Total Synthesis of Iejimalide A−D and Assessment of the Remarkable Actin-Depolymerizing Capacity of These Polyene Macrolides

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · AUGUST 2007

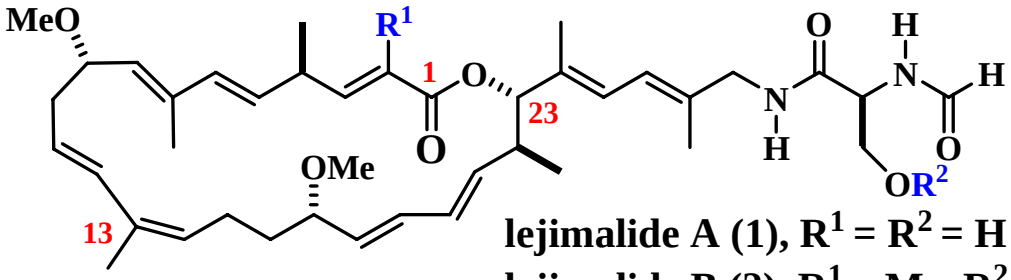
Impact Factor: 12.11 · DOI: 10.1021/ja072334v · Source: PubMed

Total Synthesis of Iejimalide A-D and Assessment of the Remarkable Actin-Depolymerizing Capacity of these Polyene Macrolides

Alois Fürstner,*† Cristina Nevado,† Mario Waser,† Martin Tremblay,†
Carine Chevrier,† Filip Teplý,† Christophe Aïssa,† Emilie Moulin,† and Oliver Müller‡

†*Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany,*
‡*Max-Planck-Institut für Molekulare Physiologie, D-44227 Dortmund, Germany*

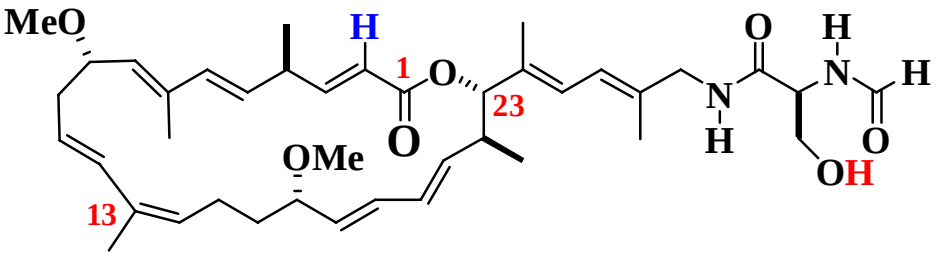
演講者：趙邦媛



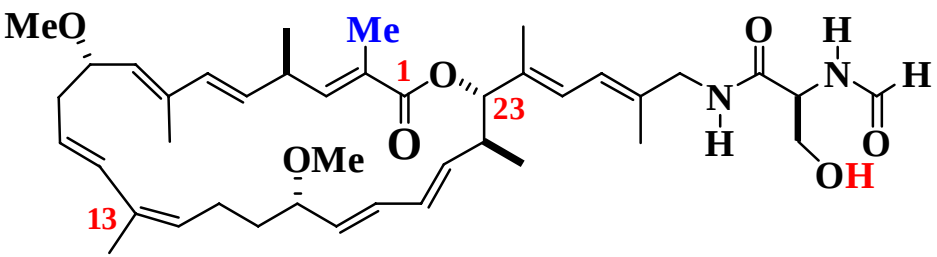
lejimalide A (1), $R^1 = R^2 = H$
lejimalide B (2), R^1 = Me, $R^2 = H$
lejimalide C (3), $R^1 = H$, $R^2 = SO_3Na$
lejimalide D (4), R^1 = Me, $R^2 = SO_3Na$

J. Am. Chem. Soc. **2007**, *129*, 9150-9161.

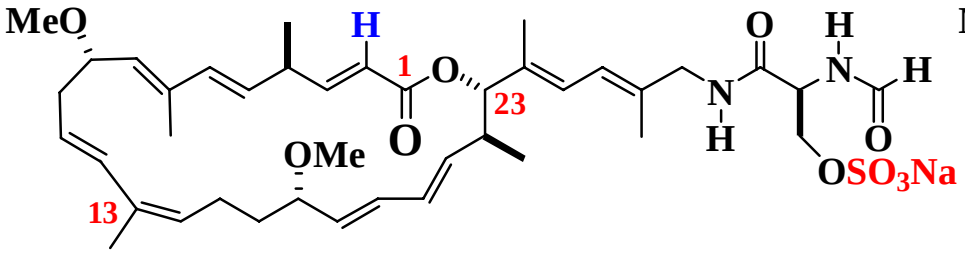
Iejimalide A-D



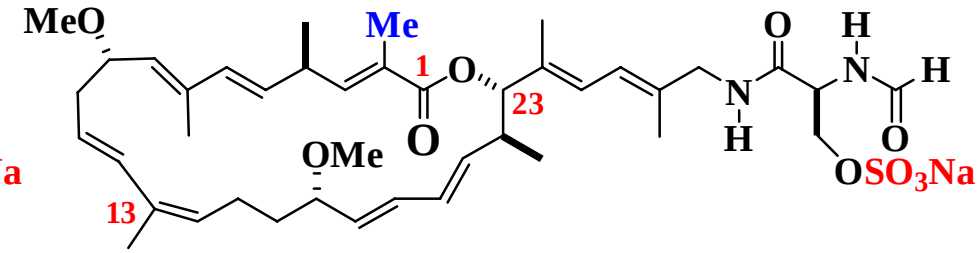
lejimalide A (1)



lejimalide B (2)



lejimalide C (3)



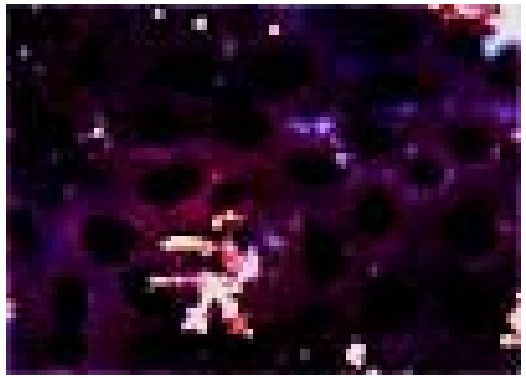
lejimalide D (4)

Alois Fürstner, Prof. Dr.

- **Research interests**
  Organometallic chemistry applied to organic synthesis.
  Homogeneous catalysis.
  Metathesis synthesis of natural products.
  Metal activation.
  Heterocyclic chemistry.

- 1962 in Bruck/Mur (Austria)
- 1987 PhD at the Technical University Graz, Austria (H. Weidmann)
- 1990-1991 postdoc at the University of Geneva, Switzerland (W. Oppolzer)
- 1992 habilitation in Organic Chemistry at the Technical University Graz, Austria
- 1993-1998 group leader at the Max-Planck-Institut für Kohlenforschung
- since 1998 apl. Professor at the University of Dortmund and Director at the Max-Planck-Institut für Kohlenforschung.

Introduction of Iejimalide A-D



Eudistoma cf. rigida

Bioassay-guided fractionation of the methanol extracts of the tunicate *Eudistoma* cf. *rigida* collected off Ie island, Okinawa, Japan.

IE Shima (伊江島) is an island in Okinawa Prefecture, Japan

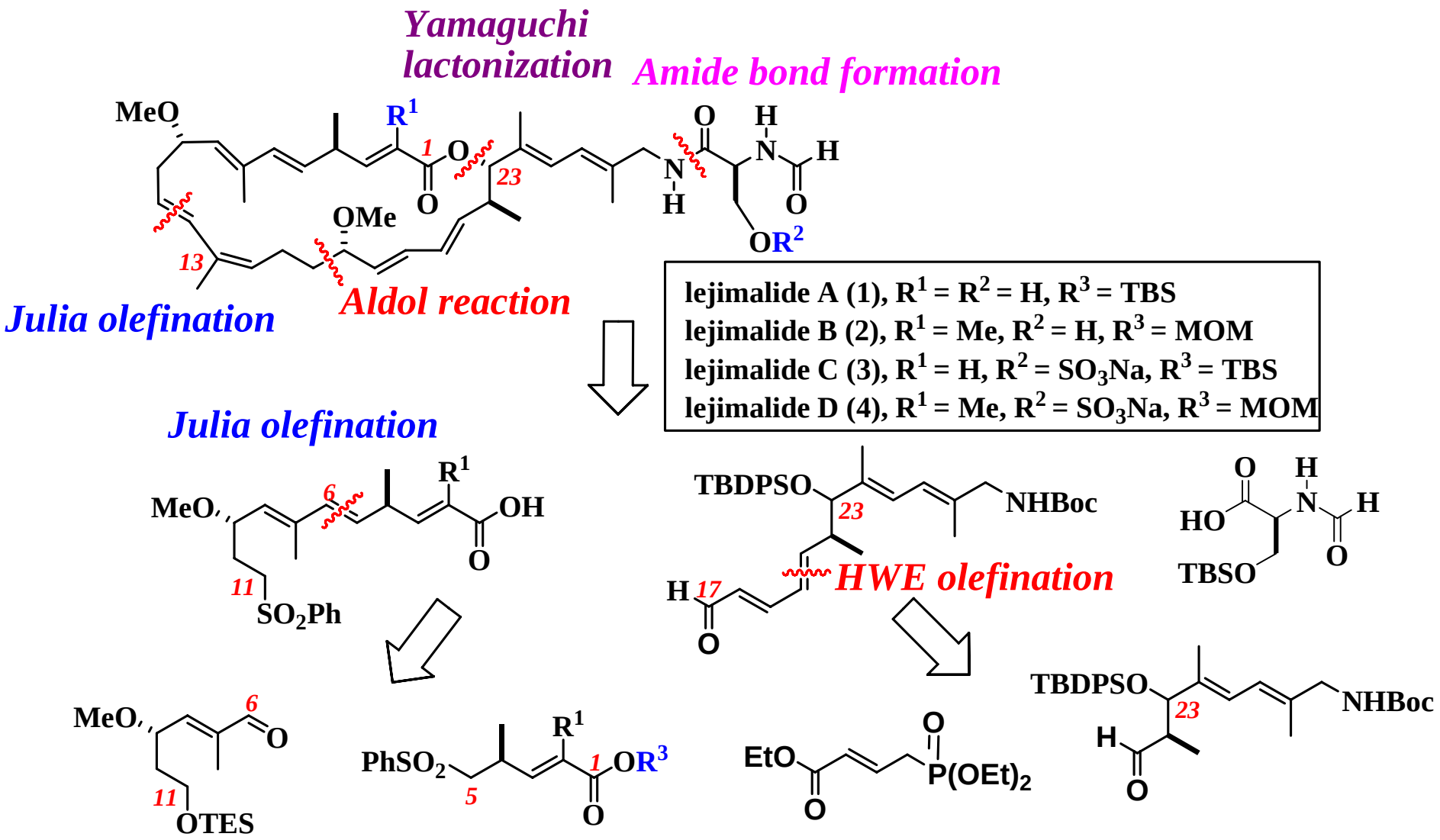
Highly cytotoxic marine natural products.

Iejimalide A against 60 different human Cancer cell lines, with GI_{50} values as low as 13 nM (MDA-MB-231/ ATCC breast cancer cell line) and total growth inhibition (TGI) values as low as 40 nM (M14 melanoma cell line).

Iejimalide B that IC_{50} = 1 ng/mL against L5178Y murine leukemia; IC_{50} = 32 ng/mL against L1210 murine leukemia.

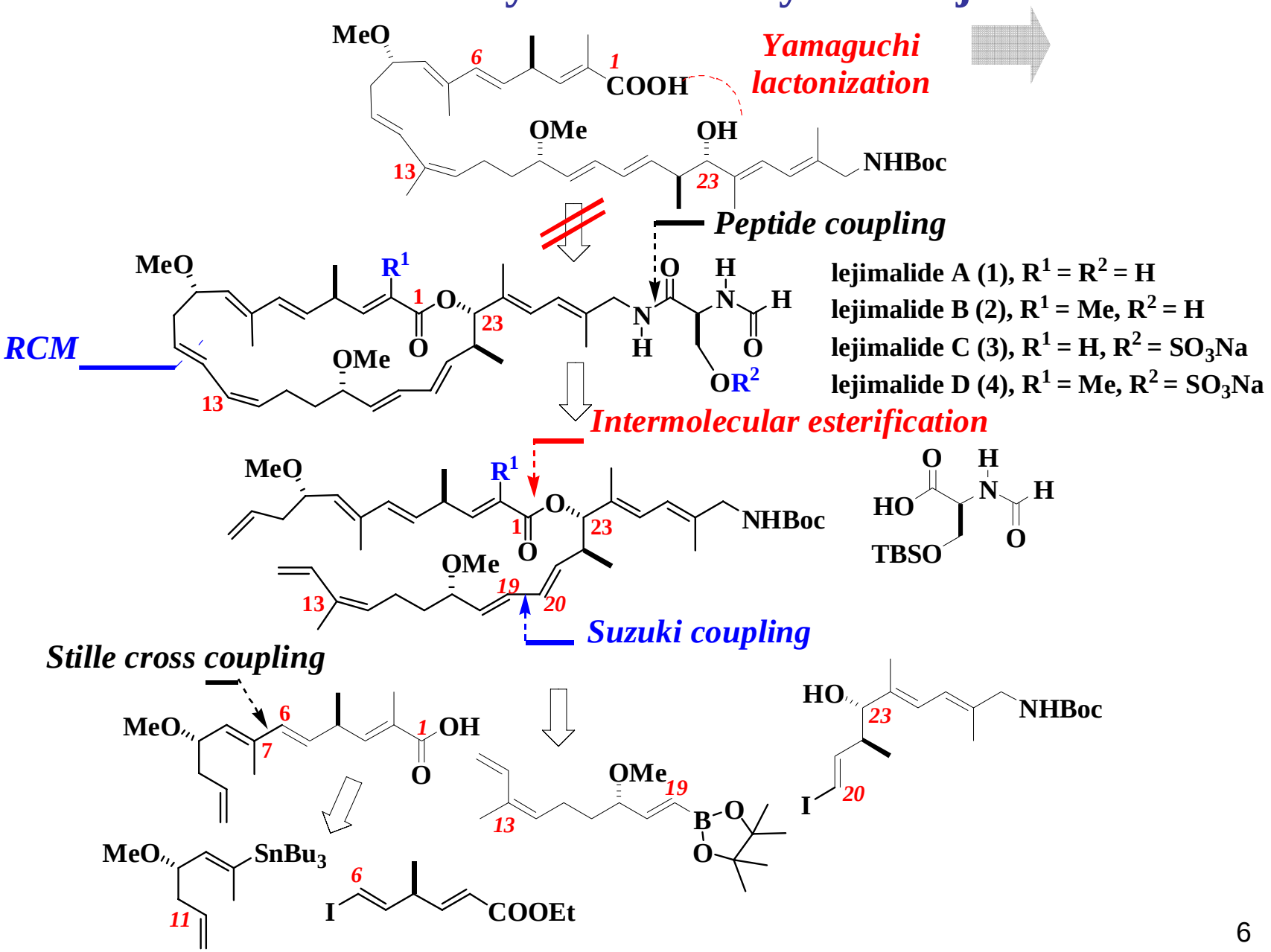
Iejimalide C and D against P388 leukemia at a dose of 200 $\mu g \cdot kg^{-1}d^{-1}$.

Scheme 1-1: Helquist's Retrosynthetic Analysis of Iejimalide A-D



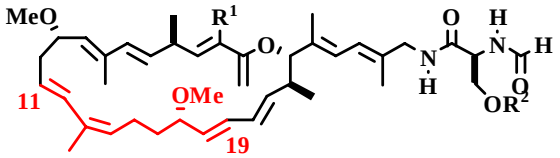
Cottard, M.; Kann, N.; Rein, T.; Åkermark, B.; Helquist, P. *Tetrahedron Lett.* **1995**, *36*, 3115.
Mendlik, M. T.; Cottard, M.; Rein, T.; Helquist, P. *Tetrahedron Lett.* **1997**, *38*, 6375.

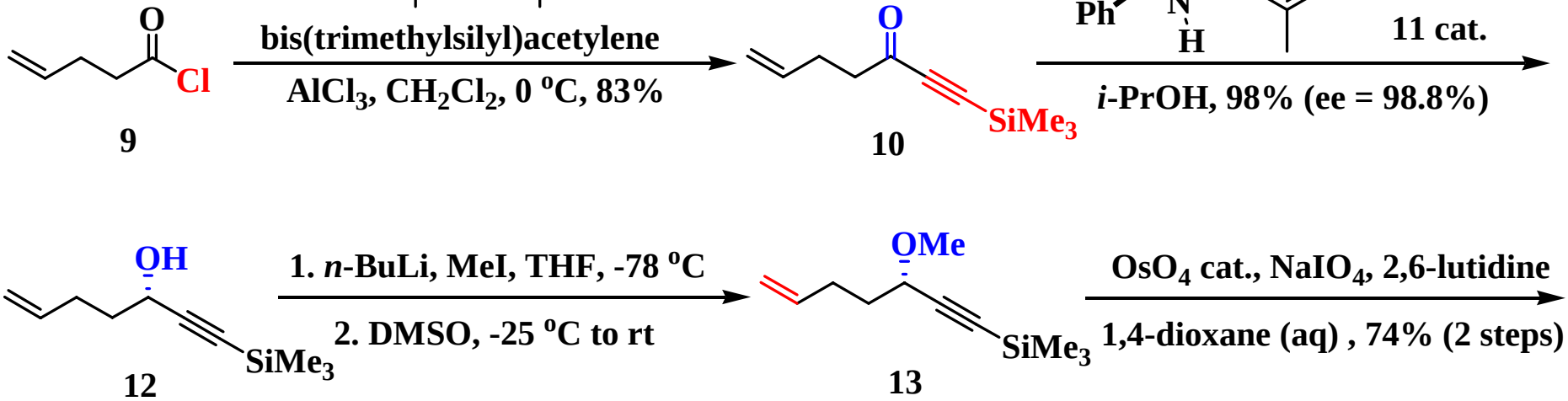
Scheme 1-2: Previous Retrosynthetic Analysis of Iejimalide A-D

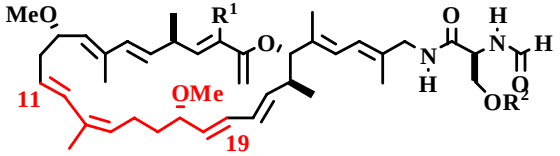


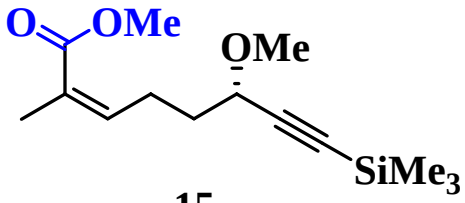
Fürstner, A.; Aïssa, C.; Chevrier, C.; Teply´, F.; Nevado, C.; Tremblay, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5832.

