Total Synthesis of (-)-Spiroxins A, C, D

2021.9.25. Literature Seminar

B4 Yuya Shiga

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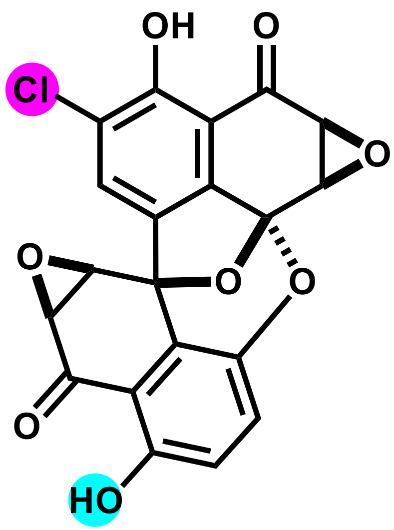
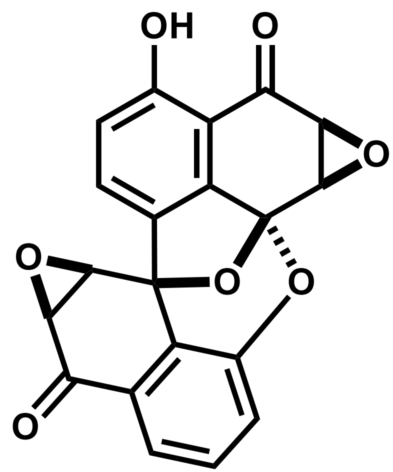
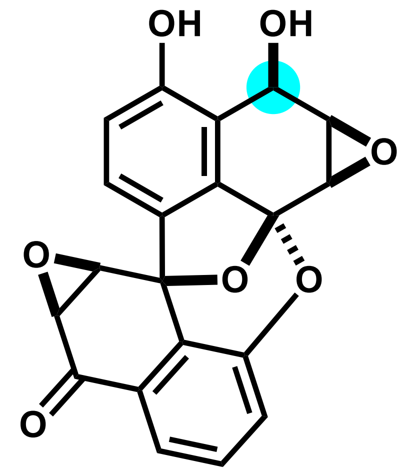
Spiroxins



Spiroxin A



Spiroxin C



Spiroxin D

Isolation[1)]

from fungal strain LL-37H248
(1999, Dixon Bay in Canada)

Biological activity

antitumor and antibacterial activities

Structural features

a unique naphthoquinone dimer structure
octacyclic ring structure

Total synthesis of spiroxin

Imanishi[2)] (2003, (±)-Spiroxin C, 15 steps)
Suzuki[3)] (2017, (-)-Spriroxin C, 20 steps)
Suzuki[4)] (2019, both enantiomers of Spiroxin A, 25 steps)
Hu[5)] (2021, (-)-Spiroxin A (14 steps), C (10 steps), D (11 steps))

Synthetic study of spiroxin

Inoue[6)] (2008)
Carrico-Moinz[7)] (2011)

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1) a) McDonald L. A.; Abbanat, D. R.; Barbieri, L. R.; Bernan, V. S.; Discafani, C. M.; Greenstein, M.; Janota, K; Korshalla, J. D.; Lassota, P.; Tischler, M.; Carter, G. T. *Tetrahedron Lett*. **1999**, *40*, 2489. b) Wang, T.; Shirota, O.; Nakanishi, K.; Berova, N.; McDonald, L. A.; Barbieri, L. R.; Carter, G. T. *Can. J. Chem.* **2001**, *79*, 1786. 2) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett*. **2003**, *5*, 2683. 3) Ando, Y.; Hanaki, A.; Sasaki,R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460. 4) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori,K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507. 5) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed*. **2021**, *60*, 18514. 6) Nabatame, K.; Hirama, M.; Inoue, M. *Heterocycles* **2008**, *76*, 1011. 7) Kwan, A.; Stein, J.; Carrico-Moinz, D. *Tetrahedron Lett*. **2011**, *52*, 3426.

Introduction of Prof. Suzuki and Hu

Prof. Keisuke Suzuki

1978 B.S. @ the University of Tokyo
1983 Ph.D @ the University of Tokyo (Prof. Teruaki Mukaiyama)
1983- Assistant professor@ Keio University (Prof. Tsuchihashi)
1987 Junior Associate Professor @Keio University
1989 Associate professor @Keio University
1990 Visiting professor @ETH (Prof. Dieter Seebach)
1994- Professor @ Keio University
1996- Professor@ Tokyo Institute of Technology
2020- Distinguished professor @ Tokyo Institute of Technology

Research topic: total synthesis, reaction development

Prof. Xiangdong Hu

1997 B.S @ Lanzhou University
2006 Ph.D @ Lanzhou University (Prof. Yongqiang Tu)
2006- Postdoctral fellow @ university of South Florida USA (Prof. Roman Manetsch)
2009- Professor @Northwest University

Research topic: total synthesis

1) http://www.org-synth.chem.sci.titech.ac.jp/suzukilab/?page_id=7#suzuki
2) https://en-chem.nwu.edu.cn/info/1006/1048.htm

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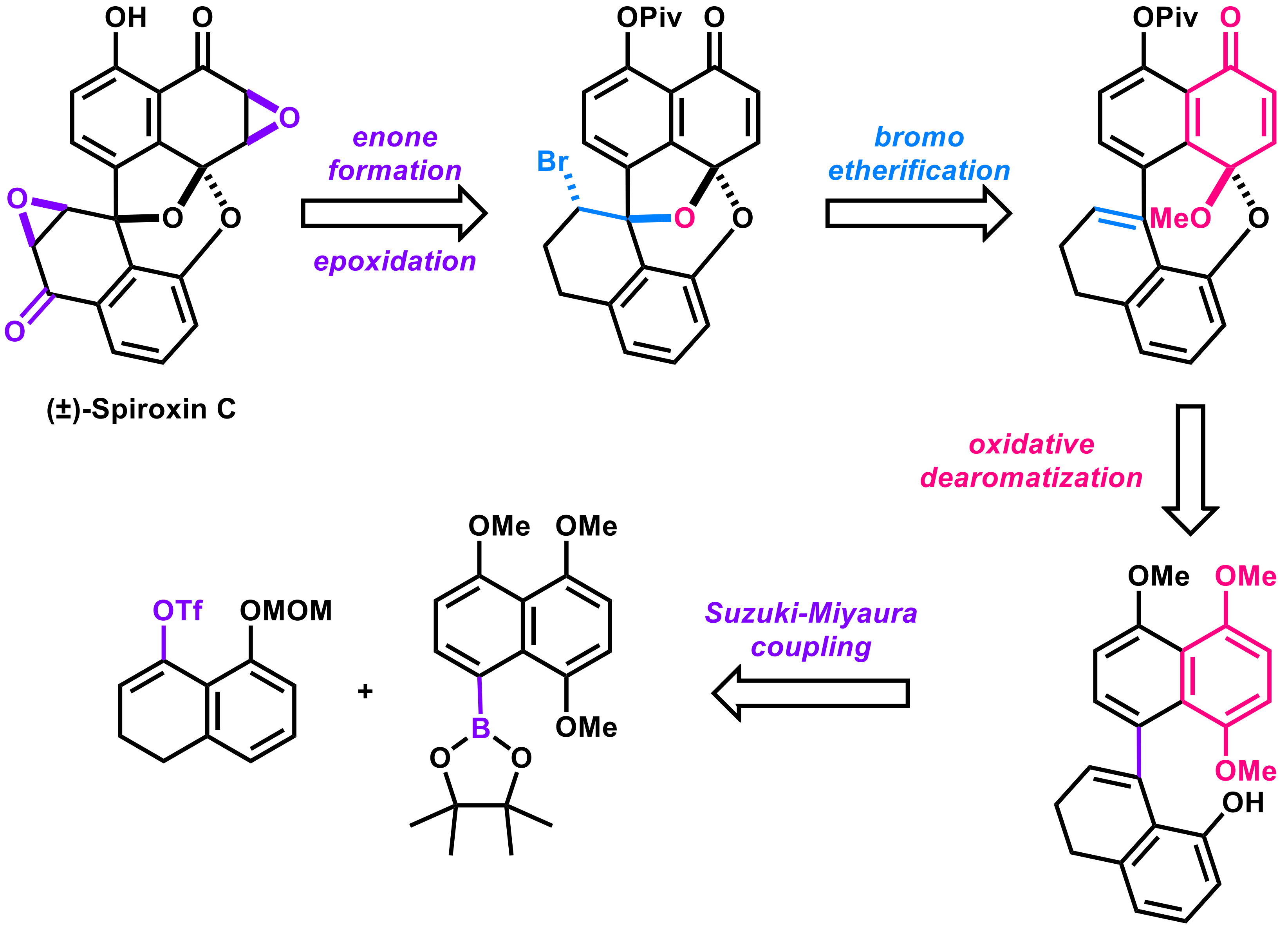
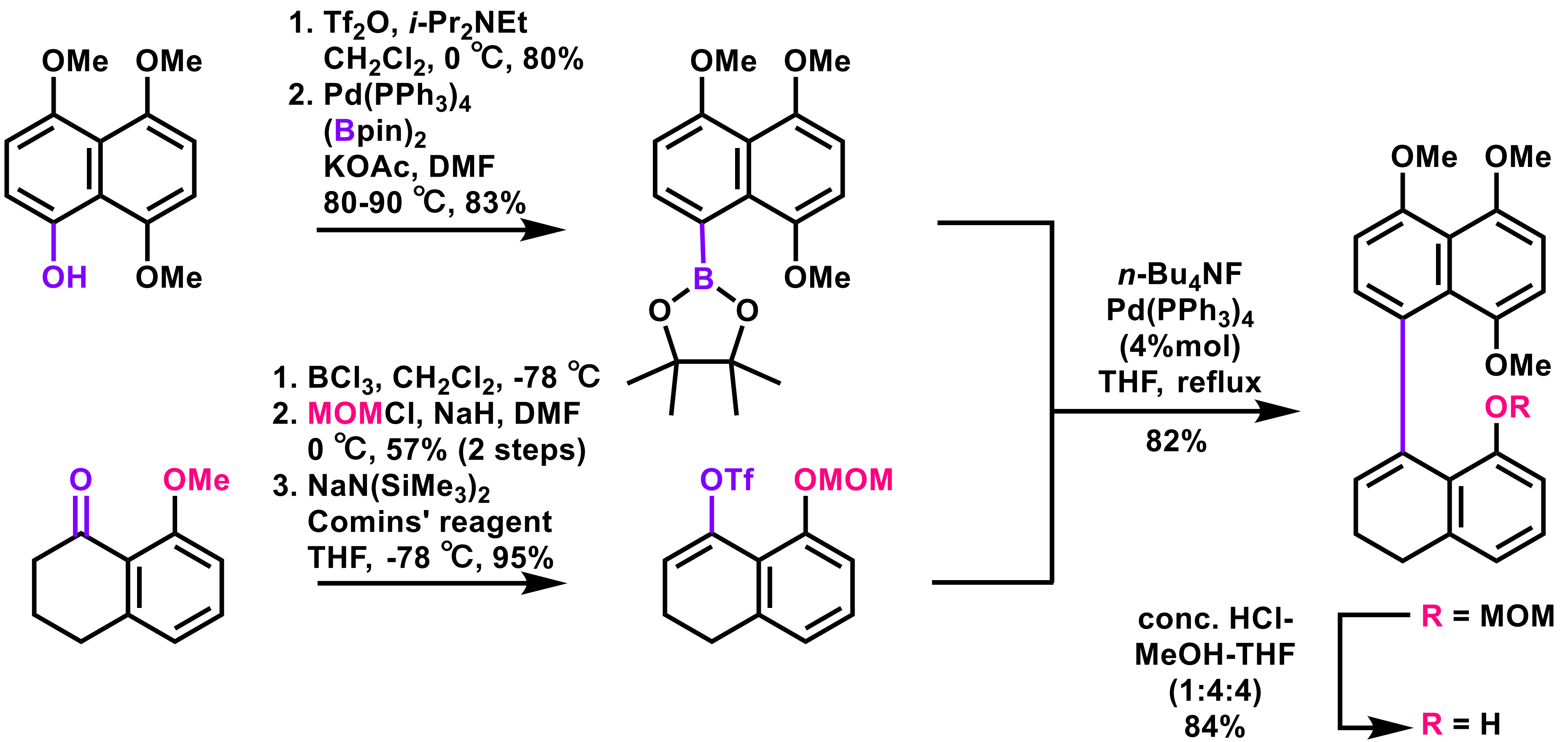
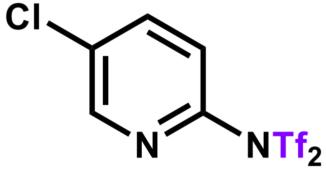
Retrosynthesis



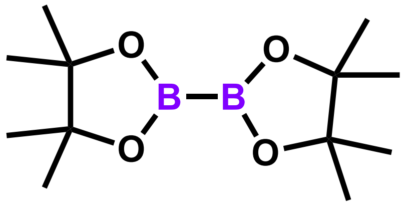
1) Miyashita, K.; Sakai, T.; Imanishi, T*. Org. Lett*. **2003**, *5*, 2683.

