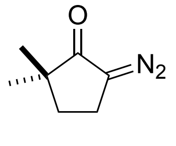
Problem Session (3)

2020.5.9 Toshiya Nagai

Please explain each reaction mechanism and stereoselectivity.

(1)

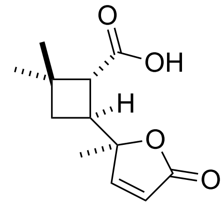


1-1

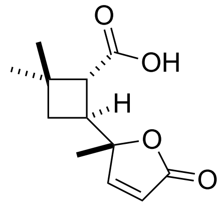
1. **A** (3 eq.), **B** (10 mol%), hν (254 nm)
   THF, rt, 62% (79% ee)
2. **C** (2 eq.), $Pd(OAc)_2$ (7.5 mol%), Ag_2CO_3 (1 eq.)
   t-BuOMe, 70 °C, 90%
3. NaOH (15 eq.), EtOH, 130 °C, 96%
4. $NaClO_2$ (3 eq.), NaH_2PO_4•H_2O (1.5 eq.)
   t-BuOH/H_2O (5:1), rt, 65%

5-1*. $TiCl_4$ (6 eq.), MeLi (24 eq.)
CH_2Cl_2, –78 °C, 60% (<u>**1-2**:***epi*-1-2** = 9:1</u>)

5-2*. (*i*-PrO)$_3$TiCl (6 eq.), MeLi (6 eq.)
THF, –78 to 23 °C, 76% (<u>**1-2**:***epi*-1-2** = 1:22</u>)



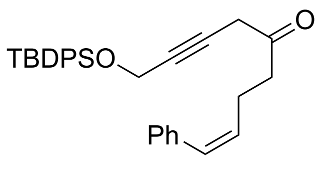
1-2



***epi*-1-2**

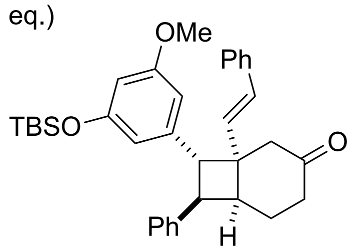
*$TiMe_4$ or (*i*-PrO)$_3$TiMe is formed firstly.
Please explain the reversed diastereoselectivity with these conditions.

(2)

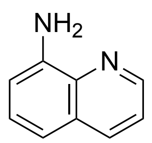


2-1

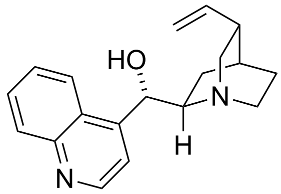
1. **D** (10 mol%), CH_2Cl_2, 0 °C;
   $Bi(OTf)_3$ (20 mol%), $MeNO_2$, 0 °C to rt
   65% (dr = >20:1, 92% ee)
2. **E** (1.2 eq.), $[Rh(COD)Cl]_2$ (2.5 mol%), LiOH•H_2O (3 eq.)
   1,4-dioxane/H_2O (10:1), 60 °C
3. TBAF (1.2 eq.), THF, 0 °C to rt
   73% (2 steps, dr = >20:1)
4. DMP (1.3 eq.), CH_2Cl_2, 0 °C to rt
5. $NaClO_2$ (5 eq.), NaH_2PO_4•H_2O (5 eq.)
   2-methyl-2-butene/*t*-BuOH/H_2O (2:10:5), 0 °C to rt
6. TCNHPI (1.1 eq.), DCC (1.2 eq.), DMAP (10 mol%)
   CH_2Cl_2, 0 °C to rt, 72% (3 steps)
7. $NiCl_2$•DME (40 mol%), BPhen (80 mol%), **F** (3 eq.)
   DMF/THF (2:3), rt, 40% (dr = >20:1)



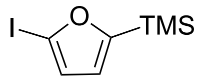
2-2



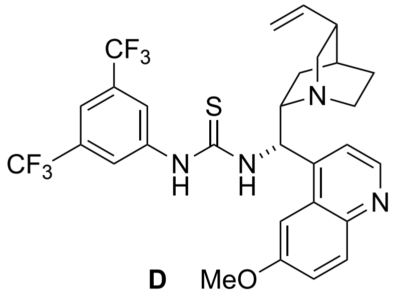
A



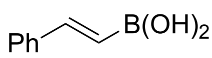
B



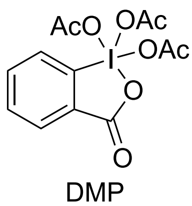
C



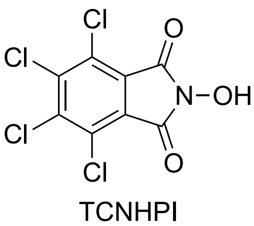
D



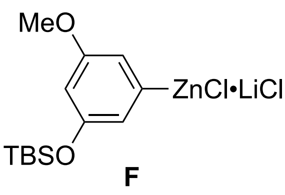
E



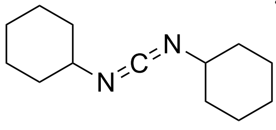
DMP



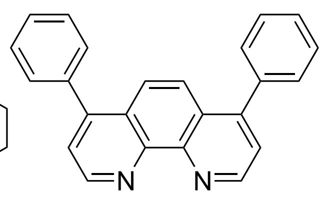
TCNHPI



F



DCC

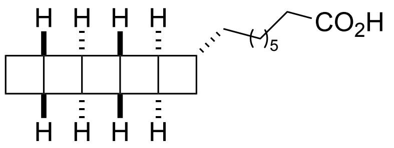


BPhen

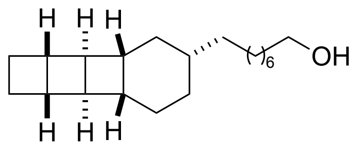
Problem session (3)- Answer

2020.5.9 Toshiya Nagai

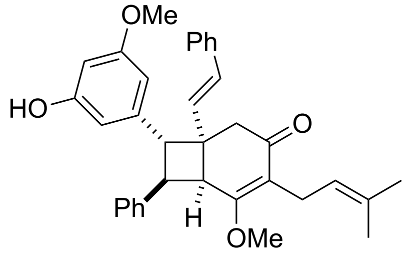
Topic: Enantioselective total syntheses of cyclobutane-containing natural products
(for construction of bridged cyclobutane, see: 160910_PS_Masanori_NAGATOMO)



[5]-ladderanoic acid*
(Corey[1]), Burns[2]))

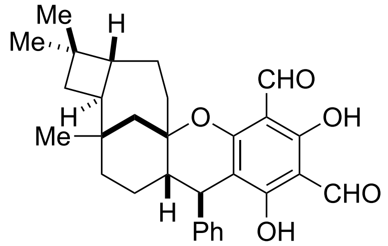


[3]-ladderanol*
(Burns[2]), Brown[3]))

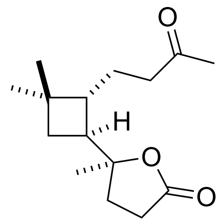


cajanusine
(Brown[4]), **problem 2**)

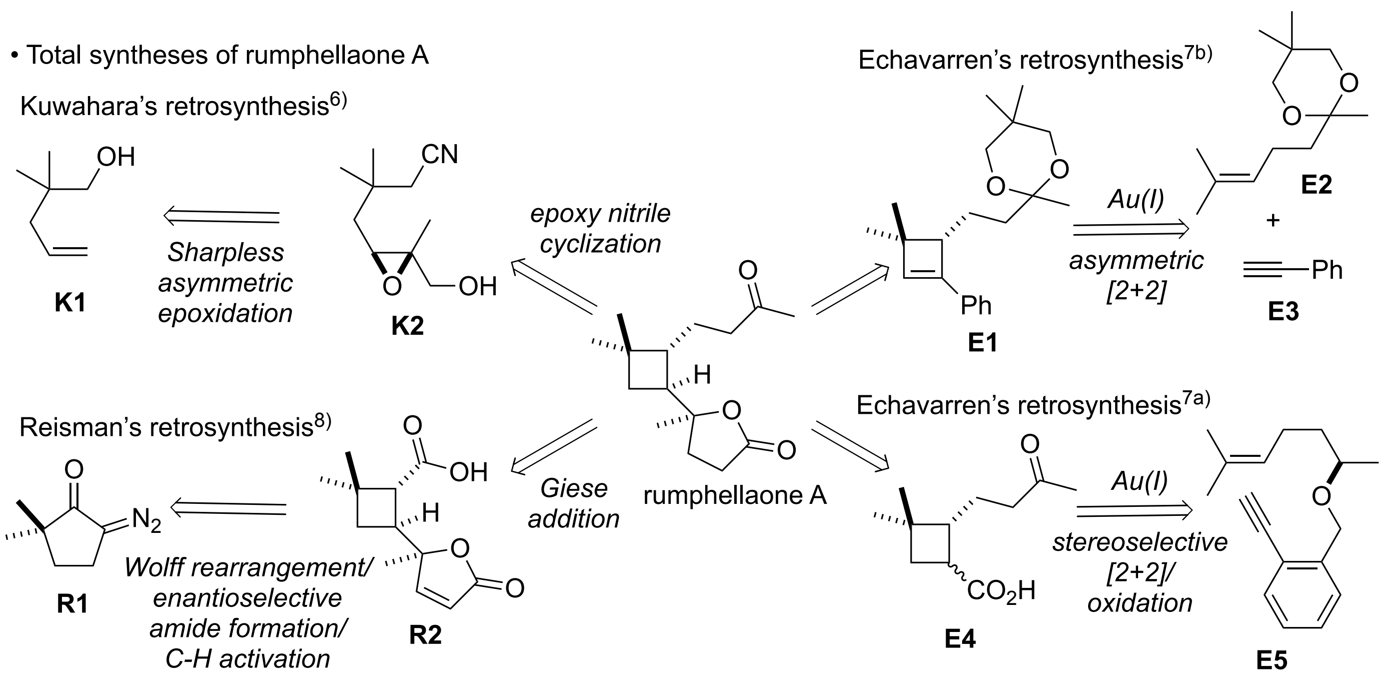
*a partial structure of ladderane phospholipid



psiguadial B
(Reisman[5]))

