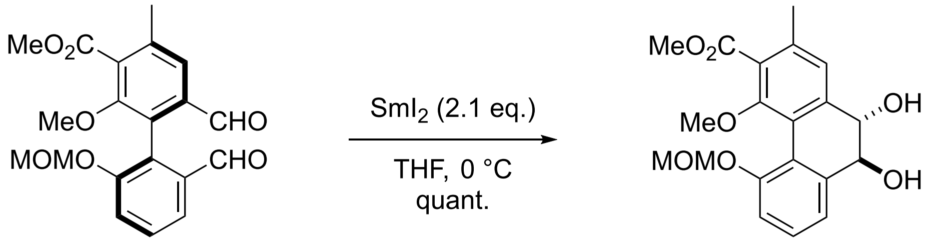
Problem Session (5)

2015. 09. 05. Kengo Masuda

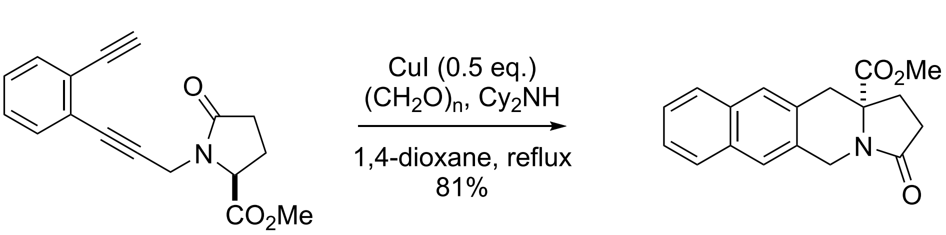
Provide the reaction mechanisms and explain the stereoselectivities.

(1)



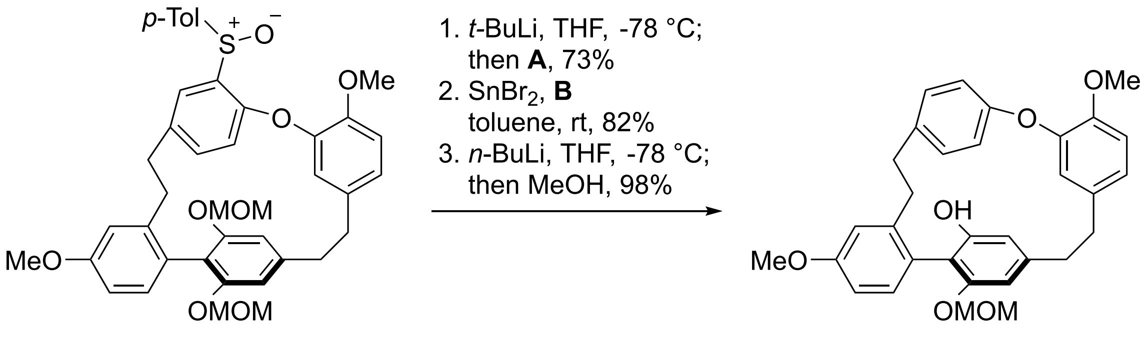
1-1 (>99% ee) **1-2** (>99% ee)* *__1-2__ has no axial chirality.

(2)

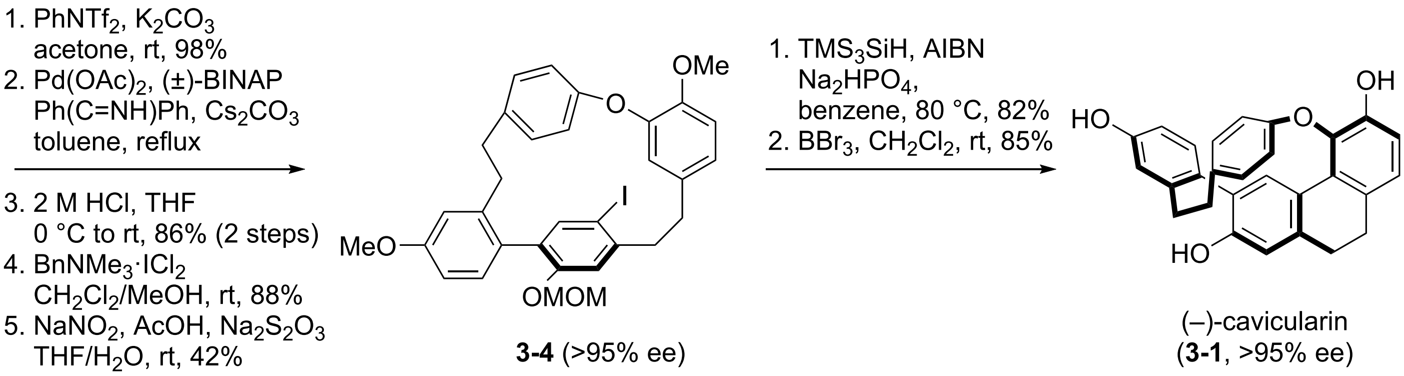


2-1 (96% ee) **2-2** (95% ee)

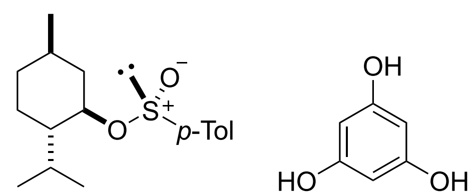
(3)



(±)-**3-2** **3-3** (>95% ee)



3-4 (>95% ee) (–)-cavicularin (**3-1**, >95% ee)



A (>99% ee) **B**

Problem Session (5): Answer

2015. 09. 05. Kengo Masuda

Topic: **Transfer of various chiralites**

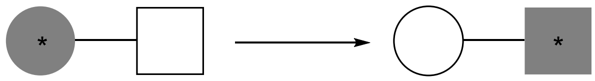
<Introduction>

For a review, see: Campolo, D.; Gastaldi, S.; Roussel, C.; Bertrand, M. P.; Nechab, M. *Chem. Soc. Rev.* **2013**, *42*, 8434.

1. definition

Chirality transfer ≡ a pocess in which new chiral element is created while the original chiral element is lost

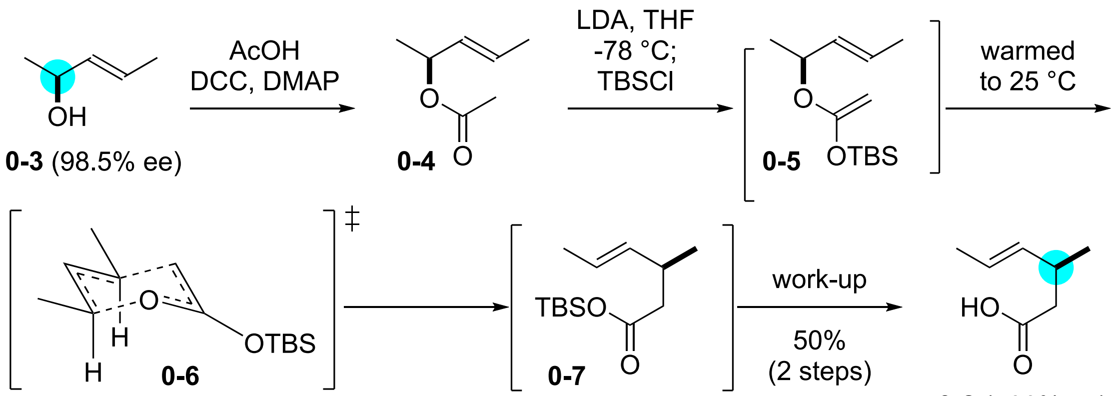
general scheme of "traceless" chirality transfer



(1)

0-1 **0-2**

example (central to central chirality): Ireland-Claisen rearrangement



0-3 (98.5% ee) **0-4** **0-5** **0-6** **0-7** **0-8** (>90% ee)

McKew, J. C.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 4589.

>91% chirality transfer

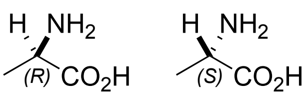
$$\text{chirality transfer level} \equiv \frac{\text{ee of product}}{\text{ee of starting material}} \quad (2)$$

- *"traceless"* chirality transfer (problem 1 and 2)
- *"extensive"* chirality transfer (problem 3, using chiral auxiliary)

2. Valious chiralities

2-1. Central chirality

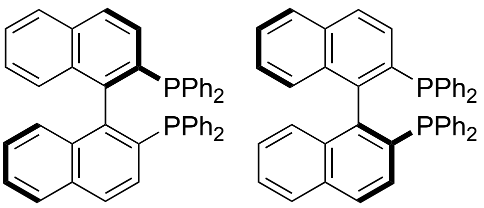
amino acids



D-alanine L-alanine

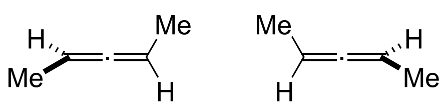
2-2. Axial chirality

biaryl compounds (atropisomerism)



(*R*)-BINAP (*S*)-BINAP

allenes

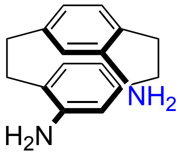


(R_a)-**0-8** (S_a)-**0-8**

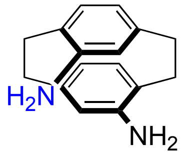
Mukai, K. PS on 2012. 01. 12. "Allenes & Transfer of Chirality"

