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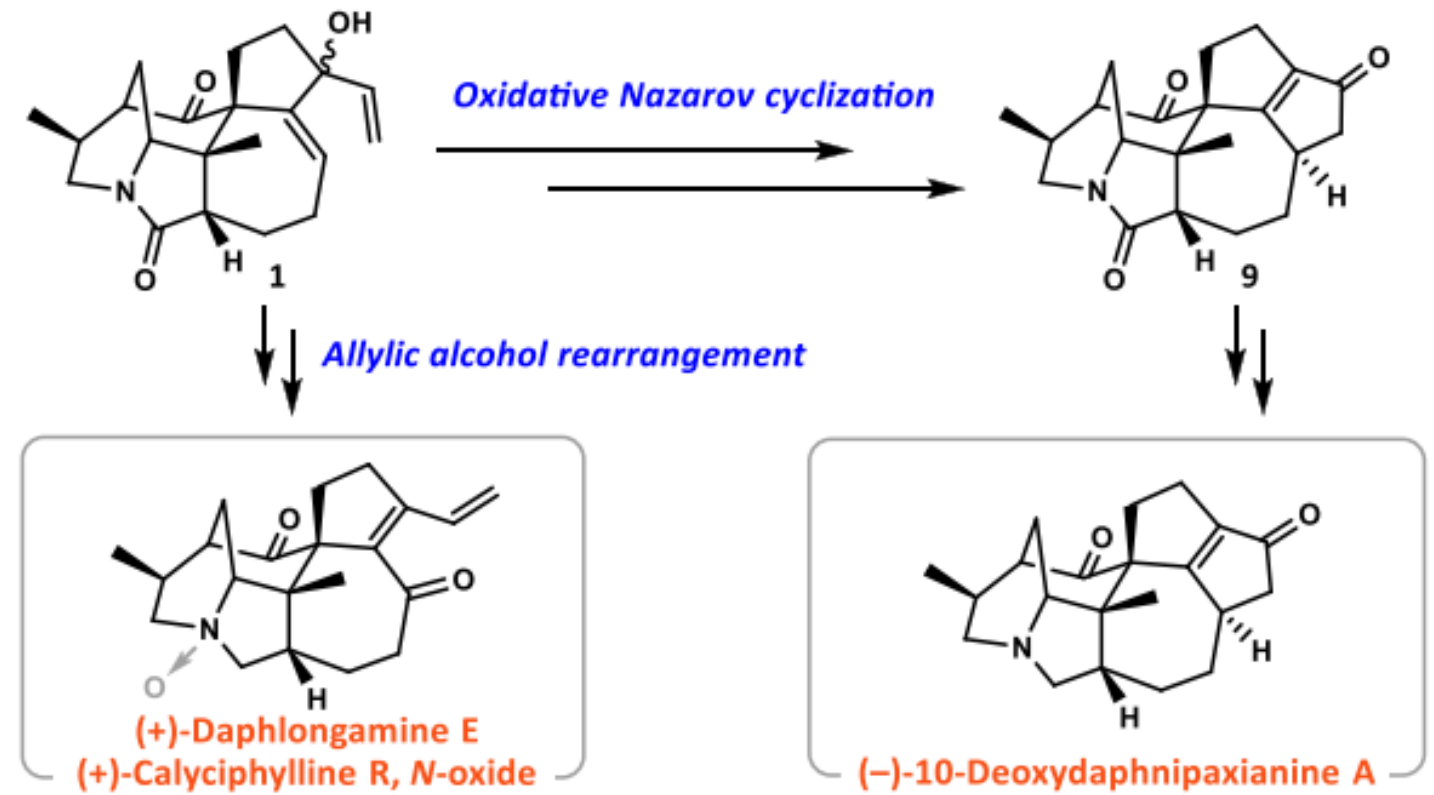
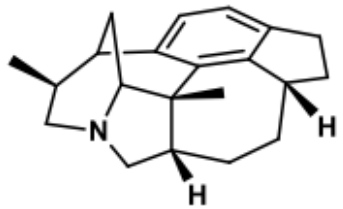
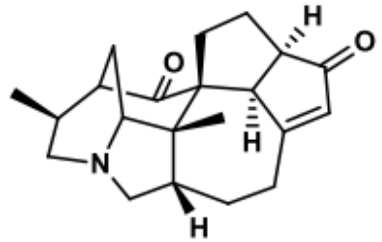
Article

Total Syntheses of Calyciphylline A-Type Alkaloids (−)-10-Deoxydaphnipaxianine A, (+)-Daphlongamine E and (+)-Calyciphylline R via Late-Stage Divinyl Carbinol Rearrangements

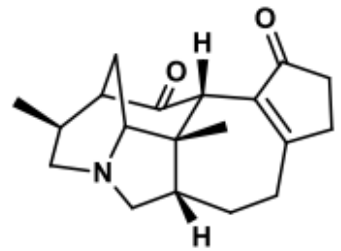




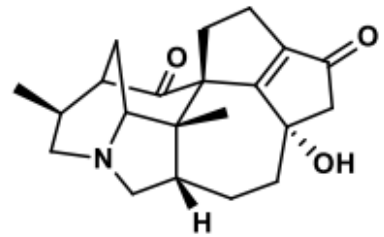
(–)-Daphenylline
Li (2013; 2018); Fukuyama/ Yokoshima (2016); Zhai (2018); Qiu (2019; 2021); Lu (2022)



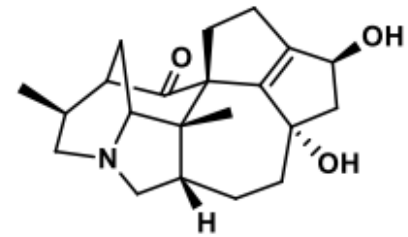
(–)-Daphniyunnine C
(Longeracinphyllin A)
Li (2017)



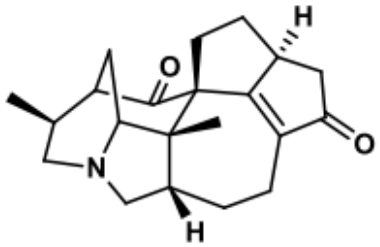
(–)-Himalensine A
Dixon (2017); Xu (2019)
Gao (2019, racemic); Qiu (2021)



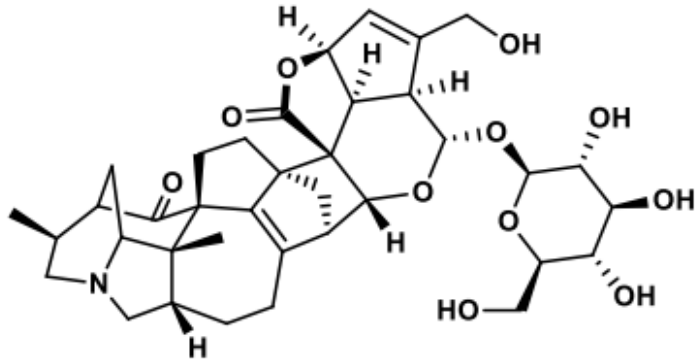
(–)-Daphnipaxianine A
Li (2018)



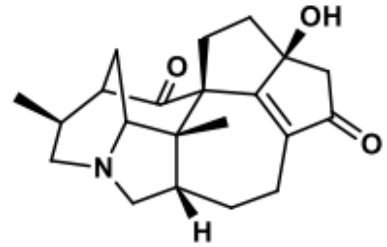
(–)-Himalenine D
Li (2018)



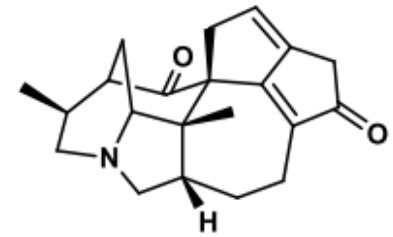
(–)-Daphnilongeranin B
Zhai (2018); Li (2018)



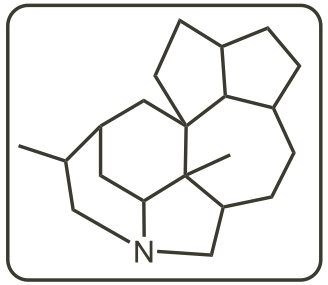
(–)-Hybridaphniphylline B
Li (2018)



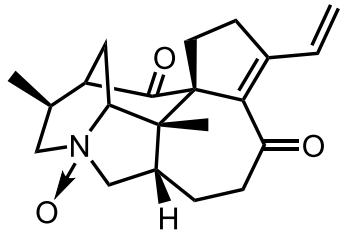
(–)-Daphniyunnine E
Li (2018)



(–)-Dehydrodaphnilongeranin B
Li (2018)

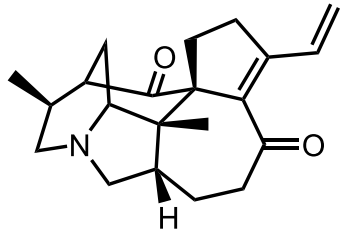


Calyciphylline A -type Alkaloids

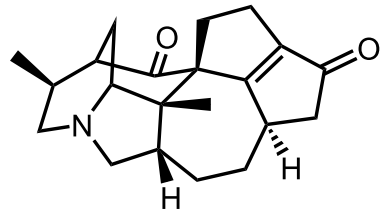


Calyciphylline R

N-oxide formation



Calyciphylline **E**

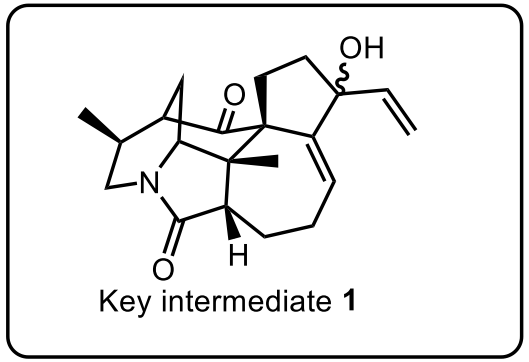


10-deoxydaphnipaxianine **A**

Regioselective allylic alcohol rearrangement

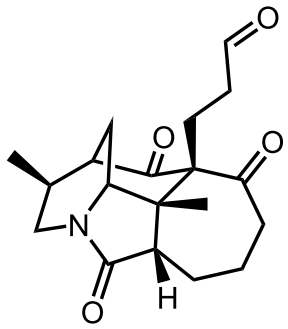
Late-stage divinyl carbinol rearrangements & Selective amide reductions

