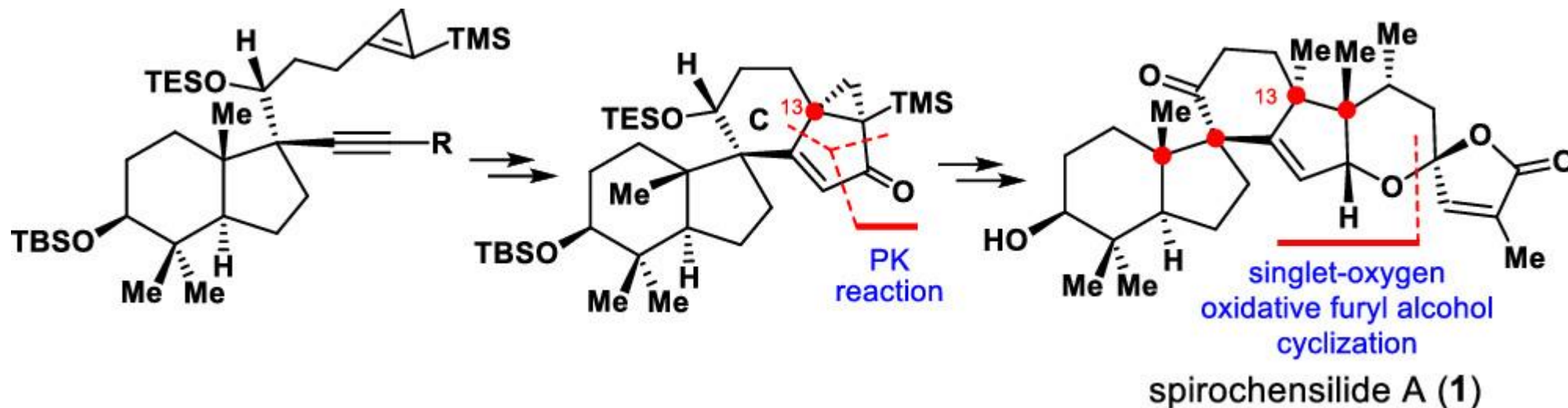


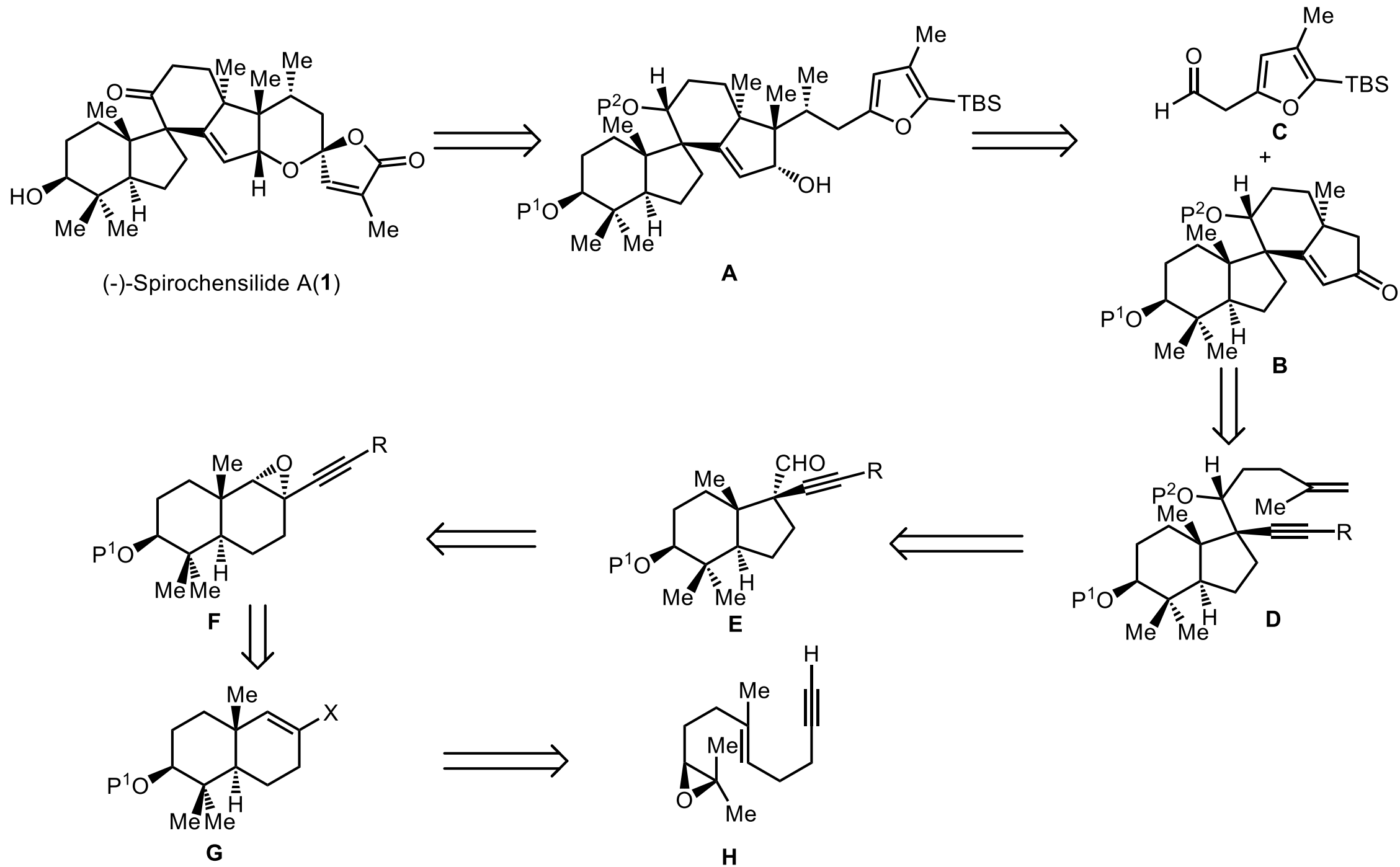
Asymmetric Total Synthesis of (–)-Spirochensilide A