2-3. Planar chirality

<u>paracyclophane (atropisomerism)</u>

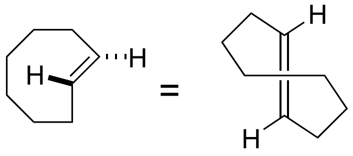


(R_p,R_p)-**0-9**

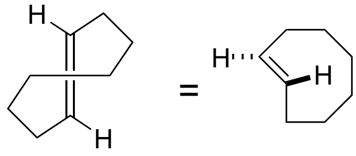


(S_p,S_p)-**0-9**

<u>*trans-cycloalkenes (atropisomerism)*</u>



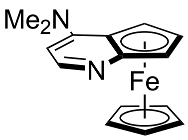
(R_p)-**0-10**



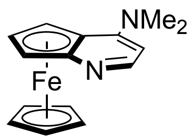
(S_p)-**0-10**

Kawamata, T. PS on 2015. 06. 13.
"Transannular reaction and rearrangement related to *trans*-cycloalkenes"

<u>*substituted metallocenes*</u>



(S_p)-**0-11**

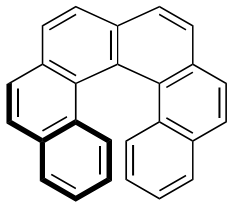


(R_p)-**0-11**

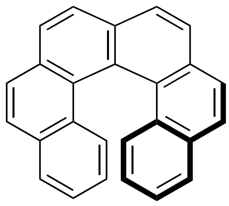
Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

2-4. Helicity

<u>*helicenes*</u>

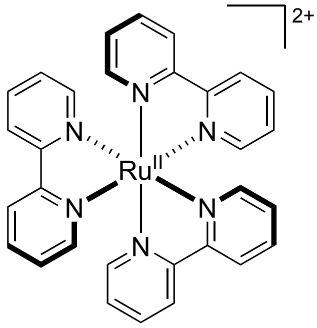


(P)-[6]helicene
((P)-**0-12**)

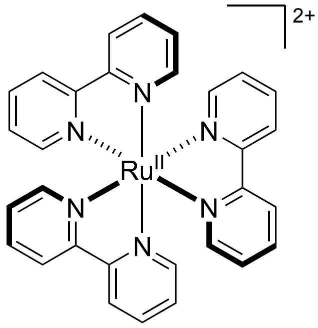


(M)-[6]helicene
((M)-**0-12**)

<u>*Octahedral complexes with tris-bidentate ligands*</u>



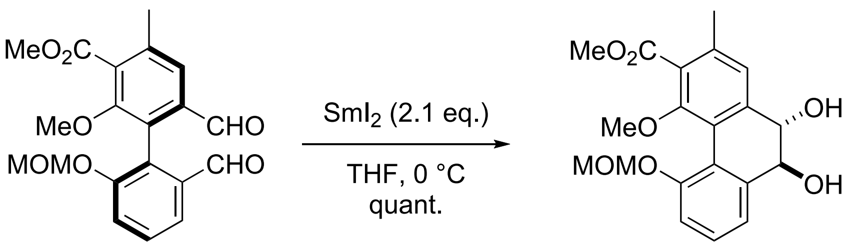
Δ-$[Ru(bpy)_3]^{2+}$
(Δ-**0-13**)



Λ-$[Ru(bpy)_3]^{2+}$
(Λ-**0-13**)

<Answer>

(1)



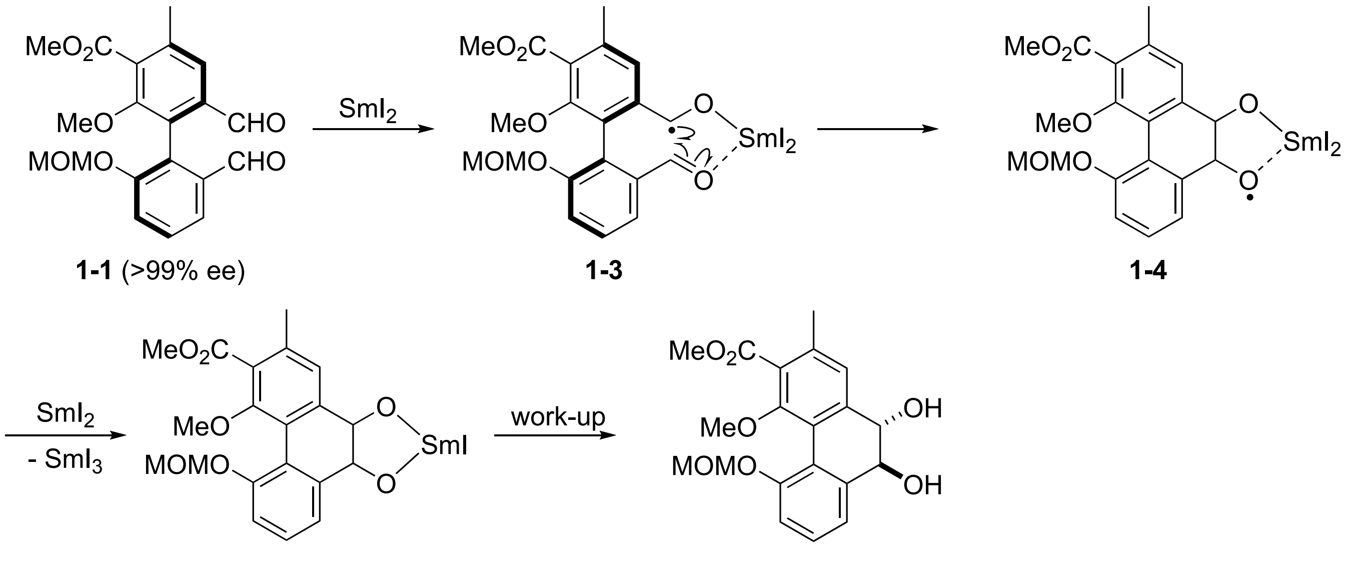
1-1 (>99% ee)

>99% chirality transfer

1-2 (>99% ee)

Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1226.

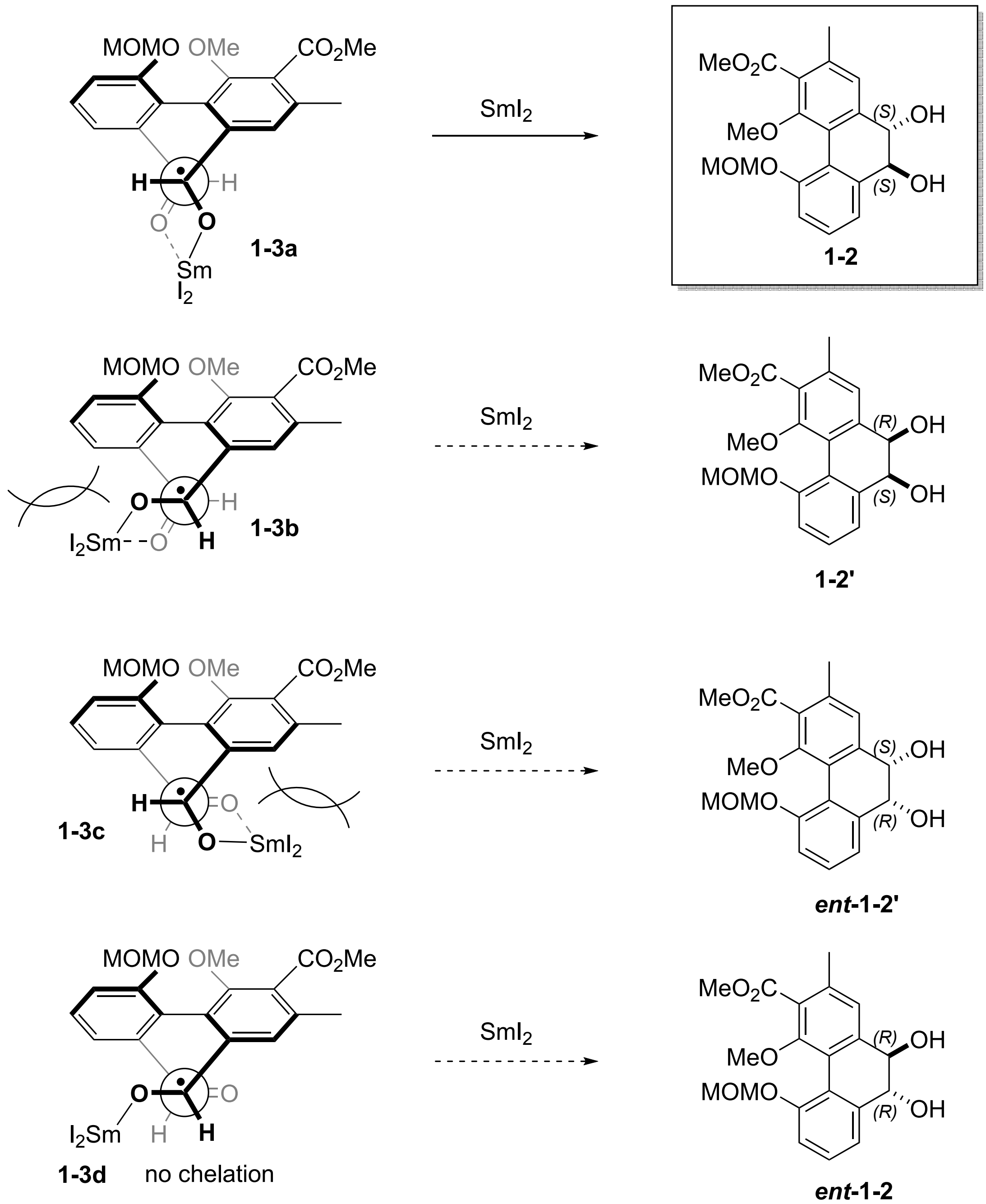
<u>"axial chirality to central chiralities"</u>