Preparation of Substrate





Comins' reagent



$(Bpin)_2$

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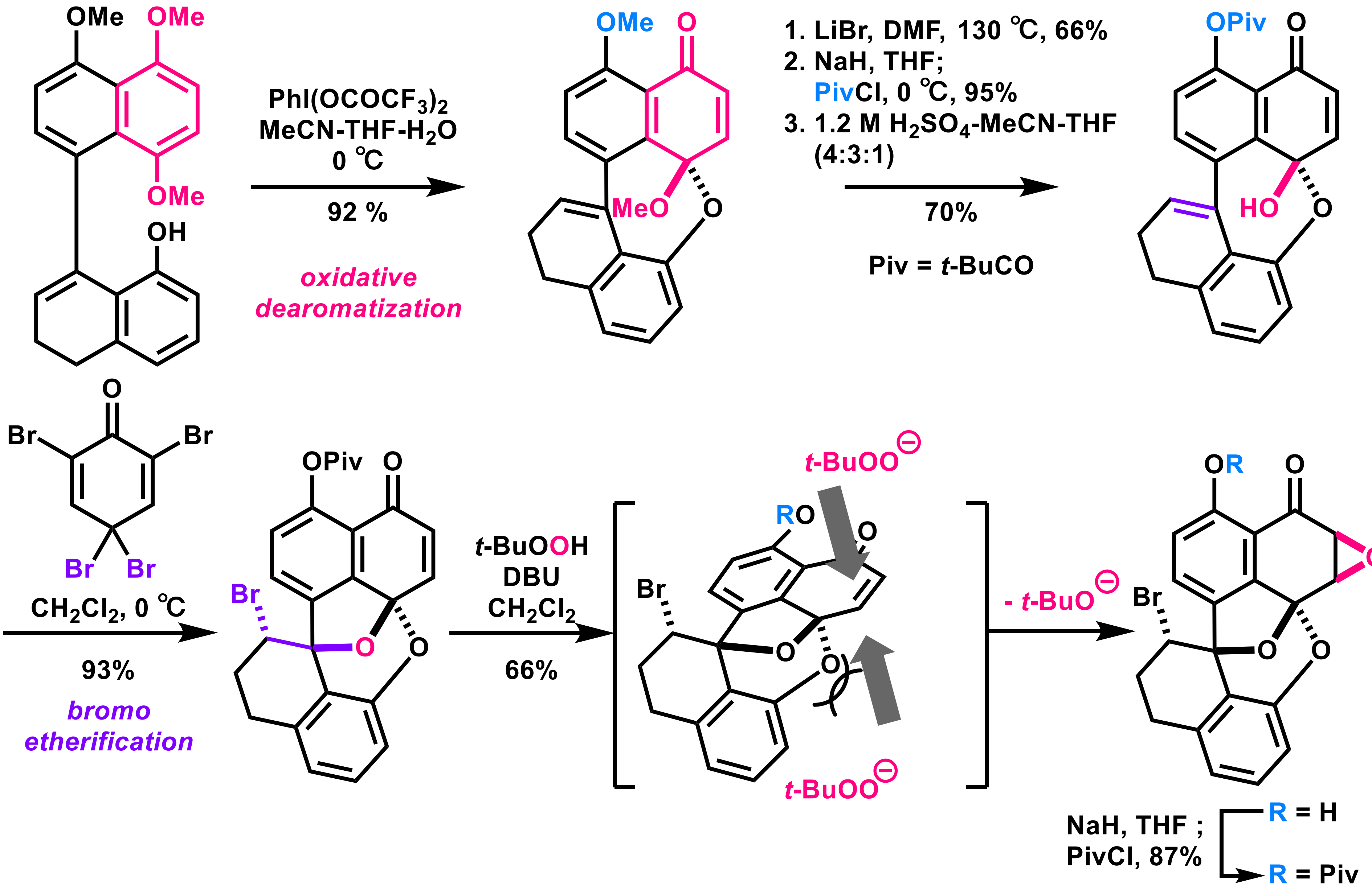
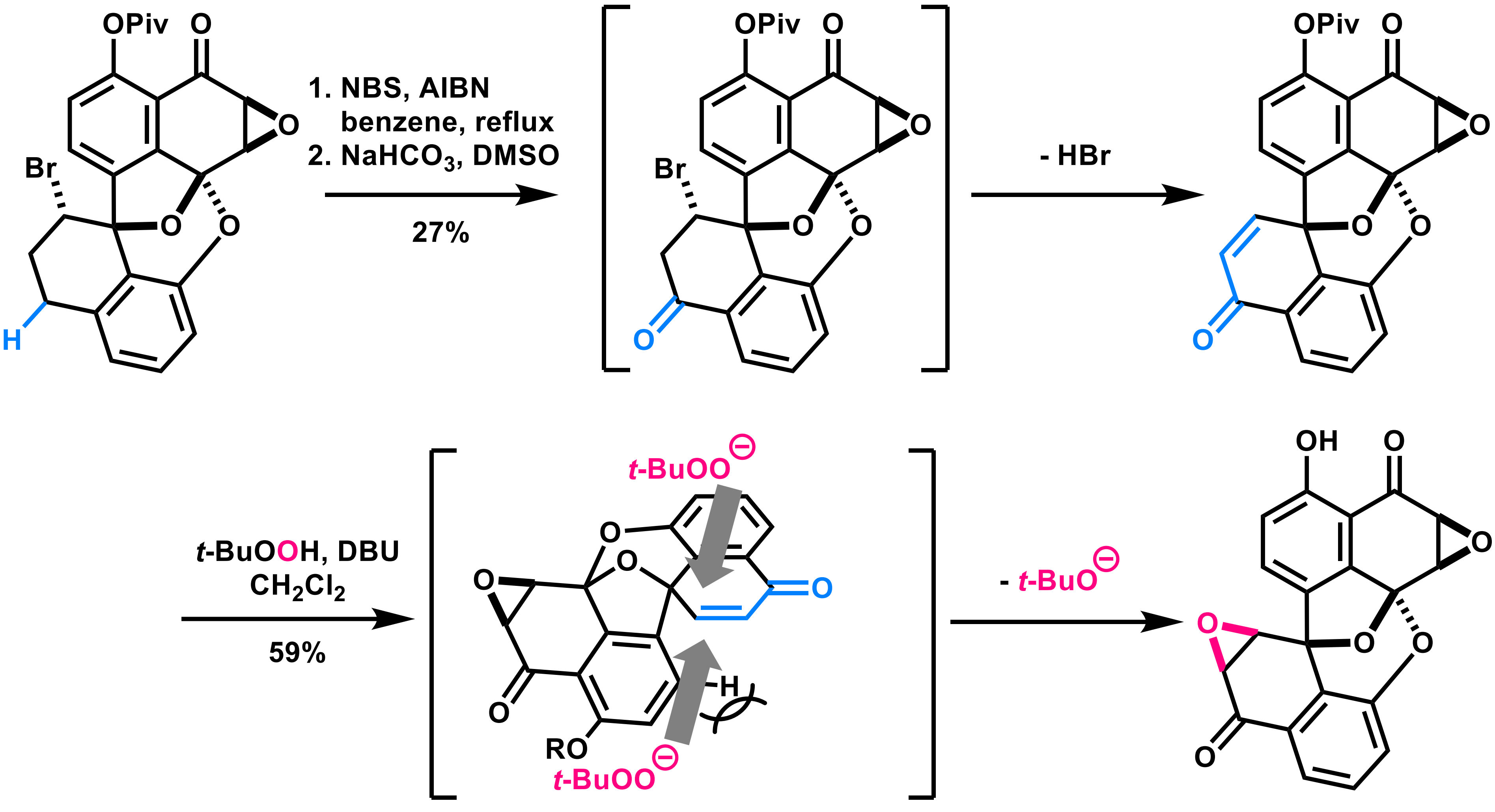
1) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett*. **2003**, *5*, 2683.

Construction of Spiroacetal Skeleton



1) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett*. **2003**, *5*, 2683.

Enone Formation and Epoxidation



(±)-Spiroxin C
(LLS: 15 steps)

1) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett*. **2003**, *5*, 2683.

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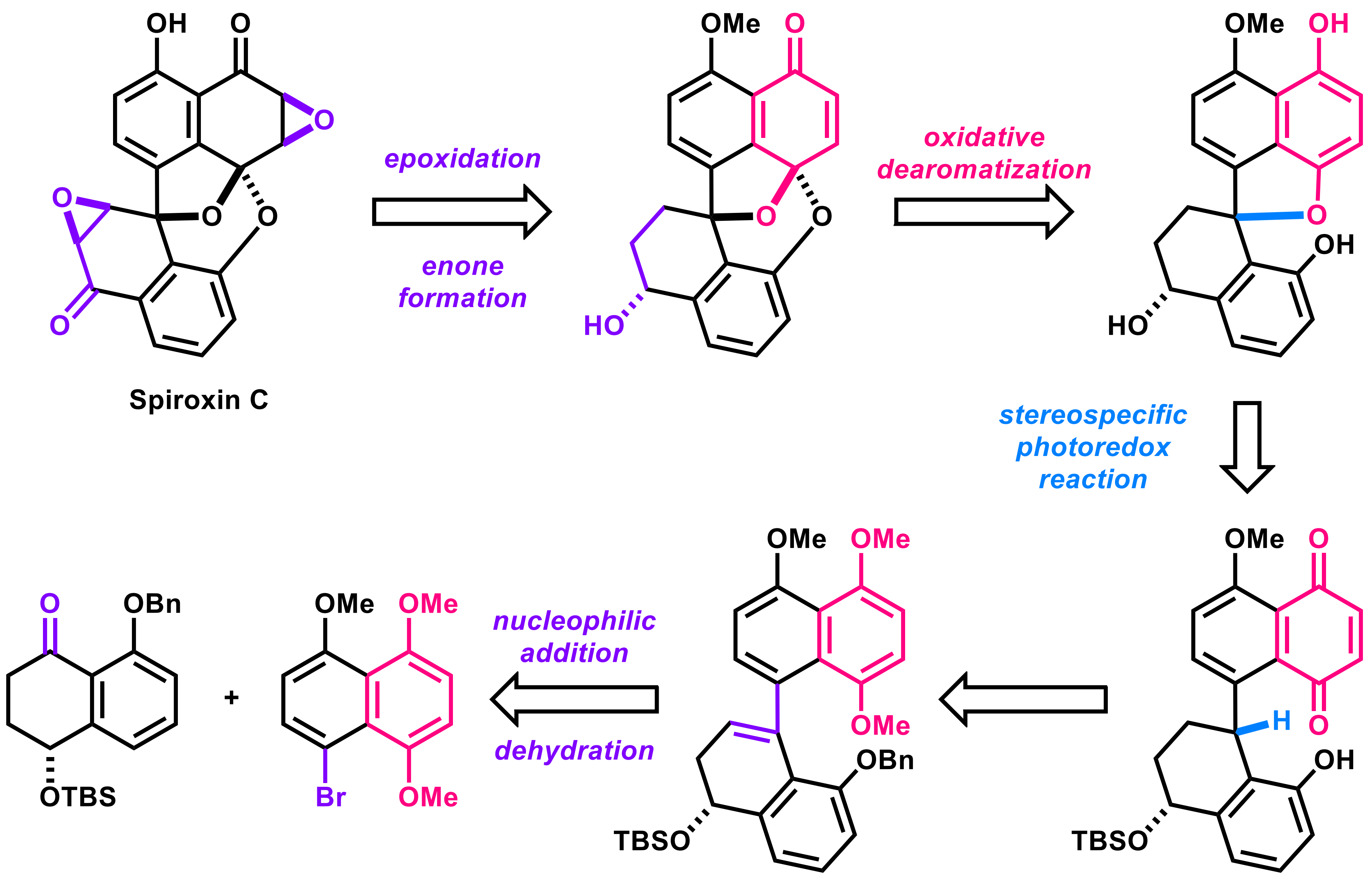
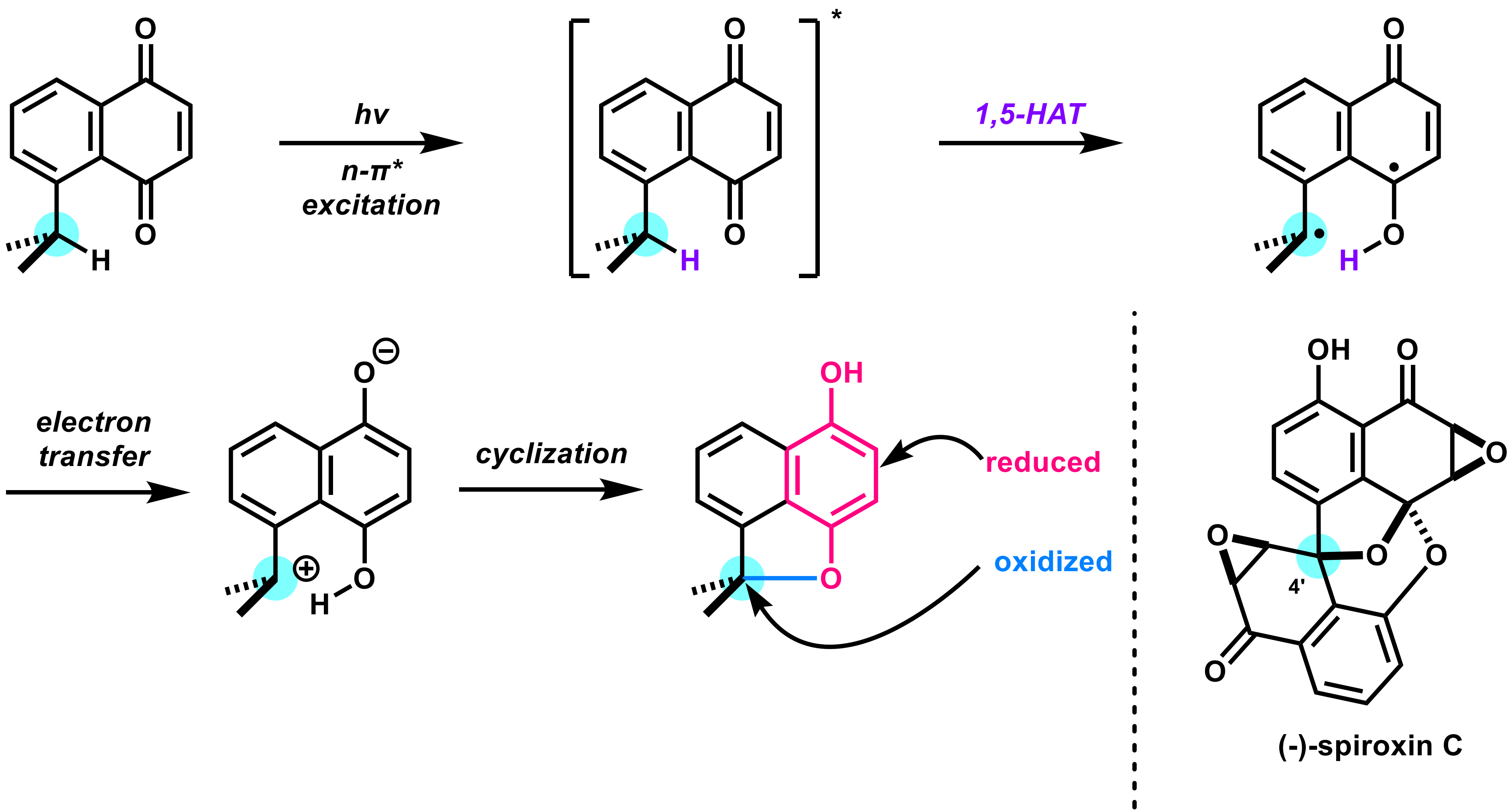
Retrosynthesis



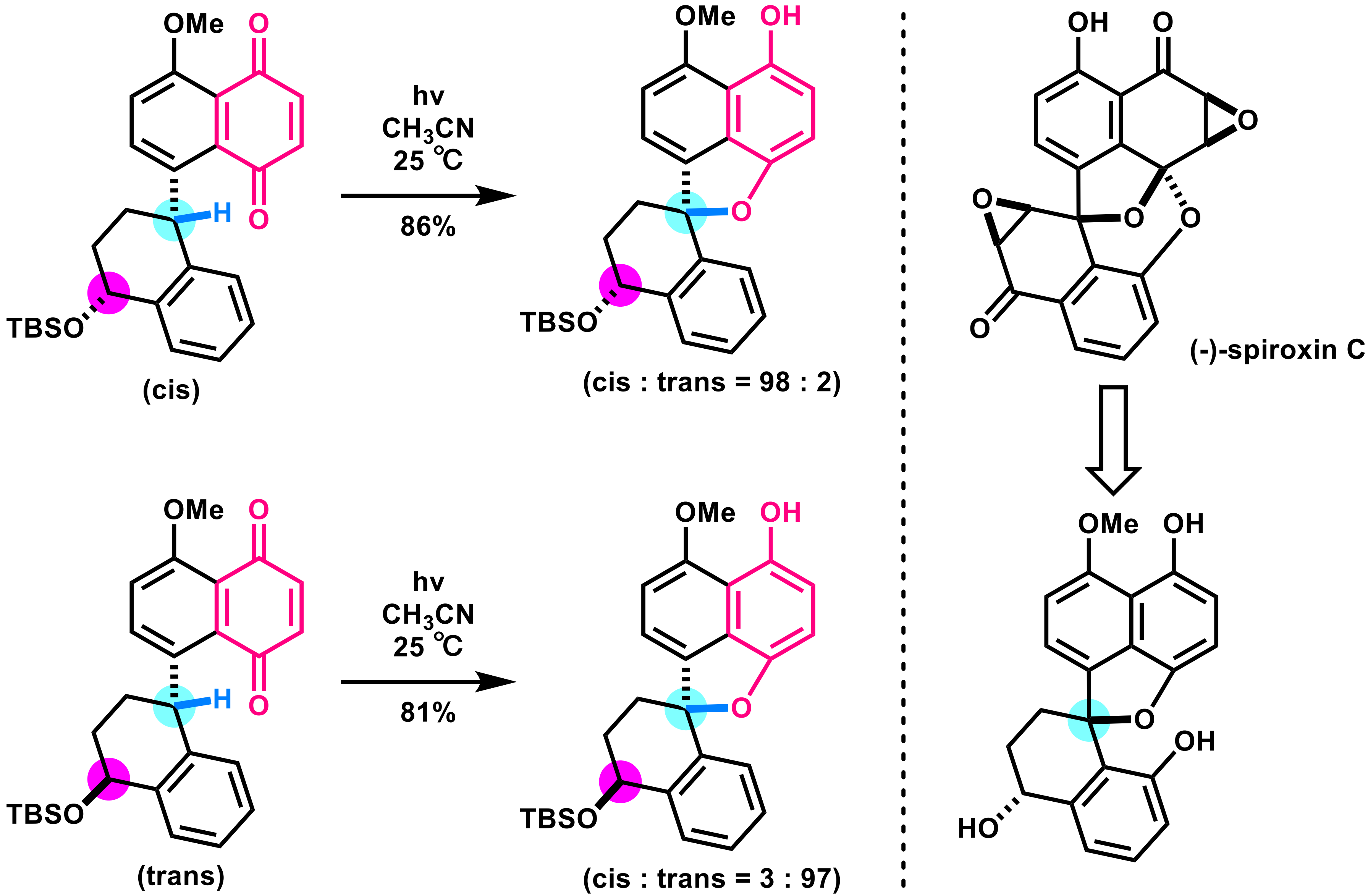
1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.

