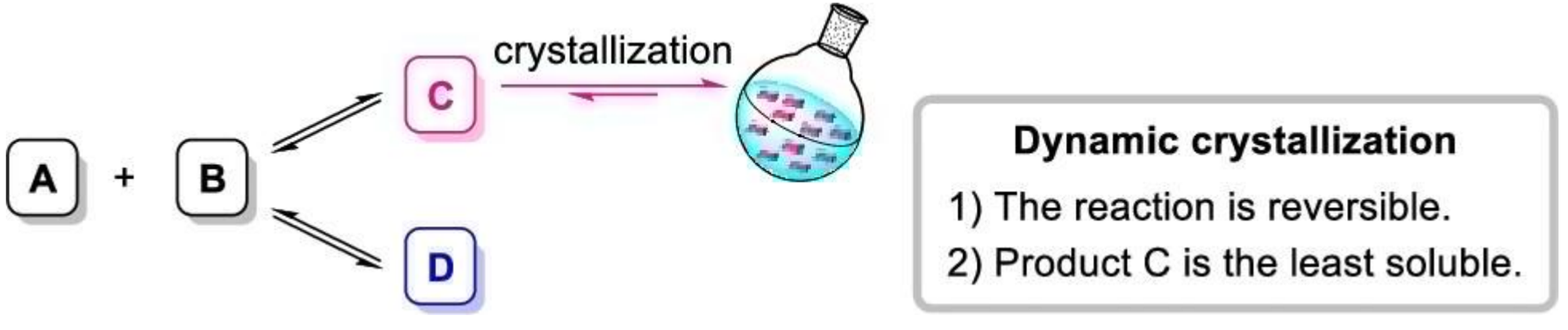
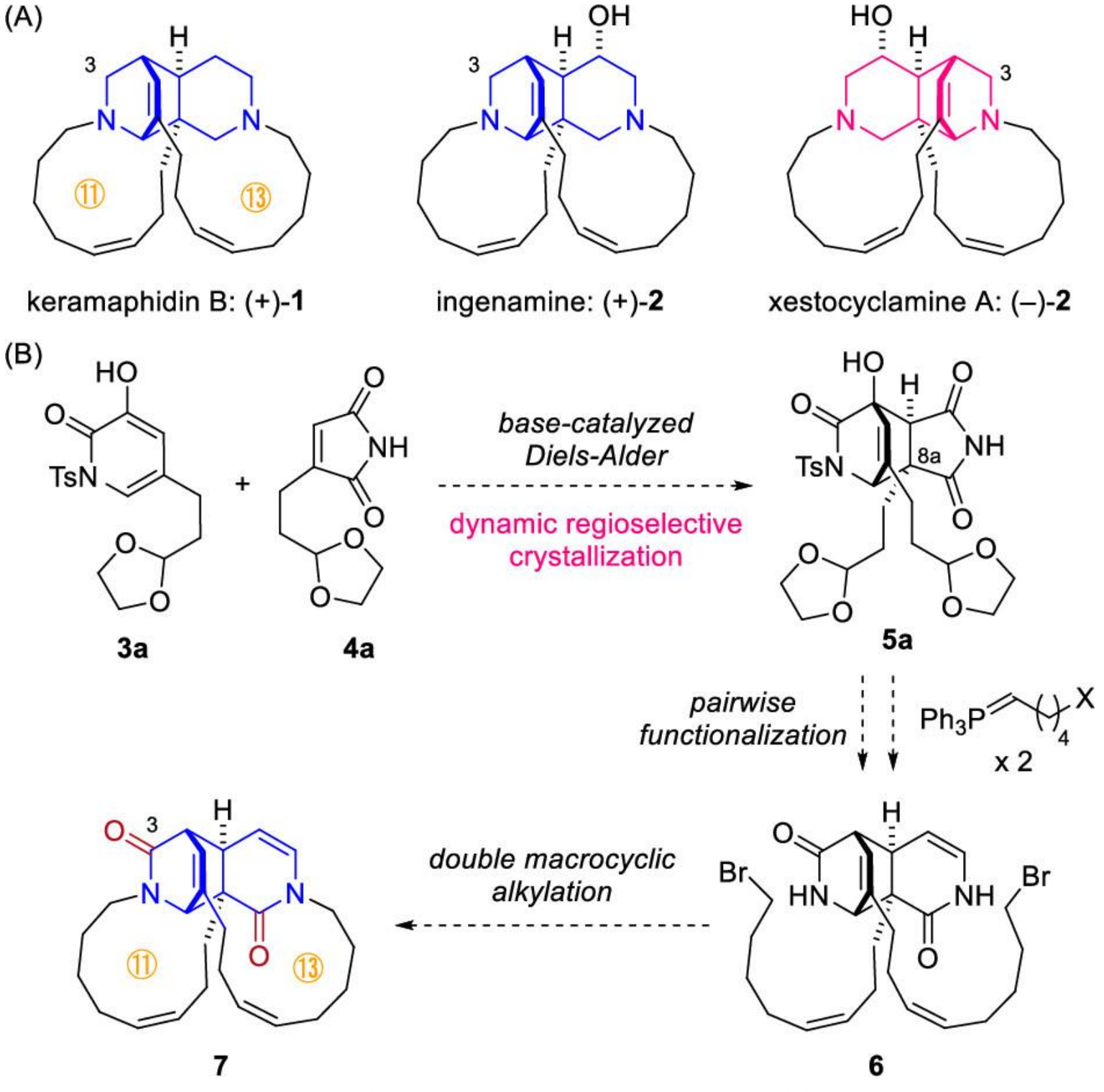
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Total Synthesis of Keramaphidin B and Ingenamine by Base-Catalyzed Diels–Alder Reaction Using Dynamic Regioselective Crystallization