1-1 (>99% ee) **1-3** **1-4** **1-5** **1-2** (>99% ee, dr >99:1)

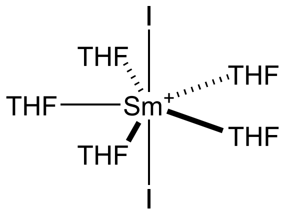
<discussion>

1. Stereoselectivity



steric congestion around Samarium center

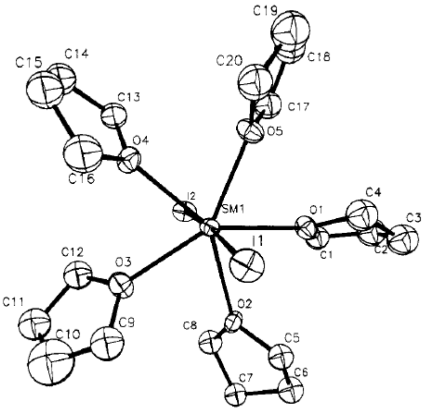
- X-ray structure of [Sm(III)I$_2$(THF)$_5$]Co(CO)$_4$



angles { (I-Sm-O): 87.5-93.7 °
(O-Sm-O): 70.4-73.3 °

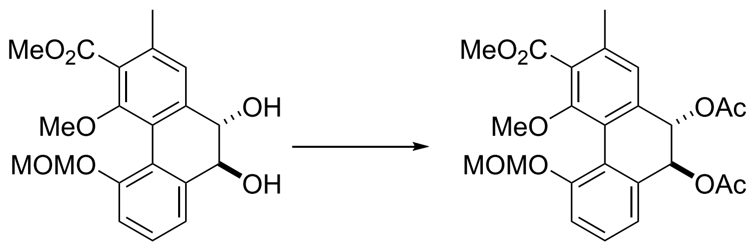
distances { (Sm-I): 3.01-3.03 Å
(Sm-O): 2.45-2.47 Å

pentagonal bipyramidal



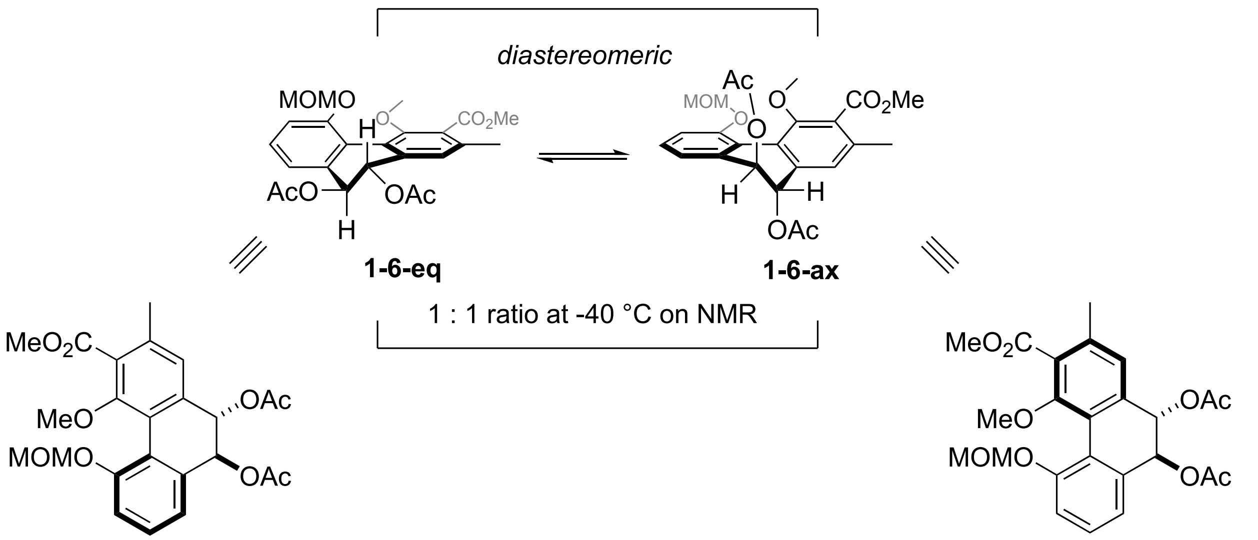
Evans, W. J.; Bloom, I.; Grate, J. W.; Hughes, L. A.; Hunter, W. E.; Atwood, J. L. *Inorg. Chem.* **1985**, *25*, 4620.

2. Unstable axial chirality (helicity) of **1-2**



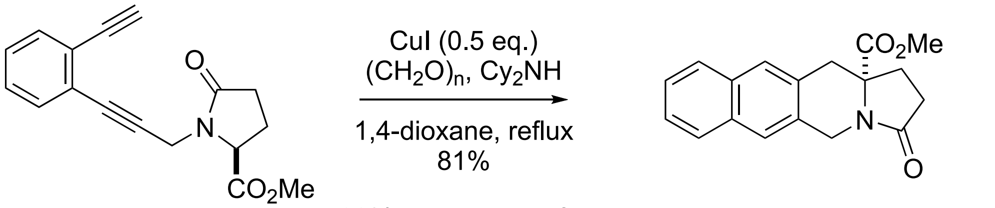
} no hydrogen bond

1-2 **1-6**



(*M*)-**1-6** (*P*)-**1-6**

(2)

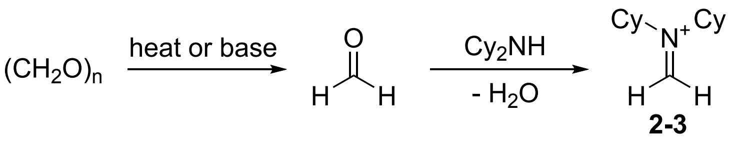


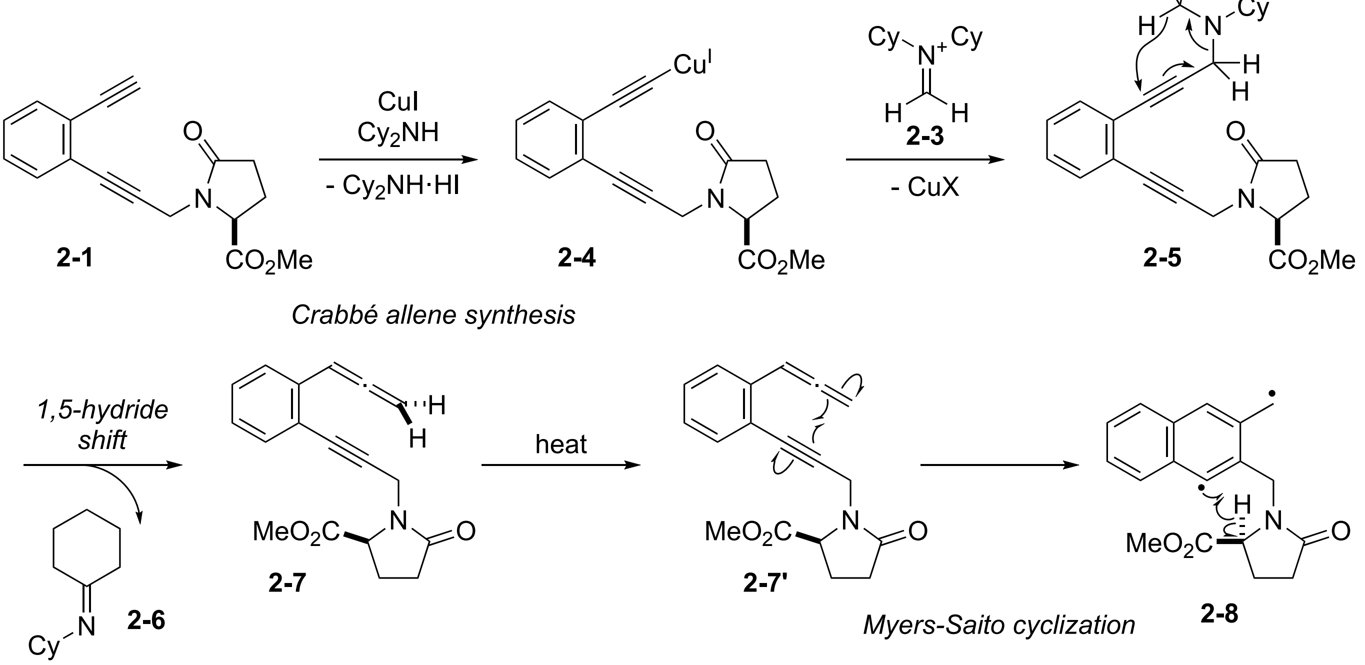
2-1 (96% ee) *99% chirality transfer* **2-2** (95% ee)

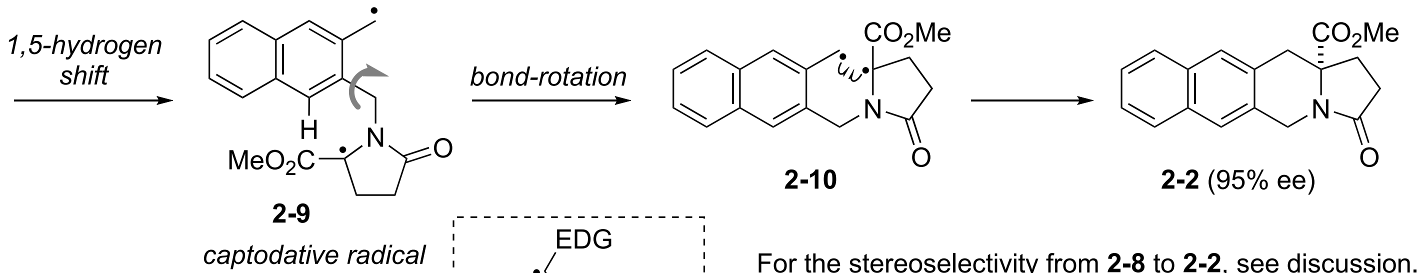
Mondal, S.; Nechab, M.; Vanthuyne, N.; Bertrand, M. P. *Chem. Commun.* **2012**, *48*, 2549.

