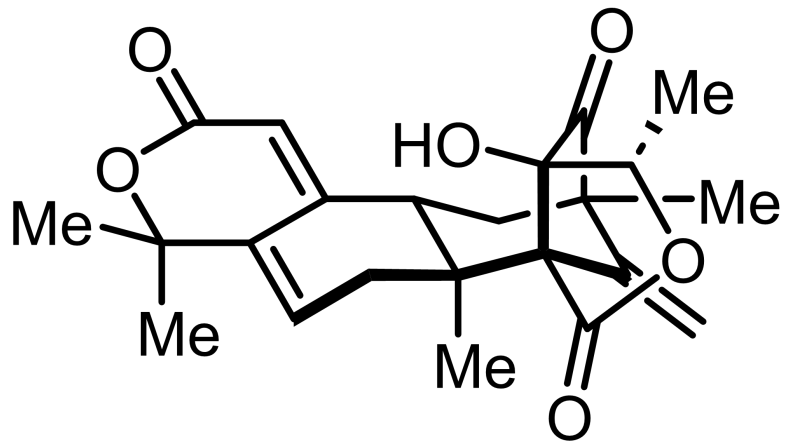
Total Synthesis of (±)-Dhilirolide U



(±)-Dhilirolide U

Wei Wang
2026.3.19

Henrik R. Wilke et al., *J. Am. Chem. Soc*. **2026**, *148*, 6, 5916-5922.

Introduction of Prof. Dr. Erick M. Carreira

1984 The University of Illinois at Urbana-Champaign, B.S.
Research advisor: Assiatant Professor Scott E. Denmark
1990 Harvard University, Ph.D.
Research advisor: Professor David A. Evans
1990-1992 California Institute of Technology, Postdoctoral Fellow
Research advisor: Professor Peter Dervan

Department of Chemistry, California Institute of Technology
1992 Assistant Professor
1996 Associate Professor
1997 Professor

Department of Chemistry, ETH Zürich
1998 Professor

Introduction of (±)-Dhilirolide U

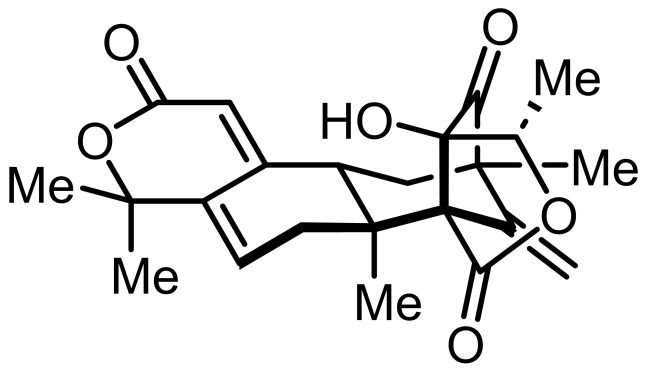
Isolation: from ***Penicillium purpurogenum*** AN13 by Lin and Fan et al. in 2024.

Structure:

a unique 6/6/6/5/5-fused ring sistem

a highly substituted bicyclo[3.2.1]octane core

an overall dense oxidation pattern

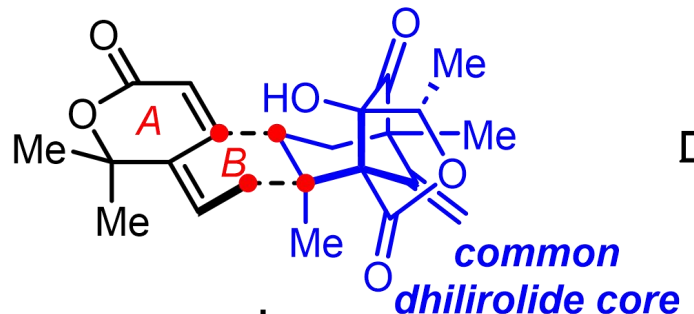


(±)-Dhilirolide U

Penicillium purpurogenum fungus

Zhaolun Sun et al.,*J.Am.Chem.Soc.***2024**,146,30242−30251.
Henrik R. Wilke et al., *J. Am. Chem. Soc*. **2026**, *148*, 6, 5916-5922.

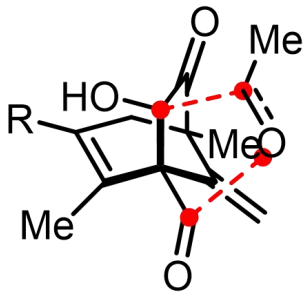
Retrosynthetic Analysis of Dhilirolide U



