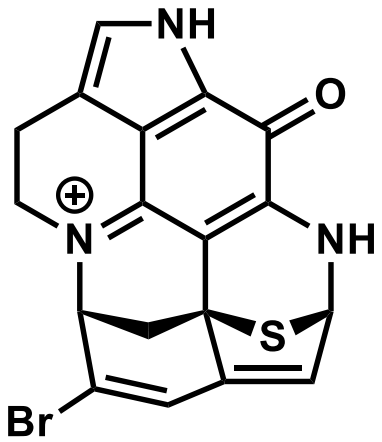
Molecule of Year



(-)-Aleutianamine

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Communication

Unified Divergent Total Synthesis of Discorhabdin B, H, K, and Aleutianamine via the Late-Stage Oxidative *N,S*-Acetal Formation

Masashi Shimomura, Kohta Ide, Juri Sakata, and Hidetoshi Tokuyama*

Published: August 9, 2023

Total Synthesis of Aleutianamine

Hao Yu,‡ Zachary P. Sercel,‡ Samir P. Rezgui, Jonathan Farhi, Scott C. Virgil, and Brian M. Stoltz*

Published: November 15, 2023

Reporter: Xin Wang

2024/13/01

Introduction

Hidetoshi Tokuyama

1967-06-24

1990, B.S., Chemistry, Tokyo Institute of Technology

1994, Ph.D., Chemistry, Tokyo Institute of Technology with Professor Eiichi Nakamura

4/1994-11/1995, Postdoctoral Fellow with Professor Amos B. Smith, Department of Chemistry, University of Pennsylvania

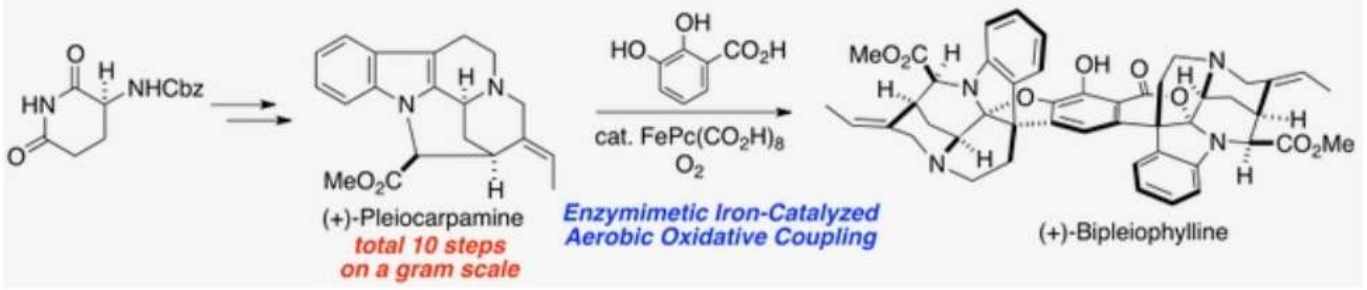
11/1995-3/2001, Assistant, Graduate School of Pharmaceutical Sciences, University of Tokyo

4/2001-1/2003, Lecturer, Graduate School of Pharmaceutical Sciences, University of Tokyo

2/2003-4/2006, Associate Professor, Graduate School of Pharmaceutical Sciences, University of Tokyo

5/2006-present, Professor, Graduate School of Pharmaceutical Sciences, Tohoku University

J. Am. Chem. Soc., **145**(30), 16337-16343 (2023) (DOI: 10.1021/jacs.3c05811).



Introduction

Brian M. Stoltz

1970-11-12

1993, B.S., Chemistry and German from Indiana University of Pennsylvania

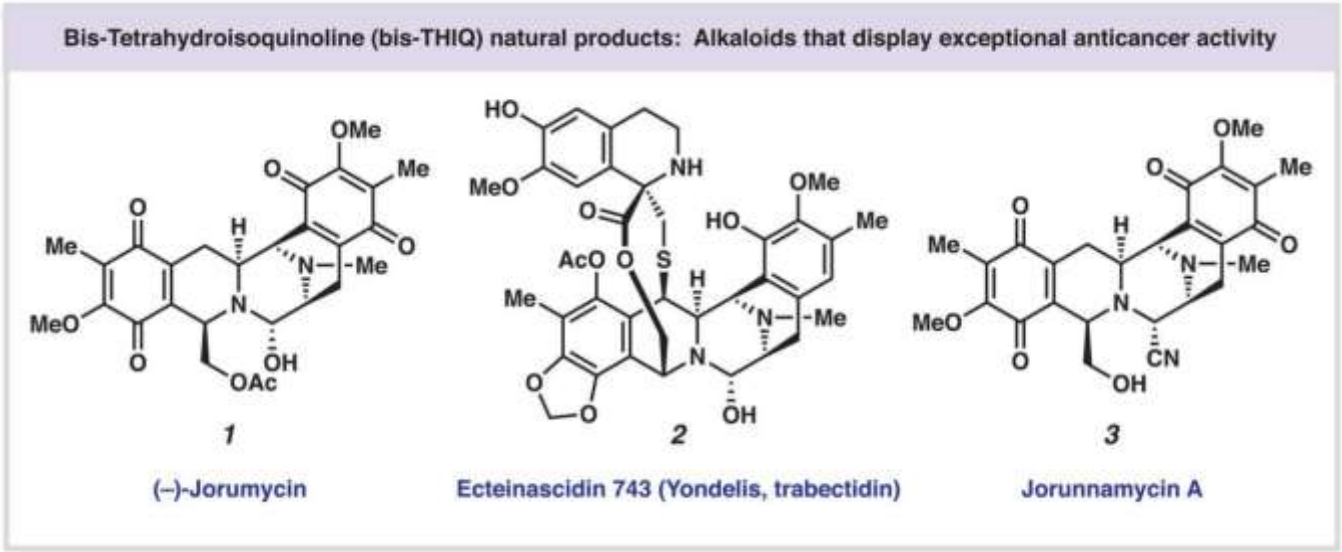
1997, Ph.D., Yale University, John L. Wood,

1998-2000, Postdoctoral Fellow with E. J. Corey at Harvard University

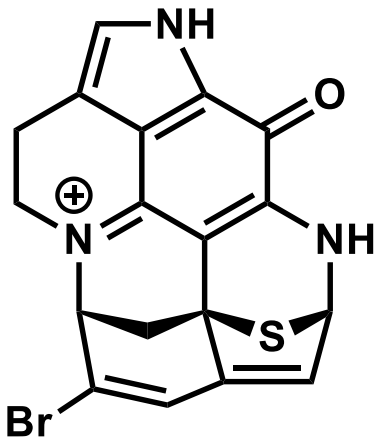
2000, Assistant Professor, Caltech

2006-now, Professor, Caltech

Brian M. Stoltz. *Science* **2019**, *363*, 270–275.



Introduction



(-)-Aleutianamine

Discovered from Latrunculia (Latrunculia) austini Samaai in 2019

Structural features

a unique heptacyclic ring system which consists of a pyrroloiminoquinone unit,

a bridged azabicyclo[3.3.1]nonane ring system substituted with a congested tertiary alkyl sulfide

an alkenyl bromide

another bridging thioaminal linkage

IC50 value

human HCT-116 colon cancer cells was 1 μM

PANC-1 pancreatic cancer cells was **25 nM**

The principal structural feature of discorhabdins is the core of **a planar iminoquinone moiety** which has been shown to **intercalate and cleave DNA as well as inhibit the action of topoisomerase II.**

Mark T. Hamann, *J. Am. Chem. Soc*. **2019**, *141*, 4338−4344

Introduction

Discorhabdins, structurally divergent **marine alkaloids**

Common Skeleton of Discorhabdins

Pyrroloiminoquinone unit

Discorhabdin C (**1**, X = Br)
(±)-Discorhabdin E (**2**, X = H)
A/B/C/D/E ring system
Class 1

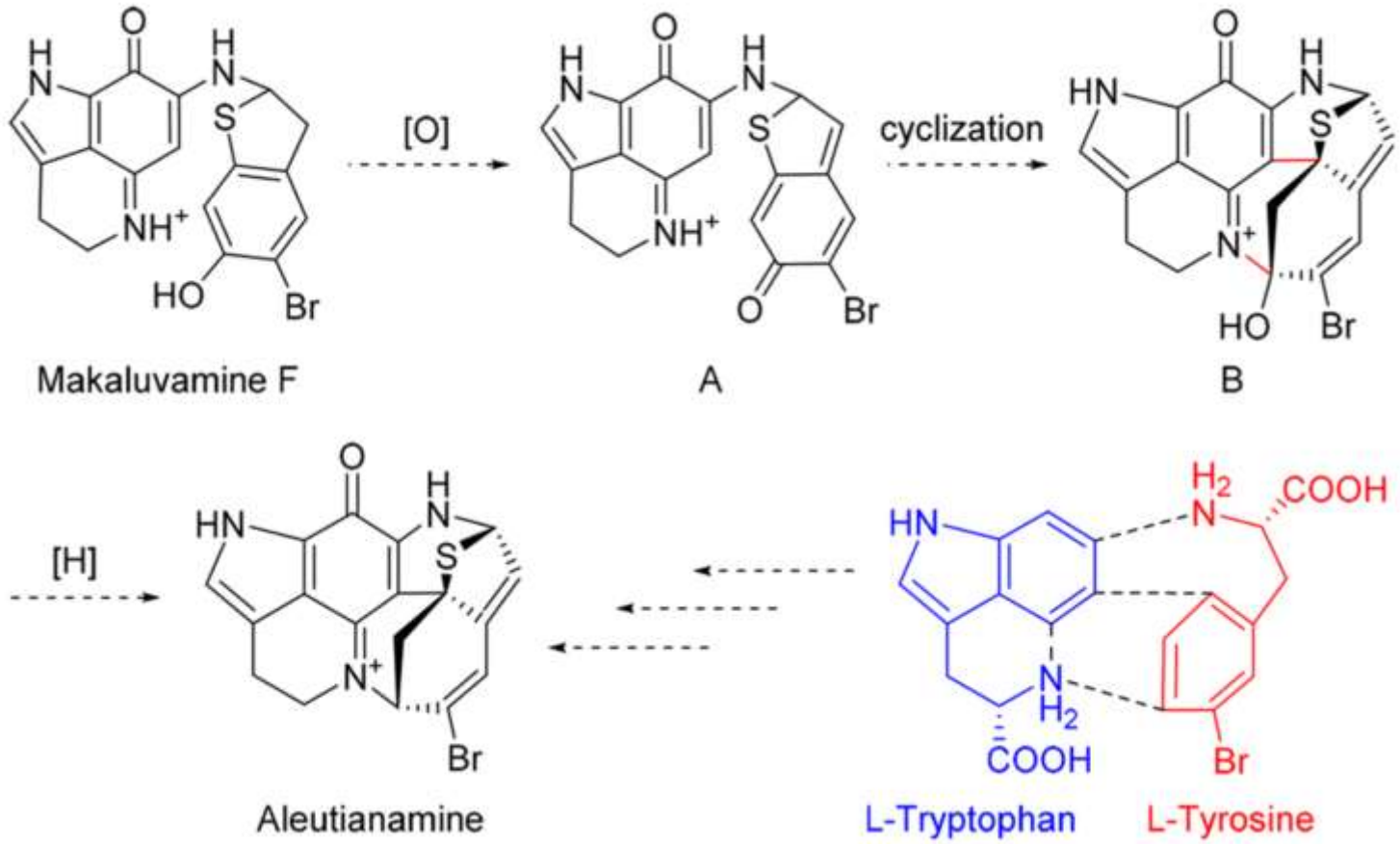
(+)-Discorhabdin A (**4**)
(+)-Discorhabdin B (**5**, Δ^4)
A/B/C/D/E/G ring system
Class 2