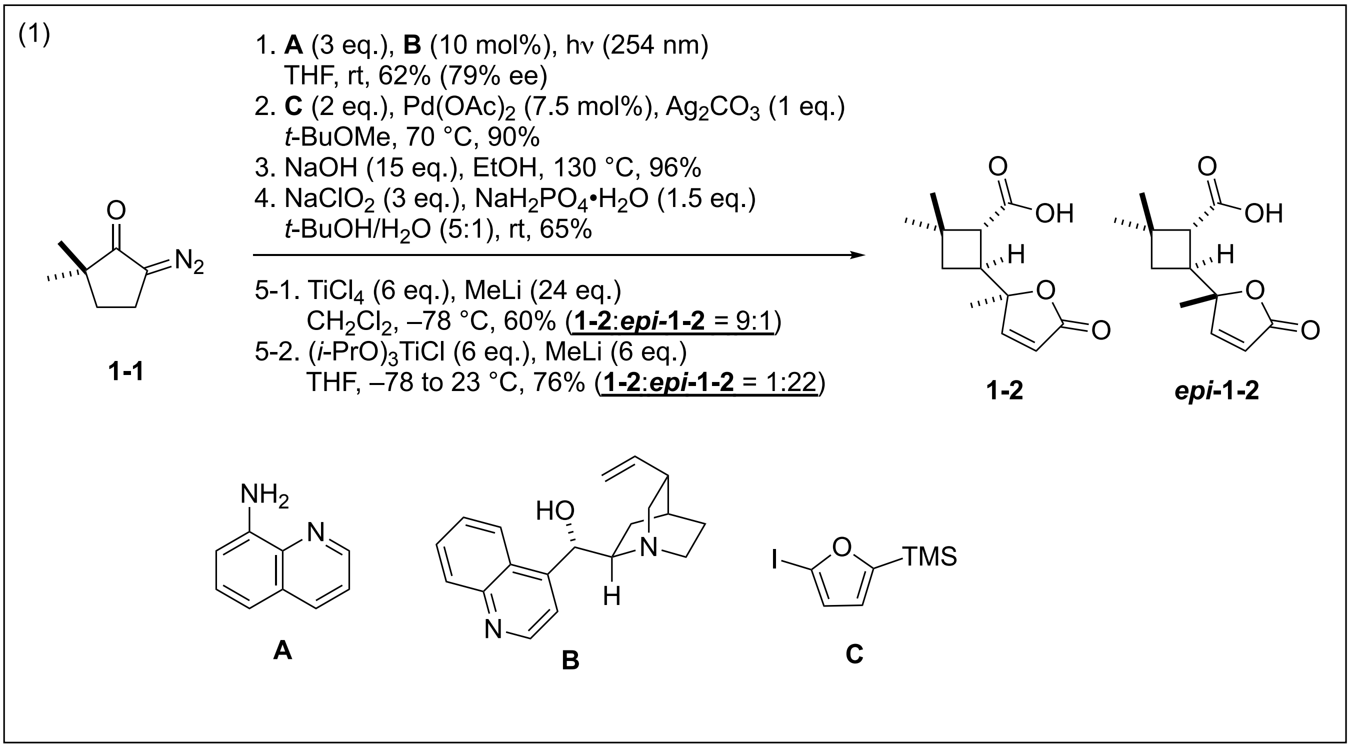


rumphellaone A
(Kuwahara[6]), Echavarren[7]), Reisman[8]))

