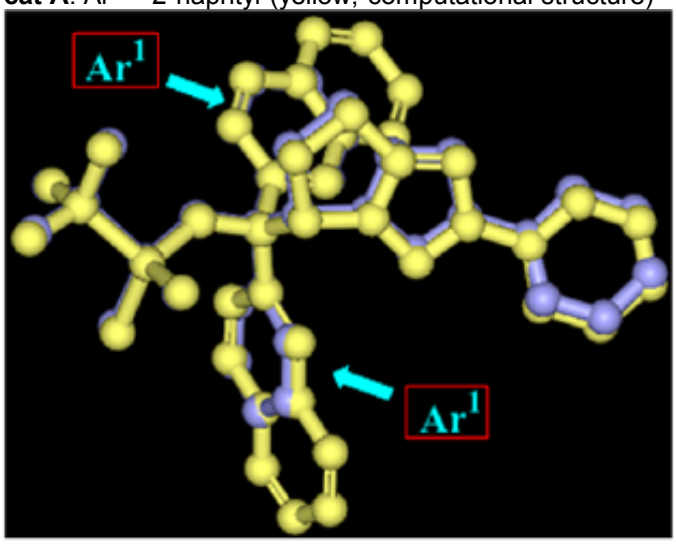
(**cat A**: Ar^1 = 2-naphtyl)