(–)-Aleutianamine (**7**)
Rearranged A/B/C/D/E/F/G ring system

Discorhabdin V (**3**)
A/B/C/D/F/E ring system
Class 3

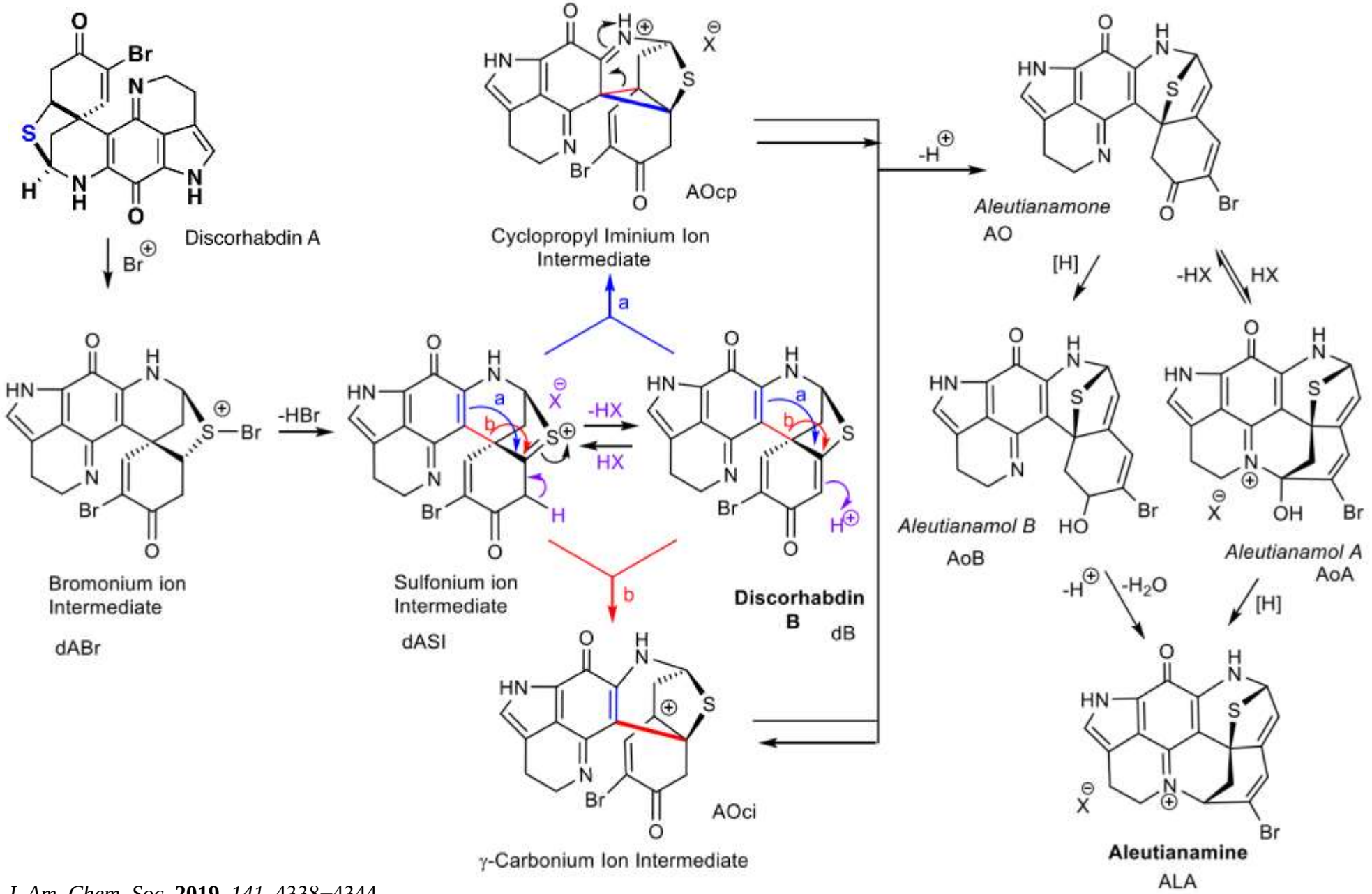
(–)-Discorhabdin H (**6**)
A/B/C/D/E/F/G ring system
Class 4

Proposed biosynthesis of Aleutianamine



Mark T. Hamann, *J. Am. Chem. Soc*. **2019**, *141*, 4338−4344

Proposed biosynthesis of Aleutianamine



Mark T. Hamann, *J. Am. Chem. Soc.* **2019**, *141*, 4338−4344

Introduction

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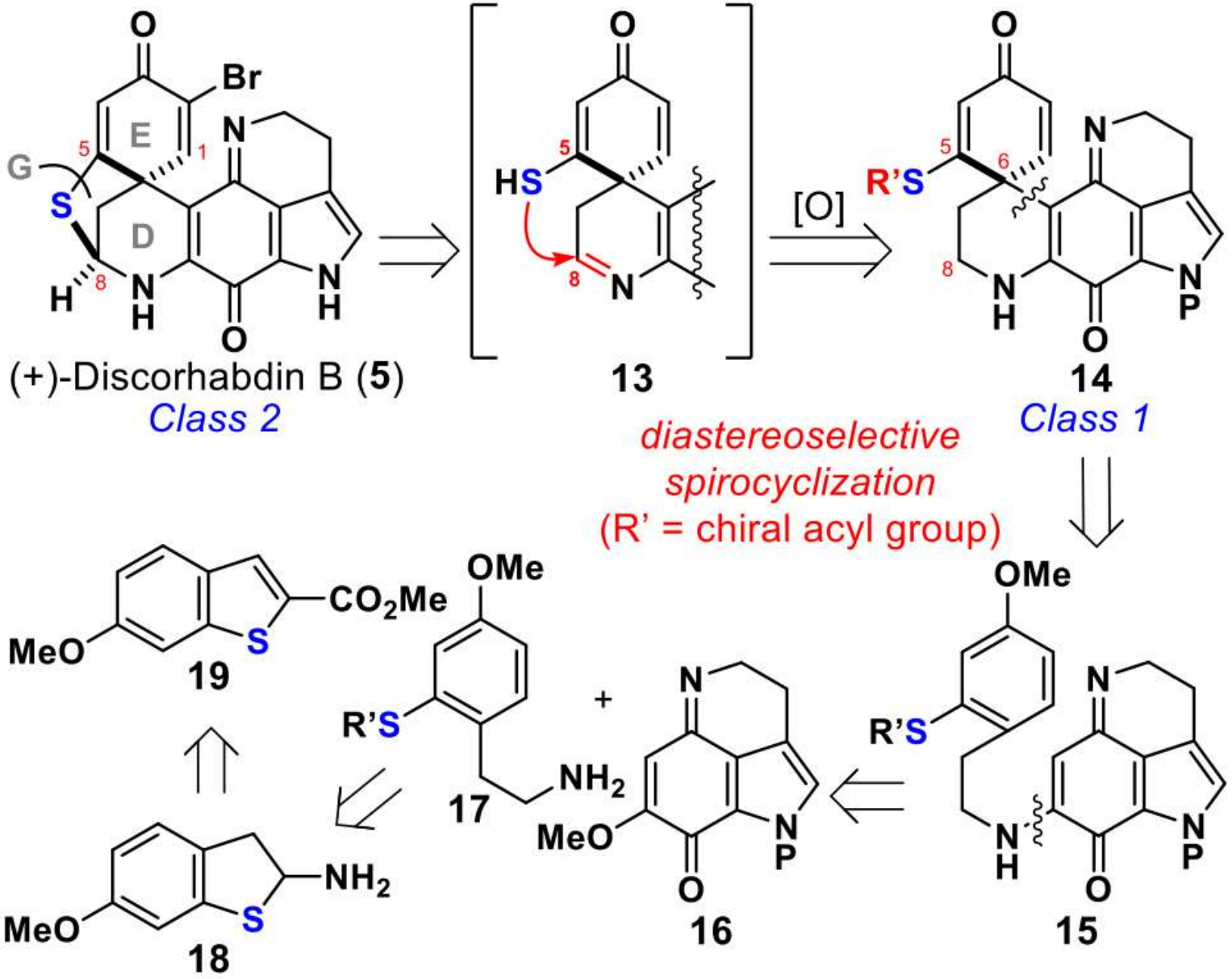
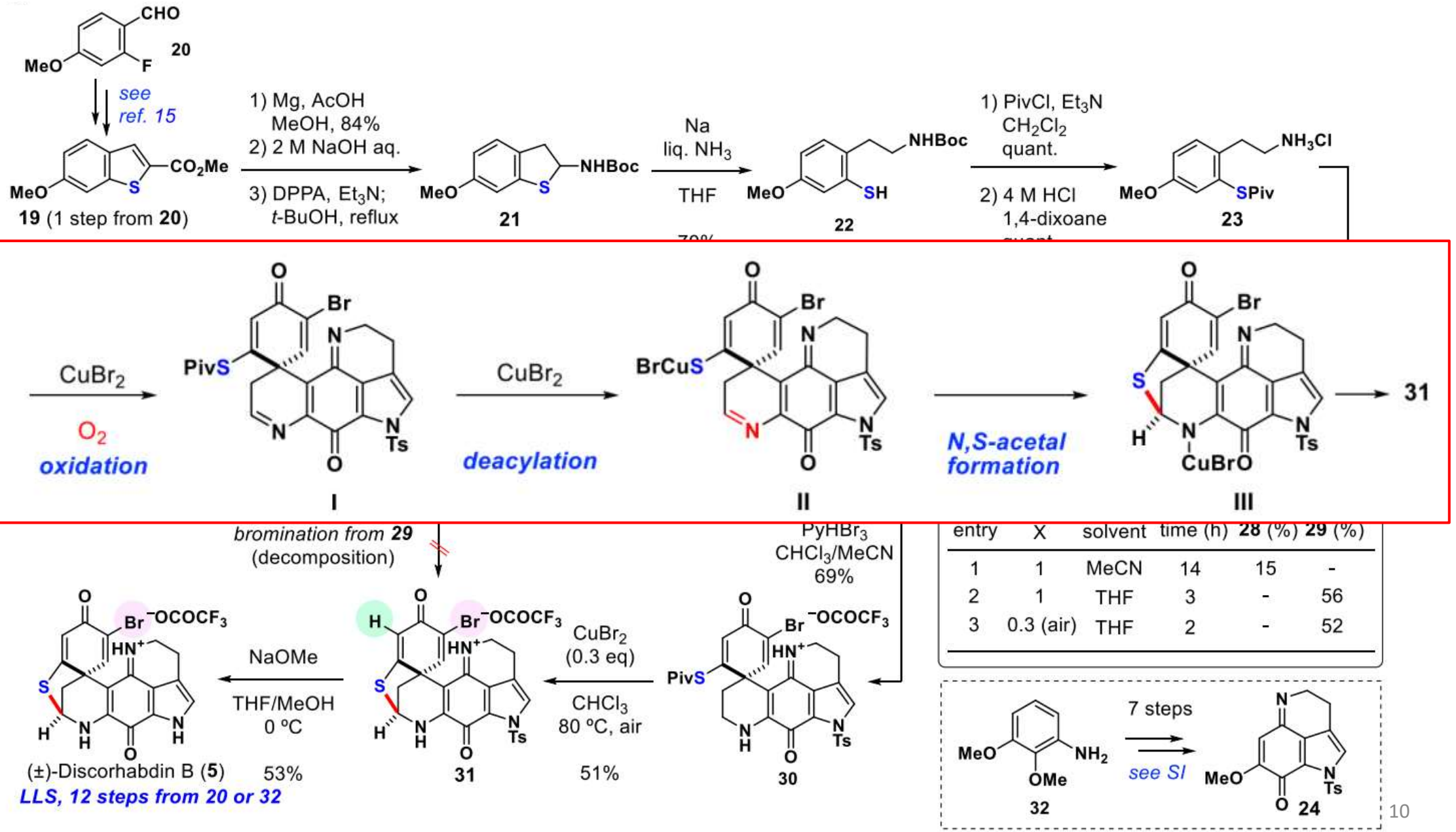
Retrosynthetic Analysis