Photoredox Reaction of Naphtoquinone



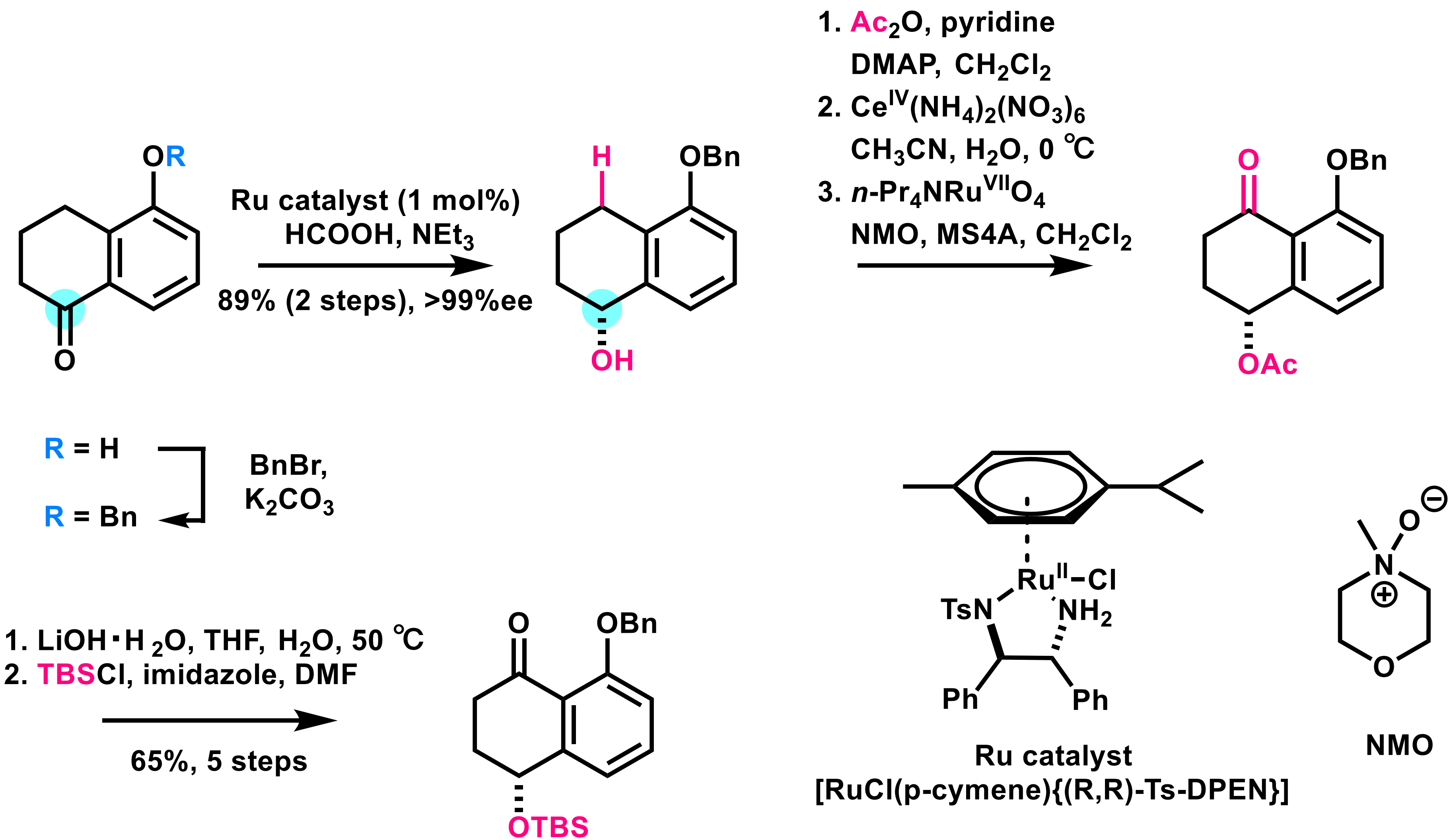
1) Ando, Y.; Matsumoto, T.; Suzuki, K*.* *Synlett* **2017**, *28*, 1040.
2) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.

Stereoselectivity of Photoredox Reaction



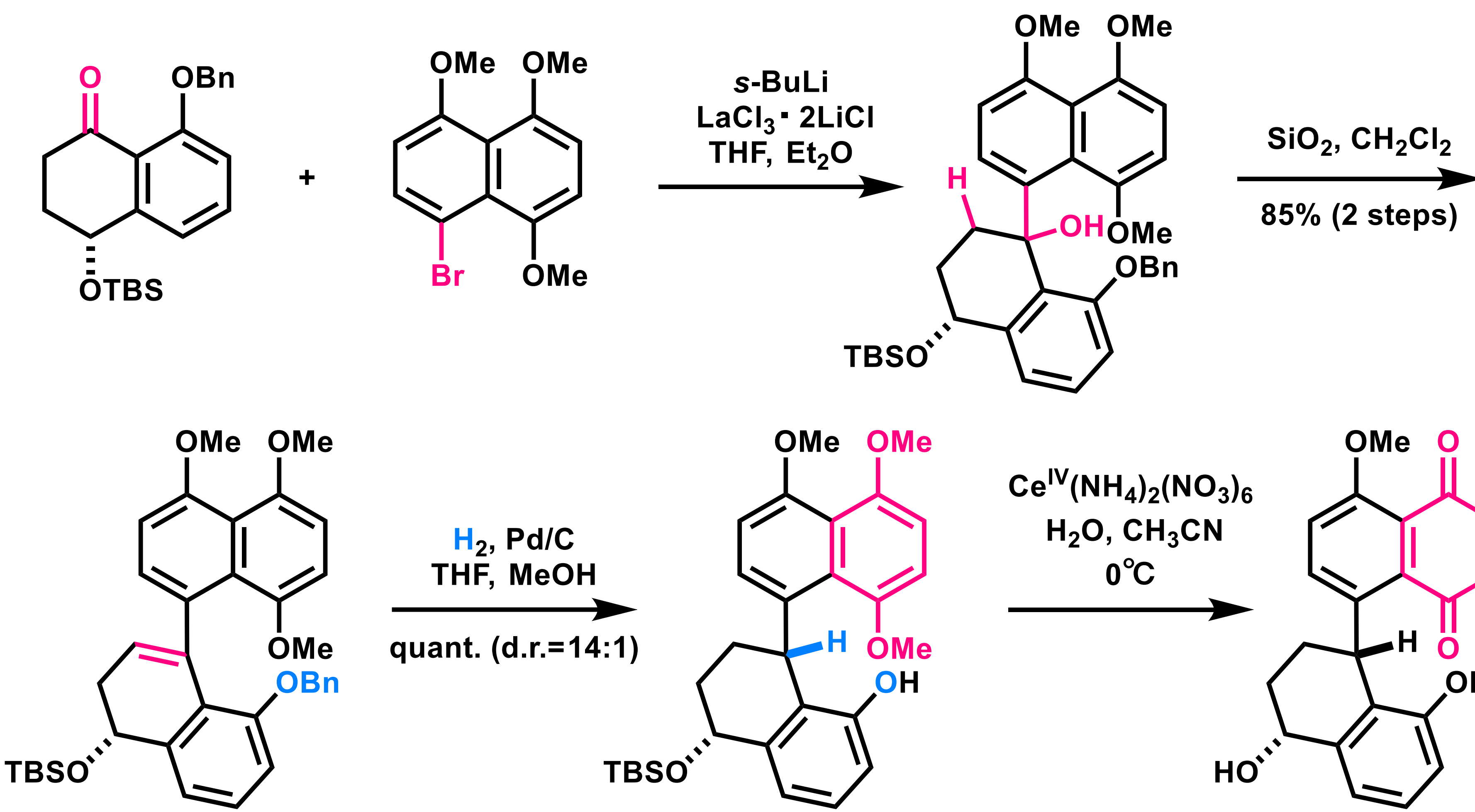
1) Ando, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **2017**, *28*, 1040.
2) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11460.

Preparation of Substates



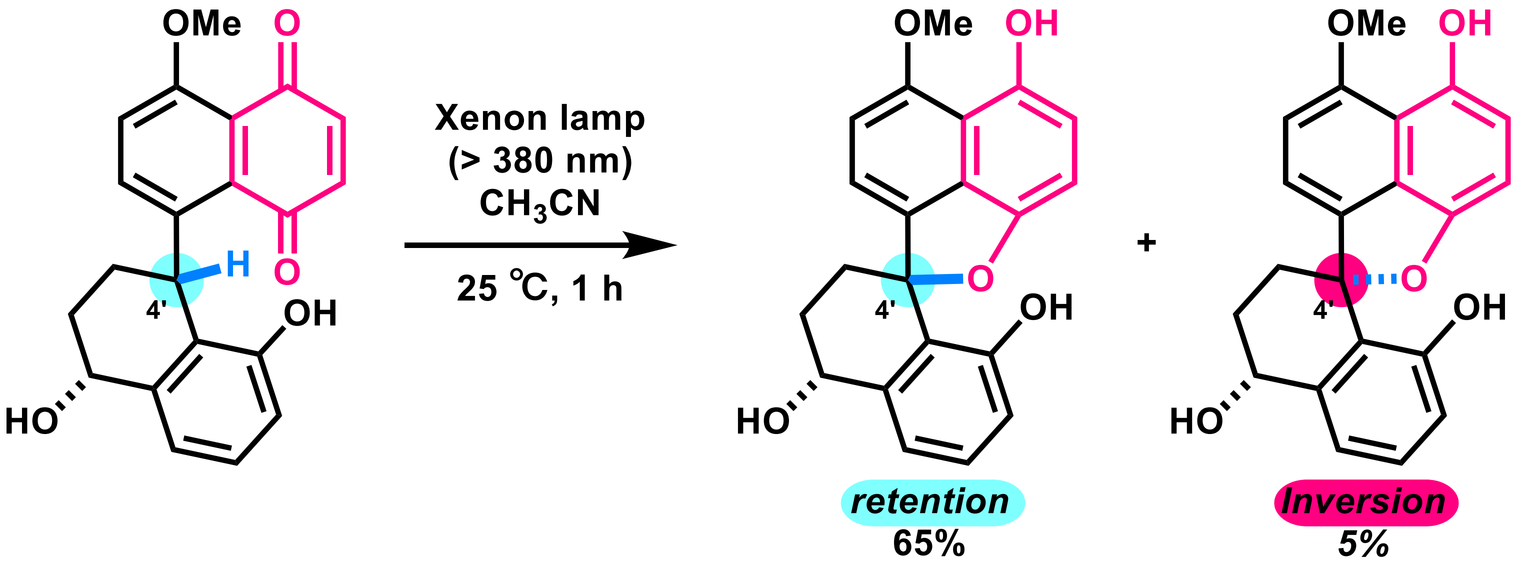
1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11460.

Preparation of Naphtoquinone



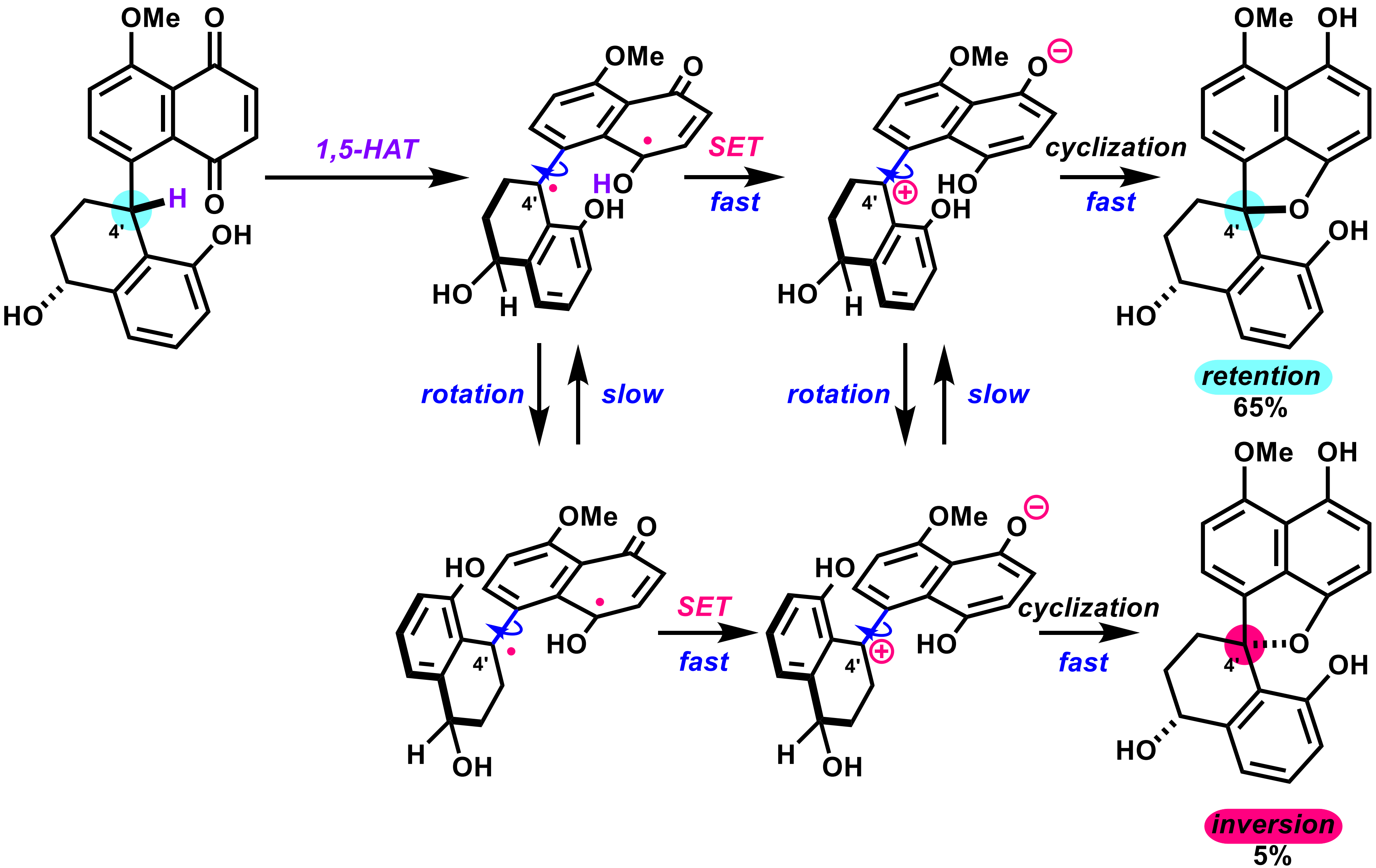
1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11460.

Photoredox Reaction



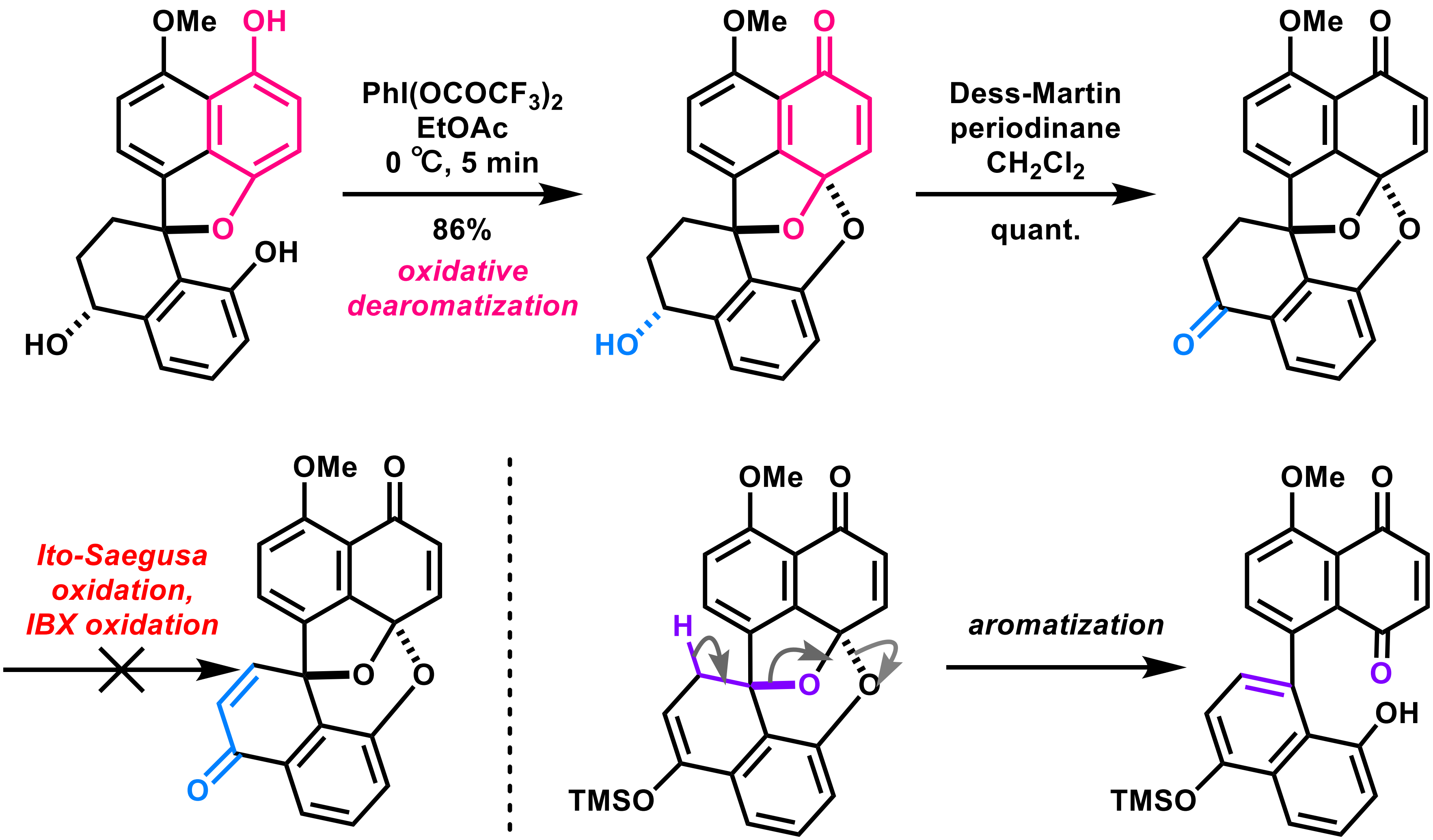
1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.