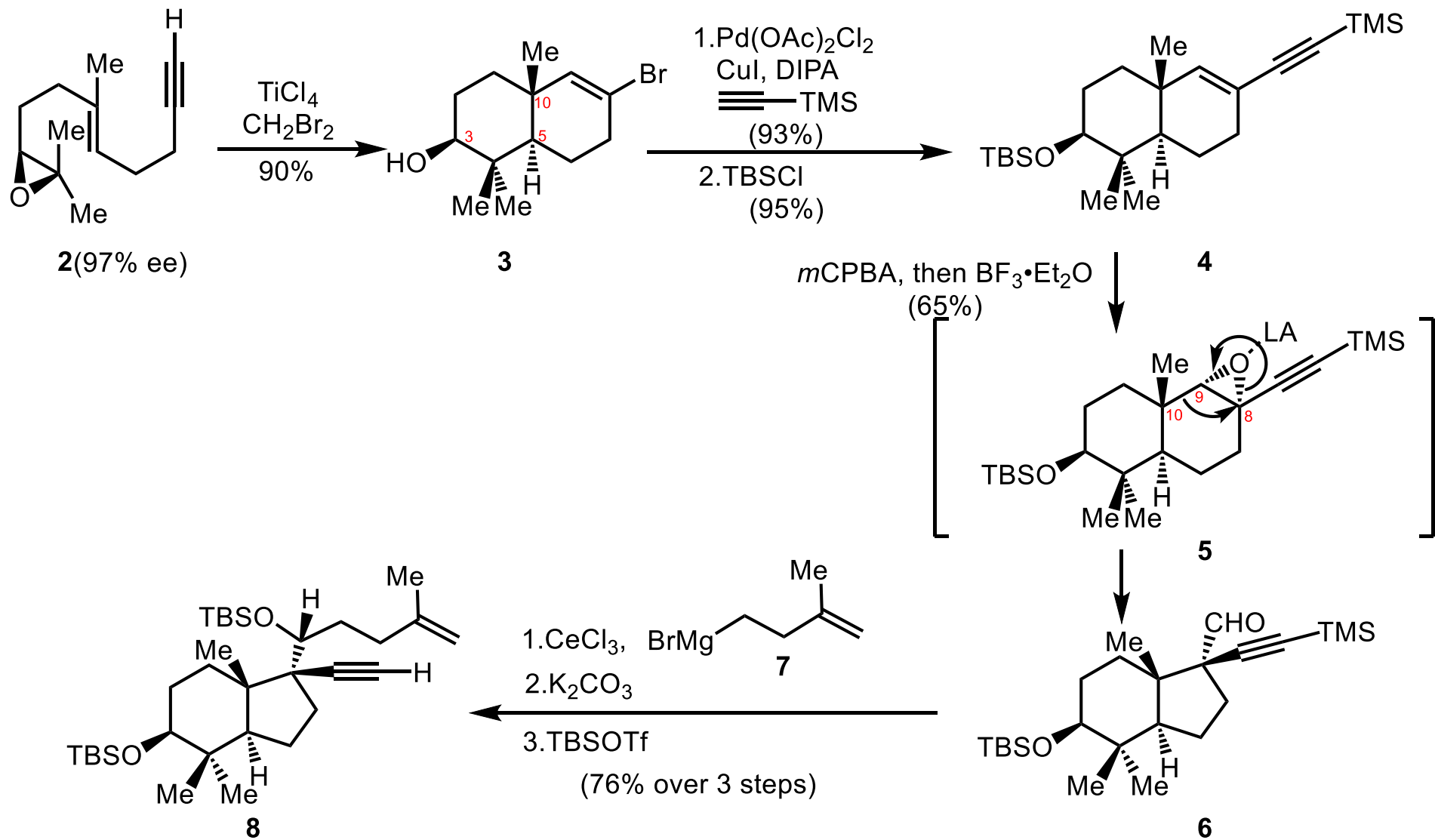
Xin-Ting Liang, Jia-Hua Chen,* and Zhen Yang*