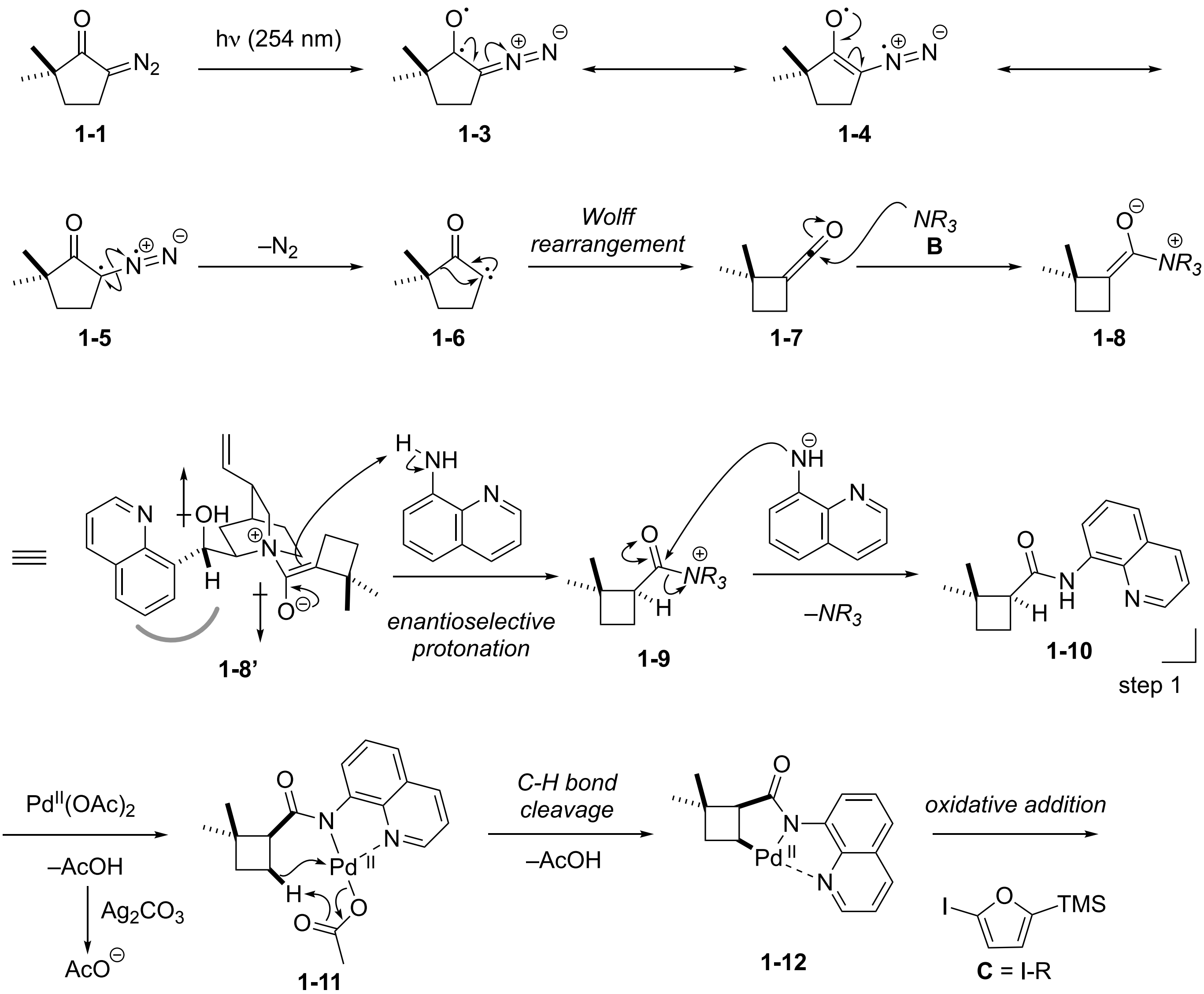


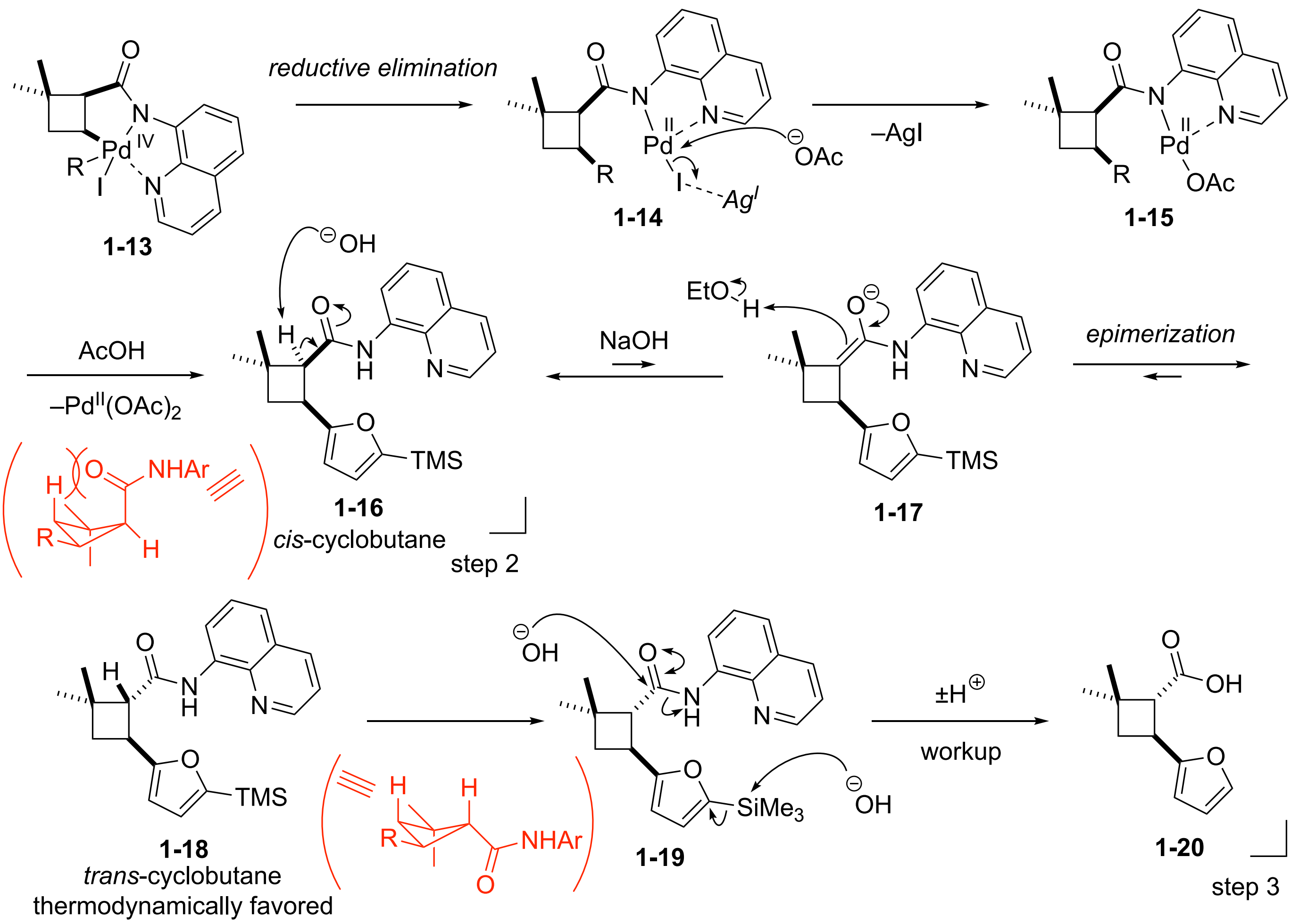
Reference

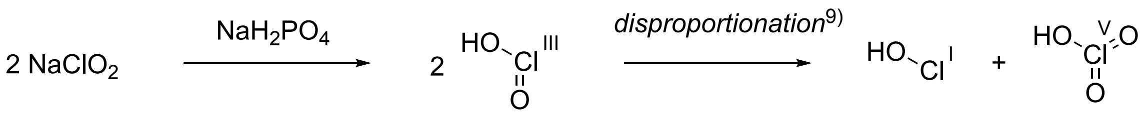
1. (a) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 15664.
   (b) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118.
2. Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R.; Smith, M. D.; Vahala, R.; Gonzalez, M. A.; Boxer, S. G.; Burns, N. Z. *J. Am. Chem. Soc.* **2016**, *138*, 15845.
3. Line, N. J.; Witherspoon, B. P.; Hancock, E. N.; Brown, M. K. *J. Am. Chem. Soc.* **2017**, *139*, 14392.
4. Guo, R.; Witherspoon, B. P.; Brown, M. K. *J. Am. Chem. Soc.* **2020**, *142*, 5002.
5. (a) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc.* **2016**, *138*, 9803.
   (b) Chapman, L. M.; Beck, J. C.; Lacker, C. R.; Wu, L.; Reisman, S. E. *J. Org, Chem.* **2018**, *83*, 6066.
6. (a) Hirokawa, T.; Nagasawa, T.; Kuwahara, S. *Tetrahedron Lett.* **2012**, *53*, 705.
   (b) Hirokawa, T.; Kuwahara, S. *Tetrahedron* **2012**, *68*, 4581.
7. (a) Ranieri, B.; Obradors, C.; Mato, M. Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614.
   (b) Garcia-Morales, C.; Ranieri. B.; Escofet, I.; López-Suarez, L.; Obradors, C.; Konovalov, A. I.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 13628.
8. Beck, J. C.; Lacker, C. R.; Chapman, L. M.; Reisman, S. E. *Chem. Sci.* **2019**, *10*, 2315.

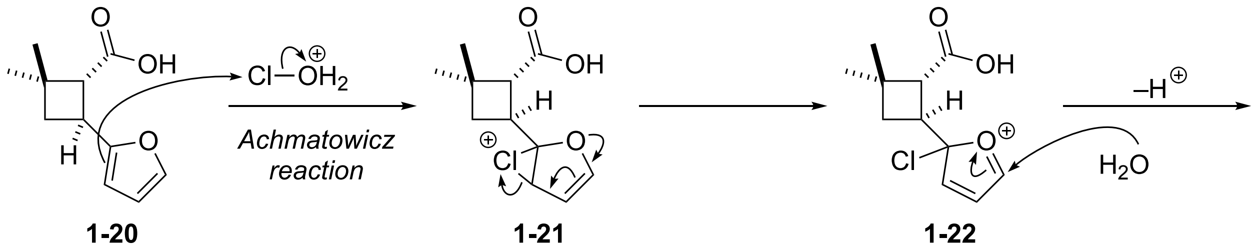

(1)
1. A (3 eq.), B (10 mol%), hν (254 nm)
THF, rt, 62% (79% ee)
2. C (2 eq.), Pd(OAc)2 (7.5 mol%), Ag2CO3 (1 eq.)
t-BuOMe, 70 °C, 90%
3. NaOH (15 eq.), EtOH, 130 °C, 96%
4. NaClO2 (3 eq.), NaH2PO4•H2O (1.5 eq.)
t-BuOH/H2O (5:1), rt, 65%
5-1. TiCl4 (6 eq.), MeLi (24 eq.)
CH2Cl2, –78 °C, 60% (1-2:epi-1-2 = 9:1)
5-2. (i-PrO)3TiCl (6 eq.), MeLi (6 eq.)
THF, –78 to 23 °C, 76% (1-2:epi-1-2 = 1:22)
1-1
1-2
epi-1-2
A
B
C
TMS

Answer

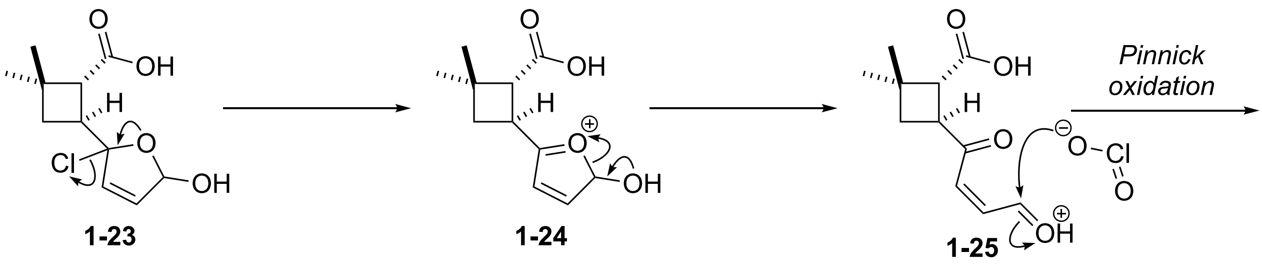

hν (254 nm)
1-1
1-3
1-4
1-5
–N2
1-6
Wolff rearrangement
1-7
NR3
B
1-8
1-8'
enantioselective protonation
1-9
–NR3
1-10
step 1
Pd^{II}(OAc)2
–AcOH
Ag2CO3
AcO⊖
1-11
C-H bond cleavage
–AcOH
1-12
oxidative addition
TMS
C = I-R