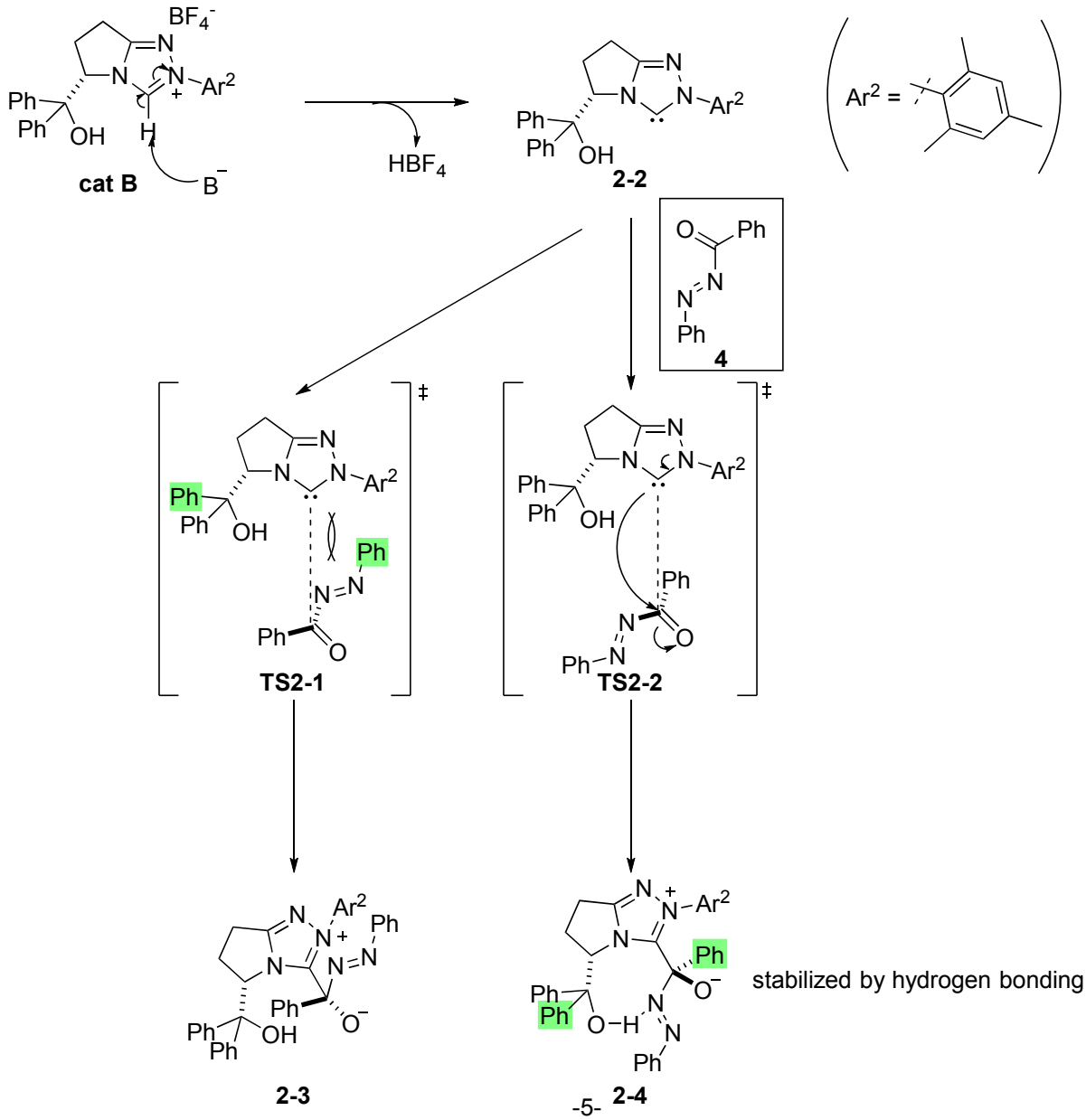
computational study

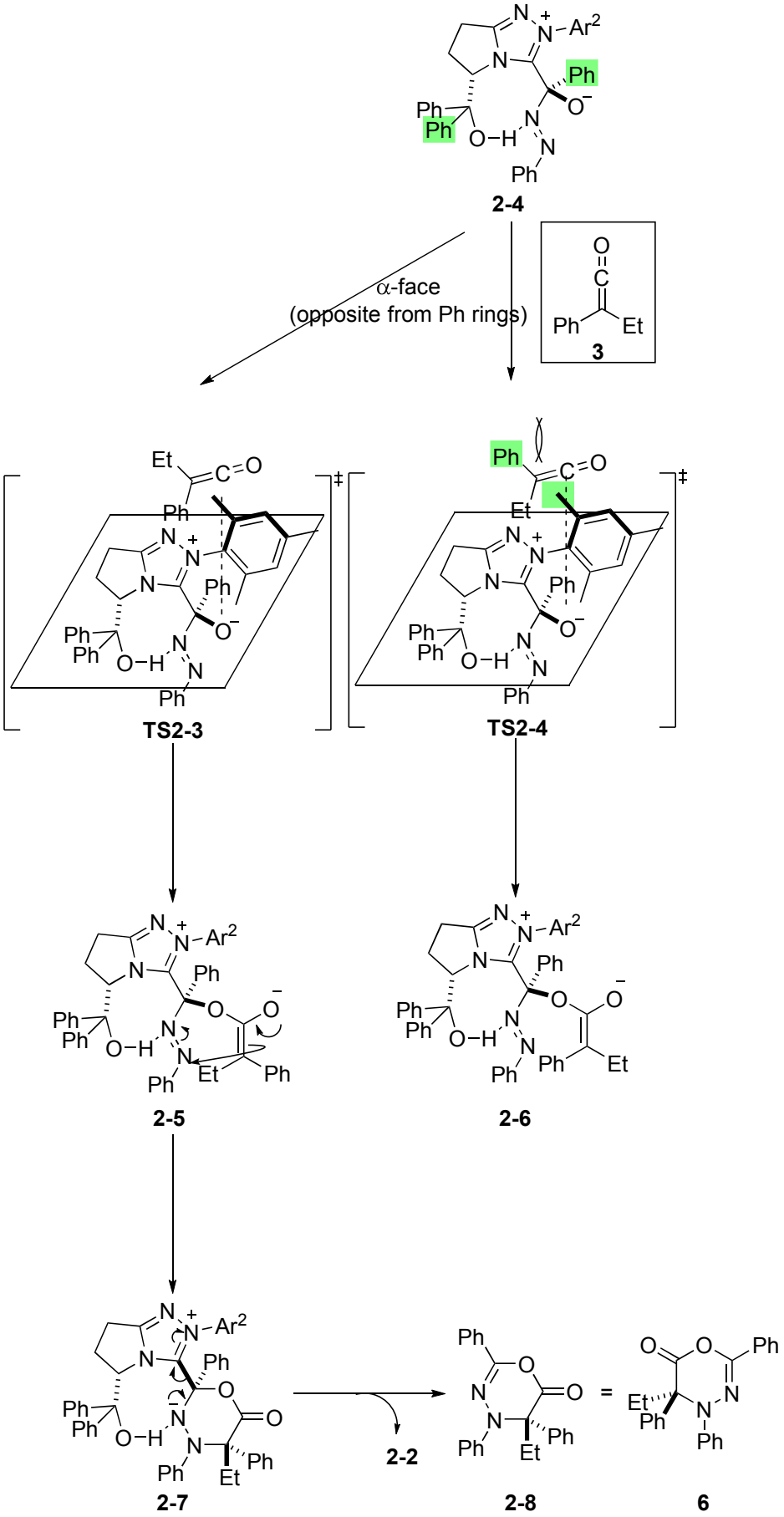
cat 2-1: Ar^1 = Ph (purple, X-ray structure)

cat A: Ar^1 = 2-naphtyl (yellow, computational structure)