ABSTRACT: An asymmetric total synthesis of (–)-spirochensilide A has been achieved for the first time. The synthesis features a semipinacol rearrangement reaction to stereoselectively construct the two-vicinal quaternary chiral centers at C8 and C10, a tungsten-mediated cyclopropene-based Pauson–Khand reaction to install the C13 quaternary chiral center, and a furan-based oxidative cyclization to stereoselectively form the spiroketal motif.

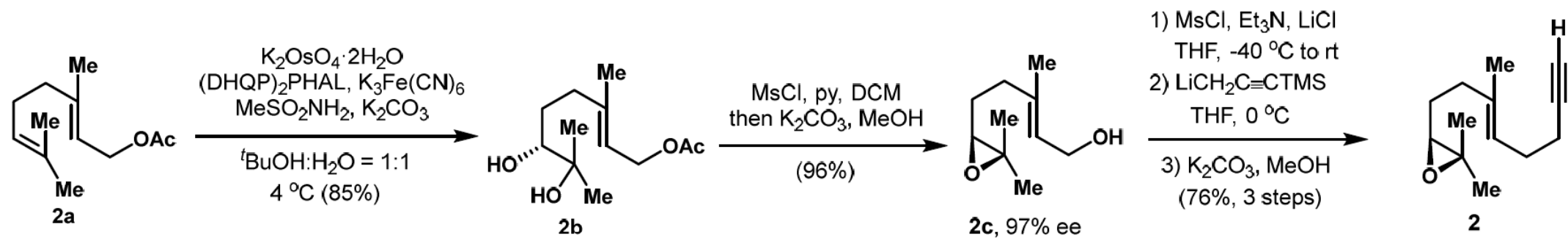


<https://dx.doi.org/10.1021/jacs.0c02522>
J. Am. Chem. Soc. 2020, 142, 8116–8121



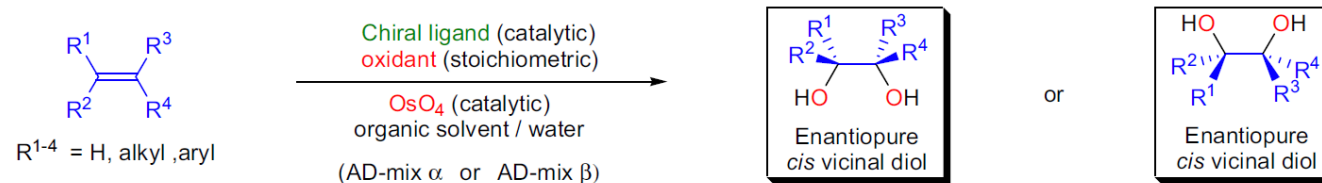


Synthetic route of the known epoxide **2** in asymmetric form:

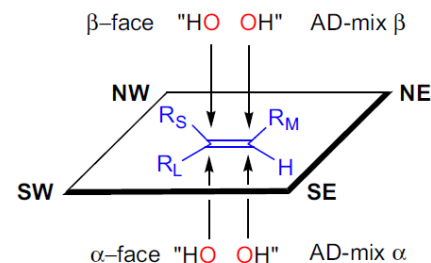


SHARPLESS ASYMMETRIC DIHYDROXYLATION

(References are on page 673)

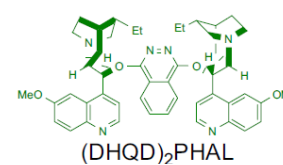
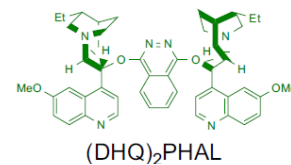


Empirical model (mnemonic device):