Oxidative Nazarov electrocyclization



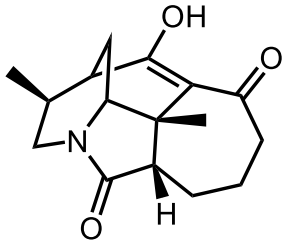
Key intermediate **1**

Pinacol coupling & Grignard



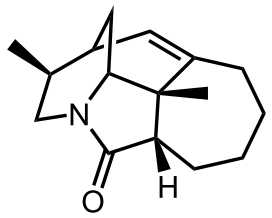
2

Tsuji-Trost allylation, Claisen rearrangement & Hydroboration



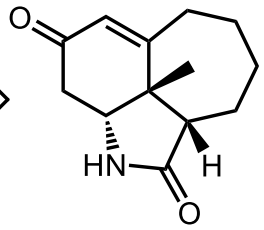
3

Sequential Oxidations



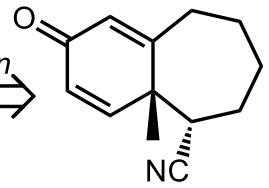
4

Hutchins-Kabalka & Heck coupling



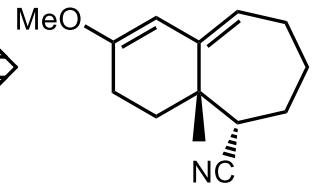
5

Pt-catalyzed nitrile hydration & Michael addition



6

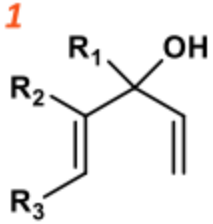
Saegusa-Ito oxidation



7

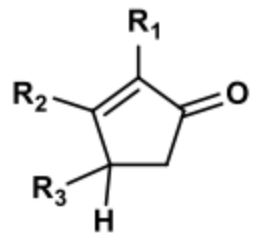
B. Key Transformations

1

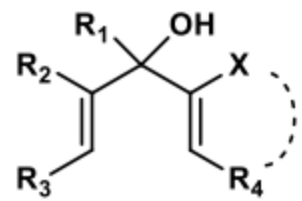


Oxidative Nazarov electrocyclization

Unprecedented transformation using unfunctionalized tertiary divinyl carbinol

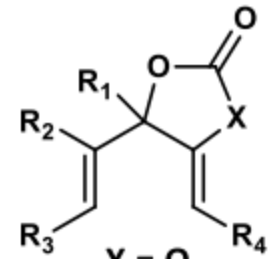


Reported examples: functionalized tertiary divinyl carbinols



X = O or S

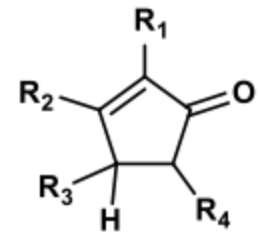
or



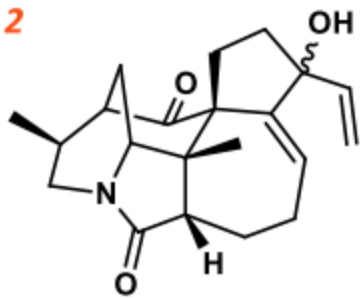
X = O

LA or H^+

ref. 27

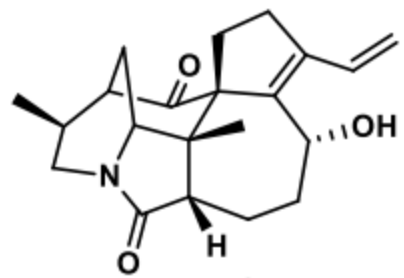


2



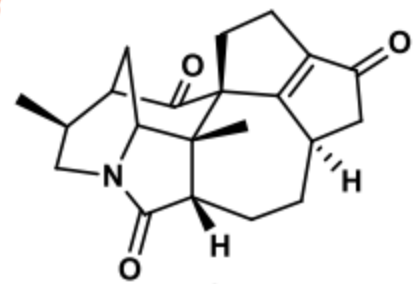
1

Regioselective allylic alcohol rearrangement



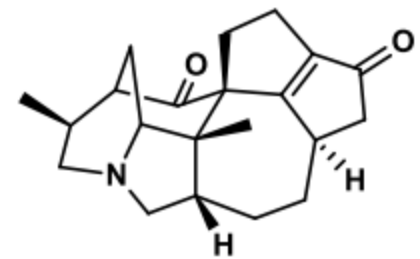
8

