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Communication

Convergent Total Synthesis of (−)-Cyclopamine

Manolis Sofiadis,[‖] Dongmin Xu,[‖] Anthony J. Rodriguez,[‖] Benedikt Nissl, Sebastian Clementson, Nadia Nasser Petersen, and Phil S. Baran*

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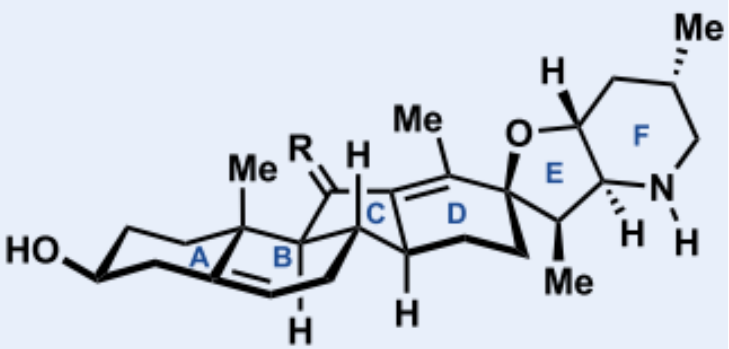
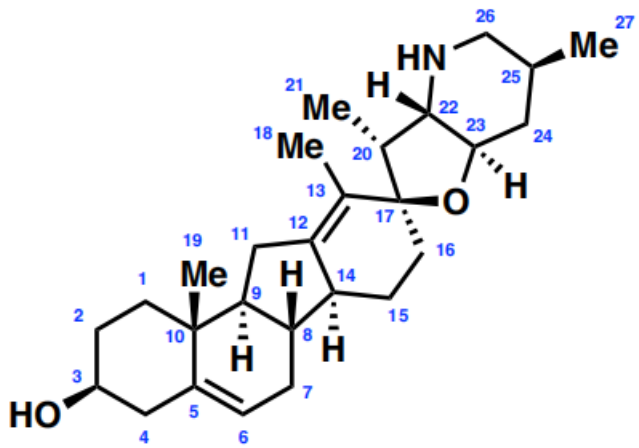


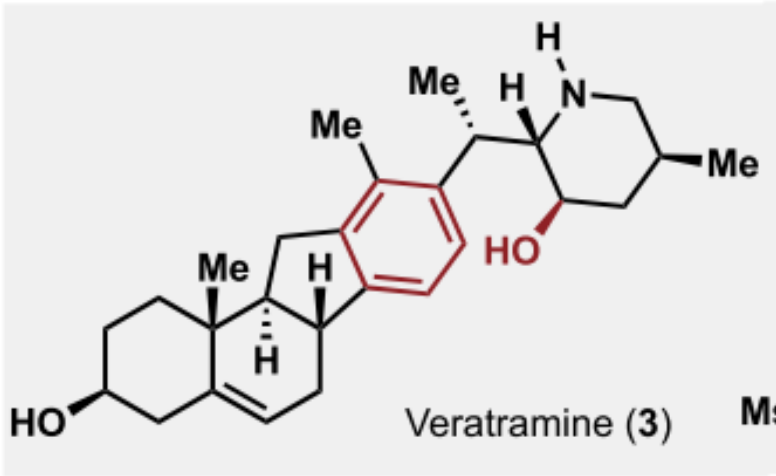
Cyclopamine (**1**): R = 2H
Jervine (**2**): R = O



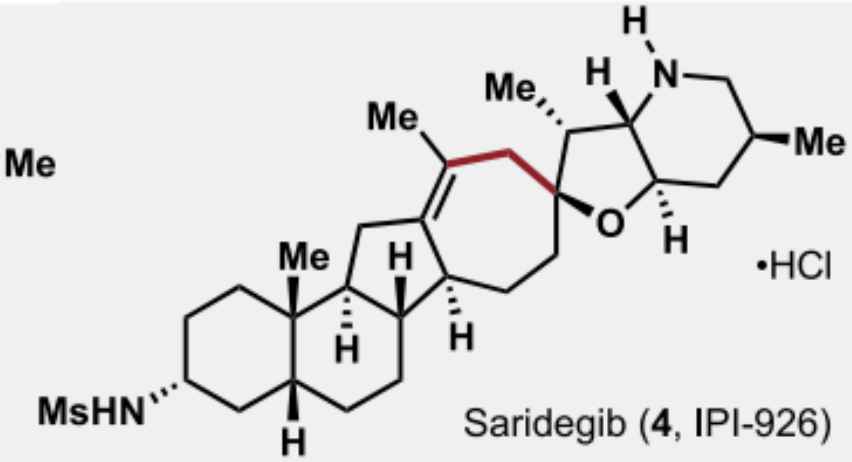
(–)-cyclopamine (1)

J. Am. Chem. Soc., **2023**, *145*, 21760.

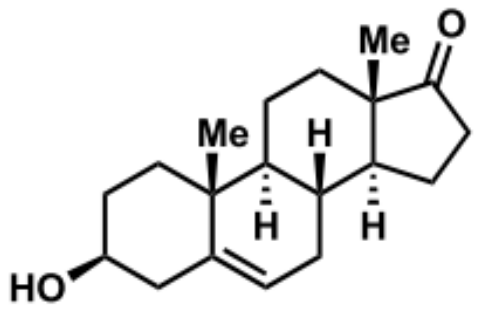
A. Previous Syntheses of Cyclopamine and Related *Veratrum* Alkaloids



Veratramine (**3**)



Saridegib (**4**, IPI-926)



Dehydroepiandrosterone (**5**)

(**R** = 2H)

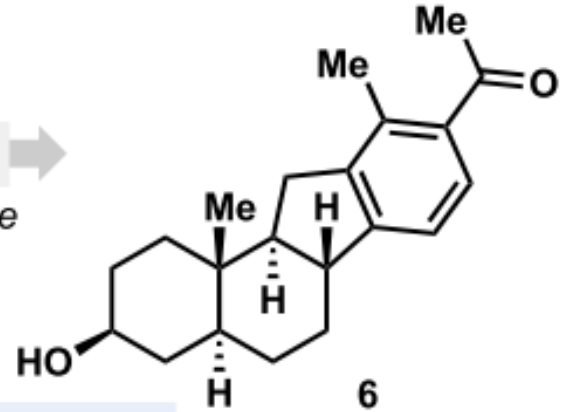
20 steps

Giannis (ref. 7h)

(**R** = O)

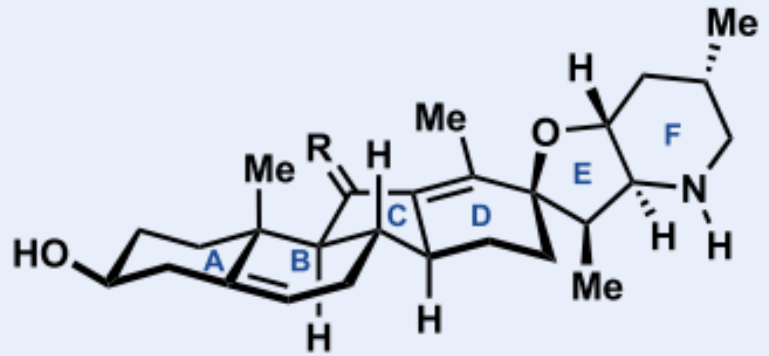
18 steps

Masamune (ref. 7a)