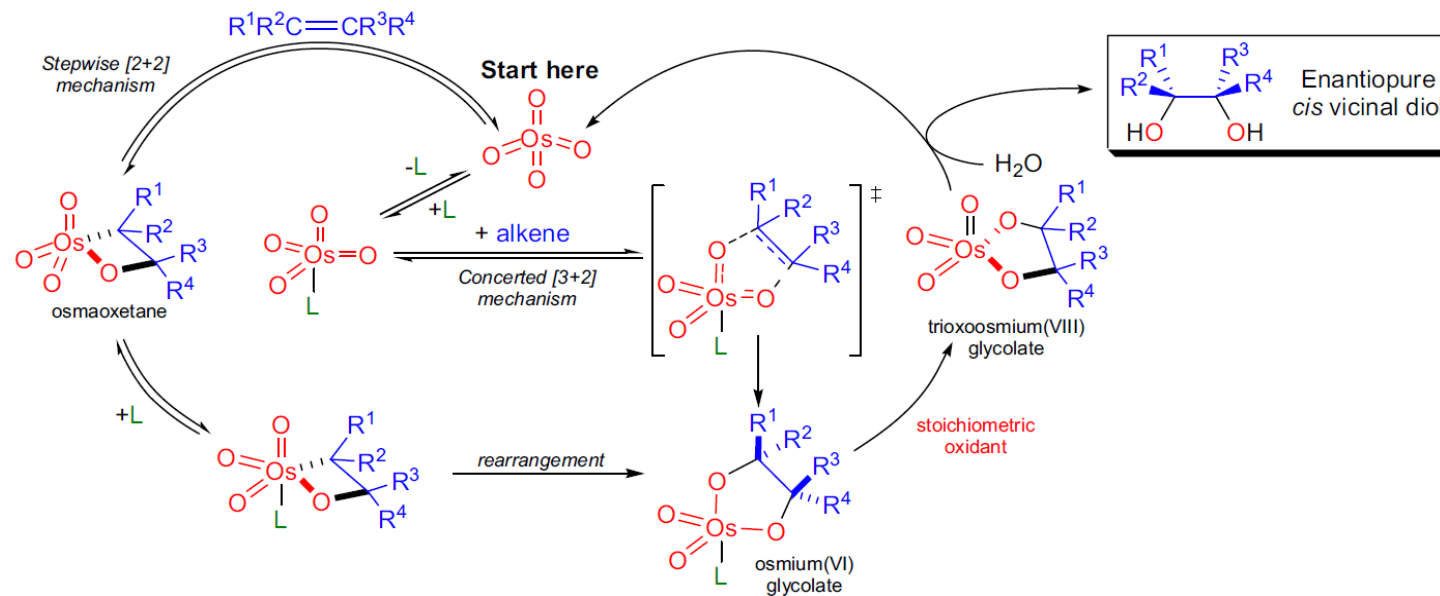


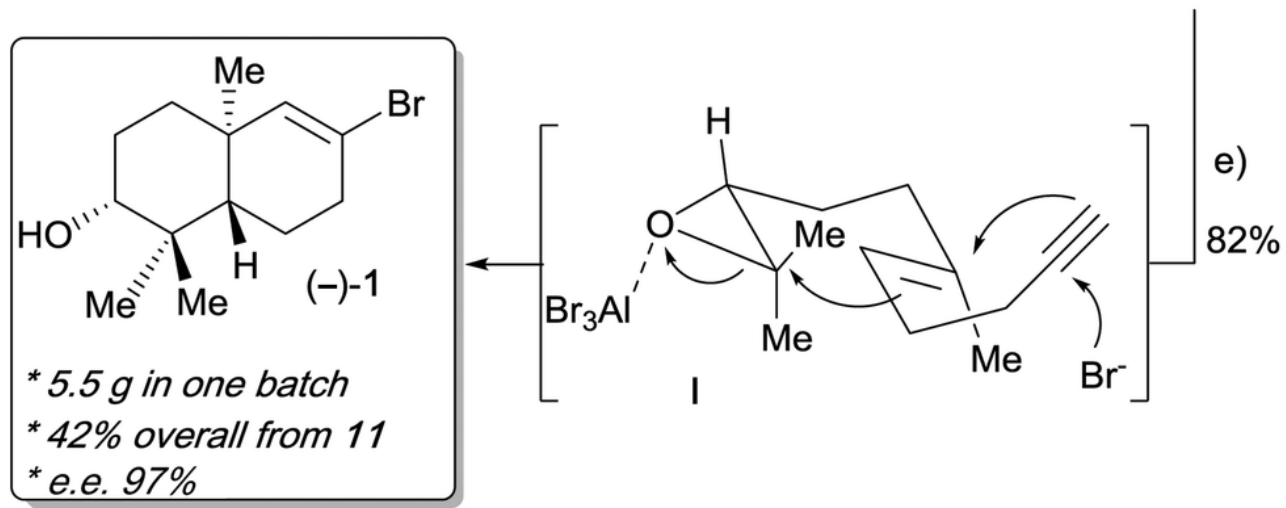
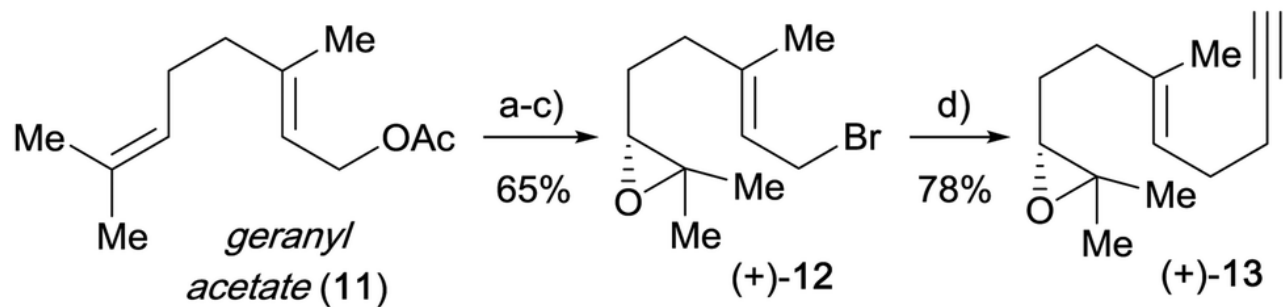
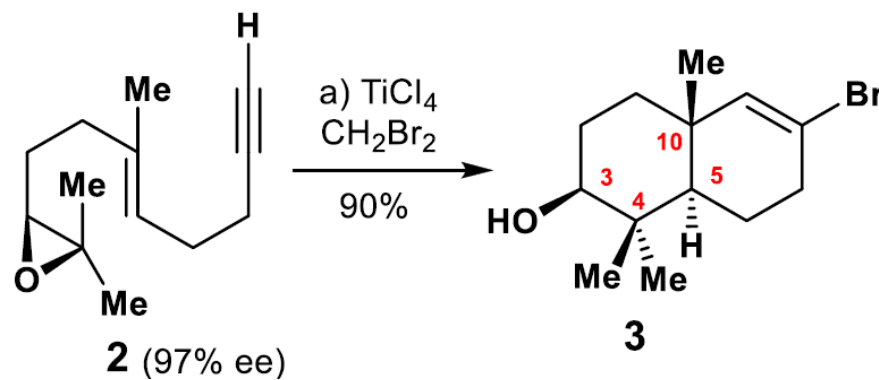
AD-mix α : (DHQ)₂PHAL + K₂OsO₂(OH)₄ + K₃Fe(CN)₆

