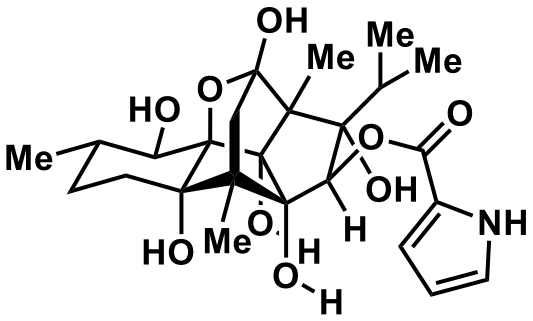
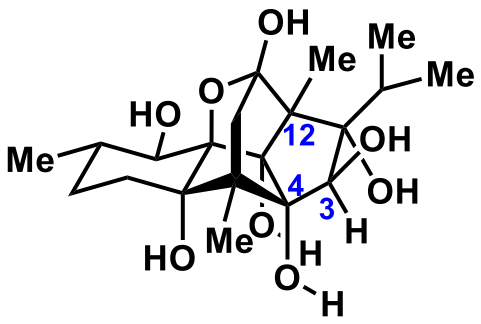
# A 15-step synthesis of (+)-ryanodol

Kangway V. Chuang,* Chen Xu,* Sarah E. Reisman†

*Science*, **2016**, *353*, 912.




(+)-ryanodine (1)

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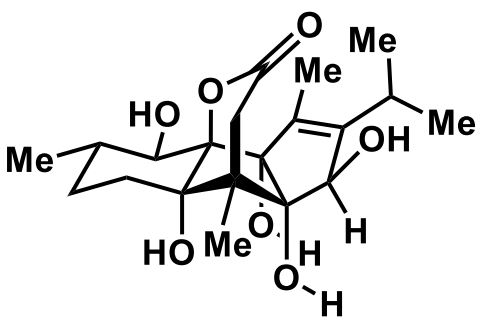
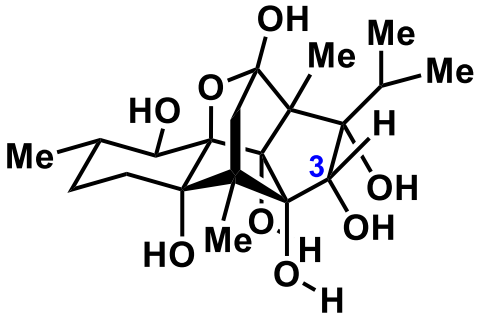
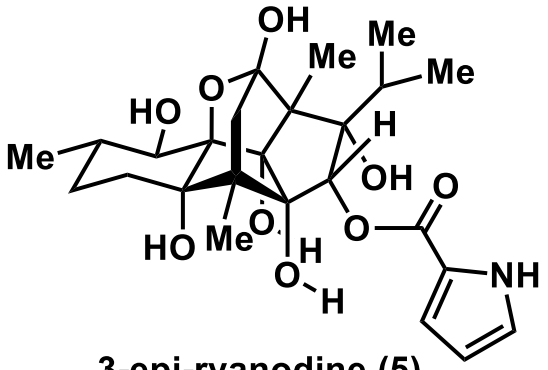


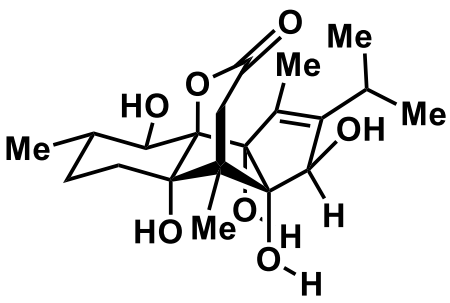

(+)-anhydroryanodol (3)




3-epi-ryanodol (4)

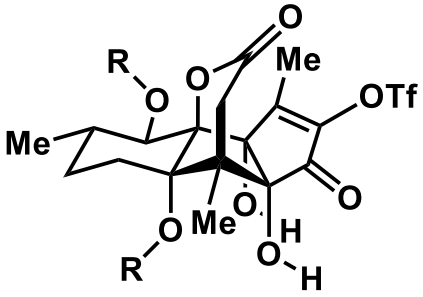



3-epi-ryanodine (5)



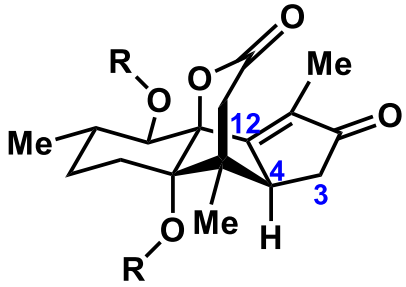

(+)-anhydroryanodol (3)

*cross-coupling*



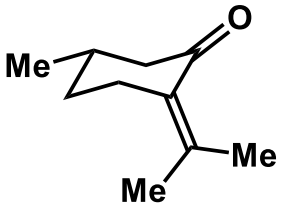

6

*hydration/ oxidation*

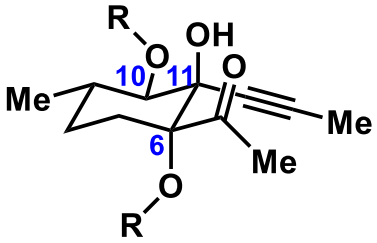



7

*intramolecular Pauson-Khand*

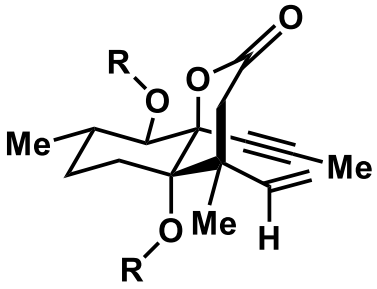



(*S*)-pulegone (10)