3

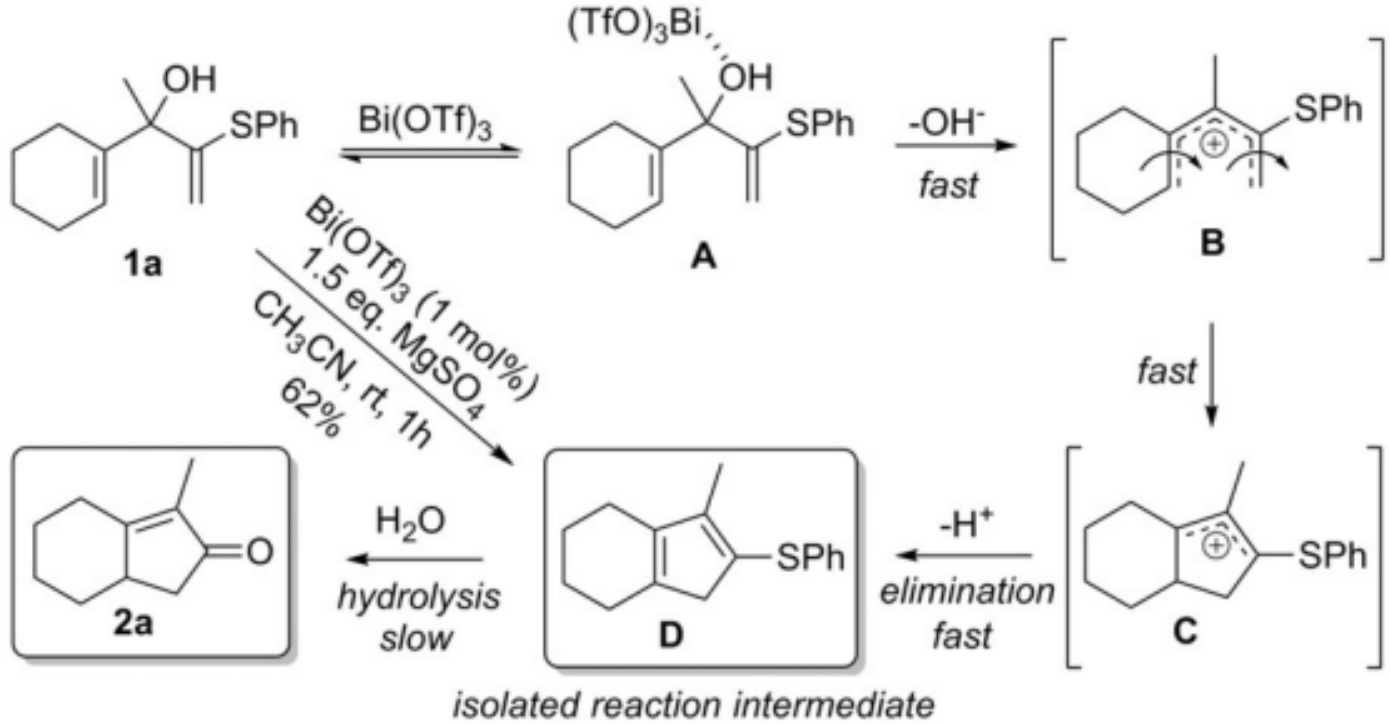


9

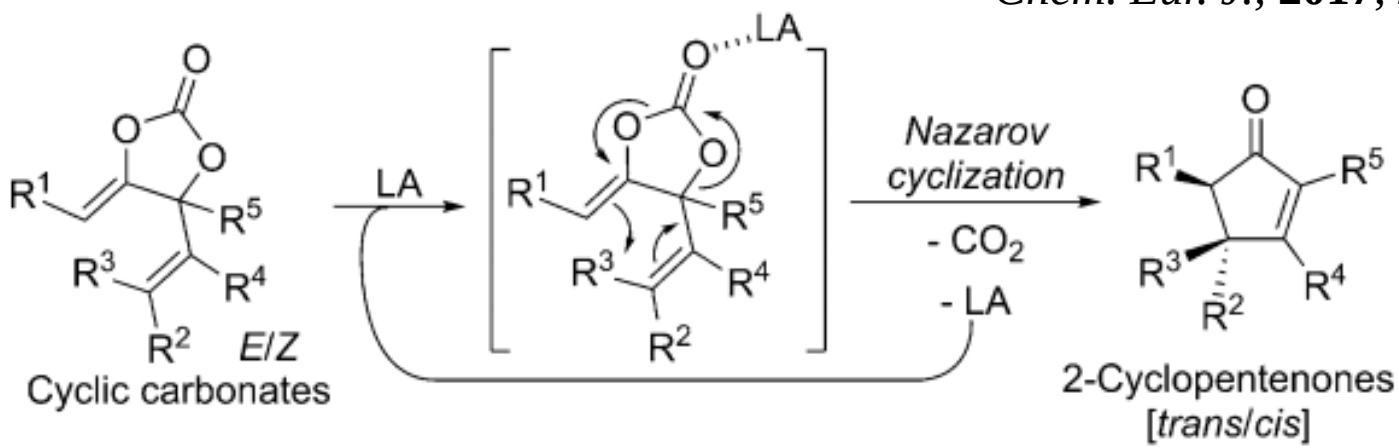
Selective amide reduction



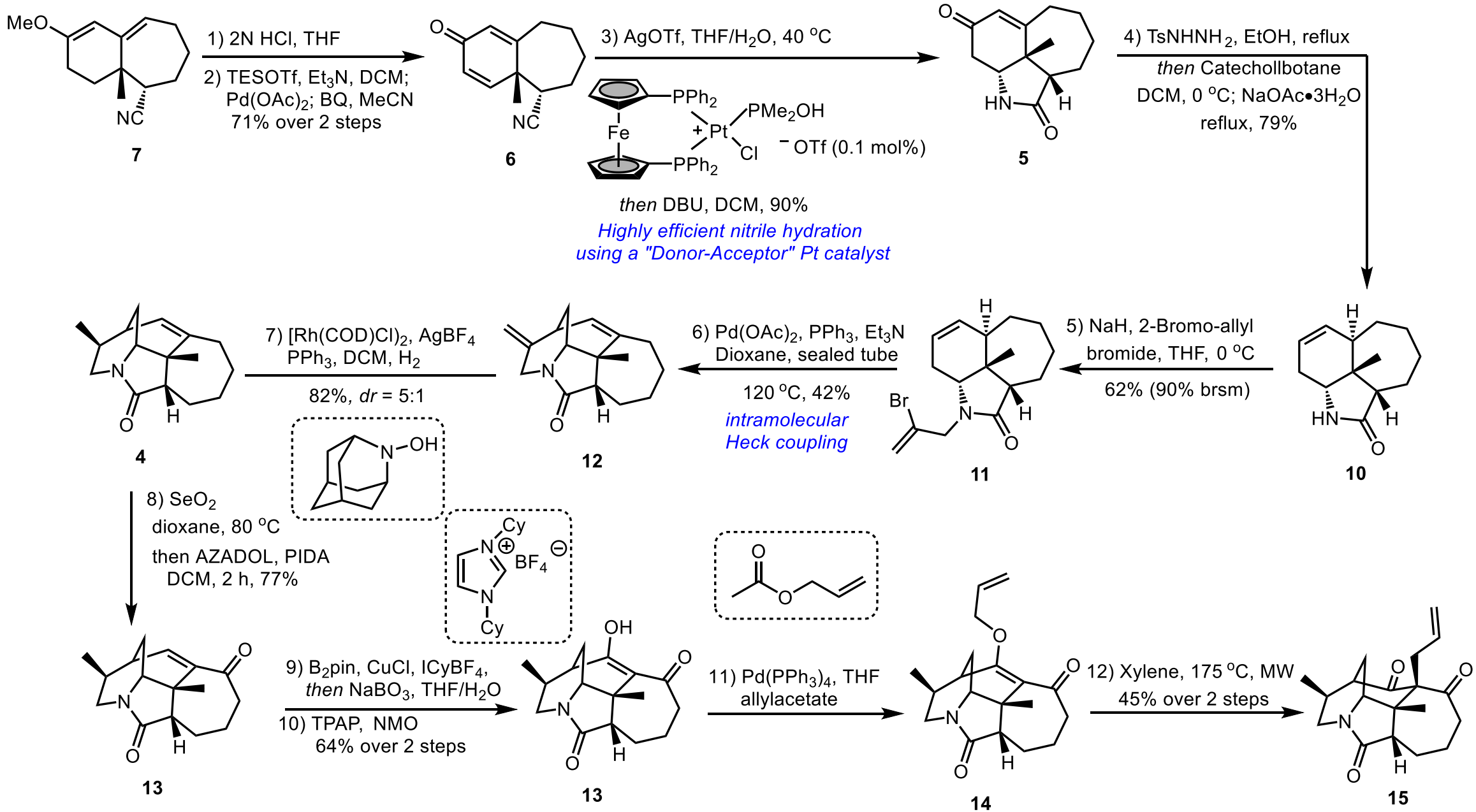
10-Deoxydaphnipaxianine A

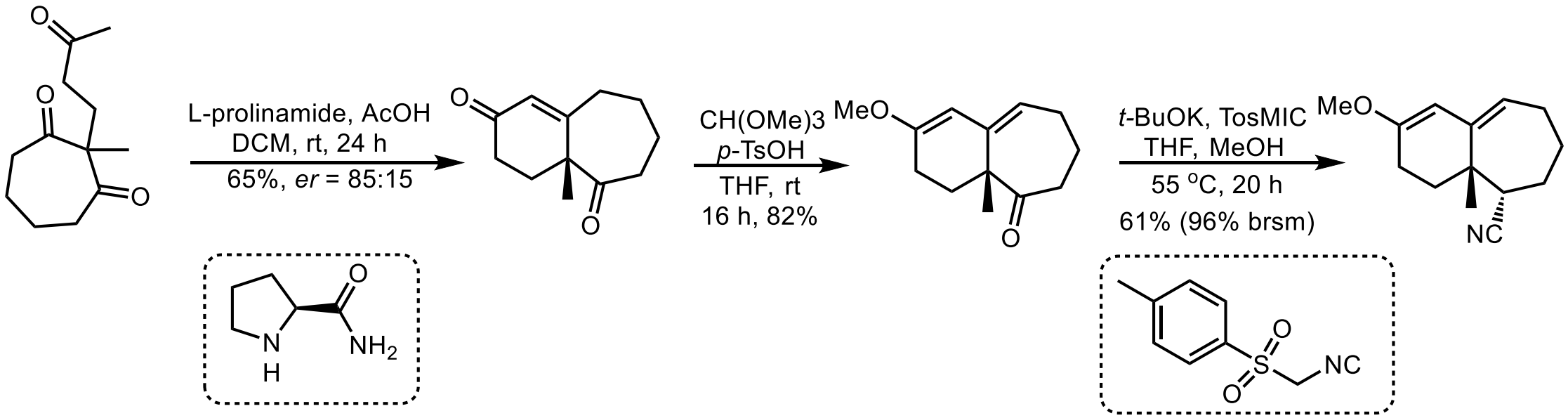


Chem. Eur. J., **2017**, *23*, 10285.



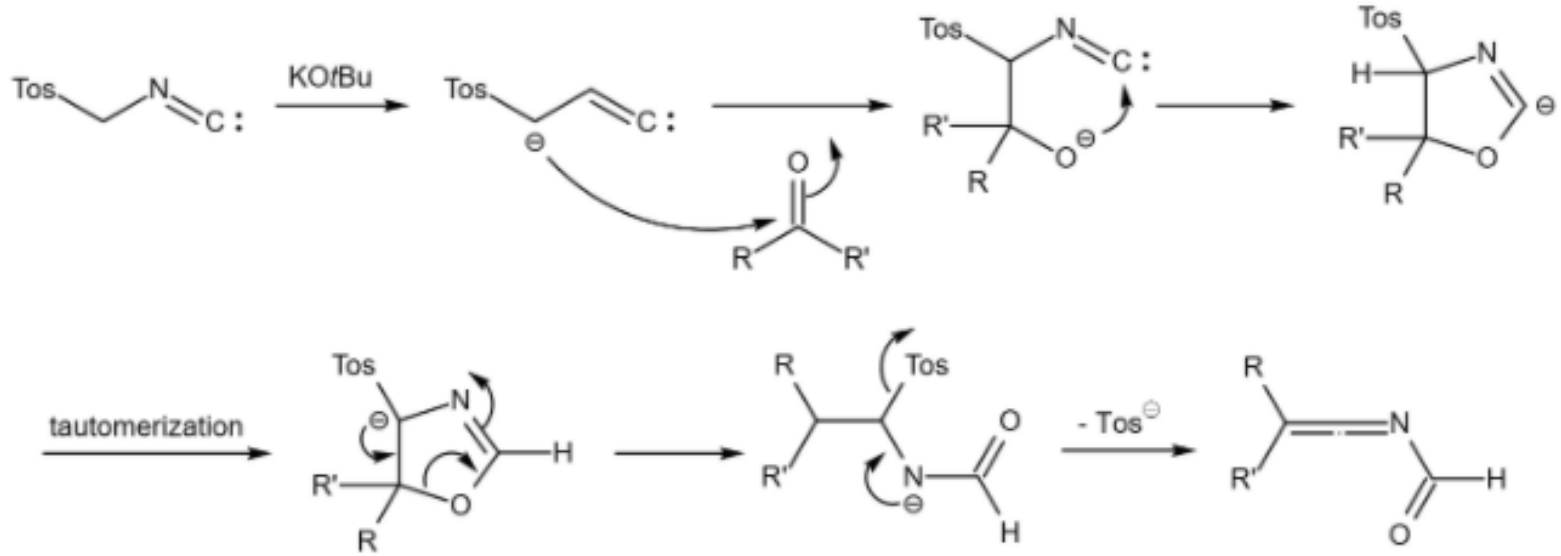
Angew. Chem. Int. Ed., **2017**, *56*, 11594.


MeO
NC
7
1) 2N HCl, THF
2) TESOTf, Et3N, DCM;
Pd(OAc)2; BQ, MeCN
71% over 2 steps
O
NC
6
3) AgOTf, THF/H2O, 40 °C
PPh2
Fe
+Pt
PMe2OH
Cl
PPh2
− OTf (0.1 mol%)
then DBU, DCM, 90%
Highly efficient nitrile hydration
using a "Donor-Acceptor" Pt catalyst
O
HN
H
O
5
4) TsNHNH2, EtOH, reflux
then Catecholborane
DCM, 0 °C; NaOAc•3H2O
reflux, 79%
H
HN
H
O
10
5) NaH, 2-Bromo-allyl
bromide, THF, 0 °C
62% (90% brsm)
H
Br
N
H
O
11
6) Pd(OAc)2, PPh3, Et3N
Dioxane, sealed tube
120 °C, 42%
intramolecular
Heck coupling
N
H
O
12
7) [Rh(COD)Cl)2, AgBF4
PPh3, DCM, H2
82%, dr = 5:1
N
H
O
4
N
OH
Cy
N
BF4
N
Cy
8) SeO2
dioxane, 80 °C
then AZADOL, PIDA
DCM, 2 h, 77%
O
N
H
O
13
9) B2pin, CuCl, ICyBF4,
then NaBO3, THF/H2O
10) TPAP, NMO
64% over 2 steps
OH
N
H
O
O
13
O
O
11) Pd(PPh3)4, THF
allylacetate
O
N
H
O
O
14
12) Xylene, 175 °C, MW
45% over 2 steps
O
O
N
H
O
15