Stereoselectivity of Photoredox Reaction



1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11460.

Construction of Spiroacetal Skeleton



1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11460.

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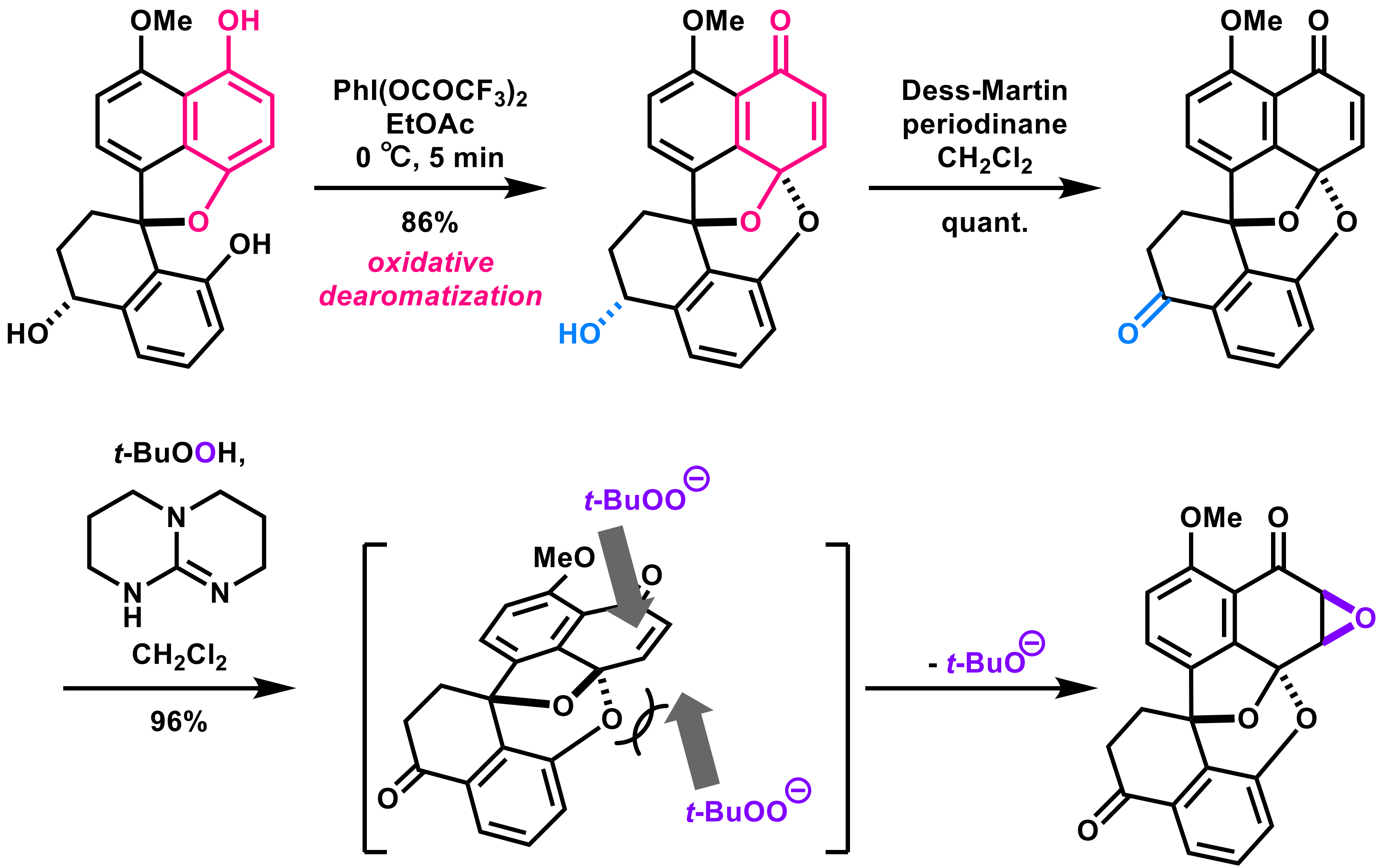
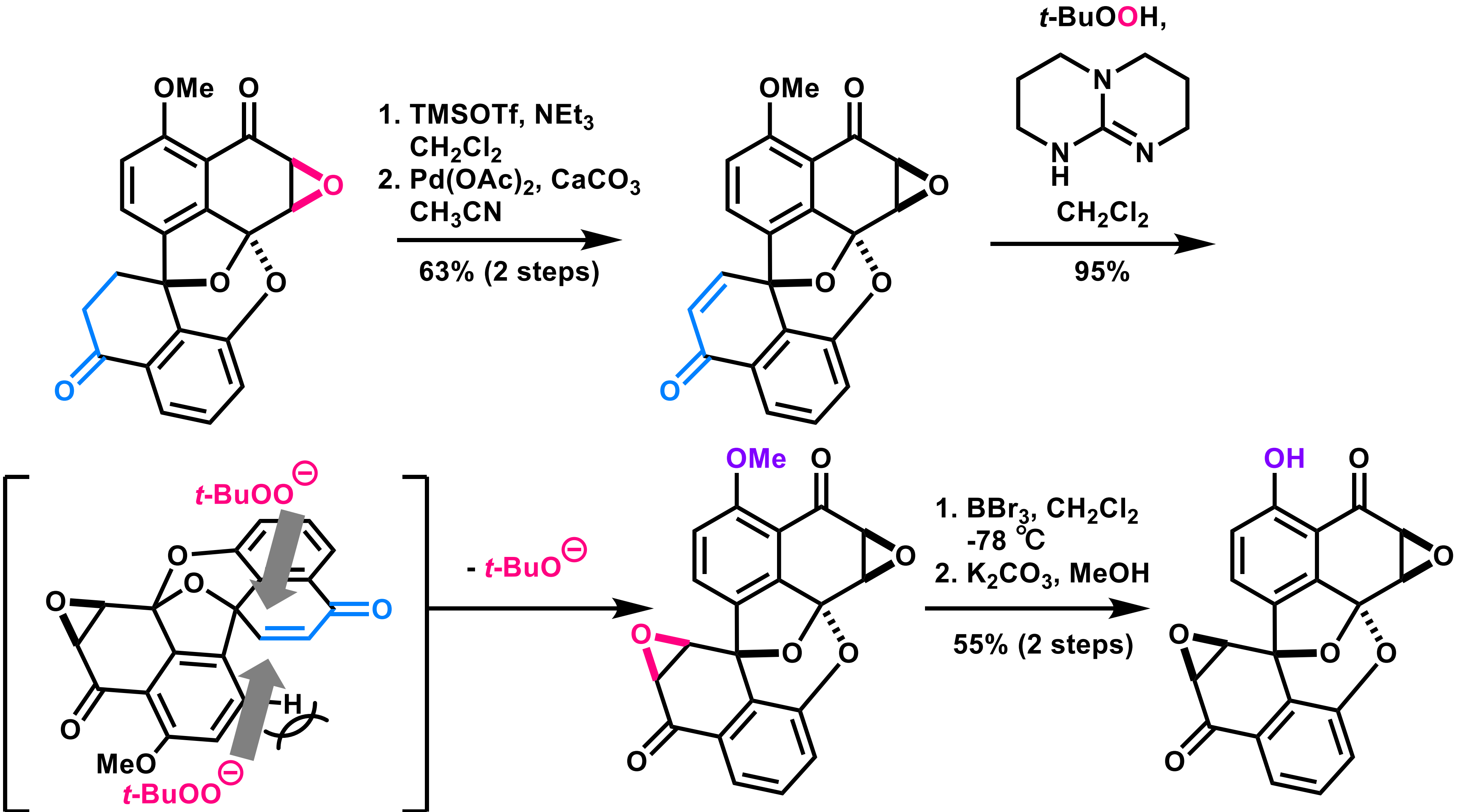


1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.

Enone Formation and Epoxidation



(-)-spiroxin C
(LLS: 20 steps)

1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.

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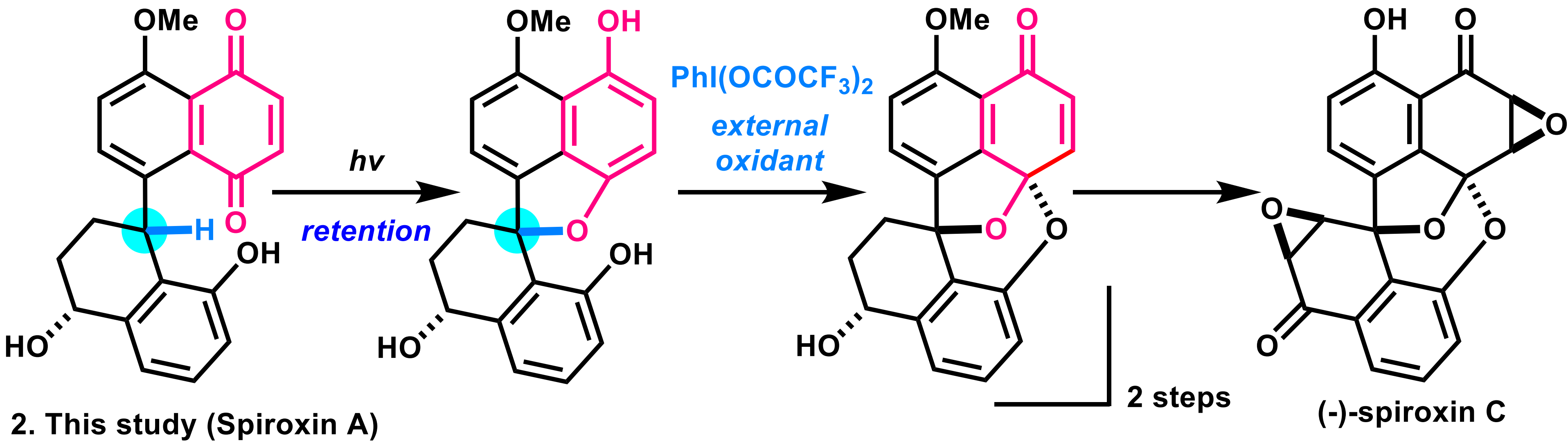
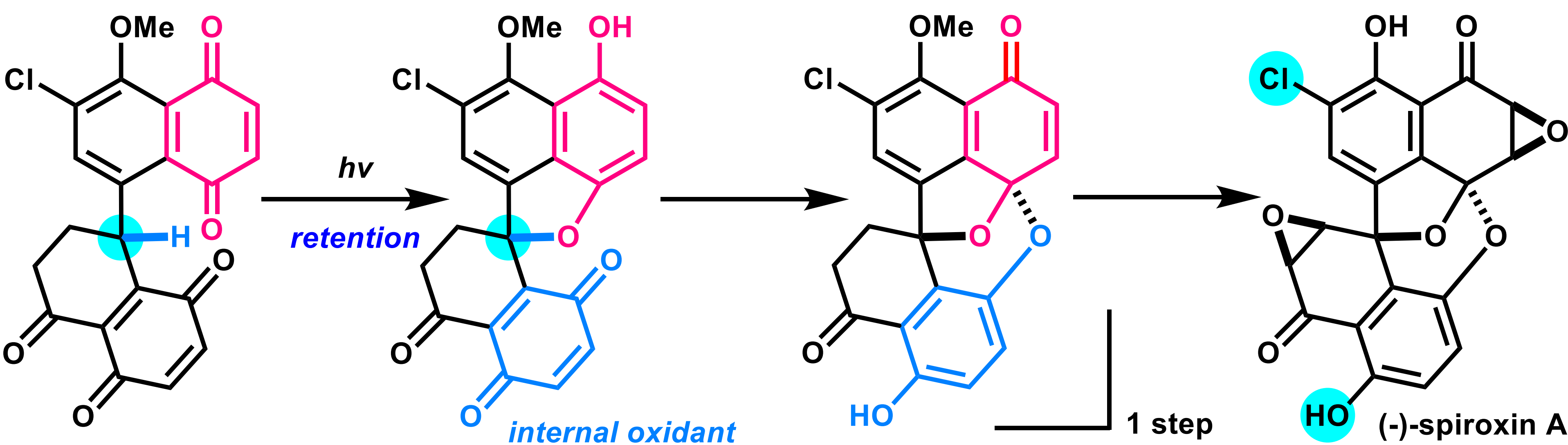
Substrate Design for Total Synthesis of Spiroxin A