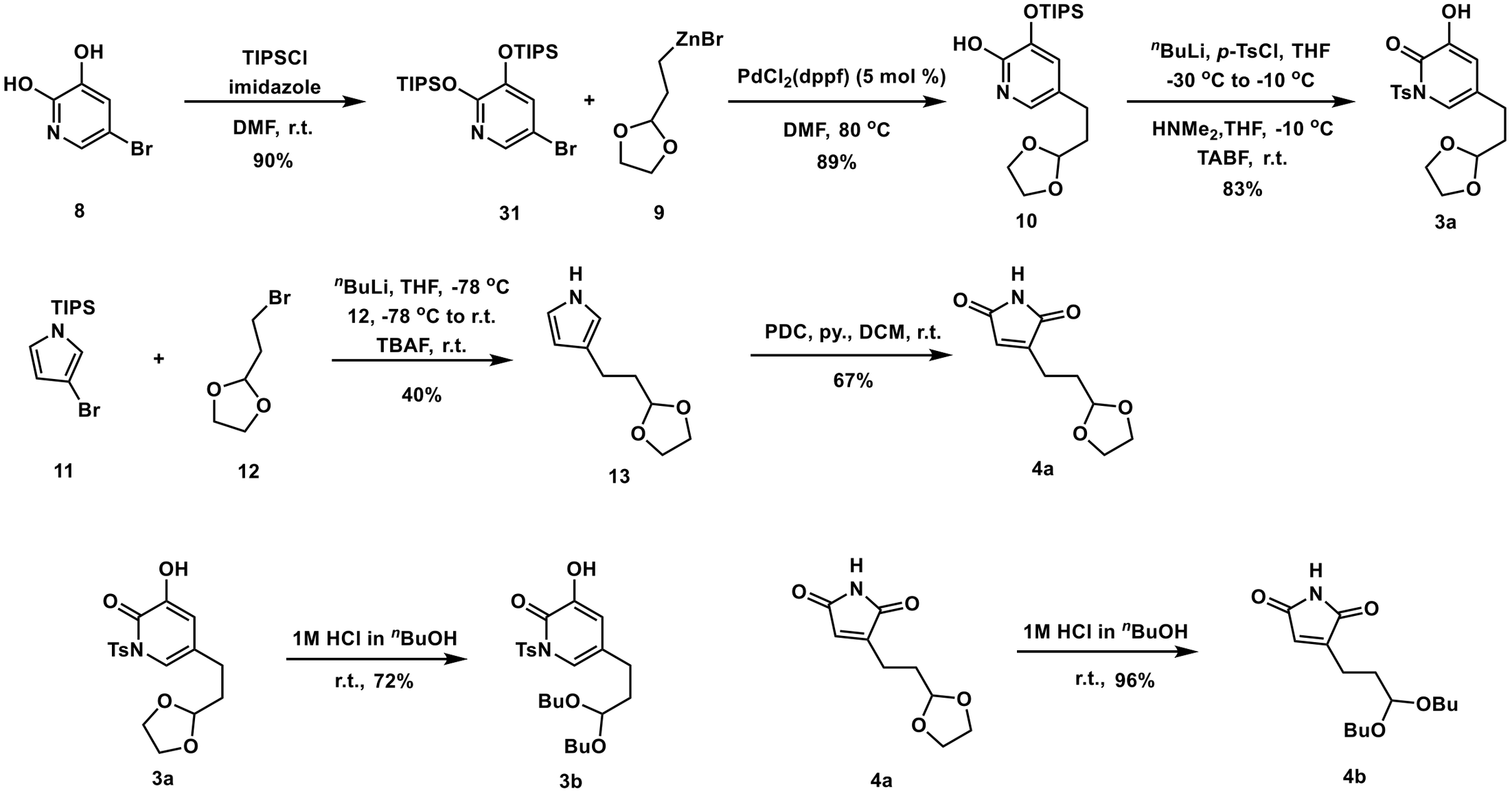
Yuki Kurihara, Minori Yagi, Takashi Noguchi, Haruka Yasufuku, Ayane Okita, Sho Yoshimura, Takeshi Oishi, Noritaka Chida, Toshitaka Okamura, and Takaaki Sato*



Scheme 1. Dynamic Crystallization Approach To Control Selectivity



Scheme 2. (A) Keramaphidin B and Ingenamine, (B) Our Synthetic Plan


TIPSCl
imidazole
DMF, r.t.
90%
PdCl2(dppf) (5 mol %)
DMF, 80 °C
89%
nBuLi, p-TsCl, THF
-30 °C to -10 °C
HNMe2,THF, -10 °C
TABF, r.t.
83%
nBuLi, THF, -78 °C
12, -78 °C to r.t.
TBAF, r.t.
40%
PDC, py., DCM, r.t.
67%
1M HCl in nBuOH
r.t., 72%
1M HCl in nBuOH
r.t., 96%
8
31
9
10
3a
11
12
13
4a
3a
3b
4a
4b