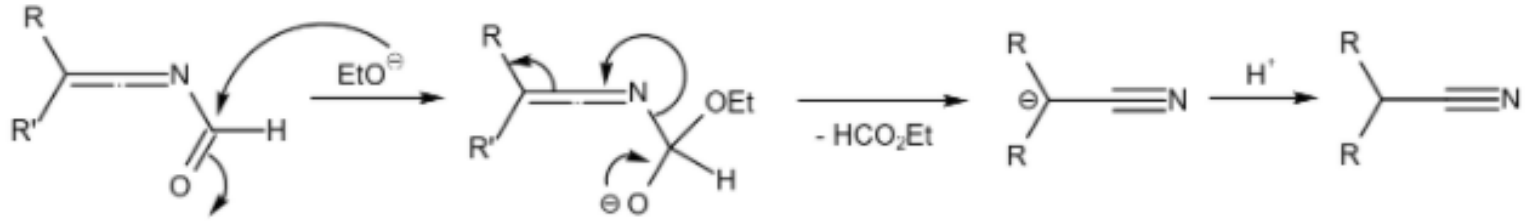


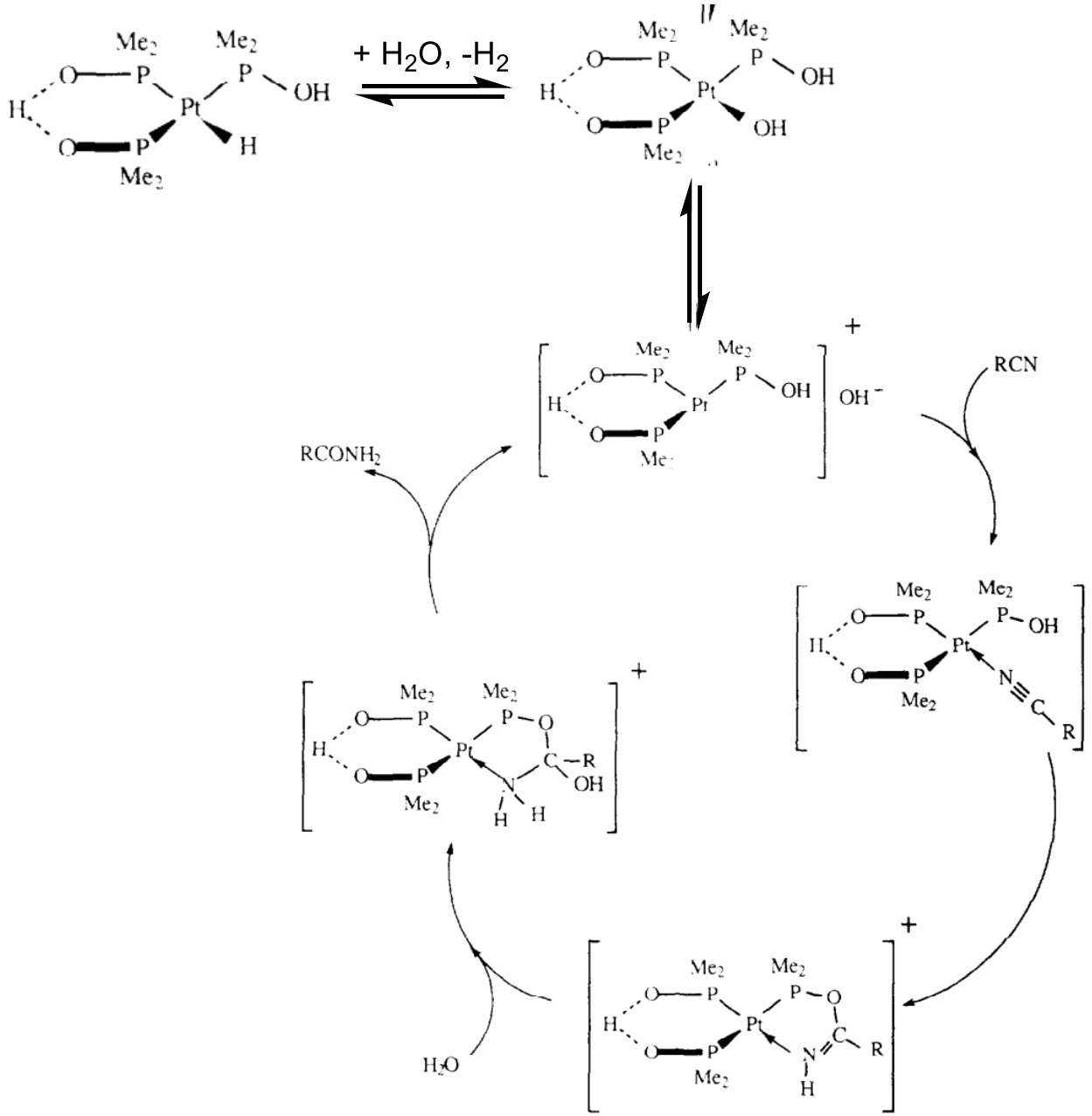
Angew. Chem. Int. Ed., **2019**, *58*, 7390.

Van Leusen homologation reaction



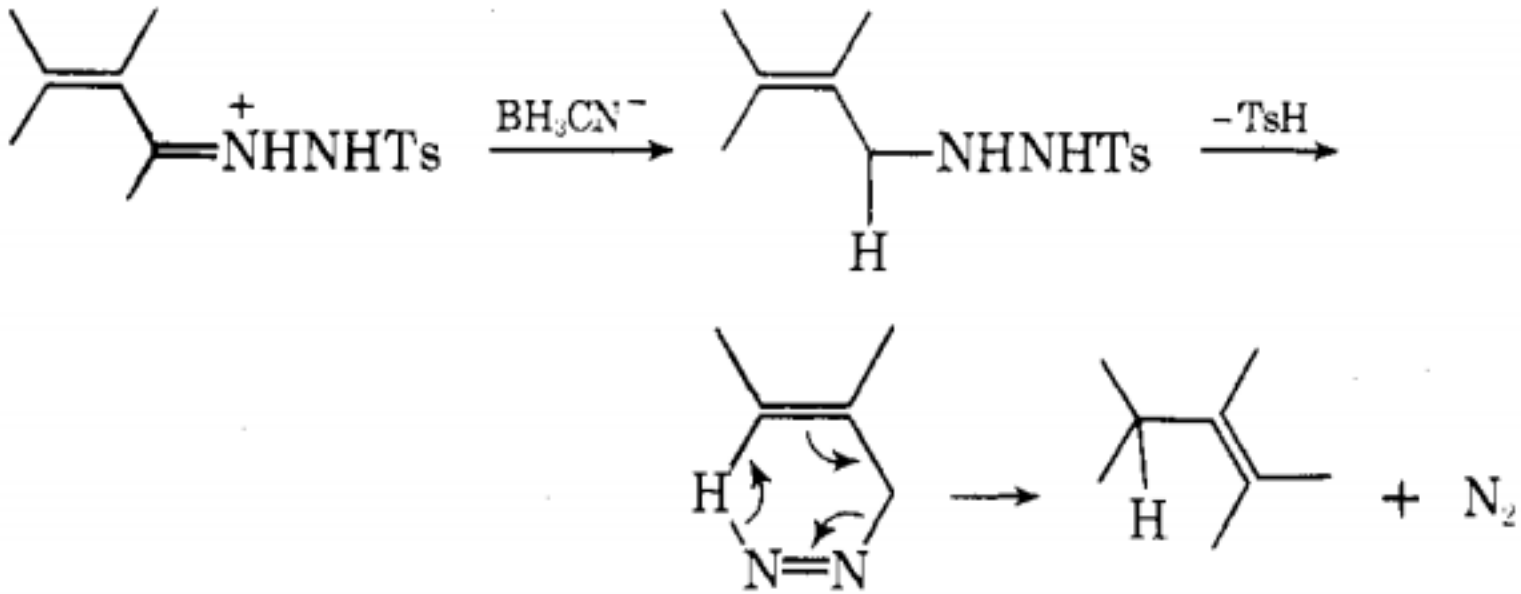
在形成腈的过程中，醇负离子在酮亚胺的脱甲酰化的过程起到很重要的亲核试剂的作用：



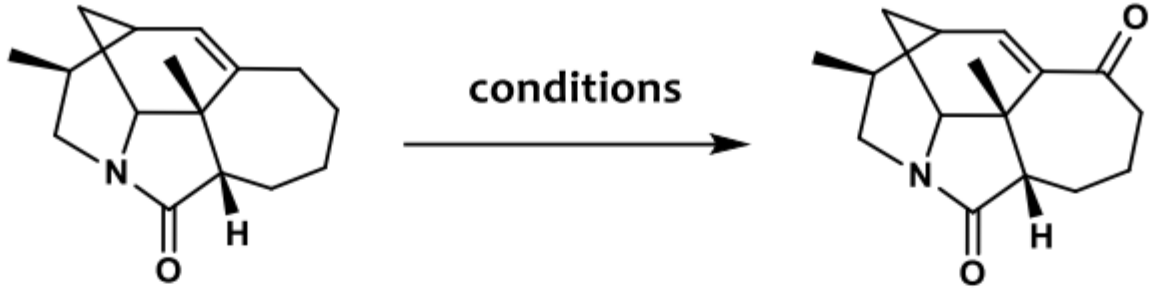


Tetrahedron Lett., **1995**, *36*, 8657.

Scheme II



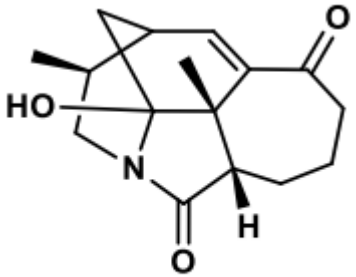
J. Org. Chem., **1975**, *40*, 923.



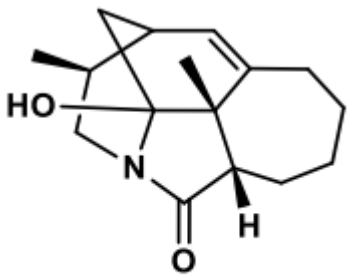
4 13

Entry	Conditions	Results[a]
1	$Mn(OAc)_3$, TBHP, 4Å MS, EtOAc, rt	No product, only **S1**(14%)
2	SeO_2 (on silica), TBHP, DCM, rt	NR.
3	SeO_2 (on silica), TBHP, DCM, 60°C	Decomposed
4	$Rh_2(cap)_4$, TBHP, K_2CO_3, DCM, rt	Messy
5	CuCl, TBHP, DCM, rt	Messy
6	$CuBr_2$, TBHP, DCM, rt.	Messy
7	SeO_2, dioxane, rt	trace
8	SeO_2, dioxane, 80°C	**13**(77%)[b]
9	$Pd(OH)_2/C$, TBHP, K_2CO_3, DCM, rt	**13**(8%) and **S2** (22%)

[a] Reactions conducted on 0.1 mmol scale. [b] After oxidation by AZADOL/PIDA.