1. Previous study (Spiroxin C)

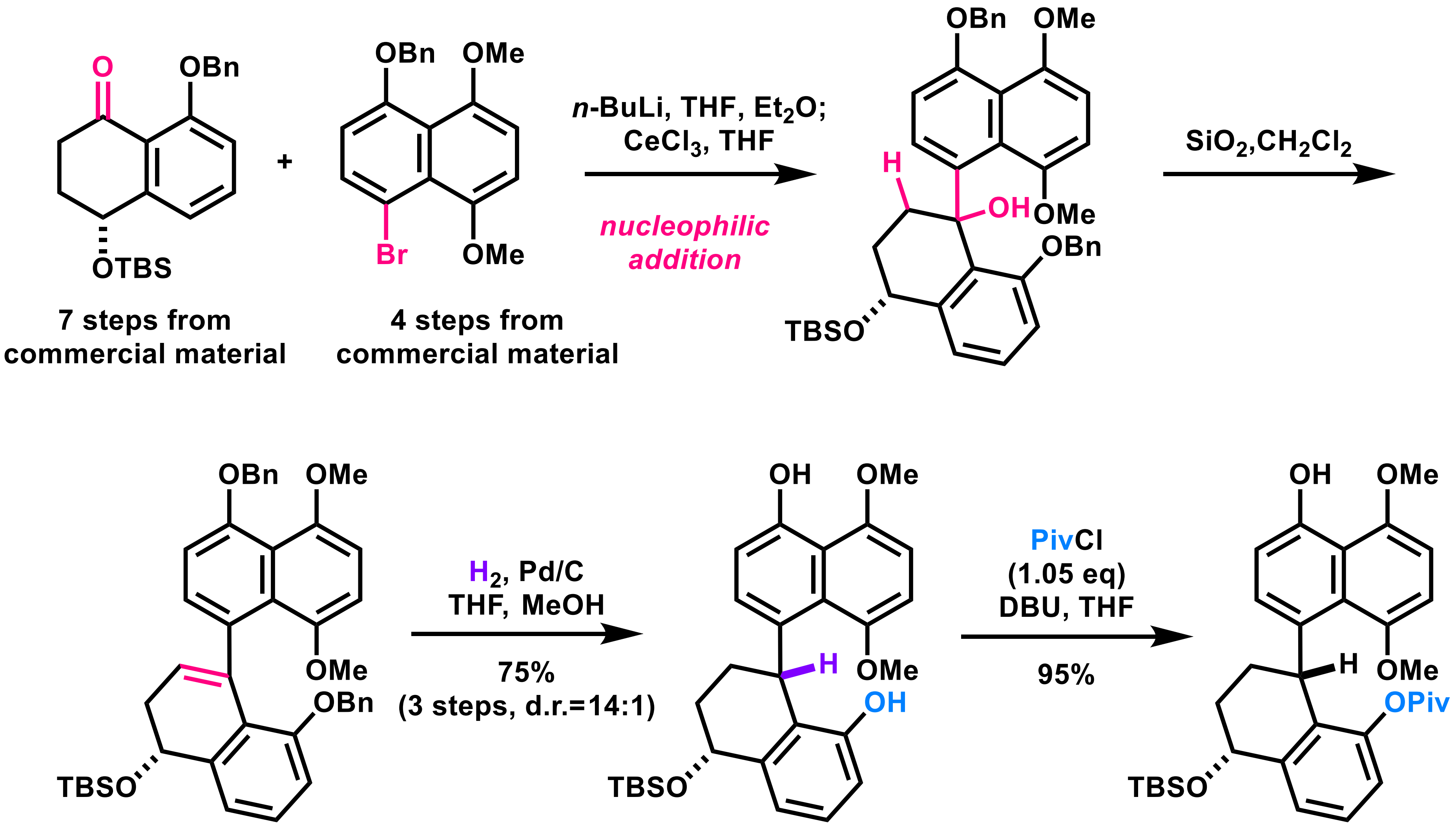


2. This study (Spiroxin A)



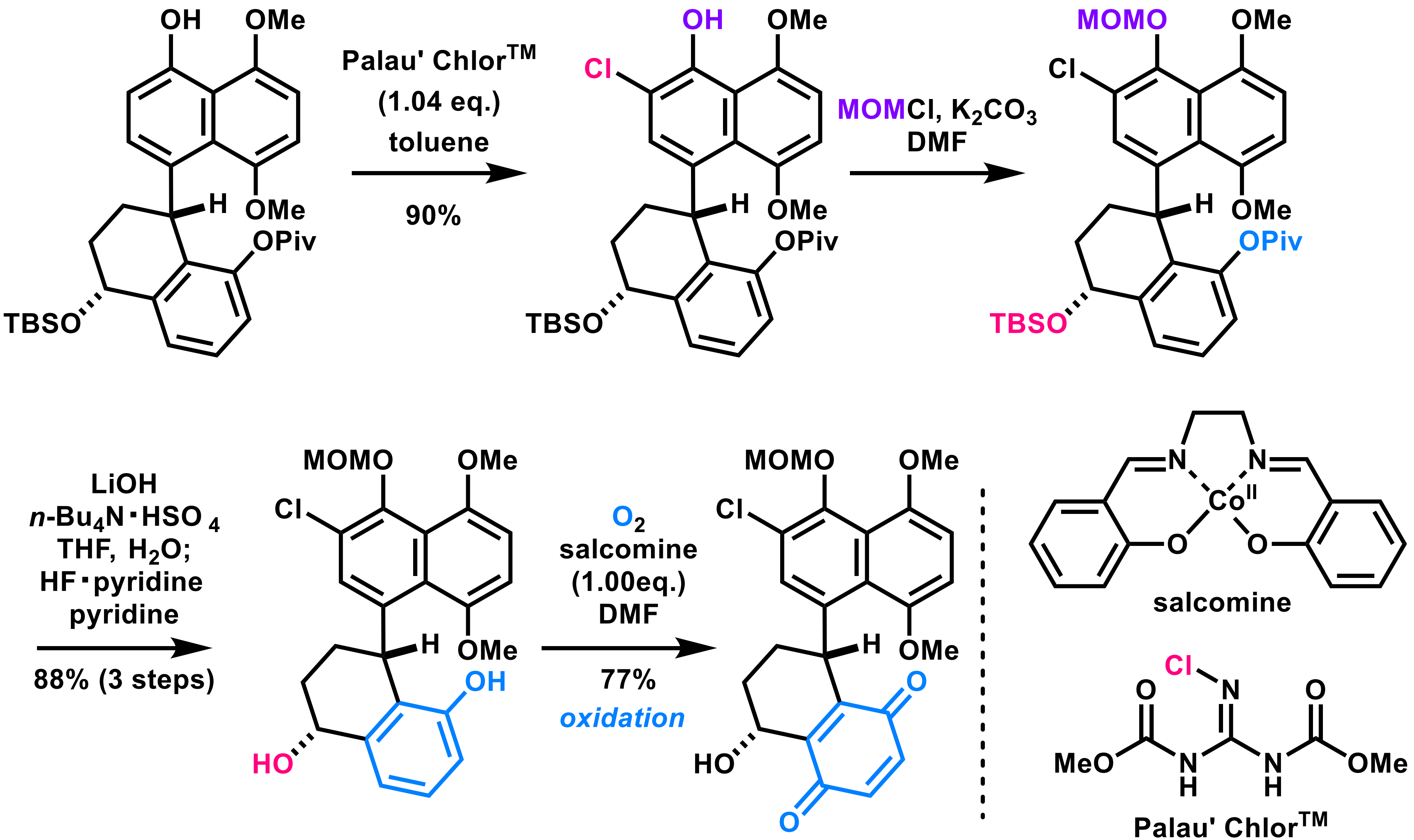
1) Ando, Y.; Hanaki, A.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed*. **2017**, *56*, 11460.
2) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

Nucleophilic Addition



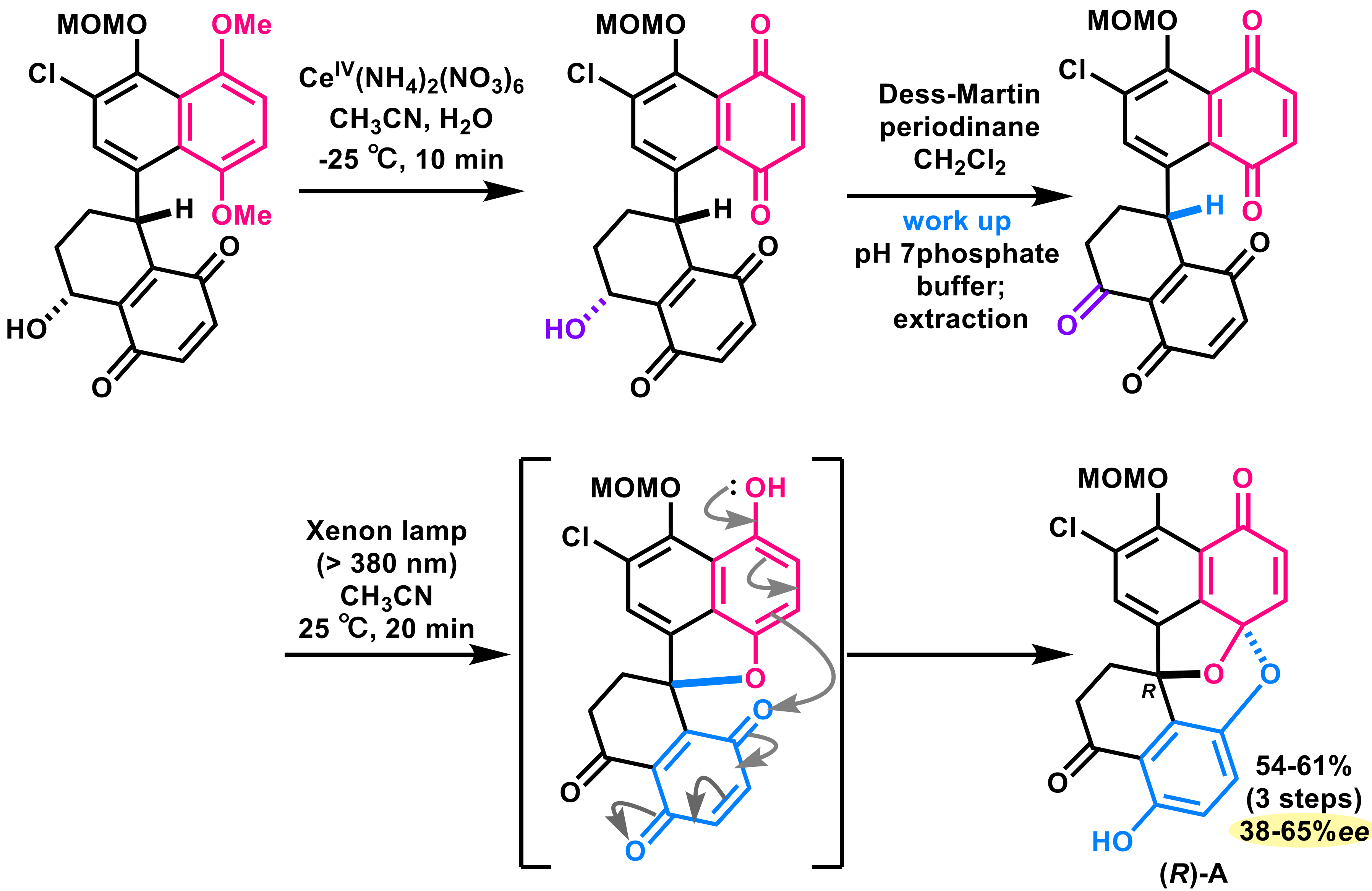
1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

Preparation of Internal Oxidant



1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

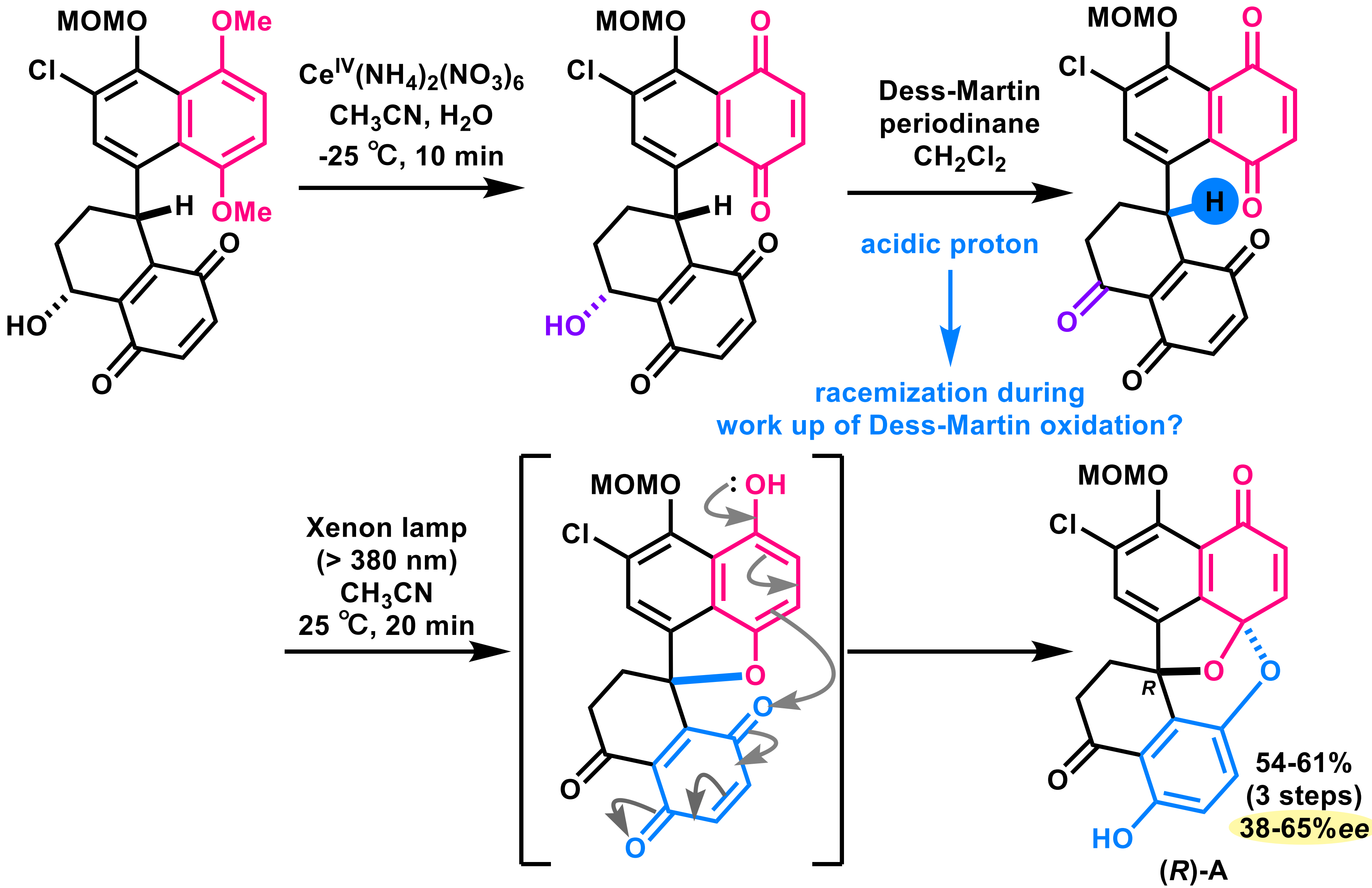
Construction of Spiroacetal Skeleton



1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

2) S. Chi, C. H. Heathcock, *Org. Lett*. **1999**, *1*, 3.

Loss of Chirality



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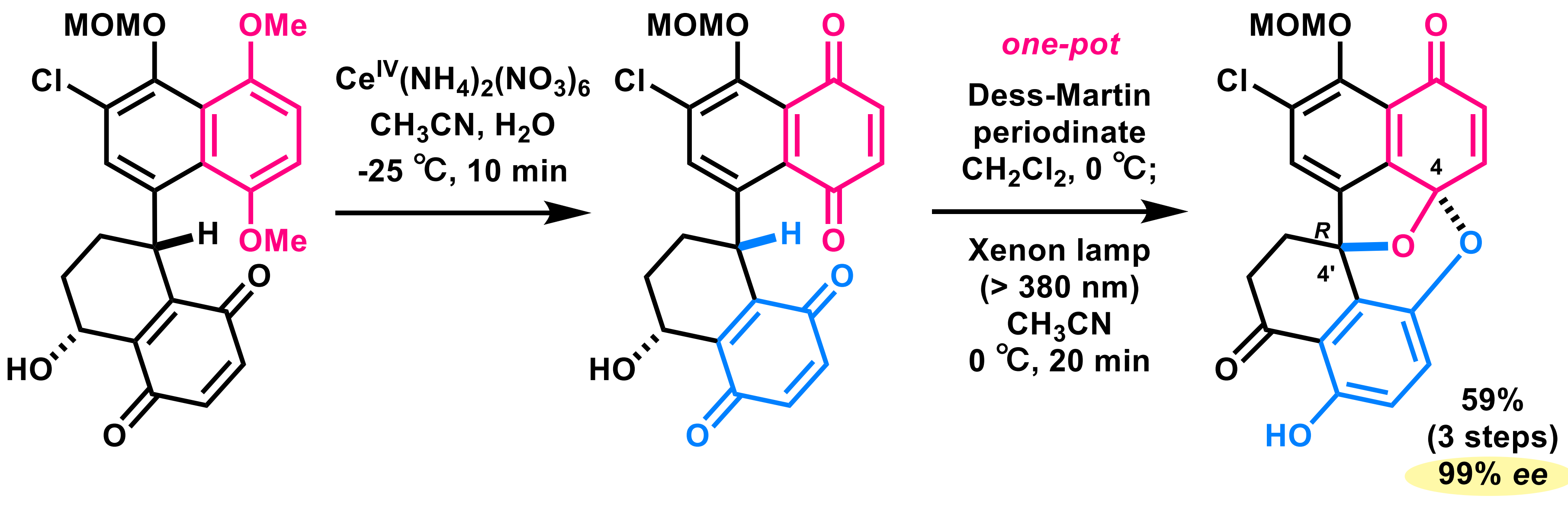
1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