Scheme 2: Synthesis of Fragment C_{11}-C_{19}





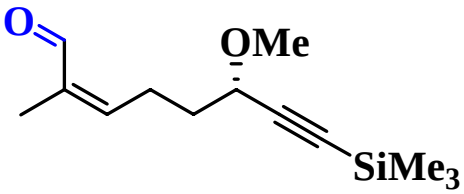




15

1. DIBAl-H, CH_2Cl_2, -78 °C

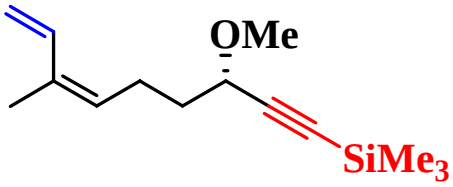
2. MnO_2, CH_2Cl_2, 96% (2 steps)



16

$[Ph_3PCH_3]^+ Br^-$, *n*-BuLi

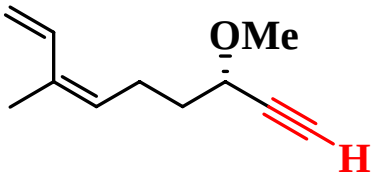
THF, -78 °C to rt



17

K_2CO_3, MeOH

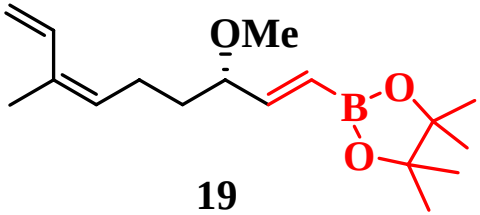
83%



18

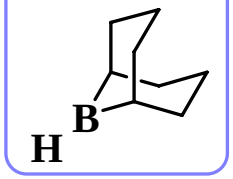
pinacolborane, 9-BBN (10 mol %)

THF, 45 °C, 56%

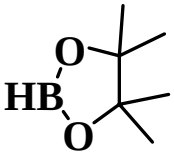


19

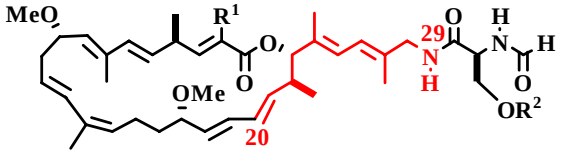
9-BBN

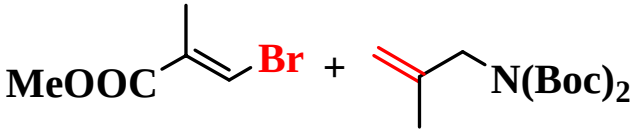


pinacolborane



Scheme 3: Synthesis of Fragment C_{20}-N_{29}



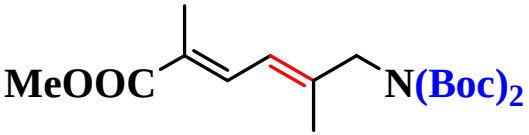


20 21

$Pd(OAc)_2$ (3 mol %), P(*o*-tol)$_3$ (6 mol%)

Et_3N, 100 °C, 84%

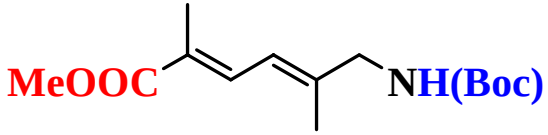
Heck reaction



22

trifluoroacetic acid

CH_2Cl_2, 87%

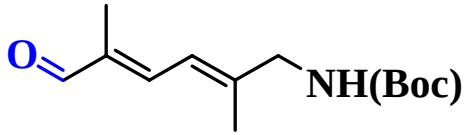


23

(i) DIBAl-H, CH_2Cl_2, -78 °C, 97%

(ii) DMSO, $(COCl)_2$; Et_3N, CH_2Cl_2
-78 °C to rt, 79%

Swern oxidation



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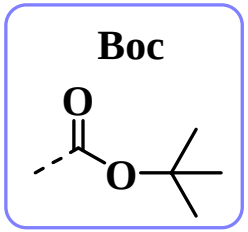
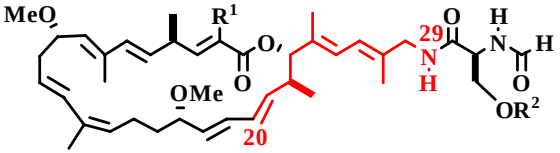
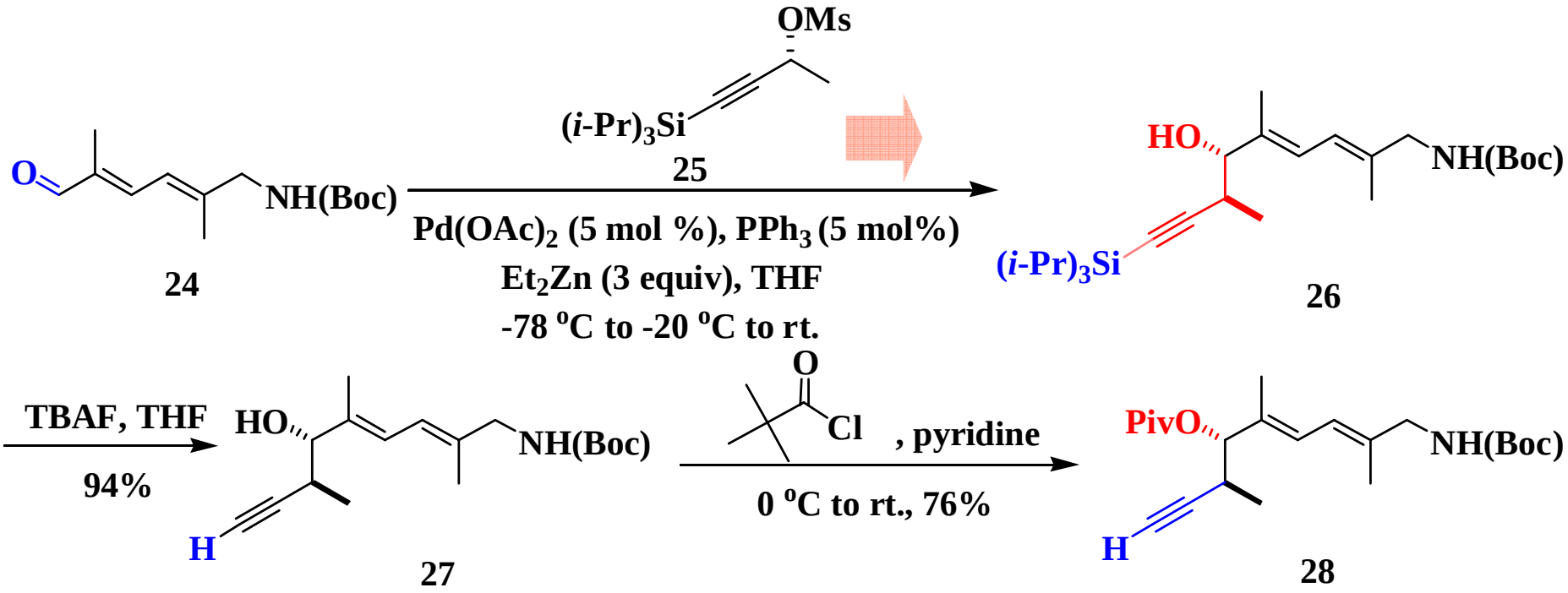
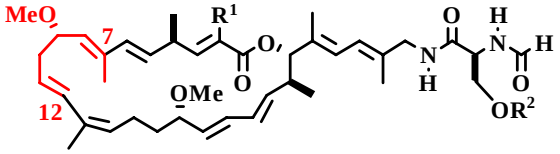
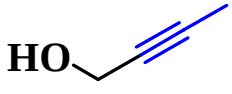



MeO
R1
O
O
OMe
20
29
N
H
O
H
N
H
O
OR2


OMs
(i-Pr)3Si
25
O
NH(Boc)
24
Pd(OAc)2 (5 mol %), PPh3 (5 mol%)
Et2Zn (3 equiv), THF
-78 °C to -20 °C to rt.
HO
NH(Boc)
(i-Pr)3Si
26
TBAF, THF
94%
HO
NH(Boc)
H
27
O
Cl
, pyridine
0 °C to rt., 76%
PivO
NH(Boc)
H
28
Cp2Zr(H)Cl, THF, then I2
0 °C to rt., 85%
PivO
NH(Boc)
I
29
DIBAl-H, CH2Cl2
-78 °C, 87%
HO
NH(Boc)
I
30
Ms
O
S
CH3
O

Scheme 4-2: Synthesis of Fragment C_7-C_{12}

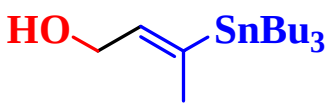




32

$Bu_3Sn(Bu)CuCNLi_2$

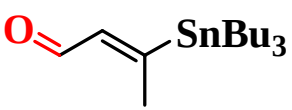
THF, MeOH, -78 °C to -10°C



33

MnO_2, CH_2Cl_2

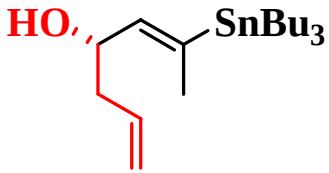
95%



34

(-)-Ipc_2BOMe, allylMgBr

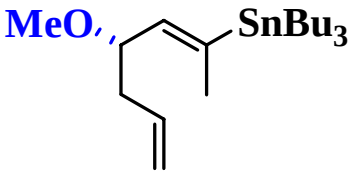
Et_2O, -78 °C, 75% (ee = 96%)



35

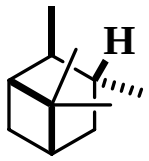
Me_3OBF_4, proton sponge

CH_2Cl_2, 88%

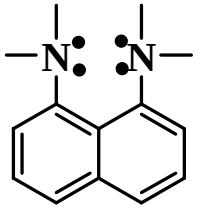


36

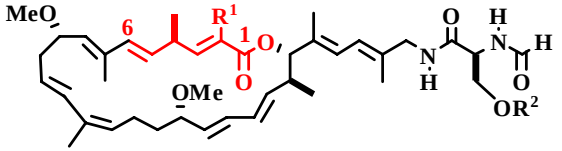
Ipc

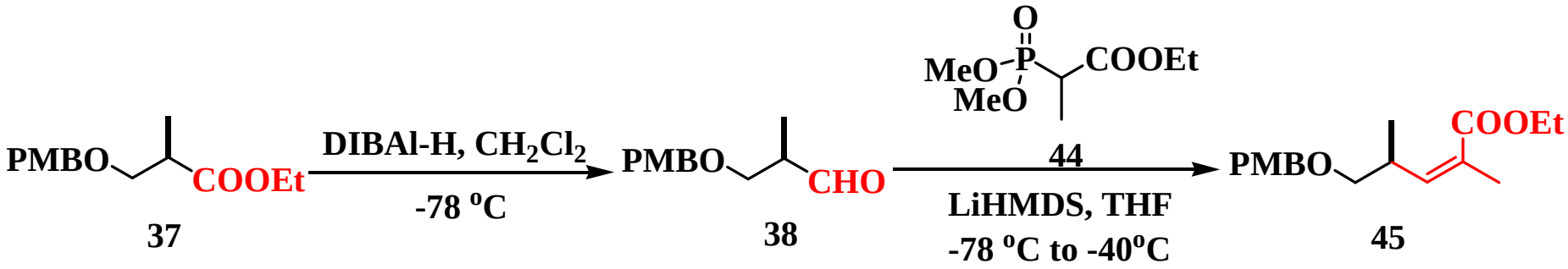


proton sponge

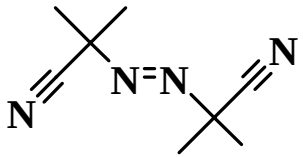


Scheme 5: Synthesis of Fragment C_1-C_6

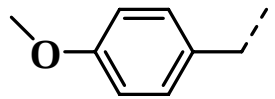




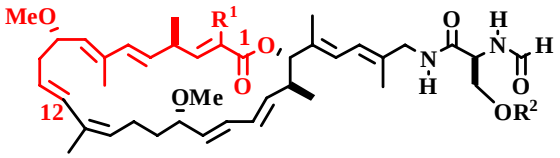
AIBN

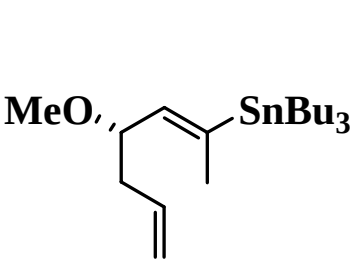


PMB



Scheme 6: Synthesis of Fragment C_1-C_{12}





36

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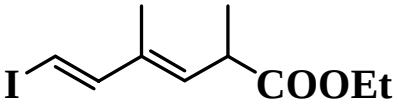
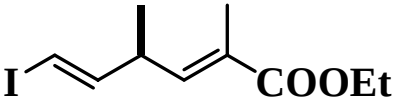


42



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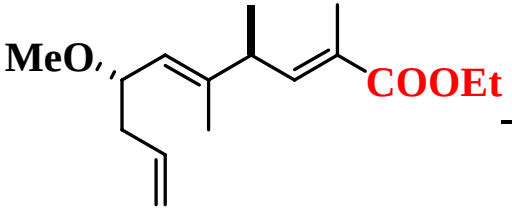
$Pd(PPh_3)_4$ (5 mol%), CuTC, $Ph_2PO_2^-NBu_4^+$

DMF, rt, 80%

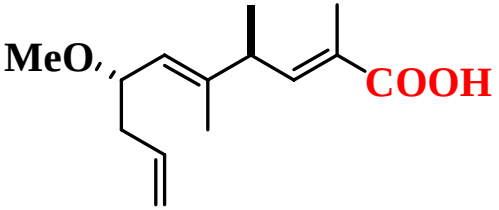
Stille coupling



46

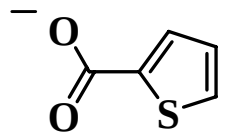
aqueous LiOH

THF/MeOH, 85%

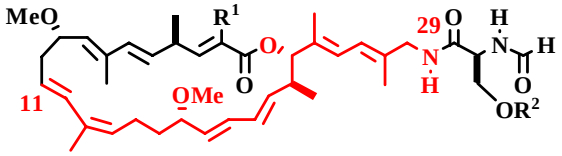


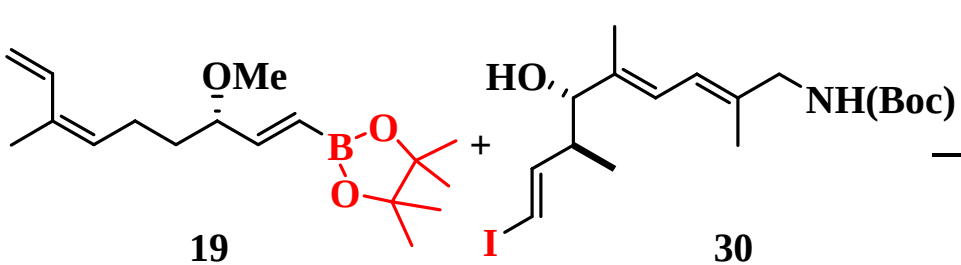
47

TC: thiophene-2-carboxylate



Scheme 7: Synthesis of Fragment C_{11}-N_{29}

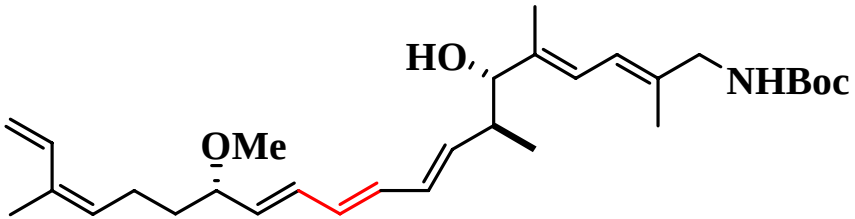




19 30

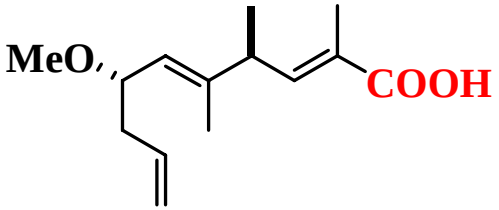
(dppf)$PdCl_2$ (15 mol%),
$Ba(OH)_2 \bullet 8H_2O$ (1.2 equiv)
DMF, 40 °C, 66%

Suzuki coupling



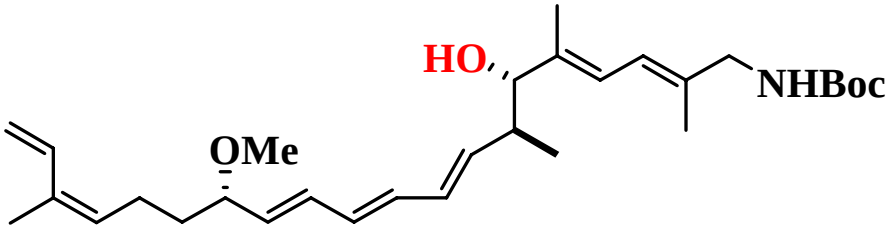
48

Scheme 8: Synthesis of Fragment C_1-N_{29}



47

+

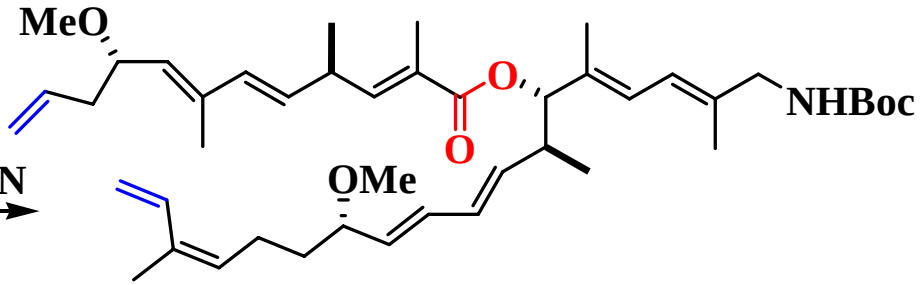


48

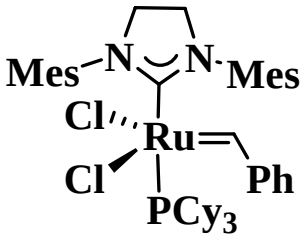
Yamaguchi esterification

2, 4, 6-trichlorobenzoyl chloride, Et_3N

DMAP cat., toluene, 73%



49

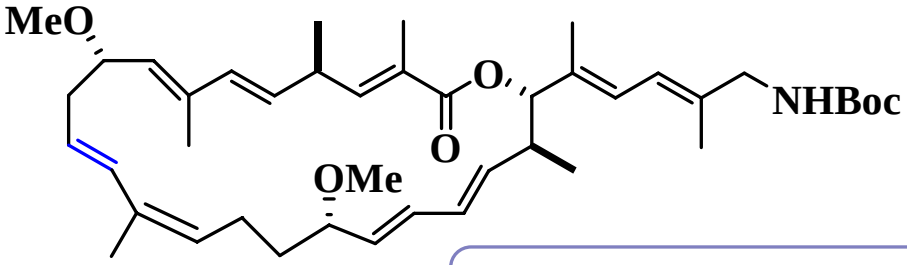


50

(2 x 10 mol %)

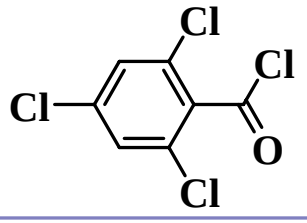
CH_2Cl_2, rt, 2d, 96%

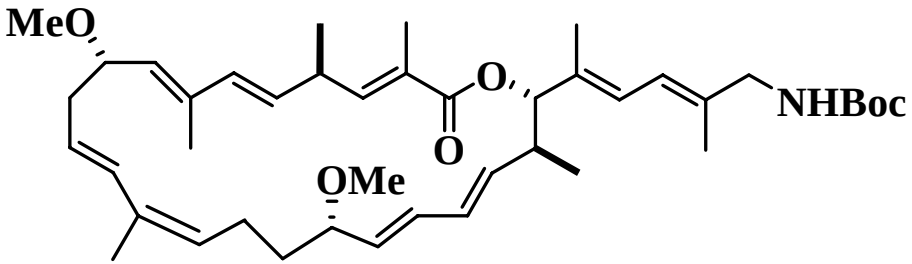
RCM



51

2, 4, 6-trichlorobenzoyl chloride

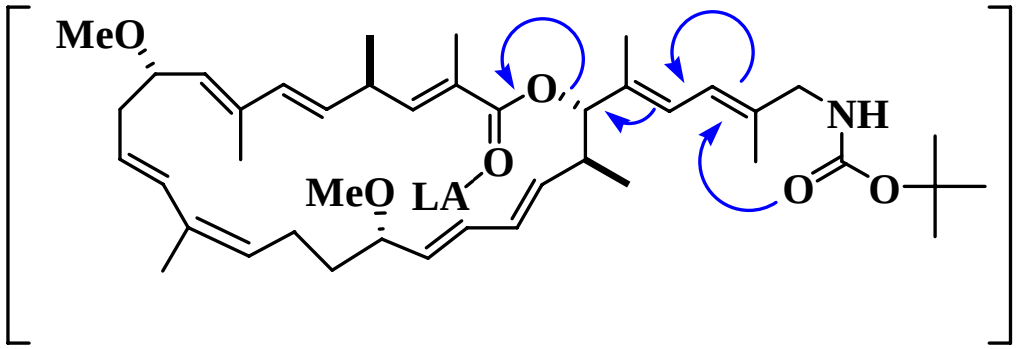




51

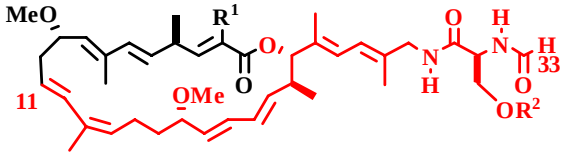
TMSOTf, 2,6-lutidine

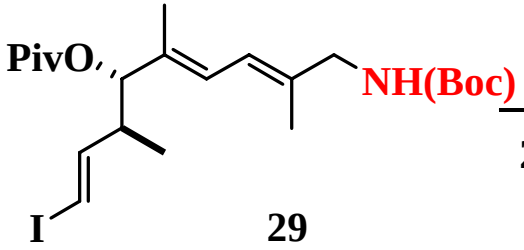
CH_2Cl_2, 0 °C



decomposition

Scheme 9: Synthesis of Fragment C_{11}-C_{33}

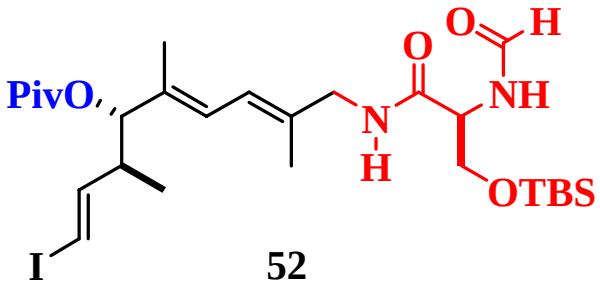




29

1. TMSOTf, 2,6-lutidine, CH_2Cl_2, then CsF, 0 °C

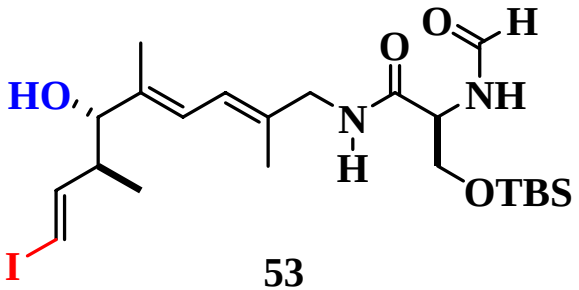
2. *O*-TBS-*N*-formyl-L-serine (57), EDC, HOBt
N-methylmorpholine (NMM), CH_2Cl_2, 85% (2 steps)