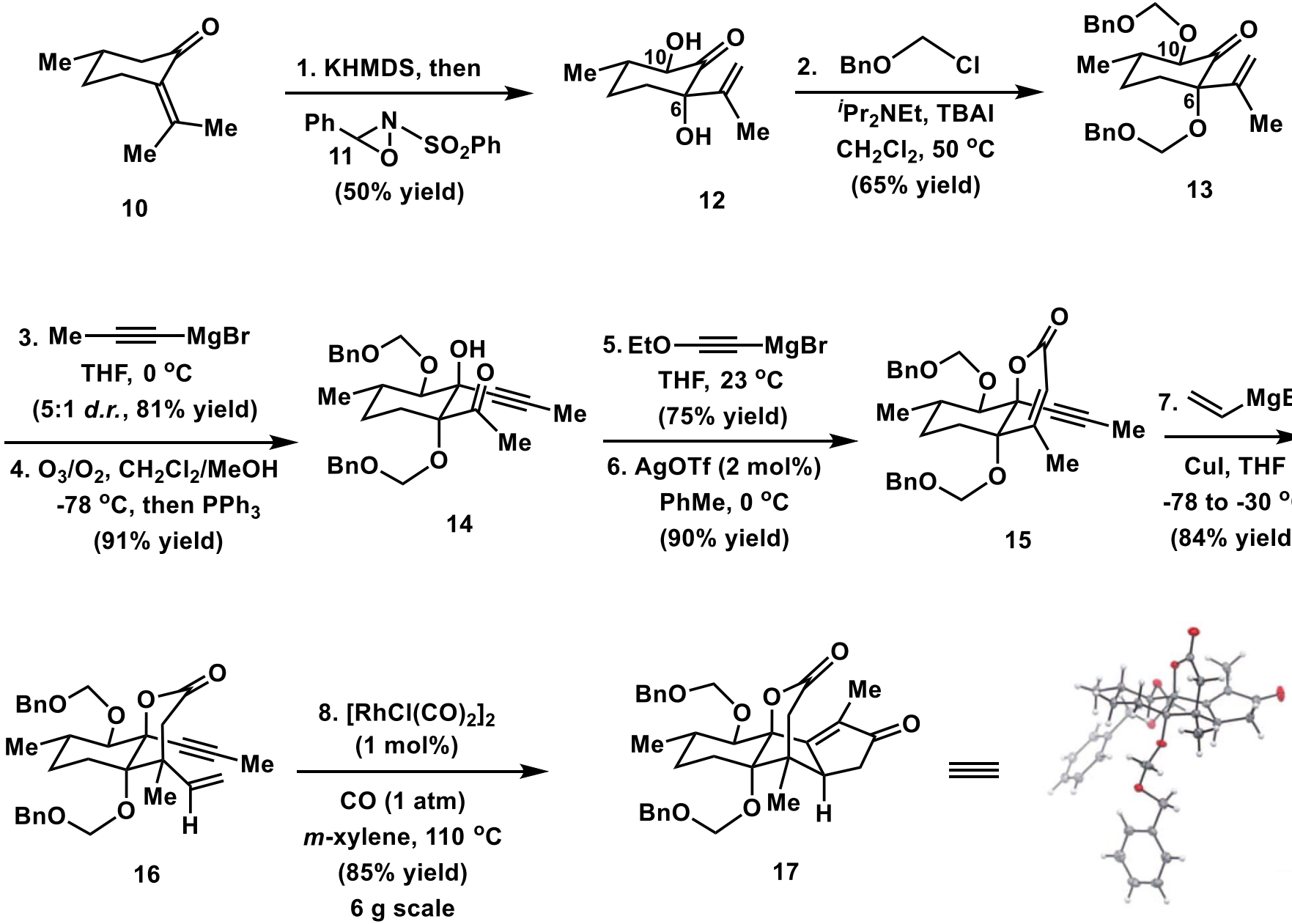


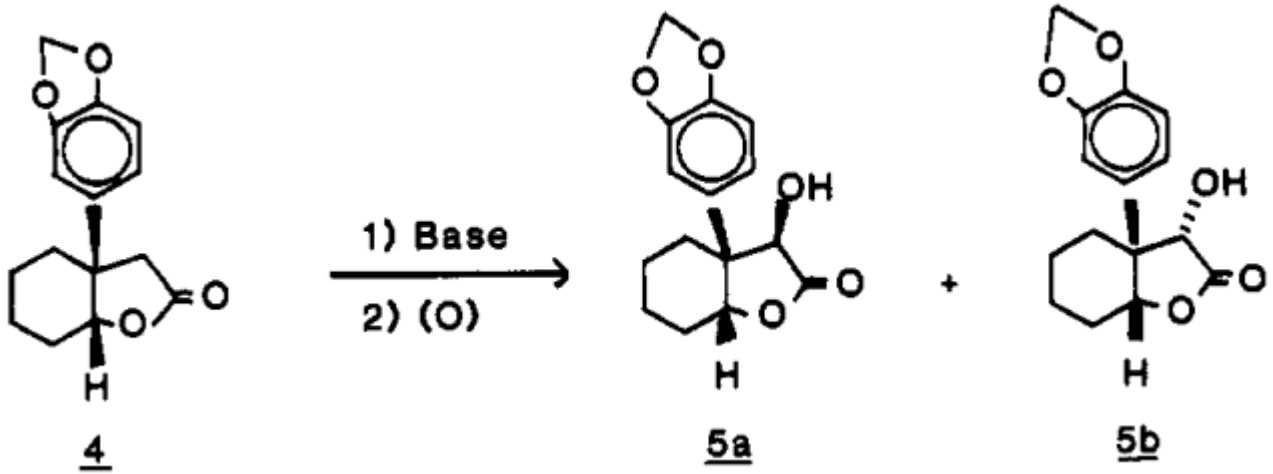

9

*lactonization/ cuprate addition*



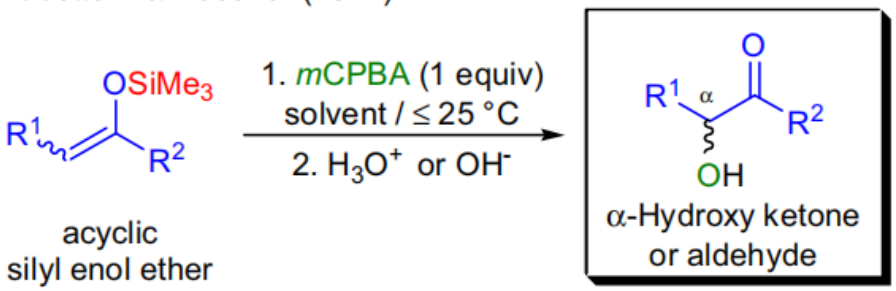

8

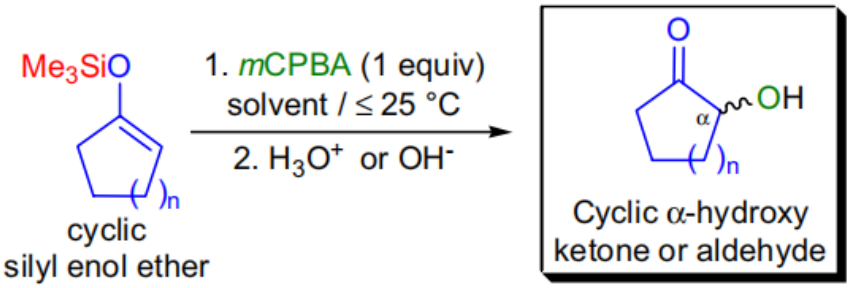

10
1. KHMDS, then
(50% yield)
12
2. BnO Cl
iPr2NEt, TBAI
CH2Cl2, 50 °C
(65% yield)
13
3. Me MgBr
THF, 0 °C
(5:1 d.r., 81% yield)
4. O3/O2, CH2Cl2/MeOH
-78 °C, then PPh3
(91% yield)
14
5. EtO MgBr
THF, 23 °C
(75% yield)
6. AgOTf (2 mol%)
PhMe, 0 °C
(90% yield)
15
7. MgBr
CuI, THF
-78 to -30 °C
(84% yield)
16
8. [RhCl(CO)2]2
(1 mol%)
CO (1 atm)
m-xylene, 110 °C
(85% yield)
6 g scale
17