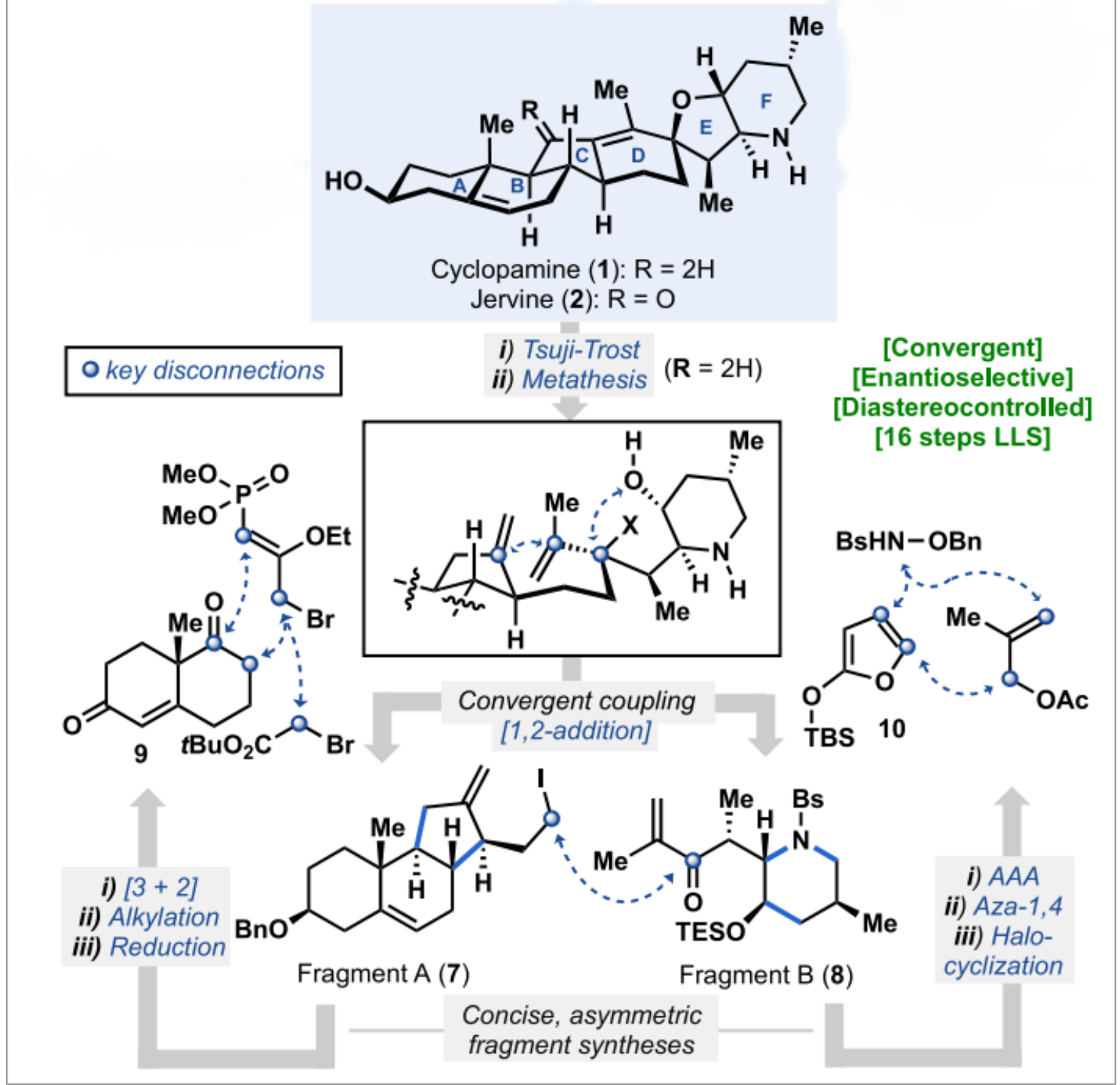


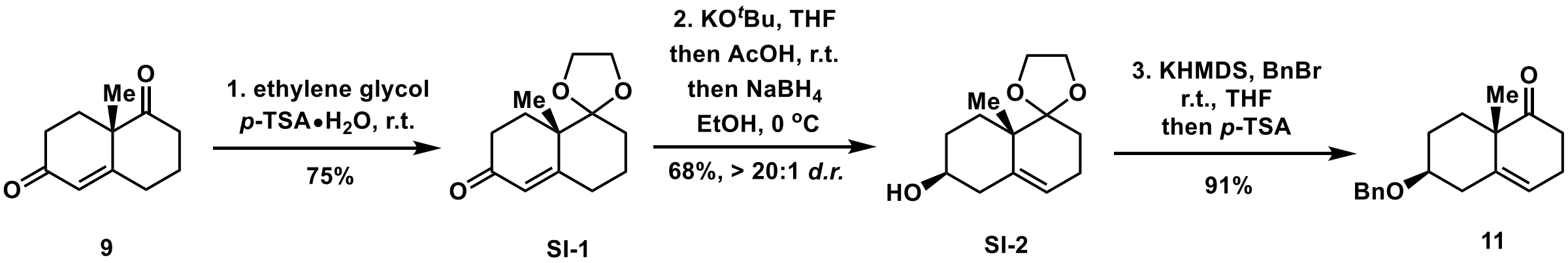
6

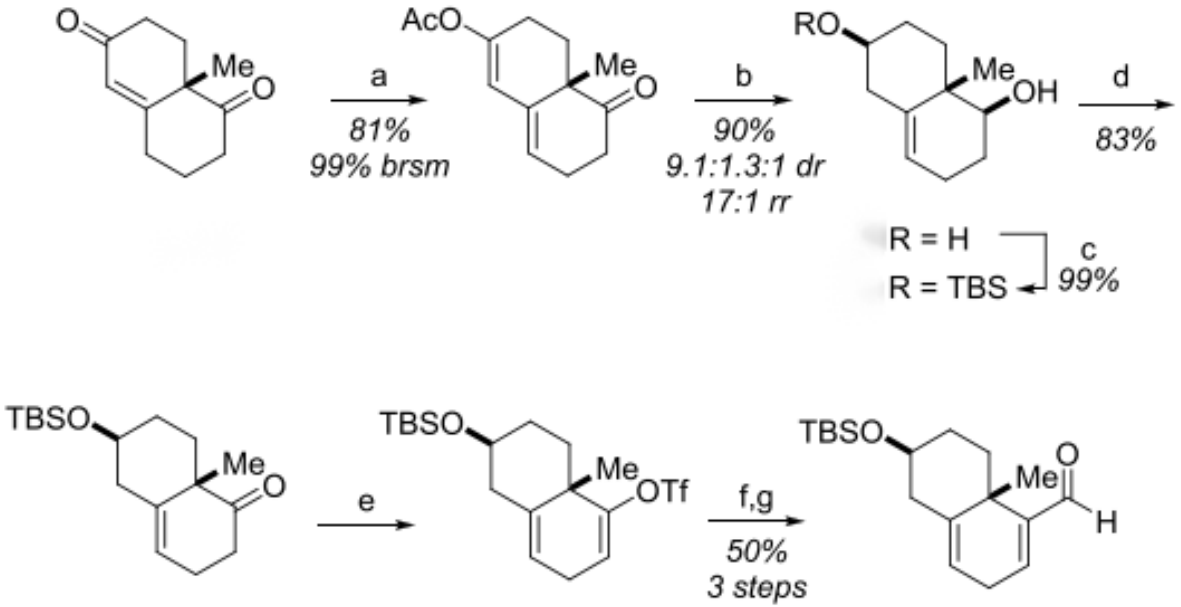
(**25 steps** from Hagemann's ester or *via* hecogenin degradation)



Cyclopamine (**1**): R = 2H
Jervine (**2**): R = O

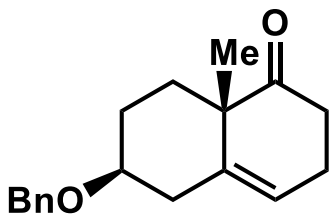

Cyclopamine (1): R = 2H
Jervine (2): R = O
key disconnections
i) Tsuji-Trost
ii) Metathesis
(R = 2H)
[Convergent]
[Enantioselective]
[Diastereocontrolled]
[16 steps LLS]
9
10
Convergent coupling
[1,2-addition]
i) [3 + 2]
ii) Alkylation
iii) Reduction
Fragment A (7)
Fragment B (8)
i) AAA
ii) Aza-1,4
iii) Halo-cyclization
Concise, asymmetric
fragment syntheses





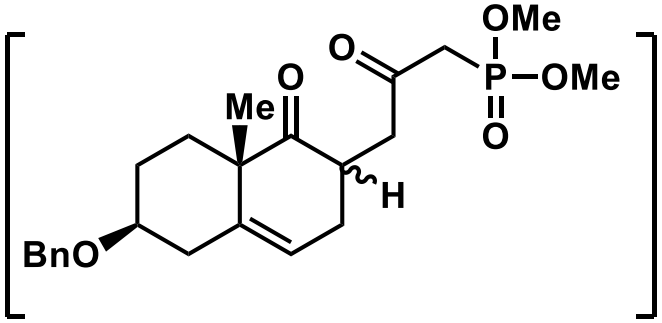
[a]Reagents and conditions: (a) Ac_2O (6 equiv), $TsOH{\cdot}H_2O$ (3 mol %), PhMe, reflux; (b) $NaBH_4$ (6 equiv), EtOH, 0 °C to rt; (c) TBSCl (1.5 equiv), imidazole (2 equiv), CH_2Cl_2, rt; (d) oxalyl chloride (2.5 equiv), DMSO (5 equiv), NEt_3 (8 equiv), CH_2Cl_2, −78 °C to rt; (e) KHMDS (2 equiv), $PhNTf_2$ (2.5 equiv), THF, −78 °C to rt; (f) Bu_3SnCH_2OH (2.2 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (3 equiv), THF, reflux; (g) Dess−Martin periodinane (1.2 equiv), sodium bicarbonate (3 equiv), CH_2Cl_2, 0 °C.

Org. Lett., **2020**, *22*, 3537.