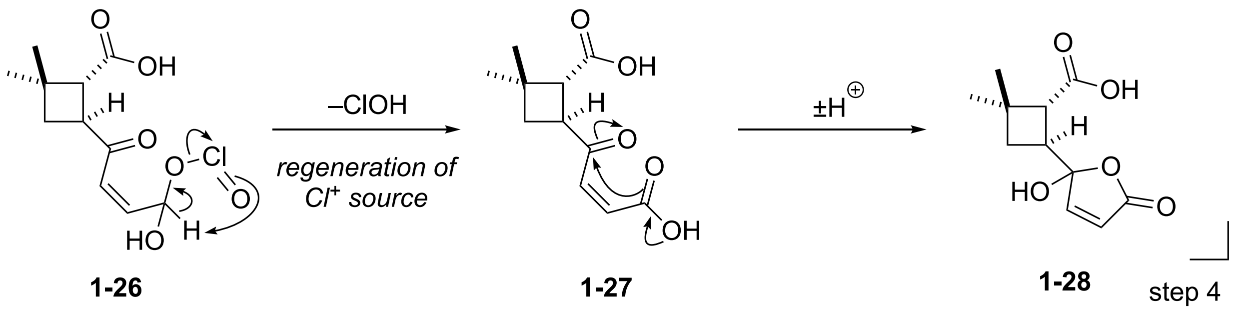






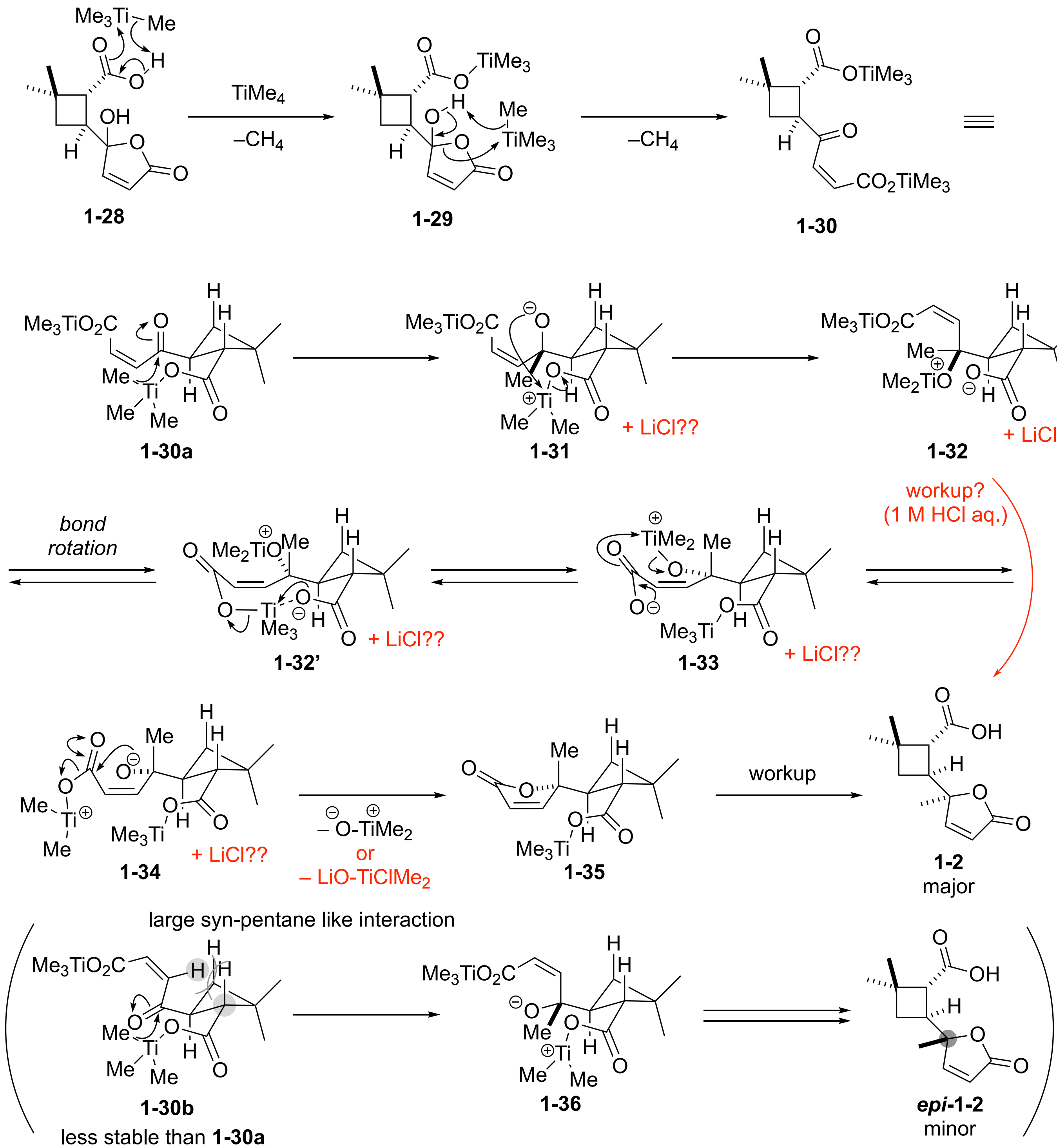
• Clive et al.[10] reported that $NaClO_2$-mediated Achmatowicz-type reaction was inhibited by the addition of scavenger (1,3-dihydroxybenzene) for HOCl. Therefore, HOCl should be generated firstly.