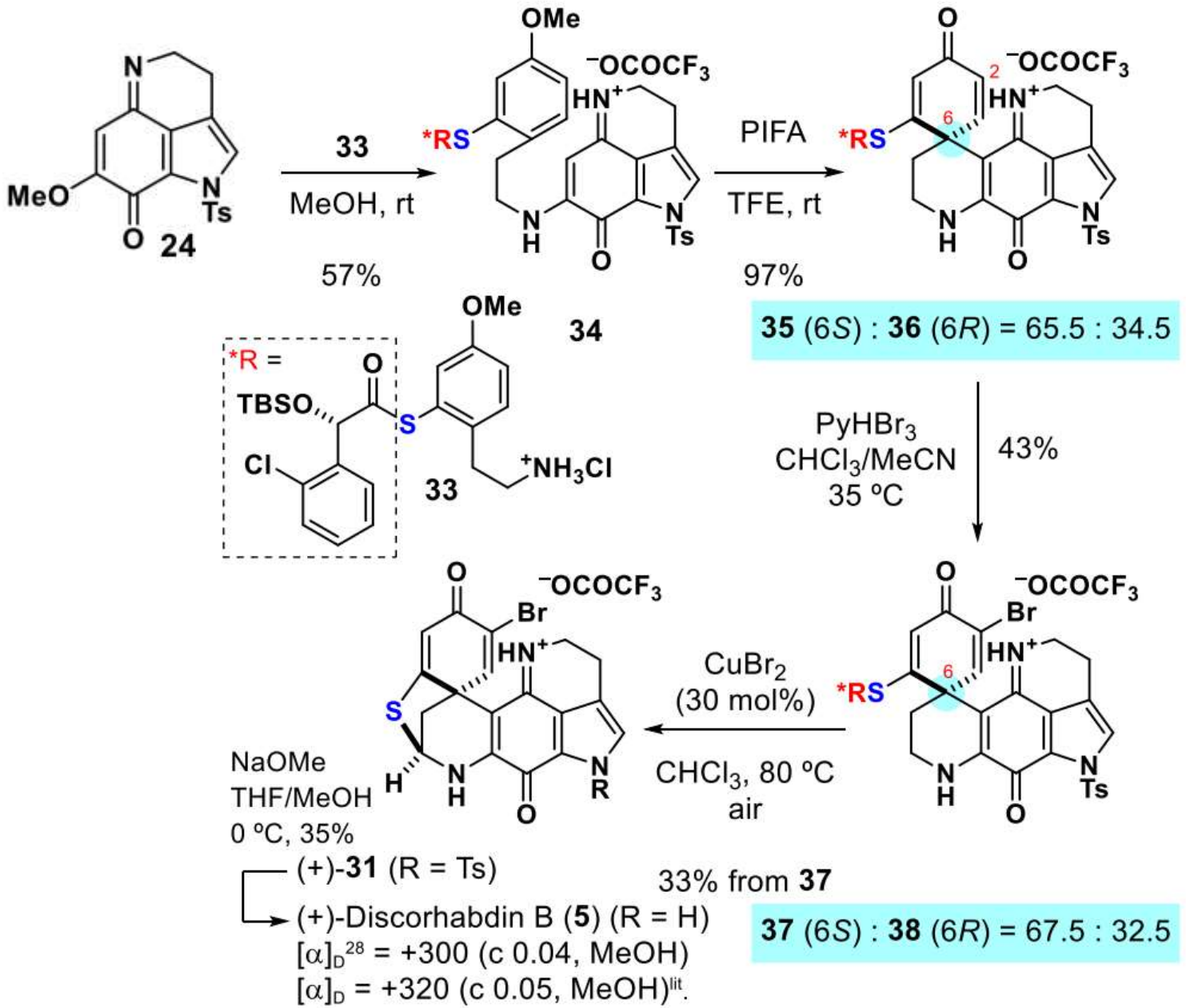


Total Synthesis of (±)-Discorhabdin B

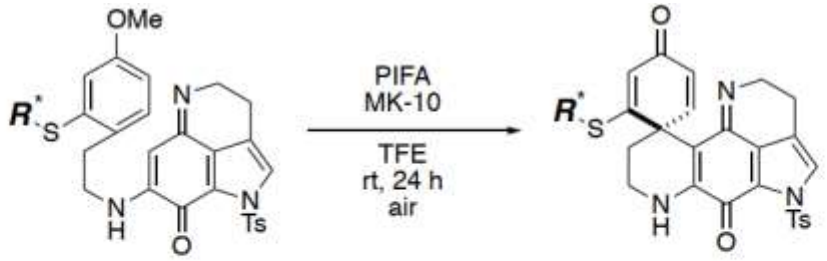


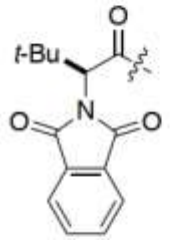
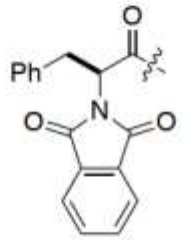
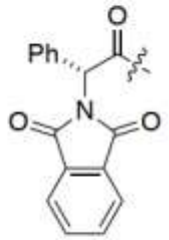
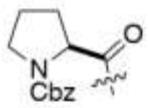
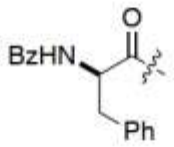
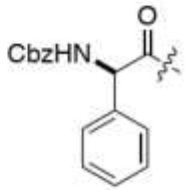
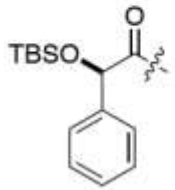
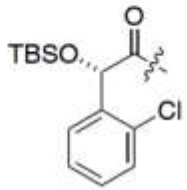
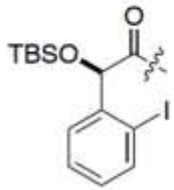
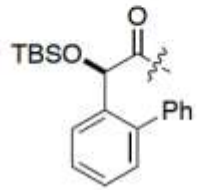
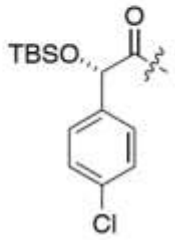
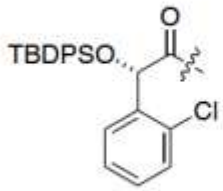
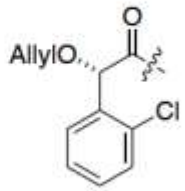
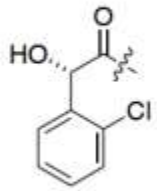
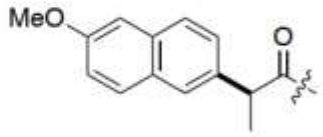
entry	X	solvent	time (h)	28 (%)	29 (%)
1	1	MeCN	14	15	-
2	1	THF	3	-	56
3	0.3 (air)	THF	2	-	52

Total Synthesis of (+)-Discorhabdin B

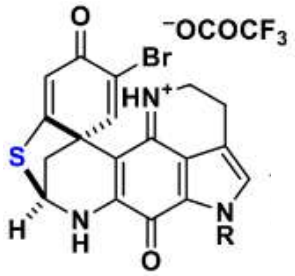


Total Synthesis of (+)-Discorhabdin B

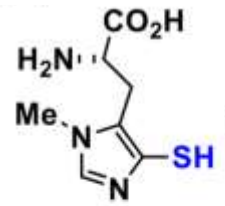


R^* =						
						
92% (21% de)[a]	86% (16% de)[a]	76% (4% de)[a]	87% (ca. 0% de)[b]	N.D.	<27% (0% de)[a]	
						
quant. (18% de)[a]	97% (31% de)[a]	36% (19% de)[a]	69% (2% de)[a]	64% (16% de)[a]		
						
61% (19% de)[a]	50% (12% de)[a]	41% (9% de)[a]	84% (2% de)[a]	N.D.		

Total Syntheses of (−)-Discorhabdin H and (+)-Discorhabdin K

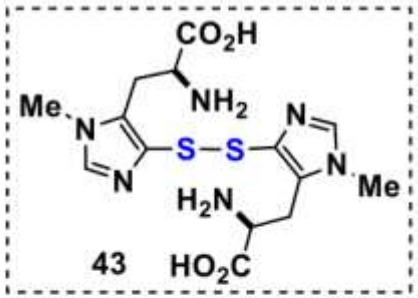


(+)-**31** (R = Ts)



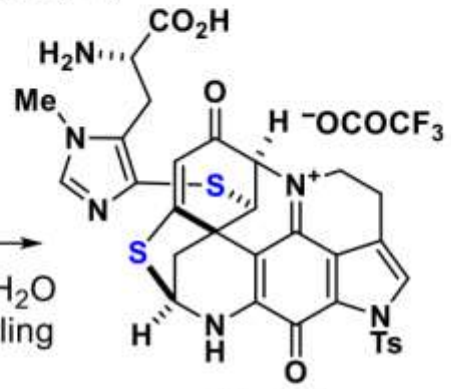
L-ovothiol A (**40**)