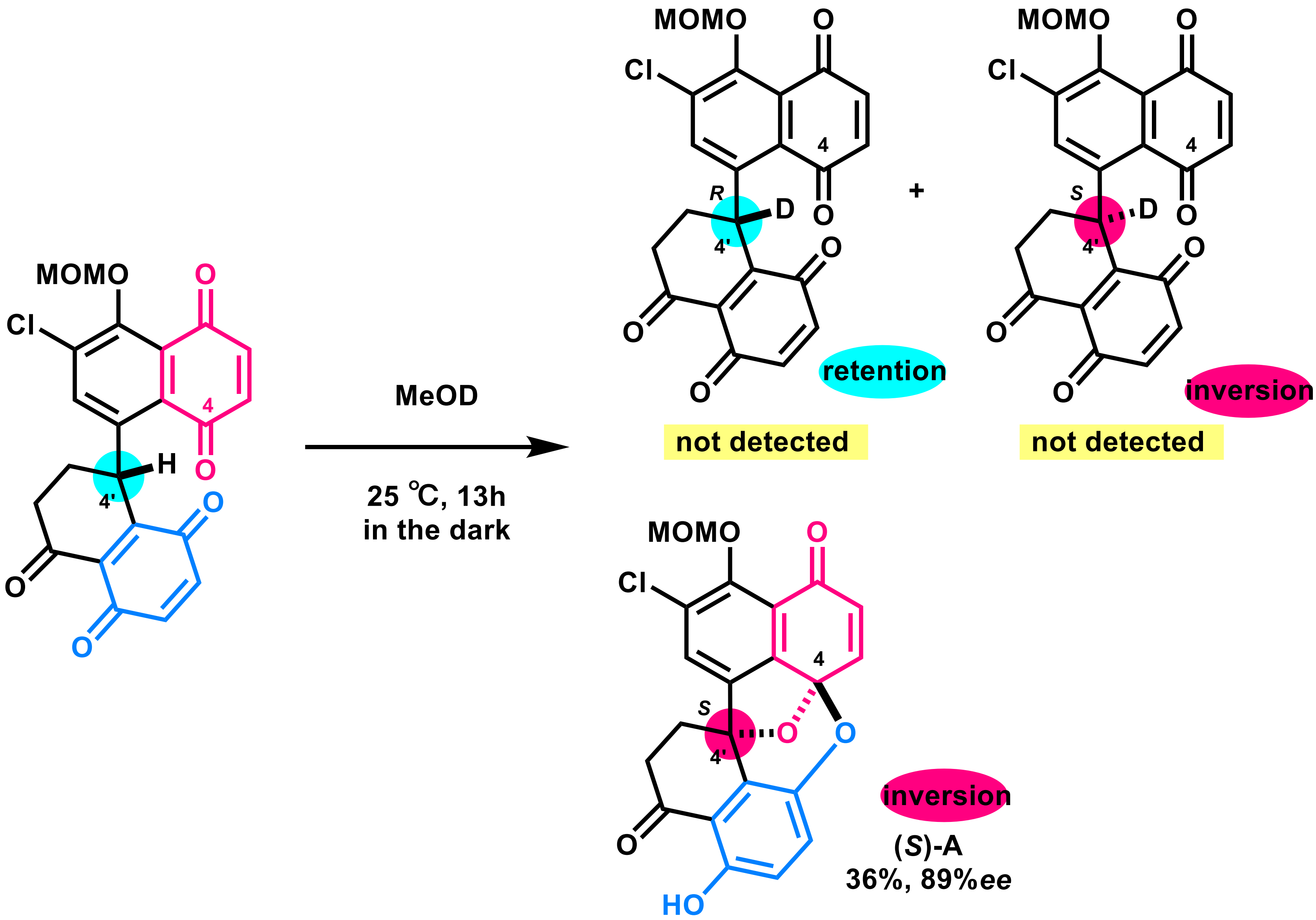
One-pot Protocol



(*R*)-A

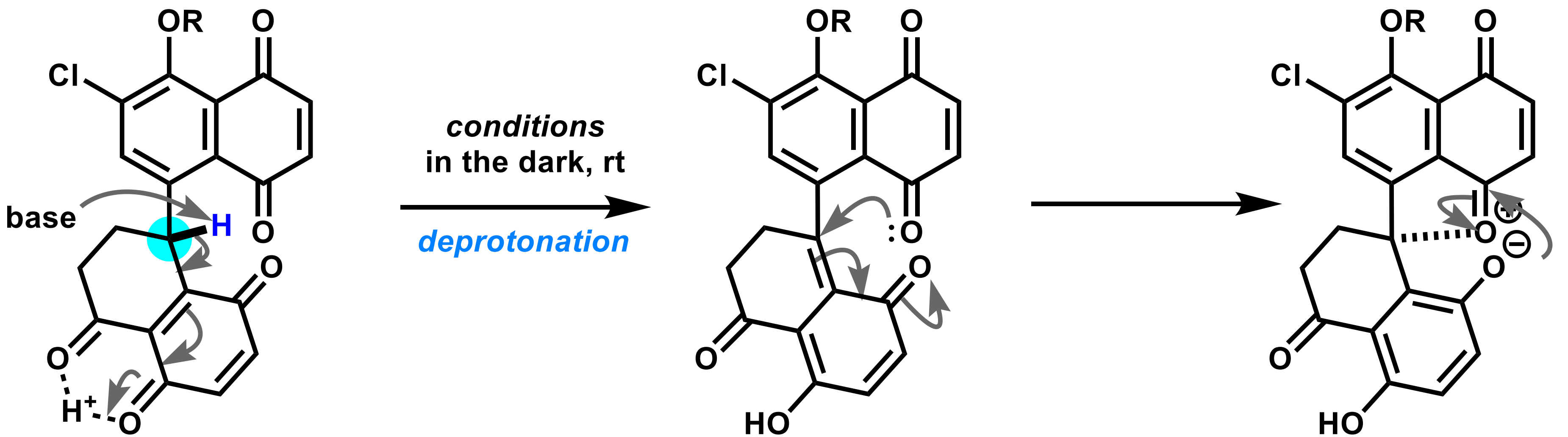
1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

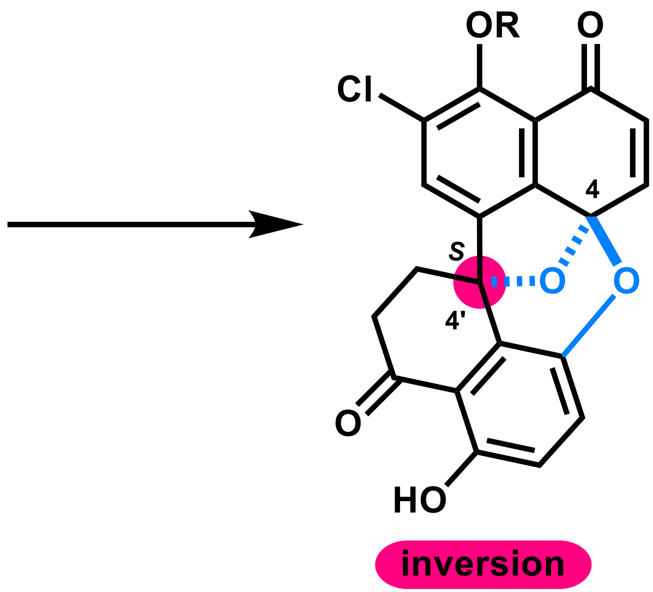
Deuterium Experiment



1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

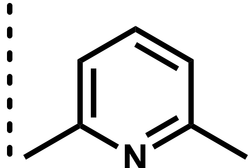
Optimization of Reaction Conditions





(*S*)-A

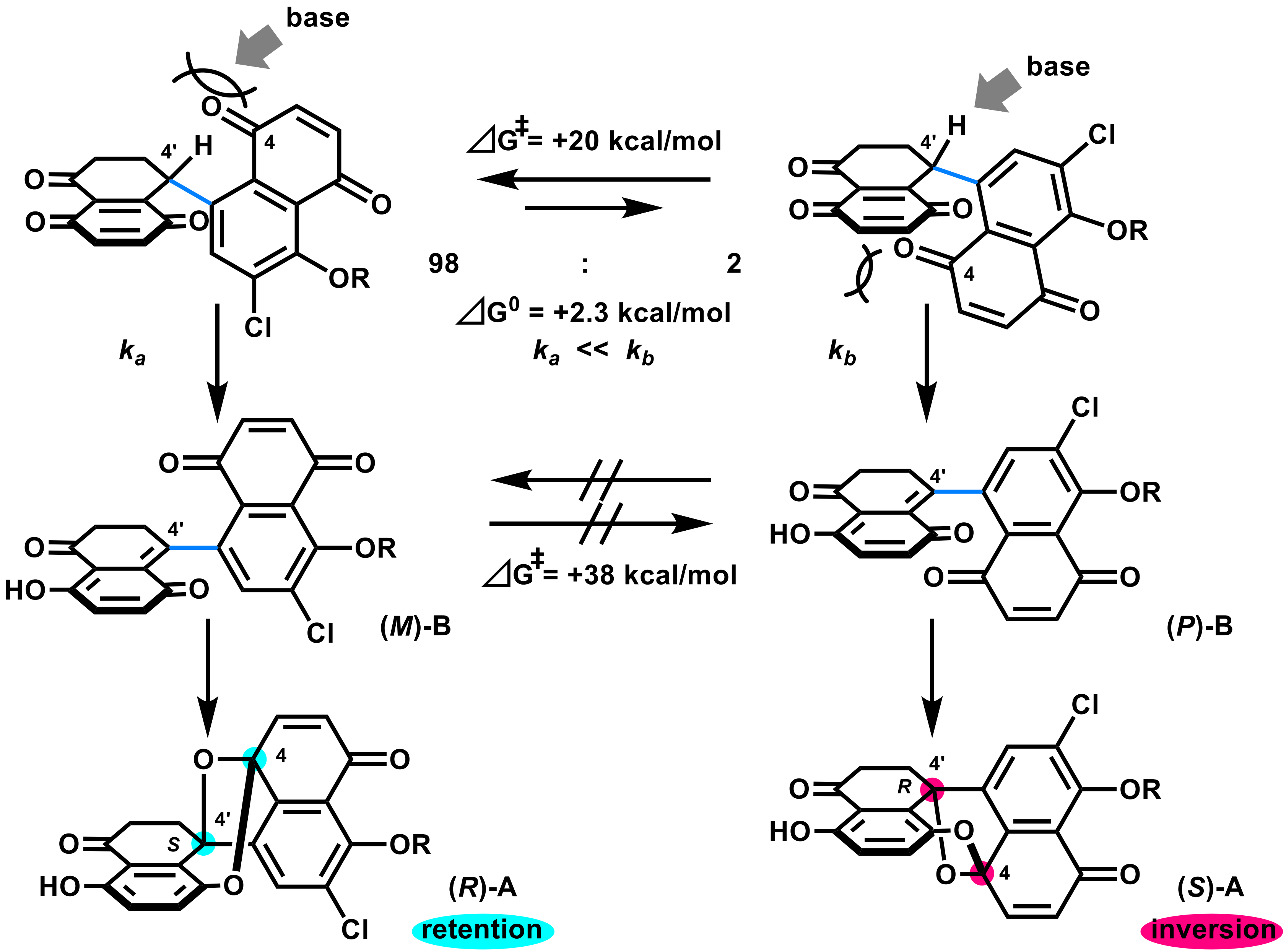
solvent	additive	t (h)	yield(%)	ee(%)
MeOH	-	22	19	82
CH_3CN	AcOH	30	51	90
CH_3CN	*t*-$BuCO_2H$	90	59	97
CH_3CN	2,6-lutidine	2.5	63	99



2,6-lutidine

1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

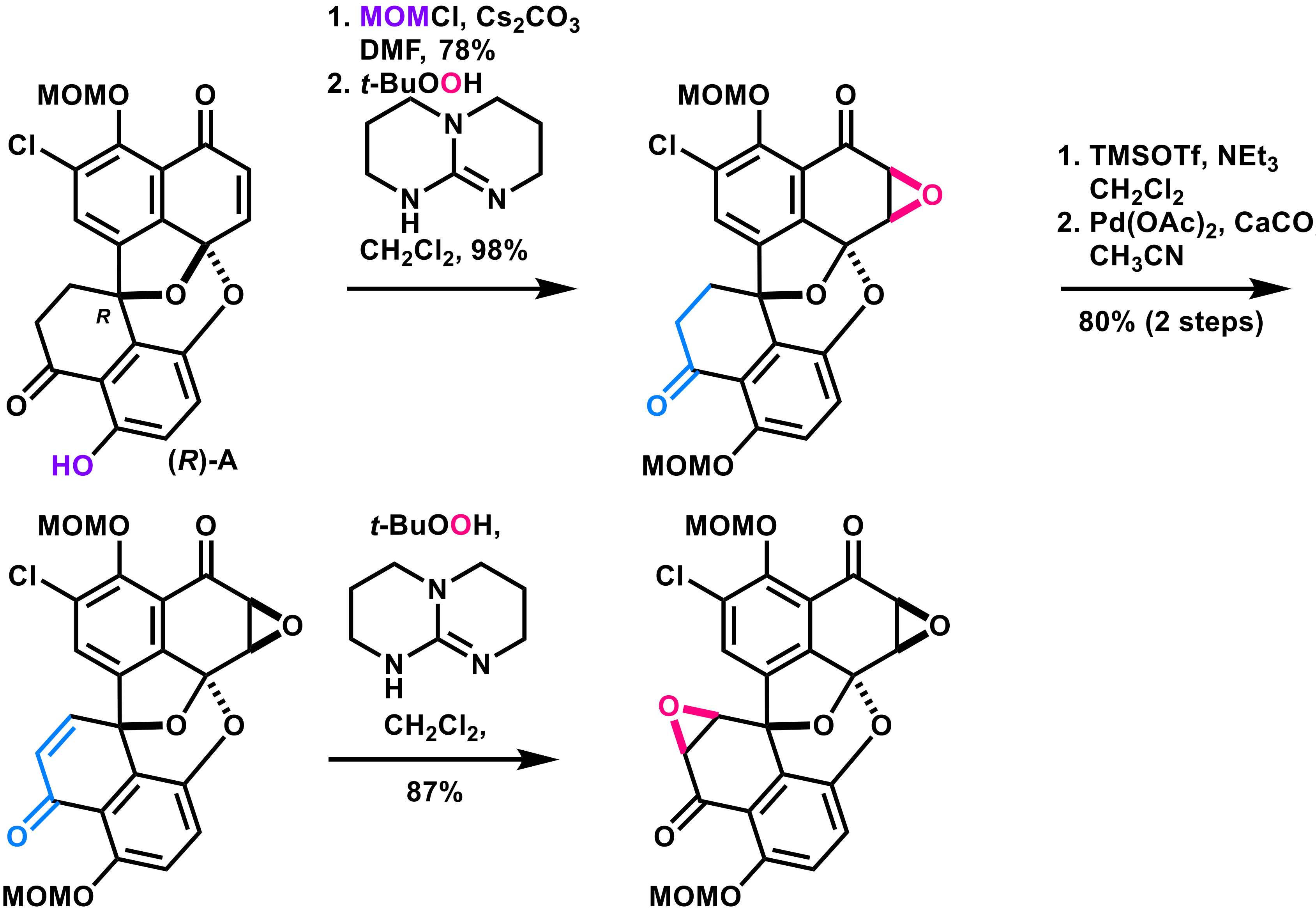
Rationale for Enantioselectivity



Calculations were conducted at the wB97X-D/6-311G(d) level of theory.

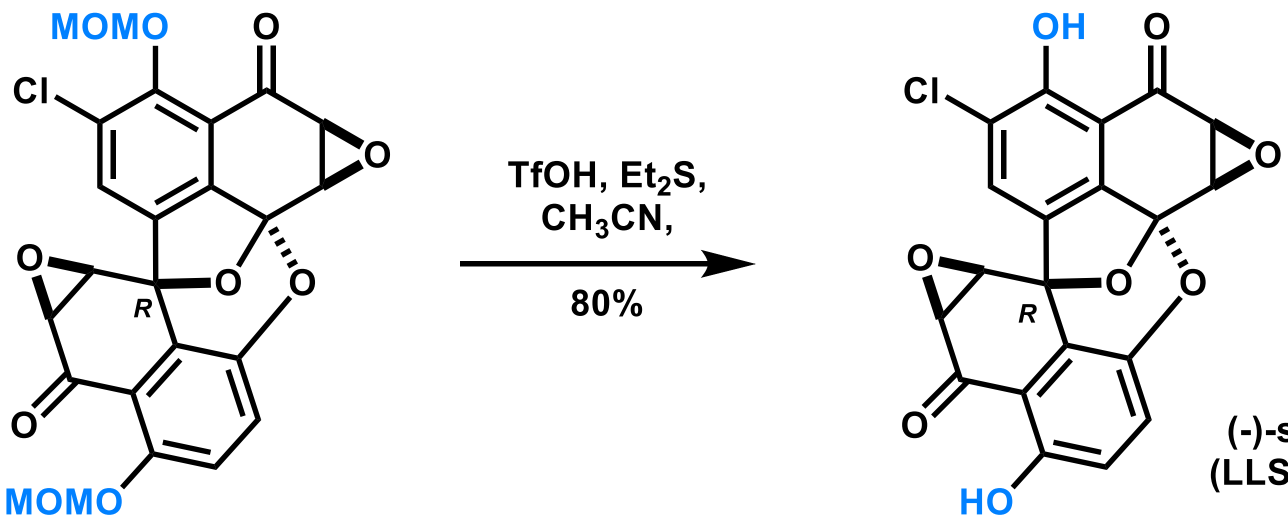
1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