common dhilirolide core

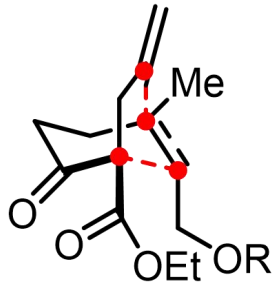
I

A/B ring installation



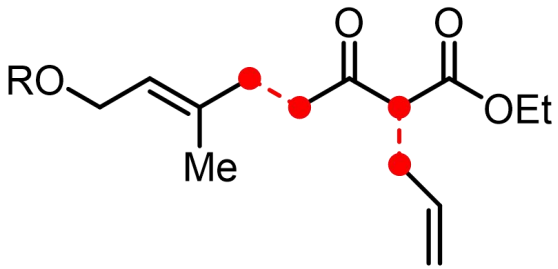
II

aldol reaction & lactonization



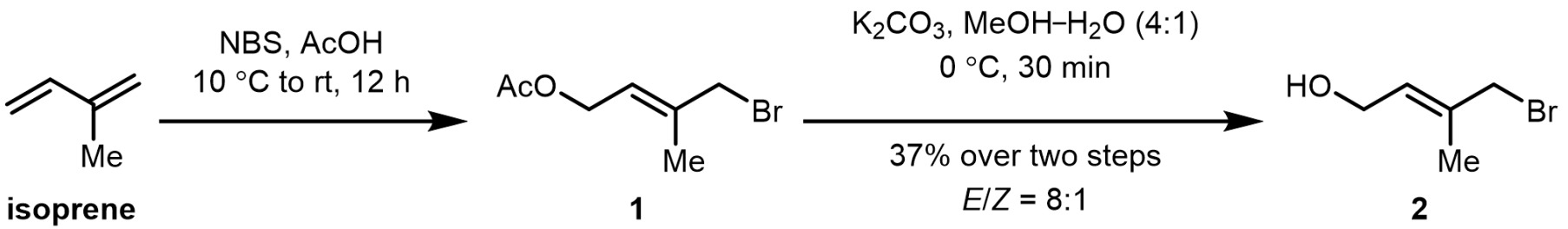
III

oxidative radical cyclization

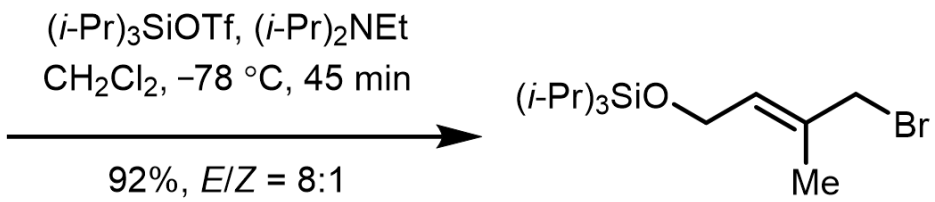


IV

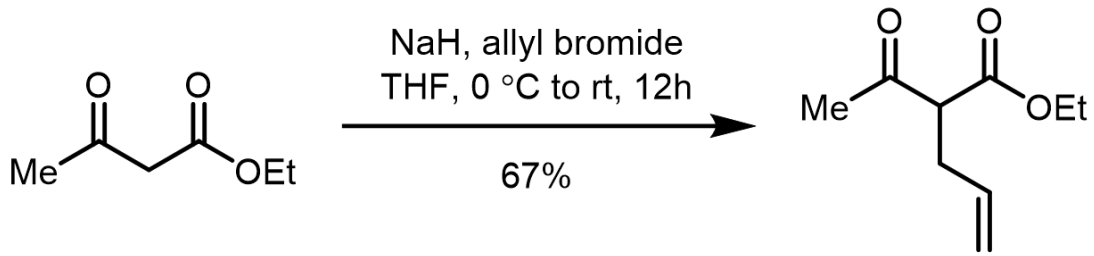
Fragment Preparation



isoprene **1** **2**

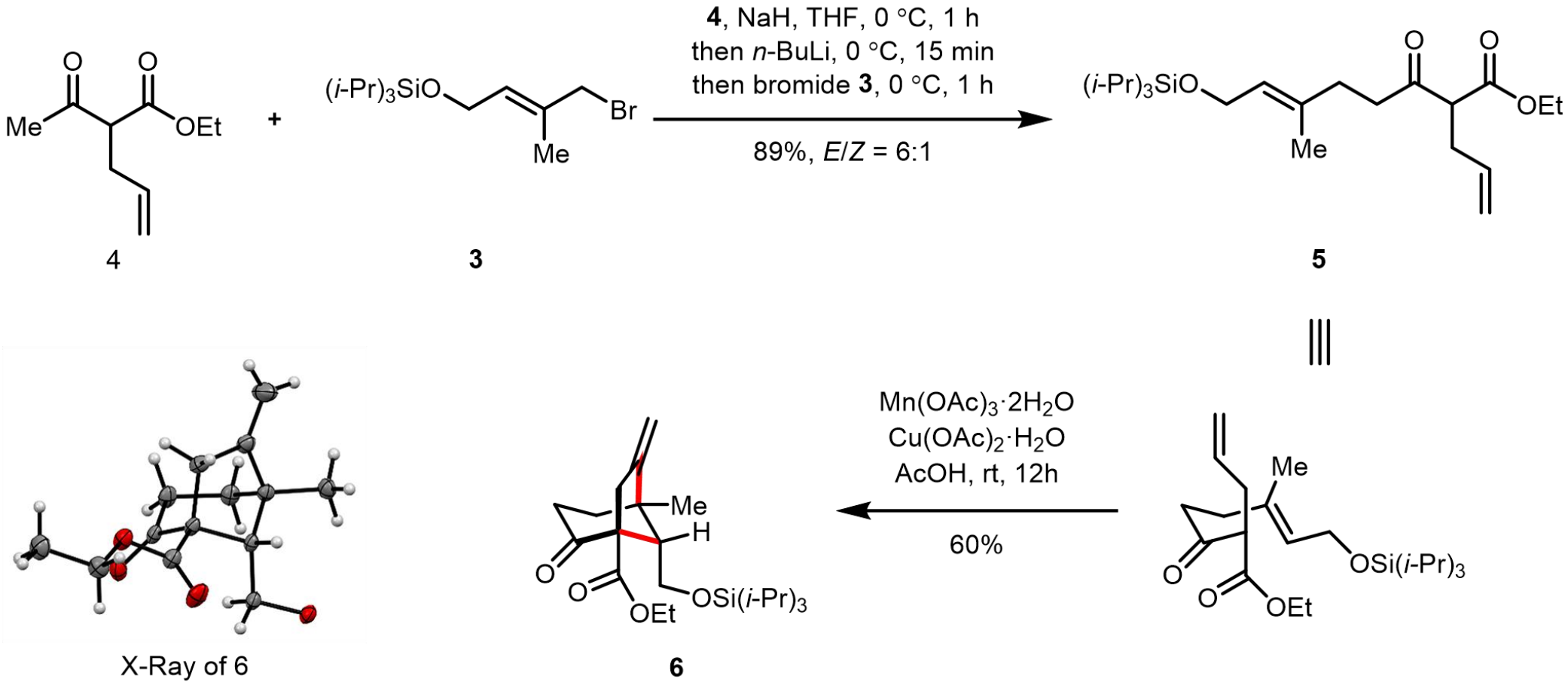