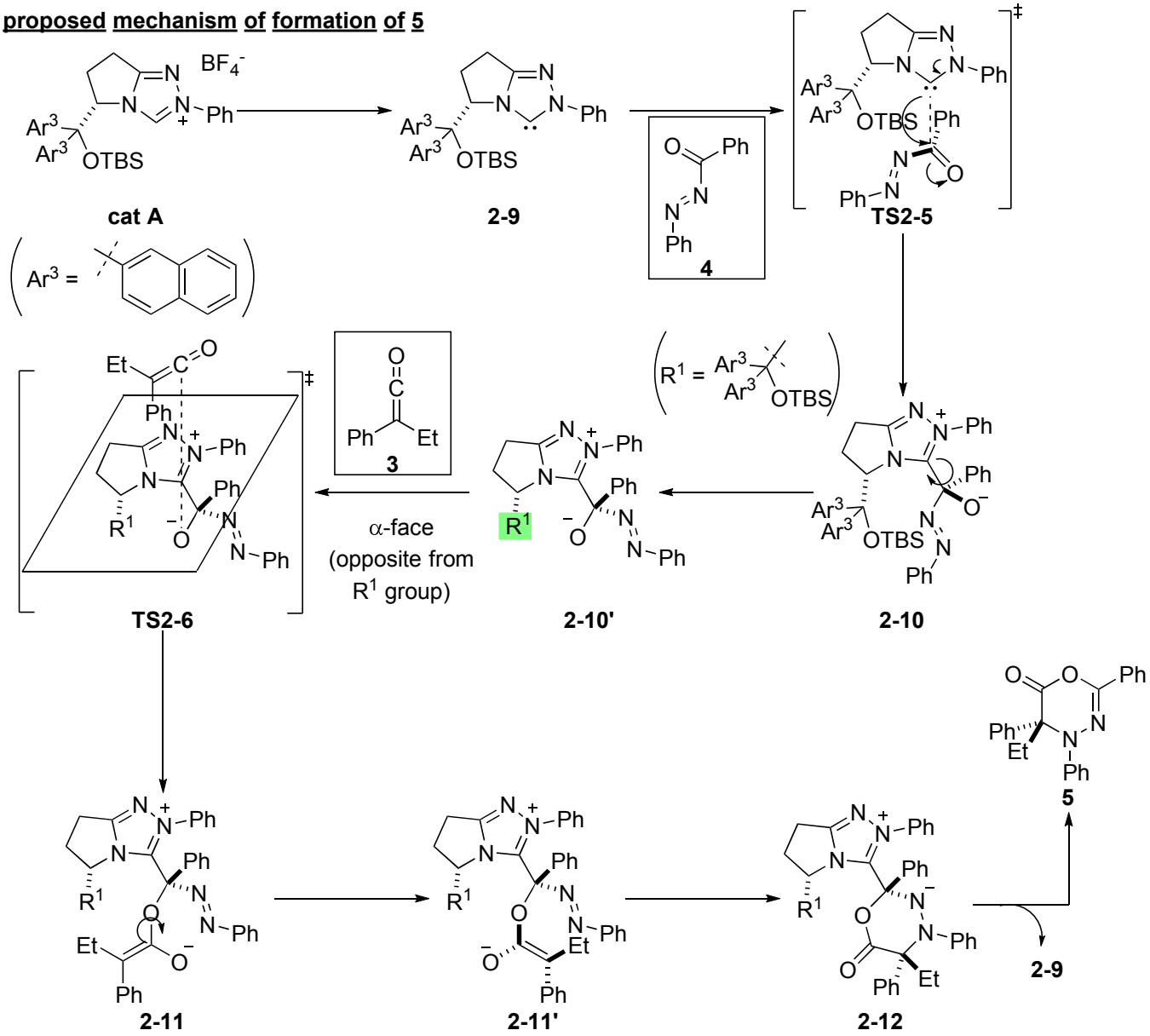


proposed mechanism of formation of 6

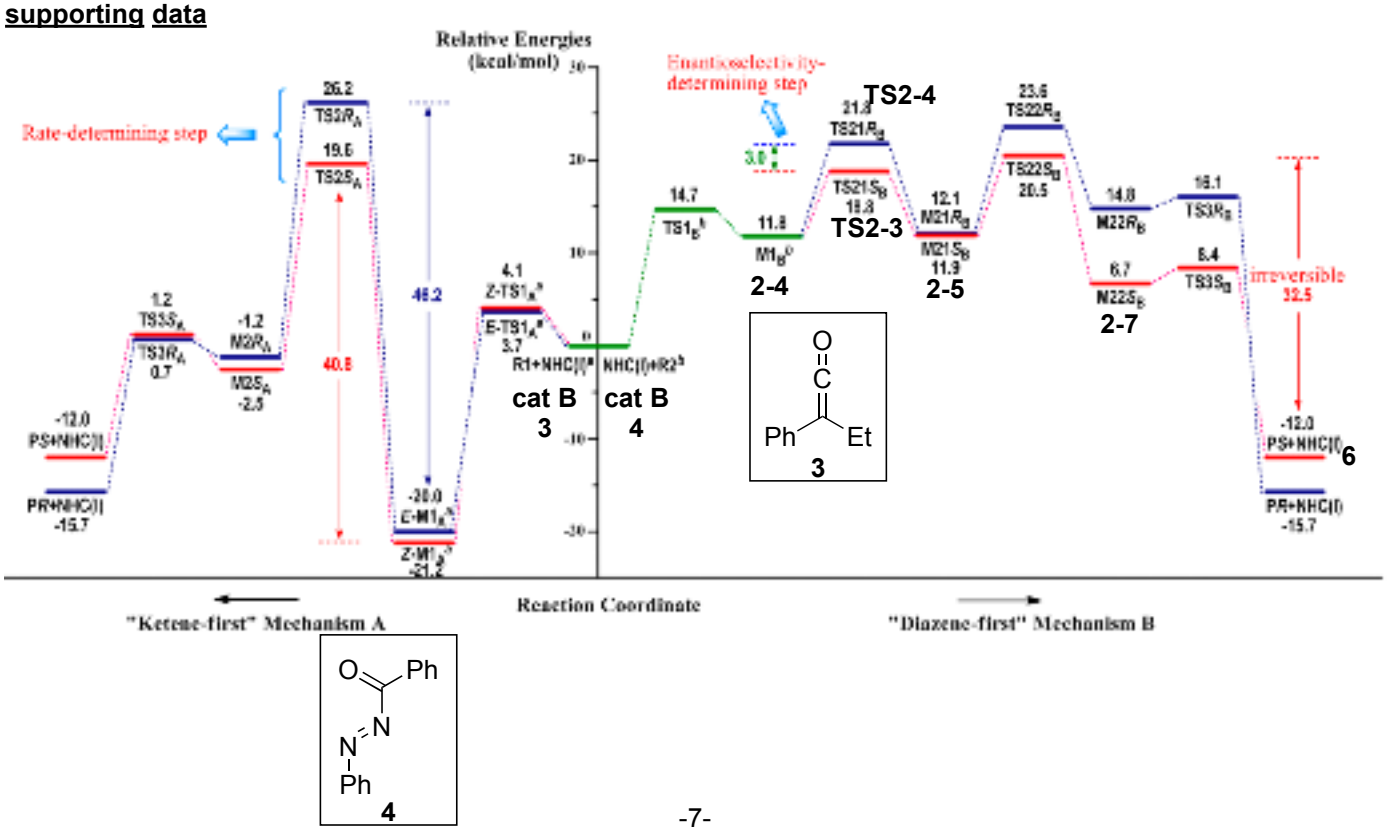


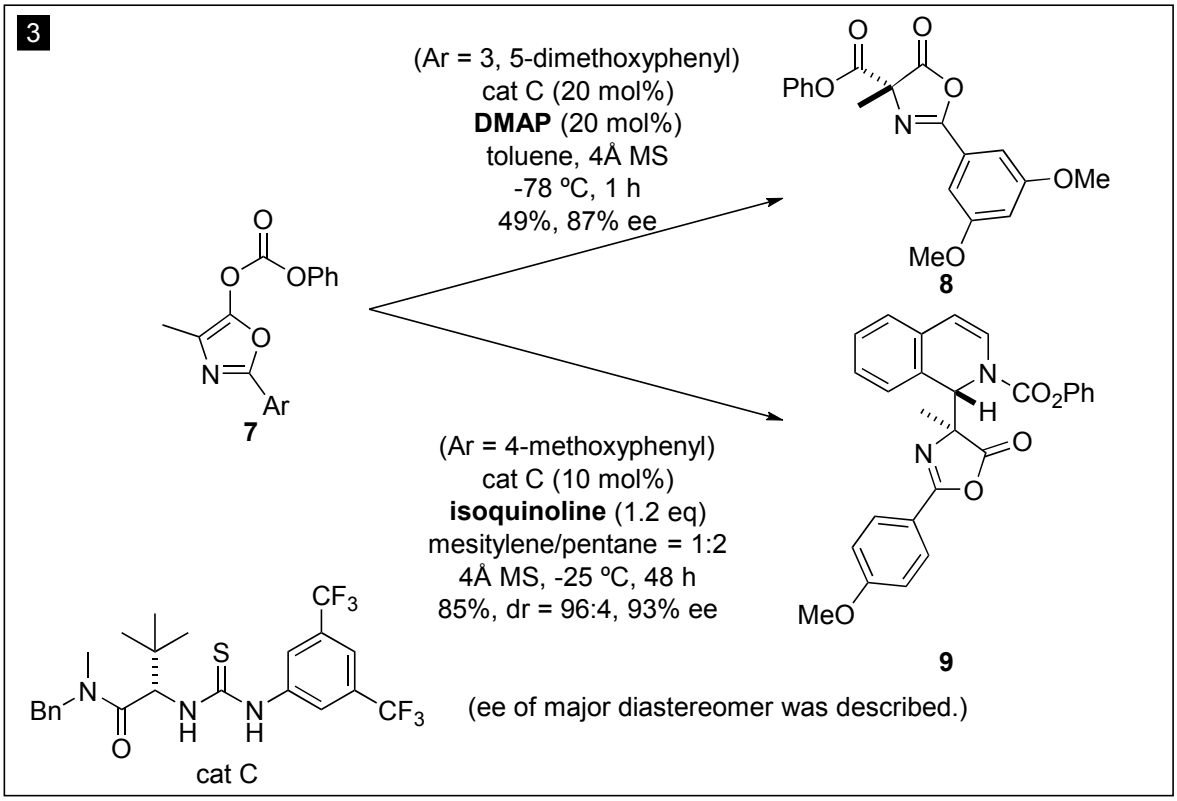

2-4
α-face
(opposite from Ph rings)
3
TS2-3