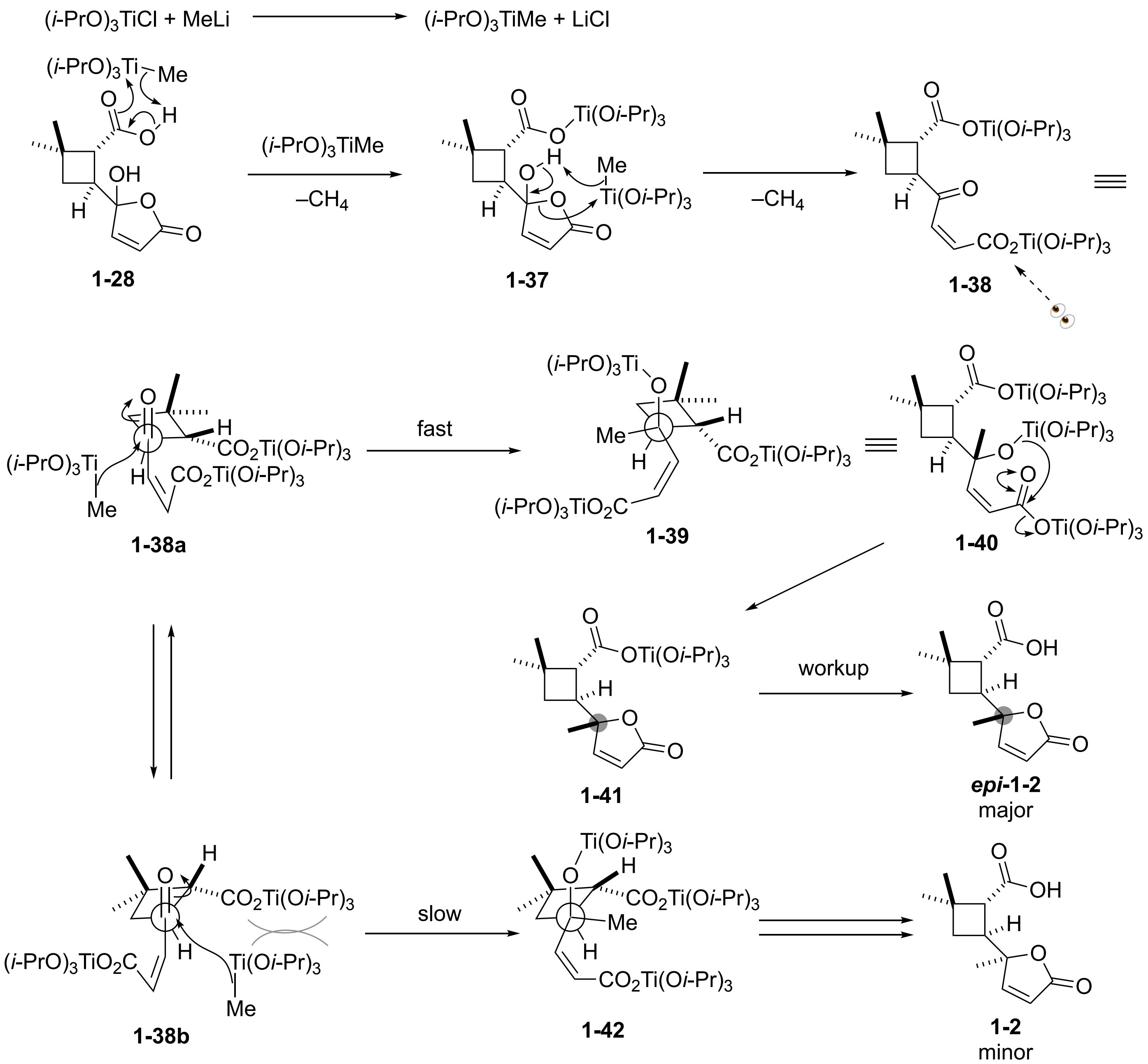


step 5-1

$TiCl_4 + 4MeLi \longrightarrow TiMe_4 + 4LiCl$

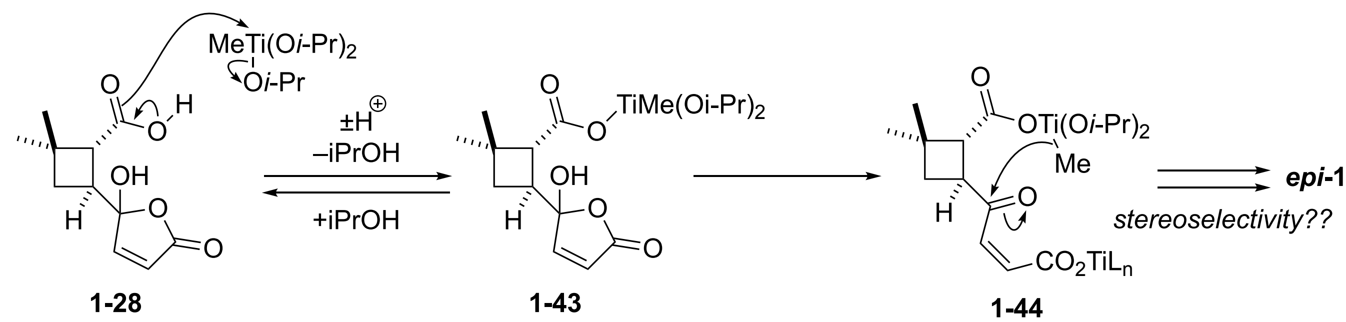


step 5-2

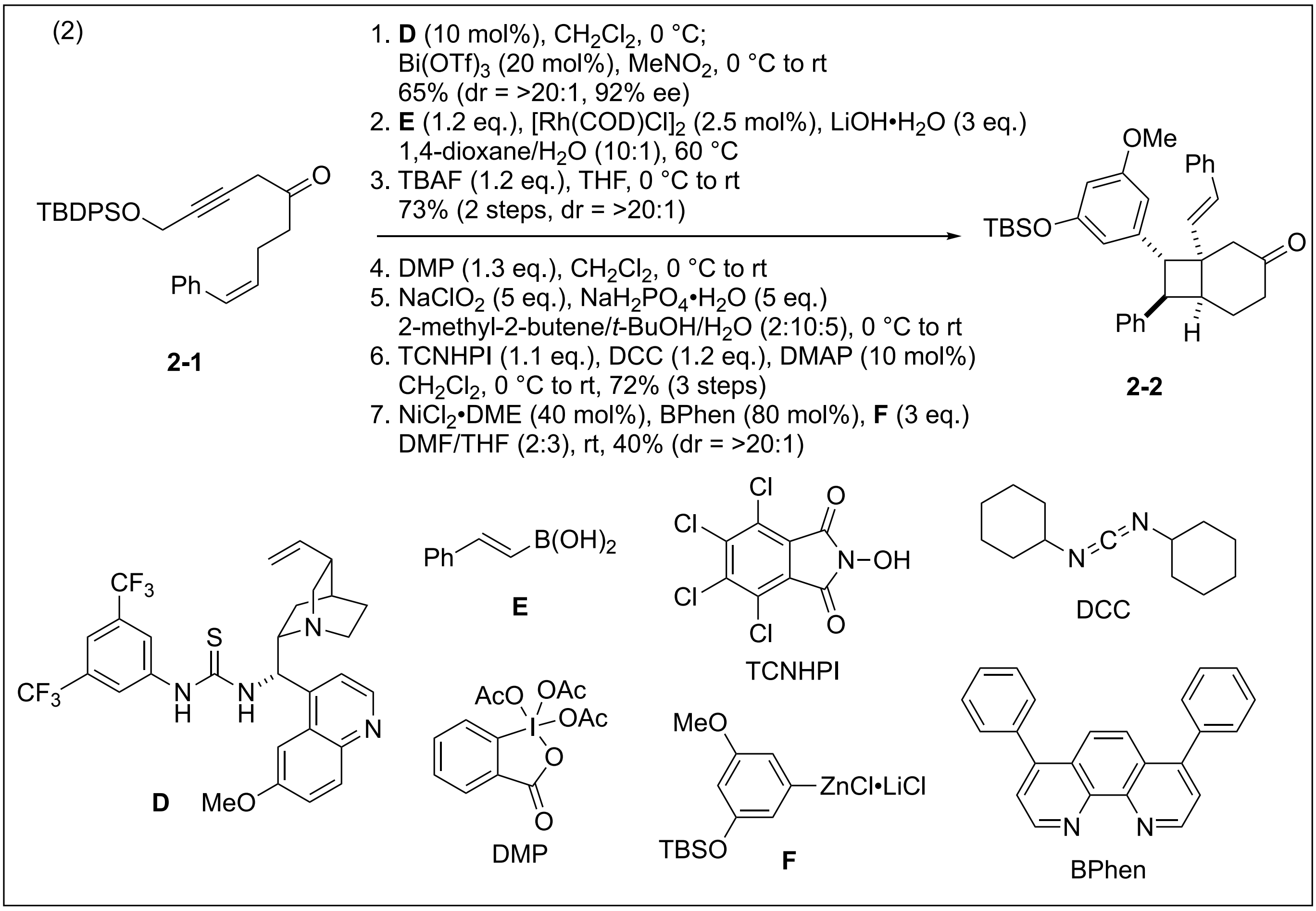


Discussion-1 (another reaction pathway in step 5-2)

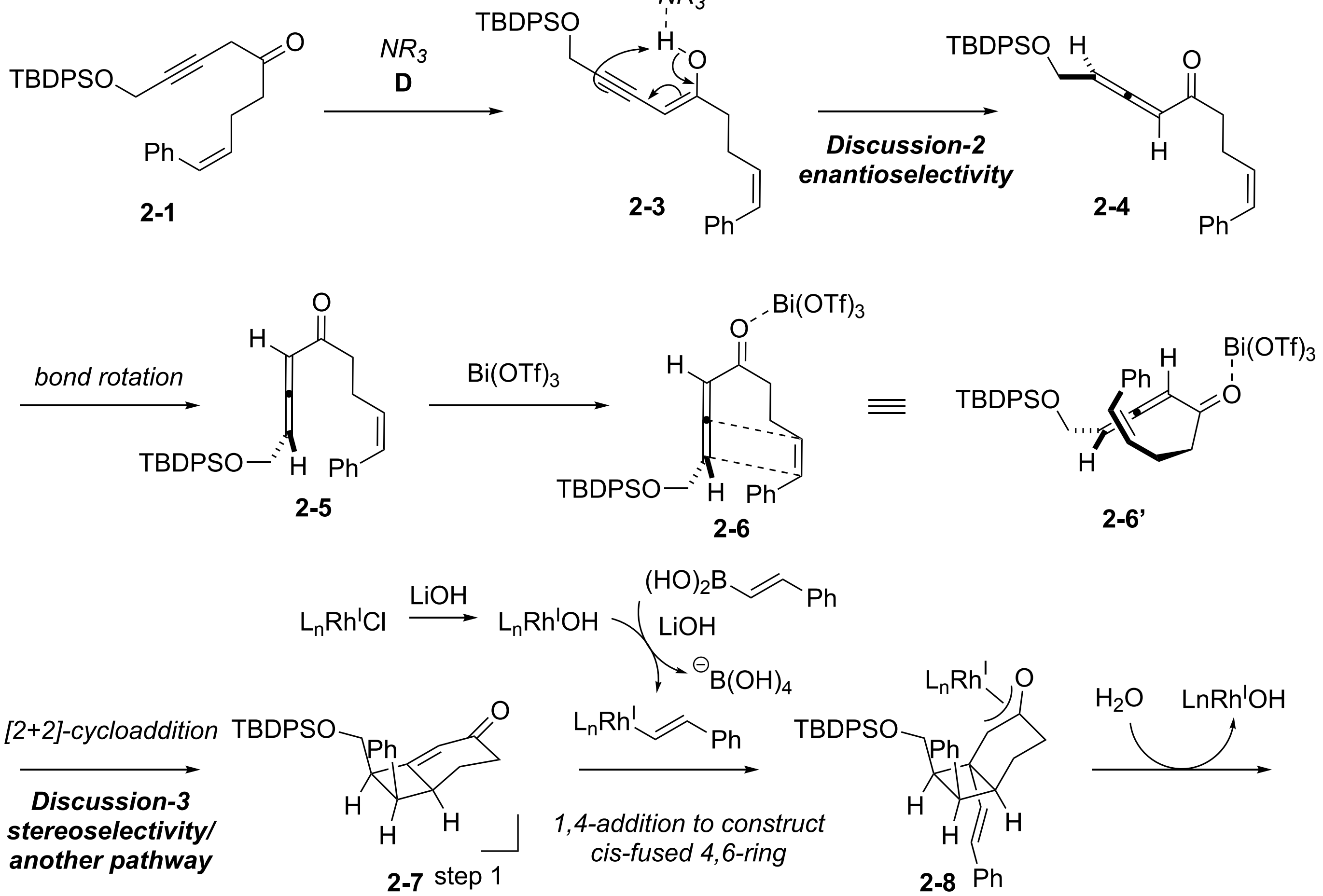
The author proposed that ***epi*-1-2** was formed by ligand exchange of the carboxylic acid of **1-28** with $(iPrO)_3TiMe$ followed by intramolecular delivery of the methyl group. ($TiMe_4$: intermolecular addition)