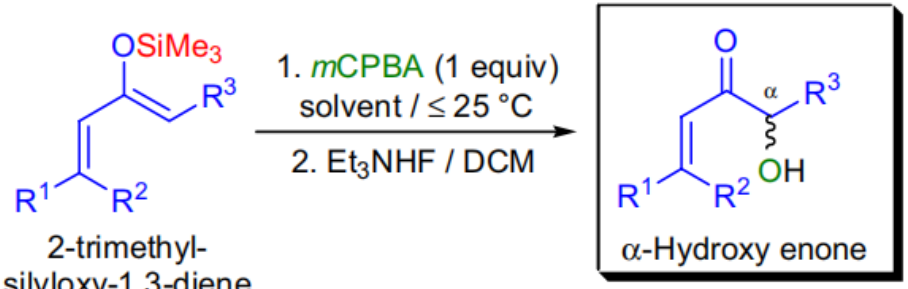

*J. Org. Chem.*, **1984**, *49*, 3241.

Rubottom & Hassner (1974):

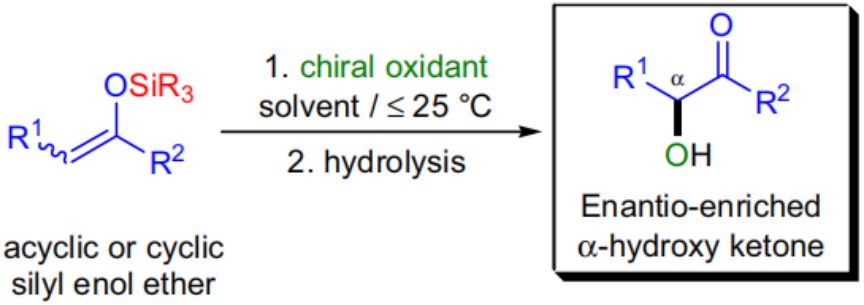


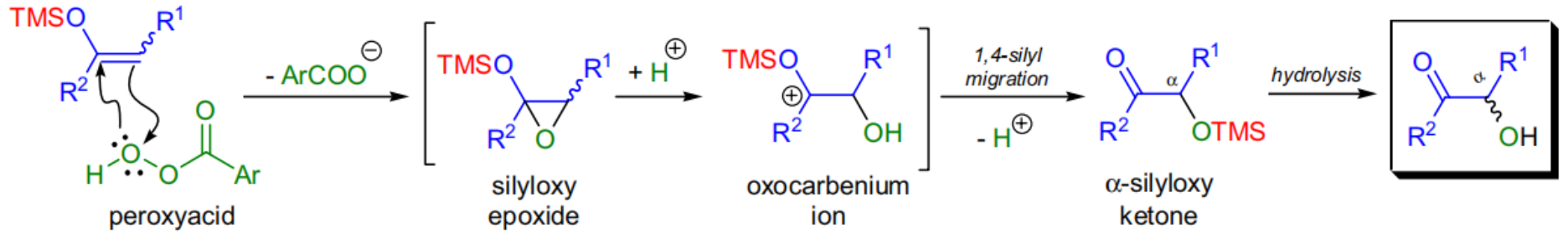

Oxidation of 2-trimethylsilyloxy-1,3-dienes:

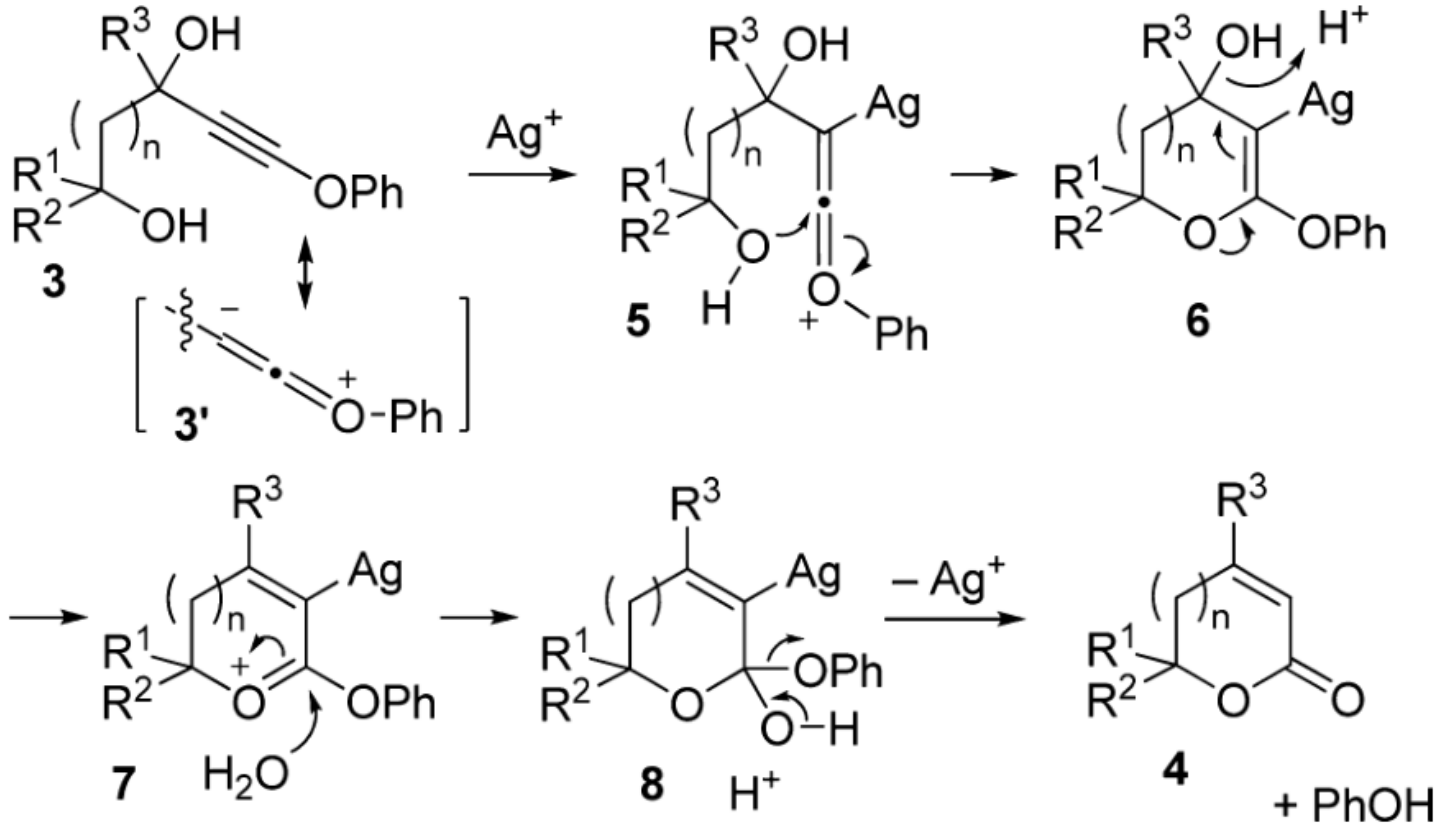



Asymmetric modification:

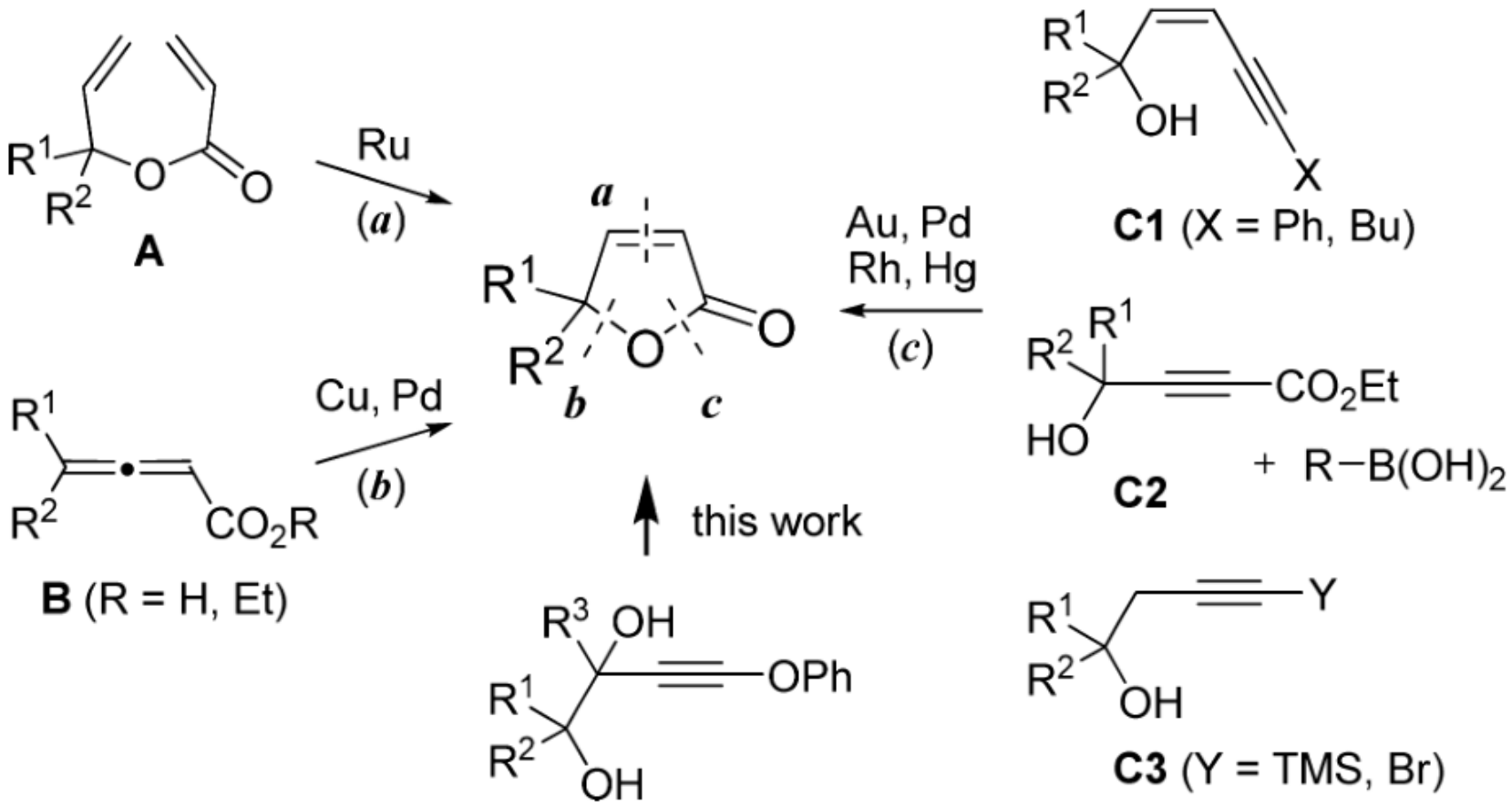



$R^{1\text{-}3}$ = H, alkyl, aryl, substituted alkyl and aryl; $SiR_3$ = $SiMe_3$, $SiMe_2$(t-Bu), $SiEt_3$; <u>solvent:</u> $CH_2Cl_2$, pentane, toluene; n = 1-3;
chiral oxidant: Davis' chiral oxaziridine, Shi's D-fructose derived ketone/Oxone, (Salen)manganese(III)-complexes/NaOCl or PhIO






*Org. Lett.*, **2013**, *15*, 4150.




*Org. Lett*., **2013**, *15*, 4150.