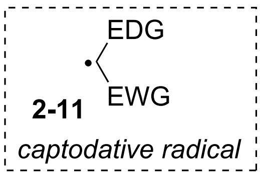
"central to pseudo-axial to central chirality"

(generation of **2-3**)







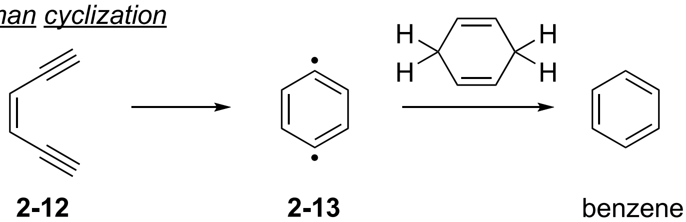


For the stereoselectivity from **2-8** to **2-2**, see discussion.

<Discussion>

1. Brief introduction about Myers-Saito cylization

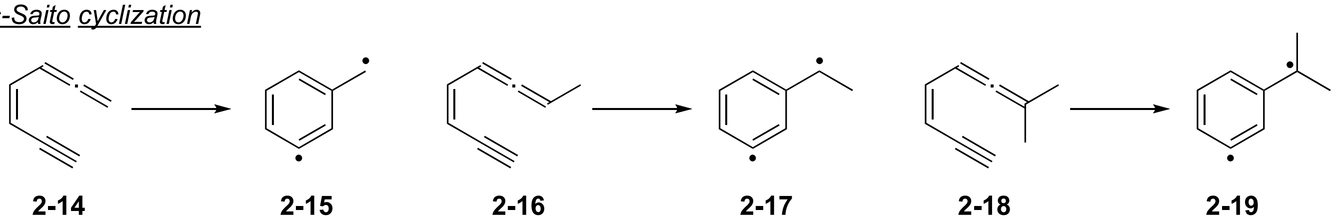
<u>Bergman</u> <u>cyclization</u>



stable at 25 °C
$t_{1/2}$ = 30 sec at 200 °C

Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

<u>Myers-Saito</u> <u>cyclization</u>

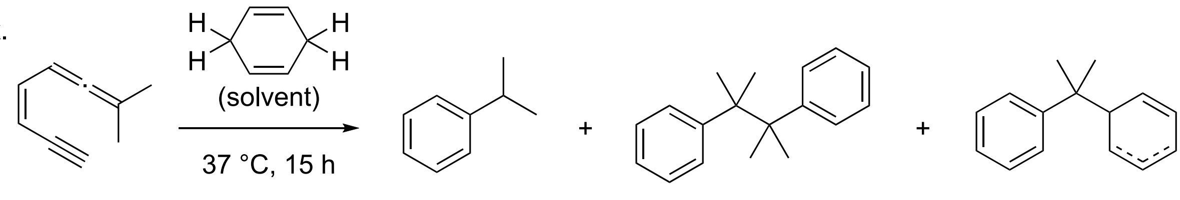


2-14: $t_{1/2}$ = 24 h at 37 °C; $t_{1/2}$ = 30 min at 75 °C

2-16: $t_{1/2}$ = ca. 4 h at 37 °C; $t_{1/2}$ = 3.6 min at 78 °C

2-18: $t_{1/2}$ = 70 min at 37 °C

ex.



2-17 **2-20** (43%) **2-21** (2%) **2-22** (15%)

Wang, K. K.; Wang, Z. *J. Org. Chem.* **1996**, *61*, 1516.

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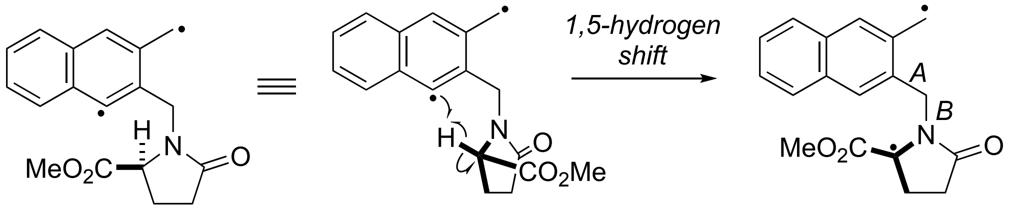
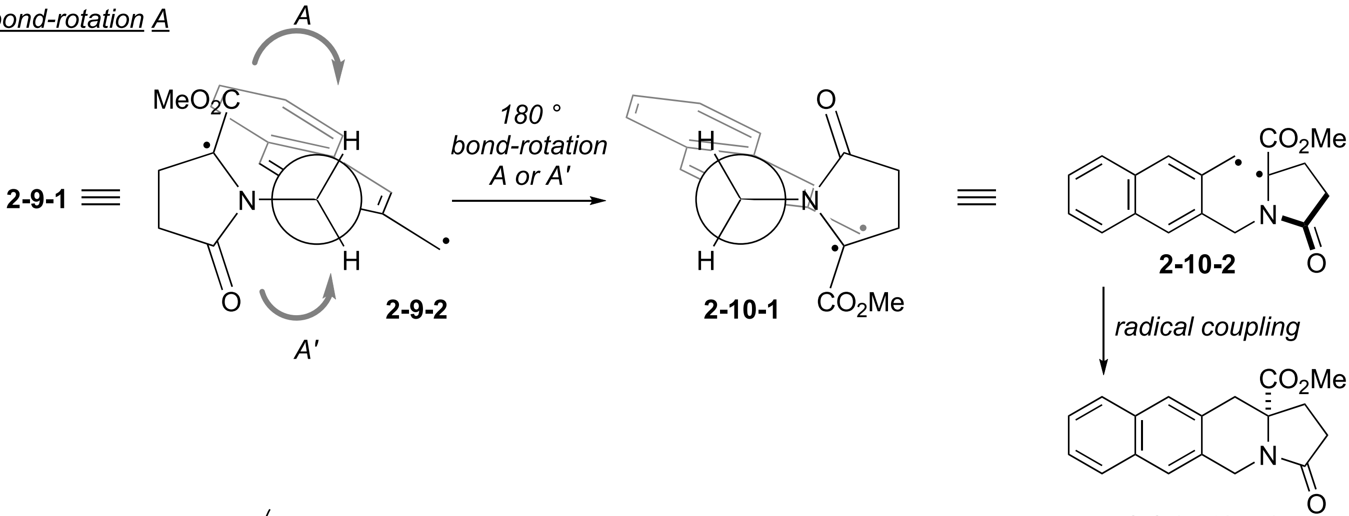
2. Stereoselectivity