\+ (+)-**31**

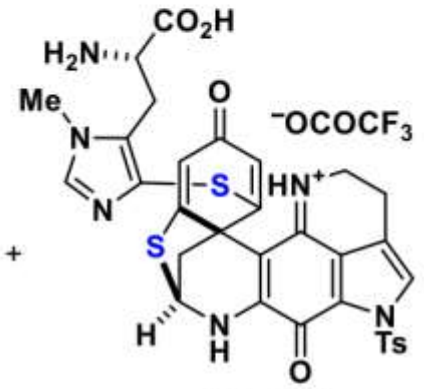


43

DMSO/H_2O
Ar bubbling
rt



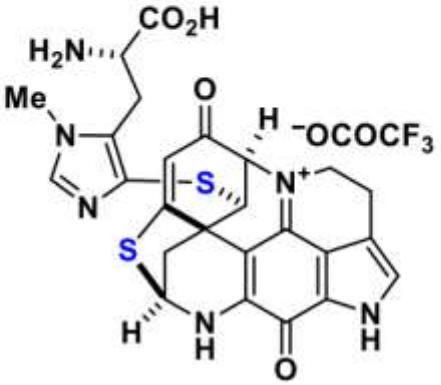
41, 39%

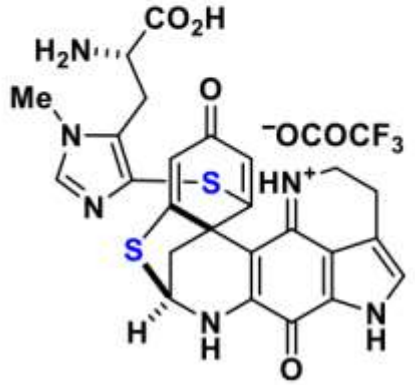


42, 26%

NaOMe
THF/MeOH
0 °C
58%

NaOMe
THF/MeOH
0 °C
37%

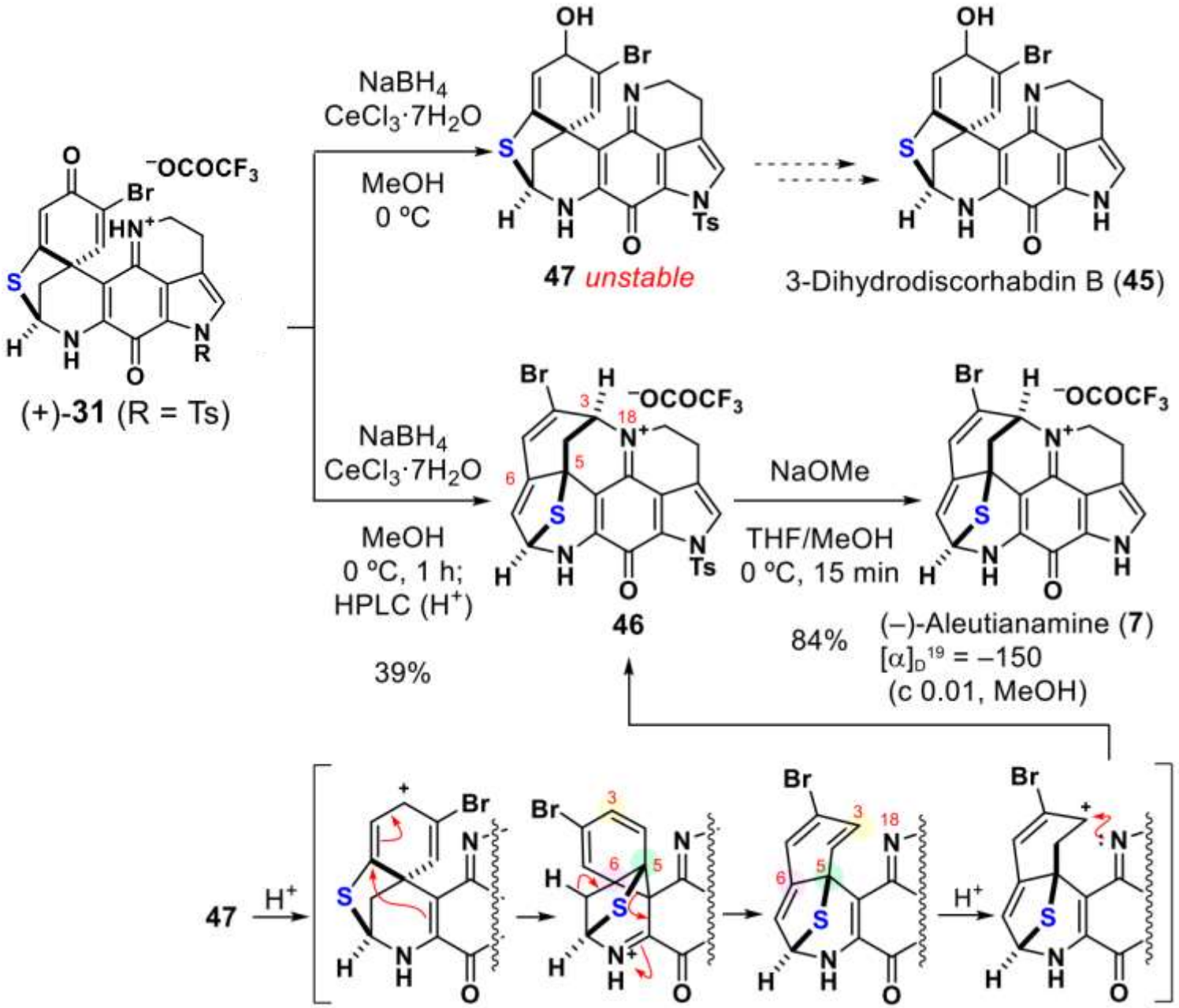




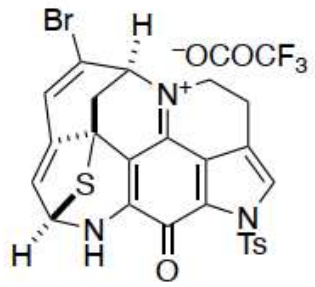
(–)-Discorhabdin H (**6**)
$[\alpha]_D^{19}$ = –66 (c 0.21, MeOH)
$[\alpha]_D^{20}$ = –77 (c 0.05, MeOH)[lit].

(+)-Discorhabdin K (**44**)
$[\alpha]_D^{21}$ = +360 (c 0.02, MeOH)
$[\alpha]_D^{20}$ = +340 (c 0.05, MeOH)[lit].

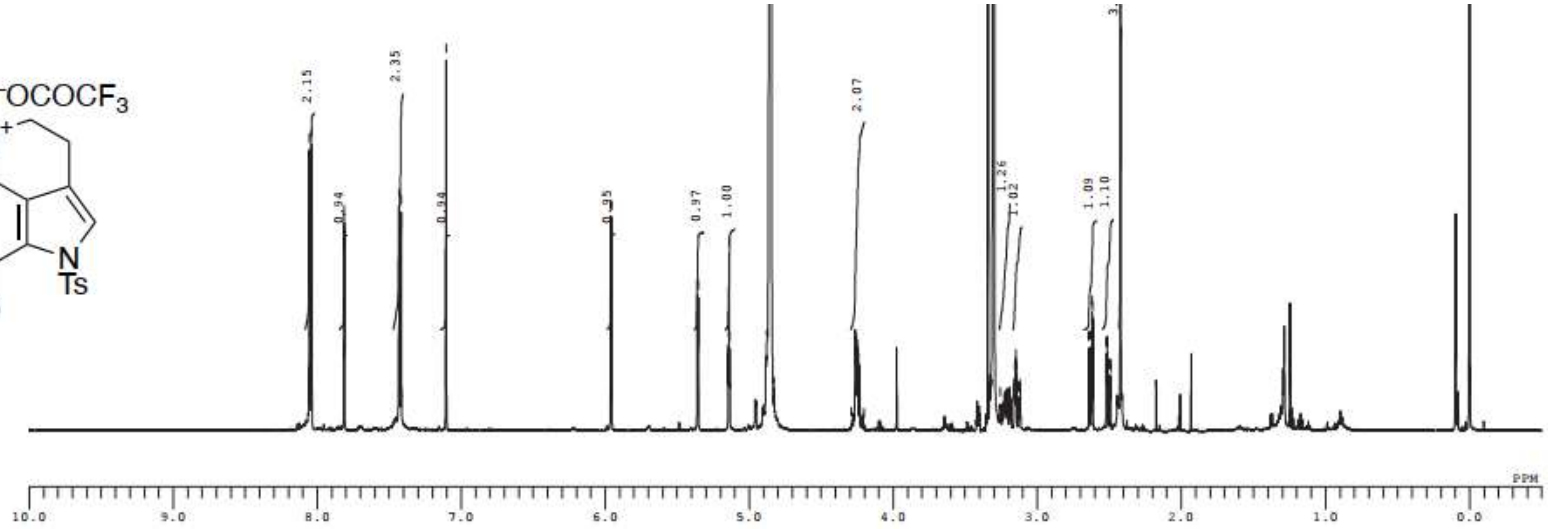
Total Synthesis of (−)-Aleutianamine

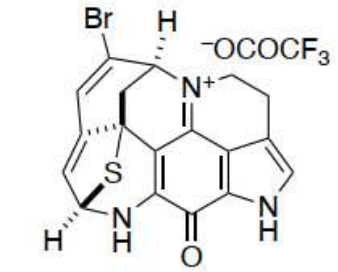


Total Synthesis of (−)-Aleutianamine

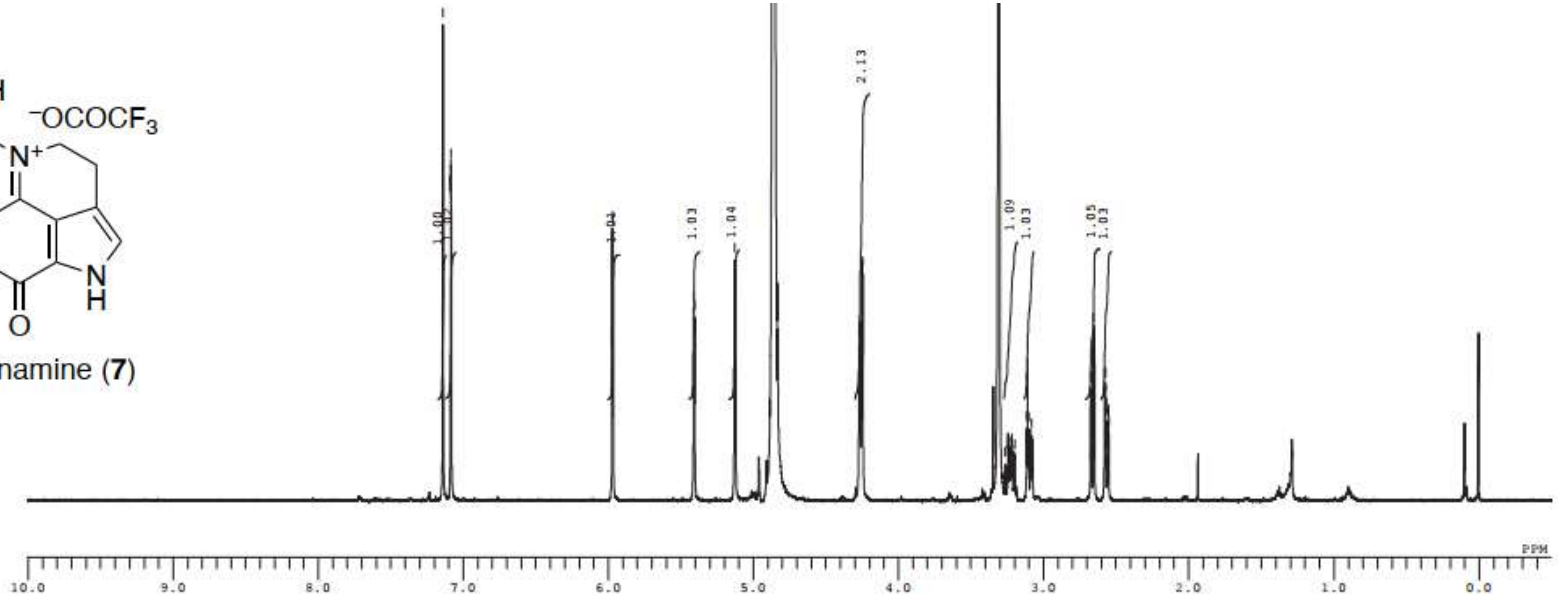


46





(–)-Aleutianamine (**7**)