3

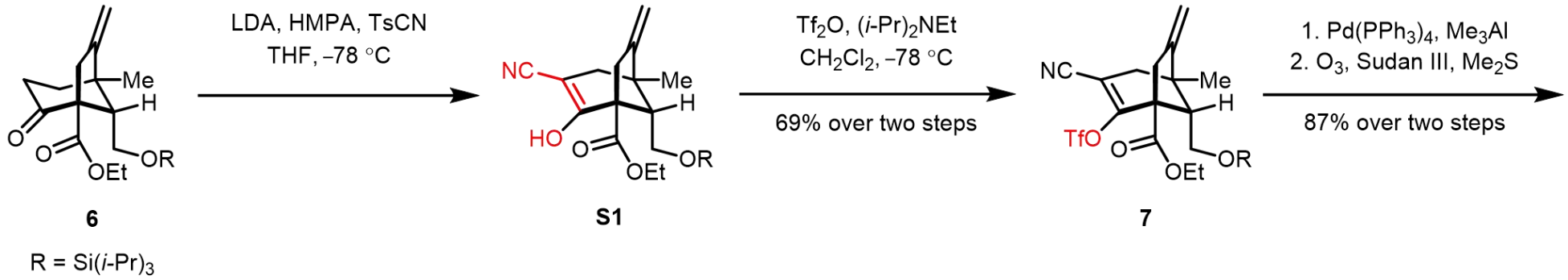


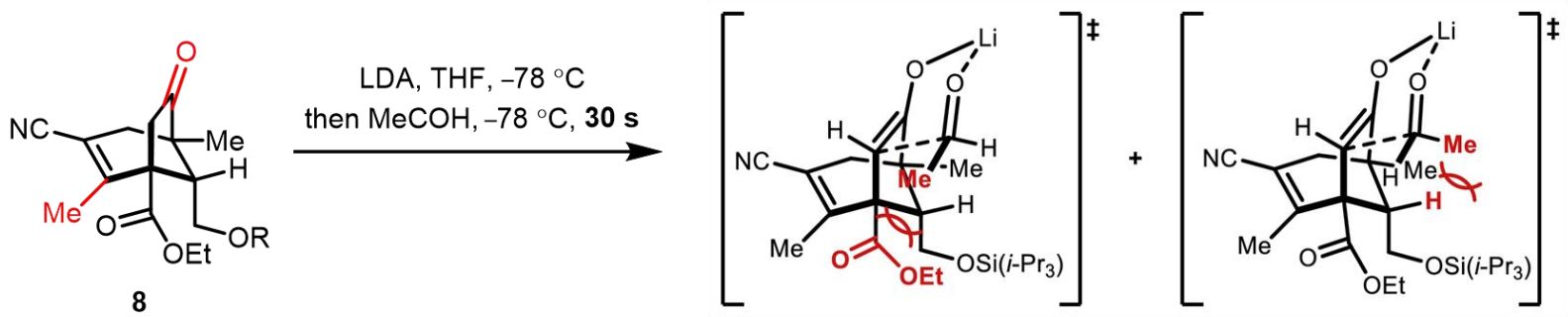
Ethyl acetoacetate **4**

Synthesis of Bicyclo[3.2.1]octane Core



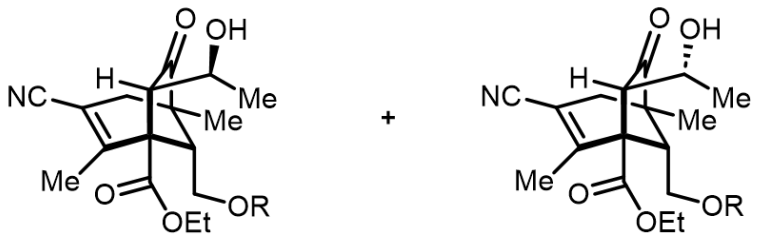
Synthesis of Lactone 13





sterical repulsion of the Me with ethyl ester **disfavored**

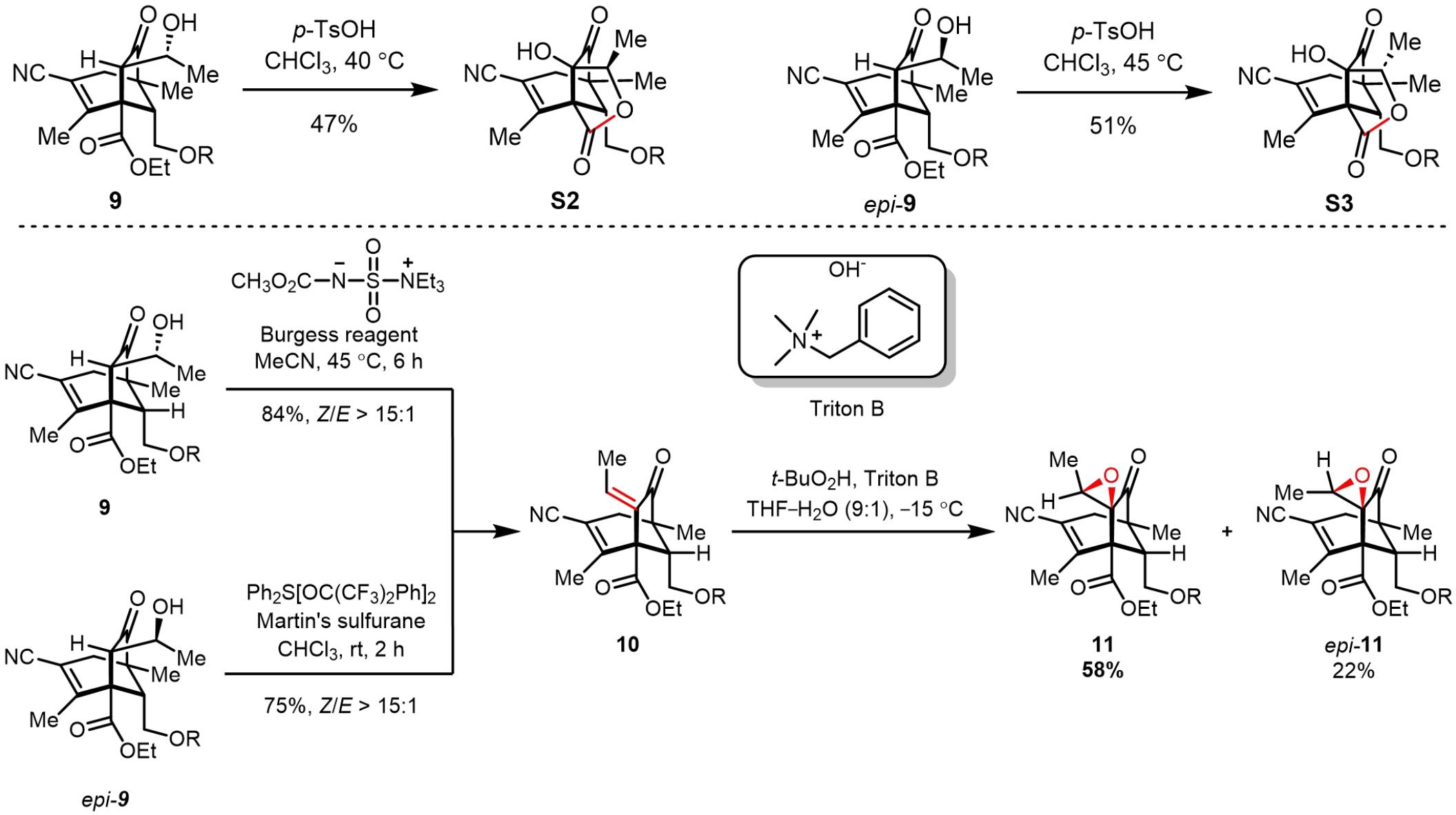
slight repulsion of the Me with methano bridge **favored**