Negishi偶联

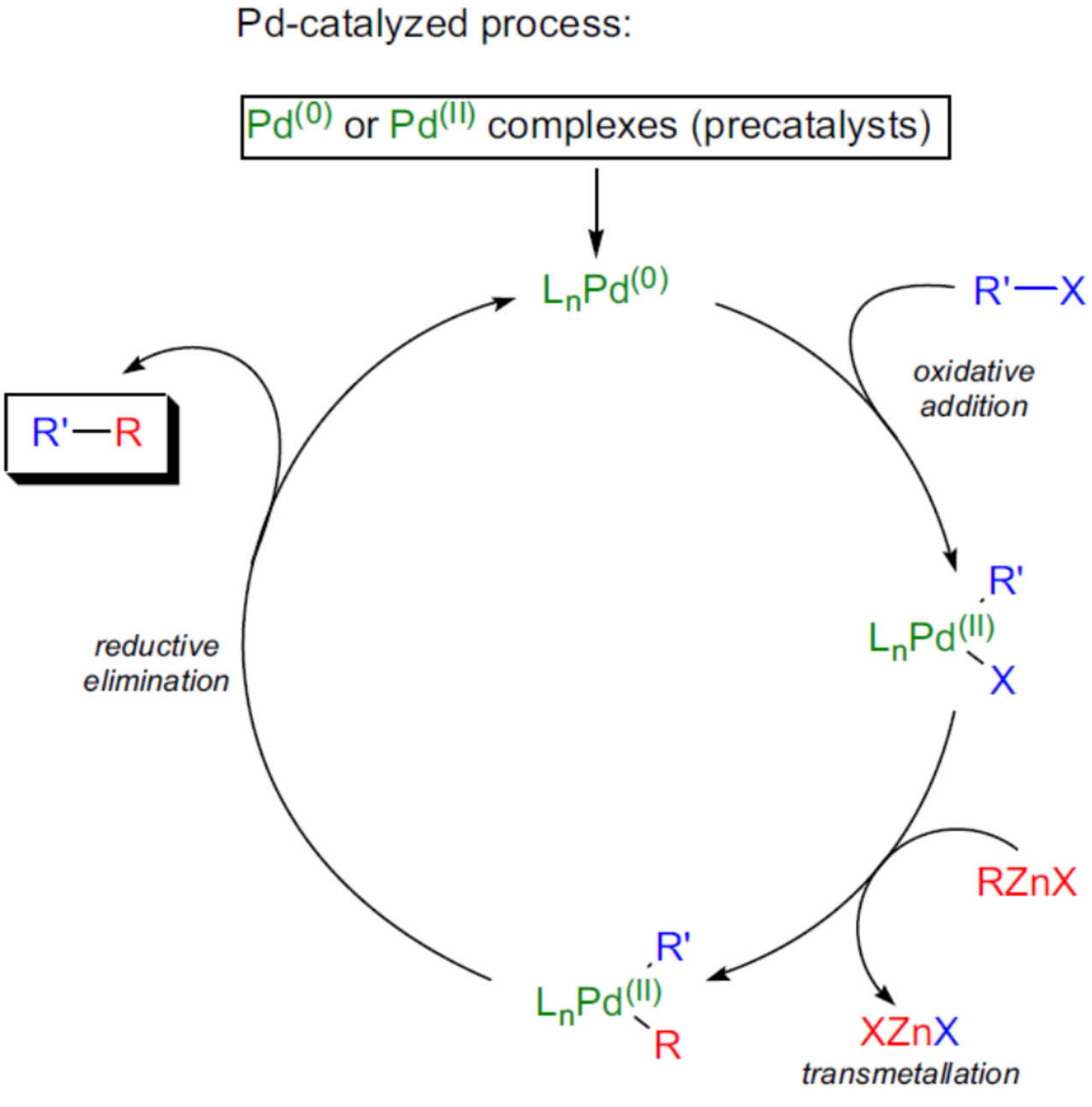
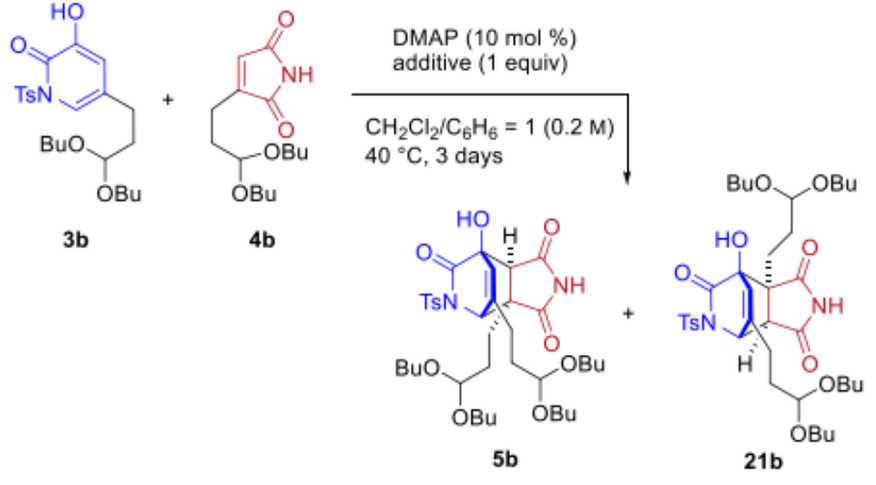

Pd-catalyzed process:
Pd(0) or Pd(II) complexes (precatalysts)
LnPd(0)
R'—X
oxidative addition
R'
LnPd(II)
X
RZnX
XZnX
transmetallation
R'
LnPd(II)
R
reductive elimination
R'—R

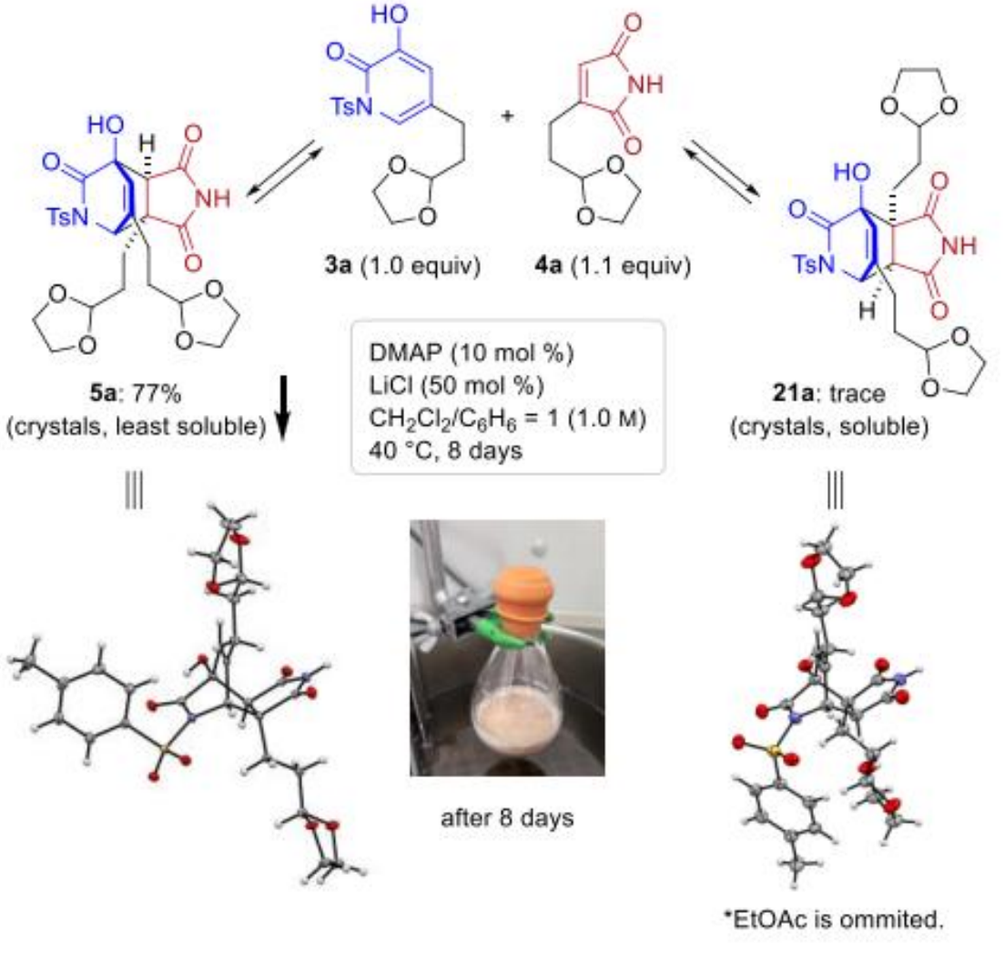
Table 1. DMAP-Catalyzed Diels–Alder Reaction between 3-Hydroxy-2-pyridone and Maleimide[a]



			yields[b]			
entry	SM	additive	**5b**	**21b**	**3b**	**4b**
1	**3b+4b**	none	5%	14%	55%	68%
2	**3b+4b**	LiCl	39%	20%	8%	22%
3	**5b**	none	98%	0%	0%	0%
4	**21b**	none	0%	97%	0%	0%
5	**5b**	LiCl	38%	15%	12%	24%
6	**21b**	LiCl	27%	11%	11%	22%