Introduction

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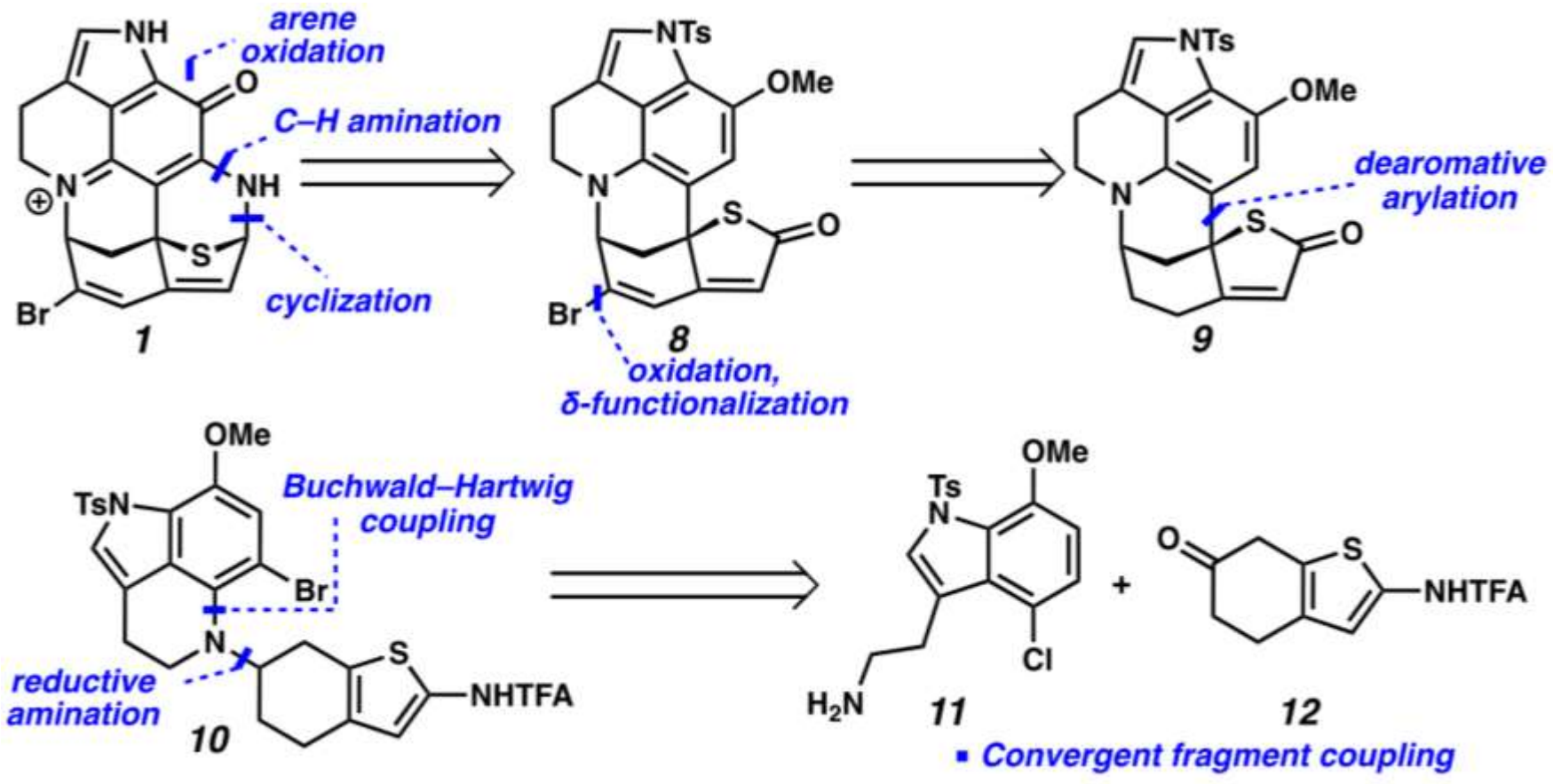
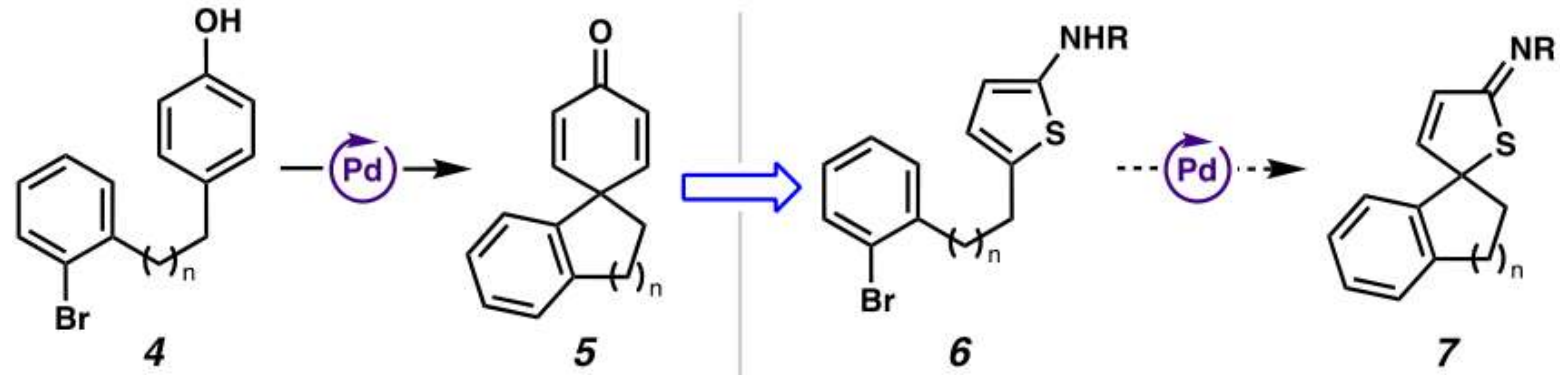
Communication

Total Synthesis of Aleutianamine

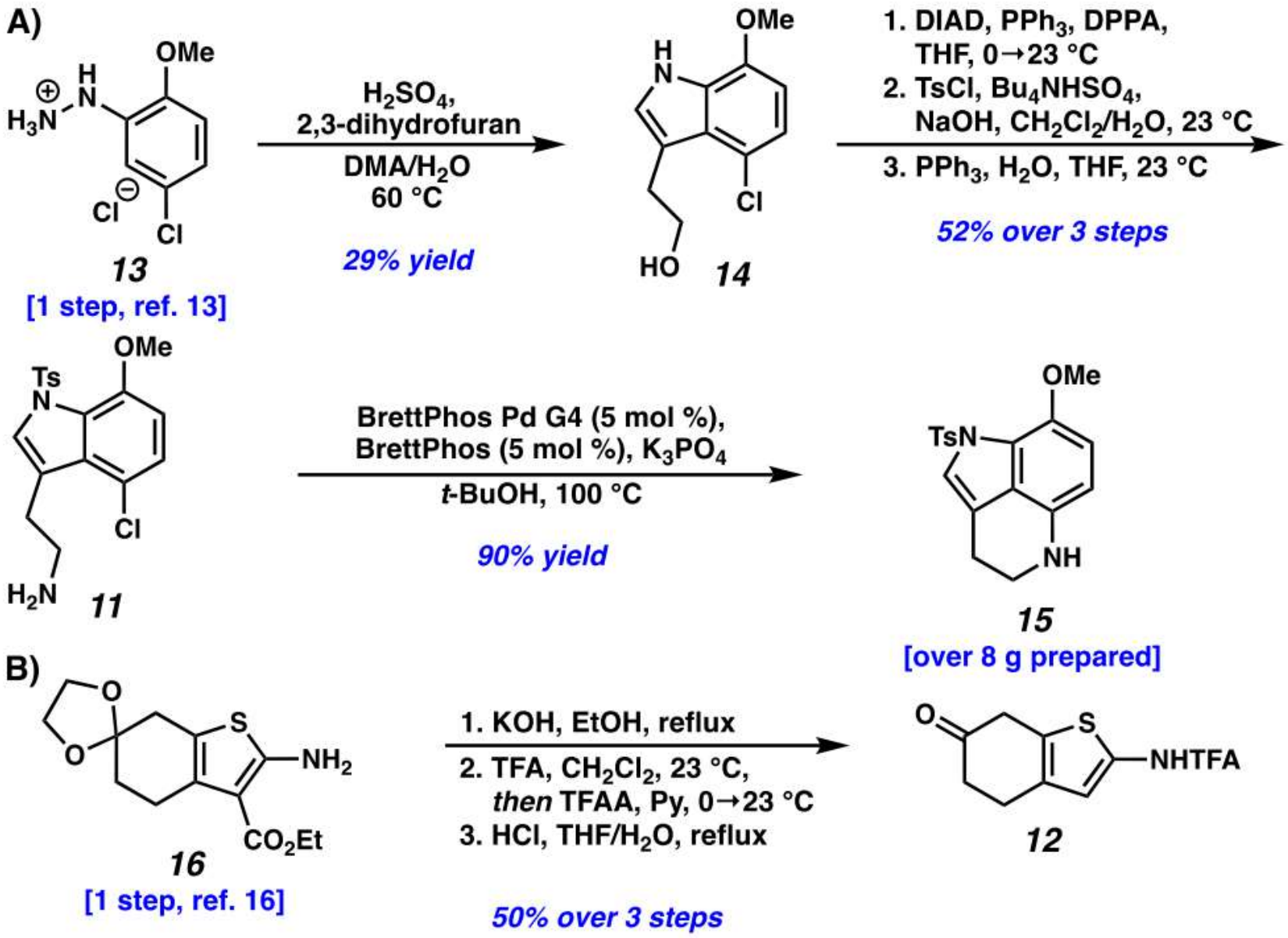
Hao Yu,[‡] Zachary P. Sercel,[‡] Samir P. Rezgui, Jonathan Farhi, Scott C. Virgil, and Brian M. Stoltz*

Retrosynthetic Analysis

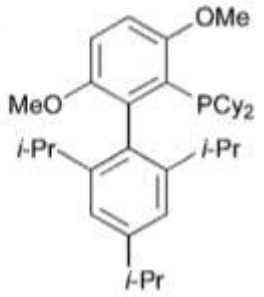




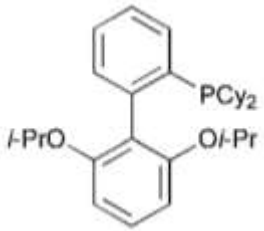
(A)Synthesis of Tricyclic Aniline 15; (B)Synthesis of Aminothiophene 12