TS2-4
2-5
2-6
2-7
2-2
2-8
6

proposed mechanism of formation of 5



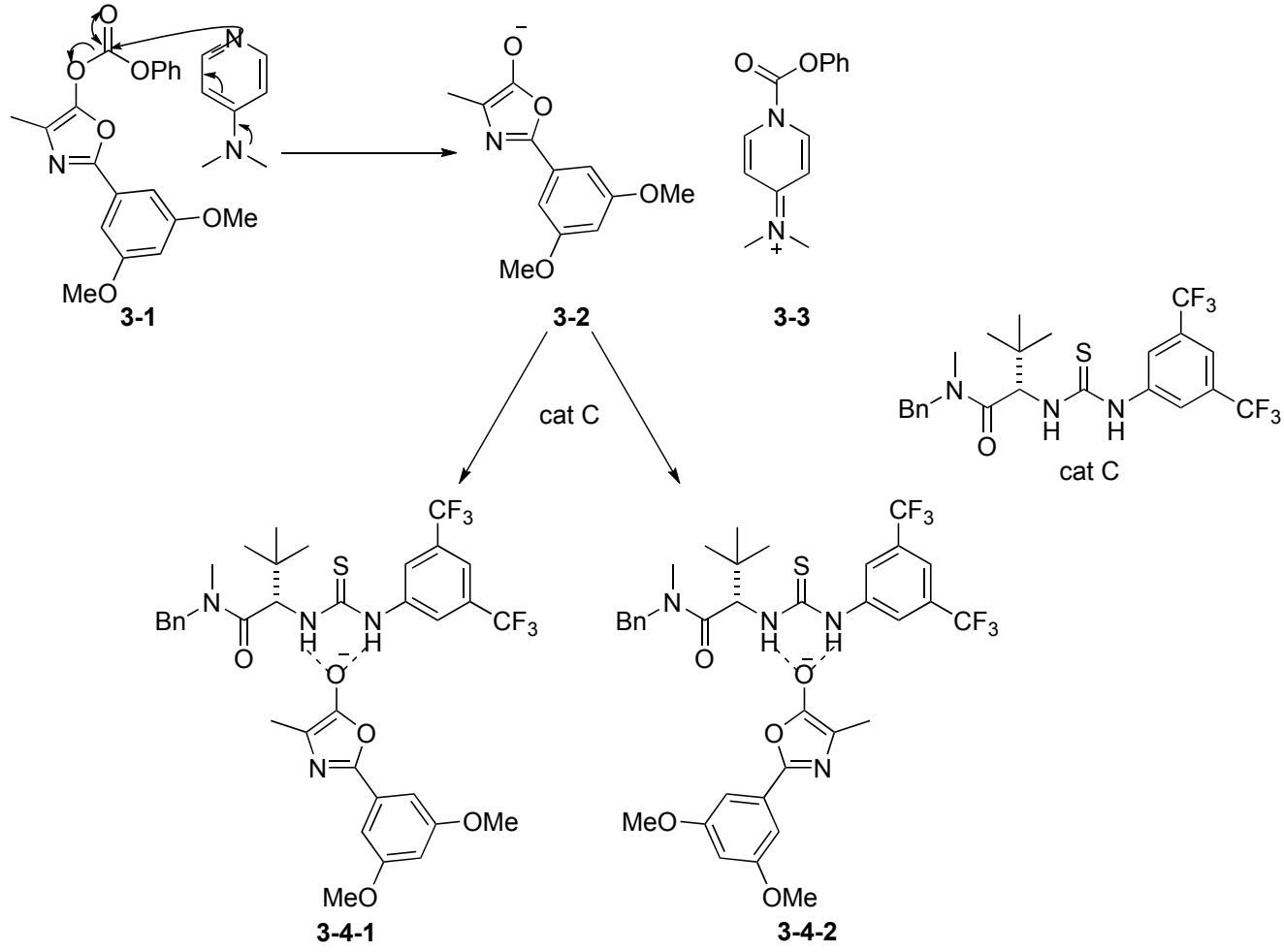
supporting data



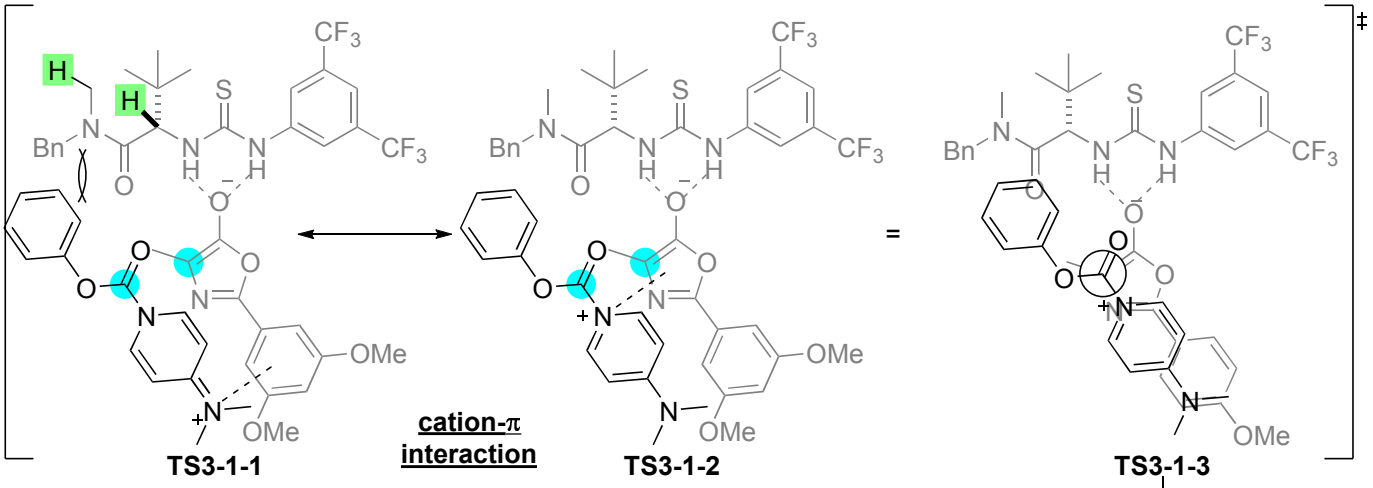


De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802.