11

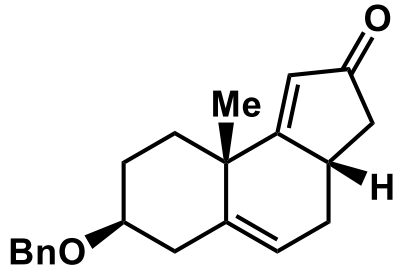
4. LDA, 12, HMPA
THF, -78 °C to r.t.
then HCl (1 M)



13

5. Cs_2CO_3, THF, 50 °C

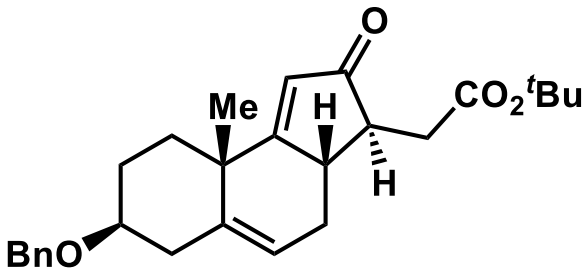
42% over 2 steps, 9:1 *d.r.*
(> 20:1 *d.r.* after recry.)



14

6. Br $CO_2{}^tBu$
LHMDS, DMI, THF
-78 °C to r.t.

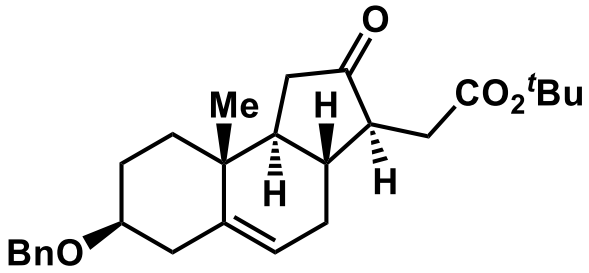
93%, > 20:1 *d.r.*



15

7. $Cu(OAc)_2$, dppbz
PMHS, toluene, 40 °C

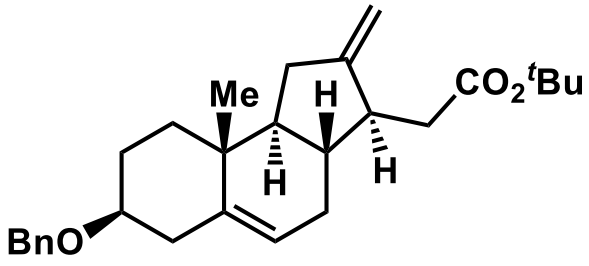
86%, > 20:1 *d.r.*



16

8. $MePPh_3Br$, KO^tBu
THF, 0 °C to r.t.

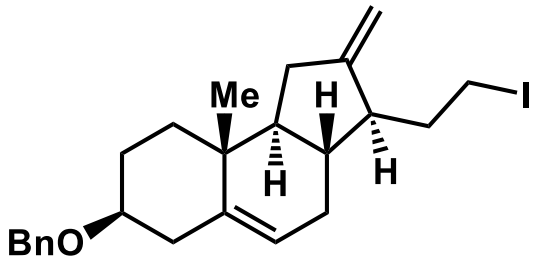
80%



SI-3

9. DIBAL-H, DCM, 0 °C
10. I_2, PPh_3, imidazole
DCM, 0 °C

57% over 2 steps



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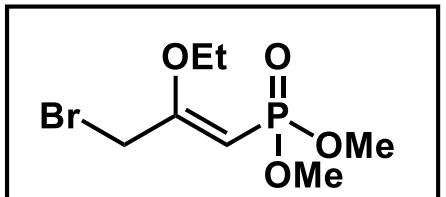
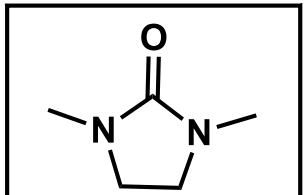
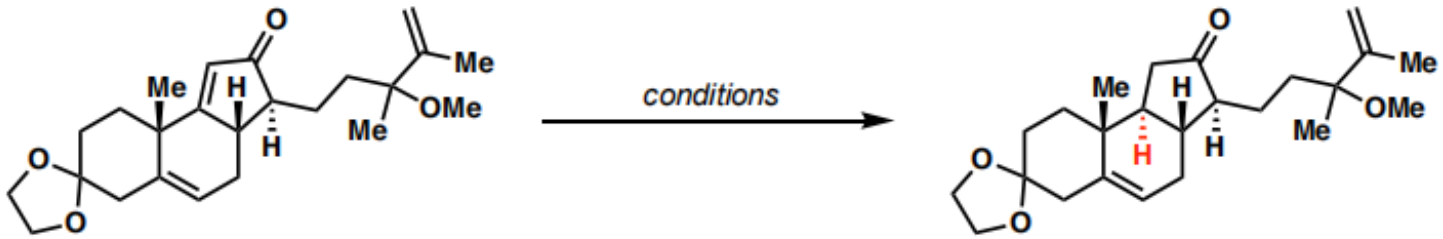


12

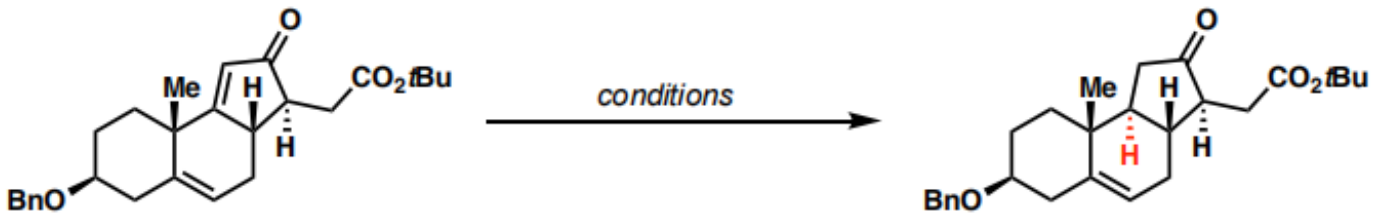


DMI

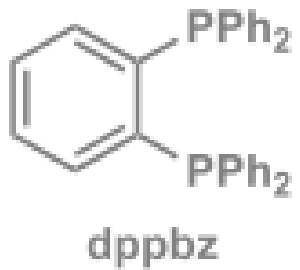
Optimization of 1,4-reduction (step 7)



conditions	results
L-selectride, THF, -78 °C to rt, 4 h	only 1,2-reduction
$[Cu(PPh_3)H]_6$ (1 eq.), PhH, 80 °C, 12 h	no reaction
$[Cu(PPh_3)H]_6$ (1 eq.), MePh, 130 °C, 12 h	no reaction
$Mn(dpm)_3$ (20 mol %), $PhSiH_3$ (1.5 eq.), THF, rt, 12 h	no reaction
$Mn(dpm)_3$ (20 mol %), $PhSiH_3$ (1.5 eq.), THF, 60 °C, 12 h	complex mixture
$Mn(dpm)_3$ (20 mol %), $PhSiH_3$ (1.5 eq.), TBHP (2 eq.), THF, rt, 2 h	non-selective reduction of all olefins
SmI_2 (2 eq.), ^{i}PrOH (10 eq.), THF, rt, 12 h	no reaction
$Cu(OAc)_2 \cdot H_2O$ (1 eq.), dppBz (0.5 eq.), PMHS (3 eq.), MePh, rt, 12 h	53% yield, 34% SM recovered