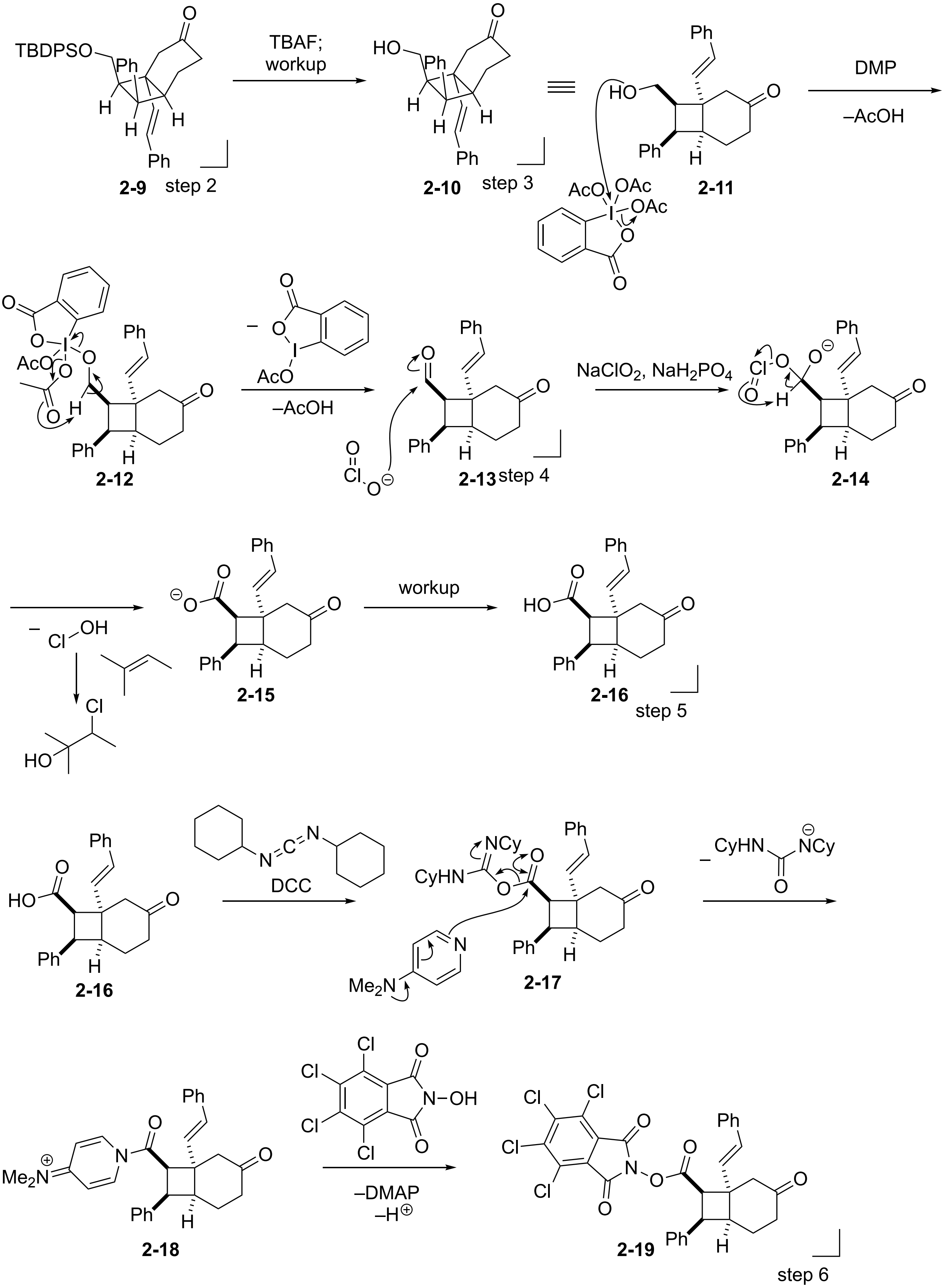


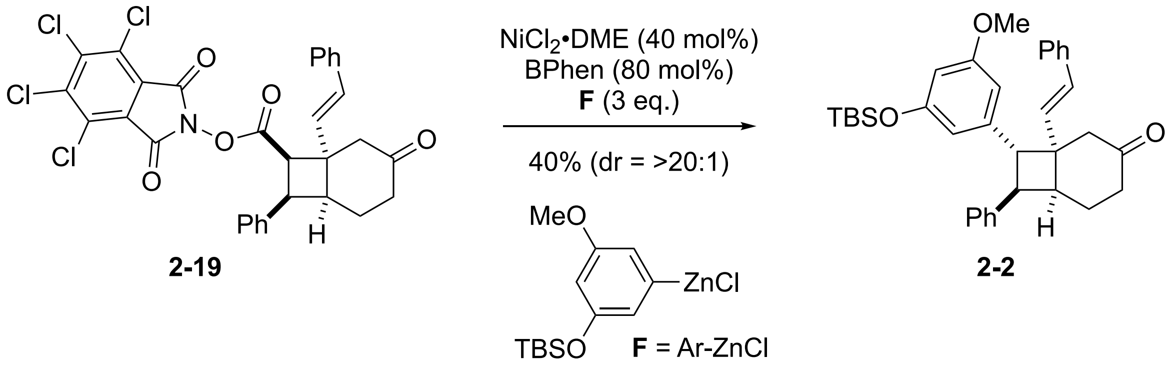
The ligand exchange to generate **1-43** would be revesible.
The reaction between carboxylic acid **1-28** and $(i\text{-PrO})_3TiMe$ should give $(i\text{-PrO})_3TiOCOR$ with release of CH_4.
Therefore, I think that the intramolecular addition of Me^- shouldn't occur in this condition.


(2)
1. D (10 mol%), CH2Cl2, 0 °C;
Bi(OTf)3 (20 mol%), MeNO2, 0 °C to rt
65% (dr = >20:1, 92% ee)
2. E (1.2 eq.), [Rh(COD)Cl]2 (2.5 mol%), LiOH•H2O (3 eq.)
1,4-dioxane/H2O (10:1), 60 °C
3. TBAF (1.2 eq.), THF, 0 °C to rt
73% (2 steps, dr = >20:1)
4. DMP (1.3 eq.), CH2Cl2, 0 °C to rt
5. NaClO2 (5 eq.), NaH2PO4•H2O (5 eq.)
2-methyl-2-butene/t-BuOH/H2O (2:10:5), 0 °C to rt
6. TCNHPI (1.1 eq.), DCC (1.2 eq.), DMAP (10 mol%)
CH2Cl2, 0 °C to rt, 72% (3 steps)
7. NiCl2•DME (40 mol%), BPhen (80 mol%), F (3 eq.)
DMF/THF (2:3), rt, 40% (dr = >20:1)
TBDPSO
Ph
2-1
OMe
Ph
TBSO
Ph
H
2-2
CF3
S
N H
N H
N
N
D
MeO
B(OH)2
E
Cl
N–OH
TCNHPI
DCC
AcO OAc
OAc
DMP
MeO
ZnCl•LiCl
TBSO
F
BPhen