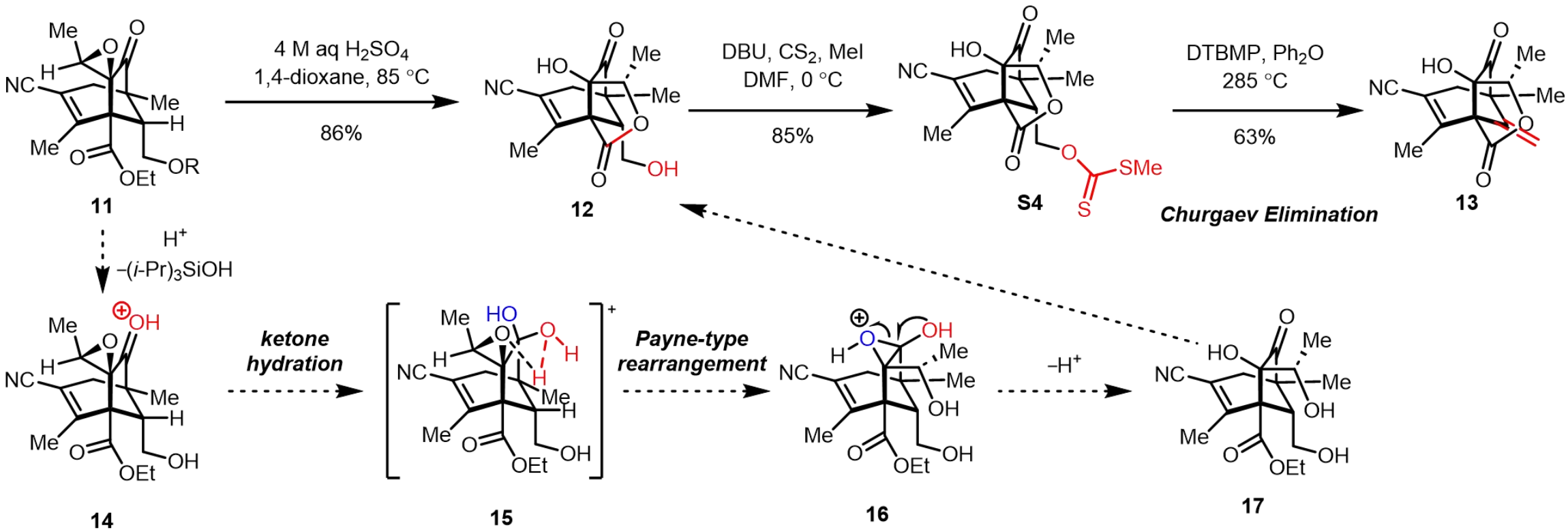
epi-**9**, 18%

9, 61%

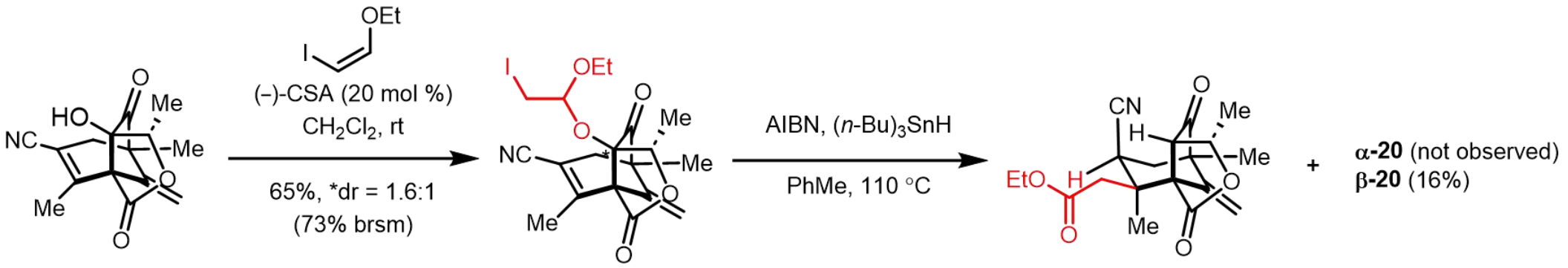
Synthesis of Lactone 13



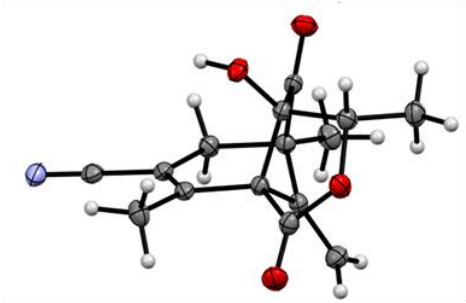
Synthesis of Lactone 13



Installation of Vicinal Quaternary Carbon Centers



13

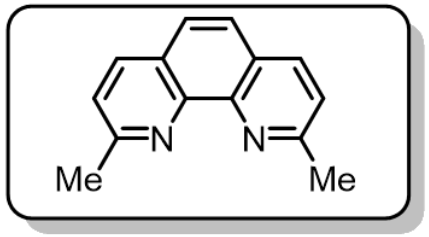


X-ray of **13**

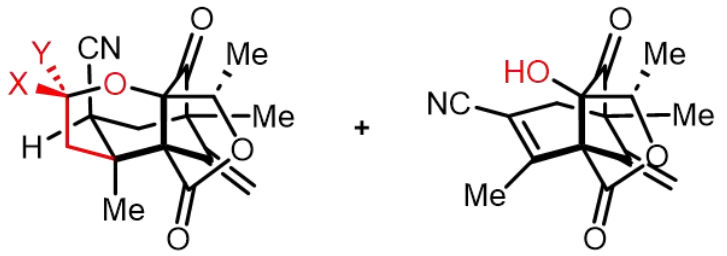
18

19
41%

$NiCl_2$·glyme
neocuproine
Rieke Zn, MeOH, 50 °C



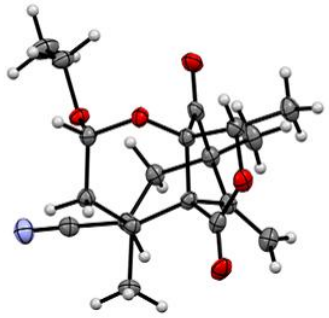
neocuproine



57%, α/β = 1:1.6
α-20 X = H, Y = OEt
β-20 X = OEt, Y = H

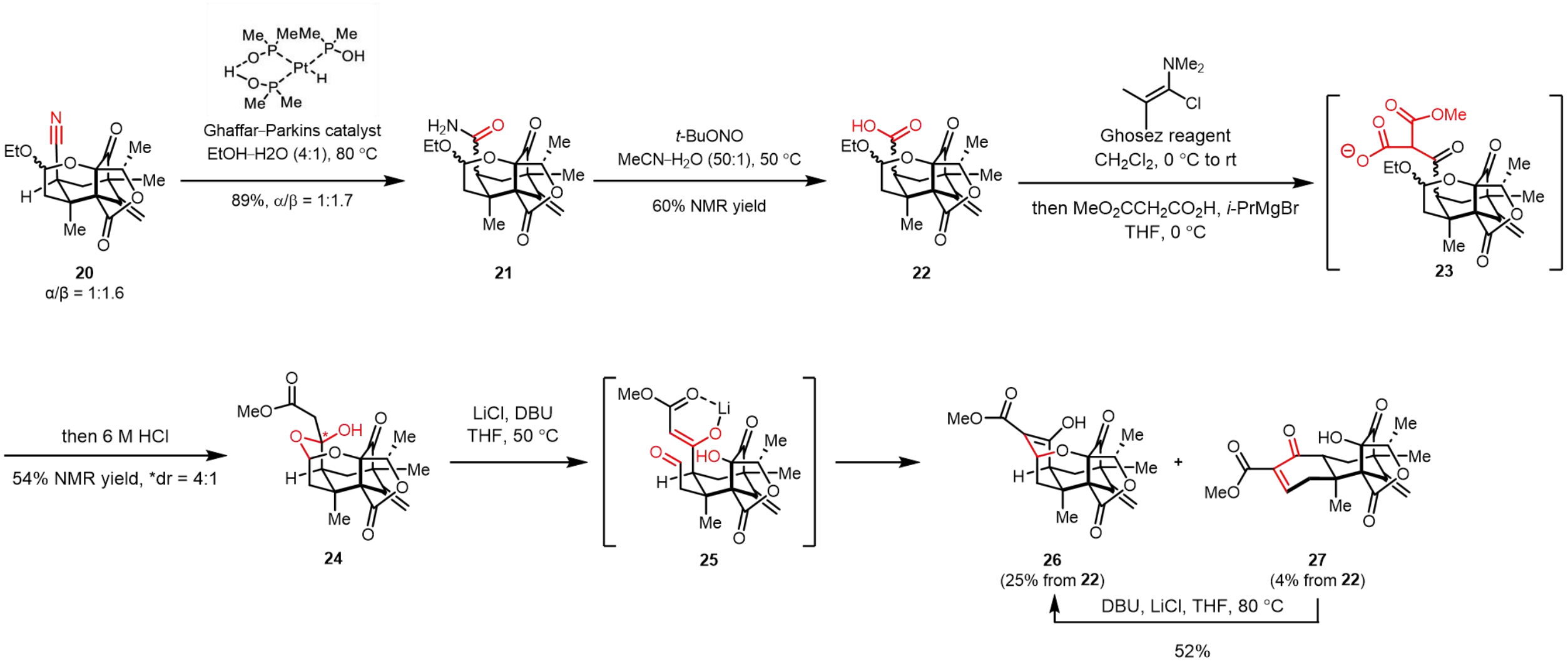
+

13
18%

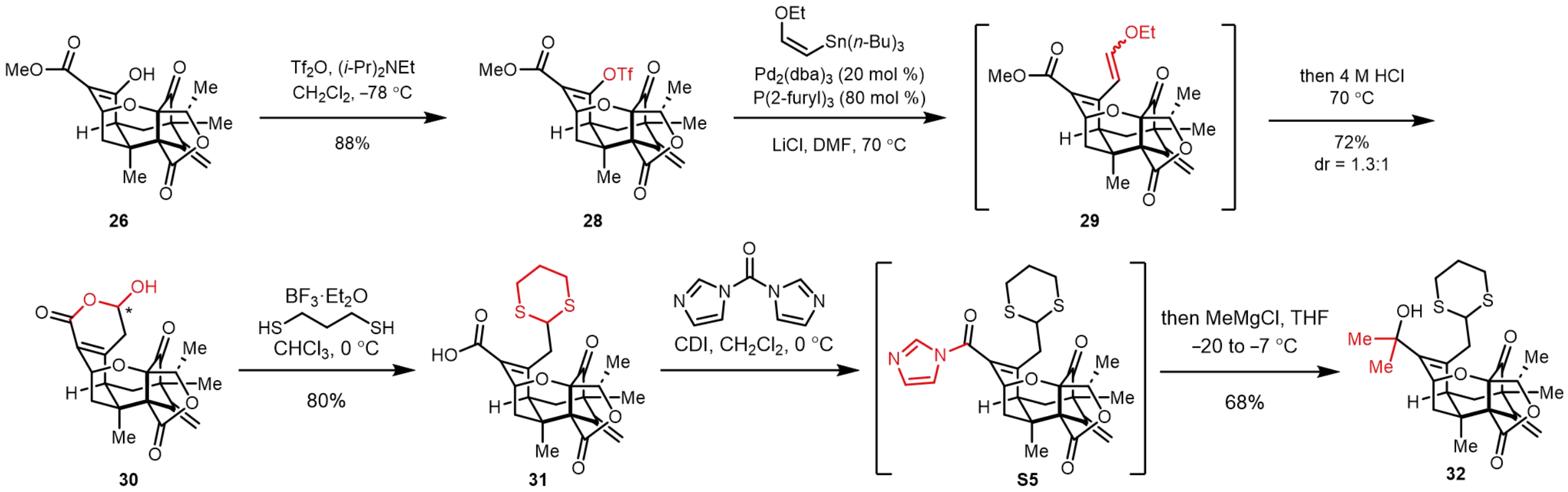


X-ray of **α-20**

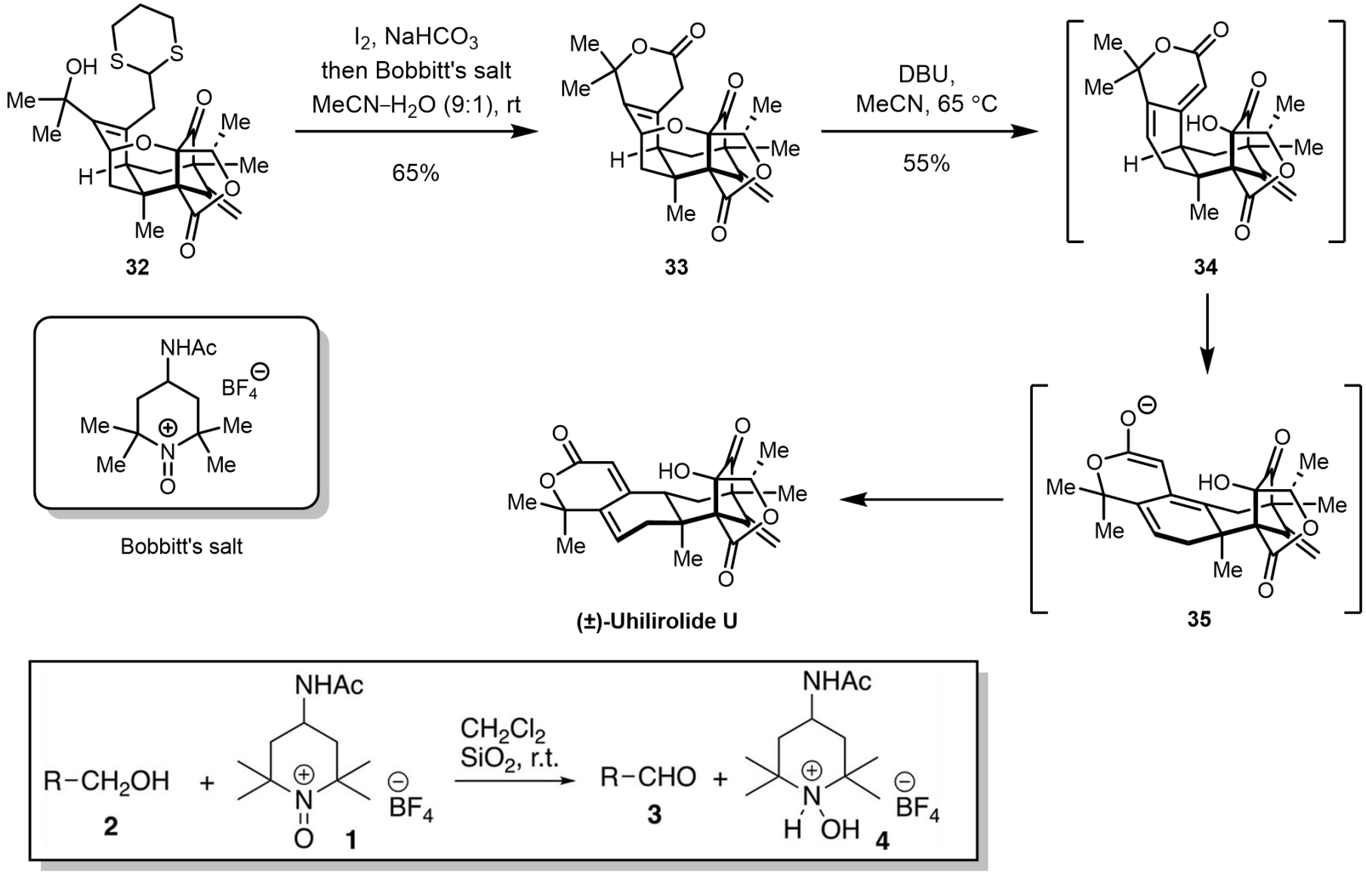
Construction of the B-Ring

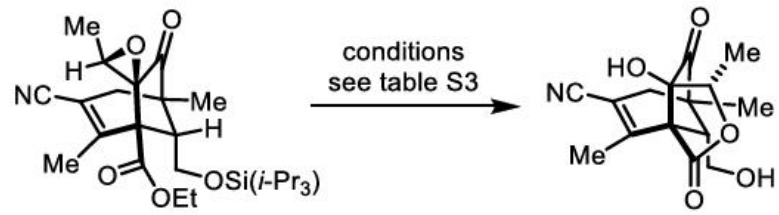