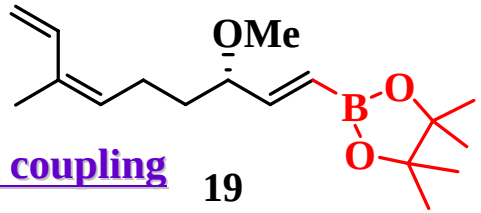
52

$LiBEt_3H$, THF

0 °C, 70%



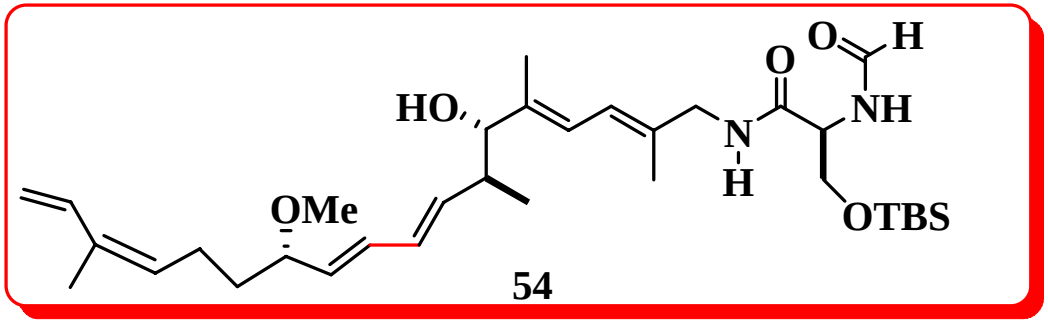
53



19

Suzuki coupling

(dppf)$PdCl_2$ (15 mol %)
$Ba(OH)_2 \bullet 8H_2O$(1.2 equiv)
DMF, rt, 70~ 80%



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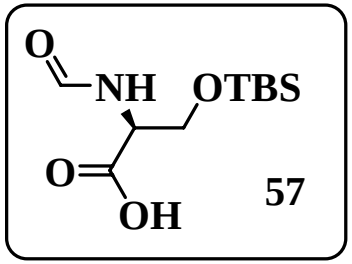
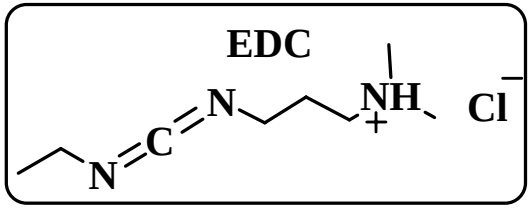
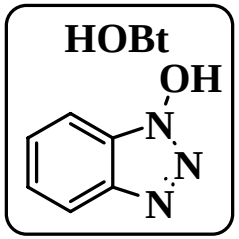
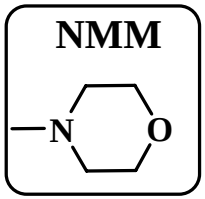


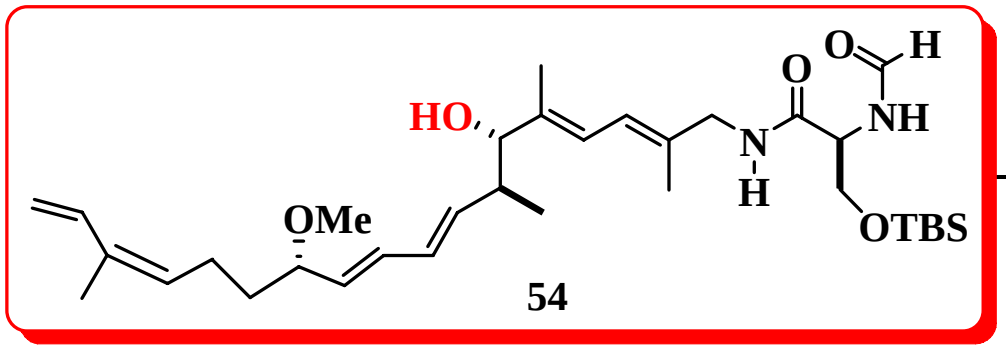
57



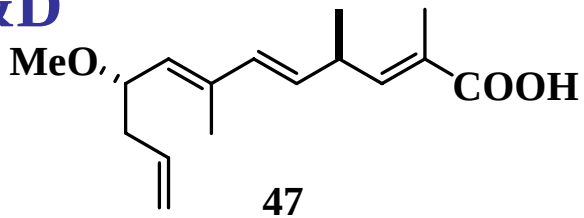




Scheme 10: Synthesis of lejimalide B&D

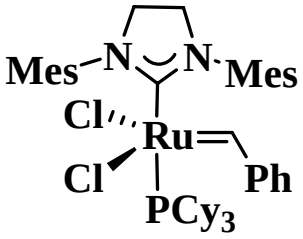


54



47

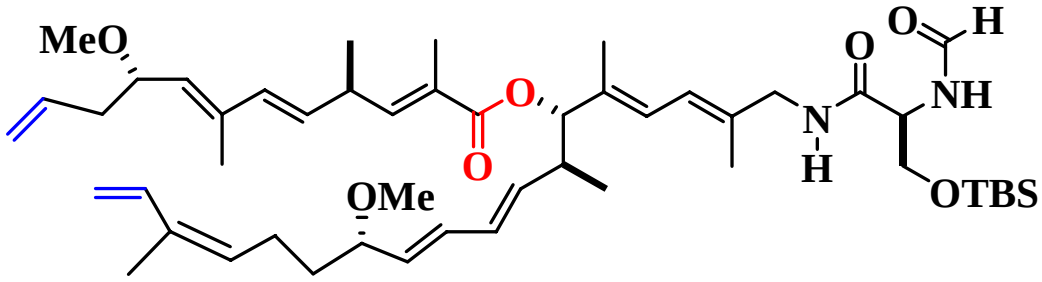
DCC, 4-pyrrolidinylpyridine (30 mol%)
CH_2Cl_2, 0 °C to rt, 85%



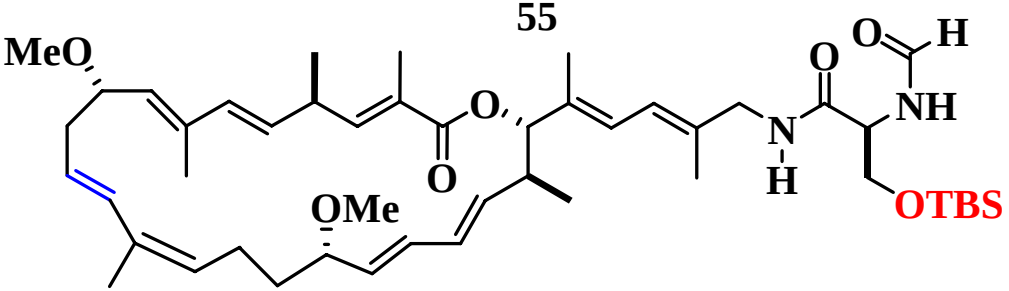
(15 mol %)

50

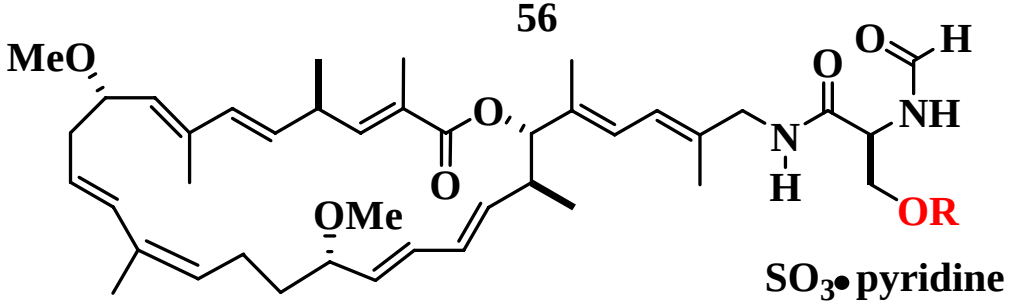
CH_2Cl_2 (5×10^{-3} M), rt, 69%



55



56

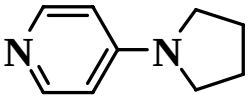


SO_3•pyridine

TBAF, THF

0 °C, 80%

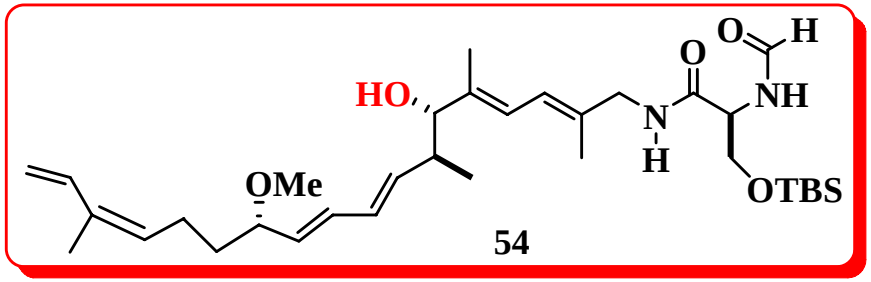
4-pyrrolidinylpyridine



lejimalide B (2) R = H

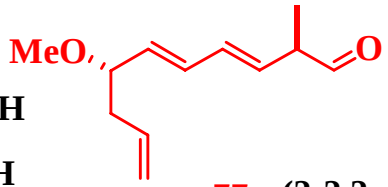
lejimalide D (4) R = SO_3Na

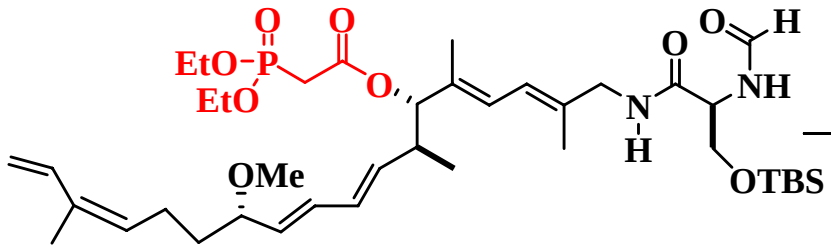
Scheme 11: Synthesis of lejimalide A&C



54

CH_2Cl_2, 0 °C to rt, 82%

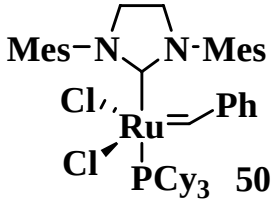




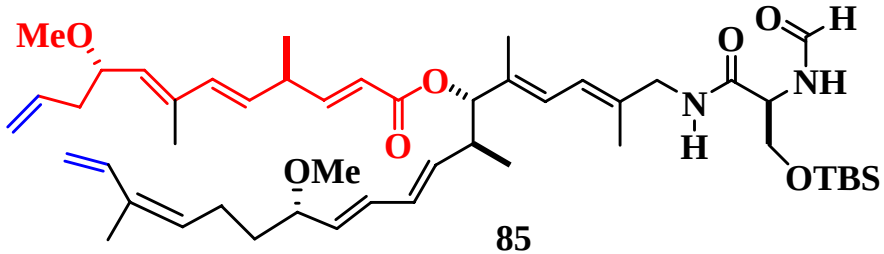
84

77 (2-2.2 equiv), LiCl, *i*-Pr_2NEt, MeCN, 36%

(65% based on recovered starting material)

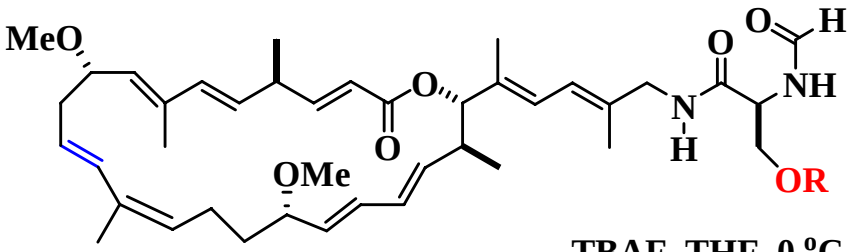


50 (20 mol%)