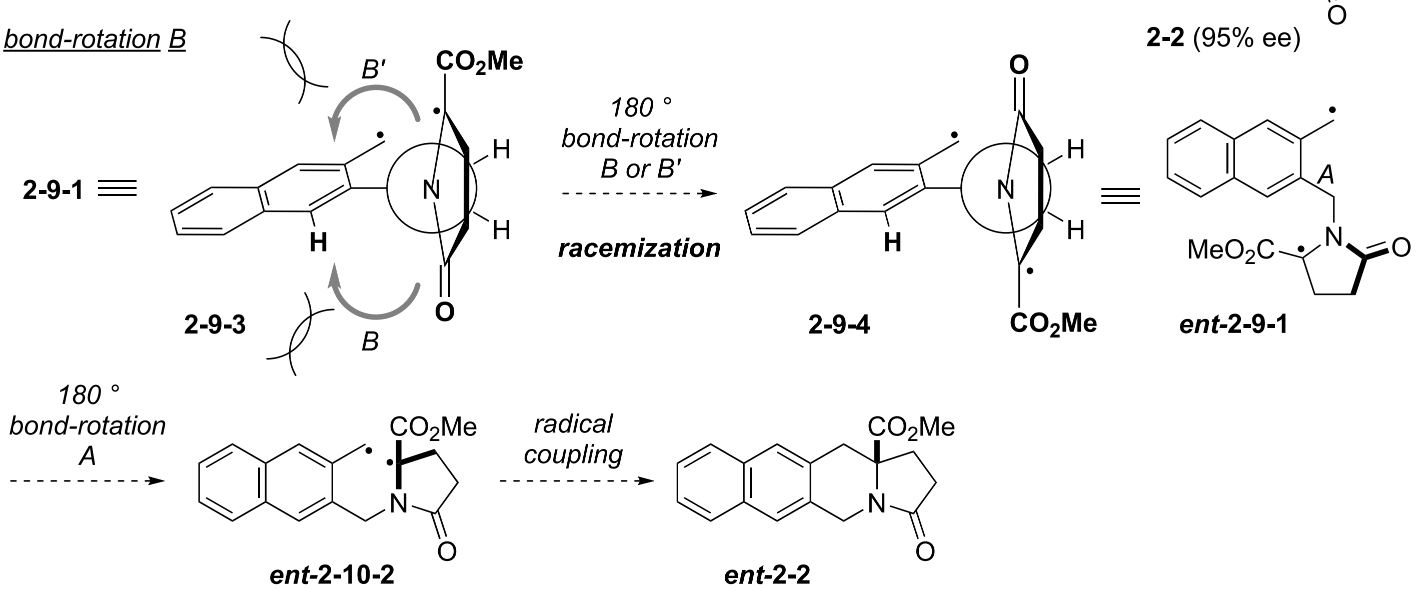


2-8 **2-8-0** **2-9-1**
pseudo-axial chirality

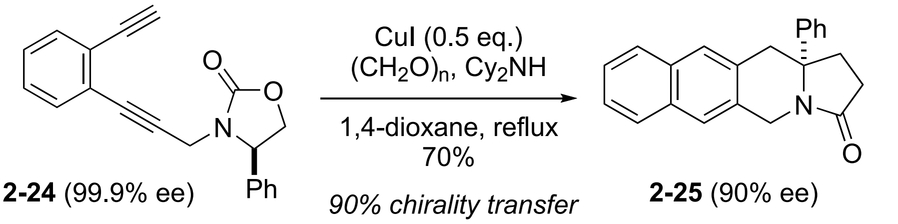
<u>*bond-rotation A*</u>



<u>*bond-rotation B*</u>

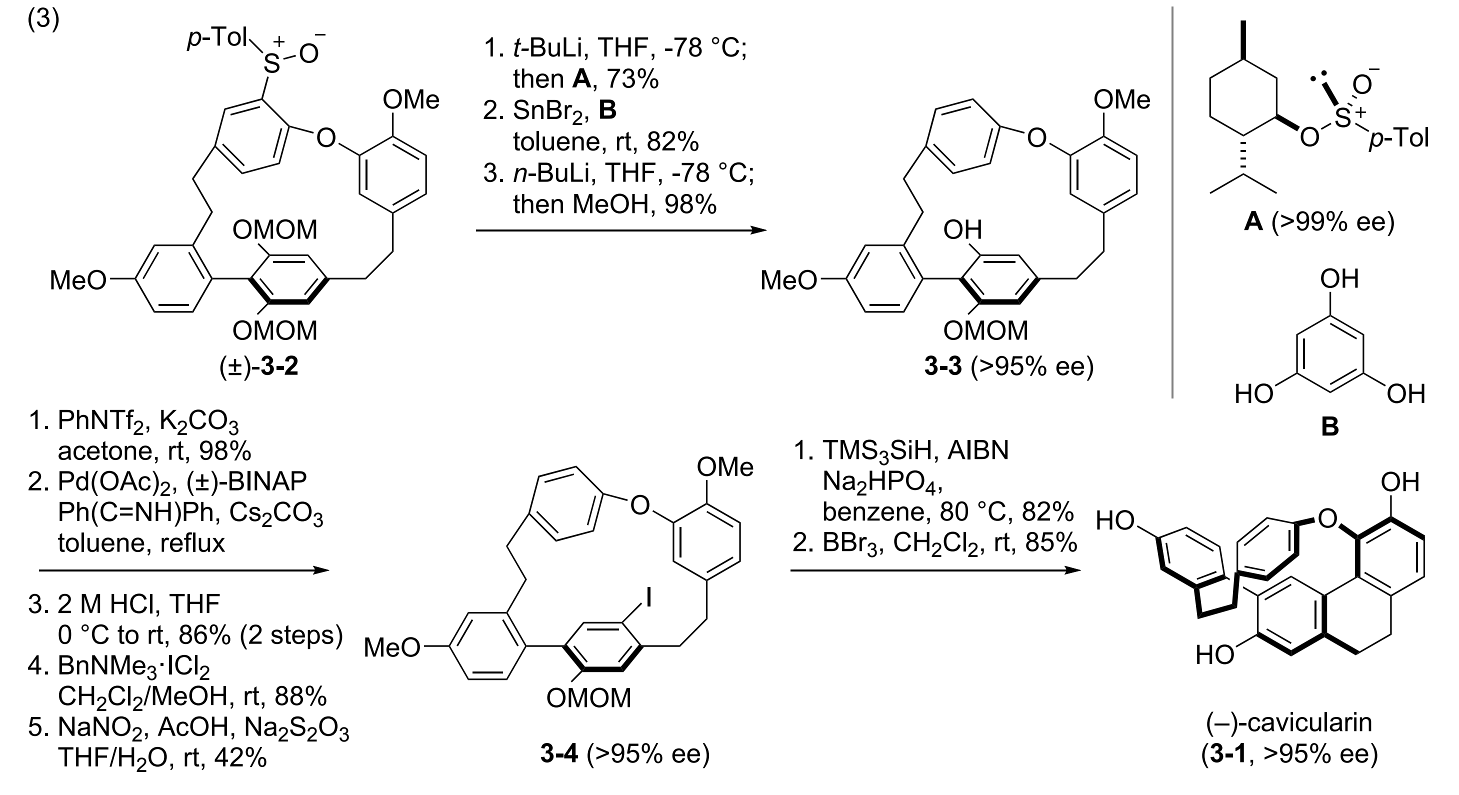


[reaction of **2-24**]



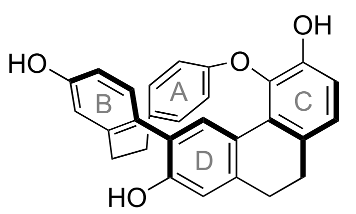
2-24 (99.9% ee) *90% chirality transfer* **2-25** (90% ee)

(3)



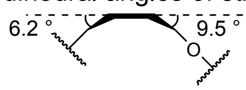
Takiguchi, H.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10472.

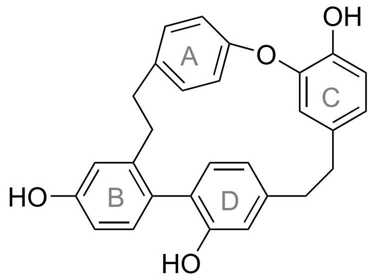
Breif introduction about cavicularin



(+)-cavicularin (**3-1**)

dihedral angles of strained A-ring





riccardin (**3-5**)
achiral

Isolation:
liverwort *Cavicularia densa* Steph.[1)]

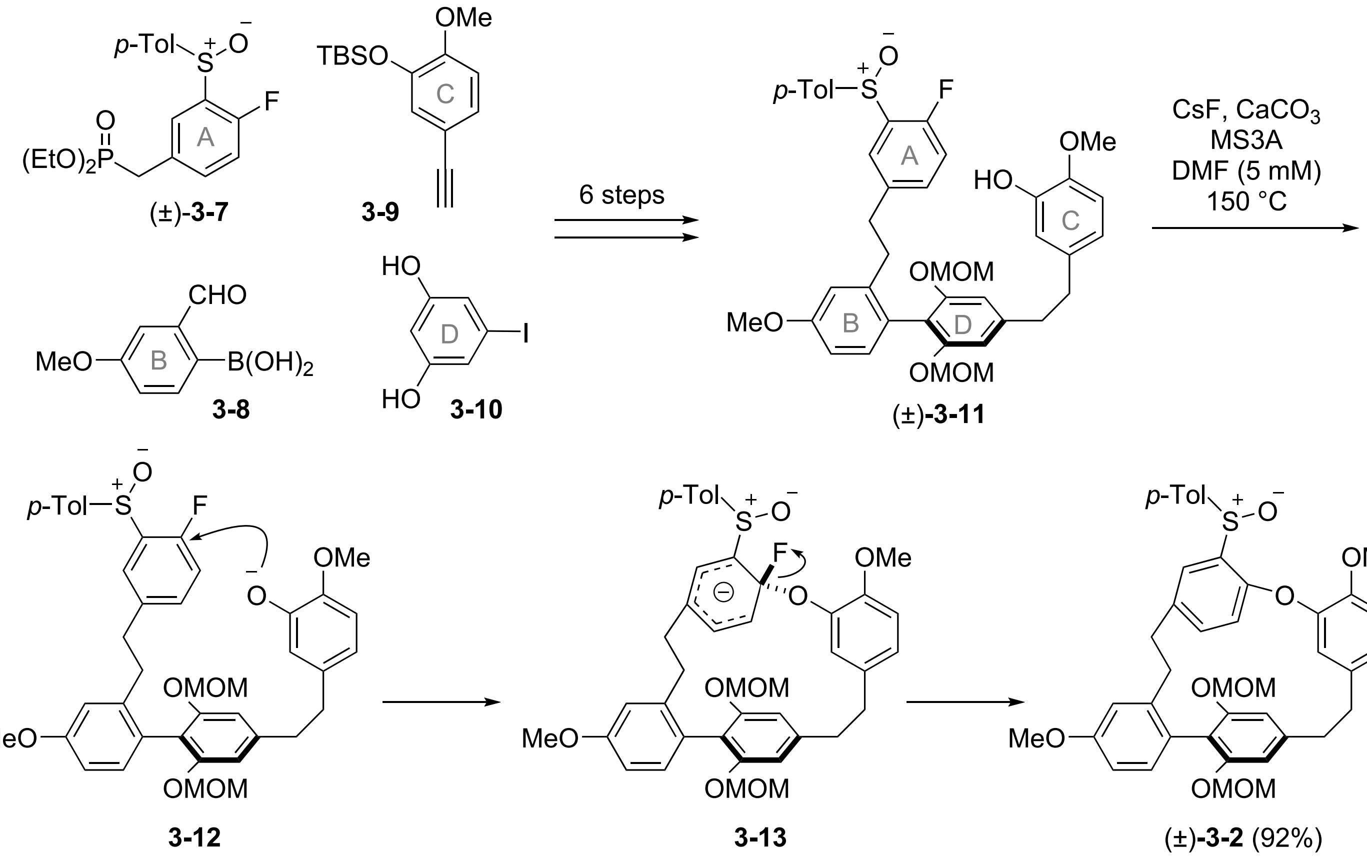
Strucural features:
- no stereocenter
- optically active compound
- planar chirality (with axial chirality and helicity)