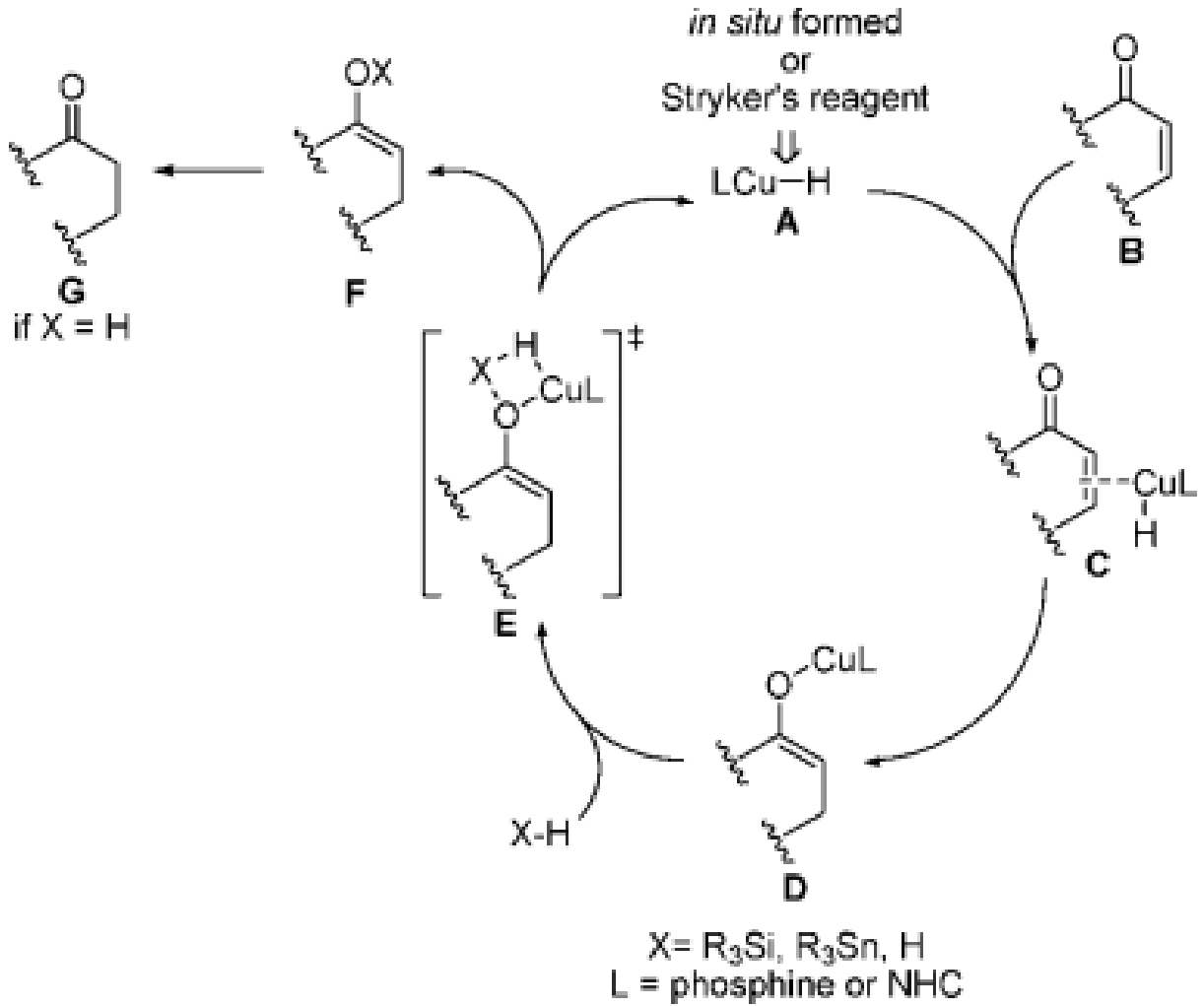


conditions	results
$Cu(OAc)_2 \cdot H_2O$ (1 eq.), dppBz (0.5 eq.), PMHS (3 eq.), MePh, rt, 2 d	47% yield, 40% SM recovered
$Cu(OAc)_2 \cdot H_2O$ (1 eq.), dppBz (0.5 eq.), PMHS (3 eq.), MePh, 40 °C, 16 h	81% yield
$Cu(OAc)_2 \cdot H_2O$ (0.2 eq.), dppBz (0.1 eq.), PMHS (4 eq.), MePh, 40 °C, 16 h	86% yield



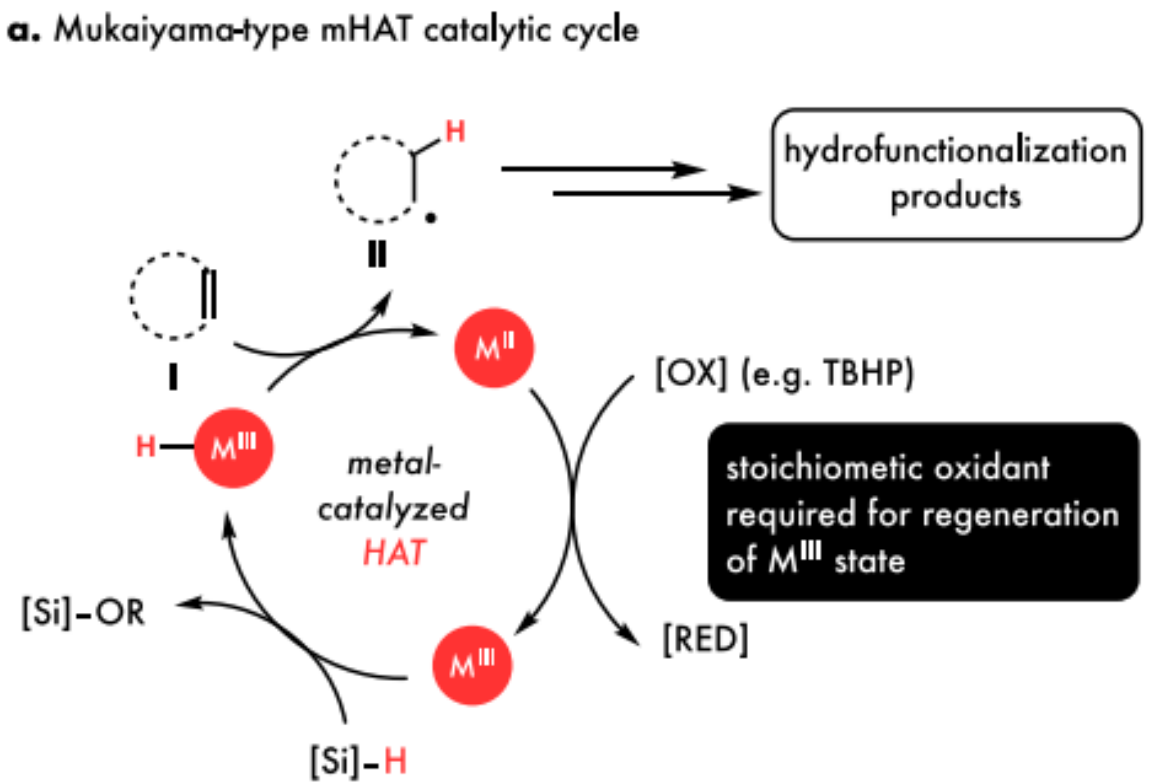
dppbz

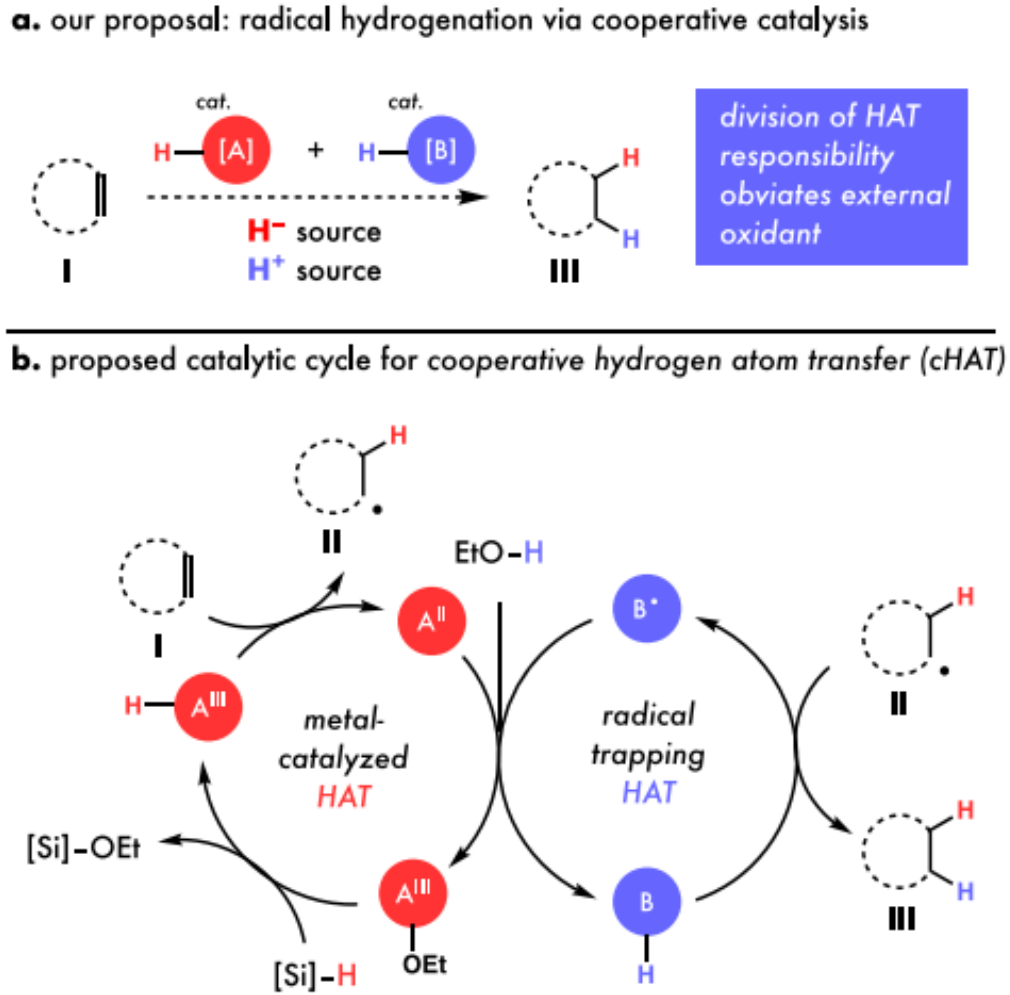
Streker试剂：



Chem. Rev., **2008**, *8*, 108.