85

CH_2Cl_2, rt, 55%



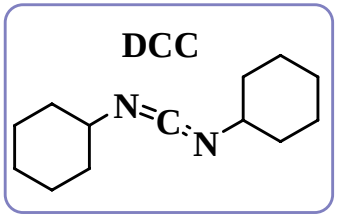
TBAF, THF, 0 °C, 67%

86 R = TBS

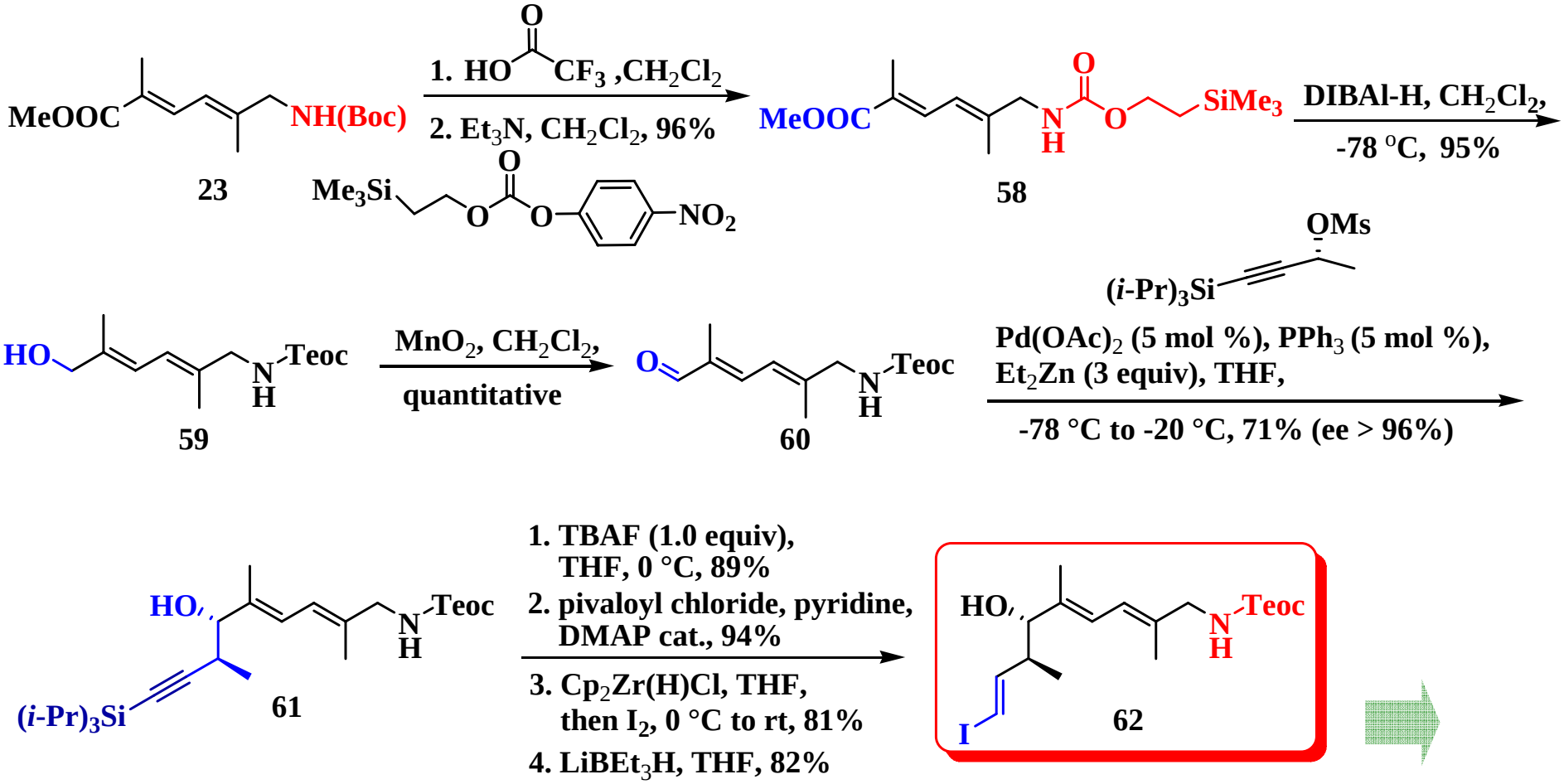
lejimalide A (1) R = H

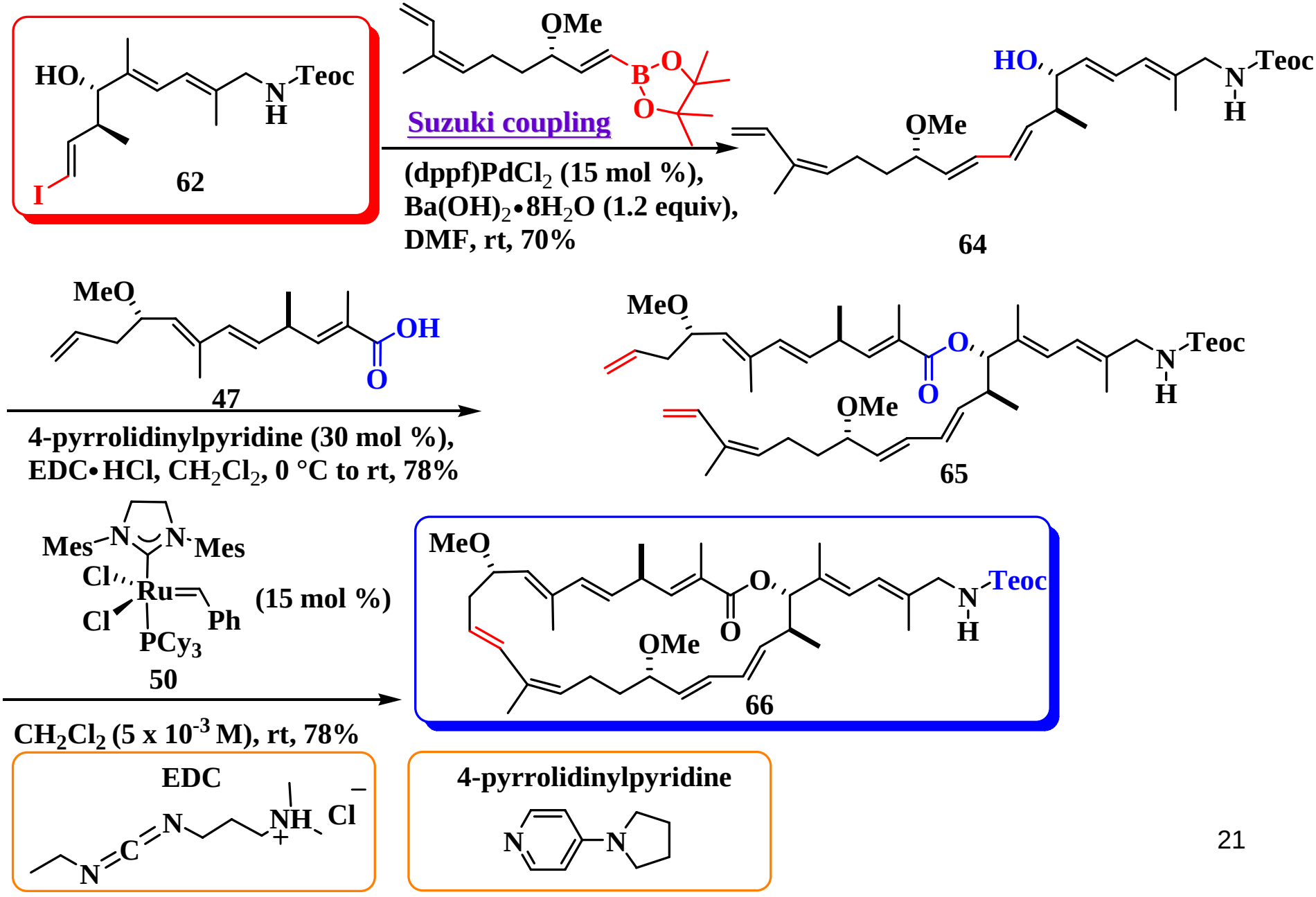
SO_3•pyridine

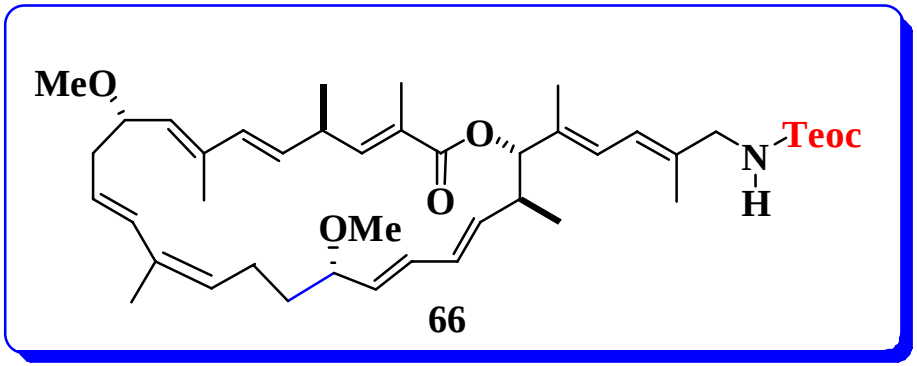
lejimalide C (3) R = SO_3Na



Scheme 12: Synthesis of lejimalide B to get lejimalide Analogues



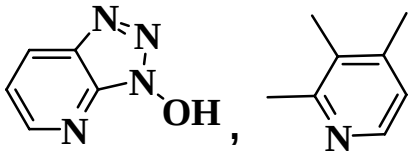

HO
Teoc
N
H
I
62
OMe
B
O
O
Suzuki coupling
(dppf)PdCl2 (15 mol %),
Ba(OH)2•8H2O (1.2 equiv),
DMF, rt, 70%
HO
Teoc
N
H
OMe
64
MeO
OH
O
47
4-pyrrolidinylpyridine (30 mol %),
EDC•HCl, CH2Cl2, 0 °C to rt, 78%
MeO
O
O
Teoc
N
H
OMe
65
Mes
N
N
Mes
Cl
Ru
Cl
Ph
PCy3
50
(15 mol %)
CH2Cl2 (5 x 10-3 M), rt, 78%
MeO
O
O
Teoc
N
H
OMe
66
EDC
N
C
N
NH
+
Cl
−
4-pyrrolidinylpyridine
N
N

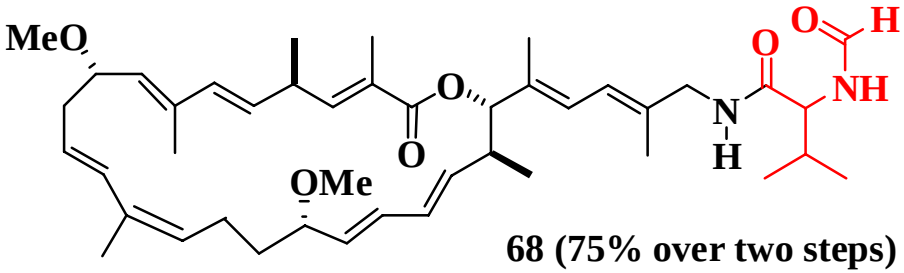


66

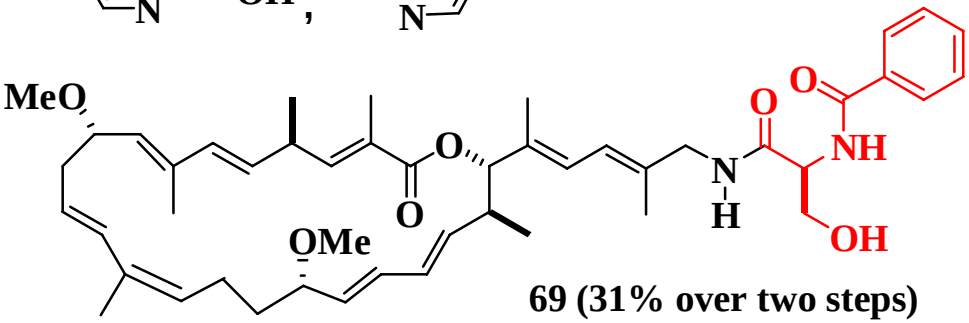
1. TBAF (4 equiv), THF, 0 °C to rt.

2. *N*-formyl-L-valine, EDC·HCl,

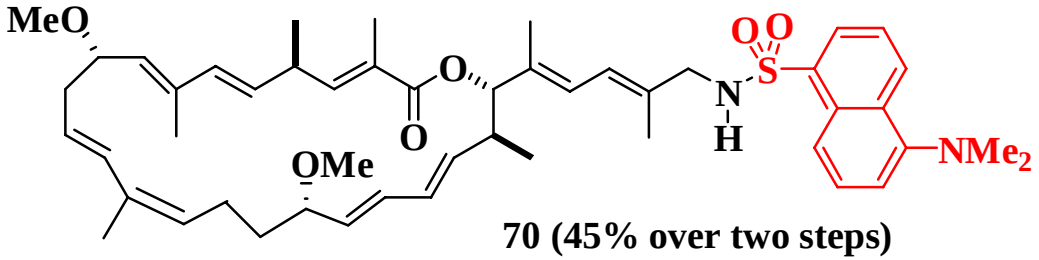




68 (75% over two steps)

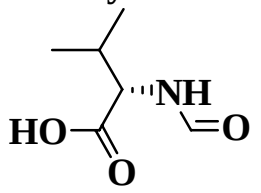


69 (31% over two steps)

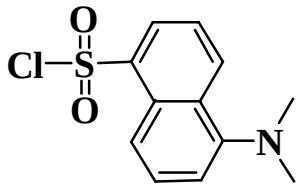


70 (45% over two steps)

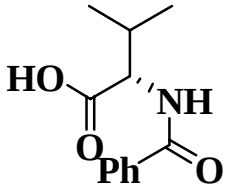
N-formyl-L-valine



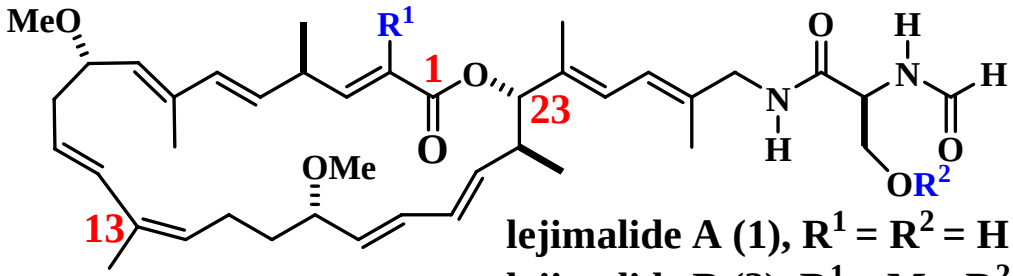
dansyl chloride



N-Benzoyl-O-TBS-L-serine



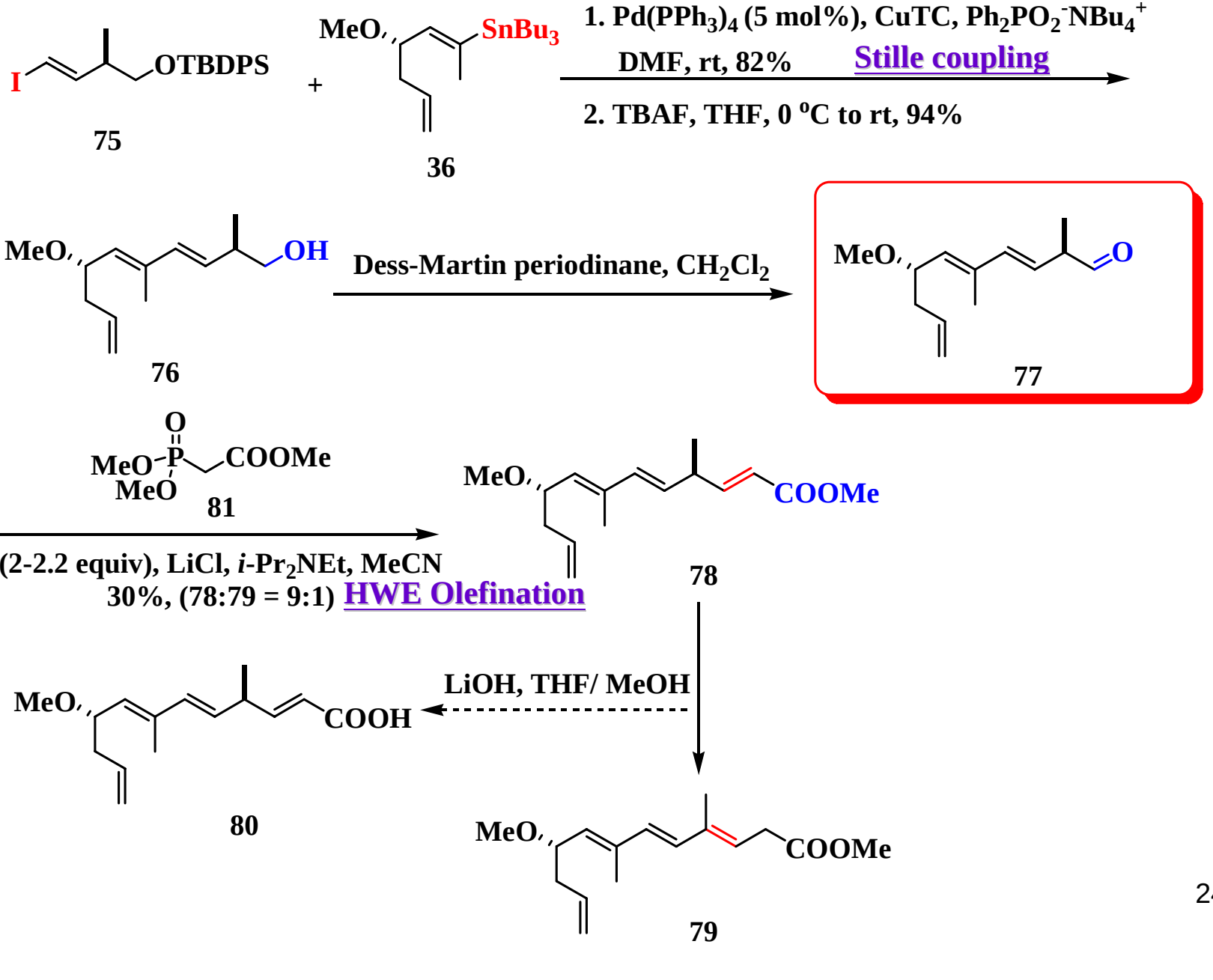
Conclusion



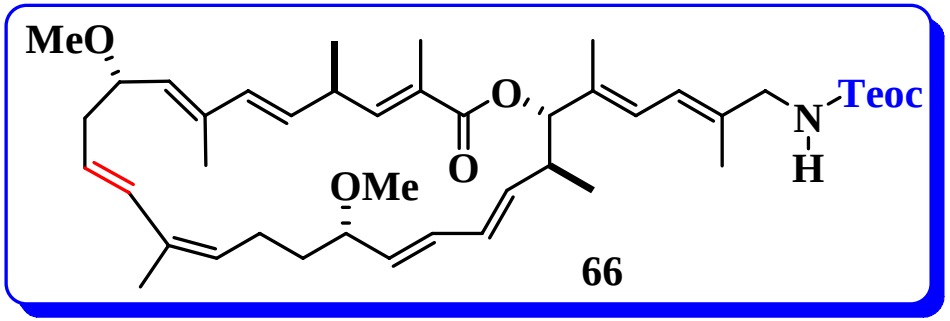
lejimalide A (1), $R^1 = R^2 = H$
lejimalide B (2), $R^1 = Me$, $R^2 = H$
lejimalide C (3), $R^1 = H$, $R^2 = SO_3Na$
lejimalide D (4), $R^1 = Me$, $R^2 = SO_3Na$

Application of RCM to appropriate cyclization precursors containing no less than 10 double bonds opened the door to a concise total synthesis of the highly cytotoxic marine natural products iejimalide A-D.

Scheme 10: Synthesis of 77

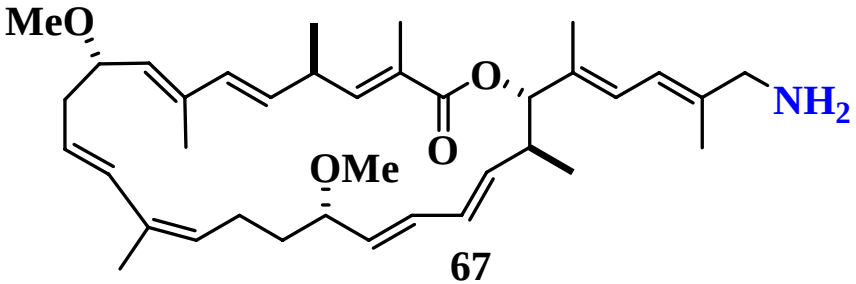


Scheme 10: Synthesis of Iejimalide B



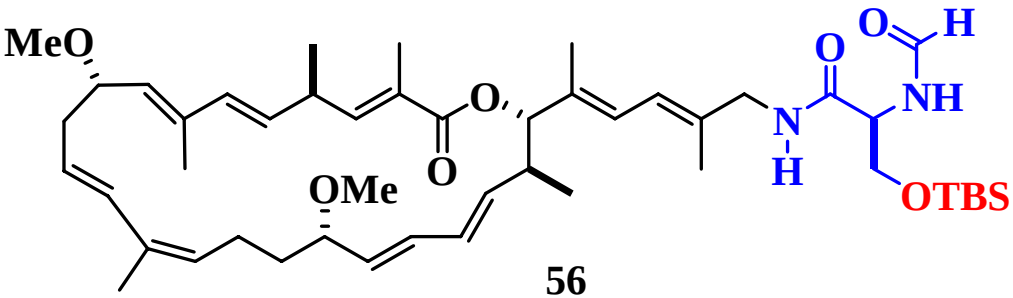
66

TBAF (4 equiv),
THF, 0 °C to rt



67

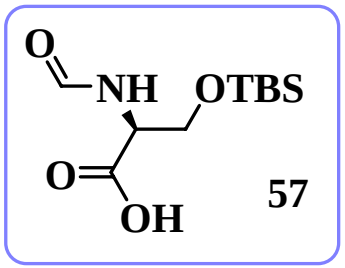
O-TBS-*N*-formyl-L-serine (57)
EDC, HOBt, NMM, 30%
(over 2 steps)