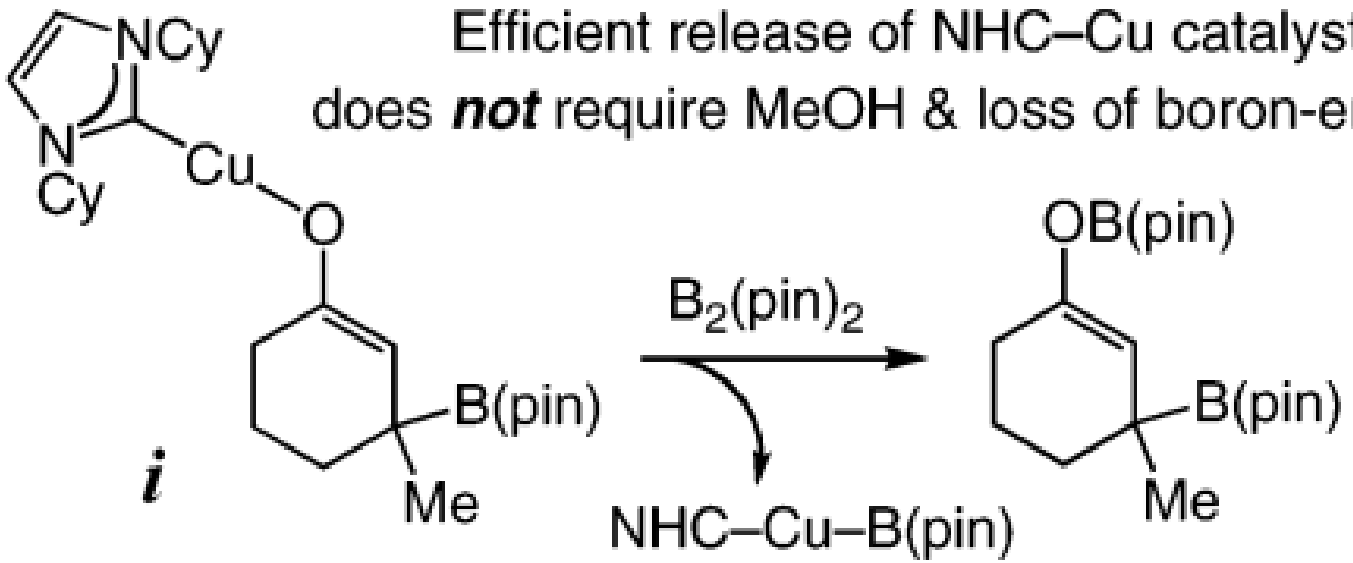


S1

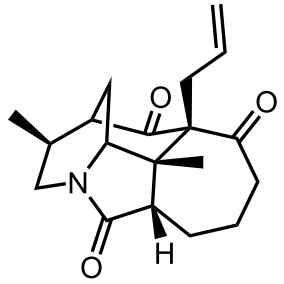


S2

Efficient release of NHC–Cu catalyst
does ***not*** require MeOH & loss of boron-enolate



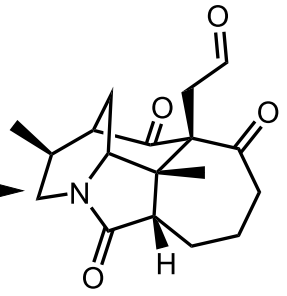
J. Am. Chem. Soc., **2009**, *131*, 7253.



15

13) Wilkinson's cat., Catecholborane THF; H_2O_2, NaOH

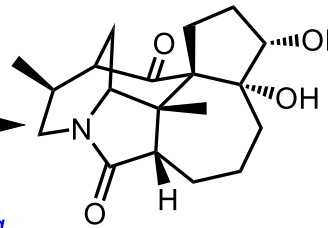
14) PCC, NaOAc, DCM 61% over 2 steps



2

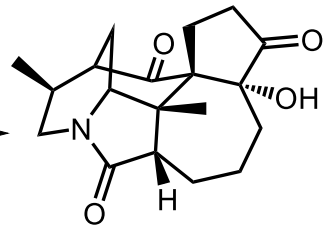
15) SmI_2, THF

Regioselective intramolecular pinacol coupling



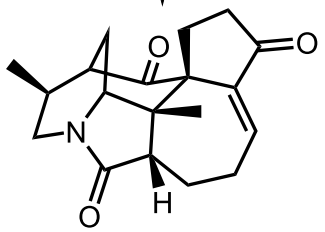
16

16) TPAP, NMO DCM



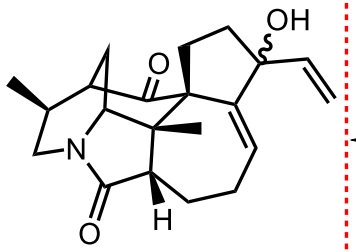
17

17) $SOCl_2$, Et_3N, THF 61% over 3 steps

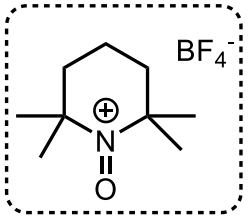


18

18)  $LaCl_3$•2LiCl THF, 81%

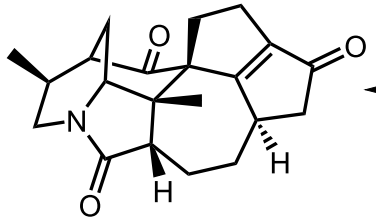


Key intermediate **1**

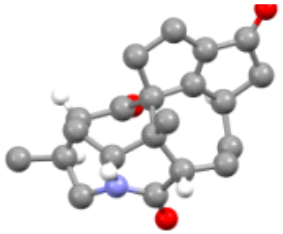


MeCN, 35 °C, 80%

Oxidative Nazarov electrocyclization unfunctionalized tertiary divinyl carbinol

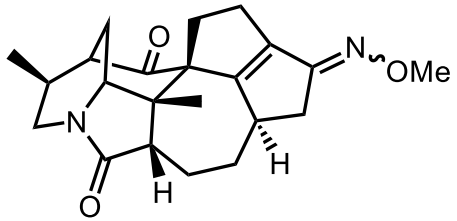


9



(XRD of 9)

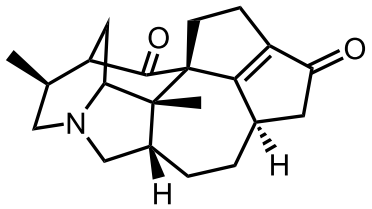
20) NH_2OMe•HCl MeOH, reflux, 84%



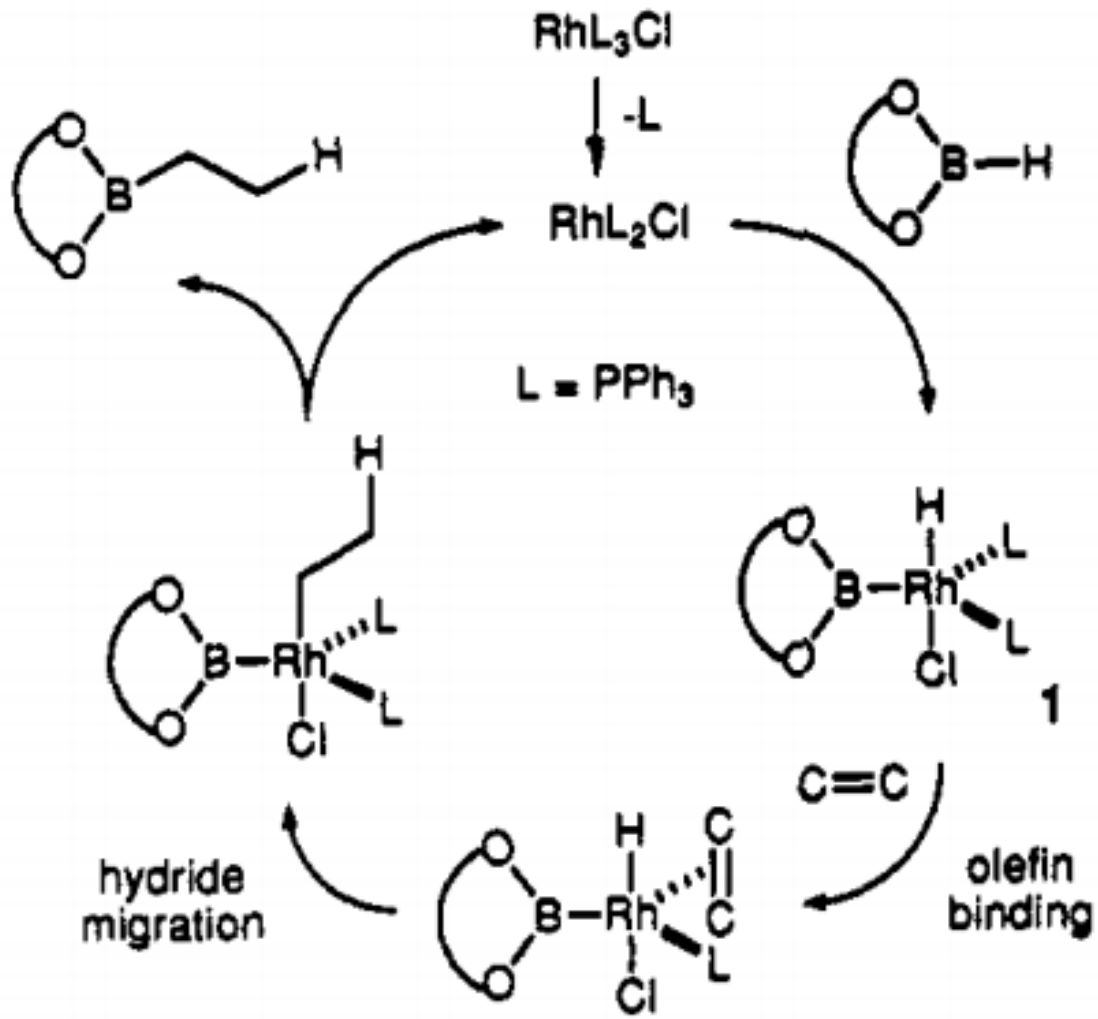
20

21) Lawesson's Reagent PhCl, MW, 125 °C

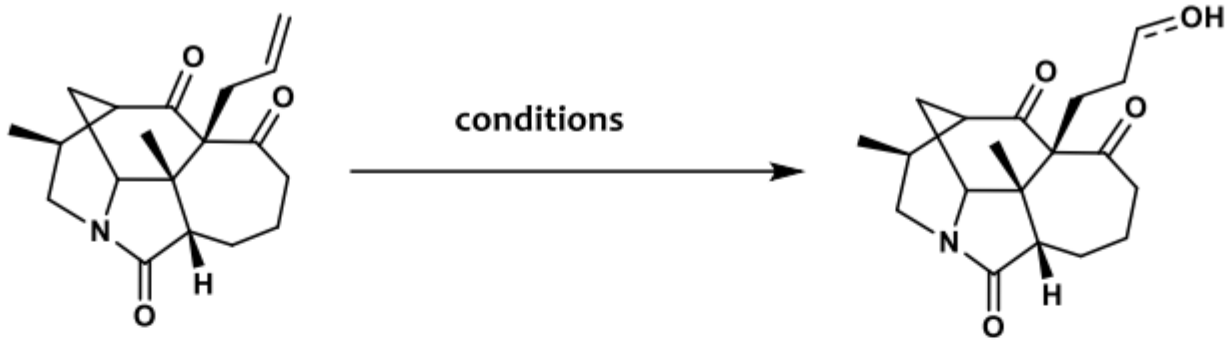
22) Raney Ni, EtOH, 80 °C 61% over 3 steps