[a]**3b** (1 equiv), **4b** (1.2 equiv), DMAP (10 mol %), additive (1 equiv), CH_2Cl_2/C_6H_6 = 1 (0.2 M), 40 °C, 3 days. [b]Yields were determined by ^1H NMR using mesitylene as an internal standard.

Scheme 4. Dynamic Regioselective Crystallization in Base-Catalyzed Diels–Alder Reaction



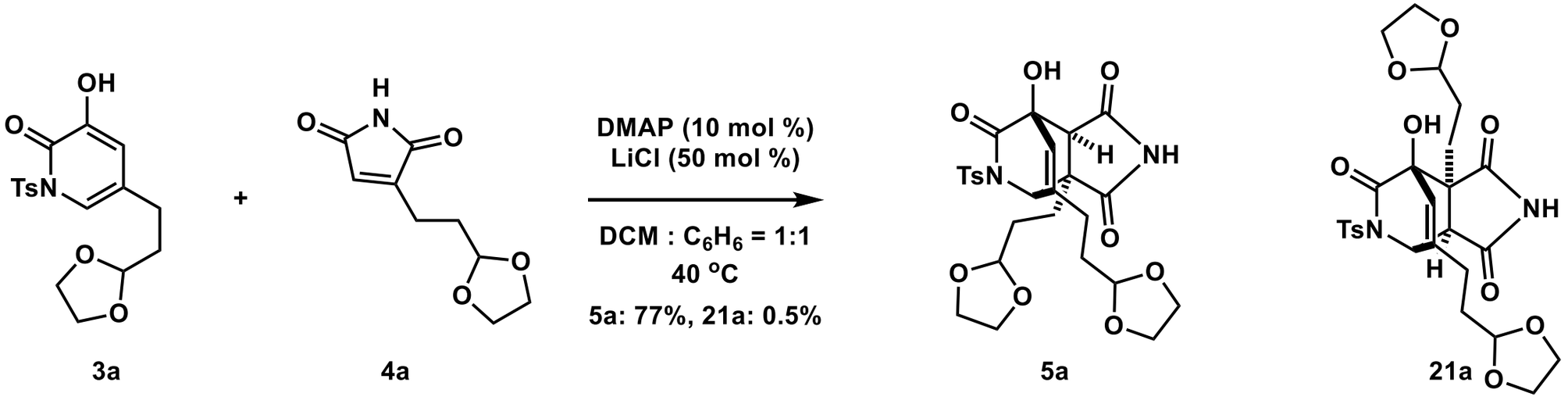
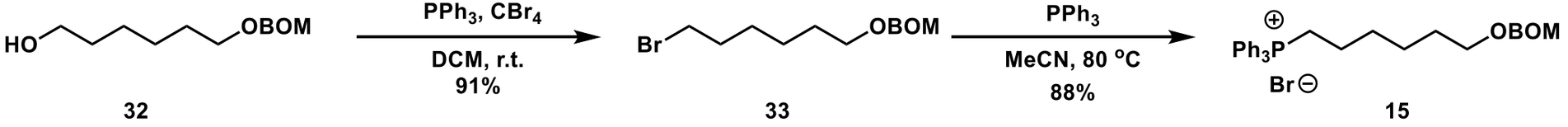


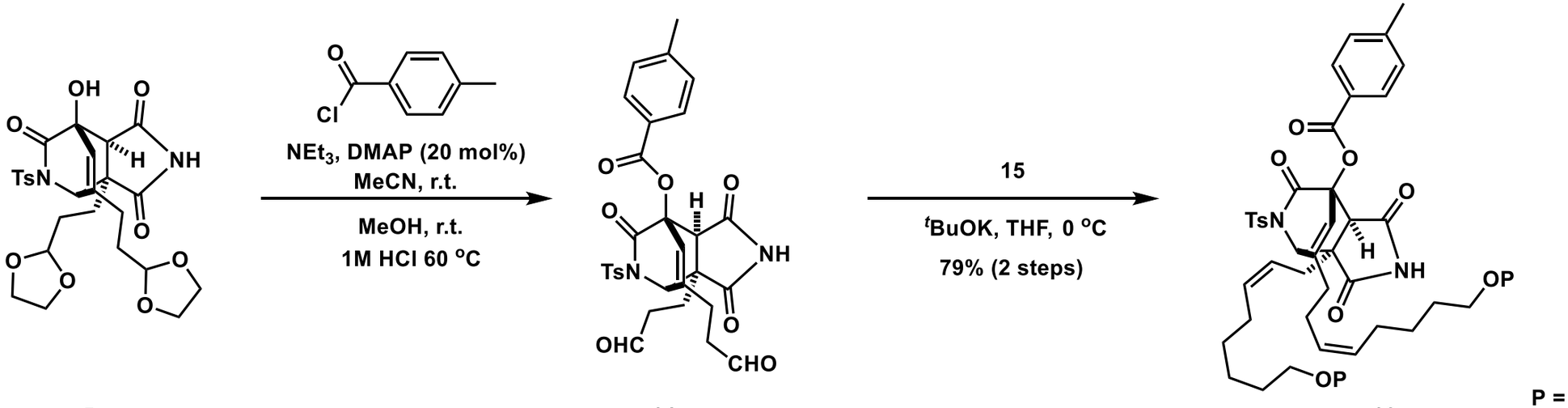
Table S3. Solubility of Related Compounds in $CH_2Cl_2/C_6H_6 = 1$ at room temperature.[a]

	3a	4a	5a[b]	21a
Solubility in $CH_2Cl_2/C_6H_6 = 1$	16 mg/mL	700 mg/mL	0.3 mg/mL	18 mg/mL