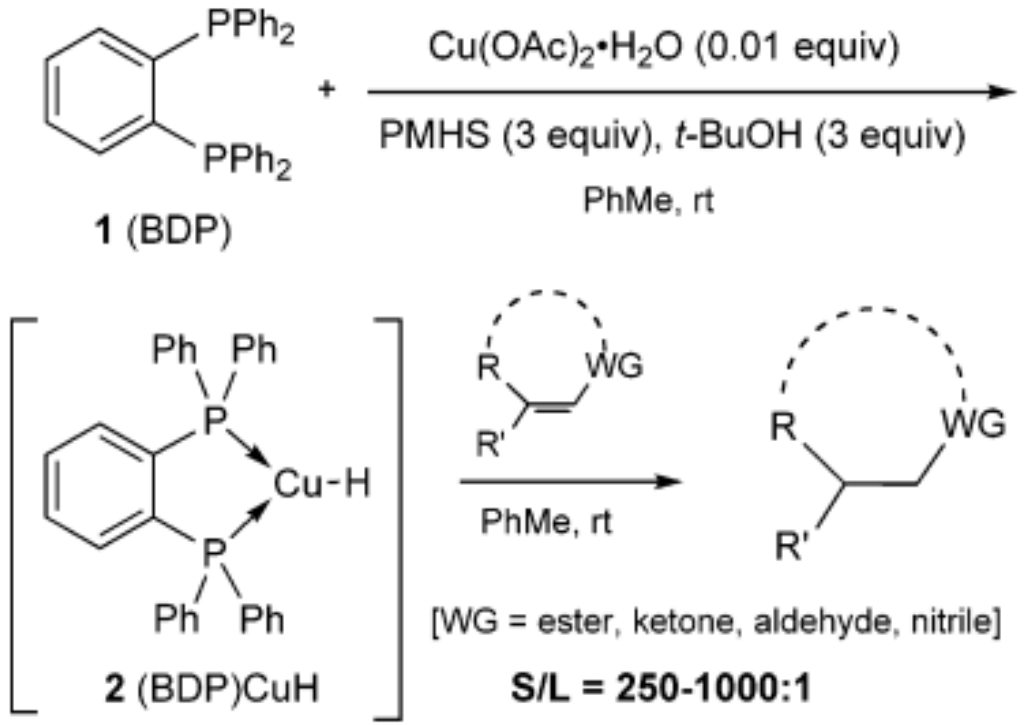
HAT烯烃氢化反应

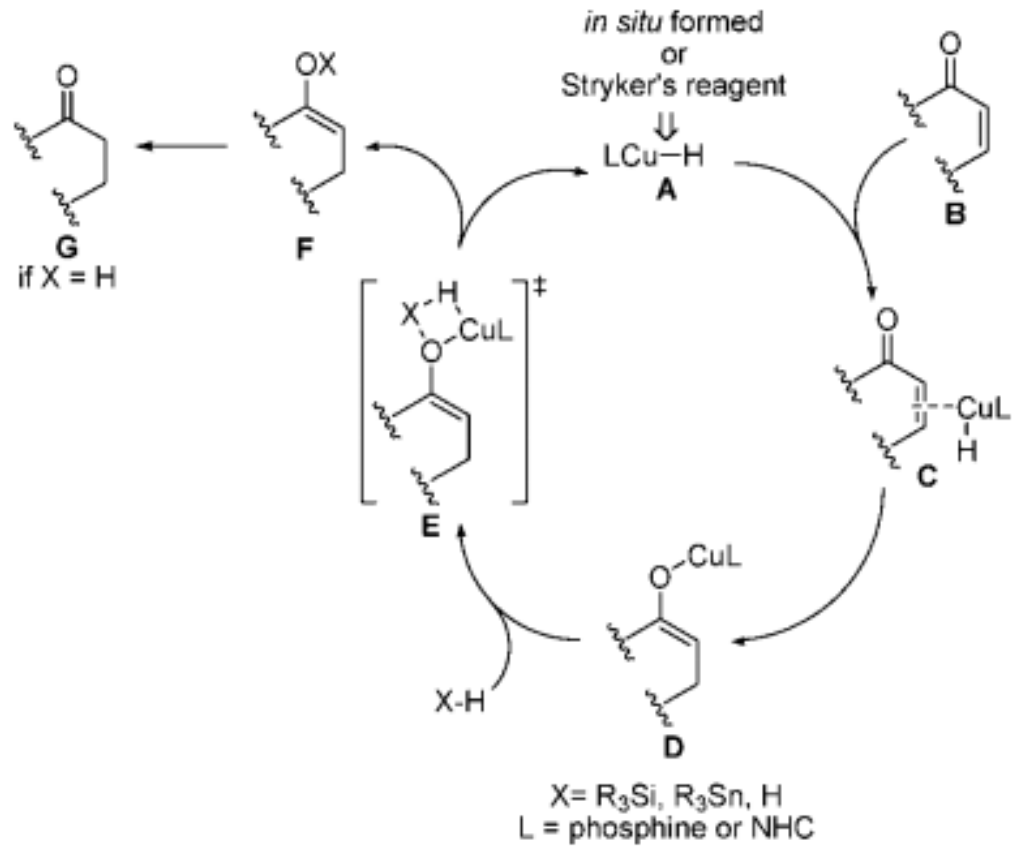




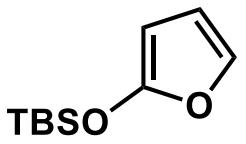
J. Am. Chem. Soc., **2020**, *142*, 19316.

Scheme 1. Preparation and Use of (BDP)CuH (**2**)





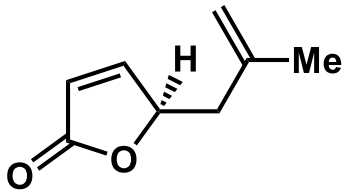
Org. Lett., **2008**, *2*, 10.



10

a. $Pd_2(dba)_3$, L1
K_2CO_3, NH_4OAc
methallyl acetate

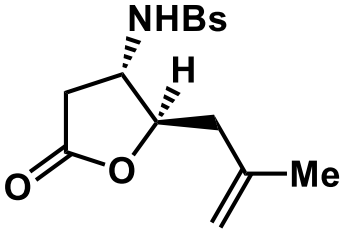
THF, -20 °C
75%, 97% *e.e.*



17

b. BsNHOBn, DBU
THF, -20 °C
then Zn^0, NH_4Cl (aq.)

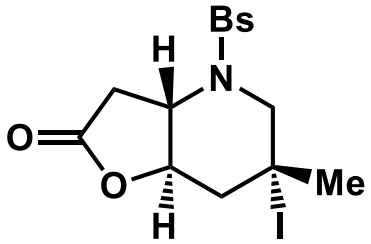
71%, 71% *e.e.*
(> 97% *e.e.* after recry.)
> 20:1 *d.r.*



18

c. KO^{t}Bu, I_2, toluene
0 °C to r.t.

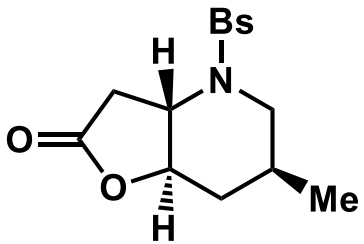
51%, 10:1 *d.r.*



19

d. AIBN, Bu_3SnH
toluene, 100 °C

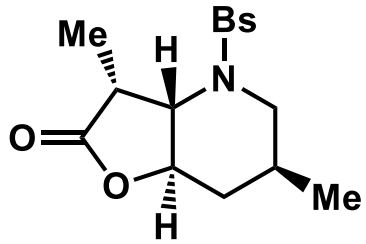
71%, > 20:1 *d.r.*



20

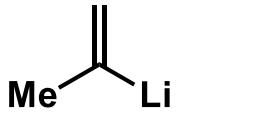
e. LHMDS, MeI, HMPA
THF, -78 °C

95%, > 20:1 d.*r.*



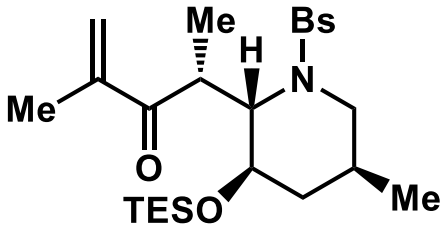
21

f.