Key dialkylbiaryl phosphine ligands for amination

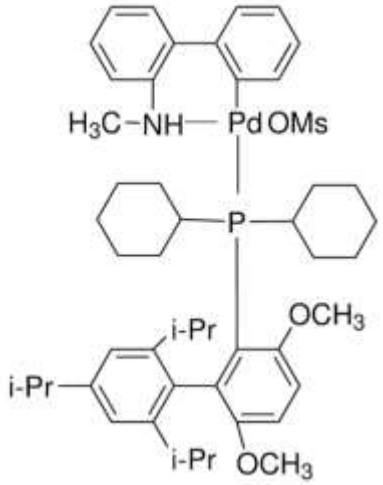


L1

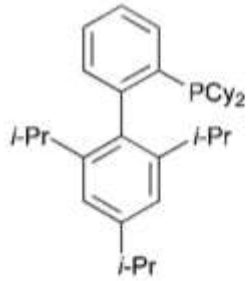


L2

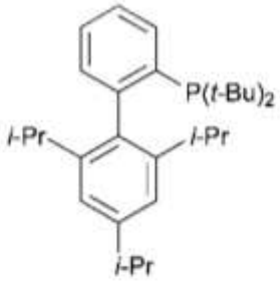
Name	*BrettPhos*	*RuPhos*
Best nucleophiles	Primary alkyl amines Primary anilines	Secondary alkyl amines Secondary anilines



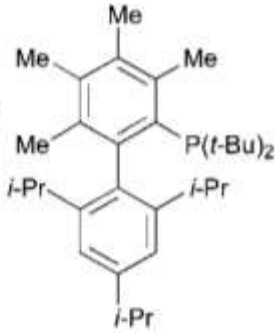
Brettphos Pd G4



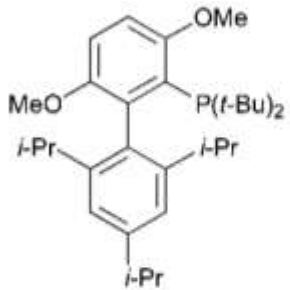
L3
XPhos



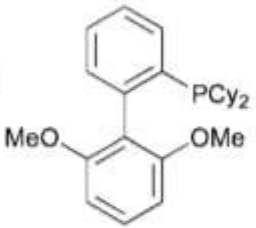
L4
tBuXPhos



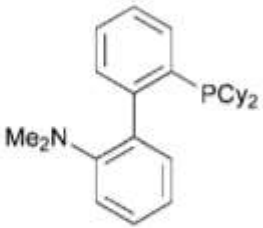
L5
Me4tBuXPhos



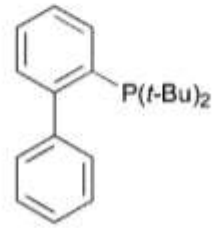
L6
tBuBrettPhos



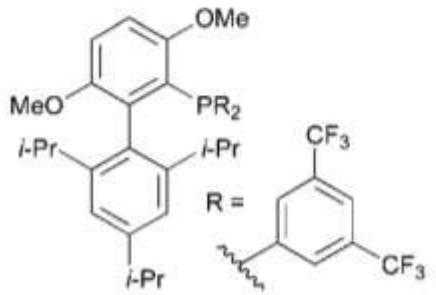
L7
SPhos



L8
DavePhos



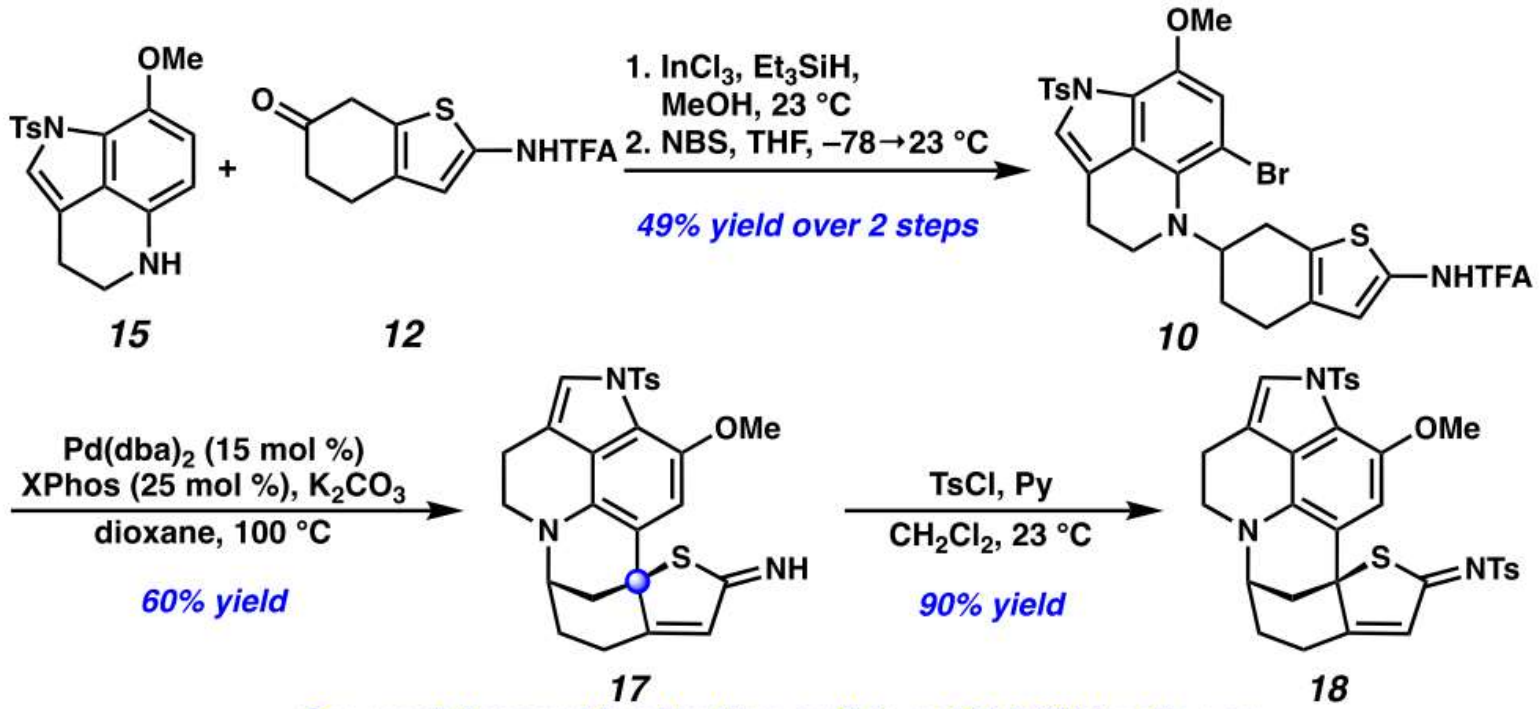
L9
JohnPhos



L10
JackiePhos

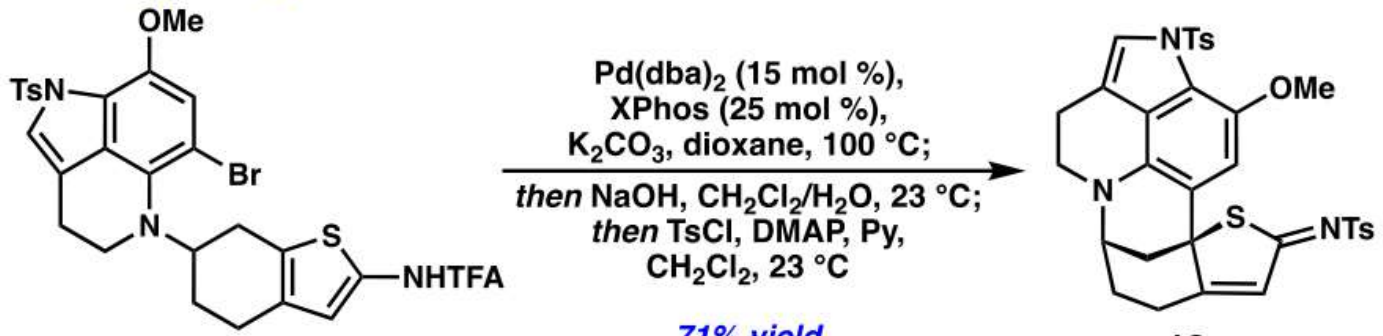
Buchwald, L. S. *Chem. Sci.* 2011, *2*, 27-50

Synthesis of Thioimidate 18 via Novel Thiophene Dearomatization

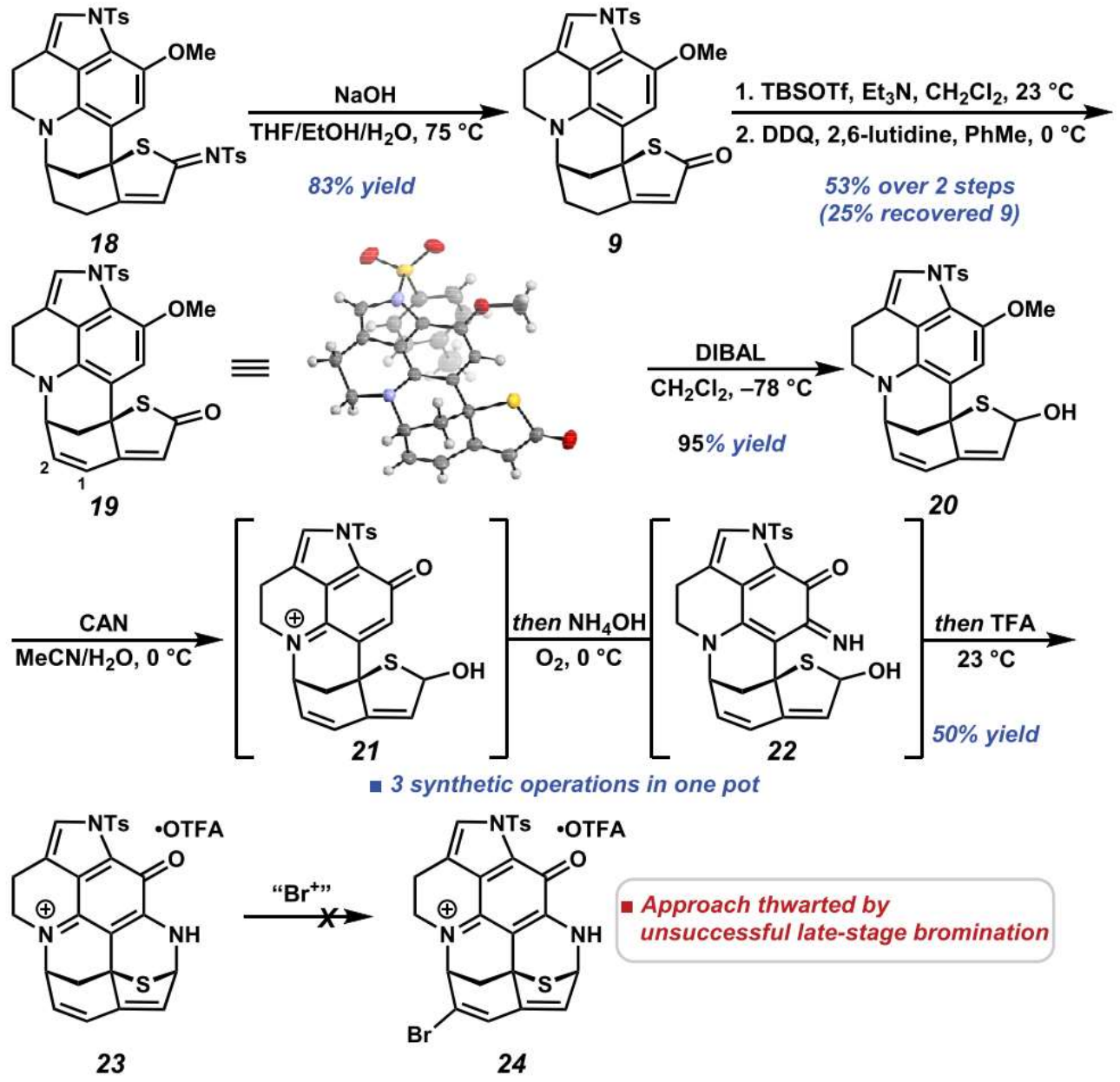


- *Successful assembly of tertiary sulfide and [3.3.1] bicyclic core*
- *Full carbon skeleton of aleutianamine established*