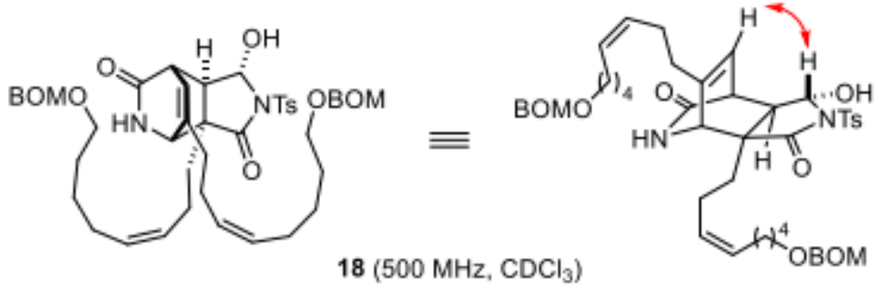
[a]The modified shake flask method was used to determine the solubility. The solvent ($CH_2Cl_2/C_6H_6 = 1$) was added to 100 mg of a compound at room temperature until the compound was dissolved. Sonication was used to check if the solid was dissolved at that volume or not. [b]20 mg of **5a** was used instead of 100 mg.



32 33 15

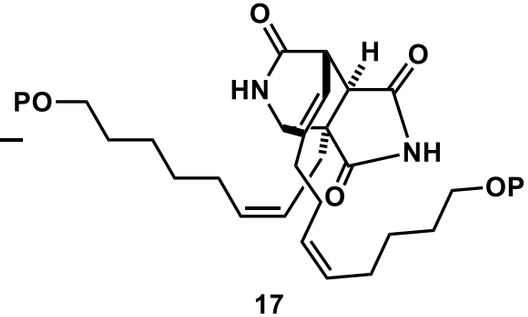


5a 14 16



18 (500 MHz, $CDCl_3$)

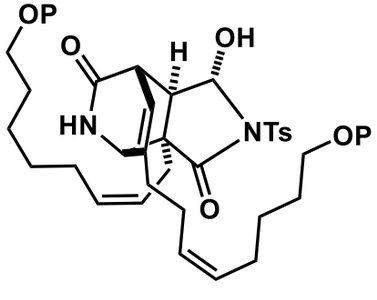
NaH, 1,4-dioxane, r.t.
$SmI_2(HMPA)_4$, 100 °C
43%



17

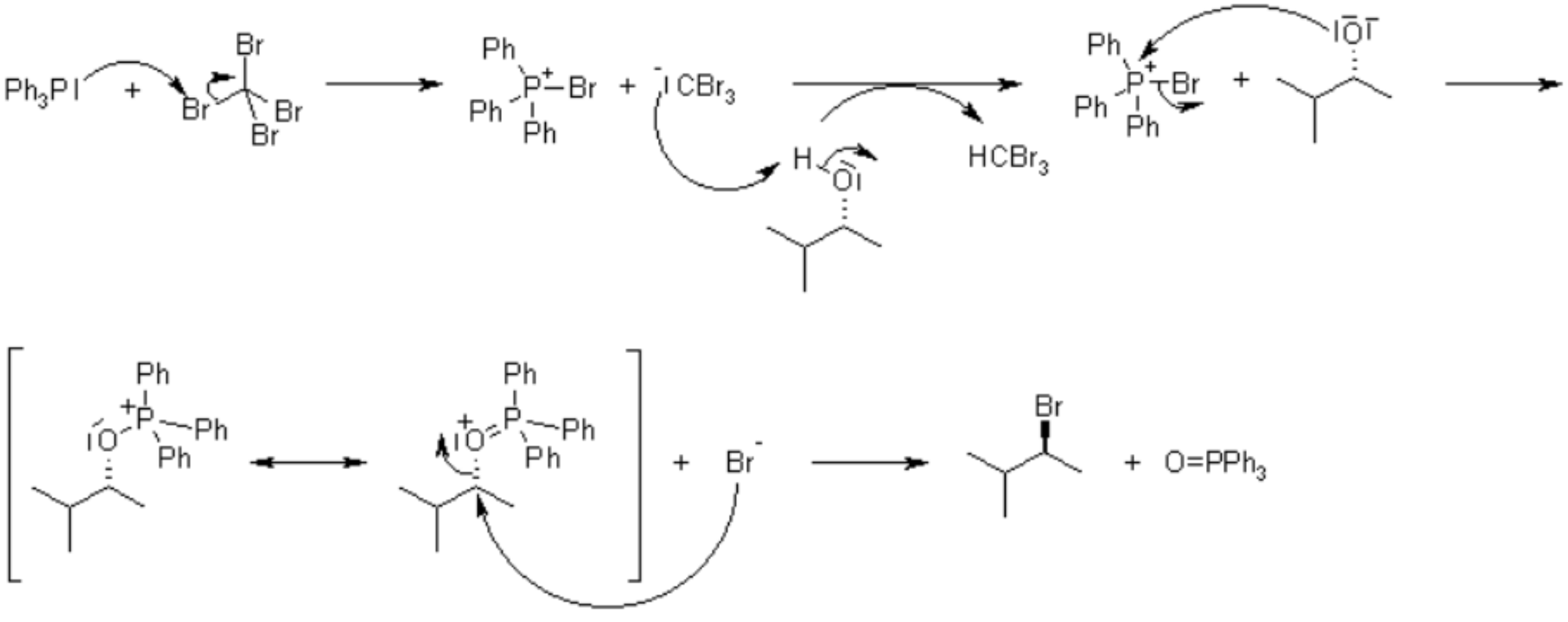
TsCl, NEt_3, NMe_3·HCl
DCM, r.t.