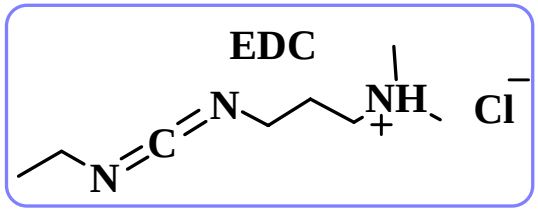
56

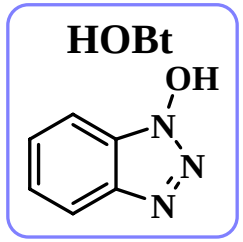
TBAF, THF
0 °C, 80%

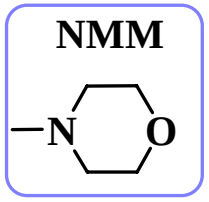
2

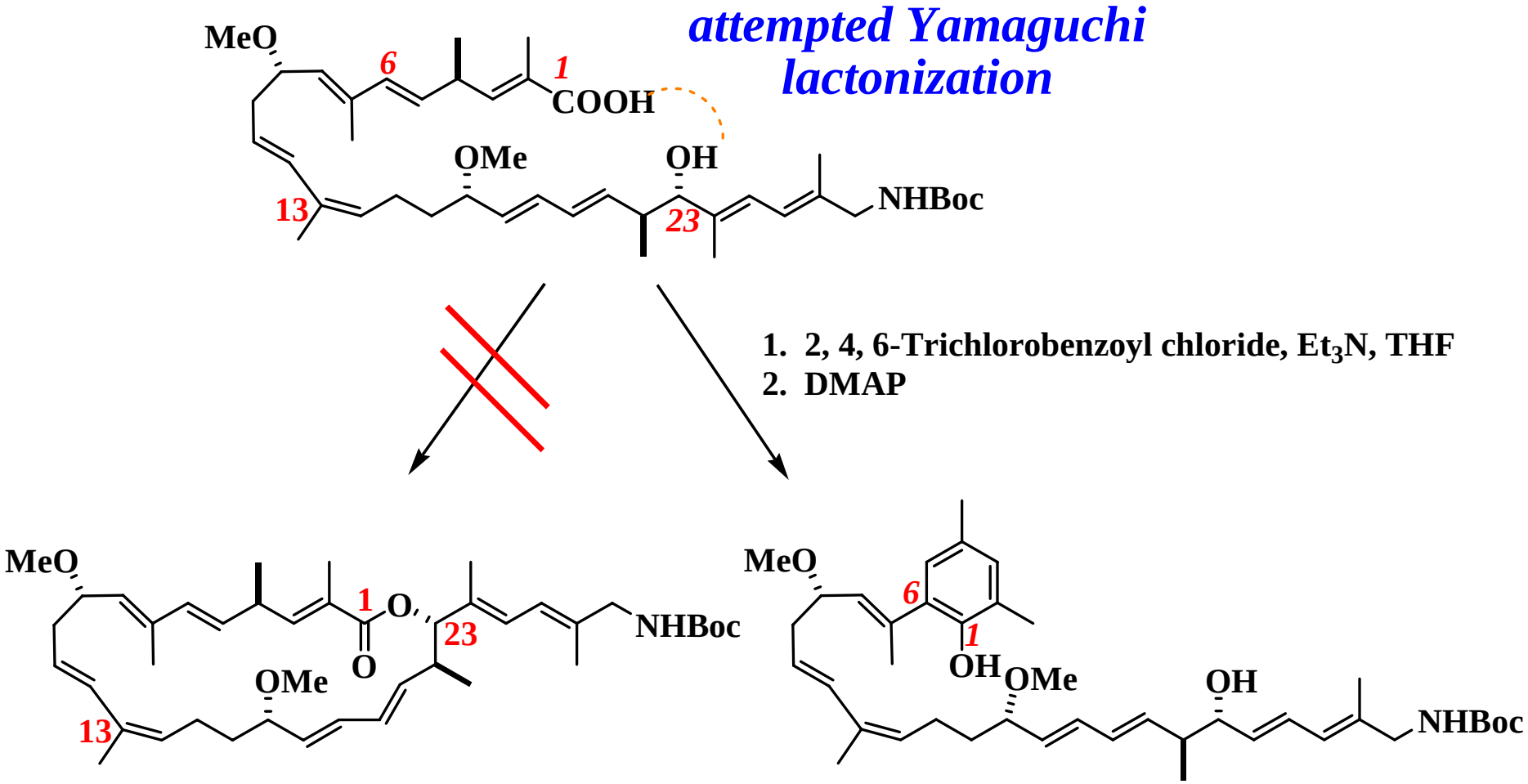


57

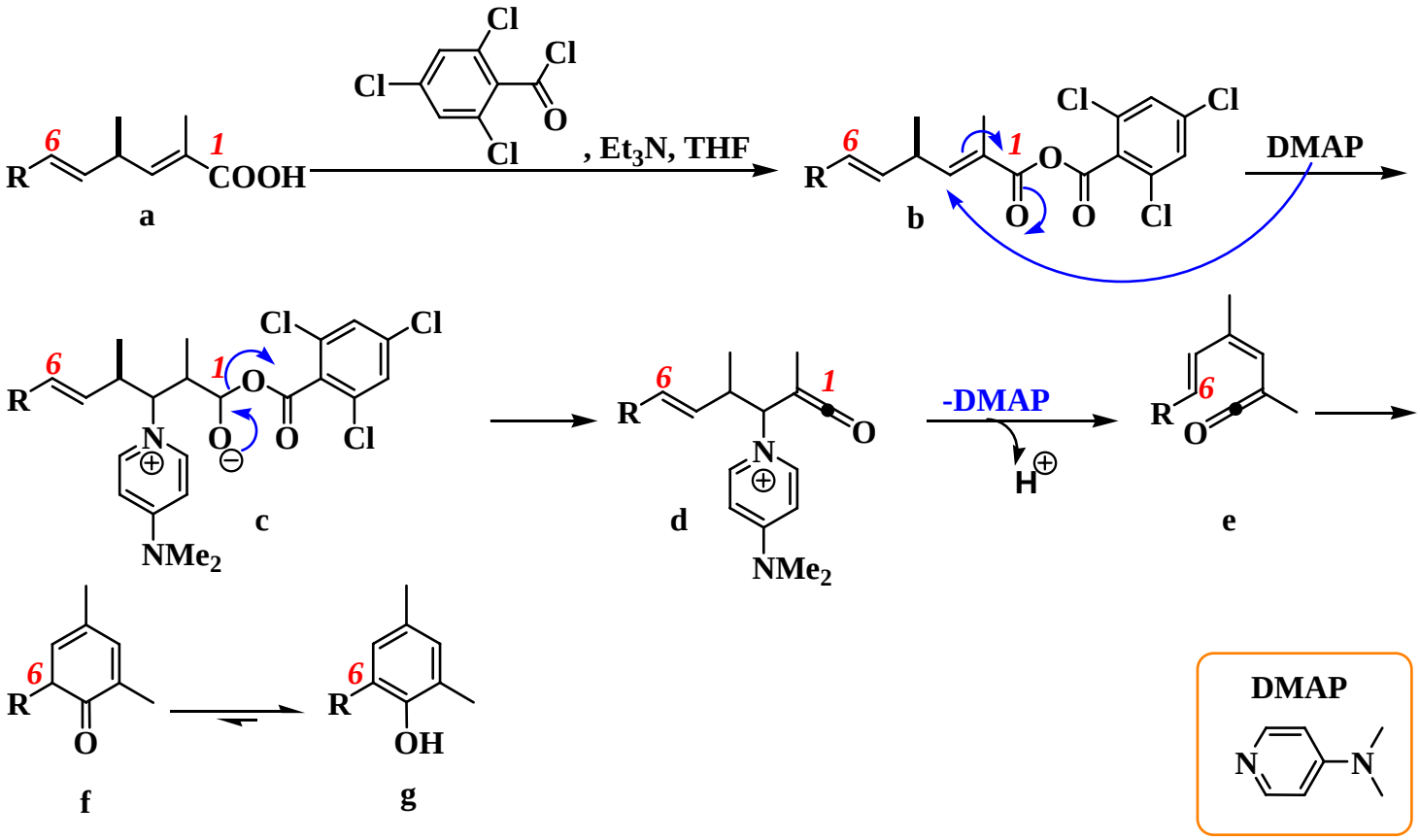




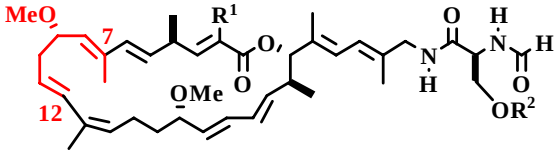



attempted Yamaguchi lactonization
MeO
6
1
COOH
OMe
OH
13
23
NHBoc
1. 2, 4, 6-Trichlorobenzoyl chloride, Et3N, THF
2. DMAP
MeO
1
O
O
23
NHBoc
OMe
13
MeO
6
1
OH
OMe
OH
NHBoc

Proposed mechanism

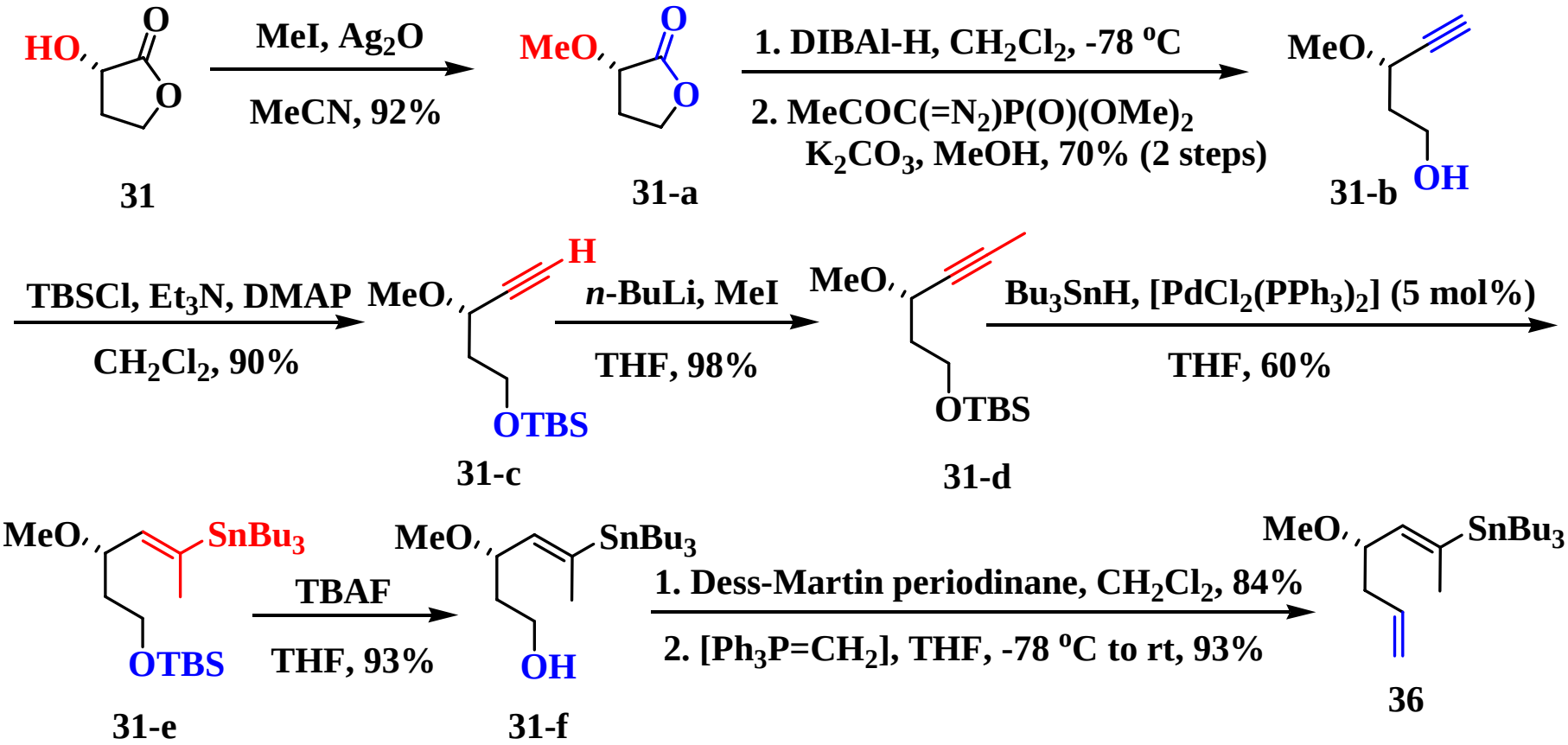


Scheme 4-1: Synthesis of Fragment C_7-C_{12}

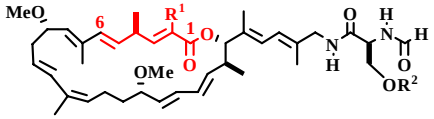


Previous synthetic methodology

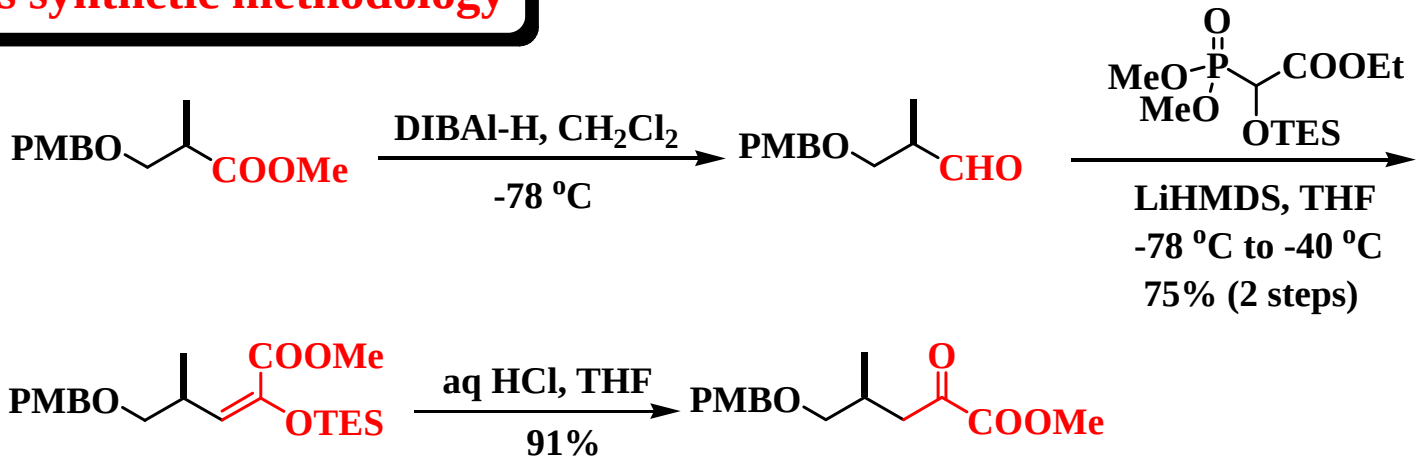
9 steps, 24% overall yield

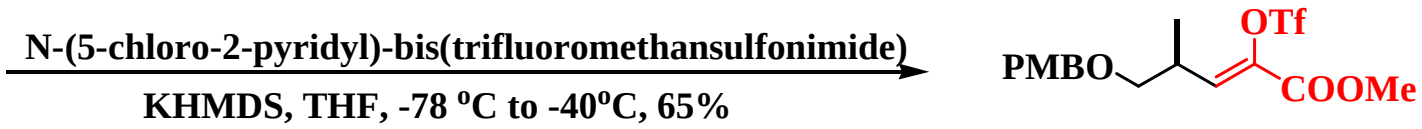


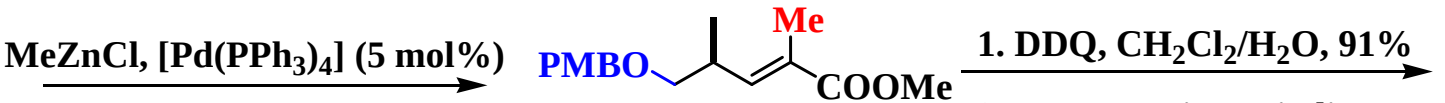
Scheme 5: Synthesis of Fragment C_1-N_6



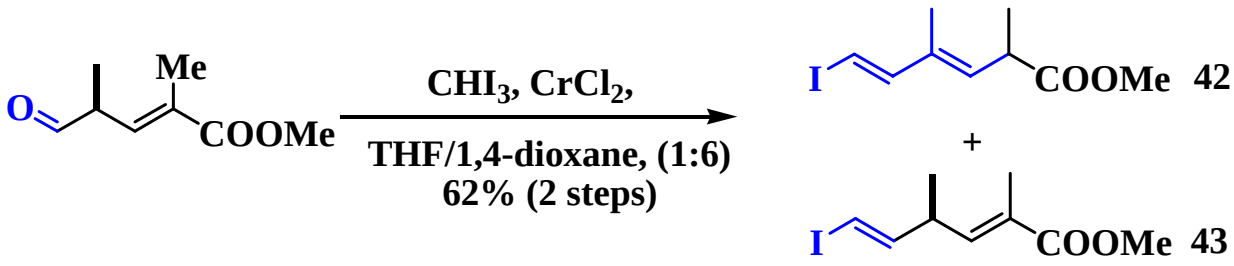
Previous synthetic methodology



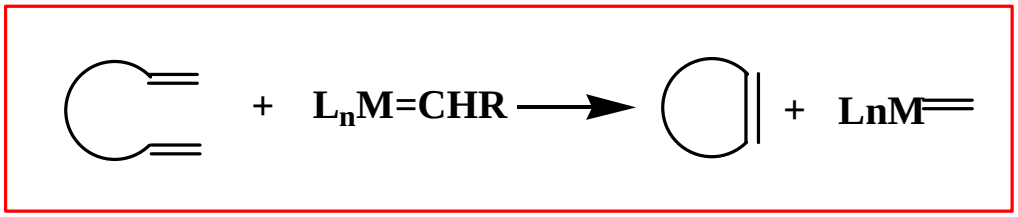


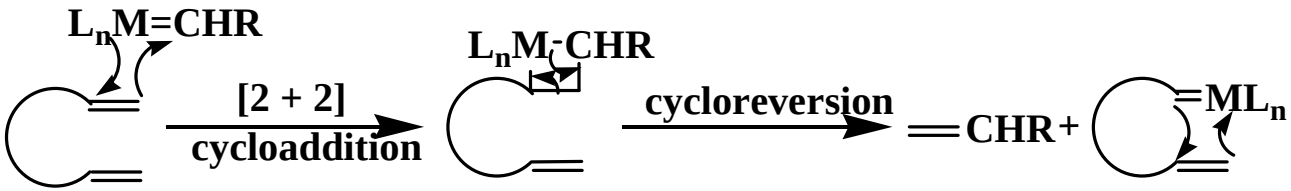


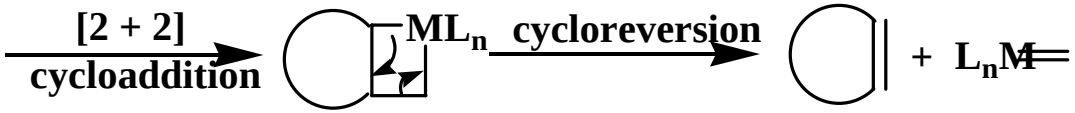
Negishi Coupling

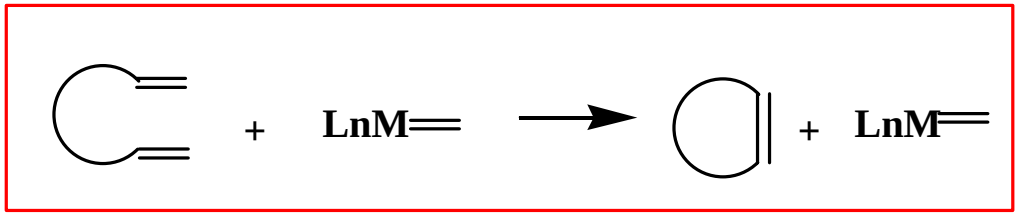


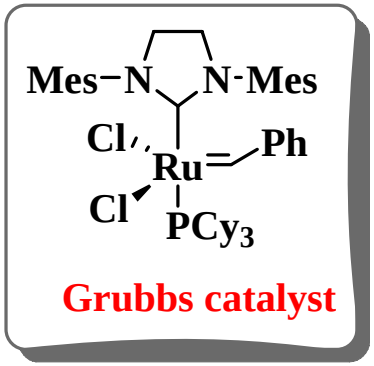
Ring-Closing Metathesis (RCM) using Grubbs Catalyst