Total synthesis:
- Harrowven (2005, 2011, racemic)[2)]
- Beaudry (racemic in 2013, asymmetric in 2014)[3)]
- Fukuyama, Y. (2013, racemic)[4)]

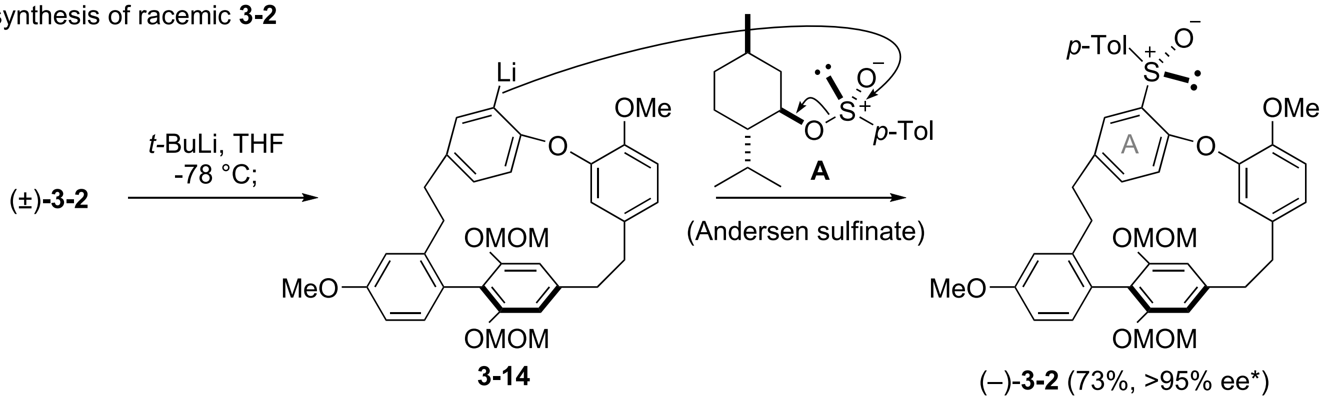
references about cavicularin:

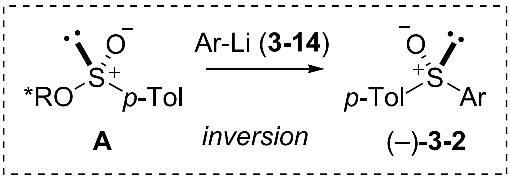
1) Toyota, M.;Yoshida, T.; Kan, Y.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4745.
2) (a) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3899.
(b) Kostiuk, S. L.; Woodcock, T.; Dudin, L. F.; Howes,P. D.; Harrowven, D. C. *Chem. Eur. J.* **2011**, *17*, 10906.
3) (a) Zhao, P.; Beaudry, C. M. *Org. Lett.* **2013**, *15*, 402. (b) Zhao, P.; Beaudry, C. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10500.
4) Harada, K.; Makino, K.;Shima, N.; Okuyama, H.; Esumi, T.; Kubo, M.; Hioki, H.; Asakawa, Y. Fukuyama, Y. *Tetrahedron* **2013**, *69*, 6959.

(synthesis of racemic **3-2**)