$NaBH_4$, EtOH, -20 °C
88%

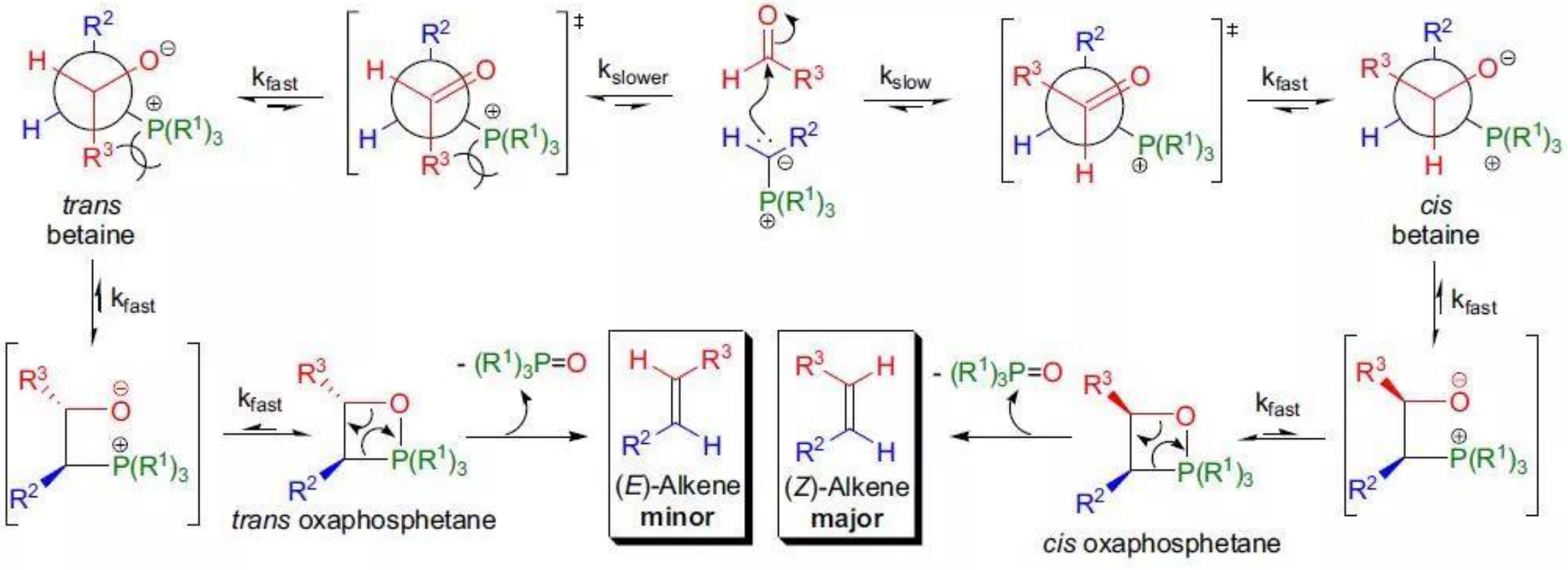


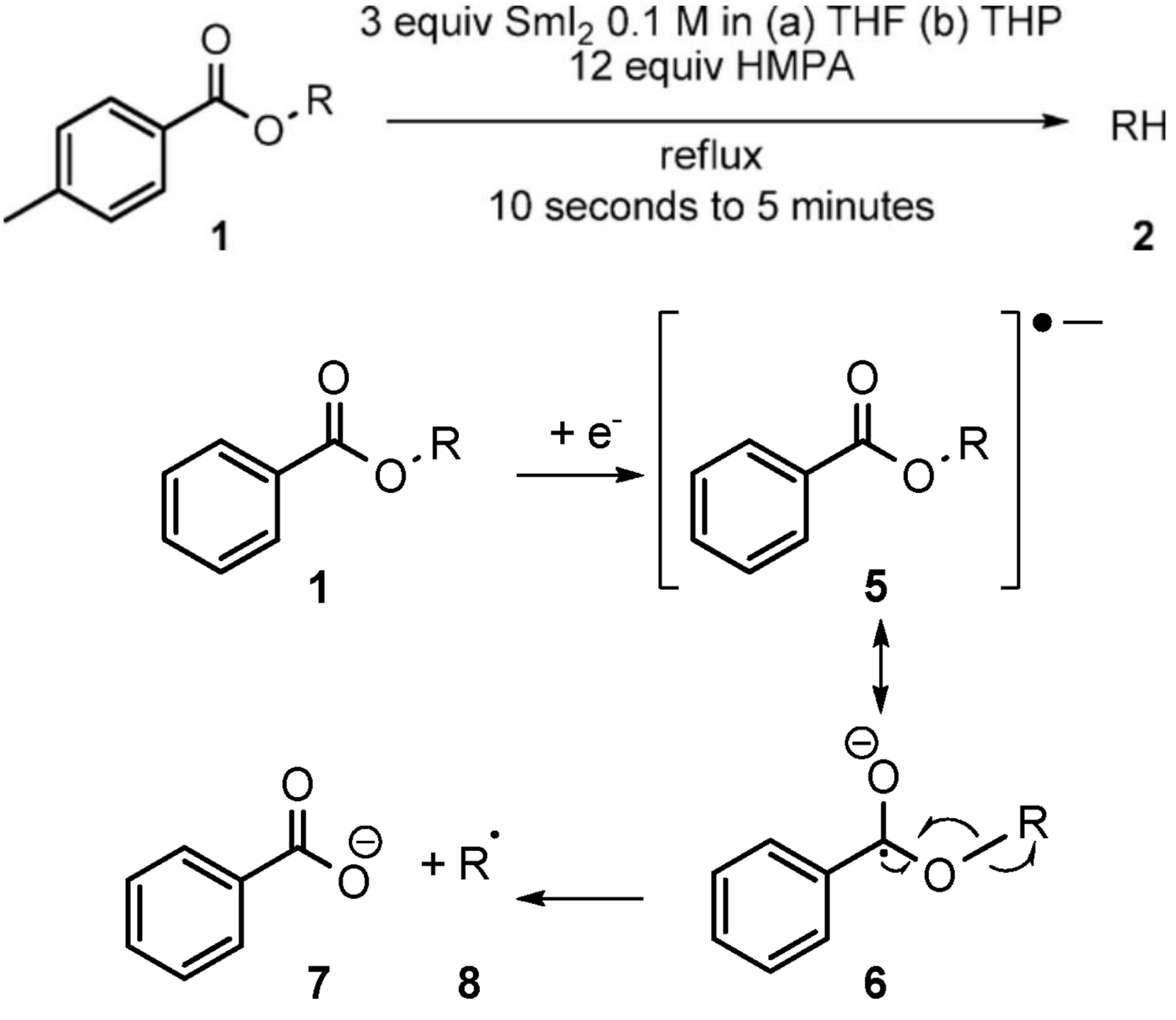
18

Appel 反应

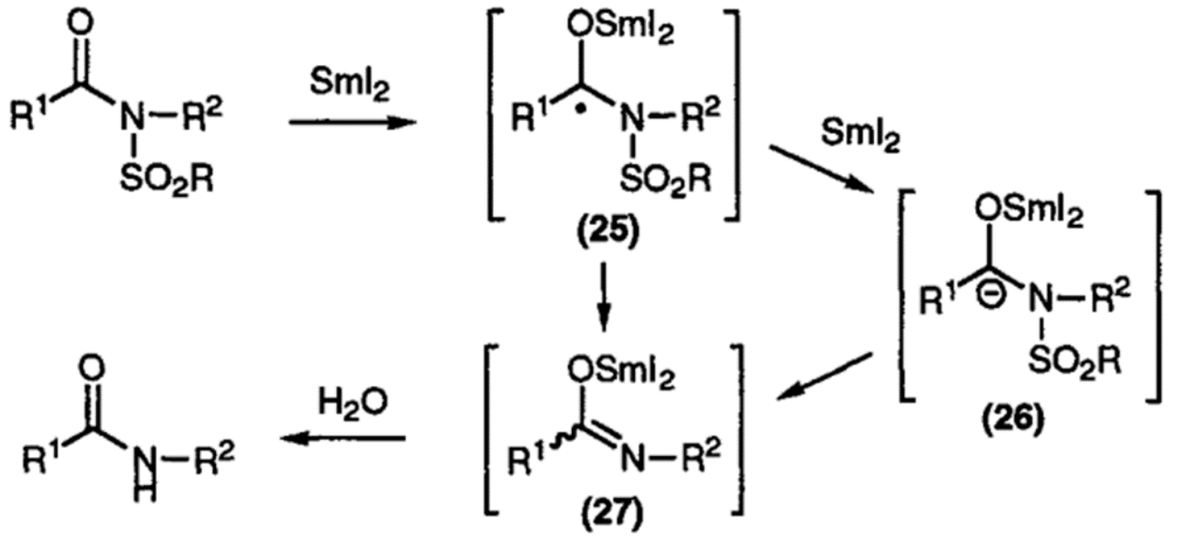

Ph3PI
Br
Br
Br
Br
Ph
Ph
Ph
Br
ICBr3
HCBr3
H
O
I
Ph
Ph
Ph
Br
IOI
Ph
Ph
Ph
O
P
Ph
I
Ph
Ph
Ph
O
P
Ph
I
Ph
Ph
Br-
Br
O=PPh3

Wittig 反应


trans betaine
cis betaine
trans oxaphosphetane