Synthesis of Bisepoxide

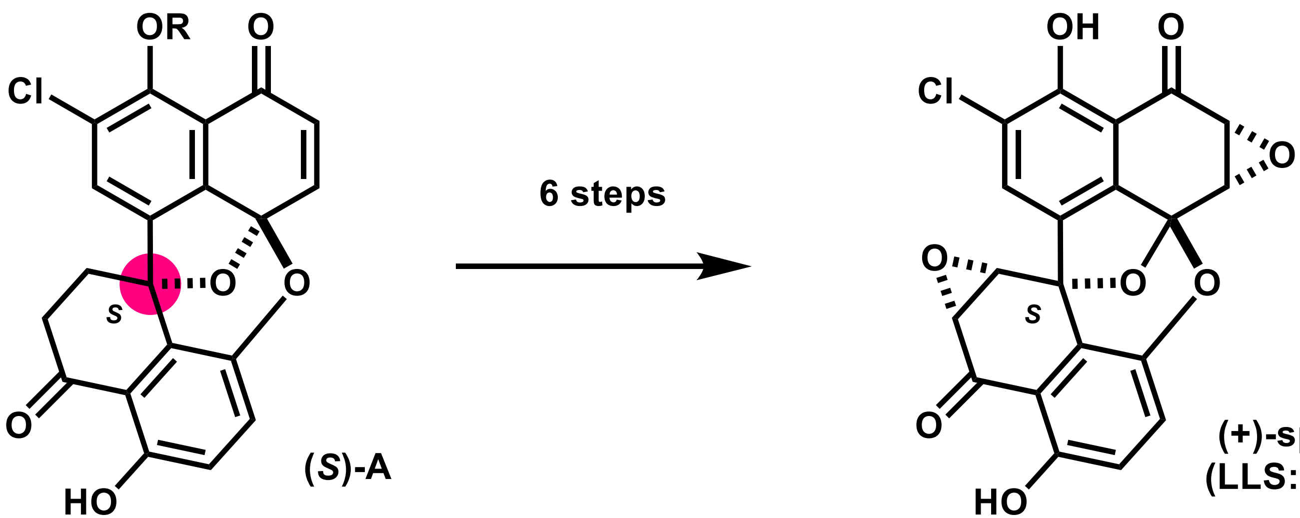


1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

Synthesis of Both Enantiomers of Spiroxin A



(-)-spiroxin A
(LLS: 25 steps)

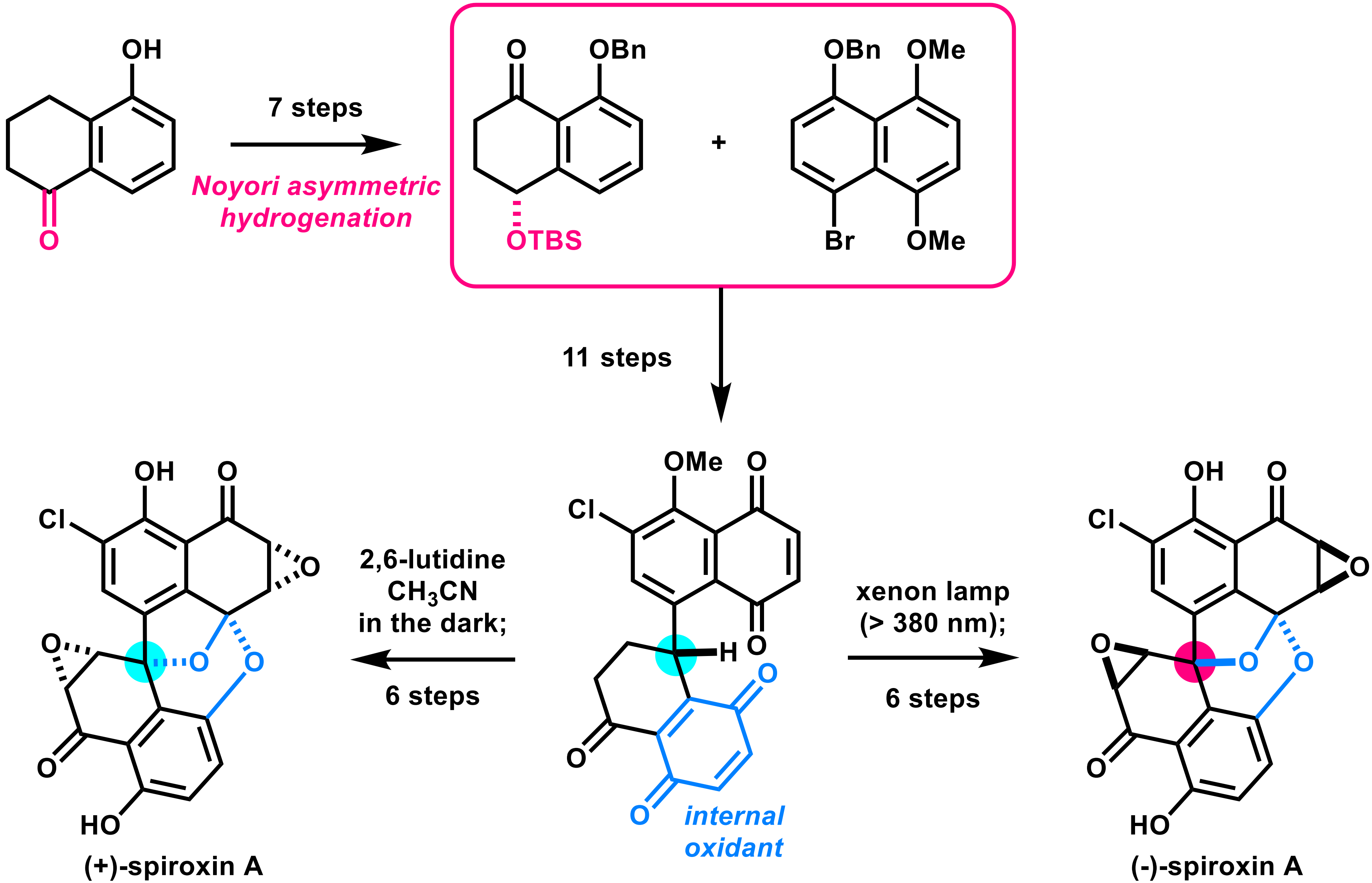


(*S*)-A

(+)-spiroxin A
(LLS: 25 steps)

1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

Summary of Suzuki's Synthesis



1) Ando, Y.; Tanaka, D.; Sasaki, R.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2019**, *58*, 12507.

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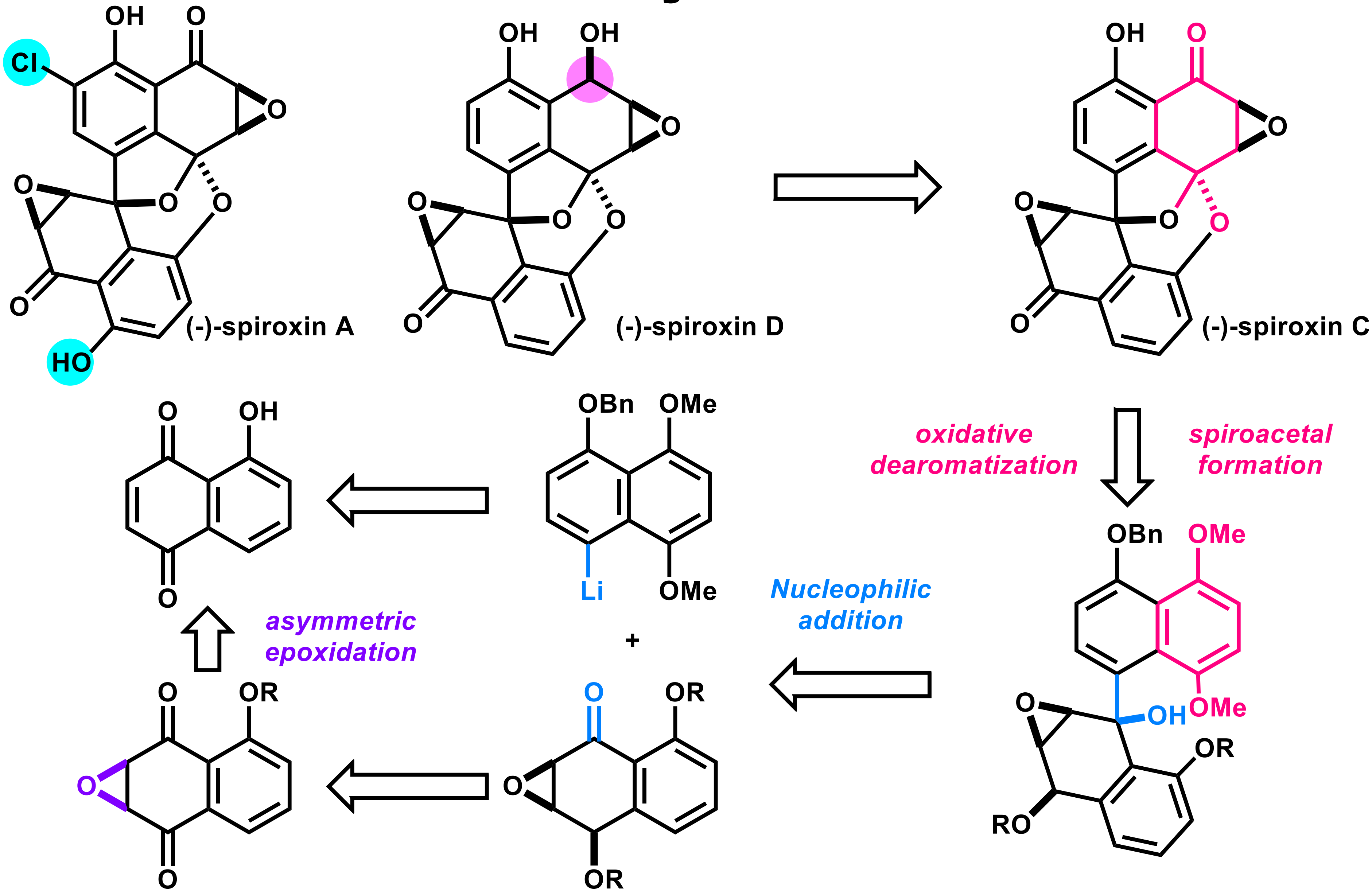
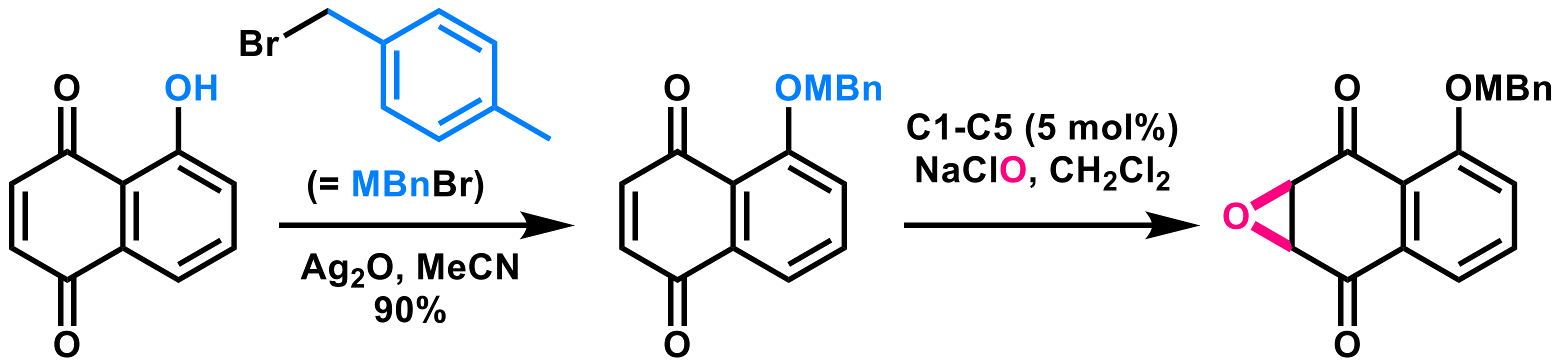
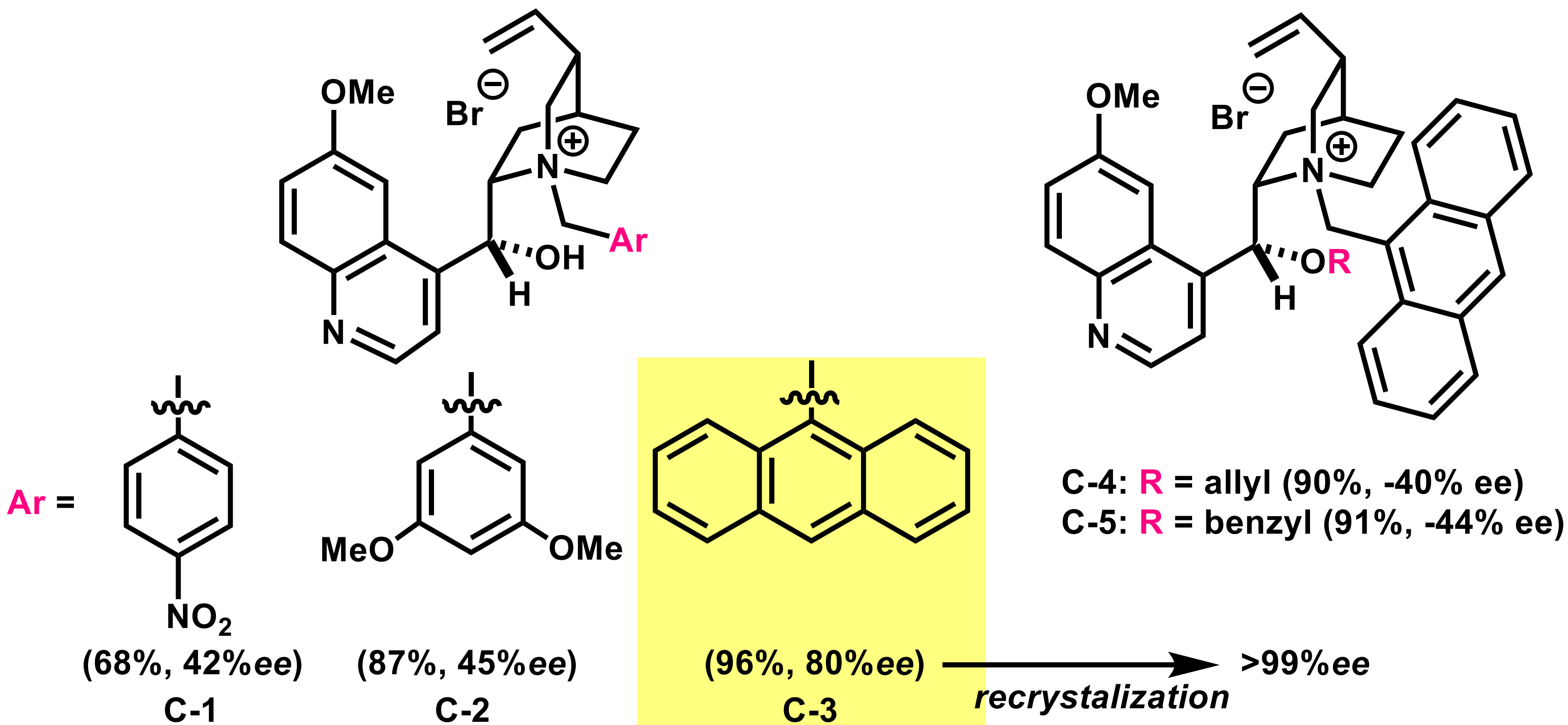
Retrosynthesis



1) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed*. **2021**, *60*, 18514.