Completion of the Synthesis



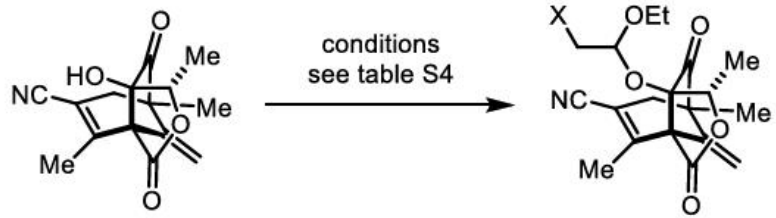
Completion of the Synthesis



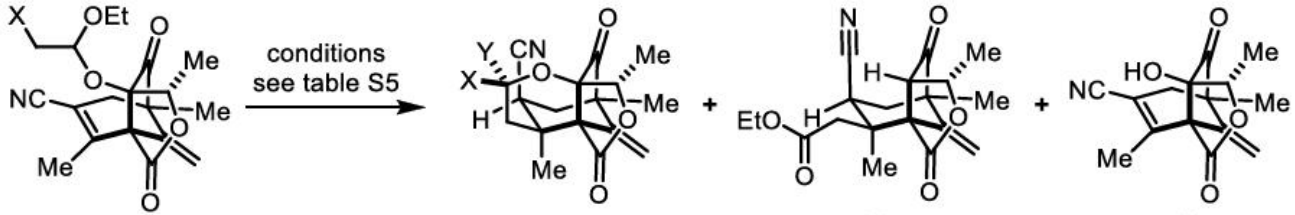


11 12

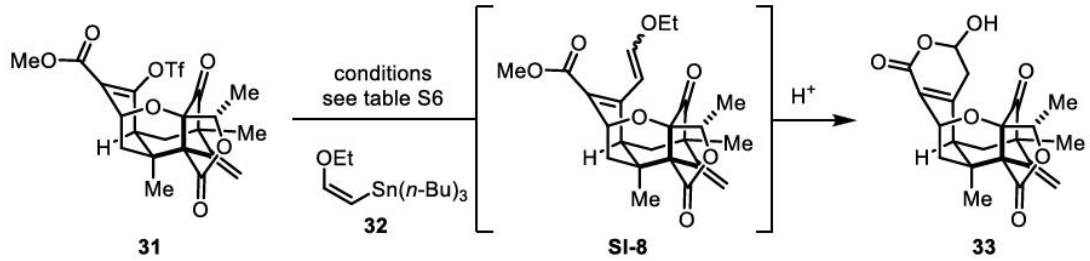
Entry	Selection of Investigated Conditions	Outcome
1	$Yb(OTf)_3$, wet THF, reflux	5%
2	$HClO_4$ (30 equiv), THF–H_2O (5:1), 95 °C (sealed flask)	27%
3	TFA–H_2O–THF (1:1:2), 95 °C (sealed flask)	28%
4	TFA–H_2O–THF (2:1:5), 95 °C (sealed flask)	41%
5	TFA–H_2O–THF (1:1:2), MW, 140 °C	decomposition
6	HCl (50 equiv), THF–H_2O (3:1), 65 °C	33%
7	H_2SO_4 (10 equiv), 1,4-dioxane–H_2O (3:1), 105 °C	58%
8	H_2SO_4 (10 equiv), 1,4-dioxane–H_2O (3:1), 95 °C	70%
9	H_2SO_4 (10 equiv), 1,4-dioxane–H_2O (3:1), 85 °C	10 mg: 83% 29.4 g-scale (isolated 86%)