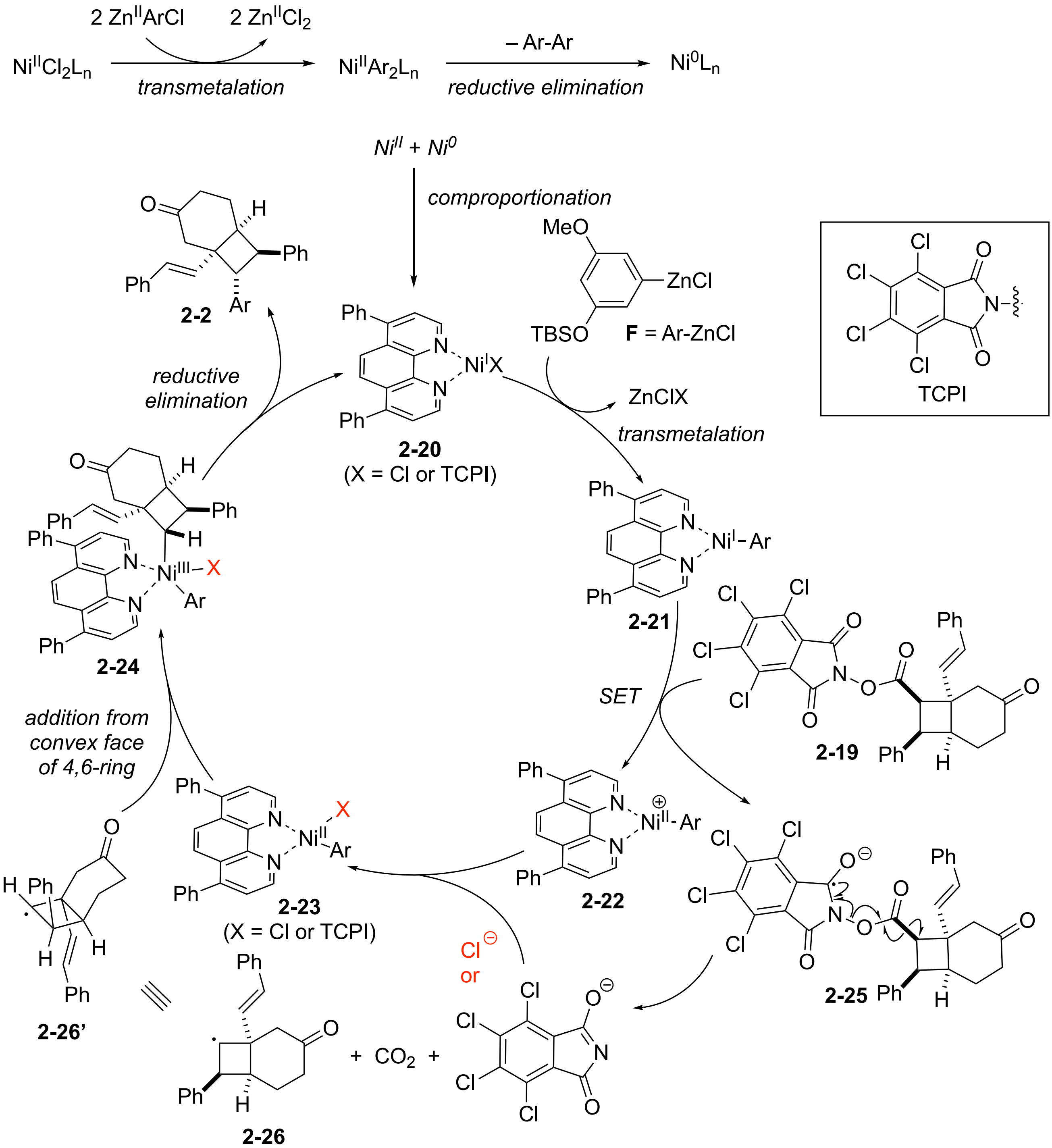
Answer


TBDPSO
Ph
2-1
NR3
D
NR3
H
2-3
Discussion-2
enantioselectivity
2-4
bond rotation
2-5
Bi(OTf)3
2-6
2-6'
LnRhICl
LiOH
LnRhIOH
(HO)2B
LiOH
B(OH)4
[2+2]-cycloaddition
Discussion-3
stereoselectivity/
another pathway
2-7 step 1
LnRhI
1,4-addition to construct
cis-fused 4,6-ring
2-8
H2O
LnRhIOH

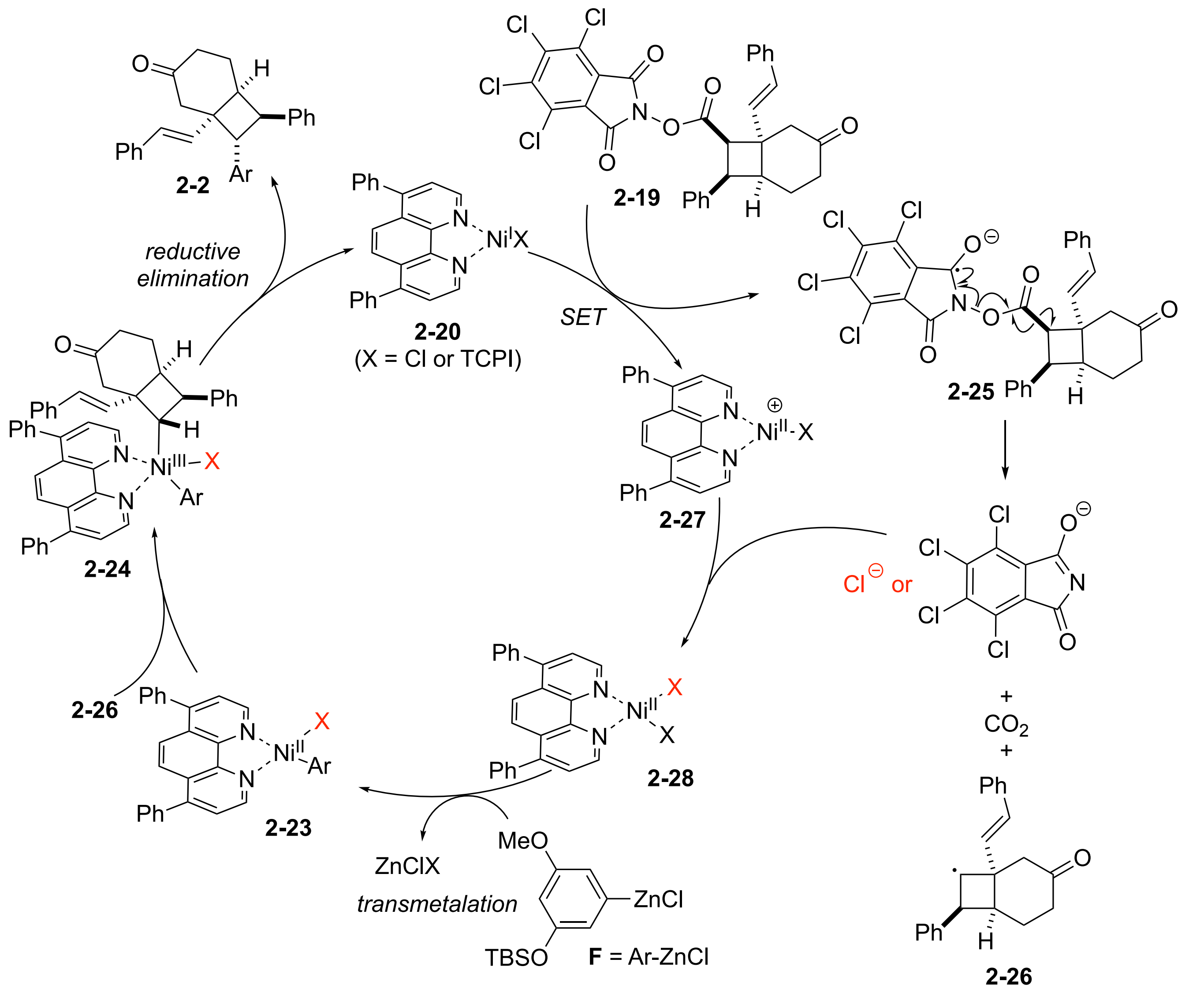

TBDPSO
Ph
H
Ph
2-9
step 2
TBAF;
workup
HO
2-10
step 3
DMP
–AcOH
AcO
OAc
2-11
2-12
AcO
–AcOH
O
Cl
2-13
step 4
NaClO2, NaH2PO4
2-14
Cl
OH
HO
2-15
workup
2-16
step 5
DCC
CyHN
NCy
2-17
Me2N
Me2N
2-18
N–OH
–DMAP
–H⊕
2-19
step 6