THF, -78 °C

then TESCl
THF/pyr., r.t., 65%



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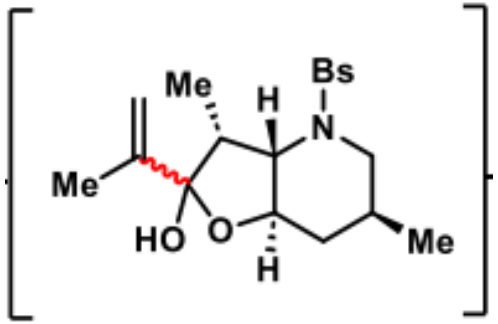
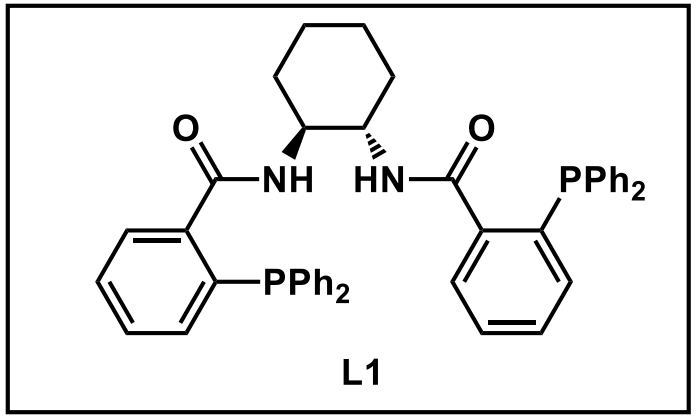
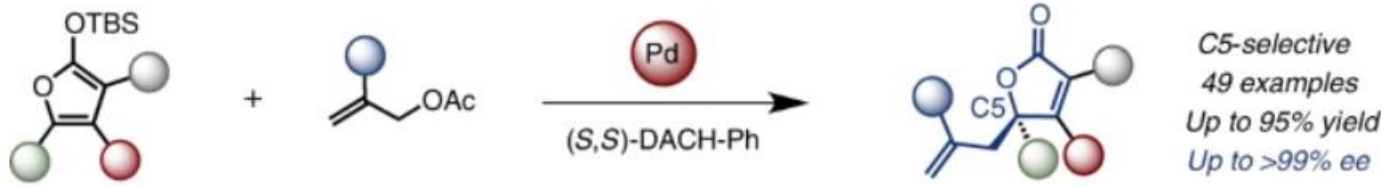
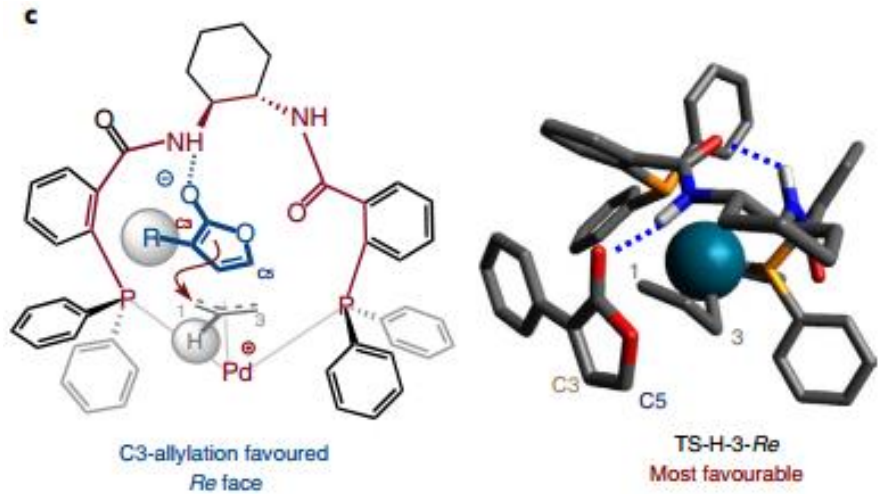
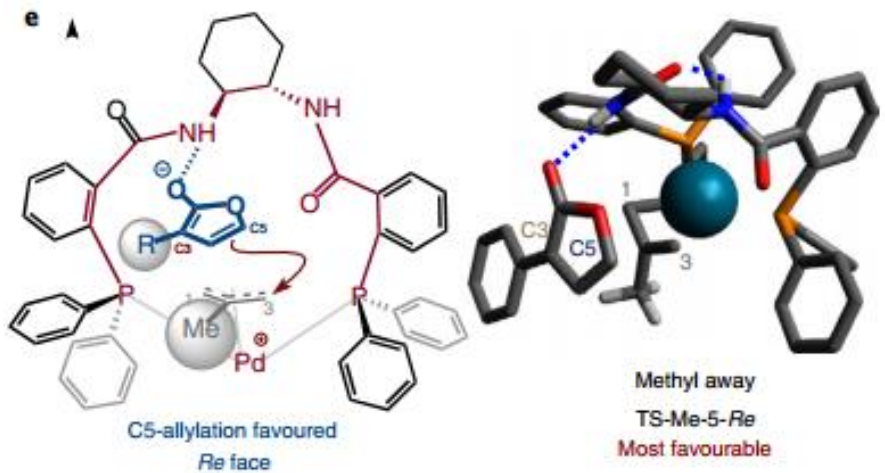




L1

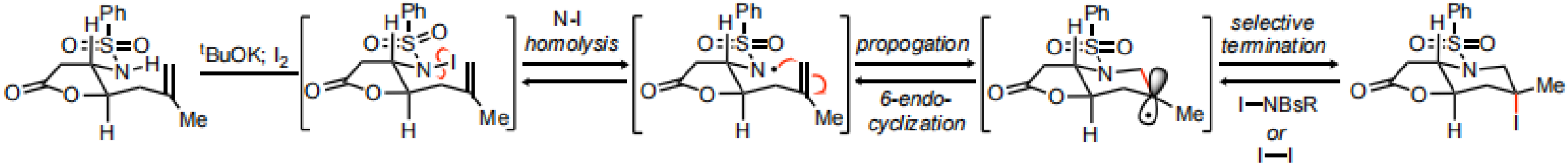




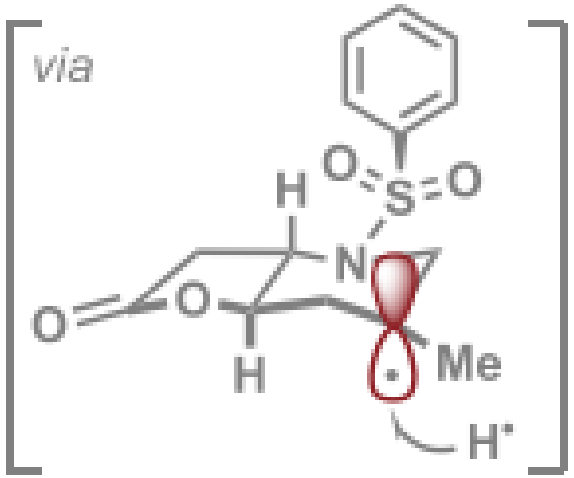


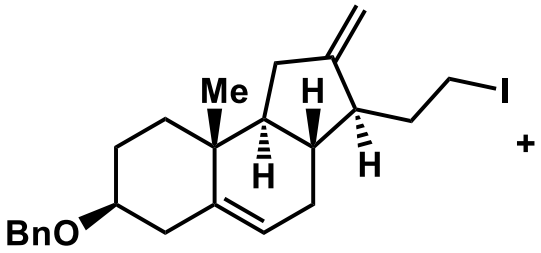
Nat. Synth., **2022**, *1*, 641.

step C:


tBuOK; I2
N-I
homolysis
propogation
6-endo-
cyclization
selective
termination
I—NBsR
or
I—I

step D:


via
H+



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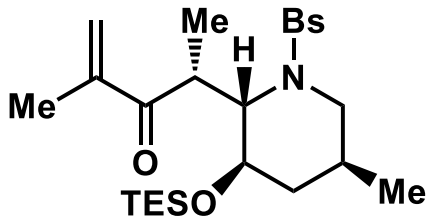
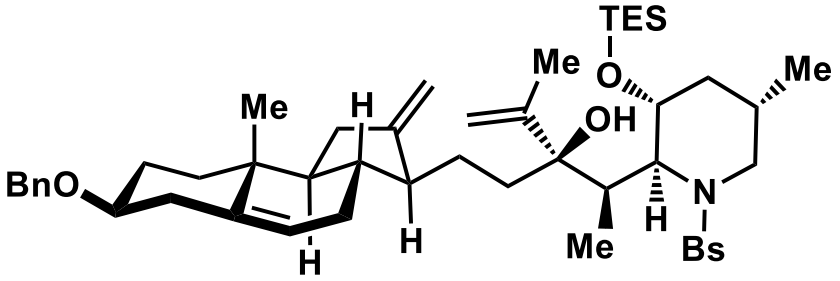