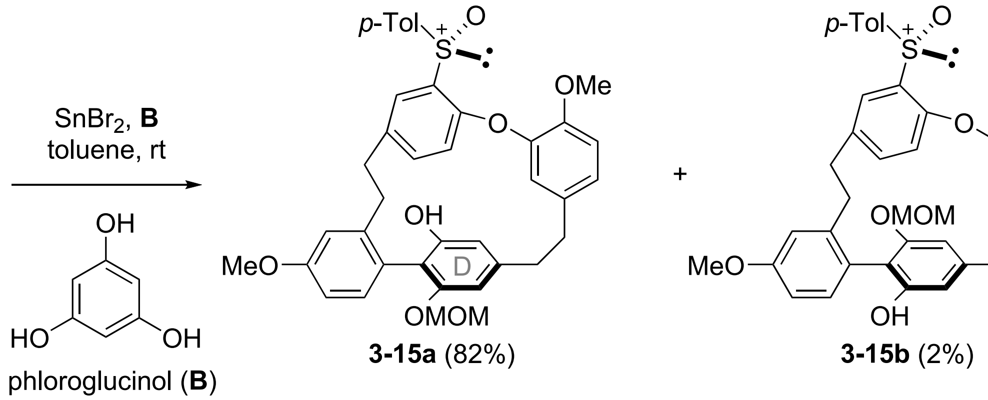


3-2. synthesis of racemic **3-2**

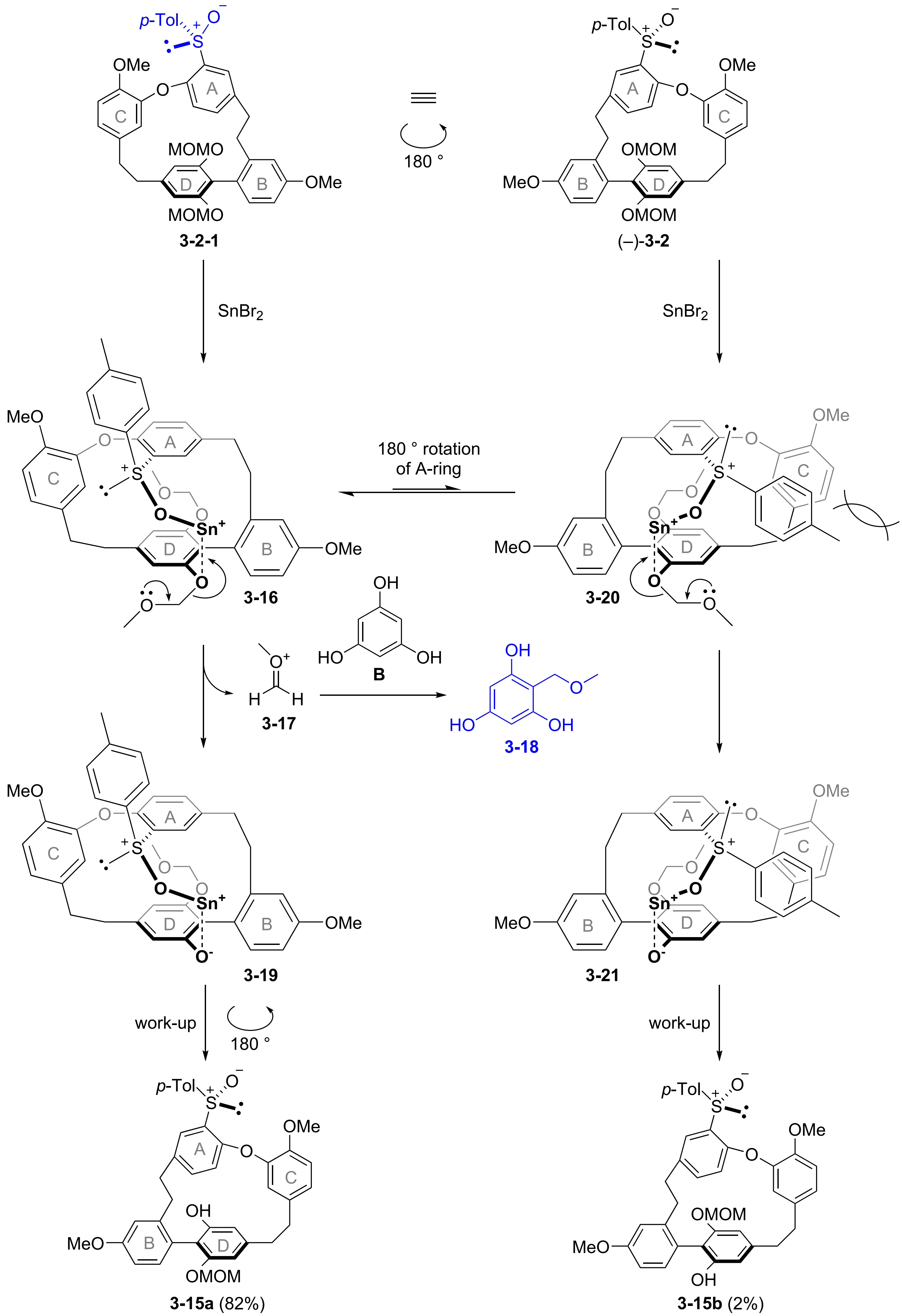


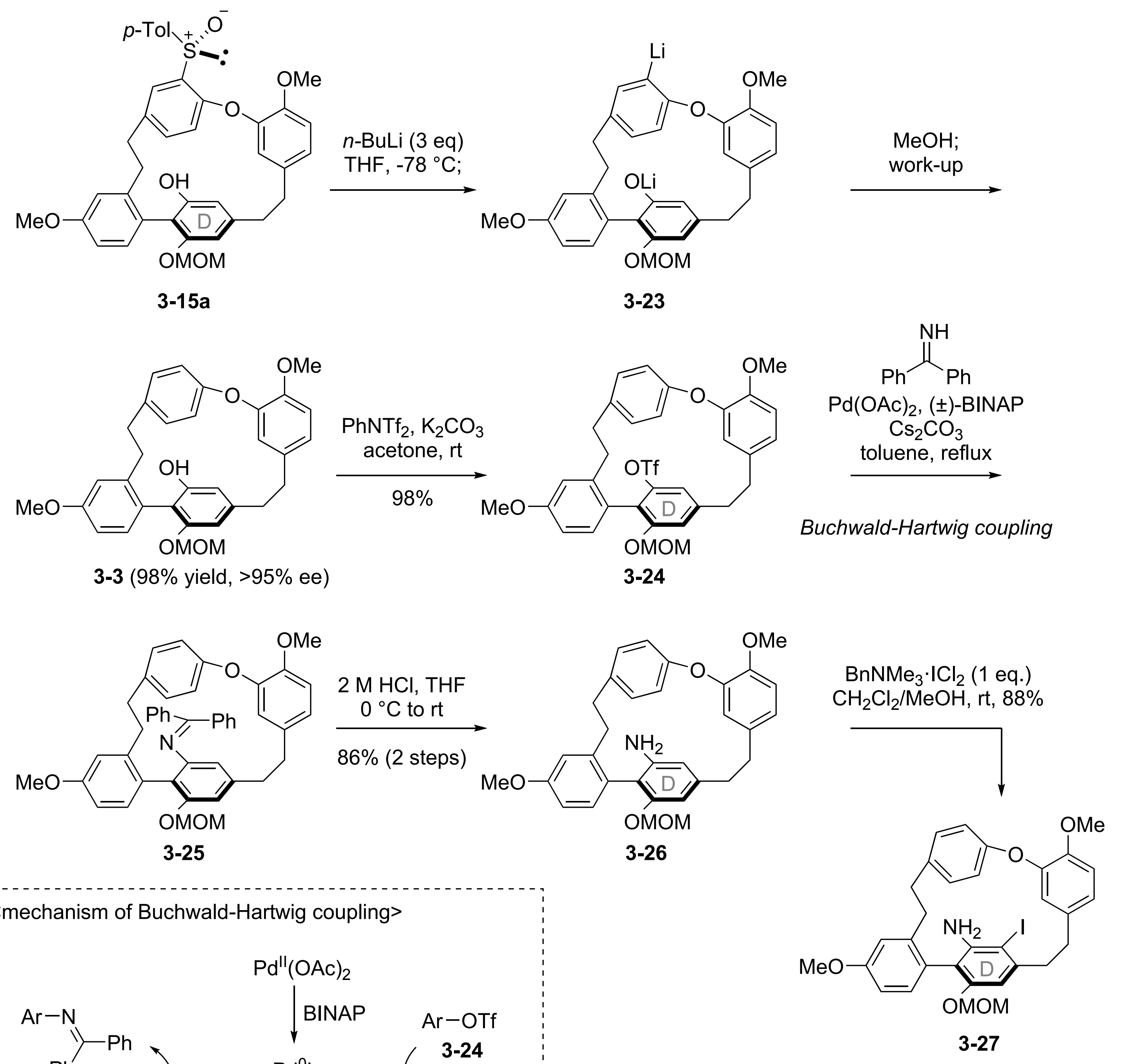


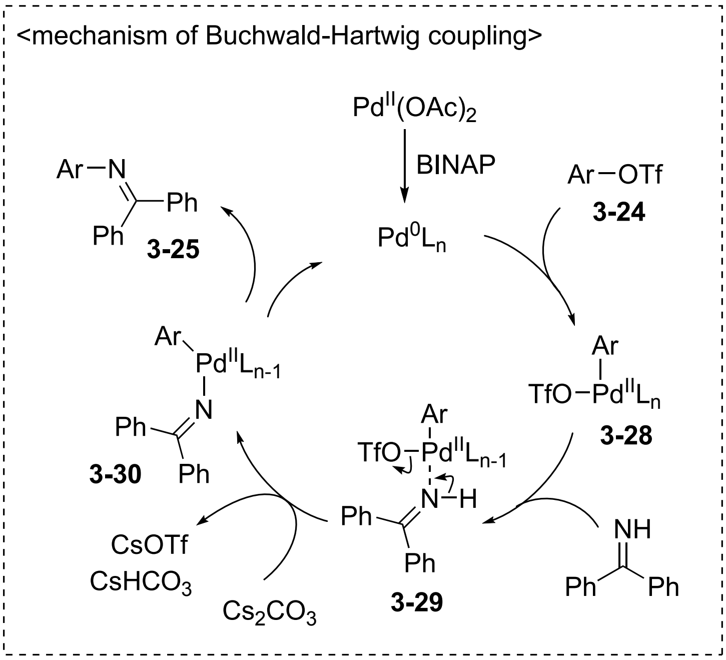
*The ee value was based on a back calculation from advanced intermediate **3-3**, because **3-2** had rotamers around A-ring.

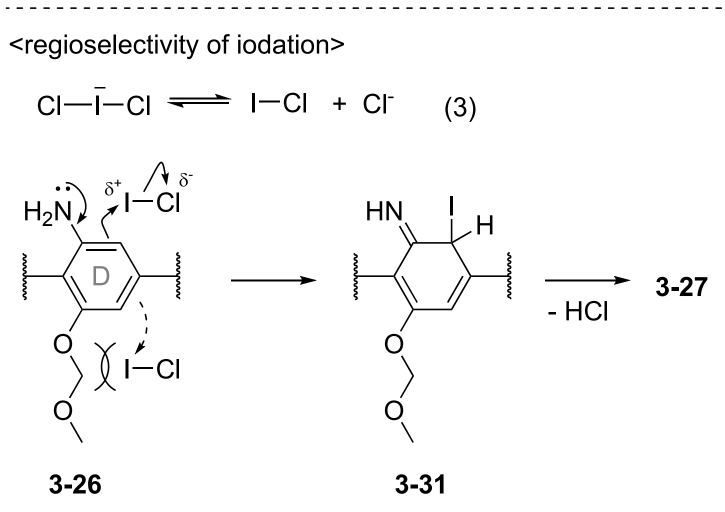


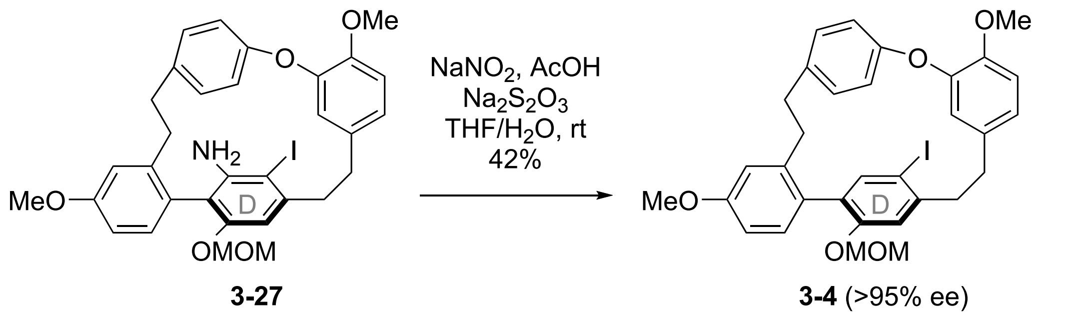
<stereoselectivity>




p-Tol
OMe
OH
D
MeO
OMOM
3-15a
n-BuLi (3 eq)
THF, -78 °C;
Li
OLi
3-23
MeOH;
work-up
3-3 (98% yield, >95% ee)
PhNTf2, K2CO3
acetone, rt
98%
OTf
3-24
NH
Ph Ph
Pd(OAc)2, (±)-BINAP
Cs2CO3
toluene, reflux
Buchwald-Hartwig coupling
Ph Ph
N
3-25
2 M HCl, THF
0 °C to rt
86% (2 steps)
NH2
3-26
BnNMe3·ICl2 (1 eq.)
CH2Cl2/MeOH, rt, 88%
I
3-27

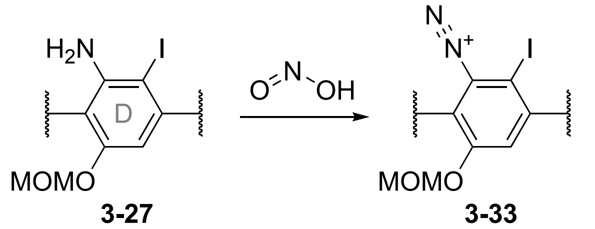

<mechanism of Buchwald-Hartwig coupling>
Pd(II)(OAc)2
BINAP
Pd(0)Ln
Ar−OTf
3-24
Ar
TfO−Pd(II)Ln
3-28
Ar−N=C(Ph)Ph
3-25
Ar
Pd(II)Ln-1
N
Ph Ph
3-30
TfO−Pd(II)Ln-1
N−H
Ph Ph
3-29
NH
Ph Ph
CsOTf
CsHCO3
Cs2CO3