Telescoped Sequence

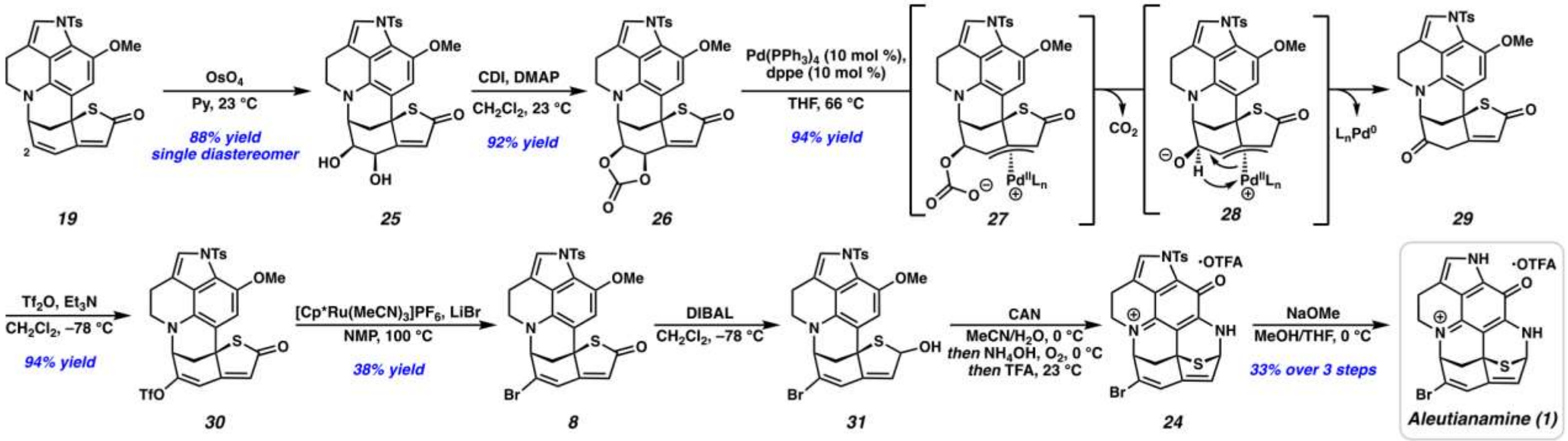


Synthesis of N-Tosyl des-Bromoaleutianamine(23) and Failed Late-Stage Bromination Attempts



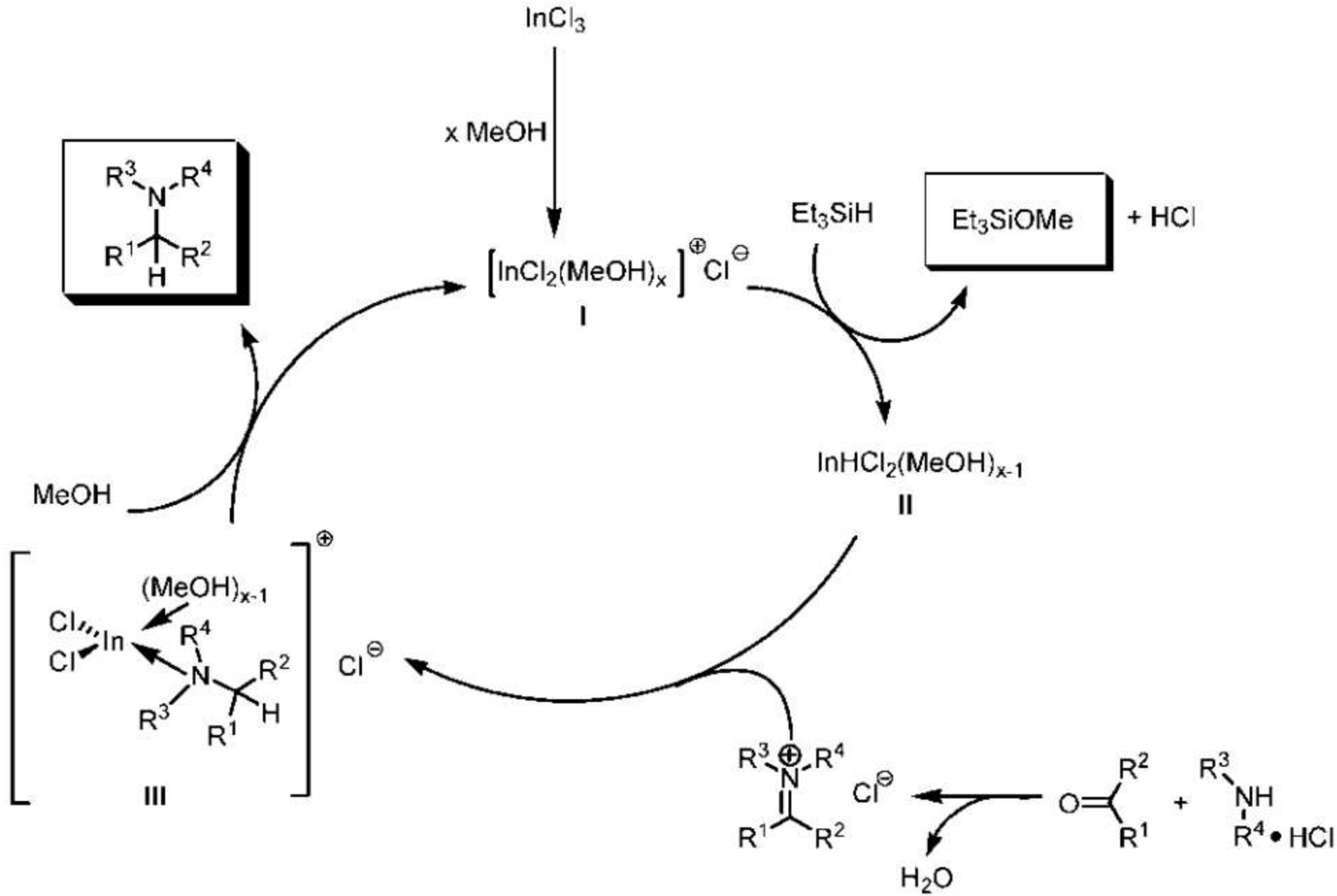
Completion of the Total Synthesis of Aleutianamine

The first palladium-catalyzed ***decarboxylative pinacol-type rearrangement*** of allylic carbonates