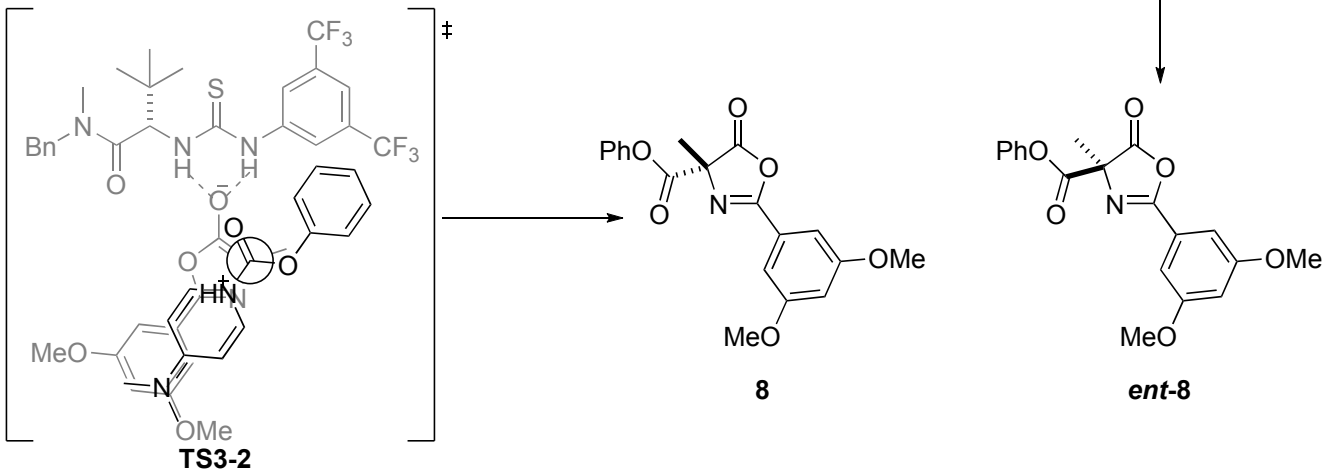
proposed mechanism of formation of 8



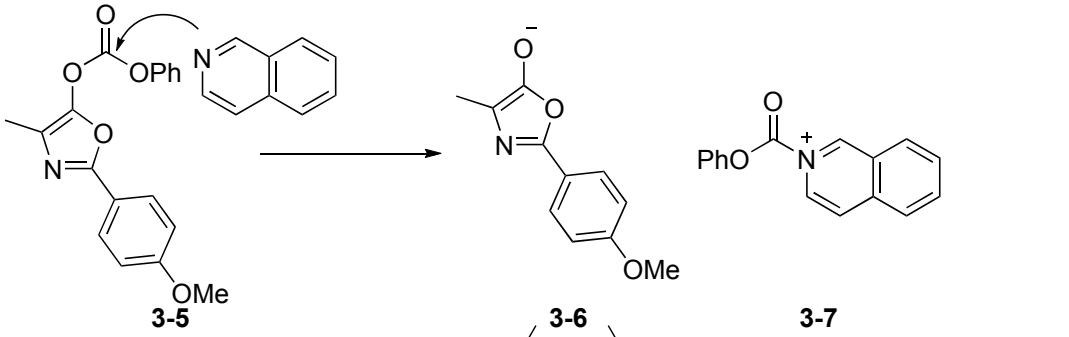
(1) **3-4-1** and **3-3**: **3-3** from α face (opposite from *t*-Bu)