(-) 10-deoxydaphnipaxianine **A**



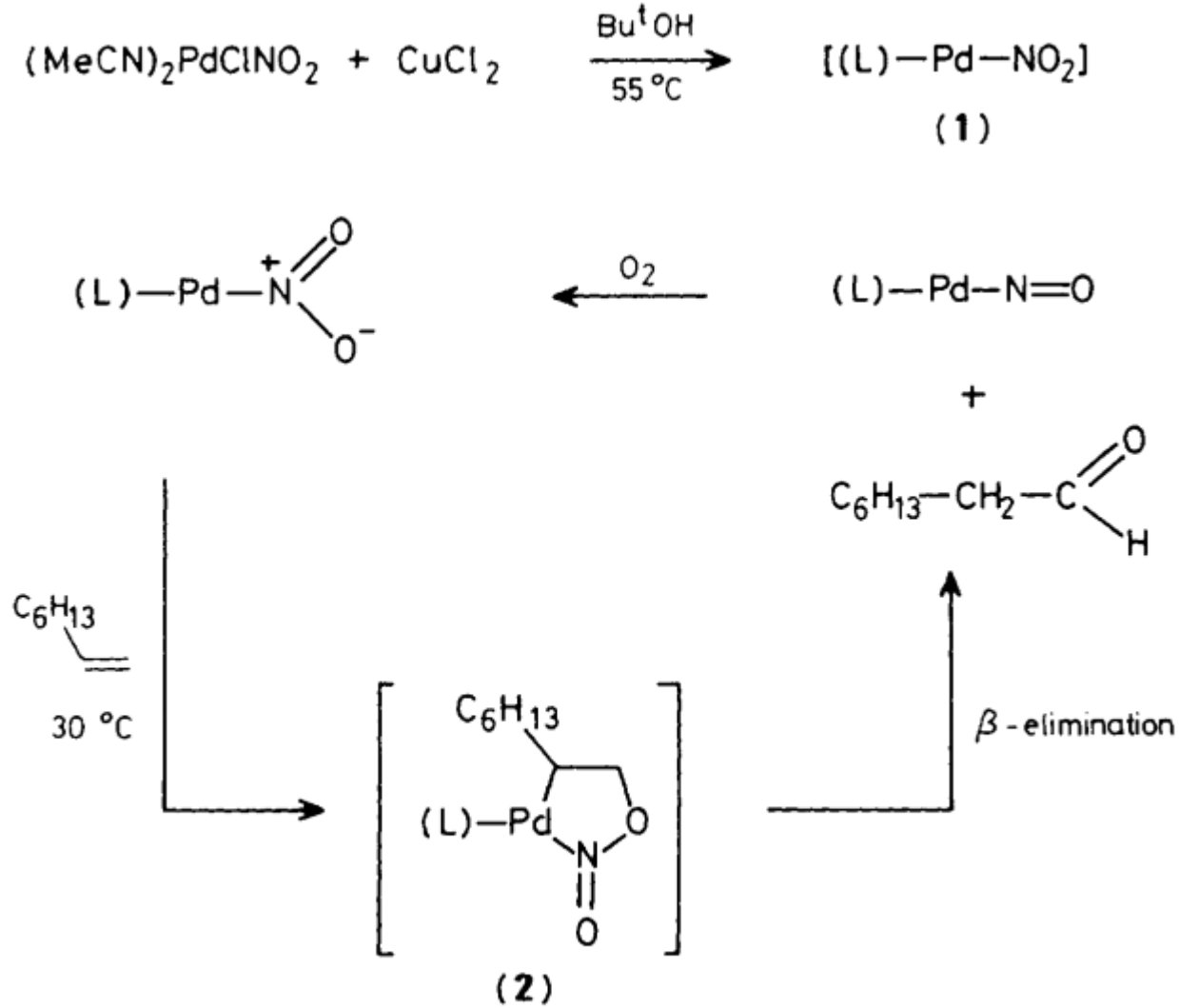
J. Am. Chem. Soc., **1992**, *114*, 6679.



15

Entry	Conditions	Results[a]
1	Cy_2BH, THF, 0°C	NR
2	9-BBN, THF, 0°C	Decomposed
3	BH_3•THF, THF, 0°C	NR
4	Wilkinson's cat., CatBH, THF, rt. Then NaOH, H_2O_2, 0°C	75%
5	$PdCl_2(PhCN)_2$, $CuCl•2H_2O$, KNO_2, tBuOH/$MeNO_2$, O_2, rt.	No desired product
6	Pinacol vinylboronate, Grubbs 2nd catalyst, DCM, 40°C	NR
7	Pinacol vinylboronate, Zhan-1-B catalyst, DCM, MW 40°C	Trace
8	Pinacol vinylboronate, Hoveyda-Grubbs 2nd catalyst, DCM, 40°C Then Me_3NO, THF, 70°C	NR[b]

[a] Reactions conducted on 0.1 mmol scale. [b] No reaction occurred at oxidation.



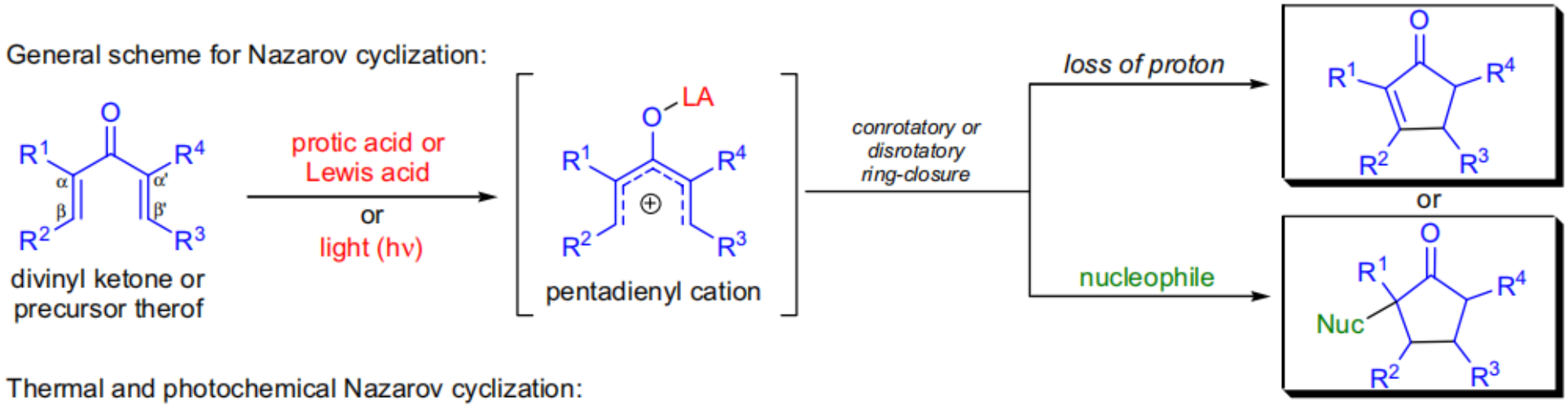
L = MeCN–$CuCl_2$–Me_3COH‡

J. Chem. Soc. Chem.Commun., **1986**, *909.*

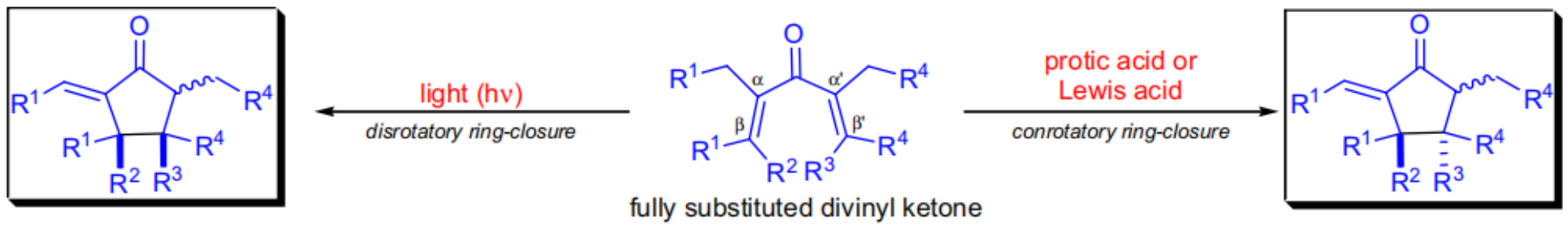
NAZAROV CYCLIZATION

(References are on page 635)

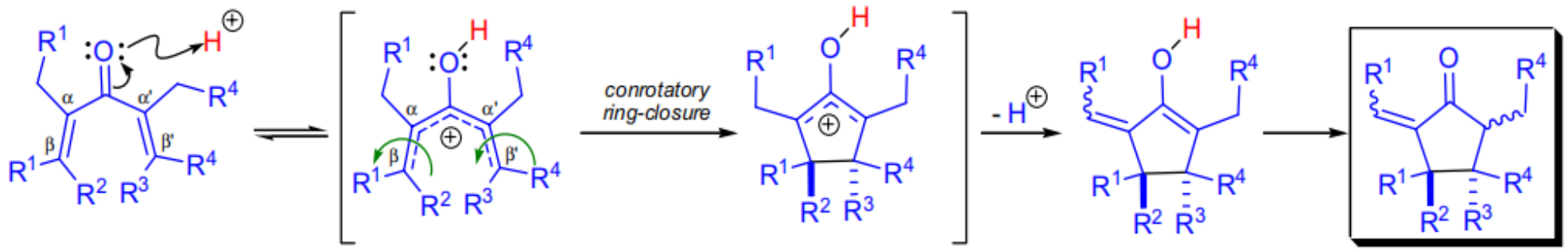
General scheme for Nazarov cyclization:



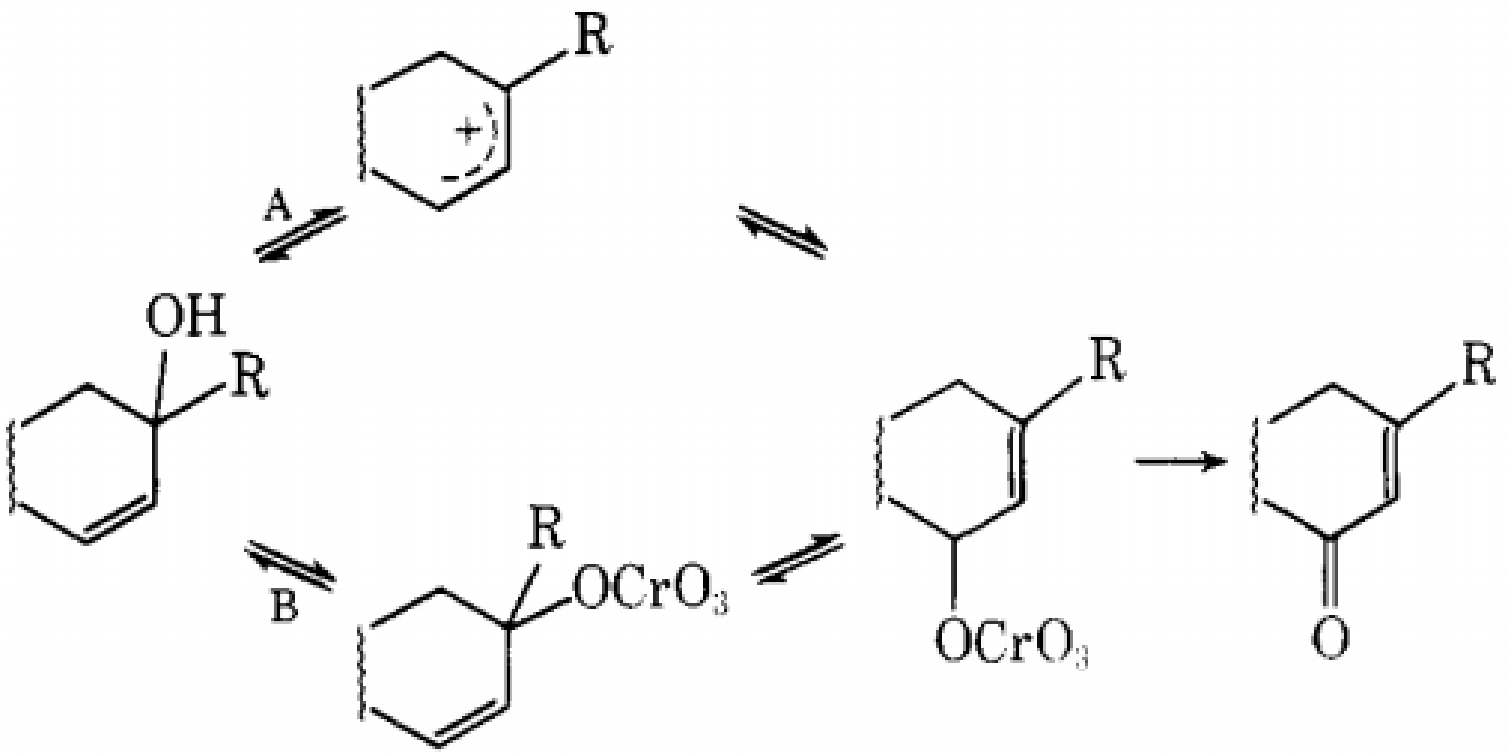
Thermal and photochemical Nazarov cyclization:



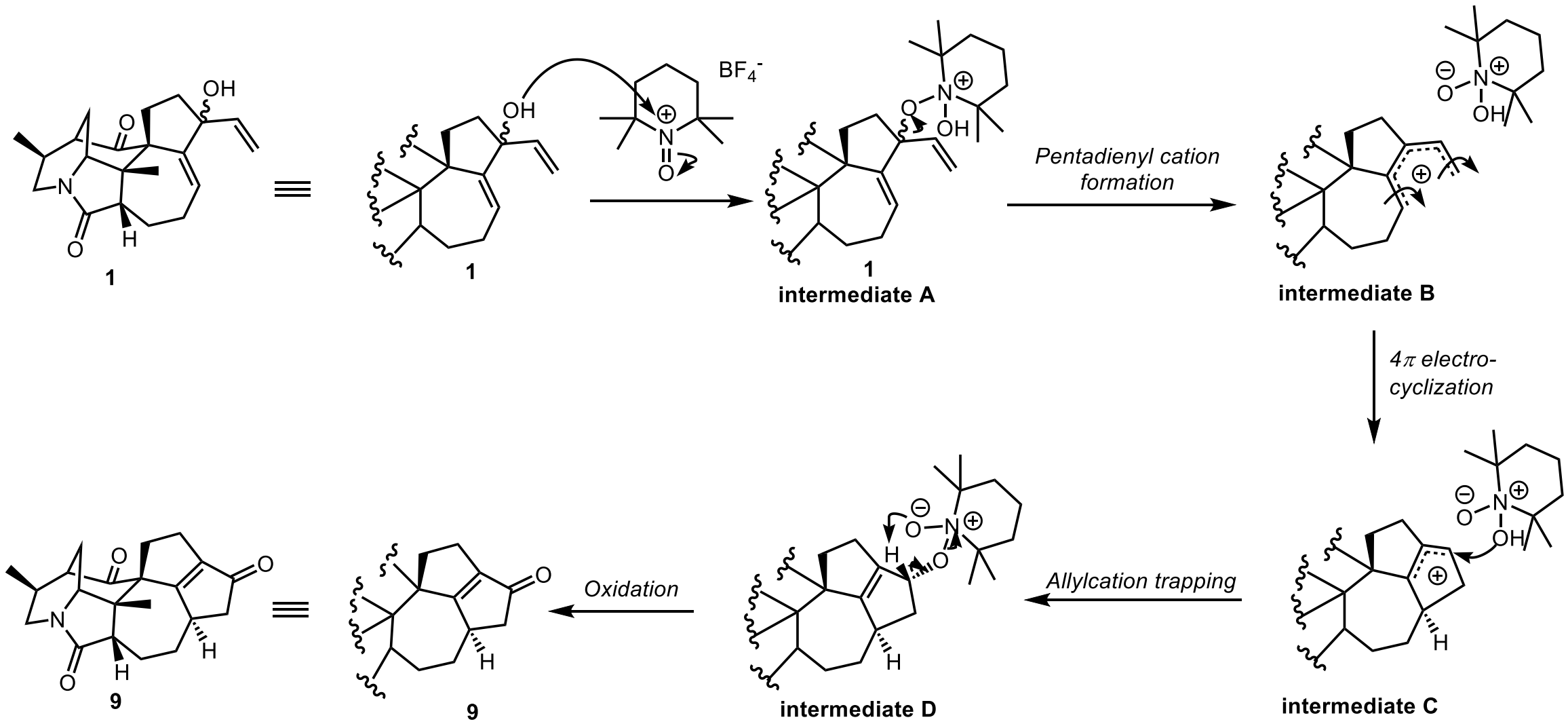
Mechanism:

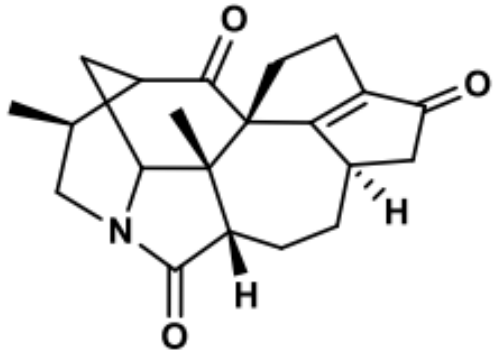


Scheme III



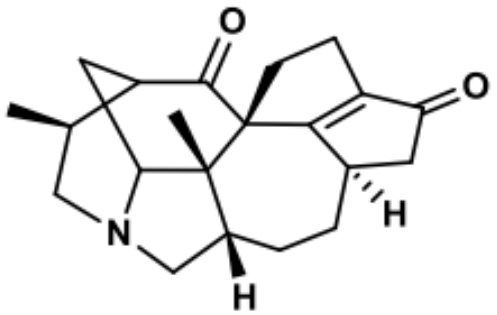
J. Org. Chem., **1977**, *42*, 682.


OH
O
N
O
H
1
≡
OH
BF4-
N
O
1
N
O
OH
1
intermediate A
Pentadienyl cation
formation
N
O
OH
intermediate B
4π electro-
cyclization
N
O
OH
H
intermediate C
Allylcation trapping
O
N
O
H
H
intermediate D
Oxidation
O
H
9
O
O
N
O
H
H
9
≡