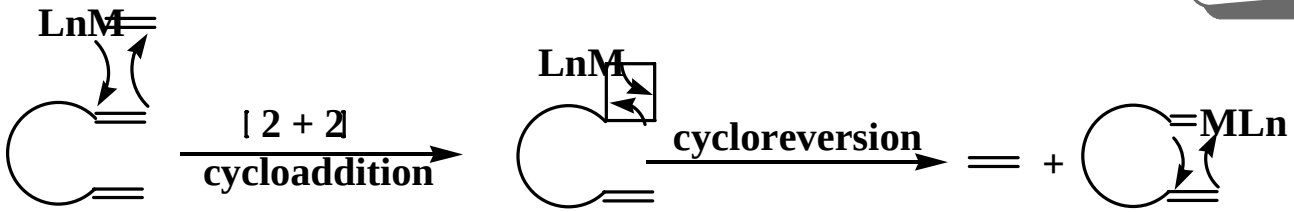




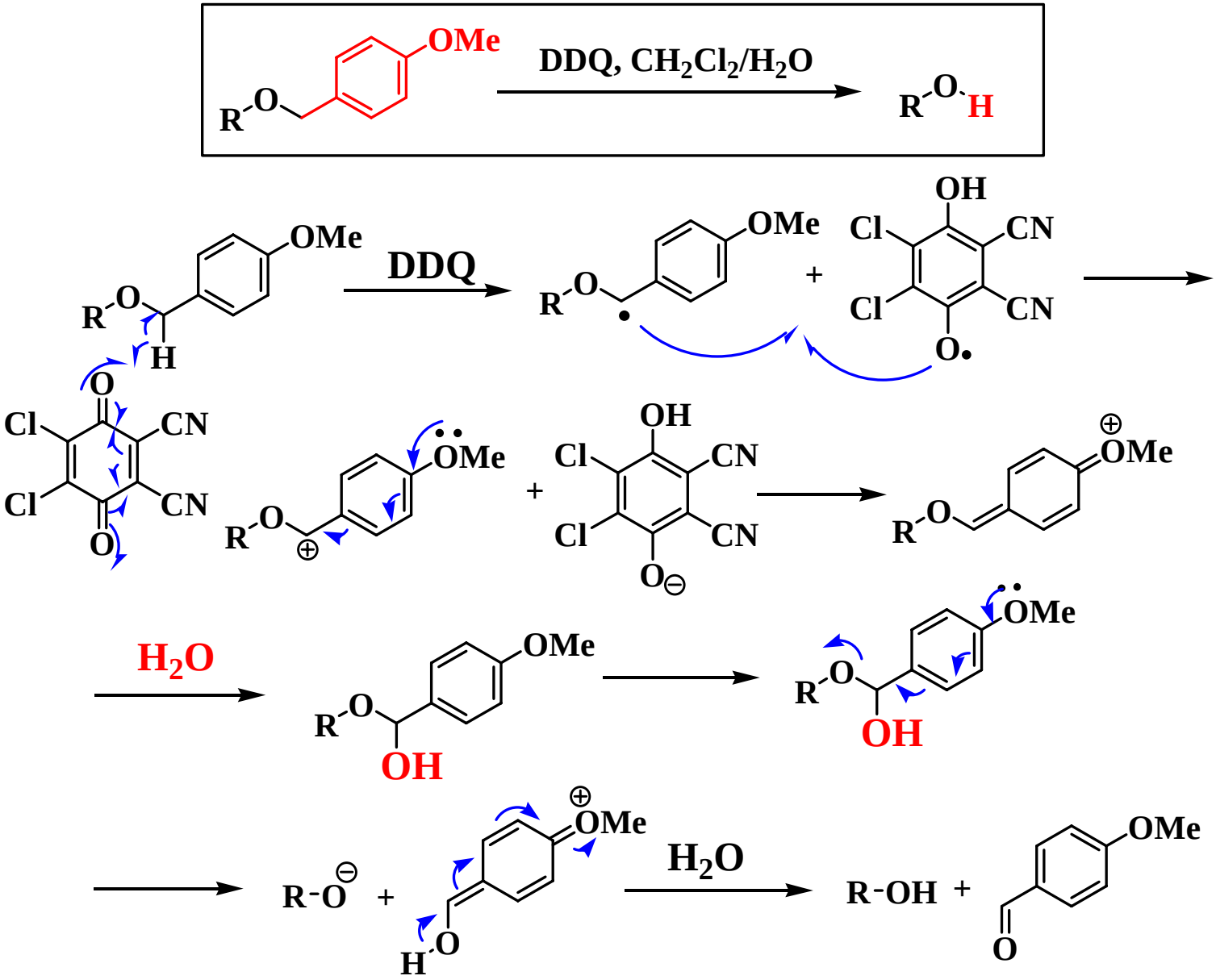




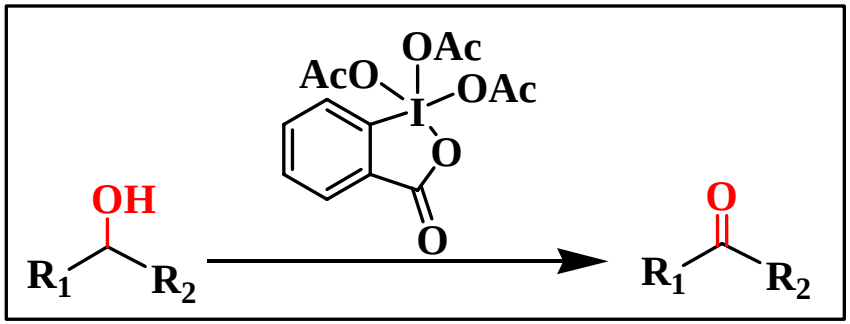


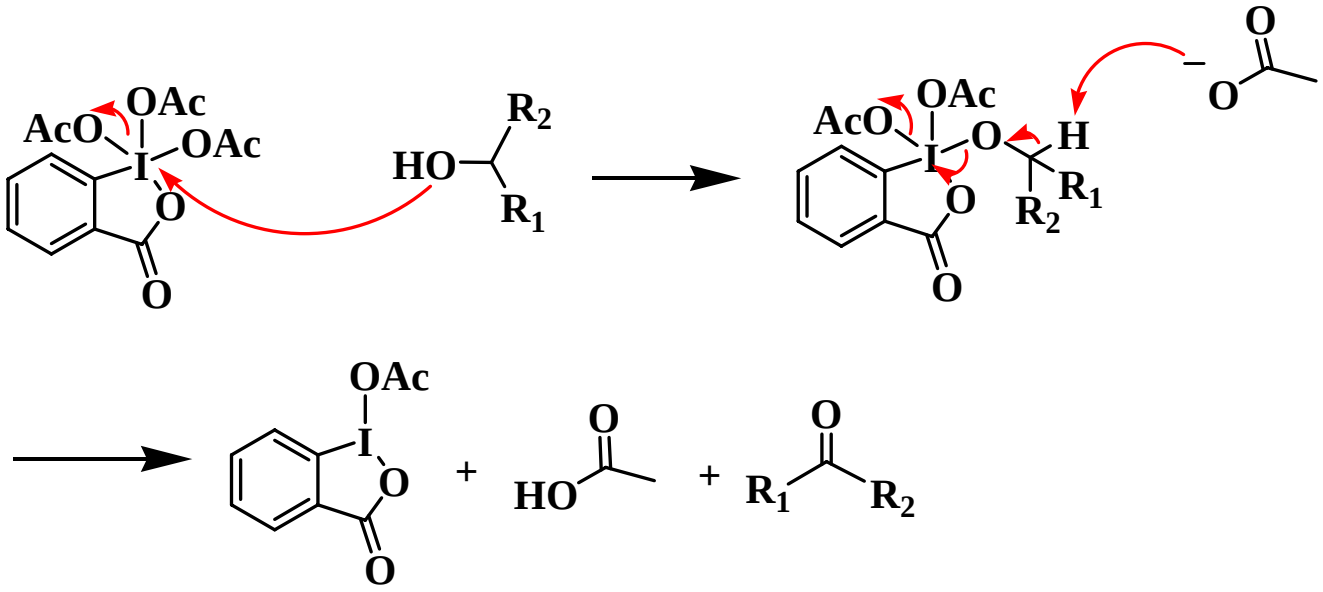


PMB Deprotection

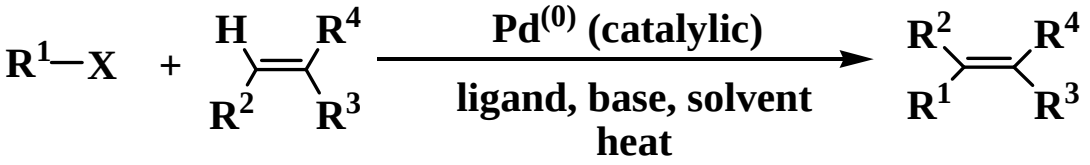


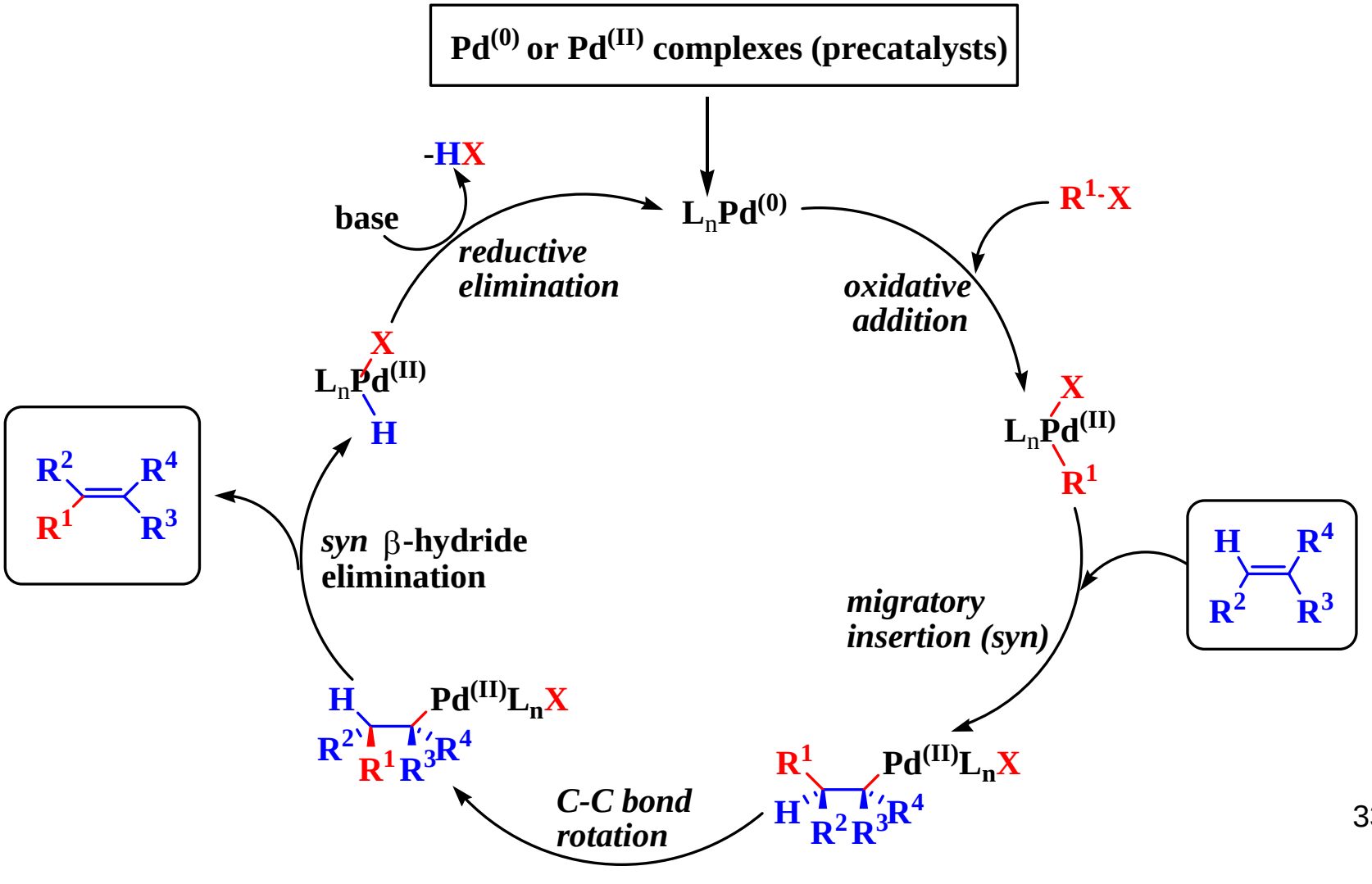
Dess-Martin Periodinane Oxidation



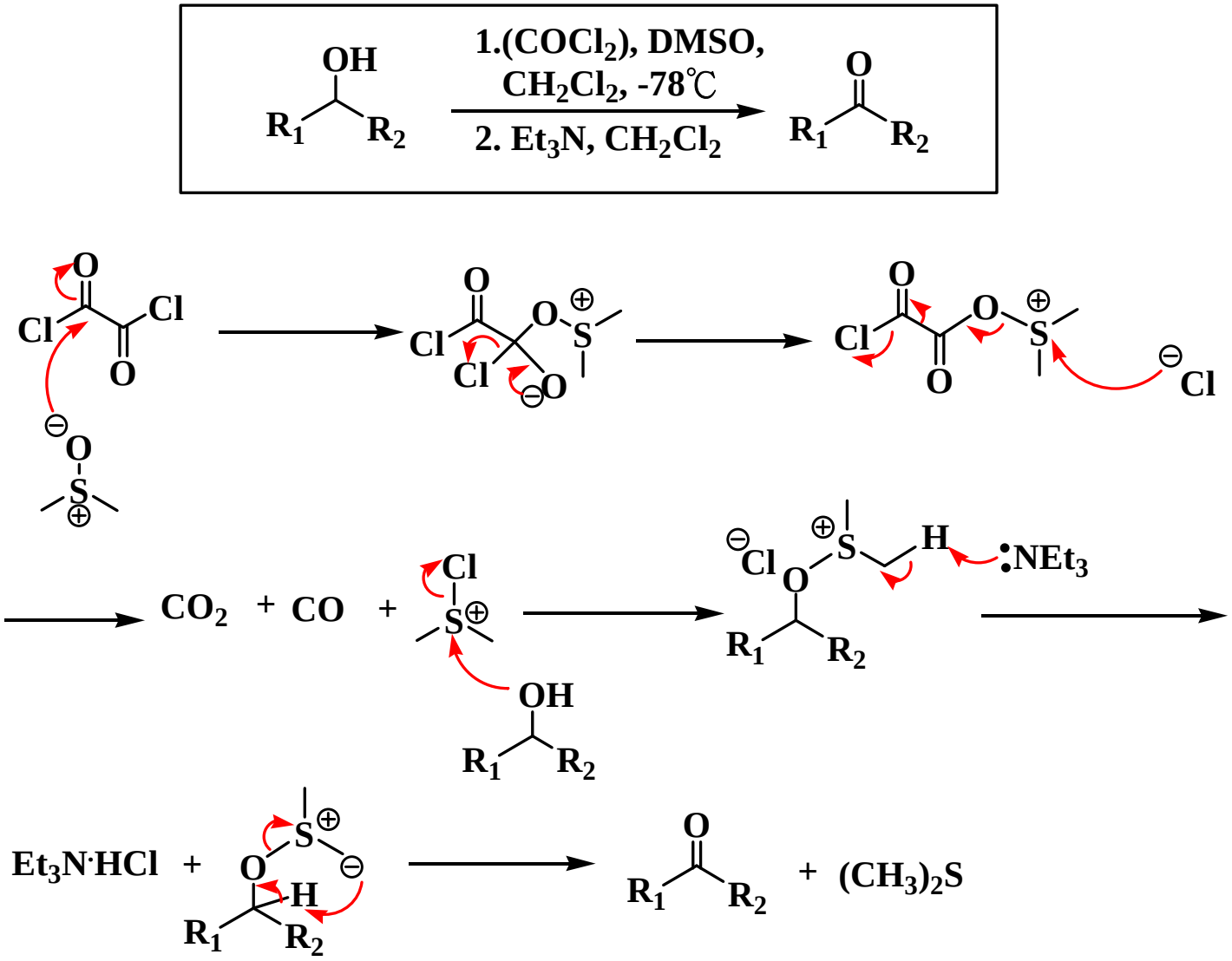


Heck Reaction

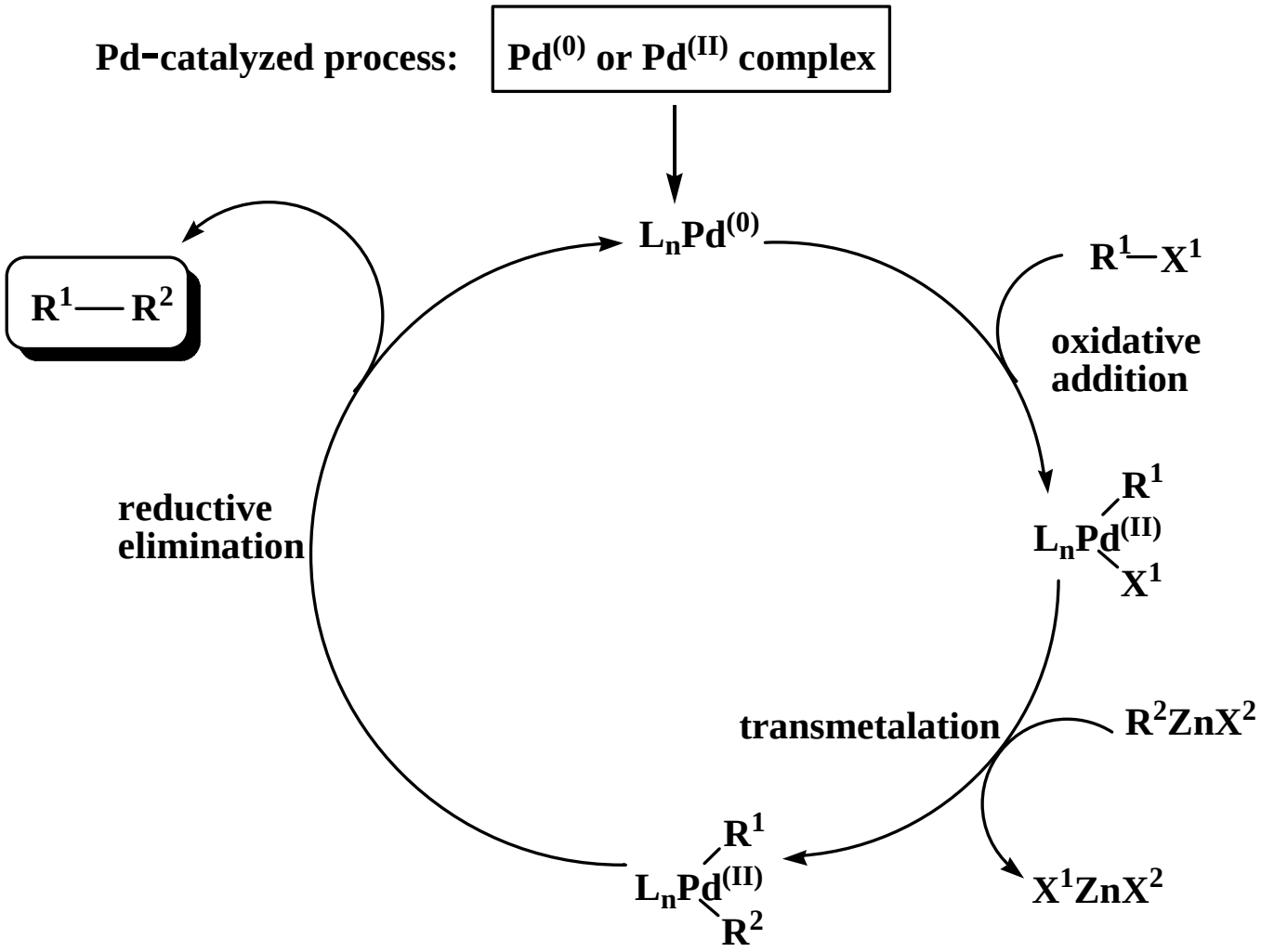


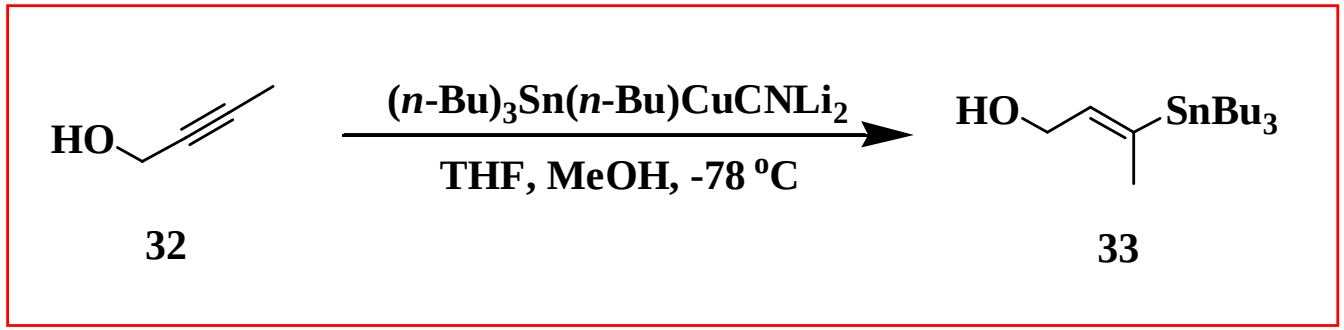


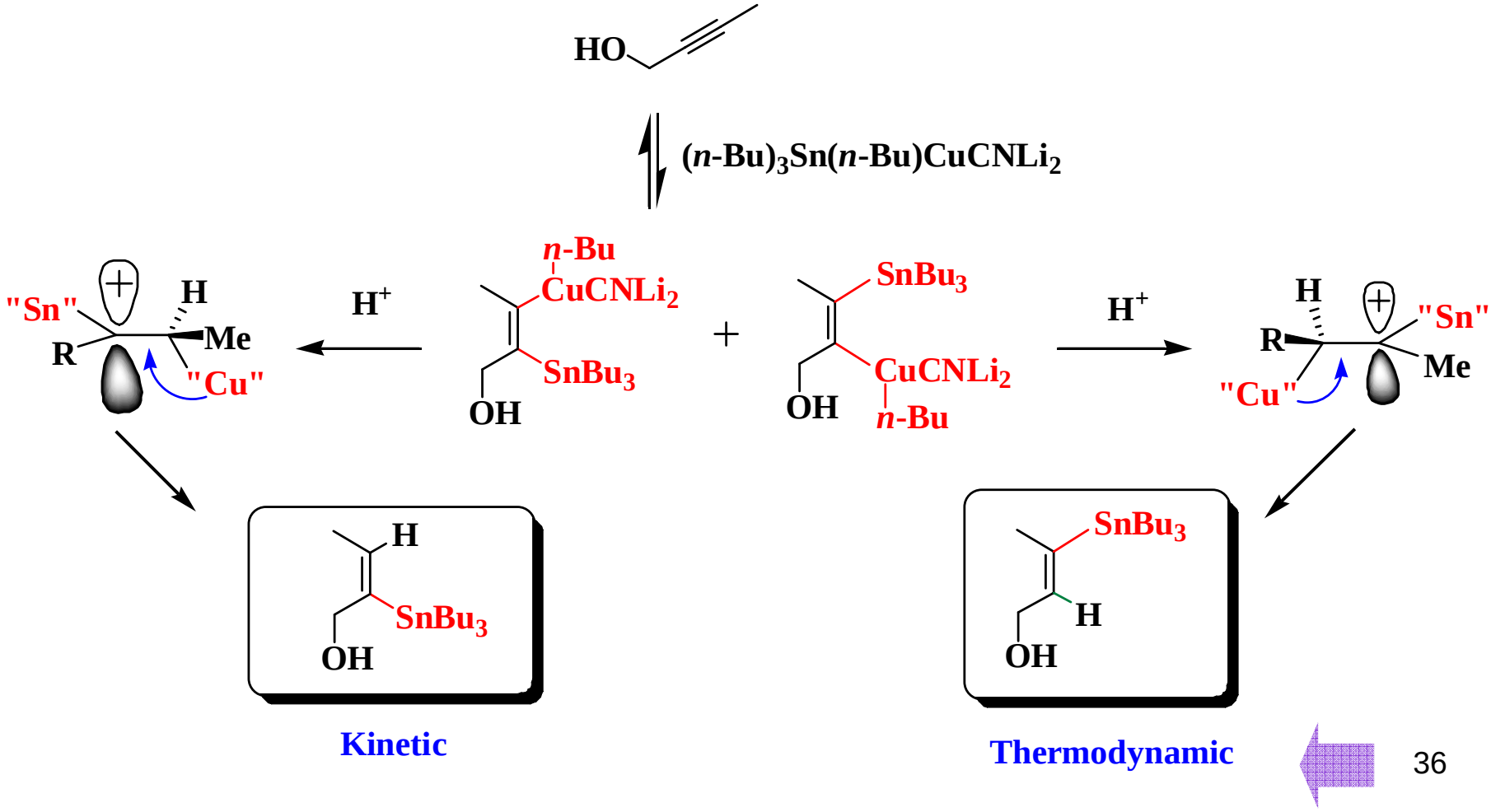
Swern Oxidation



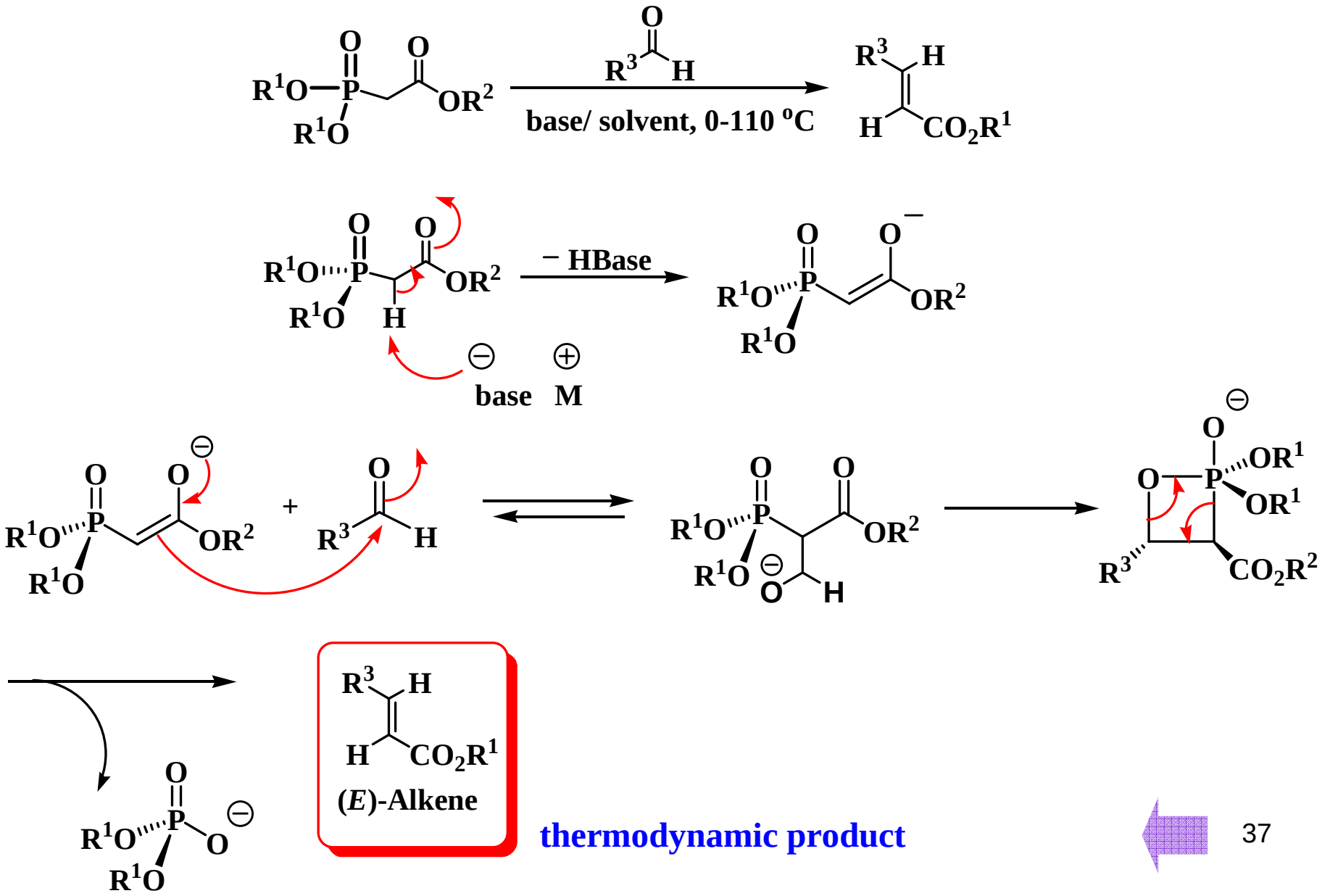
Negishi Cross-Coupling



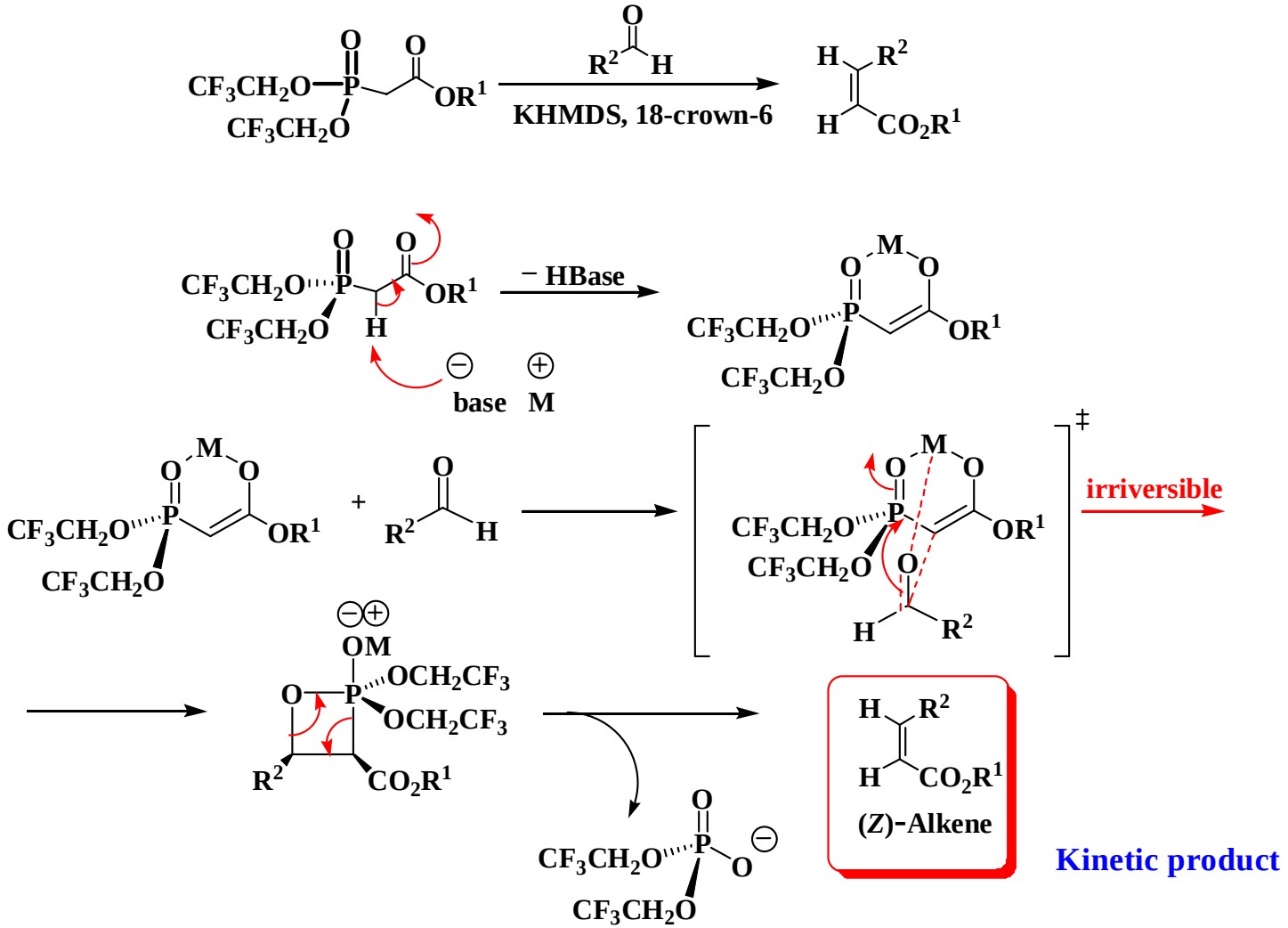

HO
(n-Bu)3Sn(n-Bu)CuCNLi2