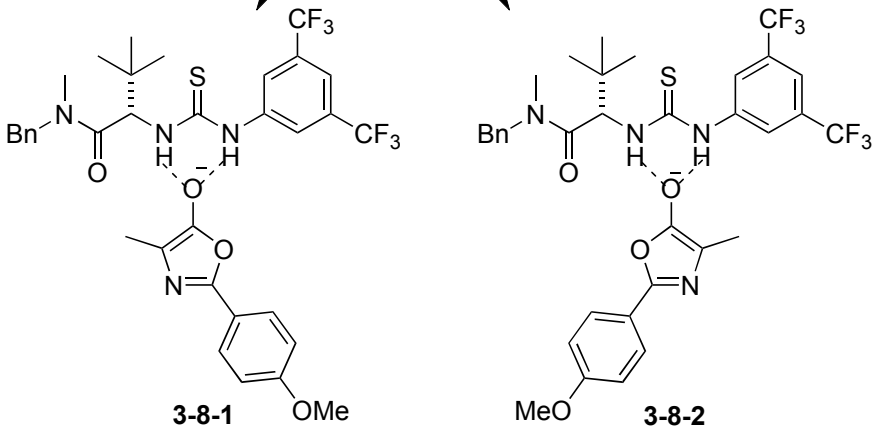
(2) **3-4-2** and **3-3**: **3-3** from α face (opposite from *t*-Bu)



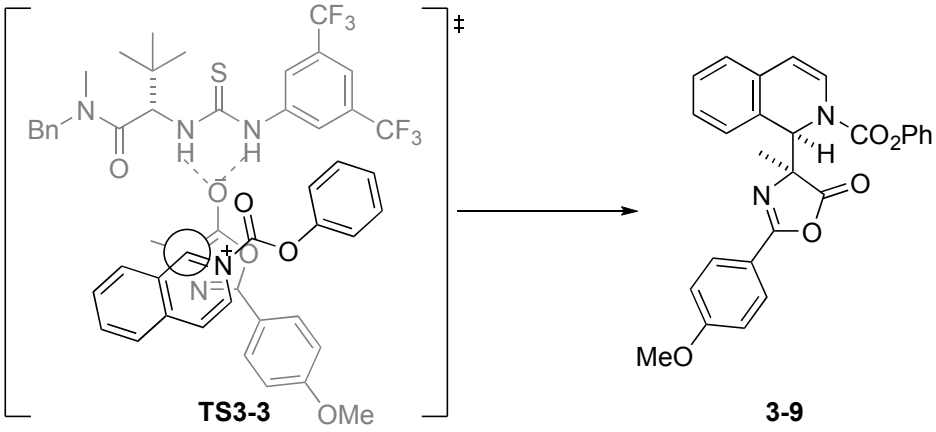
proposed mechanism of formation of 9



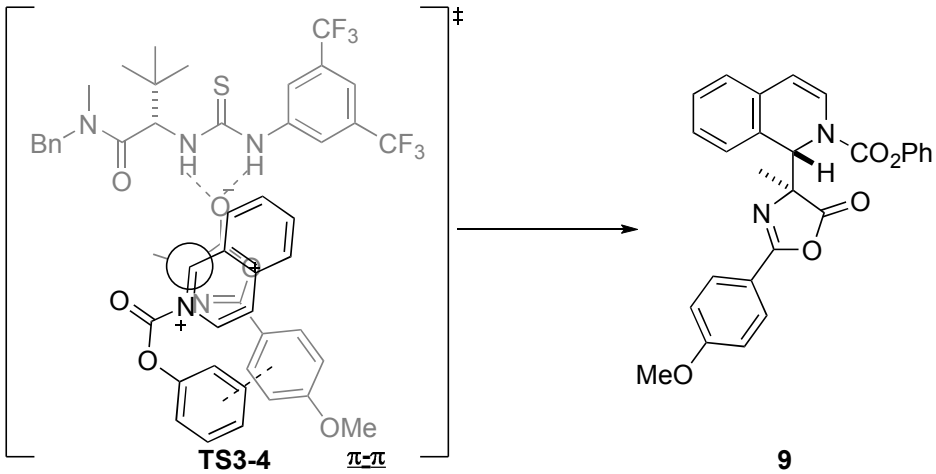
cat C



(1) **3-8-1** and **3-7**: **3-7** from α face (opposite from *t*-Bu)