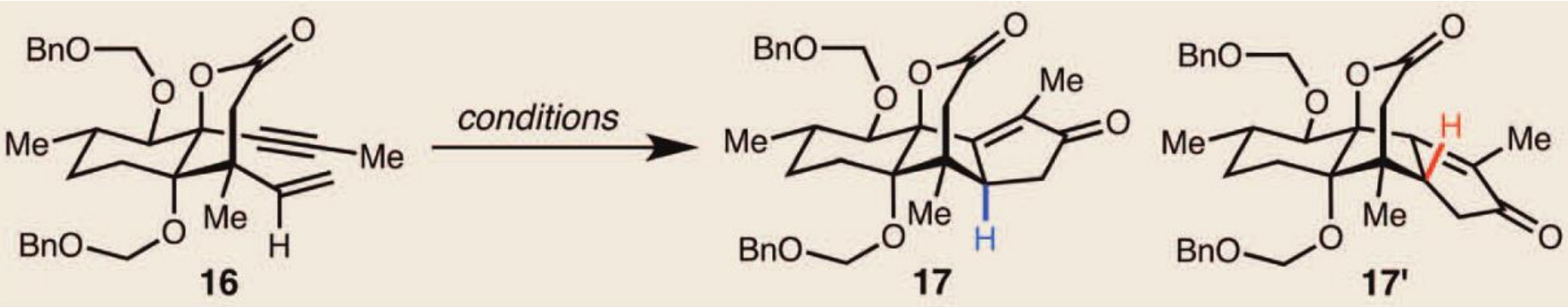


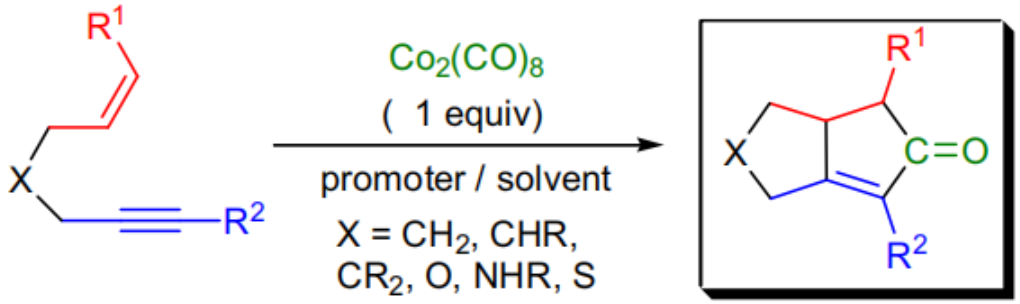

**Table 1. Evaluation of Pauson-Khand reaction conditions.**

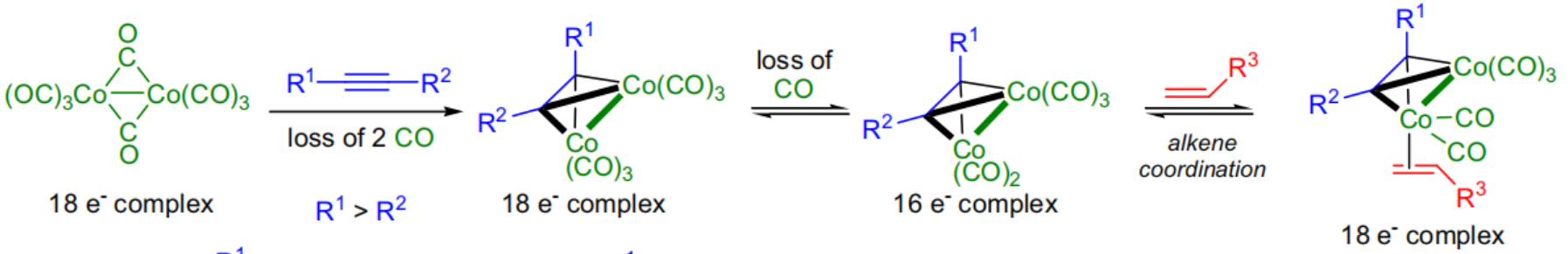
| Entry | Conditions* | dr† | Yield (%)‡ |
|---|---|---|---|
| 1 | $Co_2(CO)_8$ (1.2 equiv.), THF, 12 hours; then DMSO, 65°C | 2.2:1 | 46 |
| 2 | $Co_2(CO)_8$ (1.2 equiv.), $CH_2Cl_2$, 9 hours; then NMO, 23°C | 4.5:1 | 78 |
| 3 | $Mo(CO)_6$ (1.2 equiv.), DMSO, PhMe, 110°C | – | Trace |
| 4 | $Mo(CO)_3(DMF)_3$ (1.1 equiv.), $CH_2Cl_2$, 23°C | >20:1 | 67 |
| 5 | $[RhCl(CO)_2]_2$ (1 mol %), CO (1 atm), *m*-xylene, 110°C | >20:1 | 85 |

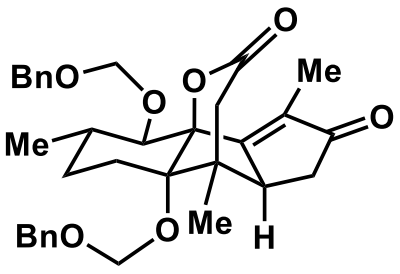
*Reactions conducted on 0.2 mmol scale. THF, tetrahydrofuran; DMSO, dimethylsulfoxide; NMO, *N*-methylmorpholine *N*-oxide; DMF, *N,N*-dimethylformamide. †Determined by $^1$H-NMR spectroscopy. ‡Isolated yield after purification by silica gel chromatography.

# PAUSON-KHAND REACTION

Intramolecular variant:





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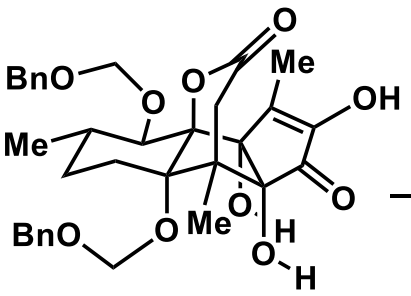
9. $SeO_2$, 4Å MS

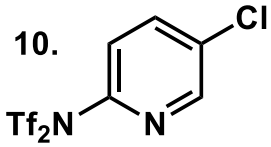
1,4-dioxane

110 °C



18

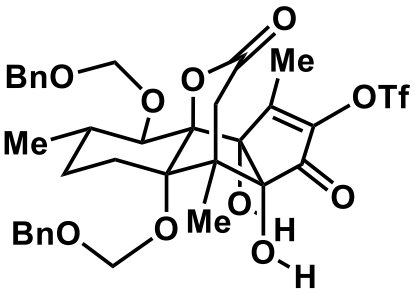
10.



$iPr_2NEt$, $CH_2Cl_2$

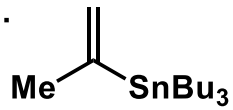
-78 to 0 °C

(28% yield, 2 steps)



19

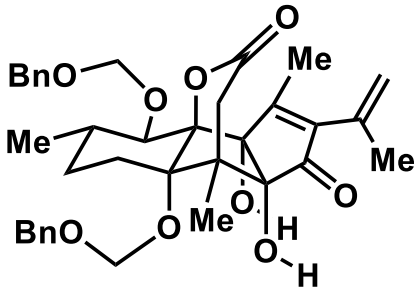
11.



$PdCl_2(PPh_3)_2$

LiCl, 2-MeTHF

(64% yield)



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12. $LiBH_4$, THF

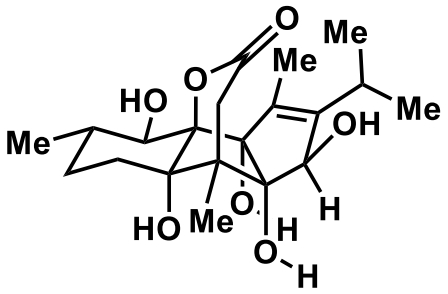
then

$KHF_2$/MeOH

13. $H_2$, $Pd(OH)_2/C$

EtOH, 22 °C

(61% yield, 2 steps)



(+)-anhydroryanodol (3)

14. $CF_3CO_3H$

$Na_2HPO_4$

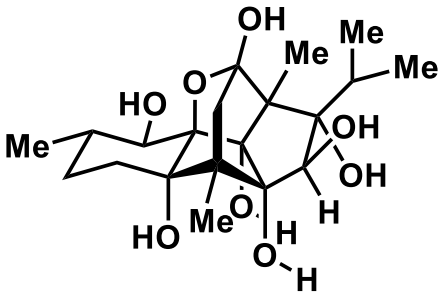
1,2-DCE, 20 °C

(86% yield)