8

11. ^{t}BuLi, $LaCl_3 \bullet 2LiCl$
THF/Et_2O, -78 °C to -40 °C

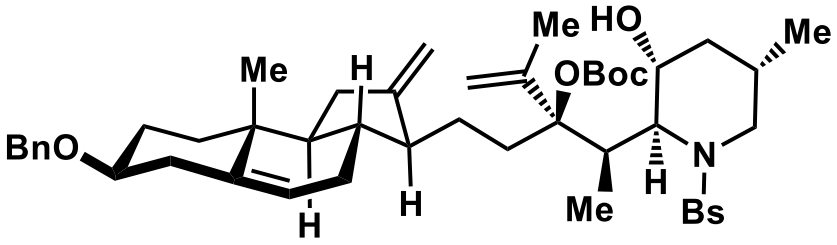
71%, > 20:1 *d.r.*



22

12. KHMDS, Boc_2O
THF, -78 °C, 64%

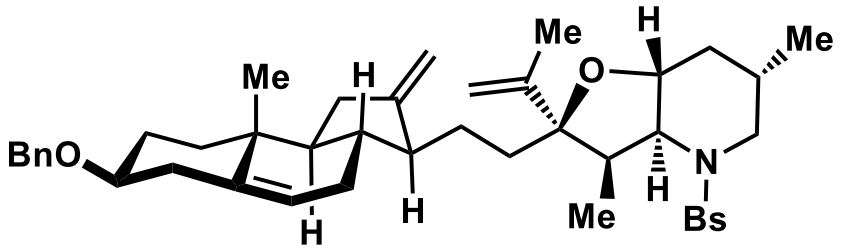
13. HF•pyr, THF
r.t., 91%



23

14. $Pd(OAc)_2$, PPh_3
DMF, 120 °C

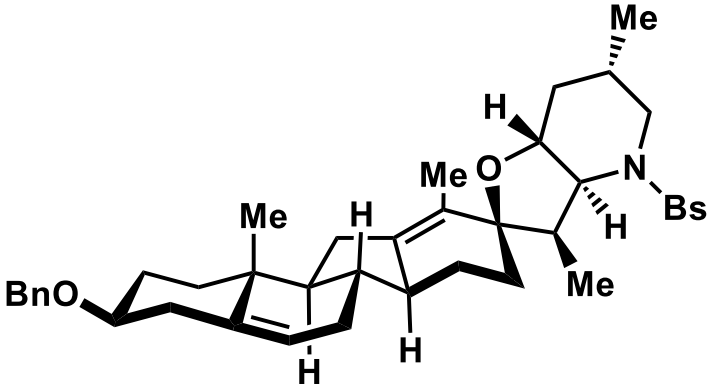
73%, > 20:1 d.*r.*



24

15. Ru-3, F_8-MePh
70 °C

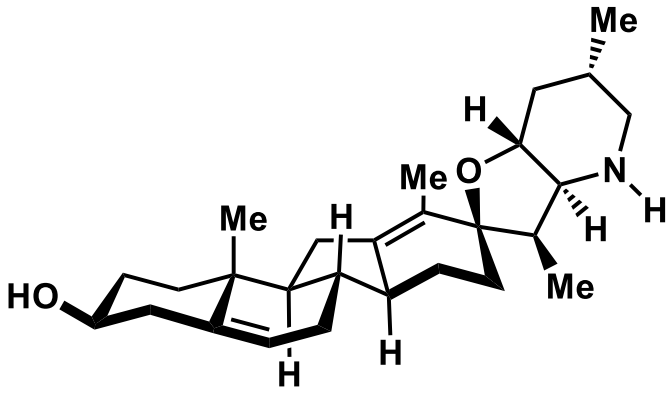
85%



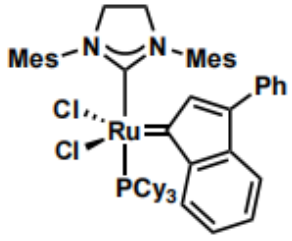
25

16. LiDBB, THF
-78 °C

78%



cyclopamine (1)



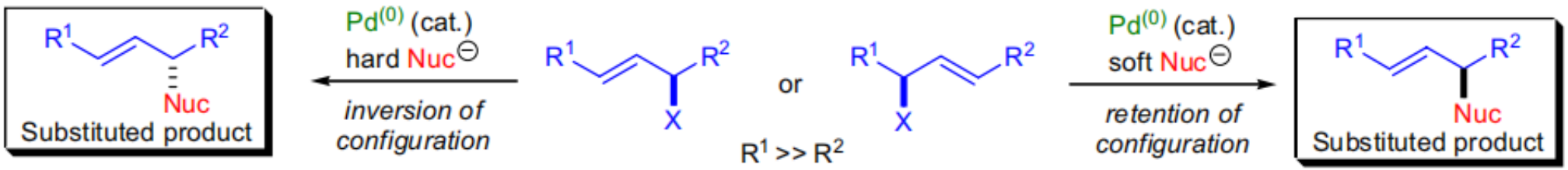
Ru-3

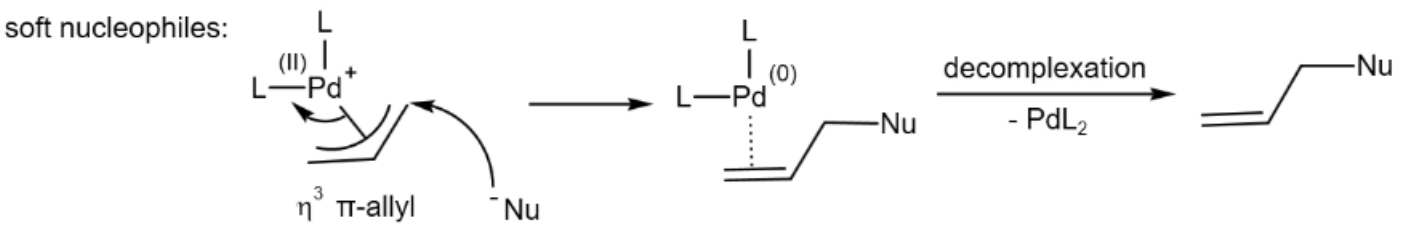
TSUJI-TROST REACTION / ALLYLATION

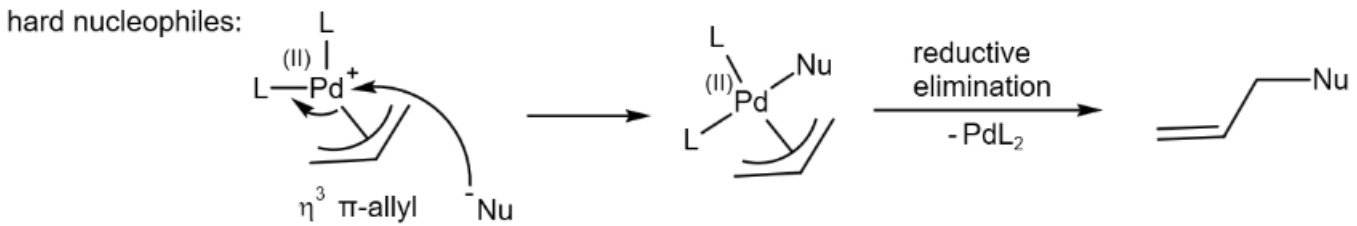
(References are on page 695)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-24]; *Modifications & Improvements*[25-30]; *Theoretical Studies*[31-37]]