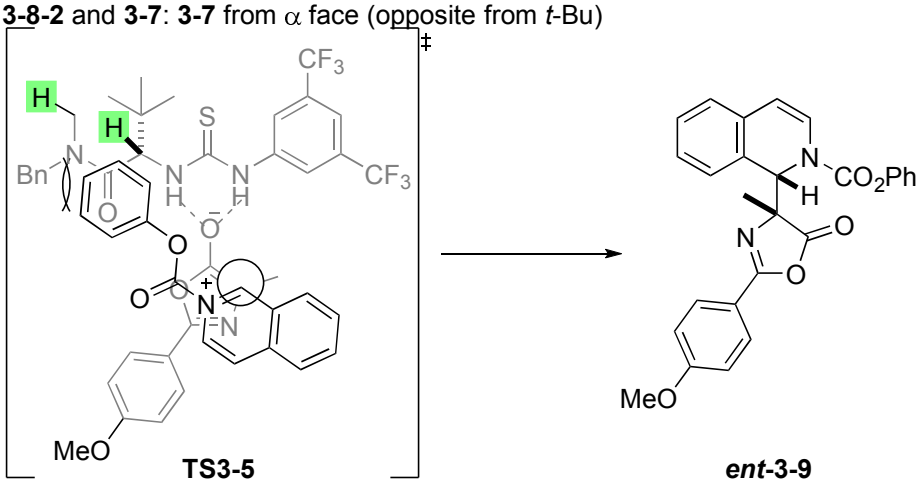


TS3-3 **3-9**

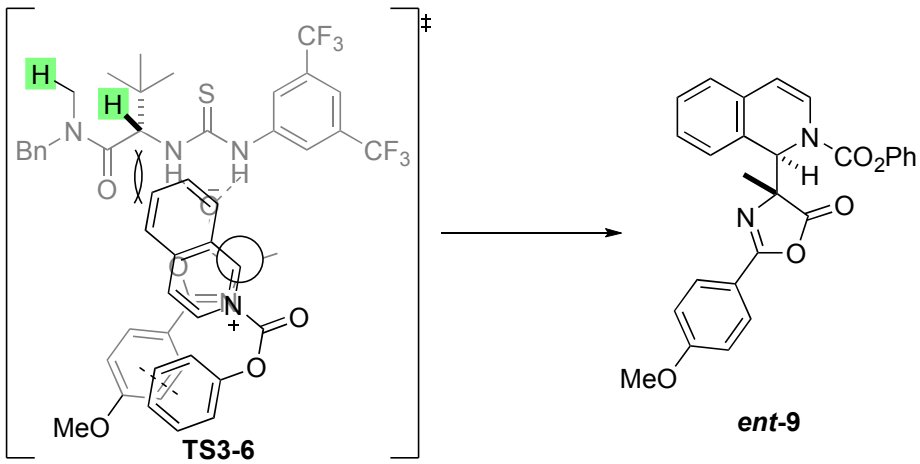


TS3-4 **π-π interaction** **9**

(2) **3-8-2** and **3-7**: **3-7** from α face (opposite from *t*-Bu)



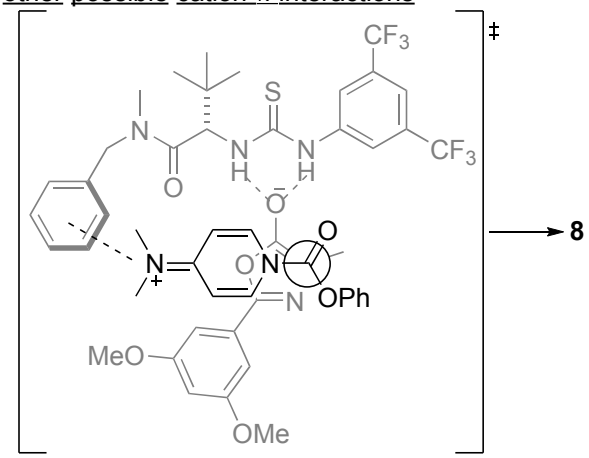
TS3-5 ***ent*-3-9**



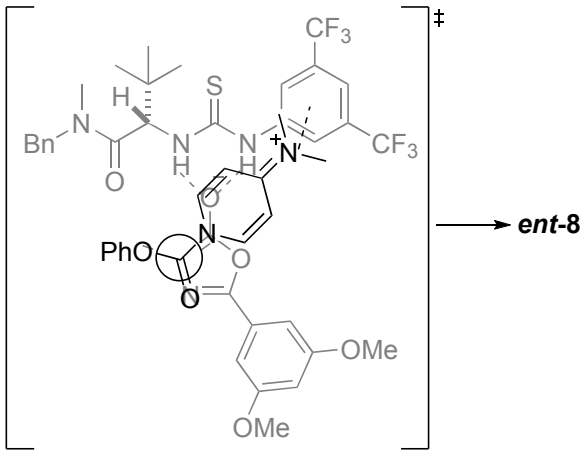
TS3-6 ***ent*-9**

supporting data

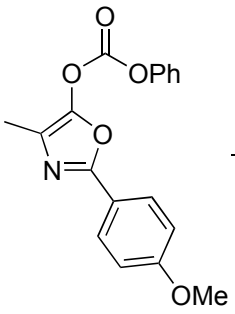
other possible cation-π interactions



TS3-7 → **8**



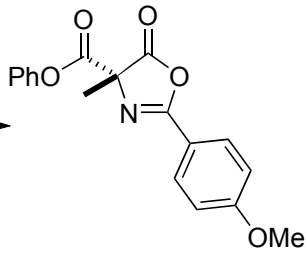
TS3-8 → ***ent*-8**



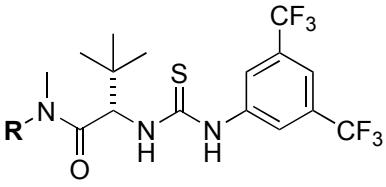
3-5

cat (20 mol%)
DMAP (20 mol%)
toluene, 4Å MS
-78 ºC, 4 h

cat C (R = **Bn**): 72%, 79% ee
cat D (R =**Me**): 52%, 55%ee

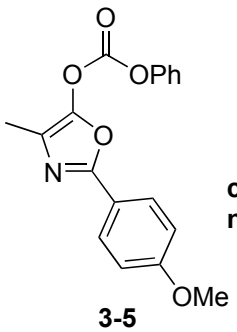


8



cat C (**R** =Bn)
cat D (**R** =Me)

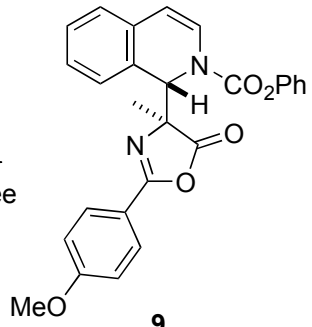
background rate (π-π interactions)