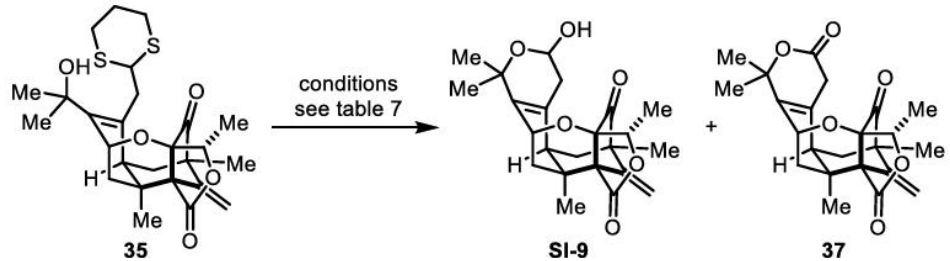
Entry	Selection of Investigated Conditions	Outcome
1	NBS (3 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), 0 °C to rt	**SI-7** (24%) **13** (68%)
2	NBS (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), 0 °C to rt	**SI-7** (32%) **13** (55%)
3	NBS (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), –50 to –25 °C	**SI-7** (44%) **13** (38%)
4	1,2-dibromo-1-ethoxyethane, *N*,*N*-dimethylaniline, CH_2Cl_2 (0.2 M), 0 °C to 40 °C	**SI-7** (17%) **13** (70%)
5	1,3-Dibromo-5,5-dimethylhydantoin (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), –20 °C to rt	**SI-7** (7%) **13** (79%)
6	Dibromoisocyanuric acid (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), –20 °C to rt	**SI-7** (<5%)
7	*N*-Bromosaccharin (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), –20 °C to rt	**SI-7** (<5%)
8	NIS (5 equiv), ethyl vinyl ether (10 equiv), CH_2Cl_2 (0.2 M), 0 °C to rt	messy reaction
9	(–)-CSA (20 mol %), (*Z*)-1-bromo-2-ethoxyethene (3 equiv), CH_2Cl_2 (0.2 M), rt	**SI-7** (52%) **13** (43%)
10	(–)-CSA (20 mol %), (*Z*)-1-bromo-2-ethoxyethene (2.0 equiv), CH_2Cl_2 (0.4 M), rt	**SI-7** (85%) **13** (4%) on 9.27 mmol scale
11	(–)-CSA (20 mol %), (*Z*)-1-iodo-2-ethoxyethene (2.0 equiv), CH_2Cl_2 (0.4 M), rt	**19** (68%, isolated 65%) **13** (13%, isolated 11%) on 403 µmol scale



Entry	Selection of Investigated Conditions	Outcome
1	**19** (X = I), AIBN (50 mol%), (n-Bu)$_3$SnH (5.0 equiv), PhMe, 110 °C, sealed flask	**α-21** (not observed) **β-21** (19%, isolated 16%) **20** (45%, isolated 41%) (messy reaction)
2	**19** (X = I), AIBN (50 mol%), Ph$_3$SnH (5.0 equiv), PhMe, 110 °C, sealed flask	**α-21** (not observed) **β-21** (11%) **20** (29%) (messy reaction)
3	**19** (X = I), Et$_3$B (50 mol %), (n-Bu)$_3$SnH (5.0 equiv), PhMe, –78 °C	**α-21** (7%) **β-21** (17%) (messy reaction)
4	**19** (X = I), Ir[dF(CF$_3$)ppy$_2$](dtbbpy)PF$_6$ (10 mol %), (i-Pr)$_2$NEt, H$_2$O (20 equiv), MeCN, rt, blue LED	**α-21** (18%) **β-21** (34%) **13** (4%)
5	**19** (X = I), NiCl$_2$·glyme (20 mol %), neocuproine (24 mol %), zinc dust, MeOH, reflux	**α-21** (<5%) **β-21** (<5%) **13** (11%)
6	**19** (X = I), NiCl$_2$·glyme (20 mol %), neocuproine (24 mol %), zinc nanopowder (Sigma Aldrich), MeOH, 50 °C	**α-21** (25%, isolated 22%) **β-21** (41%, isolated 37%) **13** (15%)
7	**19** (X = I), NiCl$_2$·glyme (20 mol %), neocuproine (24 mol %), Rieke zinc in THF, MeOH, 50 °C to 60 °C	**α-21** (7%) **β-21** (12%) **13** (65%)
8	**19** (X = I), NiCl$_2$·glyme (20 mol %), neocuproine (24 mol %), Rieke zinc, MeOH, 50 °C	**α-21** (24%, isolated 22%) **β-21** (38%, isolated 35%) **13** (21%, isolated 18%) on 5.28 mmol scale
9	**SI-7** (X = Br), NiCl$_2$·glyme (20 mol %), neocuproine (24 mol %), Rieke zinc, MeOH, reflux	**α-21** (16%) **β-21** (23%) **13** (42%)



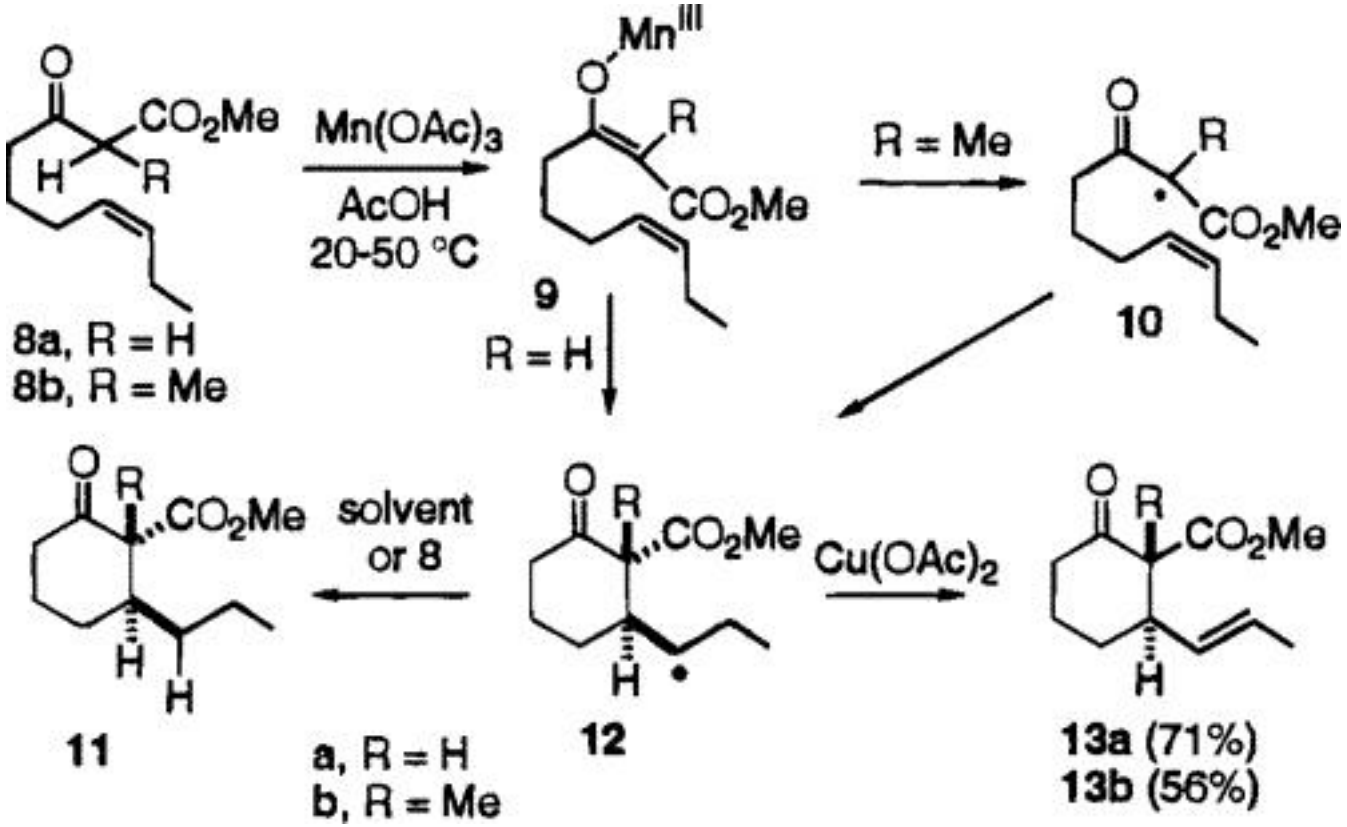
Entry	Conditions Investigated	Outcome
1	$Pd(PPh_3)_4$ (20 mol %), LiCl (5 equiv), **32** (5 equiv), THF, 65 °C	**SI-8** (<10%)
2	$Pd_2(dba)_3$ (20 mol %), $AsPh_3$ (80 mol %), LiCl (5 equiv), **32** (5 equiv), THF, 65 °C	**SI-8** (<10%)
3	$Pd_2(dba)_3$ (20 mol %), $AsPh_3$ (80 mol %), LiCl (5 equiv), **32** (5 equiv), 1,4-dioxane, 90 °C	**SI-8** (28%)
4	$Pd(OAc)_2$ (20 mol %), XPhos (40 mol %), CsCl (10 equiv), Cs_2CO_3 (50 mol %), **32** (5 equiv), 1,4-dioxane, 90 °C	**SI-8** (55%) Isolated 38%
5	$Pd(OAc)_2$ (20 mol %), XPhos (40 mol %), CsCl (10 equiv), Cs_2CO_3 (50 mol %), **32** (5 equiv), 1,4-dioxane, 90 °C; then 4 M aq HCl, 60 °C	**33** (47%) Isolated 40%
6	$Pd_2(dba)_3$ (20 mol %), P(2-furyl)$_3$ (80 mol %), **32** (5 equiv), 1,4-dioxane, 75 °C	**SI-8** (67%)
7	$Pd_2(dba)_3$ (20 mol %), P(2-furyl)$_3$ (80 mol %), **32** (5 equiv), LiCl (5 equiv), 1,4-dioxane, 75 °C	**SI-8** (76%)
8	$Pd_2(dba)_3$ (20 mol %), P(2-furyl)$_3$ (80 mol %), **32** (5 equiv), DMF, 75 °C	**SI-8** (81%) Isolated 55%
9	$Pd_2(dba)_3$ (20 mol %), P(2-furyl)$_3$ (80 mol %), **32** (5 equiv), 1,4-dioxane, 80 °C; then 4 M aq HCl, 60 °C	**33** (72%) Isolated 60%
10	$Pd_2(dba)_3$ (20 mol %), P(2-furyl)$_3$ (80 mol %), **32** (5 equiv), LiCl (5 equiv), DMF, 70 ; then 4 M aq HCl, 70 °C	**33** (76%) Isolated 72% (from 52.3 mg of **33**)