<regioselectivity of iodation>
Cl−I−Cl ⇌ I−Cl + Cl- (3)
H2N
δ+ δ-
I−Cl
D
I−Cl
3-26
HN
I H
3-31
- HCl
3-27

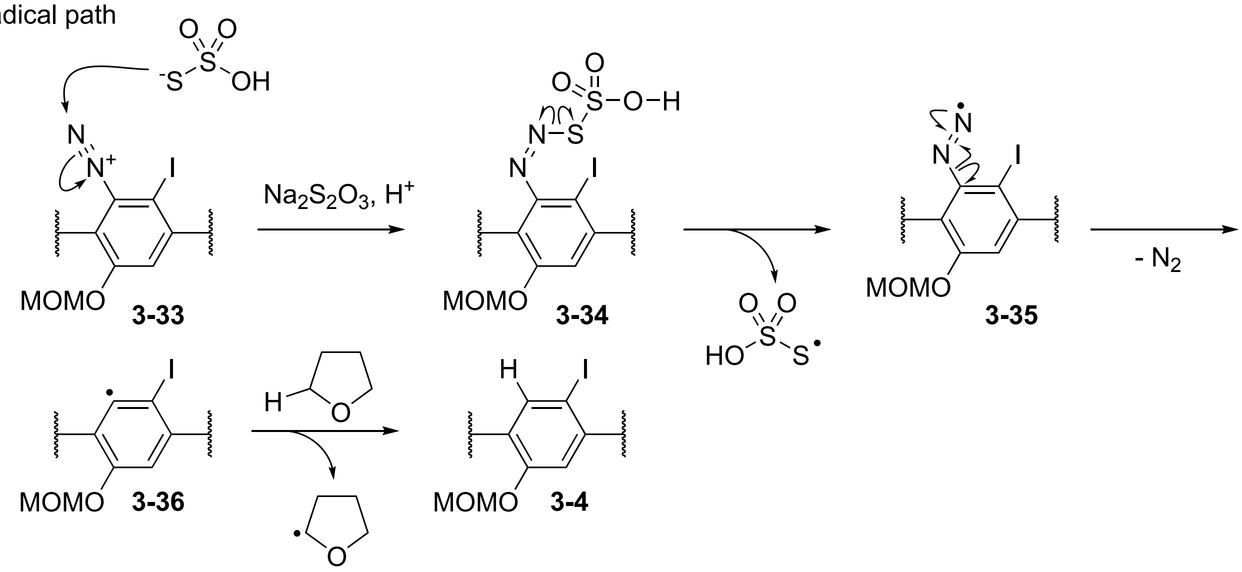


<mechanism of deamination>

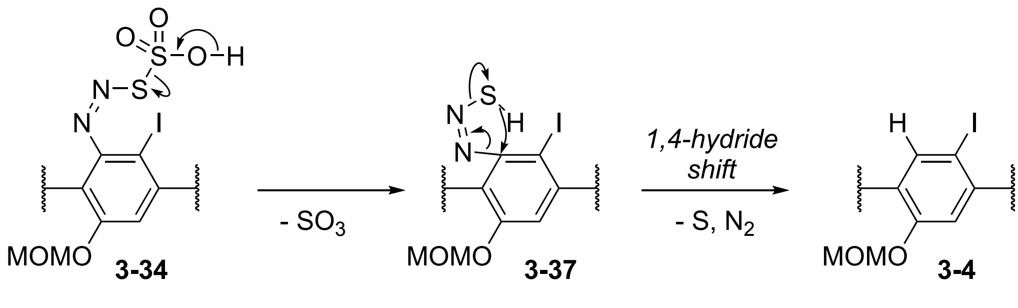
(formation of diazonium **3-33**)

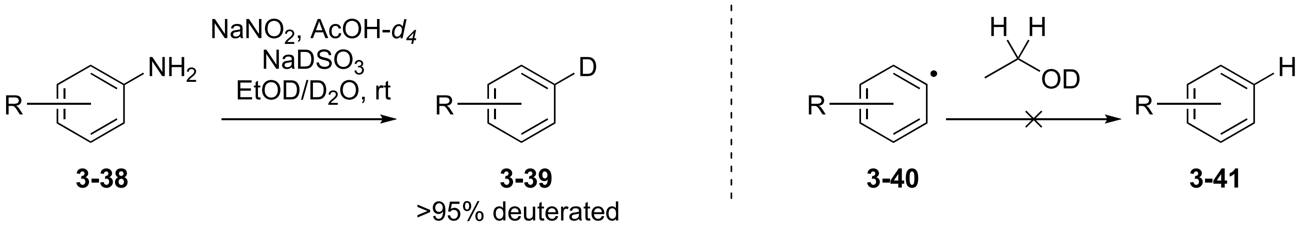


(i) radical path



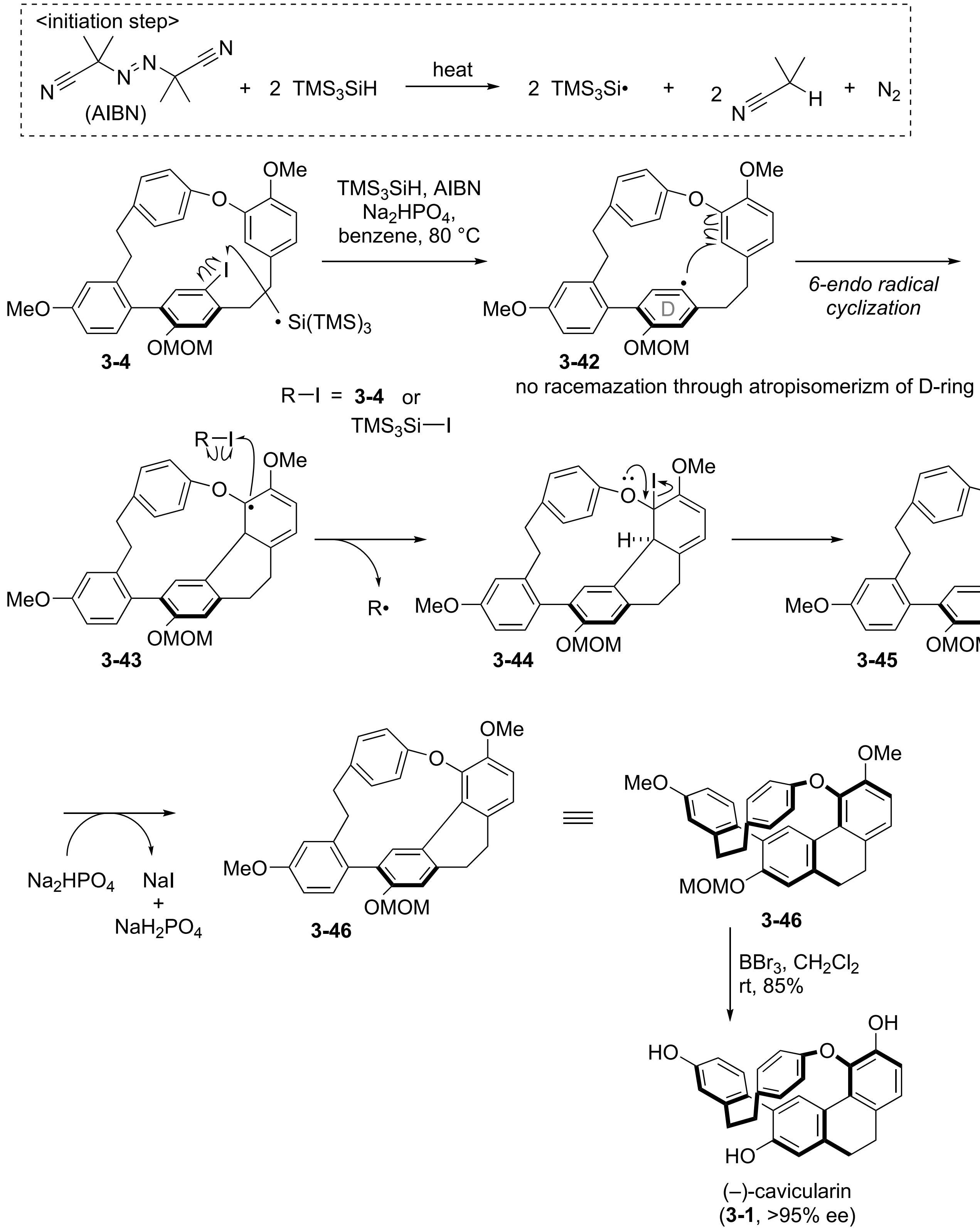
(ii) hydride shift path





Geoffroy, O. J.; Morinelli, T. A.; Meier, G. P. *Tetrahedron Lett.* **2001**, *42*, 5367.

➡ Hydride shift paht (ii) would be plausible.


<initiation step>
(AIBN)
+ 2 TMS3SiH
heat
2 TMS3Si•
+
2
H
+ N2
OMe
O
I
MeO
• Si(TMS)3
OMOM
3-4
TMS3SiH, AIBN
Na2HPO4,
benzene, 80 °C
D
3-42
no racemazation through atropisomerizm of D-ring
6-endo radical
cyclization
R—I = 3-4 or
TMS3Si—I
R—I
3-43
R•
H
3-44
O+
3-45
Na2HPO4
NaI
+
NaH2PO4
3-46
MOMO
BBr3, CH2Cl2
rt, 85%
OH
HO
(–)-cavicularin
(3-1, >95% ee)