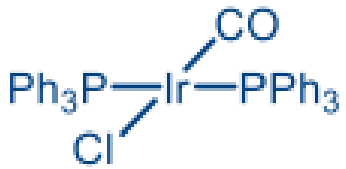
9

conditions



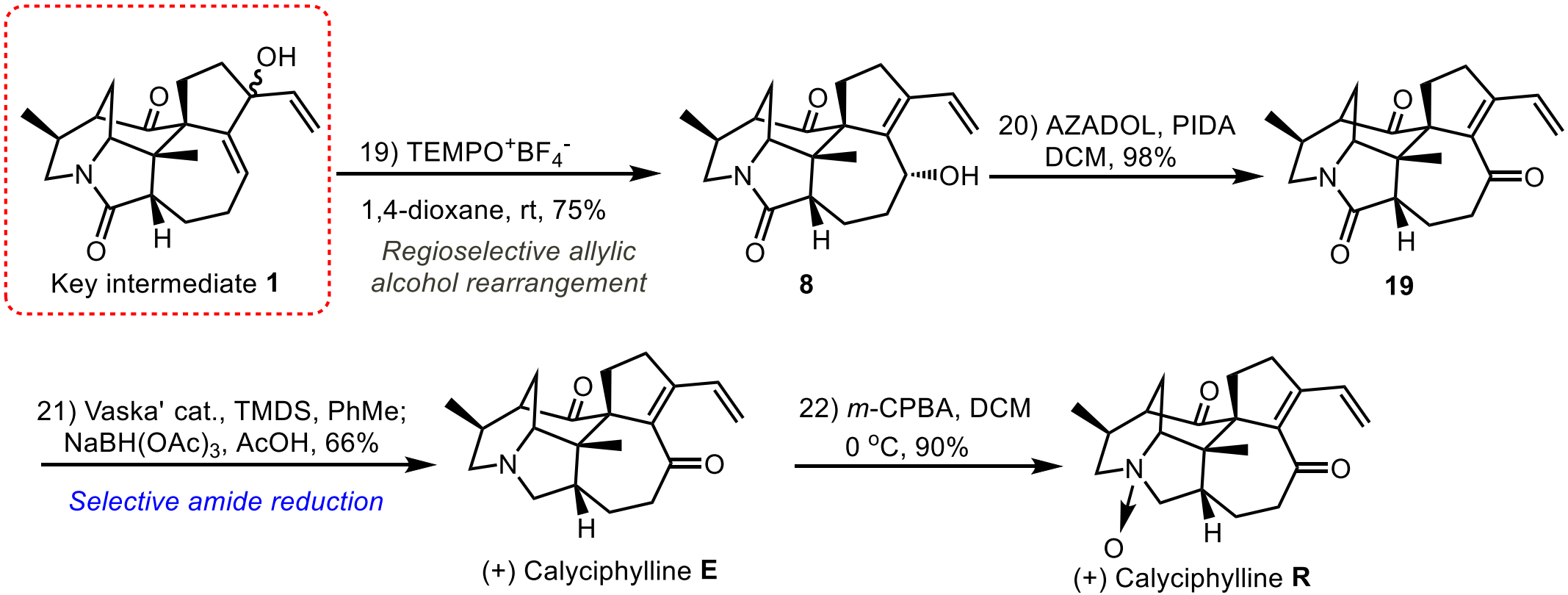
10-Deoxydaphnipaxianine A

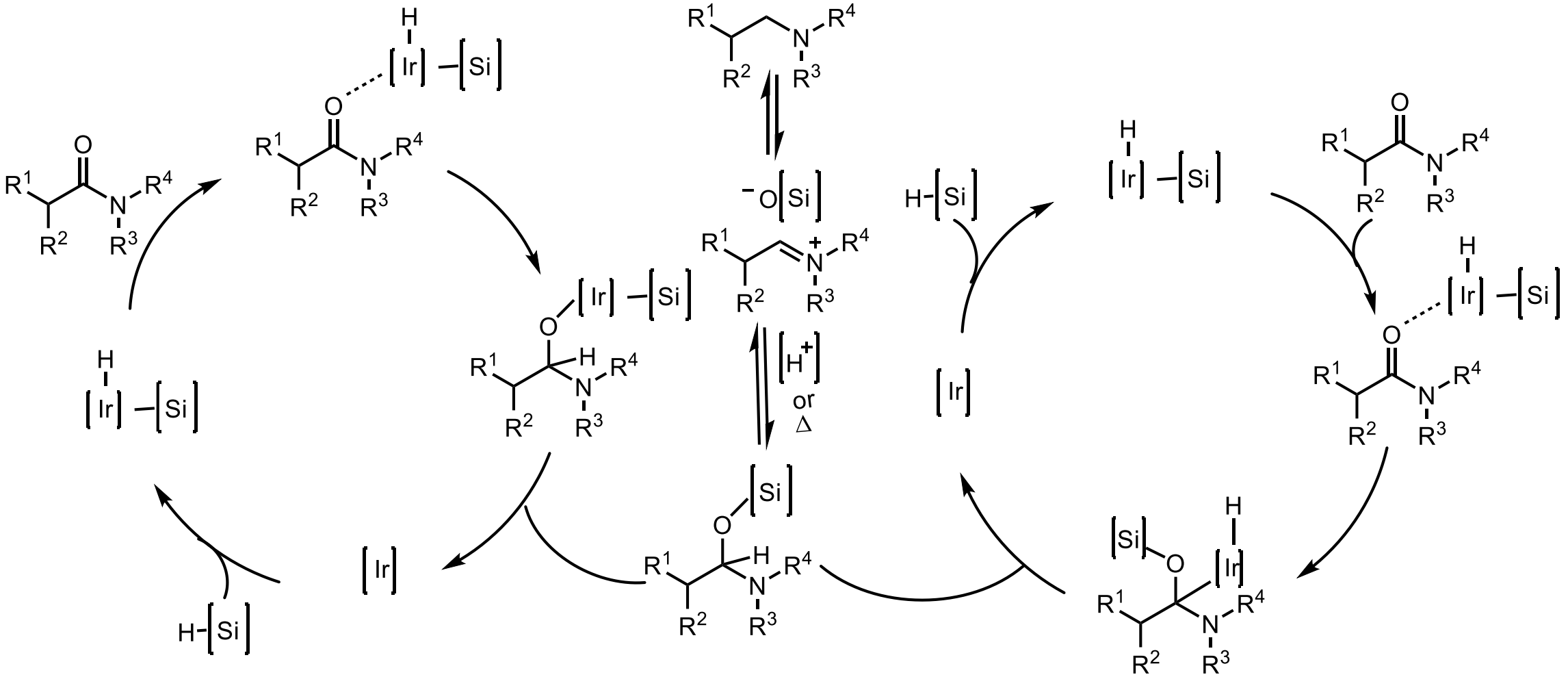
Entry	Conditions	Results[a]
1	Vaska's catalyst, TMDS, DCM; then $NaBH(OAc)_3$, HOAc	trace
2	LAH. THF, 0°C to MW 90°C then DMP	trace
3	LAH. THF, 0°C to MW 100°C then PCC	complex
4	LAH. THF, 0°C to MW 90°C then Jones' reagent	trace
5	LAH. THF, 0°C to MW 90°C then $RuCl_3 \cdot nH_2O$, $K_2S_2O_8$, aq. KOH	complex
6	LAH. THF, 0°C to MW 90°C then $Cu(MeCN)_4OTf$, NMI, ^{MeO}bpy, ABNO, air	complex
7	LAH. THF, 0°C to MW 90°C then CuCl, DMAP, bpy, AZADO, air	complex
8	LAH. THF, 0°C to MW 90°C then TPAP, NMO	complex



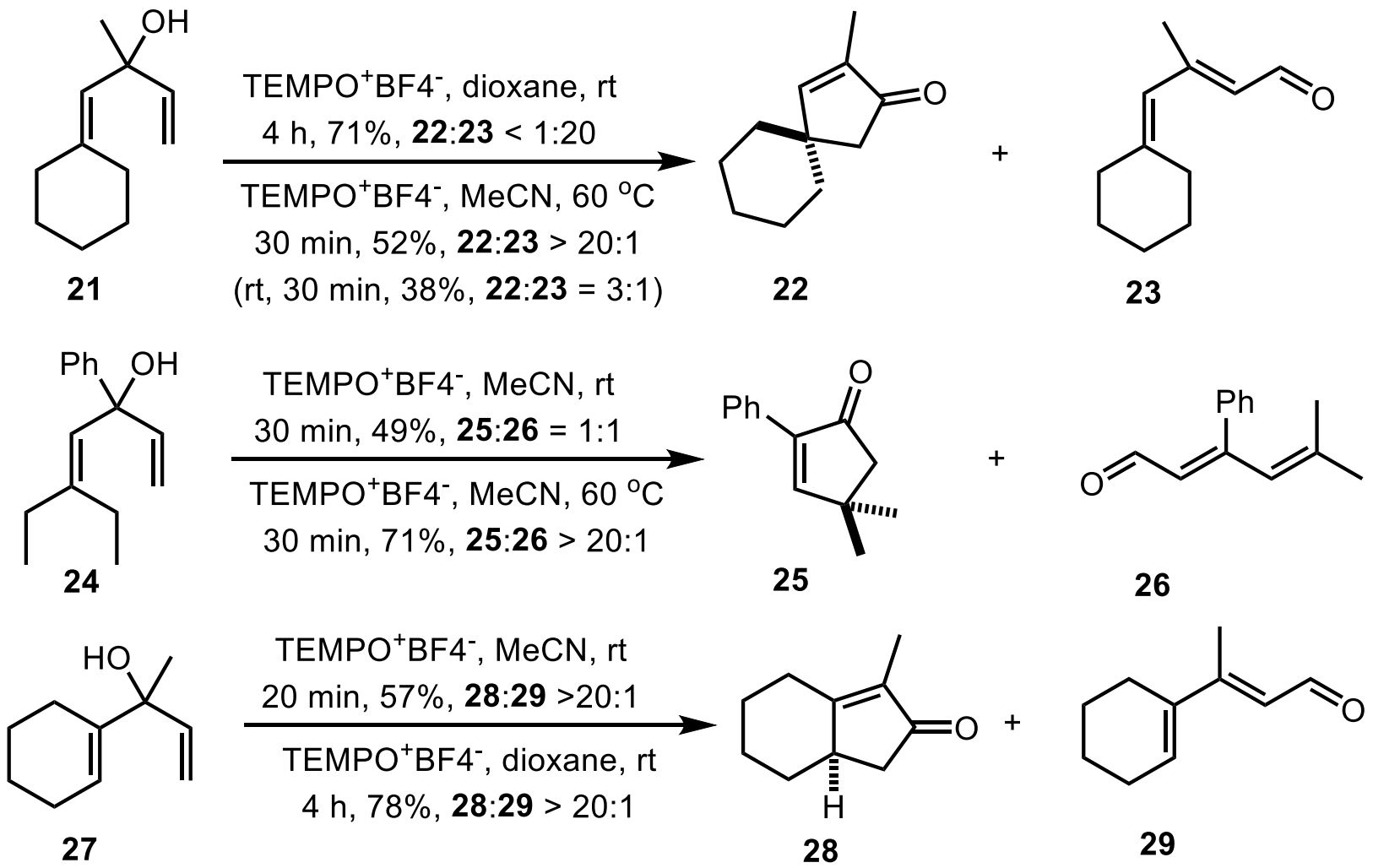
9	LR, PhMe, rt.	No desired product
10	LR, PhMe, 40°C.	No desired product
11	LR, THF, 40°C	No desired product
12	LR, PhMe, 70°C	No desired product
13	LR, PhMe, 90°C	No desired product
14	LR, PhMe, reflux	No desired product
15	LR, *o*-DCB, 170°C	complex
16	P_2S_5, PhH, 70°C	No desired product
17	P_2S_5, PhMe, reflux	No desired product
18	LR, Ph_2O, 180°C	complex
19	LR, Hexafluorobenzene, 80°C	No desired product

[a] Reactions conducted on 0.05 mmol scale.


OH
O
N
O
H
Key intermediate 1
19) TEMPO+BF4-
1,4-dioxane, rt, 75%
Regioselective allylic alcohol rearrangement
OH
8
20) AZADOL, PIDA
DCM, 98%
19
21) Vaska' cat., TMDS, PhMe;
NaBH(OAc)3, AcOH, 66%
Selective amide reduction
(+) Calyciphylline E
22) m-CPBA, DCM
0 °C, 90%
(+) Calyciphylline R



ACS Catal., **2020**, *10*, 8880.


OH
TEMPO+BF4-, dioxane, rt
4 h, 71%, 22:23 < 1:20
TEMPO+BF4-, MeCN, 60 °C
30 min, 52%, 22:23 > 20:1
(rt, 30 min, 38%, 22:23 = 3:1)
O
O
+
21
22
23
Ph
OH
TEMPO+BF4-, MeCN, rt
30 min, 49%, 25:26 = 1:1
TEMPO+BF4-, MeCN, 60 °C
30 min, 71%, 25:26 > 20:1
O
Ph
Ph
O
+
24
25
26
HO
TEMPO+BF4-, MeCN, rt
20 min, 57%, 28:29 >20:1
TEMPO+BF4-, dioxane, rt
4 h, 78%, 28:29 > 20:1
O
H
O
+
27
28
29