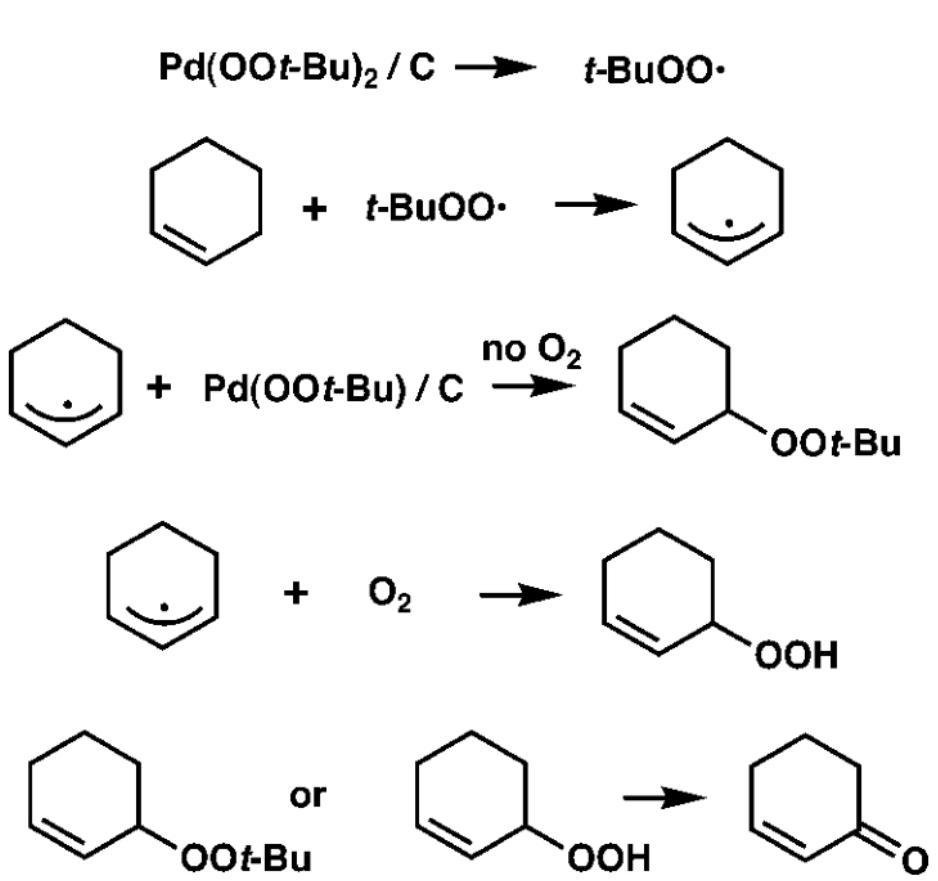
15. $Li^0$, $NH_3$/THF

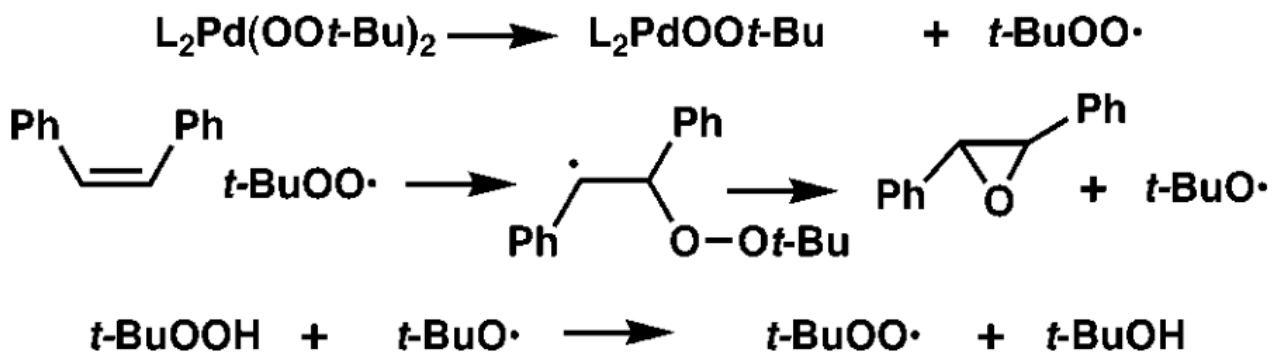
-78 °C

(38% yield)