AD-mix β : (DHQD)₂PHAL + K₂OsO₂(OH)₄ + K₃Fe(CN)₆



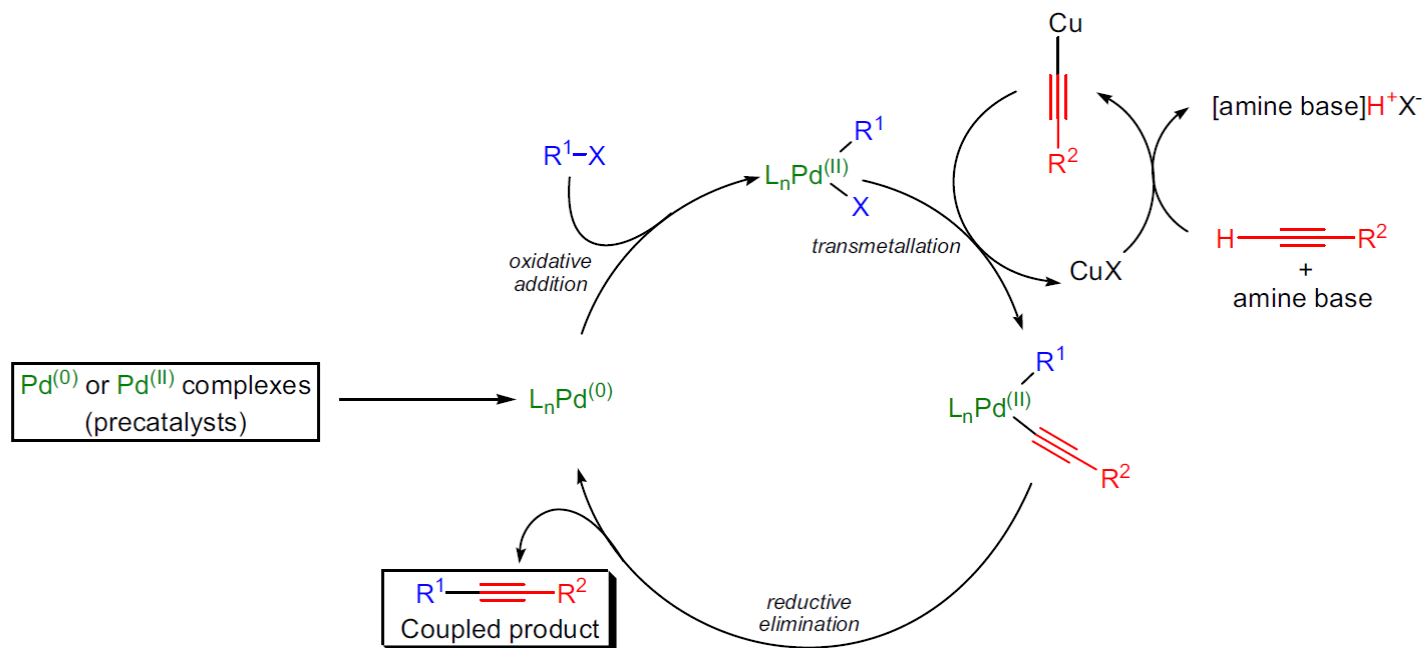
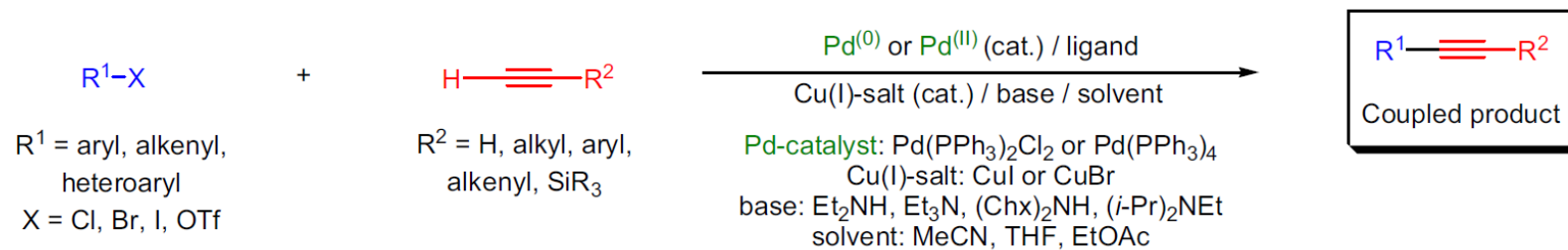
Mechanism: 53-77





SONOGASHIRA CROSS-COUPLING

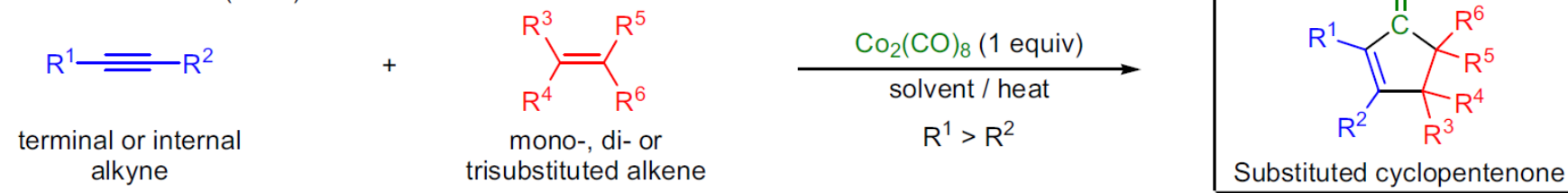
(References are on page 681)



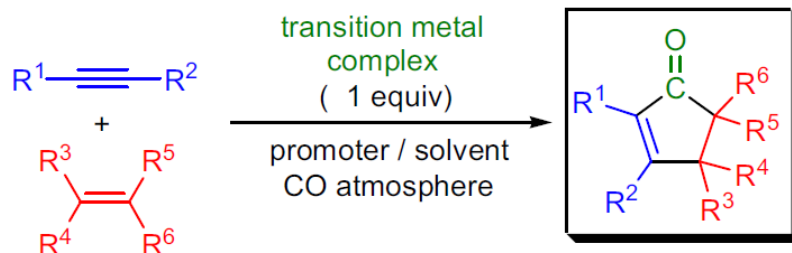
PAUSON-KHAND REACTION

(References are on page 647)