Preparation of Substrates





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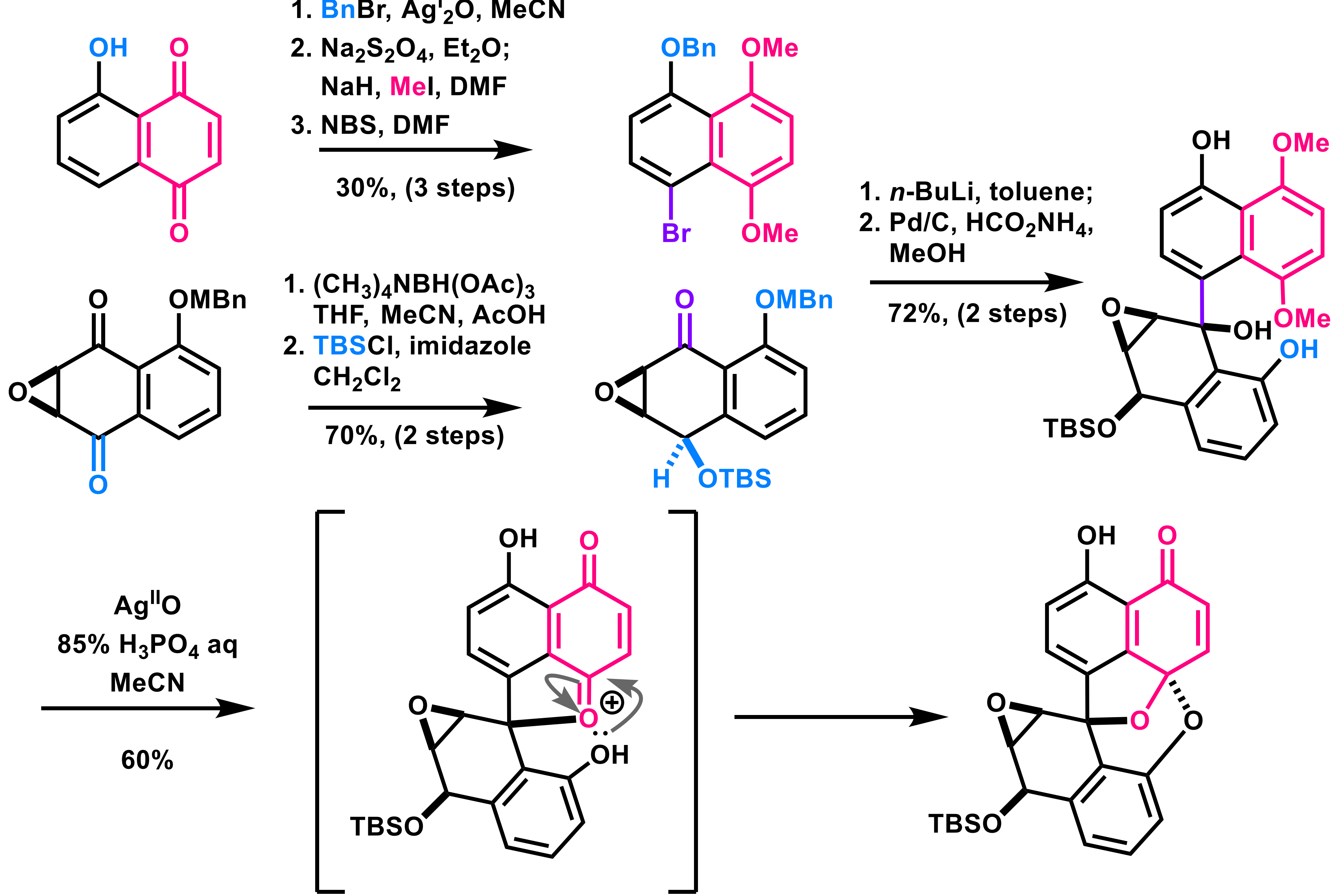
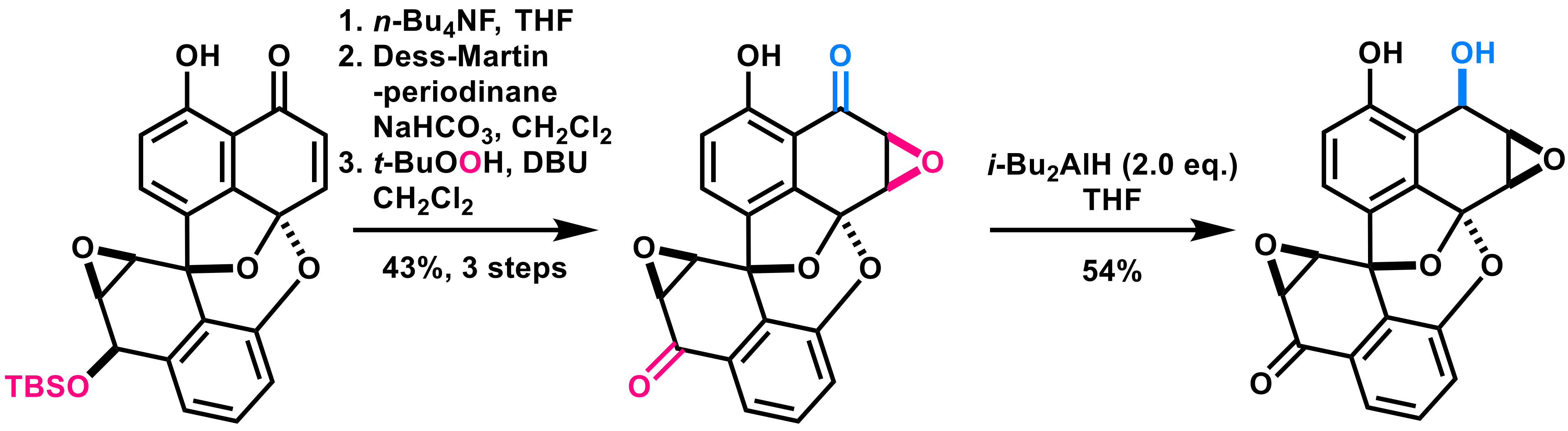
Construction of Spiroacetal Skeleton



1) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed.* **2021**, *60*, 18514.

Total Synthesis of Spiroxins C and D

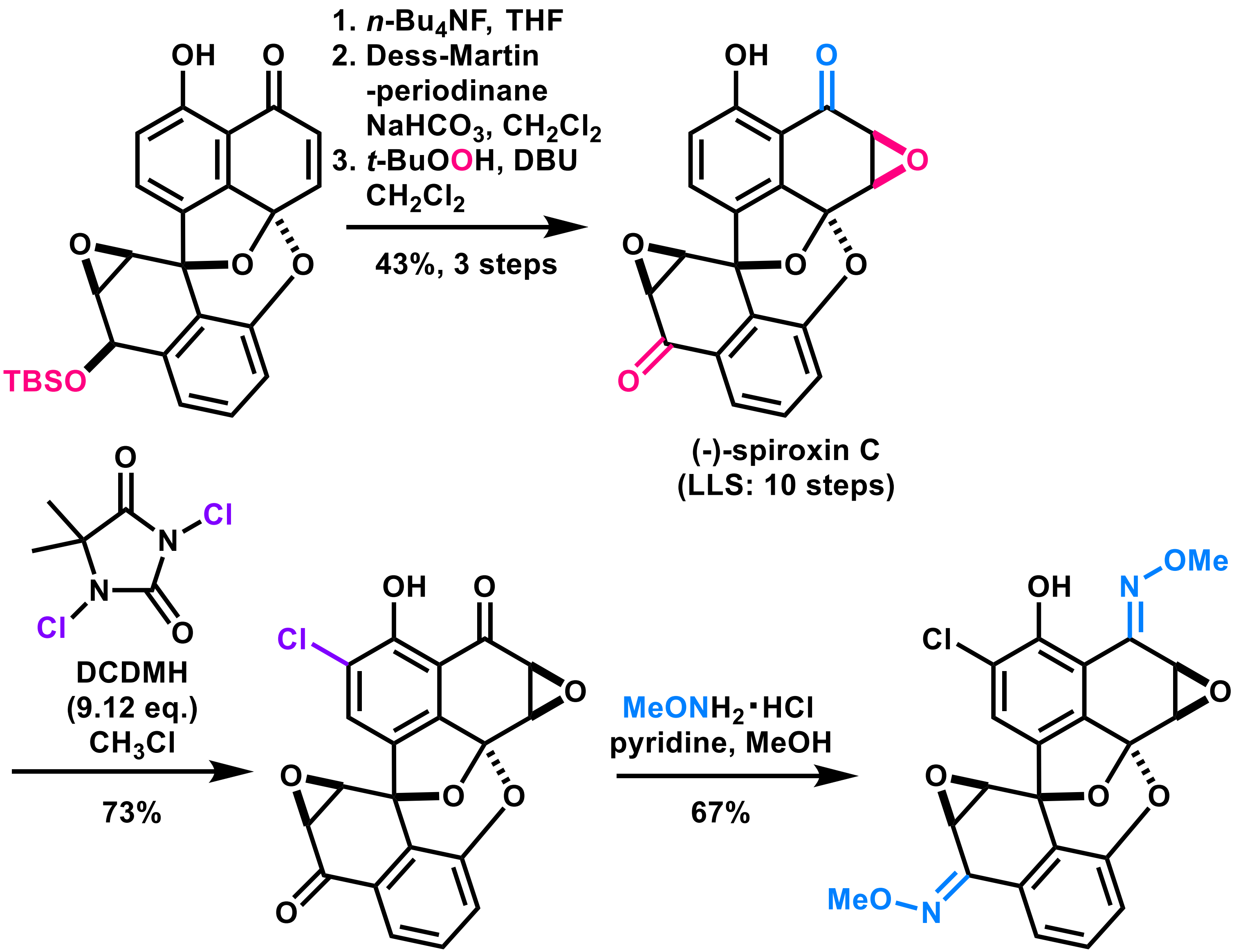


(-)-spiroxin C
(LLS: 10 steps)

(-)-spiroxin D
(LLS: 11 steps)

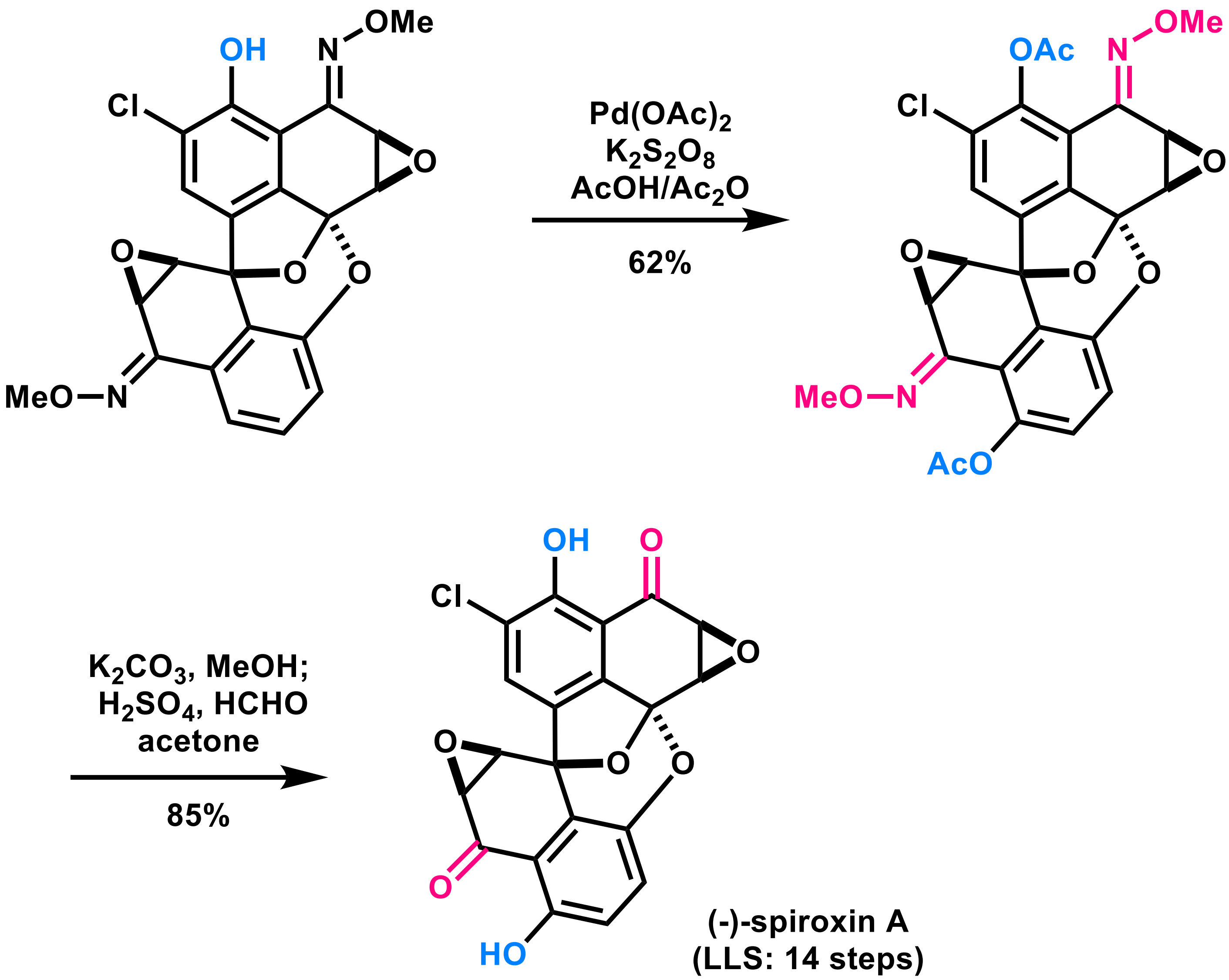
1) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed*. **2021**, *60*, 18514.

Preparation of Oxime Ether



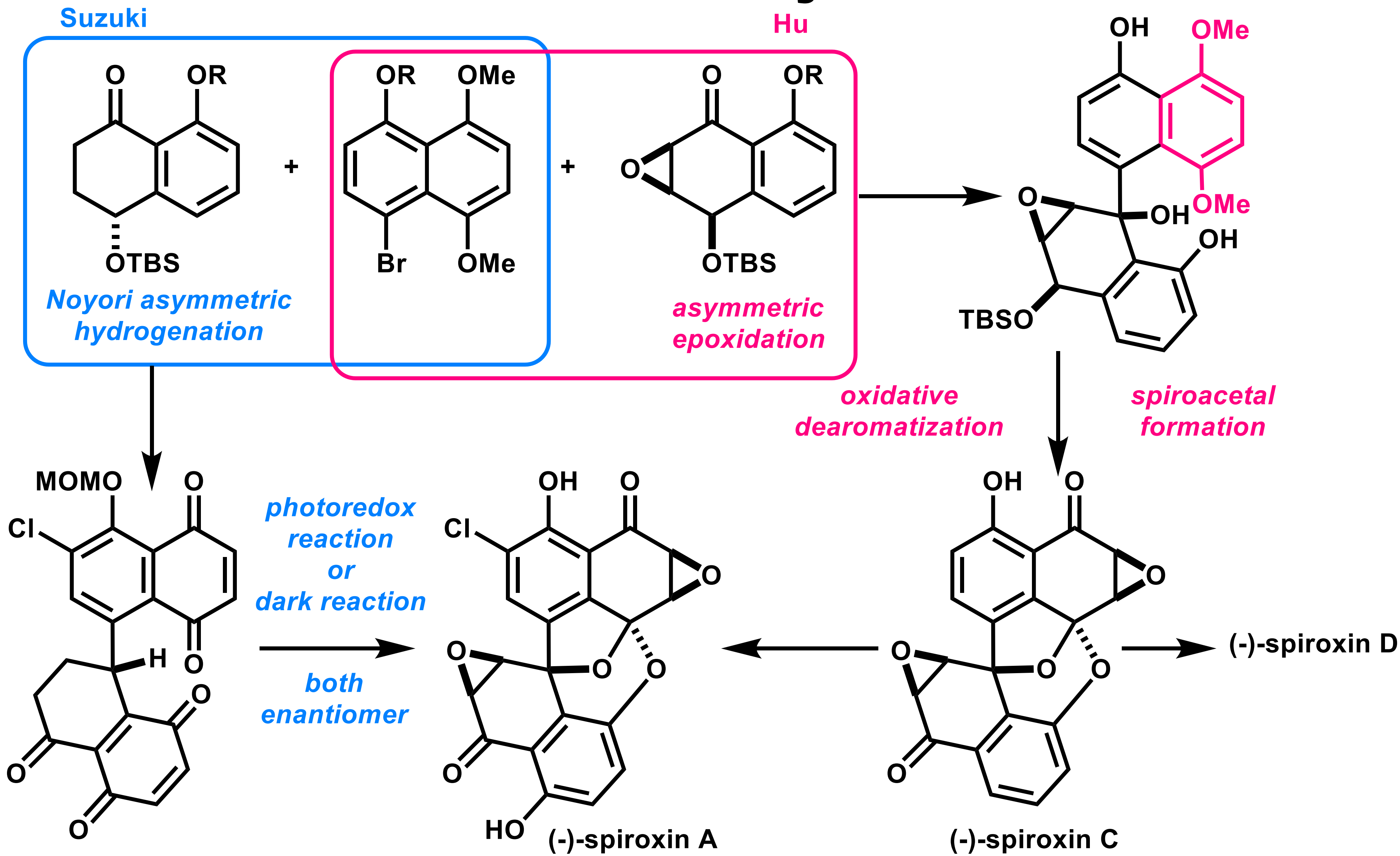
1) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed*. **2021**, *60*, 18514.

Oxime-Directed C-H Oxidation



1) Shu, X.; Chen, C.; Yu, T.; Yang, J.; Hu, X. *Angew. Chem. Int. Ed*. **2021**, *60*, 18514.

Summary



Suzuki
- synthesis of both enantiomers of spiroxin A from common intermediate
- application of an unique photoredox reaction

Hu
- divergent synthesis of spiroxins
- Use of starting materials having epoxide