35 **SI-9** 37

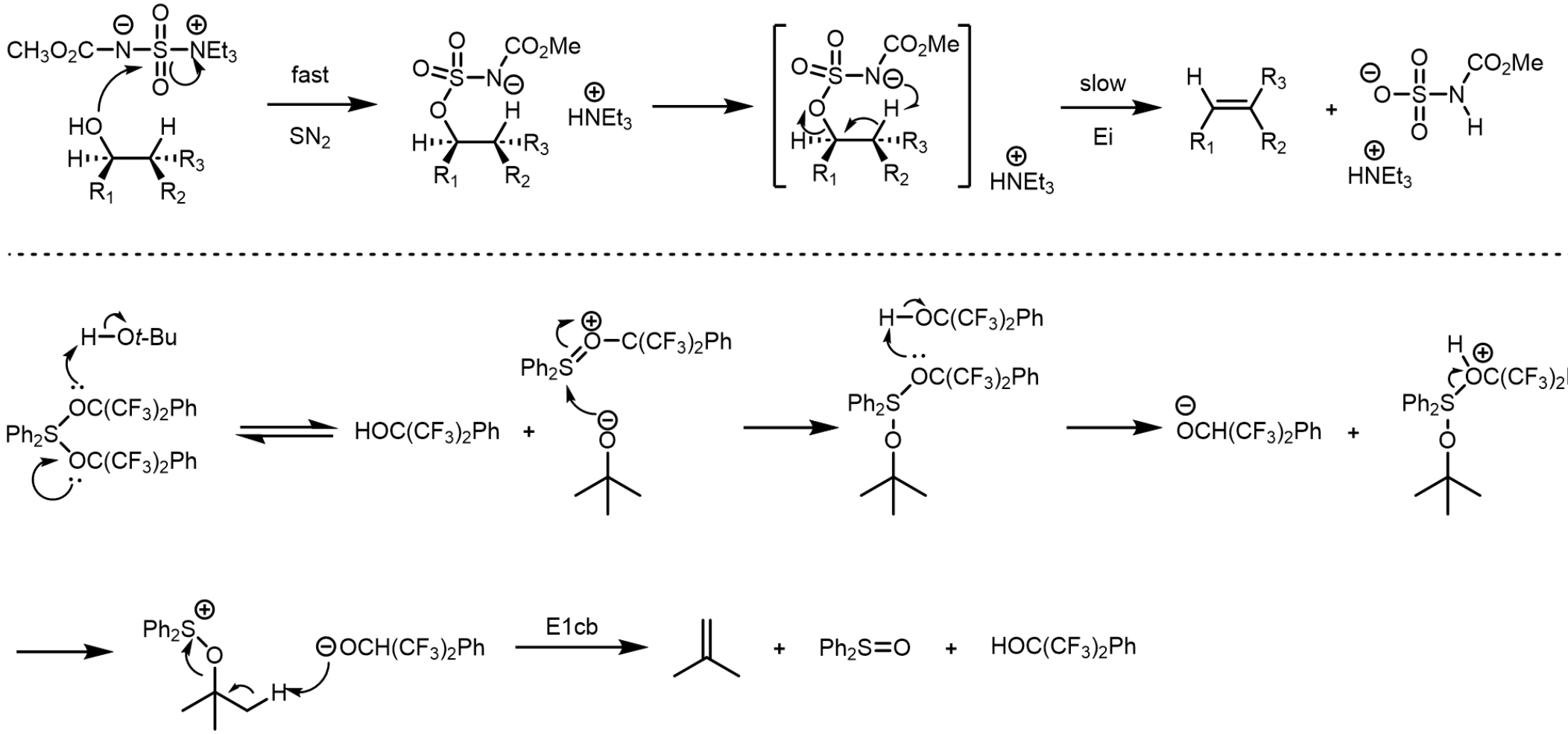
Entry	Conditions Investigated	Outcome
1	$PhI(OCOCF_3)_2$, MeCN–H_2O, 0 °C	**SI-9** (<5%)
2	NBS, aq acetone; then TEMPO	**SI-9** (31%)
3	Selectfluor, MeCN–H_2O (20:1), 0 °C	**SI-9** (<5%)
4	DMP, MeCN–H_2O–CH_2Cl_2, 60 °C	**SI-9** (23%) **37** (<5%)
5	DDQ, MeCN–H_2O (9:1), reflux	**SI-9** (7%)
6	I_2 (5 equiv), $NaHCO_3$ (10 equiv), acetone–H_2O (5:1), rt	**SI-9** (67%) **37** (17%)
7	I_2 (10 equiv), $NaHCO_3$ (20 equiv), acetone–H_2O (5:1), rt	**SI-9** (56%) **37** (23%)
8	I_2 (50 equiv), $NaHCO_3$ (100 equiv), acetone–H_2O (5:1), rt	**SI-9** (28%) **37** (55%) Isolated 43% of **37**
9	I_2 (50 equiv), $NaHCO_3$ (100 equiv), acetone–H_2O (5:1), rt, then TEMPO (5 equiv)	**SI-9** (25%) **37** (55%)
10	I_2 (10 equiv), $NaHCO_3$ (20 equiv), acetone–H_2O (5:1), rt, then Bobbitt's salt (10 equiv)	**SI-9** (18%) **37** (58%)
11	I_2 (5 equiv), $NaHCO_3$ (10 equiv), MeCN–H_2O (9:1), rt, then Bobbitt's salt (10 equiv)	**SI-9** (<5%) **37** (75%) Isolated 65% of **37** on 5.1 mg scale