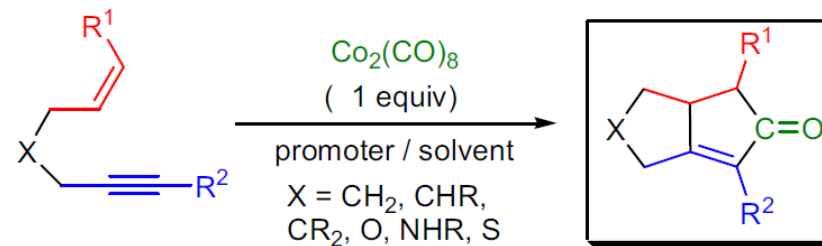
Pauson & Khand (1973):



Modified P-K reaction:



Intramolecular variant:



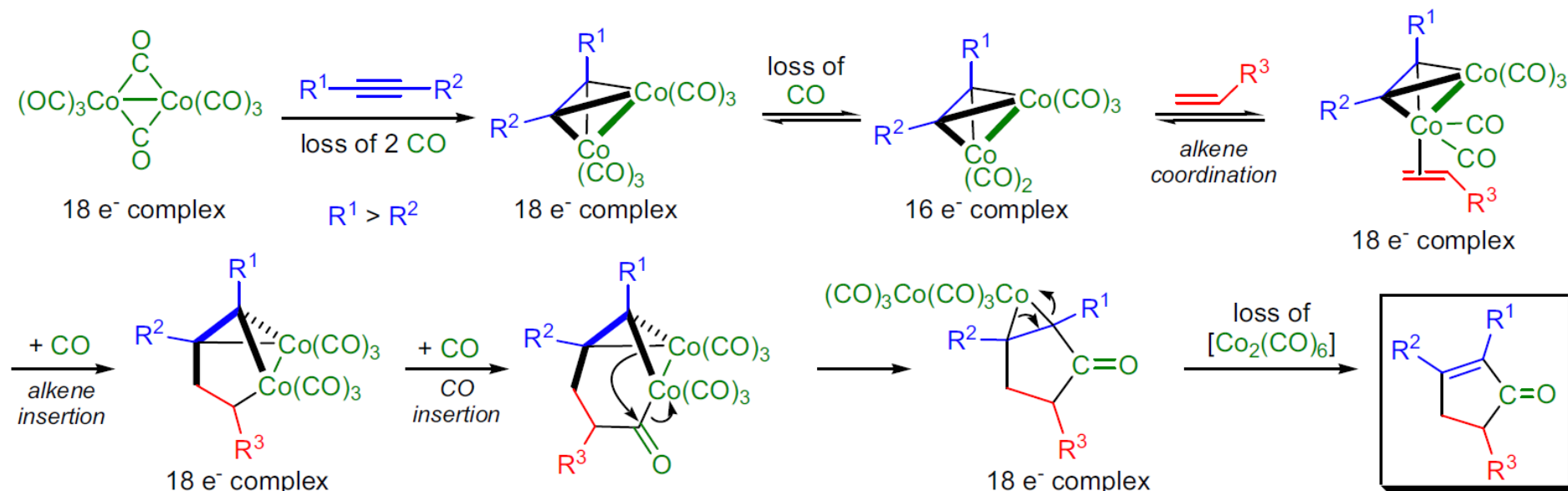
$R^{1-6} = \text{H, alkyl, aryl, substituted alkyl and aryl}$; transition metal complex: $\text{Co}_2(\text{CO})_8$, $\text{Fe}(\text{CO})_5$, $\text{Ru}_2(\text{CO})_{12}$, Cp_2TiR_2 , $\text{Ni}(\text{COD})_2$, $\text{W}(\text{CO})_6$, $\text{Mo}(\text{CO})_6$, $[\text{RhCl}(\text{CO})_2]_2$; promoter: NMO, TMAO, RSCH_3 , high-intensity light/photolysis, "hard" Lewis base