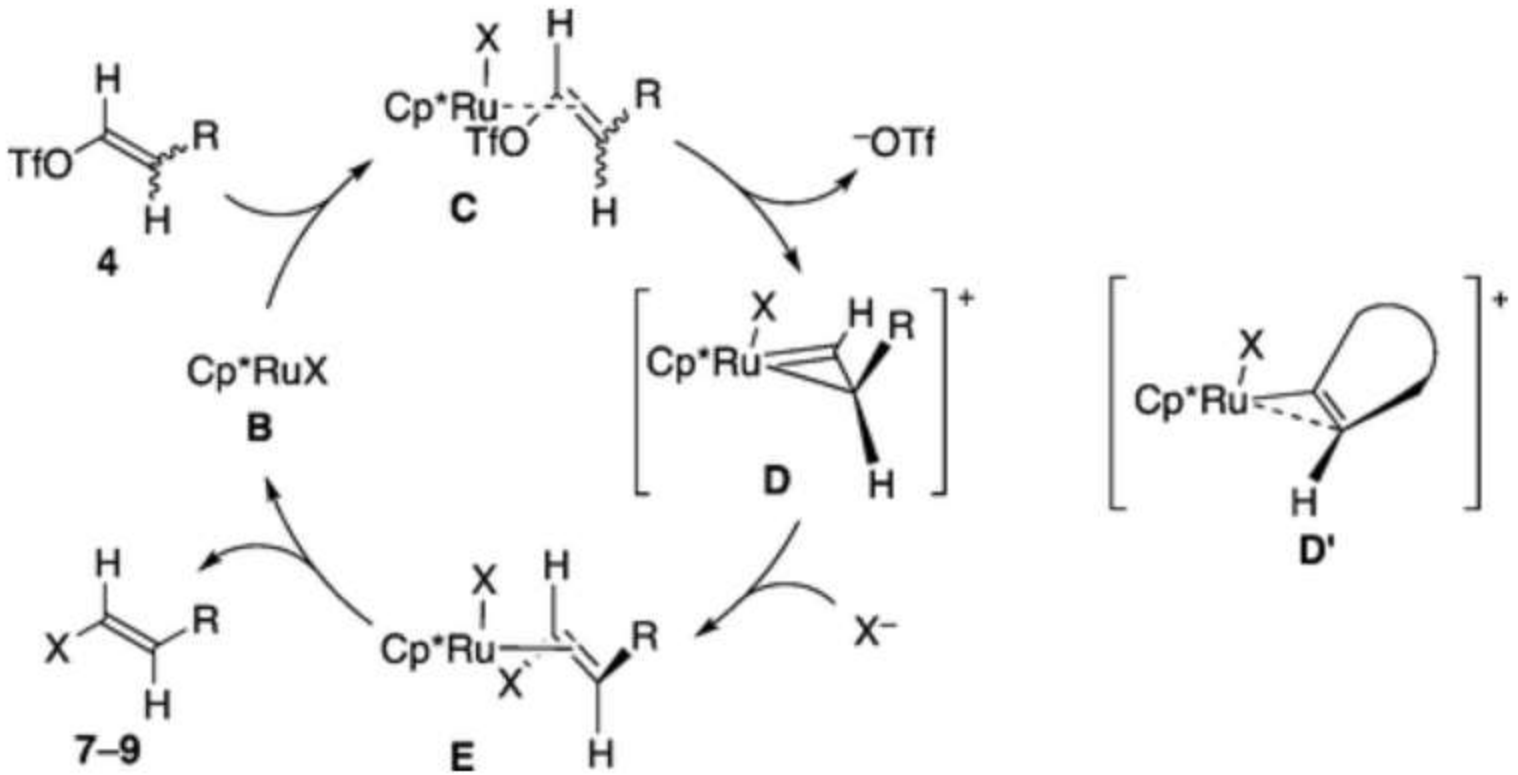


a longest linear sequence of ***20 steps***

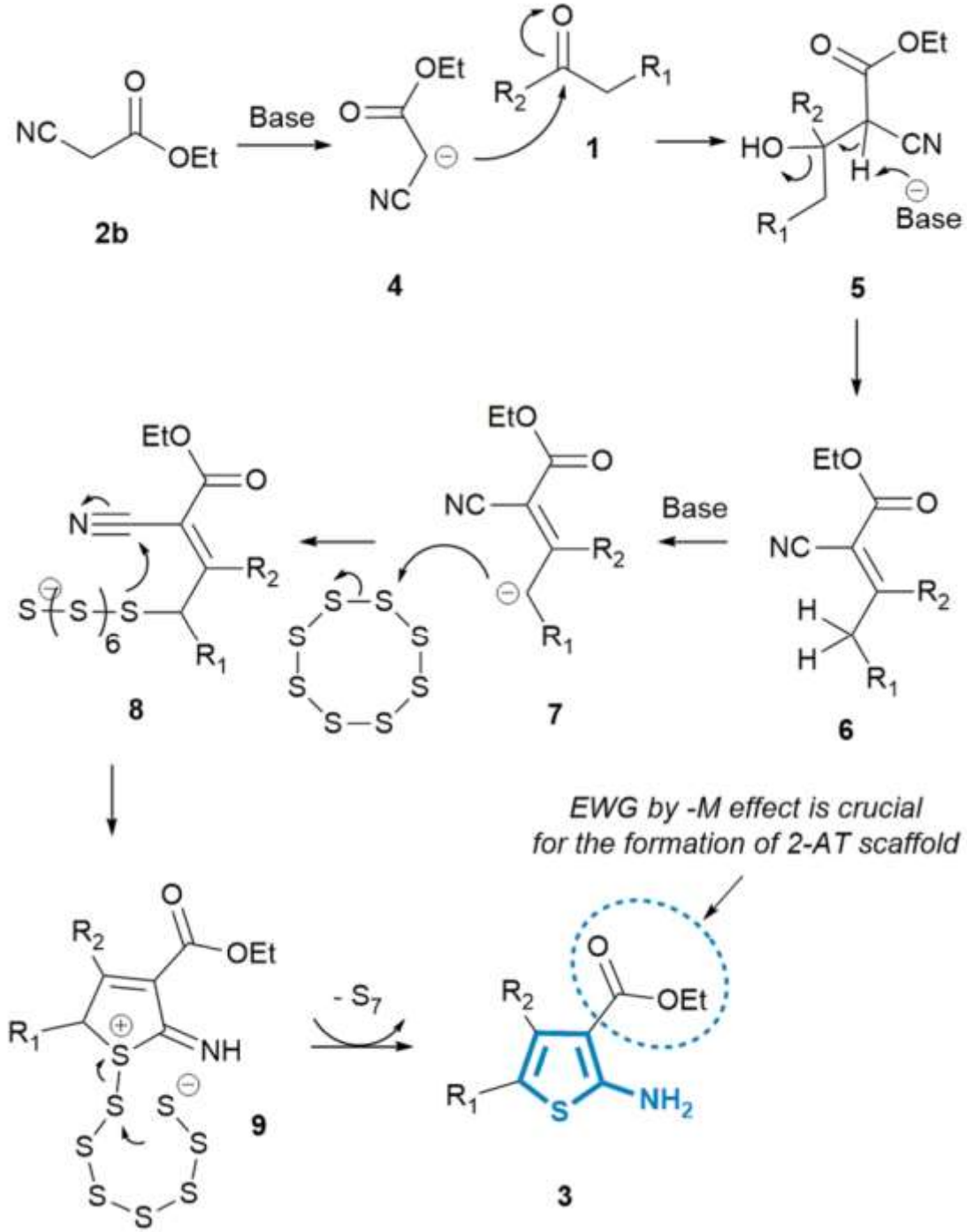
Thanks for your attention!



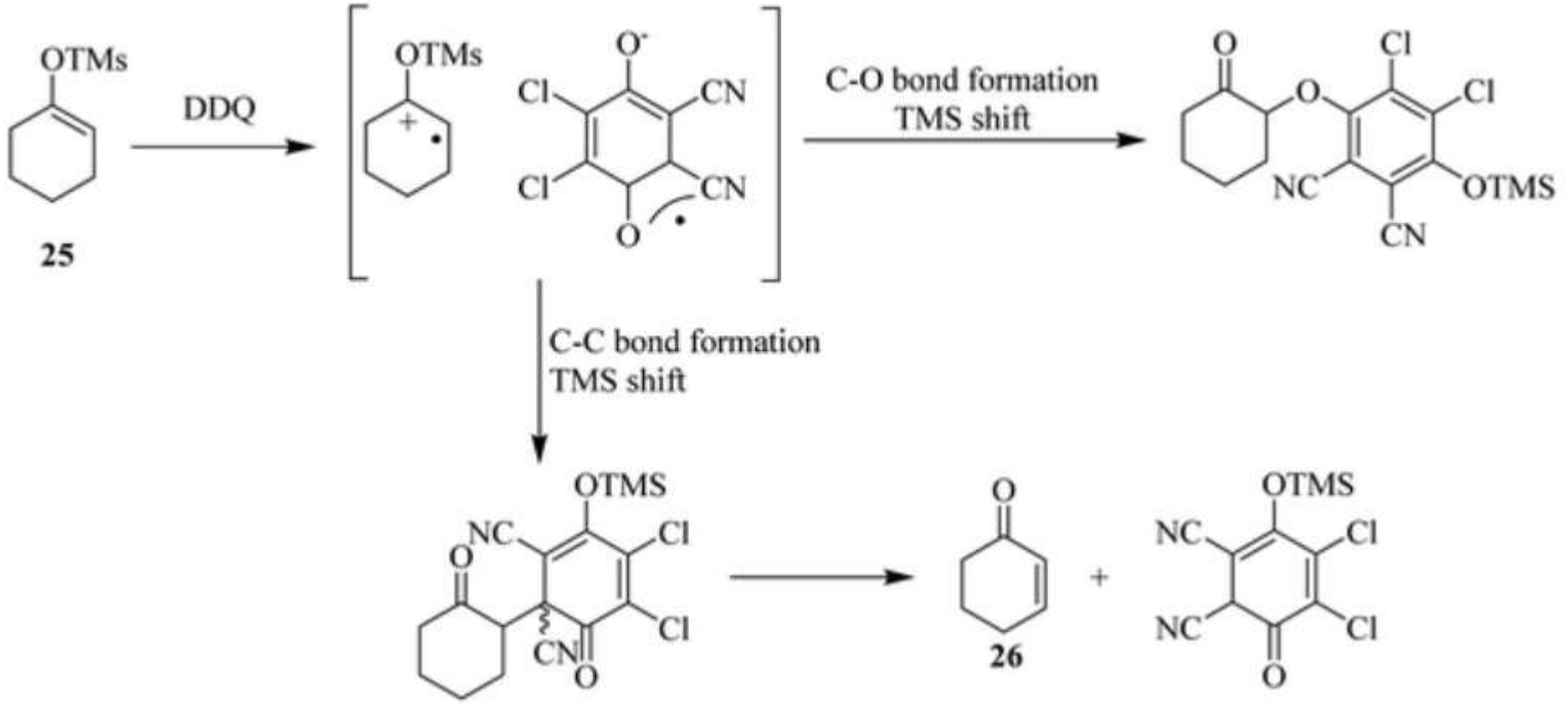
Yang, D. *J. Org. Chem.* 2008, *73*, 8829-8837



Hayashi, T. *J. Am. Chem. Soc.* 2012, *134*, 14760-14763.

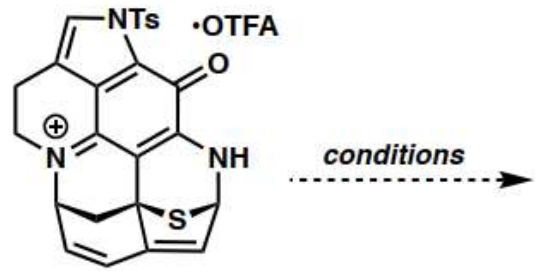


Møller, N. P. H. *J. Med. Chem.* 2002, *45*, 4443-4459.



Saleh A. Ahmed, RSC Adv., **2021**, *11*, 29826-29858

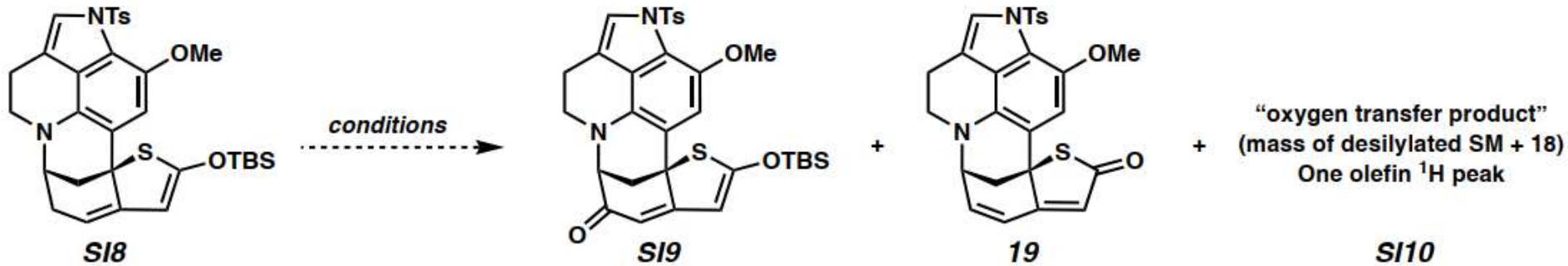
Table S4: Attempted conditions for bromination of 23



23

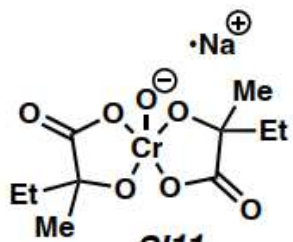
entry	conditions	result
1	NBS , THF, 23 °C	complex mixture
2	NBS, MeCN, 23 °C	unidentified rearrangement product
3	Br_2, CH_2Cl_2, 23 °C	unidentified rearrangement product
4	$PyHBr_3$, CH_2Cl_2, 23 °C	No reaction

Table S3: Attempted conditions for allylic oxidation



SI8 *SI9* *19* *SI10*

entry	conditions	result
1	$Pd(OH)_2/C$, TBHP, Cs_2CO_3, CH_2Cl_2, 0 °C	complex mixture, including *19*
2	PIDA, TBHP, $Mg(OAc)_2 \cdot 4H_2O$, n-BuOC(O)*n*-Pr, 0 °C	complex mixture, few olefin peaks by NMR
3	$Mn(OAc)_3 \cdot 2H_2O$, TBHP, 4 Å MS, O_2, EtOAc, 23 °C	complex mixture by NMR, trace mass of *SI9* by LC–MS
4	$Rh_2(esp)_2$, TBHP, EtOAc, 23 °C	SM + 2–3 new products. Major new product is *SI10*
5	$Rh_2(cap)_4$, TBHP, K_2CO_3, CH_2Cl_2, 40 °C	complex mixture; tosyl peaks are visible but no clear olefinic peaks
6	*SI10* (10 equiv), MnO_2 (20 equiv), 15-crown-5, DCE, 80 °C, 2 d	decomp to basline
7	*SI10* (5 equiv), MnO_2 (10 equiv), 15-crown-5, DCE, 80 °C, 4.5 h	low yield of *19*
8	PDC, 4 Å MS, CH_2Cl_2, 60 °C	SM, many oxidized products



SI11

Scheme S1: Failed attempts at C2 functionalization