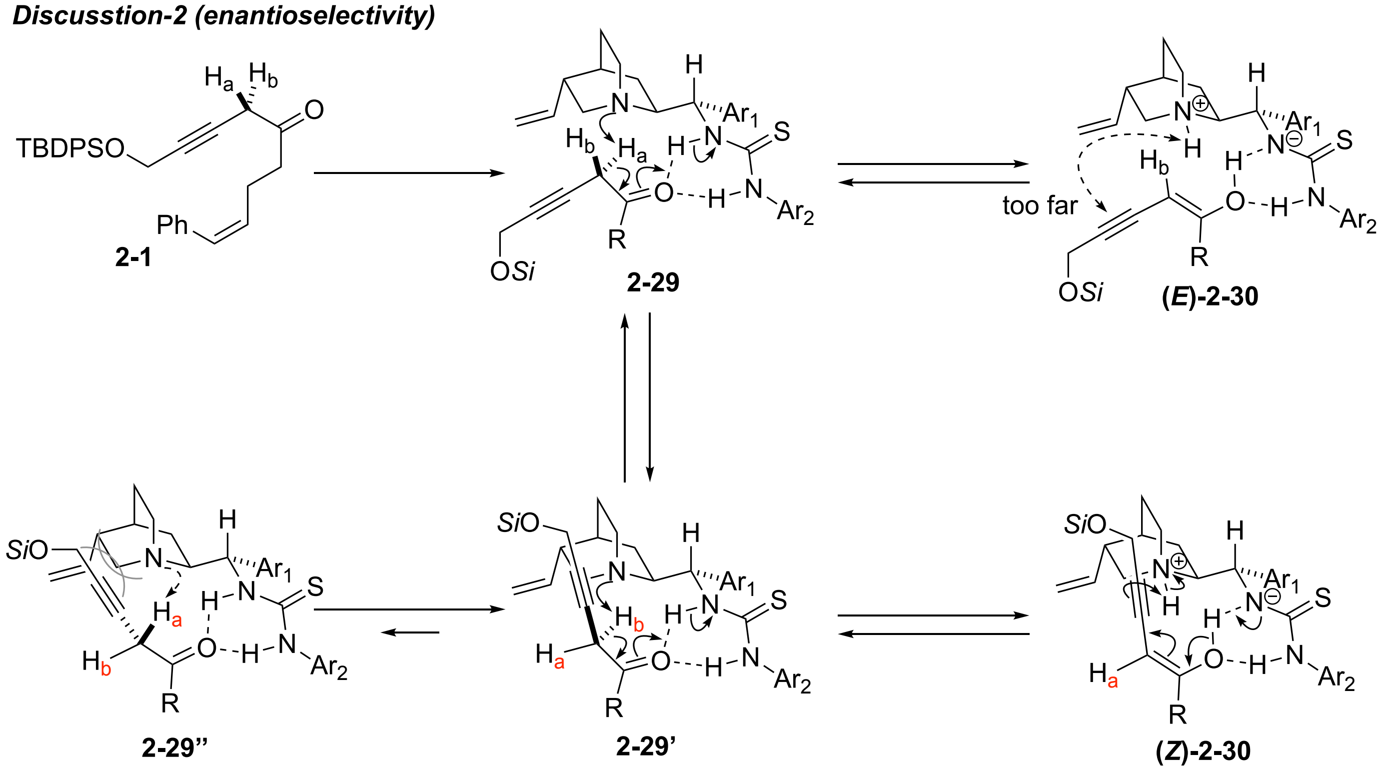
• proposed catalytic cycle-1 (transmetalation –> SET –> radical addition –> reductive elimination)[11]

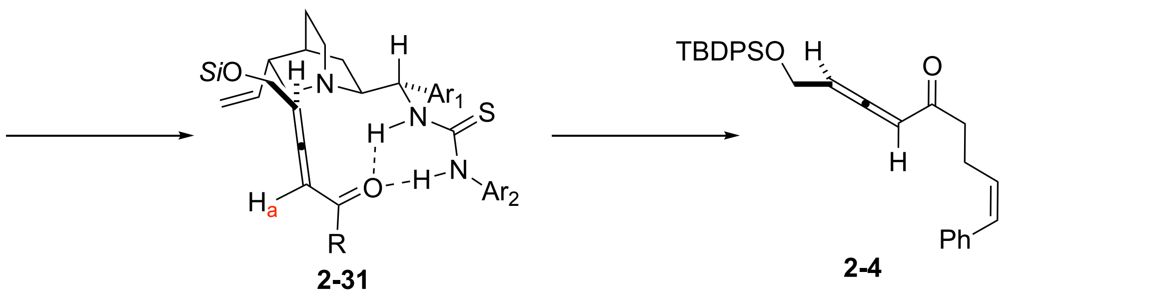


• proposed catalytic cycle-2 (SET –> transmetalation –> radical addition –> reductive elimination)



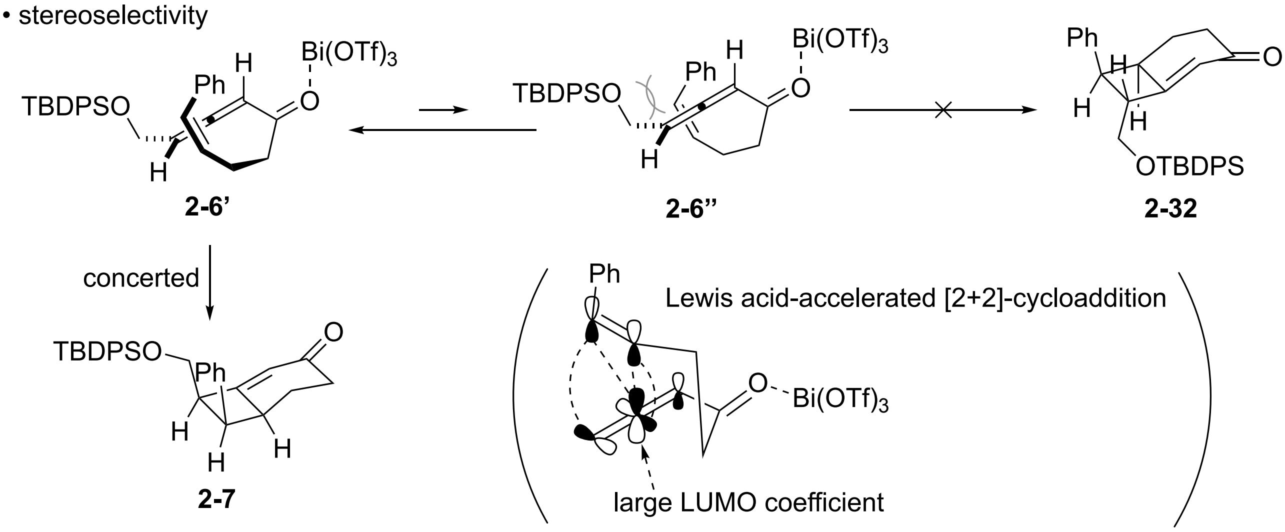
Discusstion-2 (enantioselectivity)



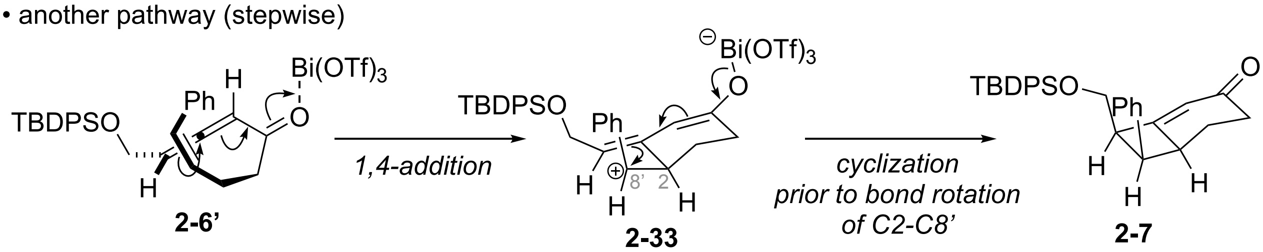


Discussion-3 ([2+2]-cycloaddition)

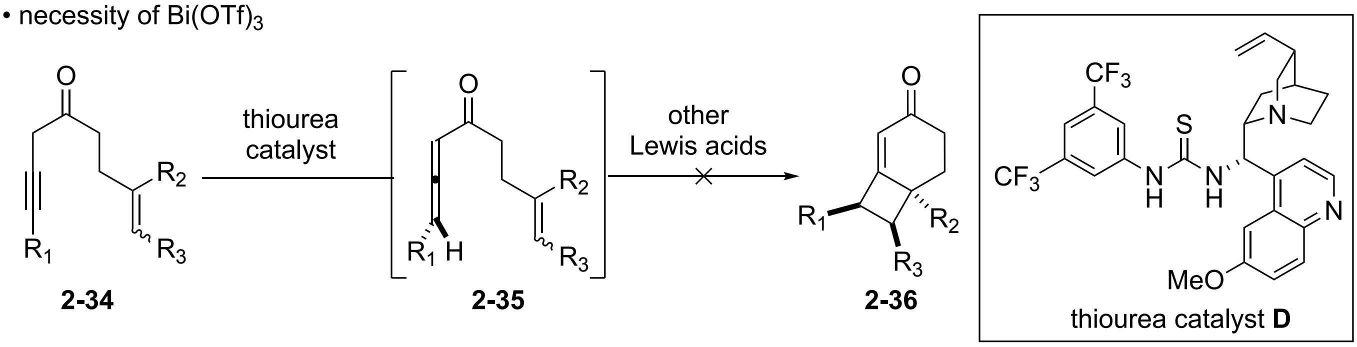
• stereoselectivity



• another pathway (stepwise)



• necessity of $Bi(OTf)_3$



In the author's previous synthetic study[3)], $Bi(OTf)_3$ was found to be effective for the one-pot isomerization-cycloaddition sequence. Other Lewis acids such as $In(OTf)_3$ or $Sc(OTf)_3$ were ineffective and only delivered recovered allene **2-35**. On the other hand, if the allene **2-35** was isolated prior to cycloaddition (free of thiourea catalyst), Lewis acids such as $In(OTf)_3$ or $Sc(OTf)_3$ were comparable to $Bi(OTf)_3$. From this data, it is suggested that $In(OTf)_3$ or $Sc(OTf)_3$ are sequestered by the thiourea catalyst whereas $Bi(OTf)_3$ is not.

Reference

9. Hong, C. C.; Rapson, W. H. *Can. J. Chem*. **1968**, *46*, 2053.
10. Clive, D. L.; Minaruzzaman; Ou, L. *J. Org. Chem.* **2005**, *70*, 3318.
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