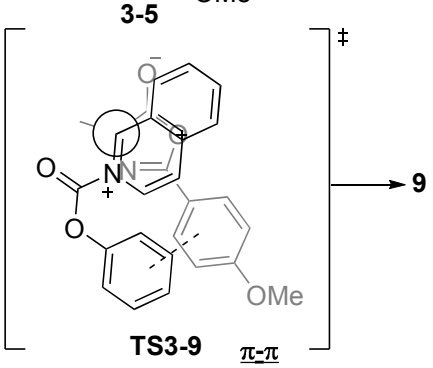
3-5

cat (10 mol%)
isoquinoline (1.2 eq)
mesitylene
4Å MS, -10 ºC

cat C: 3 h, 88%, dr = 88:12, 73% ee
none: 11.5 h, 95%, dr = 64:36

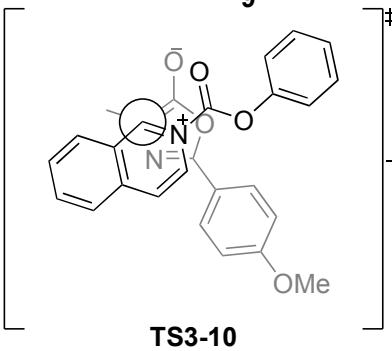


9



TS3-9 → **9**

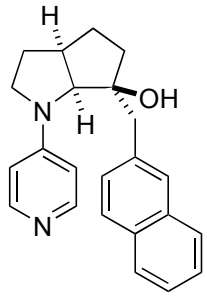
π-π interaction



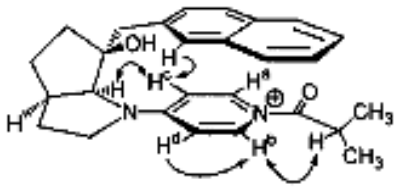
TS3-10 → **3-9 (diastereomer of 9)**

cation-π interactions (intramolecular)

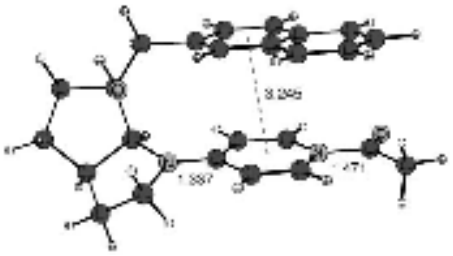
kinetic resolution of racemic alcohols



3-10



NOE

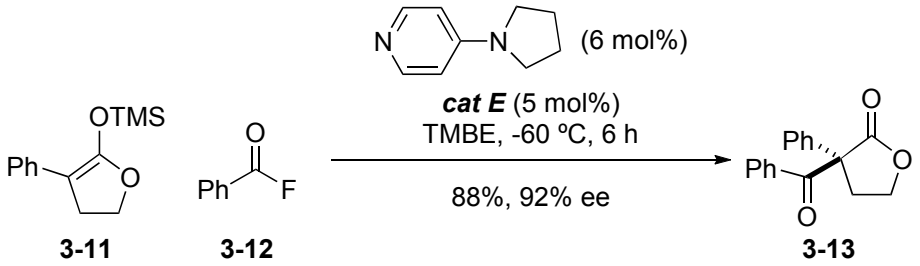


computational study

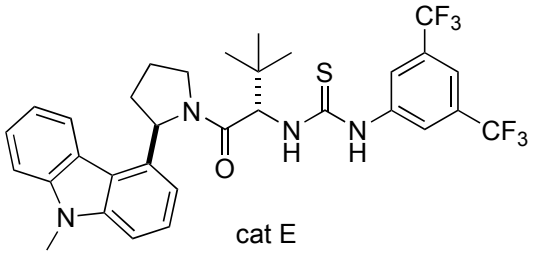
Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.
Wei, Y.; Held, I.; Zipse, H. *Org. Biomol. Chem.* **2006**, *4*, 4223.

cation-π interactions (intermolecular)

Enantioselective acylation of silyl ketene acetals



3-11 **3-12** **3-13**



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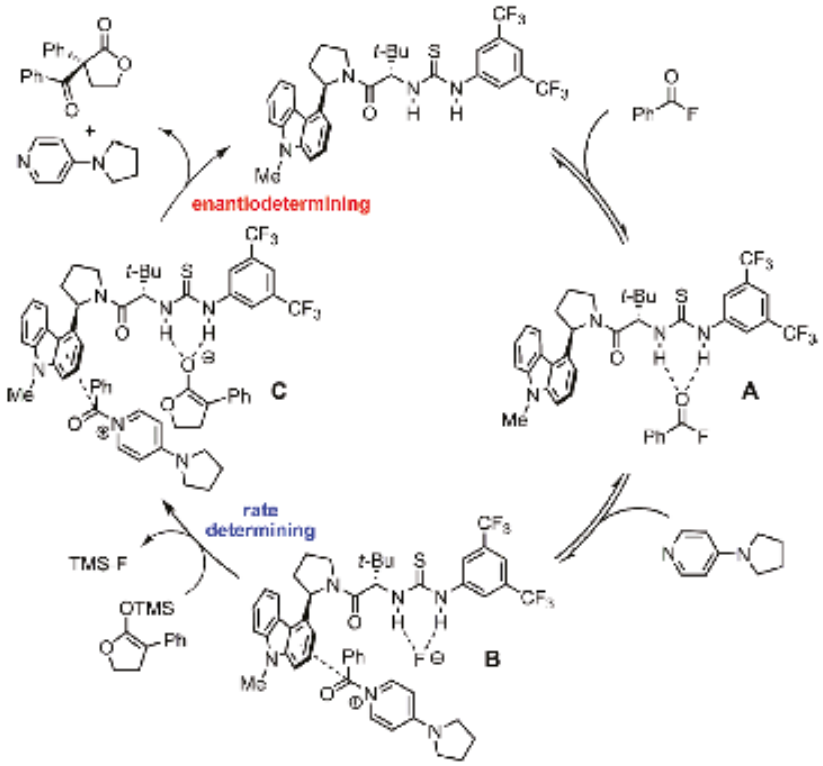

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