THF, MeOH, -78 °C
HO
SnBu3
32
33


HO
(n-Bu)3Sn(n-Bu)CuCNLi2
"Sn"
H
R
Me
"Cu"
H+
n-Bu
CuCNLi2
SnBu3
OH
+
SnBu3
CuCNLi2
OH
n-Bu
H+
H
R
"Sn"
Me
"Cu"
H
SnBu3
OH
SnBu3
H
OH
Kinetic
Thermodynamic

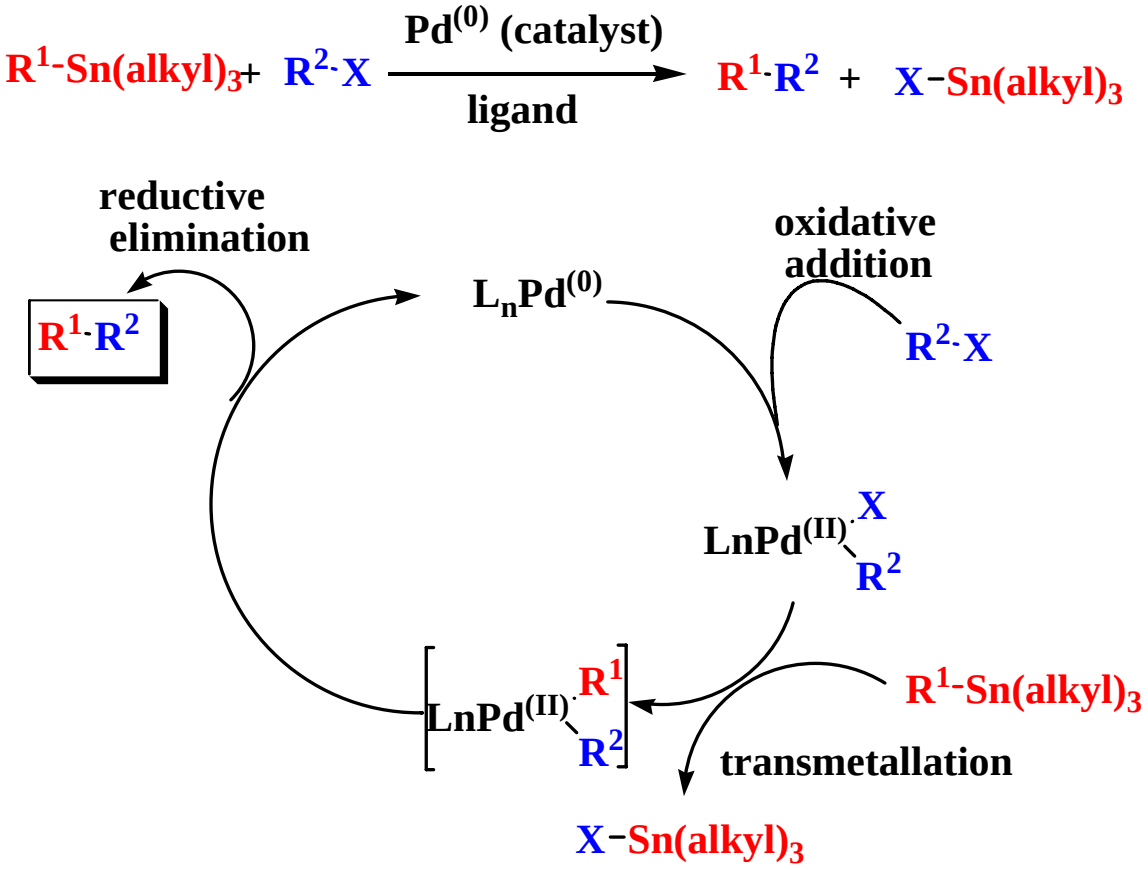
Horner-Wadsworth-Emmons Olefination



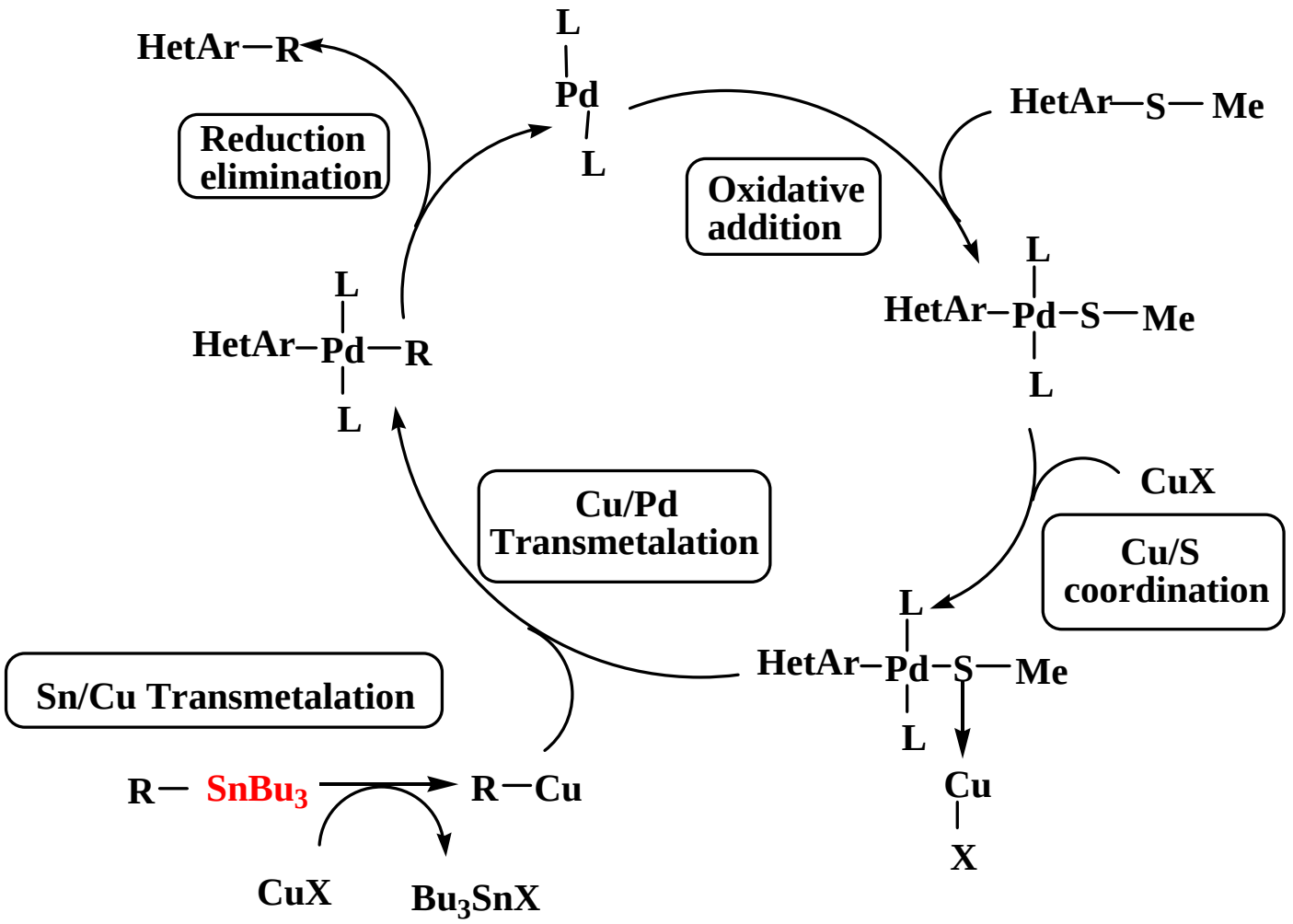
Horner-Wadsworth-Emmons Olefination-Still-Gennari Modification



Stille Coupling

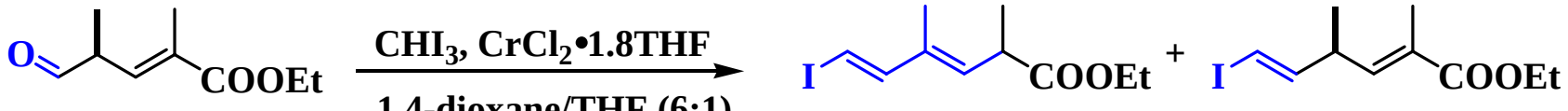


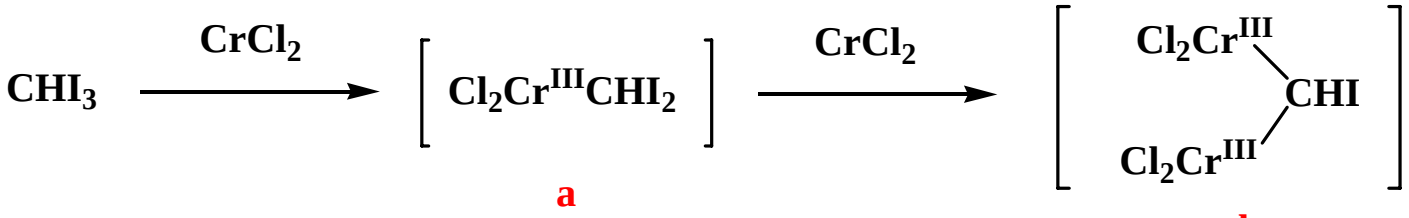
Possible Palladium Catalytic Coupling Cycle



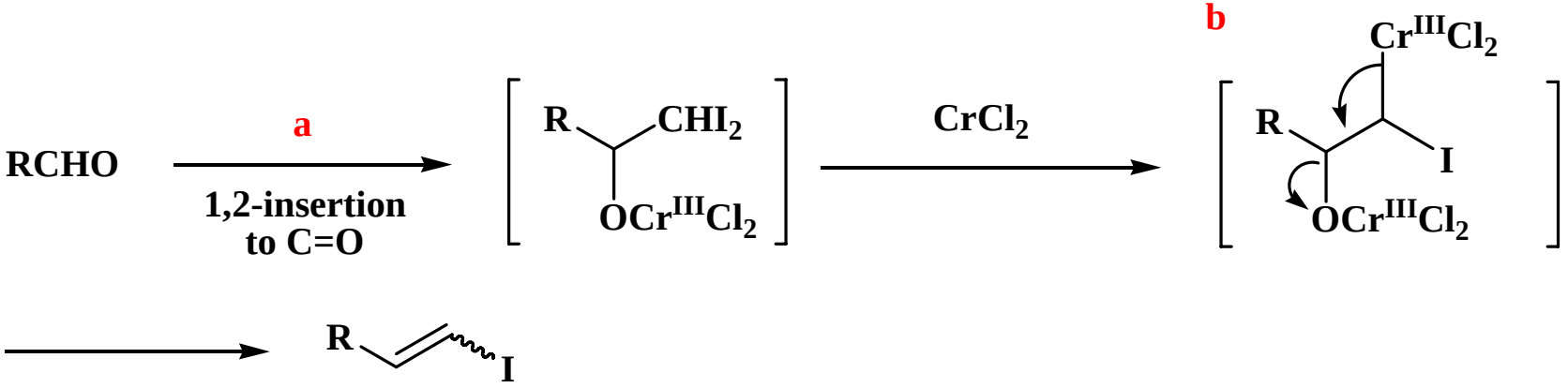
Alphonse, F. -A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803-805.