cis oxaphosphetane
(E)-Alkene minor
(Z)-Alkene major
k_fast
k_slower
k_slow
- (R1)3P=O

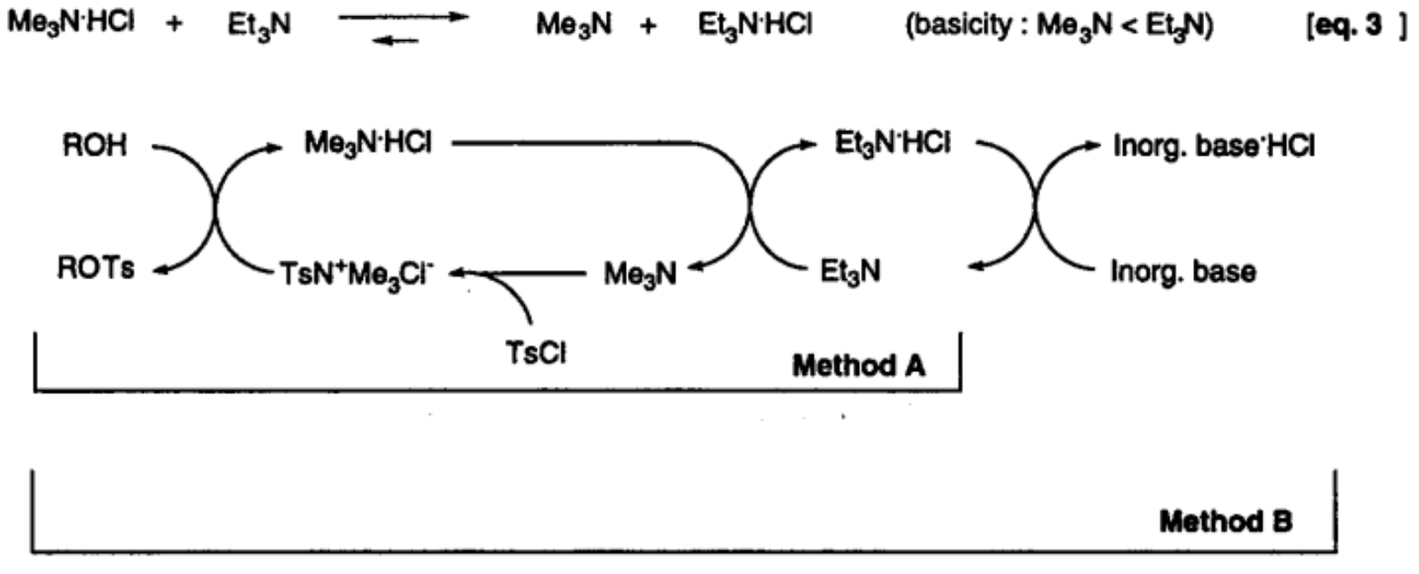


Org. Lett., **2008**, *10*, 2773.



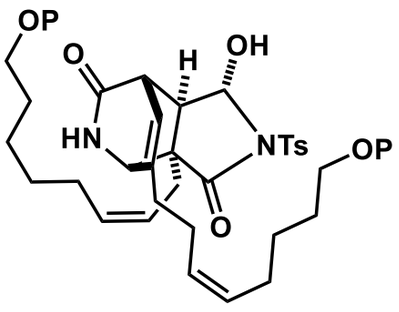
Scheme 4

Synlett, **1997**, *3*, 271.



Scheme 2

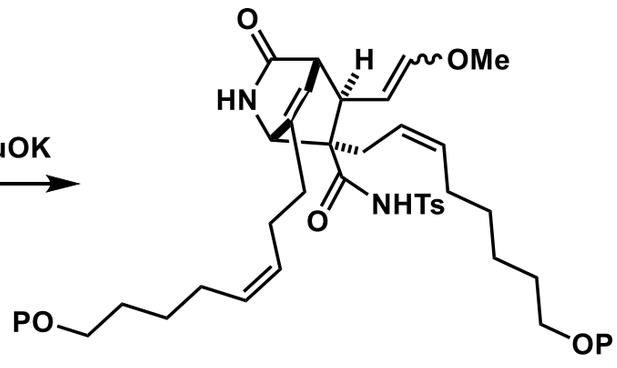
Tetrahedron, **1999**, *55*, 2183.