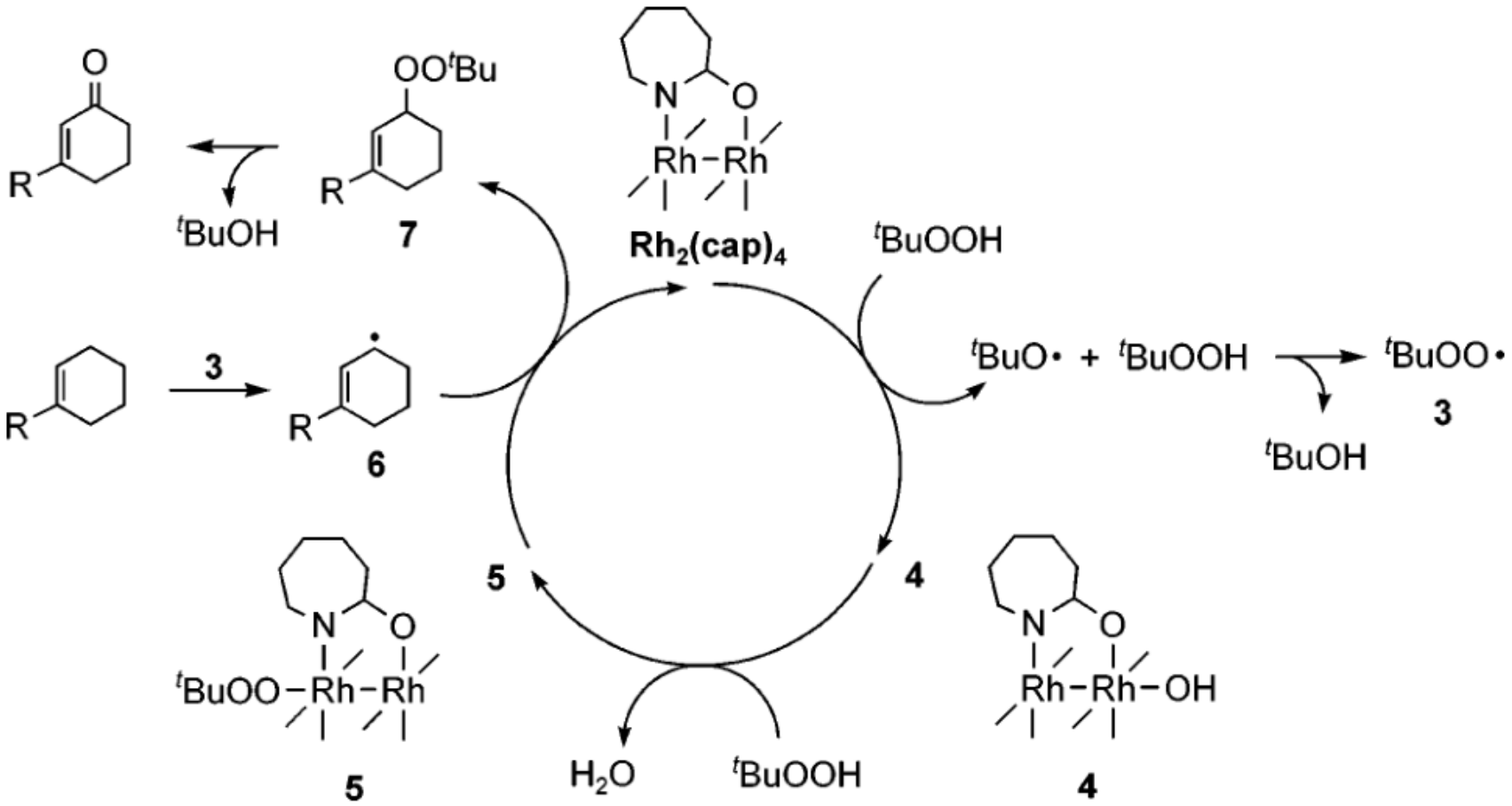


(+)-ryanodol (2)

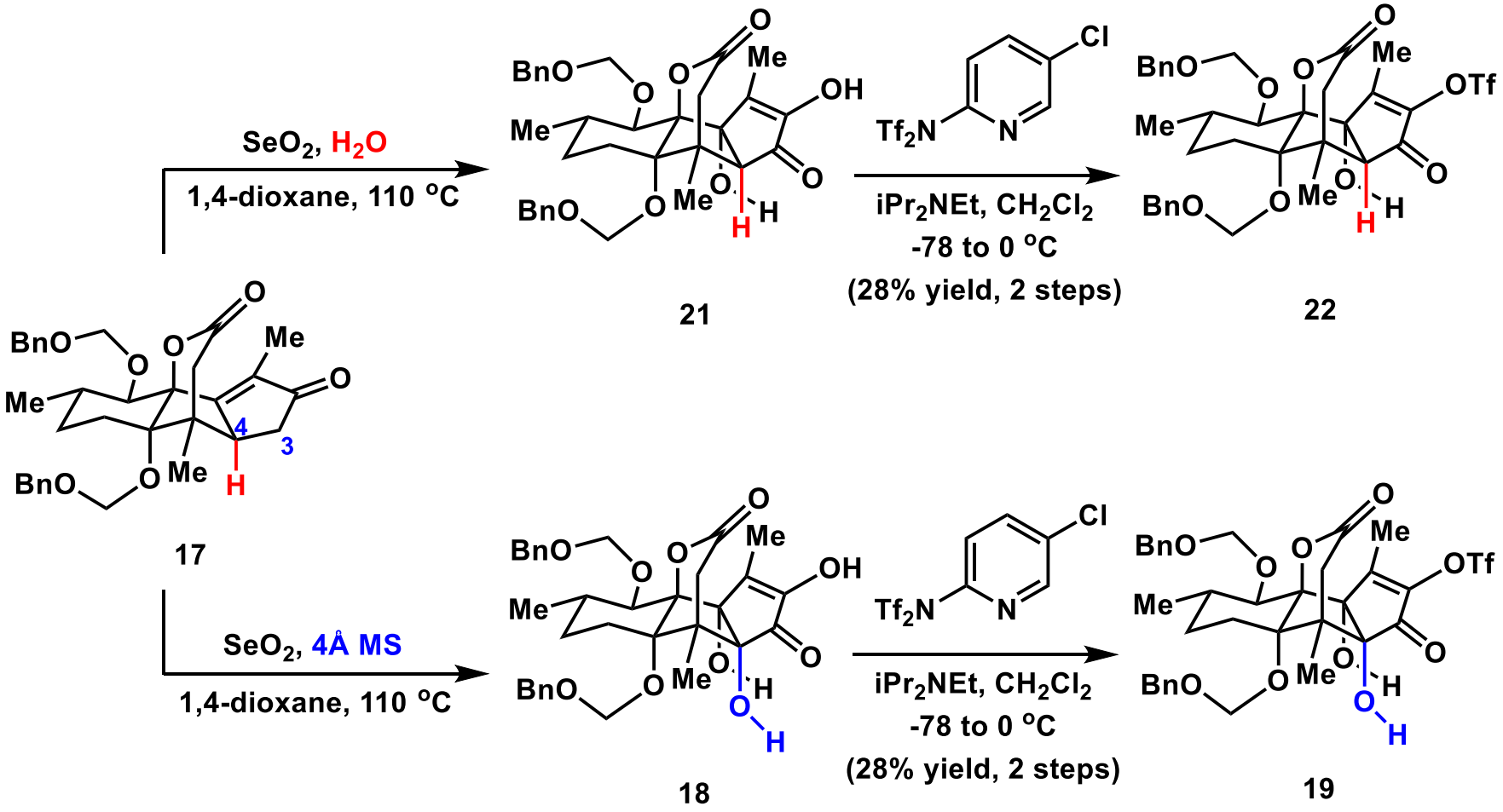


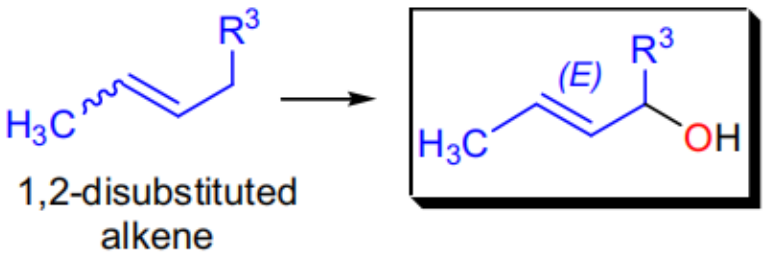

*Org. Lett.*, **2002**, *4*, 2727.

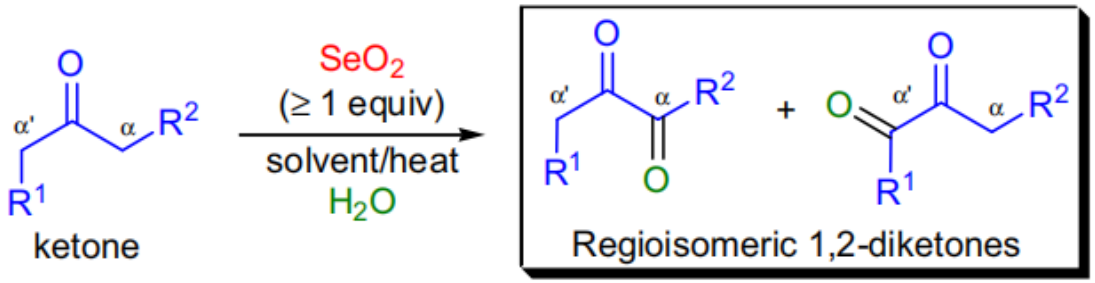



*J. Am. Chem. Soc.*, **2004**, *126*, 13622.