Manganese(III)-Based Oxidative Free-Radical Cyclizations

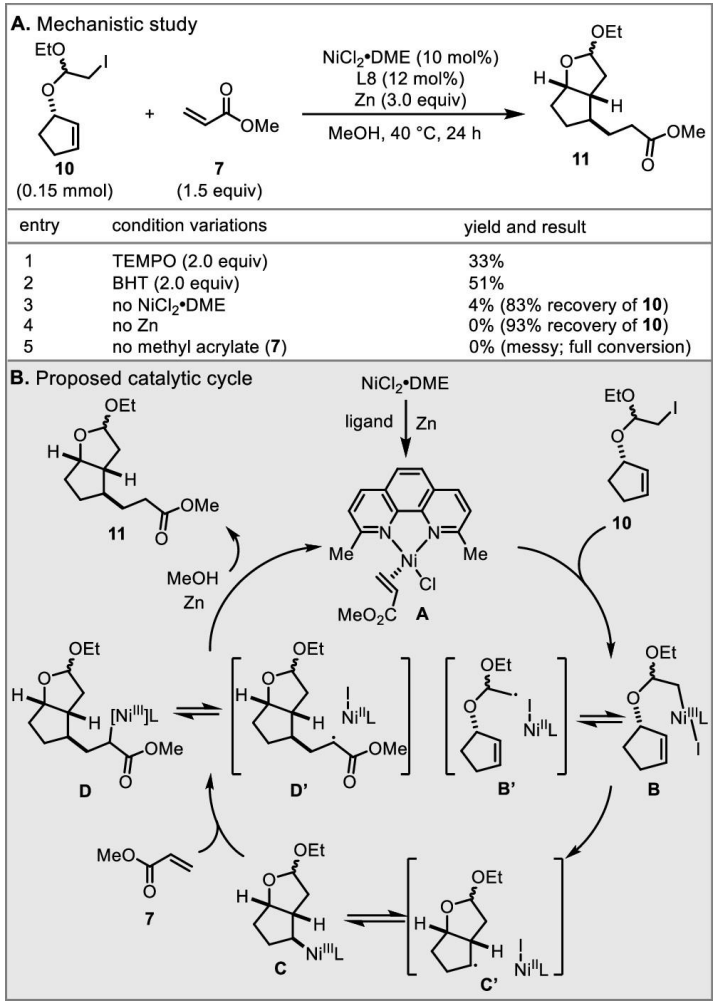


Barry B. Snider. Chem. Rev. 1996, 96, 1, 339–364.

Burgess reagent and Martin's sulfurane

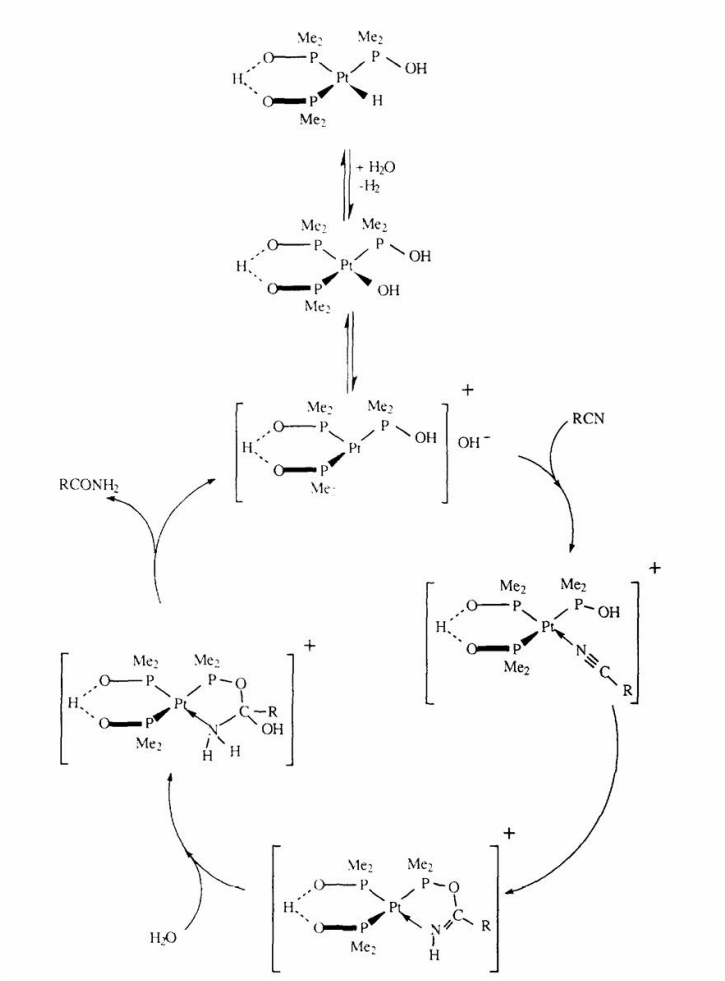


Ueno–Stork cyclization



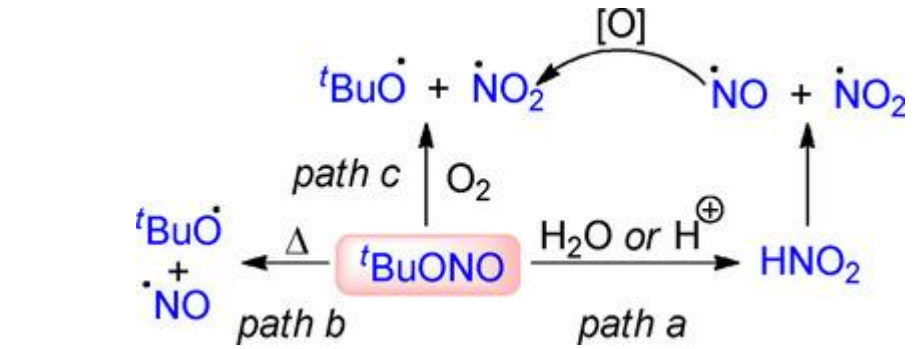
Horn, P. d. A. *J. Org. Chem*. **2022**, 87, 13, 8796–8801.

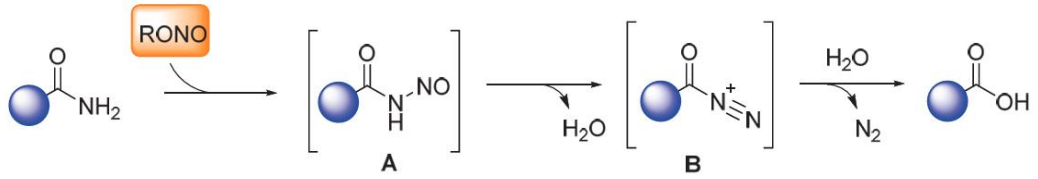
Ghaffar-Parkins catalyst



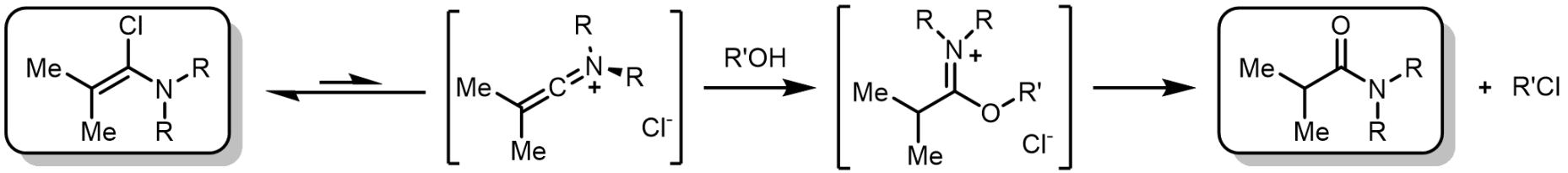
Talit Ghaffar and Adrian W. Parkins, *Tetrahedron Lett*. **1995**, 36, 8657–8660.

Amide Hydrolysis Reaction Using tert-Butyl Nitrite





The Replacement of a Hydroxyl Group by Halogen



R' = Alkyl or carboxylic acids

F. Munyemana et al.,*Tetrahedron Lett.***2016**, 72, 420–430.