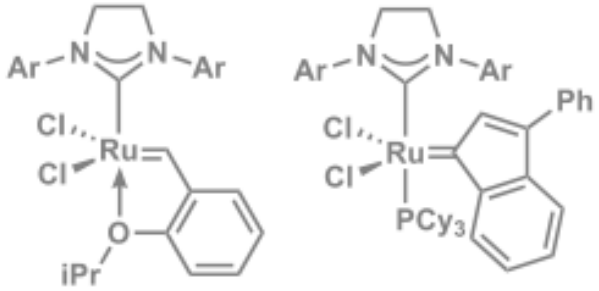






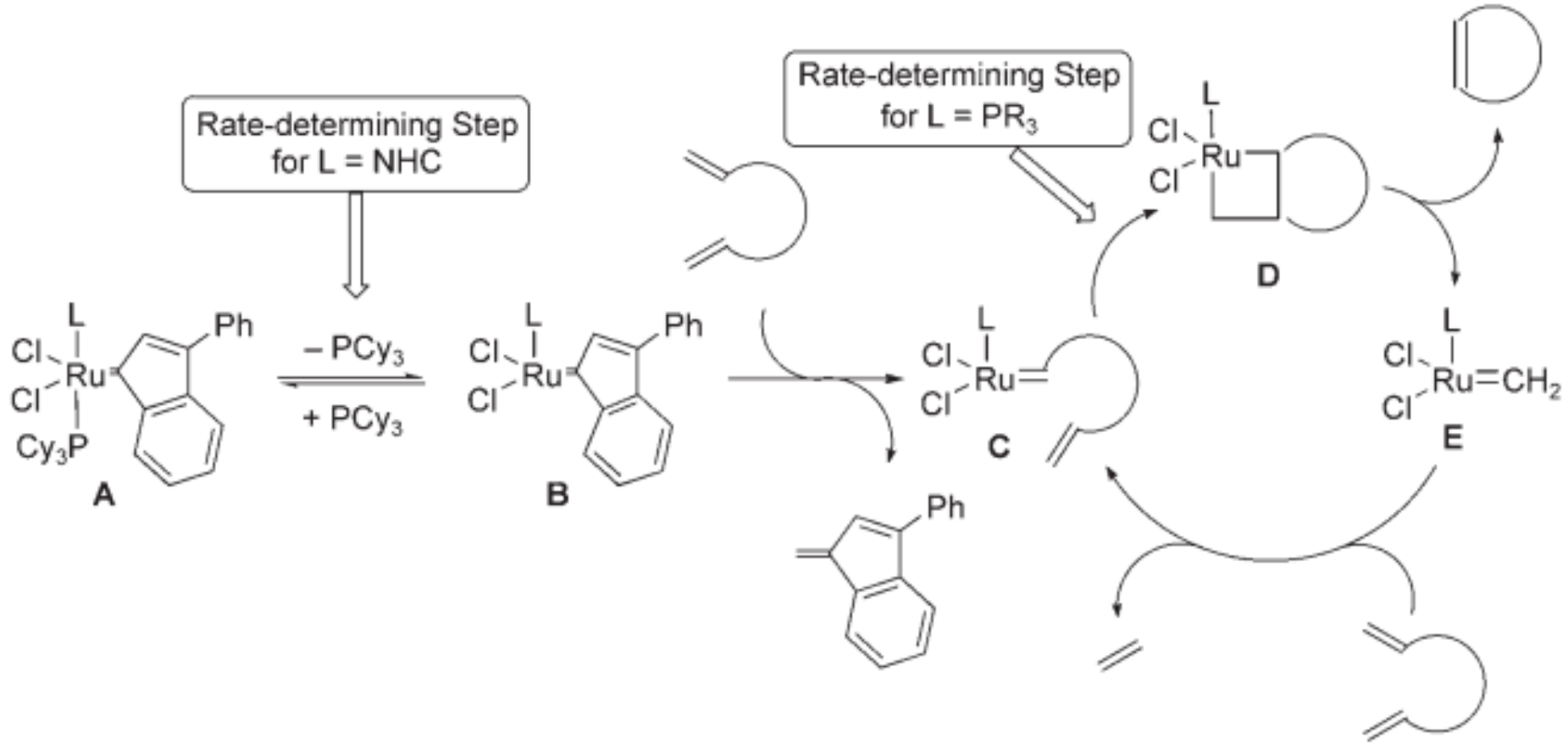
Chem. Rev., **1996**, *96*, 1.

RCM reaction:

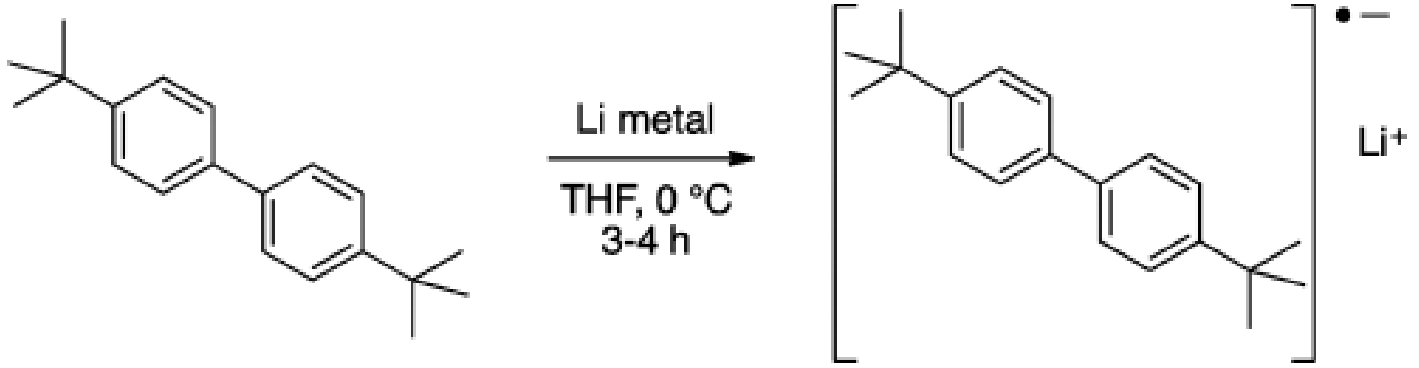


Ru-1: Ar = mesityl
Ru-2: Ar = o-tolyl

Ru-3: Ar = mesityl

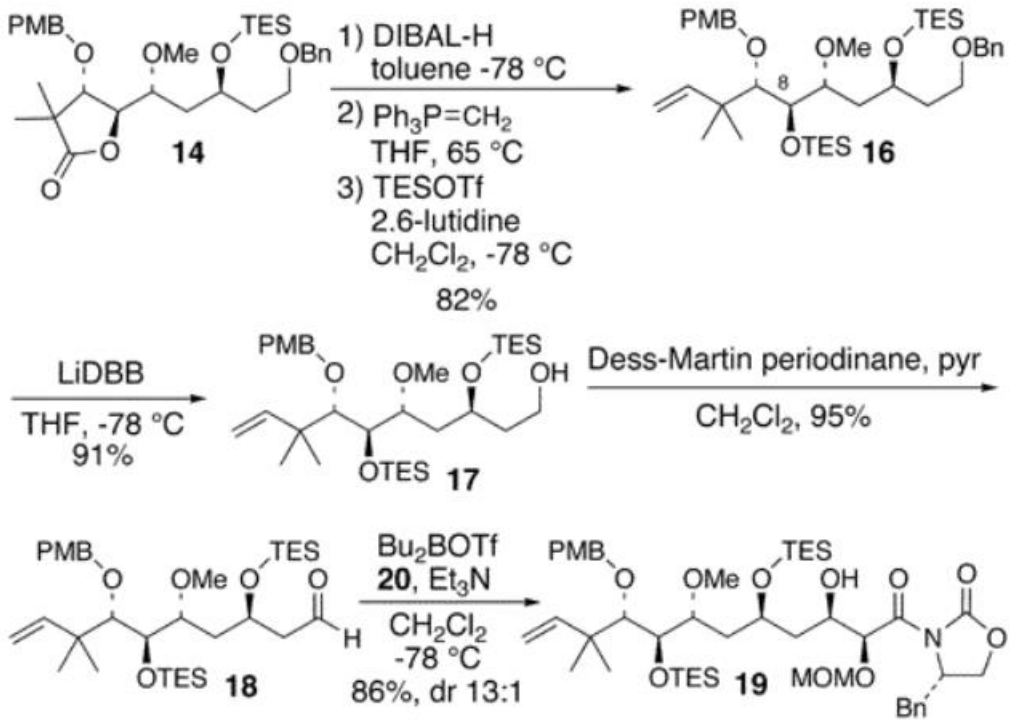


Chem. Eur. J., **2007**, *13*, 8029.

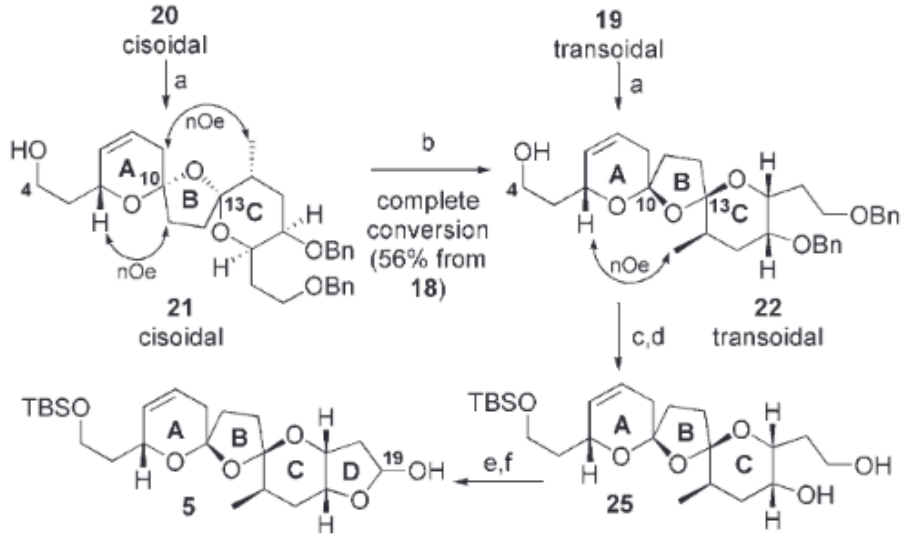


DBB: 0.20 M

LiDBB: ca. 0.17 M



Org. Lett., **2005**, *7*, 3941.



Scheme 4. Equilibration of C4-hydroxy bis-spiroketals. Reagents and conditions: a) TBAF, THF; b) CSA, *t*BuOH/PhMe (1:1), 18 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 99%; d) LiDBB, THF, −78 °C, 95%; e) TPAP, NMO, CH_2Cl_2, M.S.; 67%; f) DIBAL-H, CH_2Cl_2, 90%. TBAF = tetra-*n*-butylammonium fluoride; DBB = lithium 4,4-di-*tert*-butylbiphenylide.

Angew. Chem. Int. Ed., **2006**, *45*, 1787.