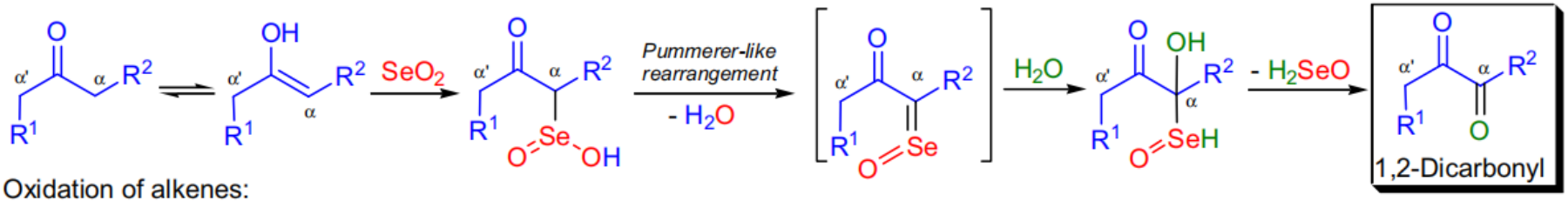

SeO2, H2O
1,4-dioxane, 110 °C
21
iPr2NEt, CH2Cl2
-78 to 0 °C
(28% yield, 2 steps)
22
17
SeO2, 4Å MS
1,4-dioxane, 110 °C
18
iPr2NEt, CH2Cl2
-78 to 0 °C
(28% yield, 2 steps)
19

# RILEY SELENIUM DIOXIDE OXIDATION

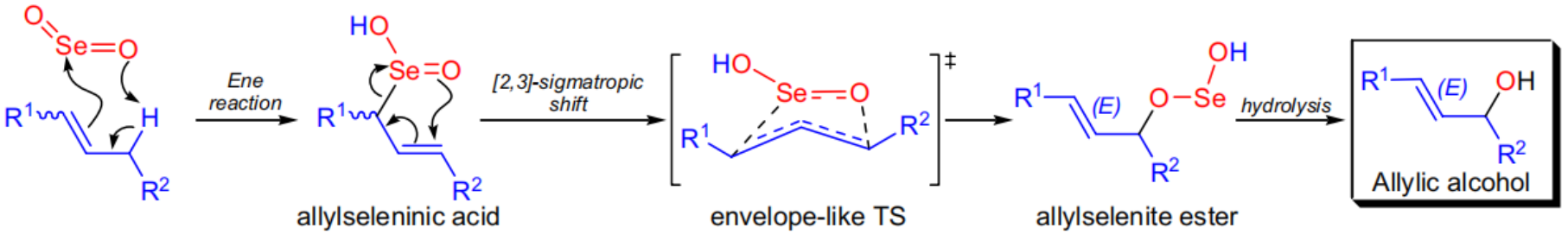


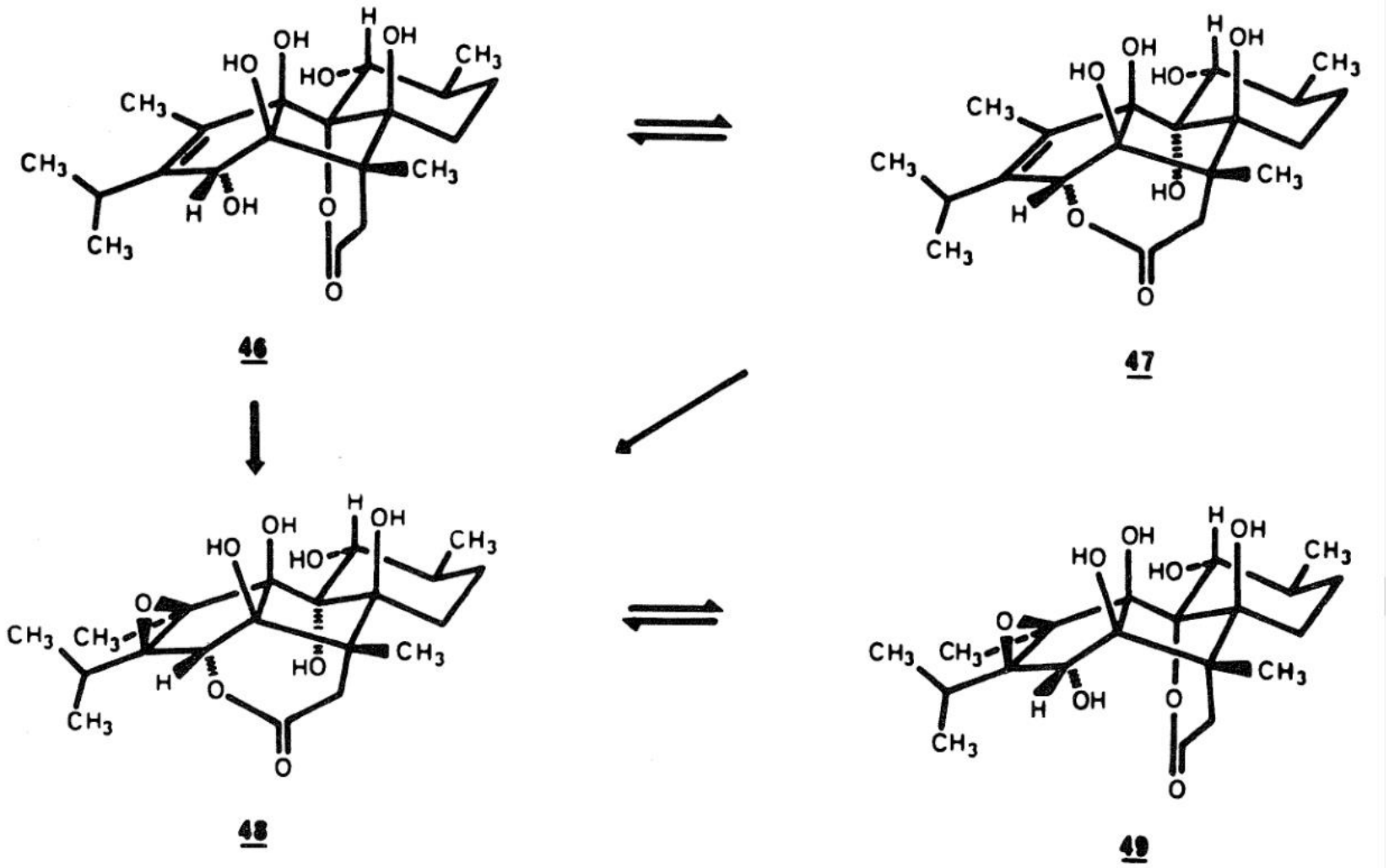




Oxidation of carbonyl compounds:




Oxidation of alkenes:






*Can. J. Chem.*, **1979**, *57*, 3348.