18

$MeOCH_2PPh_3Cl$, ^tBuOK

THF, r.t.

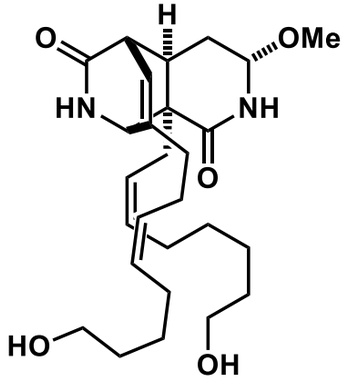


19

SmI_2, H_2O, THF, r.t.

1 M HCl MeOH, r.t.

77%



20

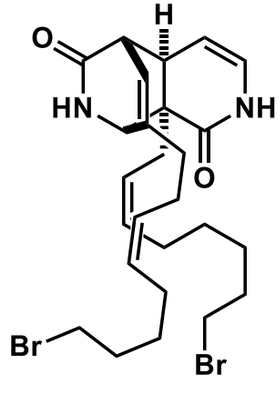
PPh_3, CBr_4

imidazole

DCE, 40 °C

TFA, 40 °C

51%

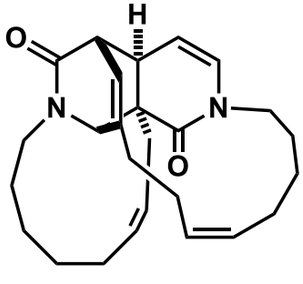


6

Cs_2CO_3, DMSO, r.t.

Cs_2CO_3, 60 °C

46%

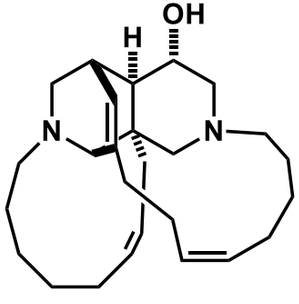


7

m-CPBA, DCM, -10 °C

DIBAL-H, Et_2O, r.t.

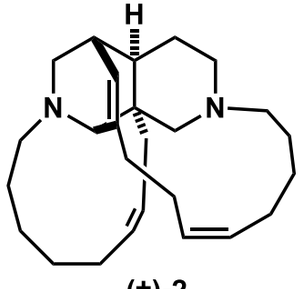
31% (2 setps)



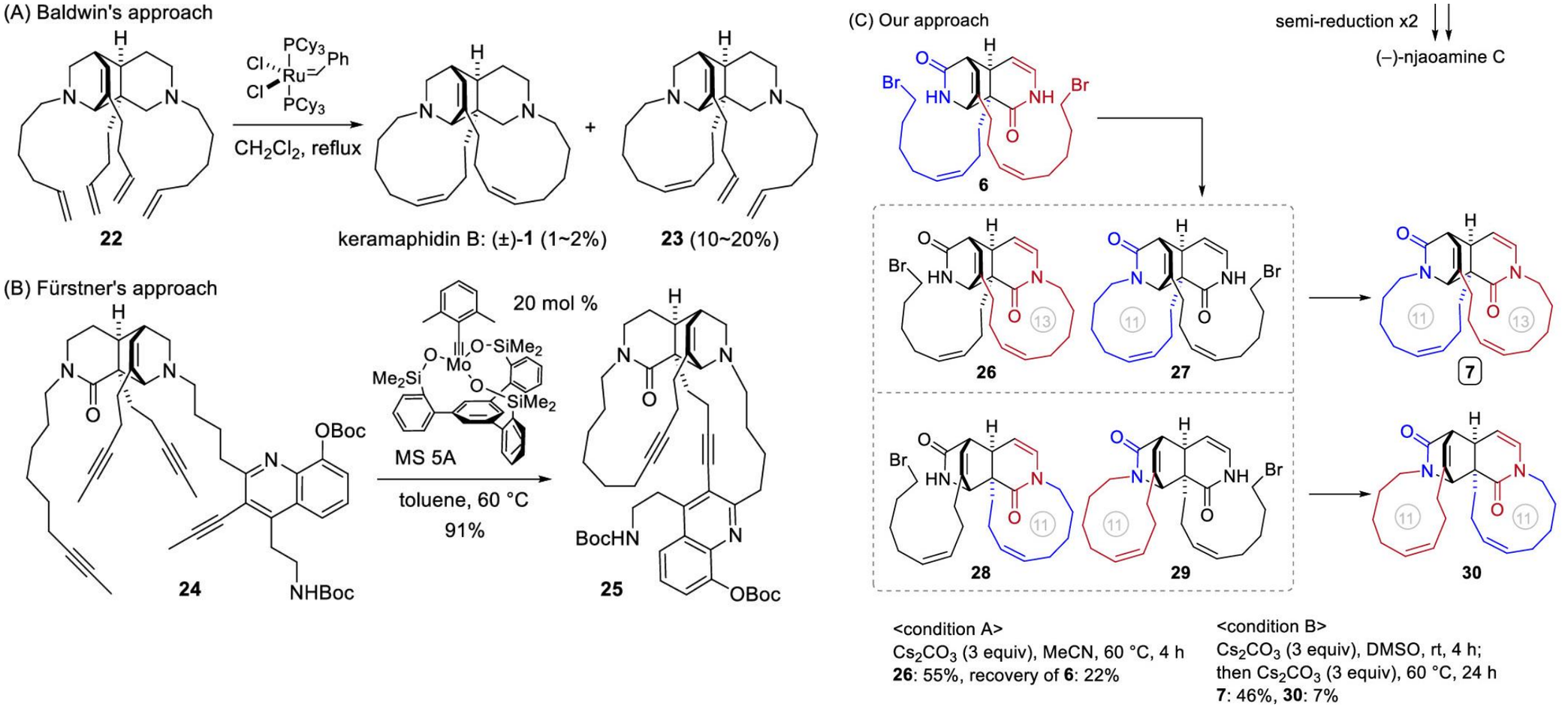
(±)-1

DIBAL-H, Et_2O, r.t.

41%



(±)-2



Scheme 5. Double Macrocyclic Formation by (A) Ring-Closing Alkene Metathesis, (B) Ring-Closing Alkyne Metathesis, (C) Alkylation