Takai Reaction

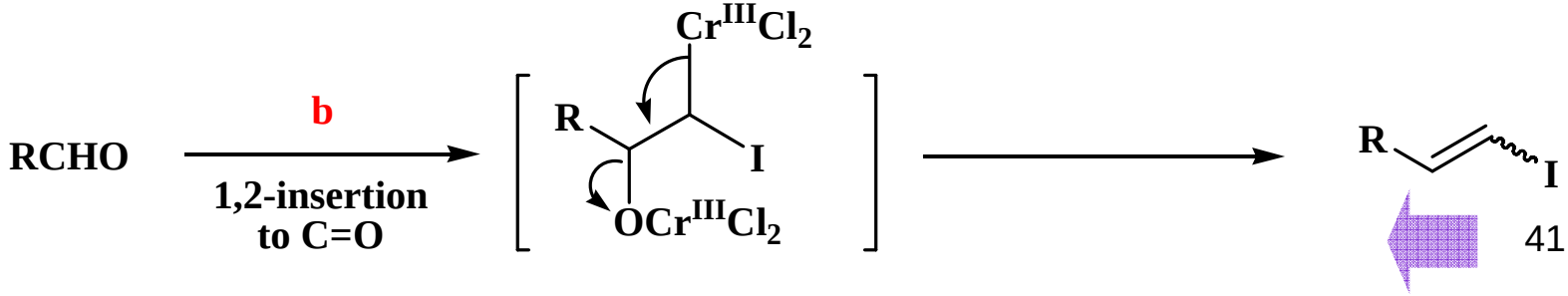


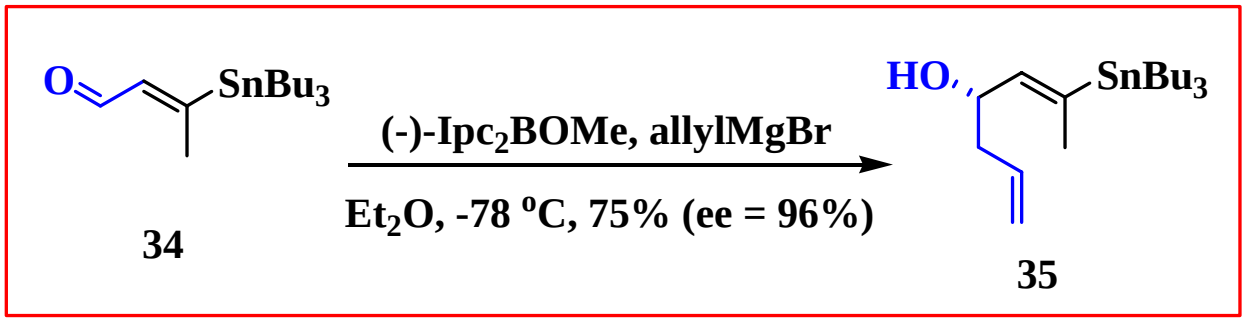


Path A



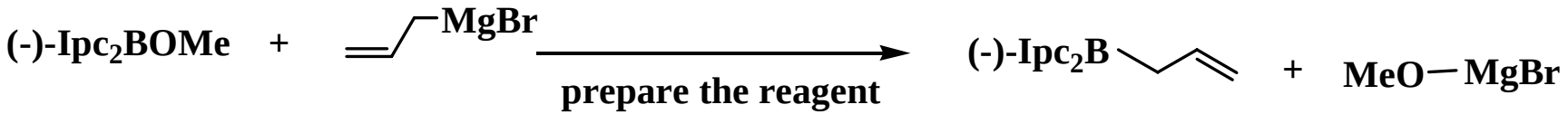
Path B

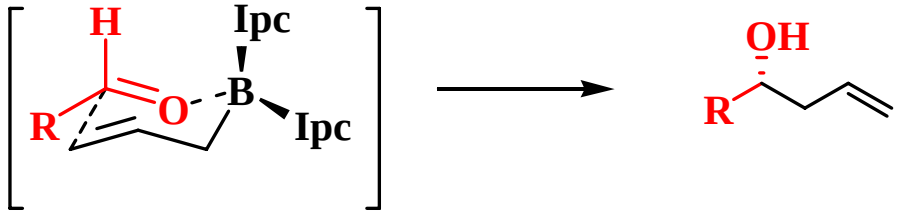



O
SnBu3
(-)-Ipc2BOMe, allylMgBr
Et2O, -78 °C, 75% (ee = 96%)
HO
SnBu3

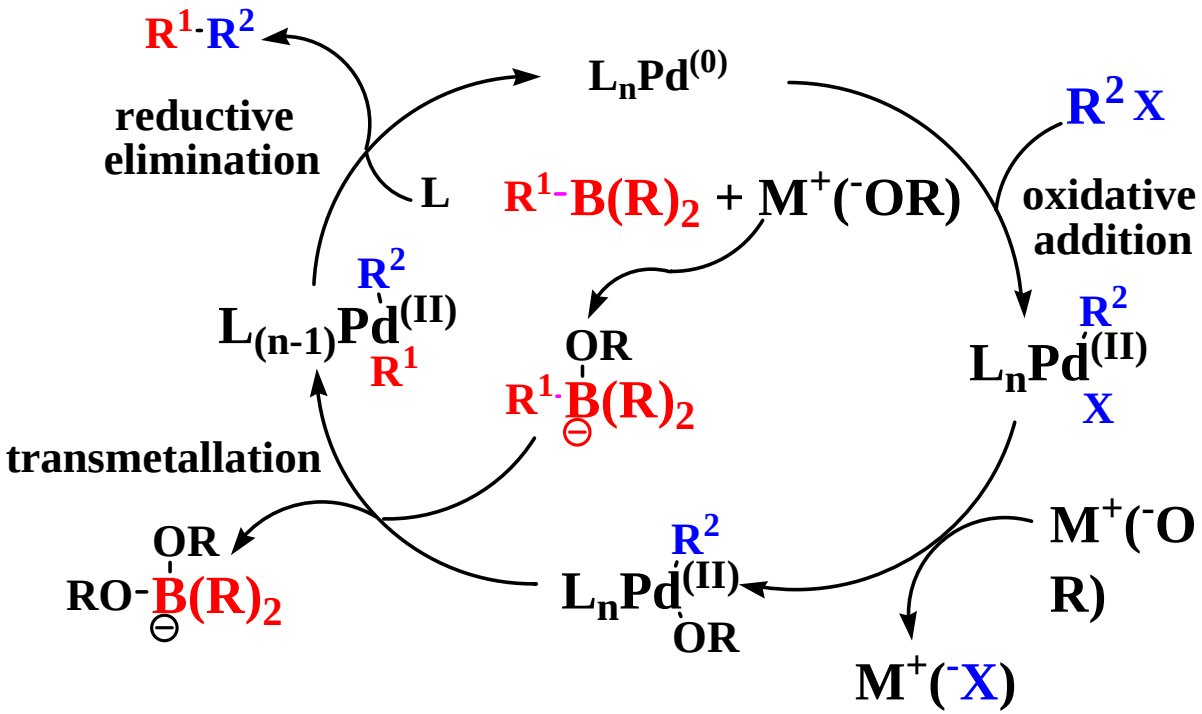
34

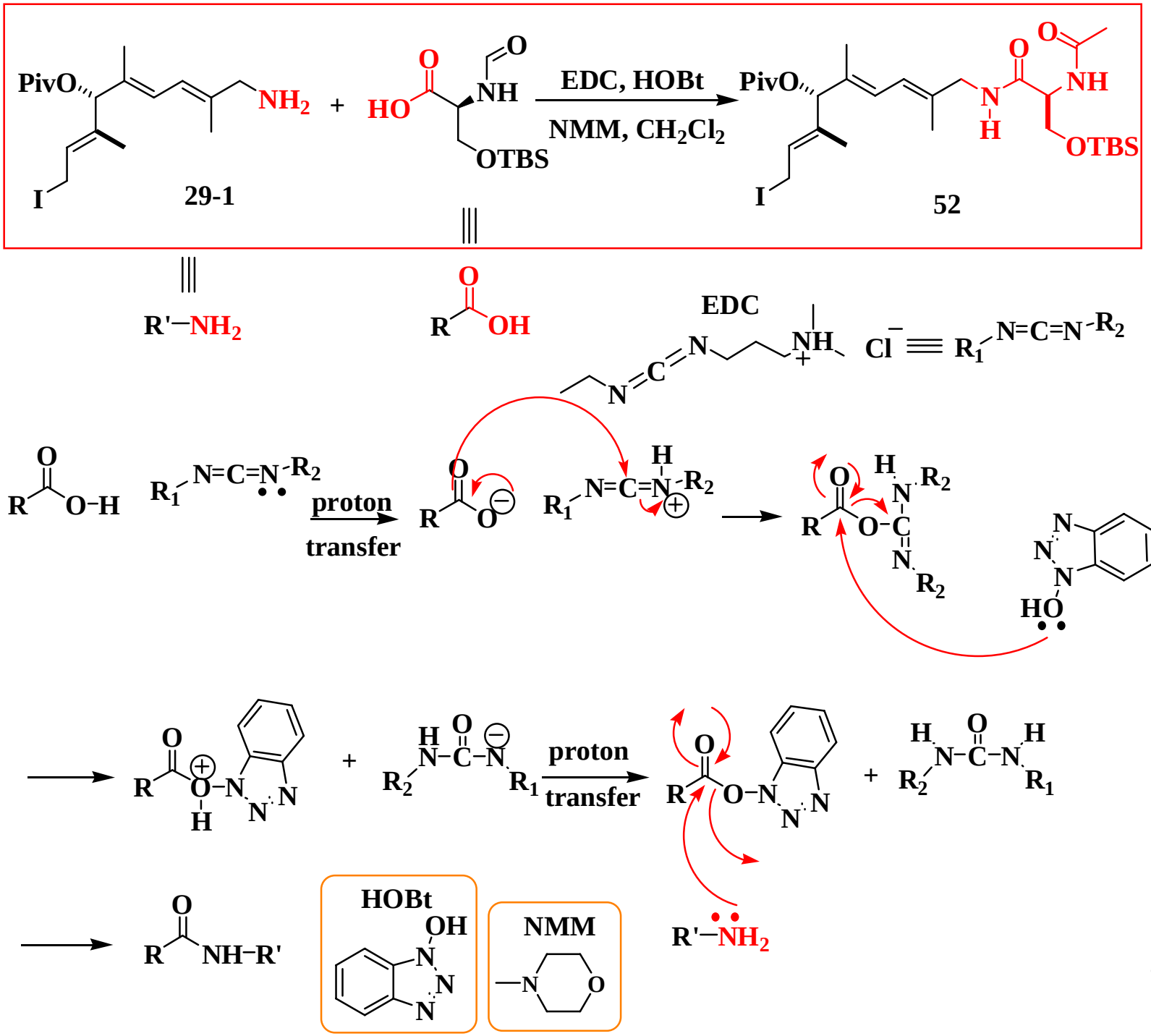
35


(-)-Ipc2BOMe
+
MgBr
prepare the reagent
(-)-Ipc2B
+
MeO
MgBr

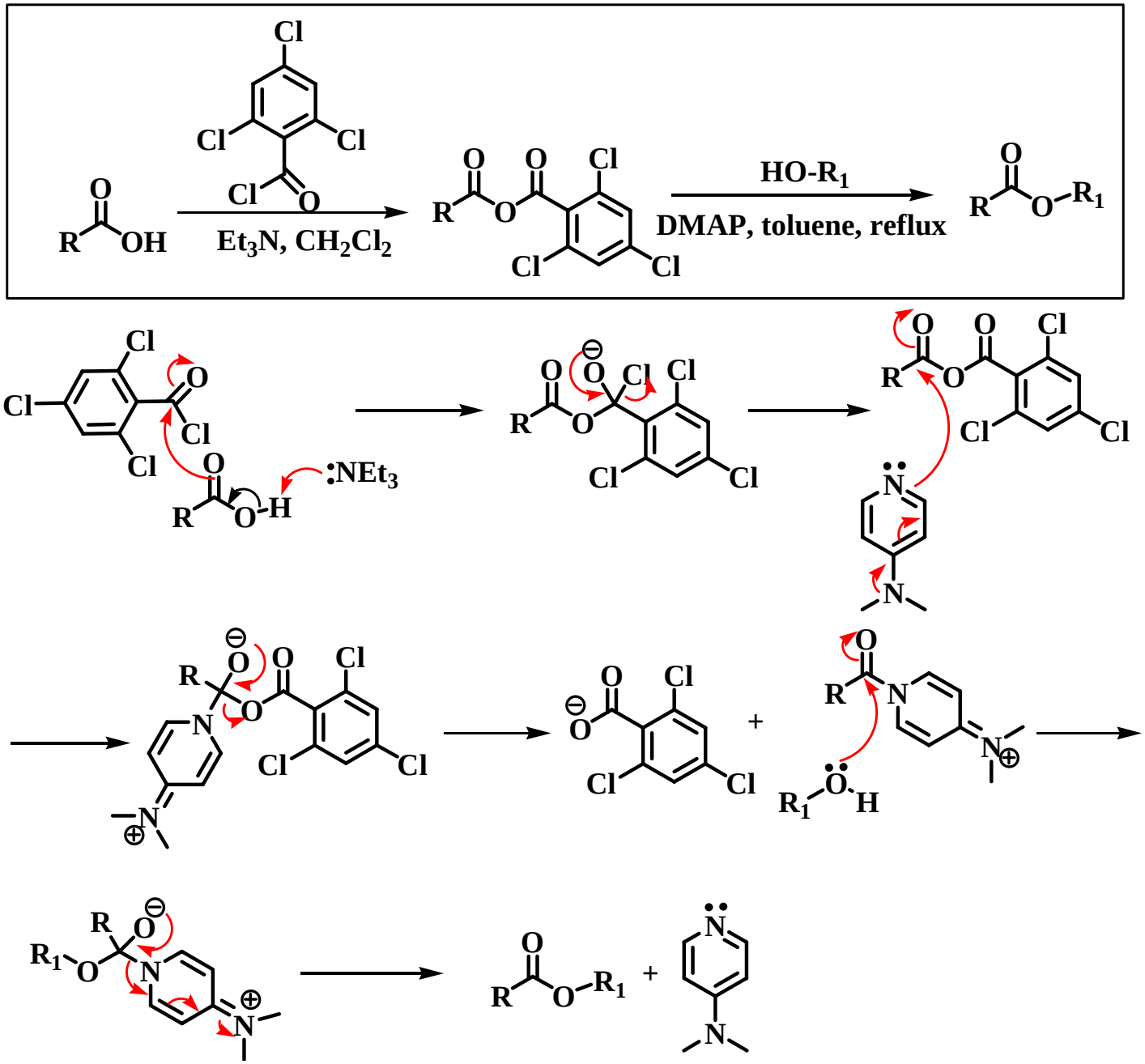

H
Ipc
R
O
B
Ipc
OH
R

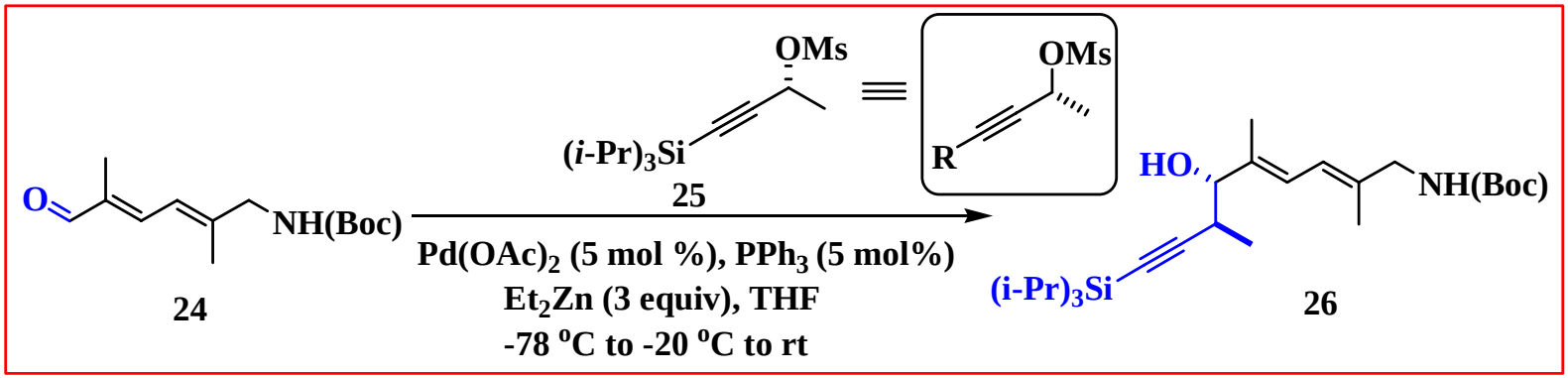
Suzuki Coupling



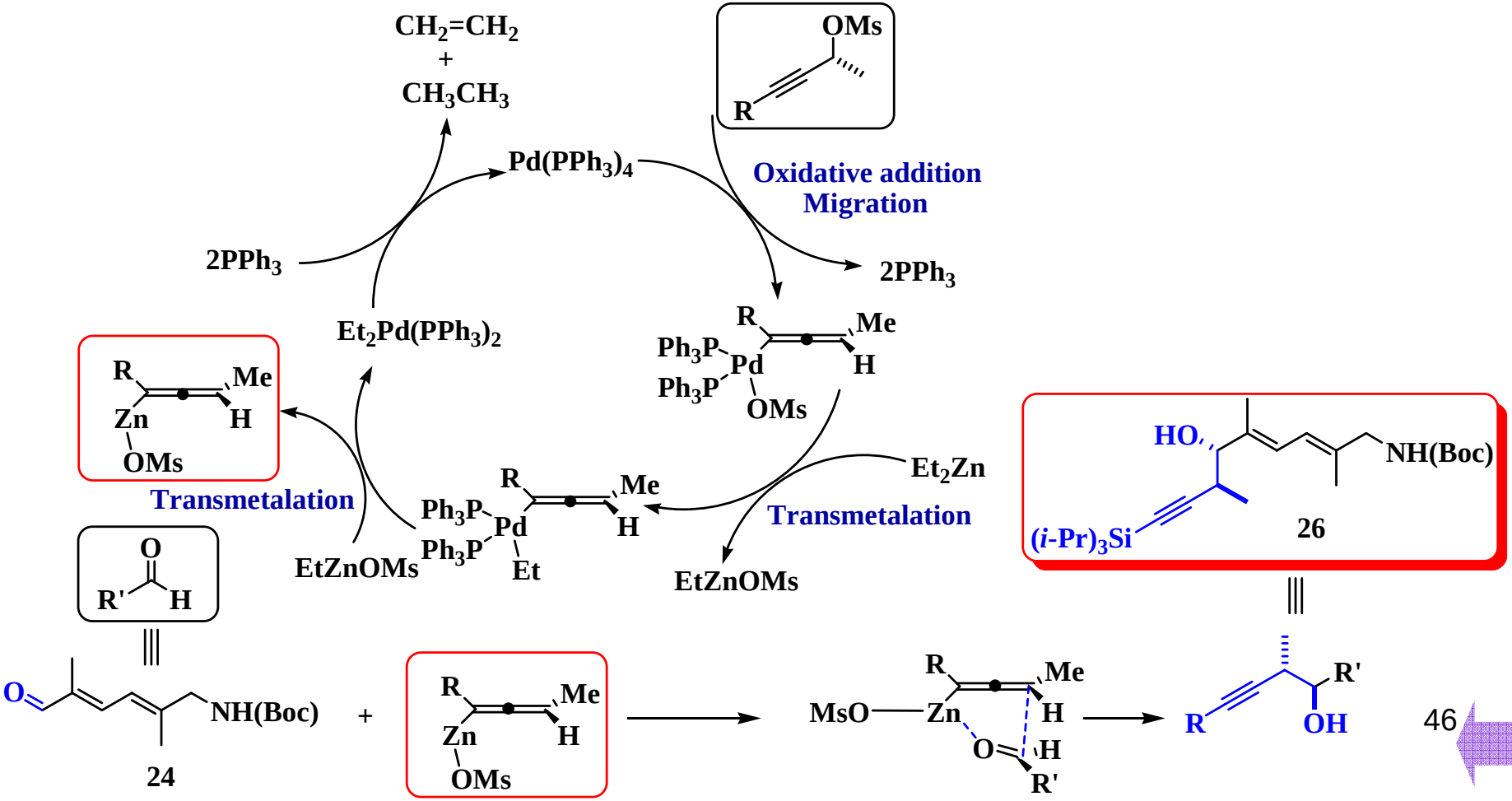

PivO
NH2
I
29-1
HO
O
NH
OTBS
EDC, HOBt
NMM, CH2Cl2
PivO
N
H
O
NH
OTBS
I
52
R'–NH2
R
OH
EDC
NH
Cl
R1
N=C=N
R2
R
O–H
proton
transfer
H
HO
HOBt
OH
NMM
R'–NH2
R
NH–R'

Yamaguchi Macrolactonization




OMs
(i-Pr)3Si
25
R
O
NH(Boc)
24
Pd(OAc)2 (5 mol %), PPh3 (5 mol%)
Et2Zn (3 equiv), THF
-78 °C to -20 °C to rt
HO
NH(Boc)
(i-Pr)3Si
26


Pd(OAc)2 + PPh3
Pd(PPh3)4 + Ac2O + Ph3PO


CH2=CH2
+
CH3CH3
OMs
R
Pd(PPh3)4
Oxidative addition
Migration
2PPh3
2PPh3
Et2Pd(PPh3)2
R
Me
Ph3P
Pd
Ph3P
H
OMs
R
Me
Zn
H
OMs
Transmetalation
EtZnOMs
R
Me
Ph3P
Pd
Ph3P
H
Et
Et2Zn
Transmetalation
EtZnOMs
HO
NH(Boc)
(i-Pr)3Si
26
O
R'
H
O
NH(Boc)
24
+
R
Me
Zn
H
OMs
R
Me
MsO
Zn
H
O
H
R'
R
R'
OH

Noyori asymmetric hydrogenation