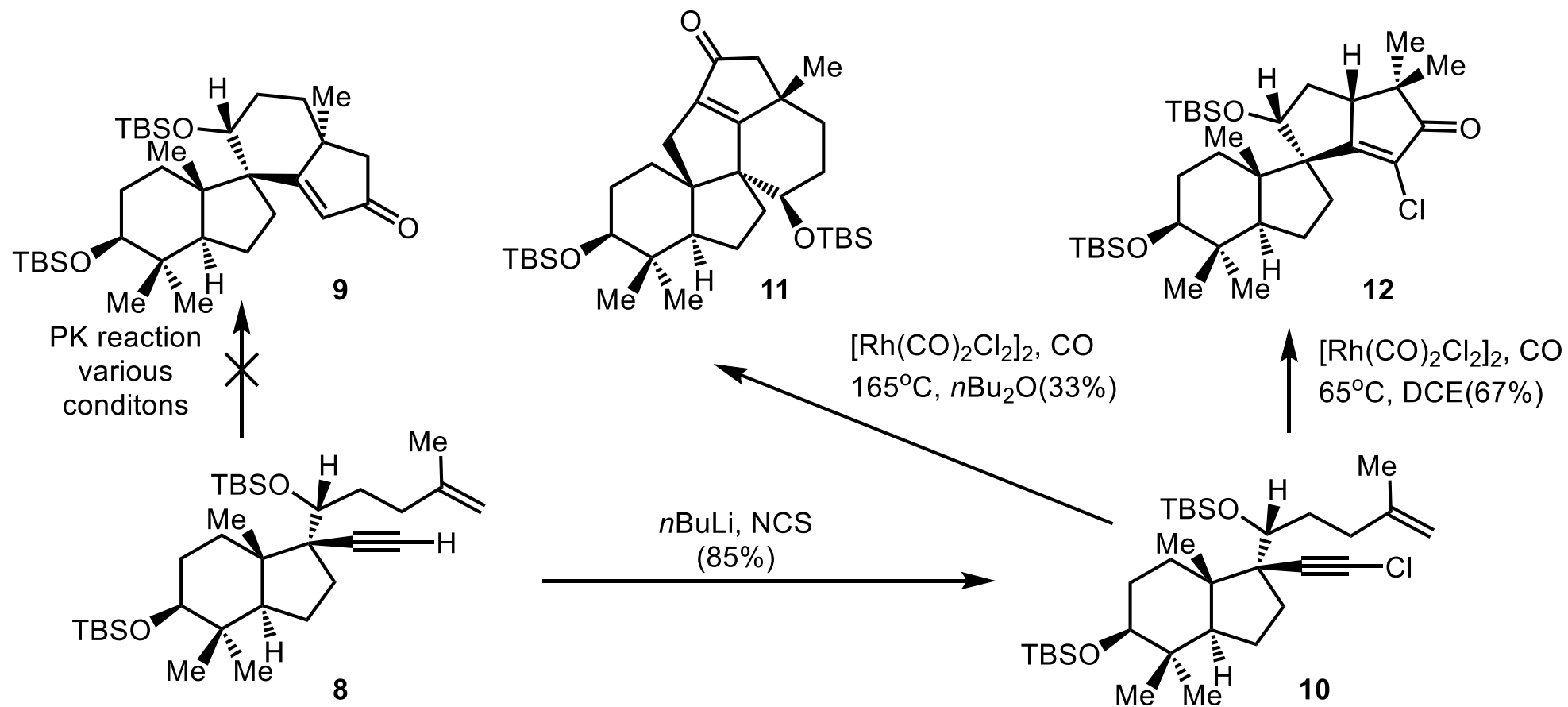
PAUSON-KHAND REACTION

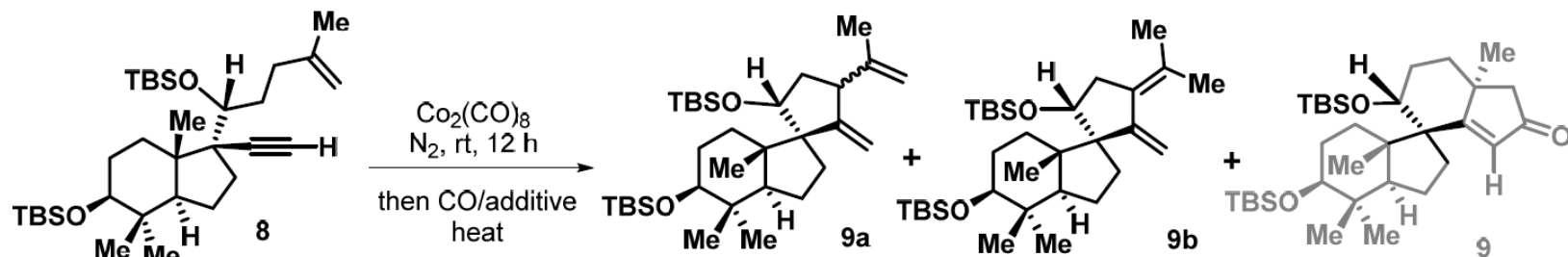
(References are on page 647)

Mechanism:

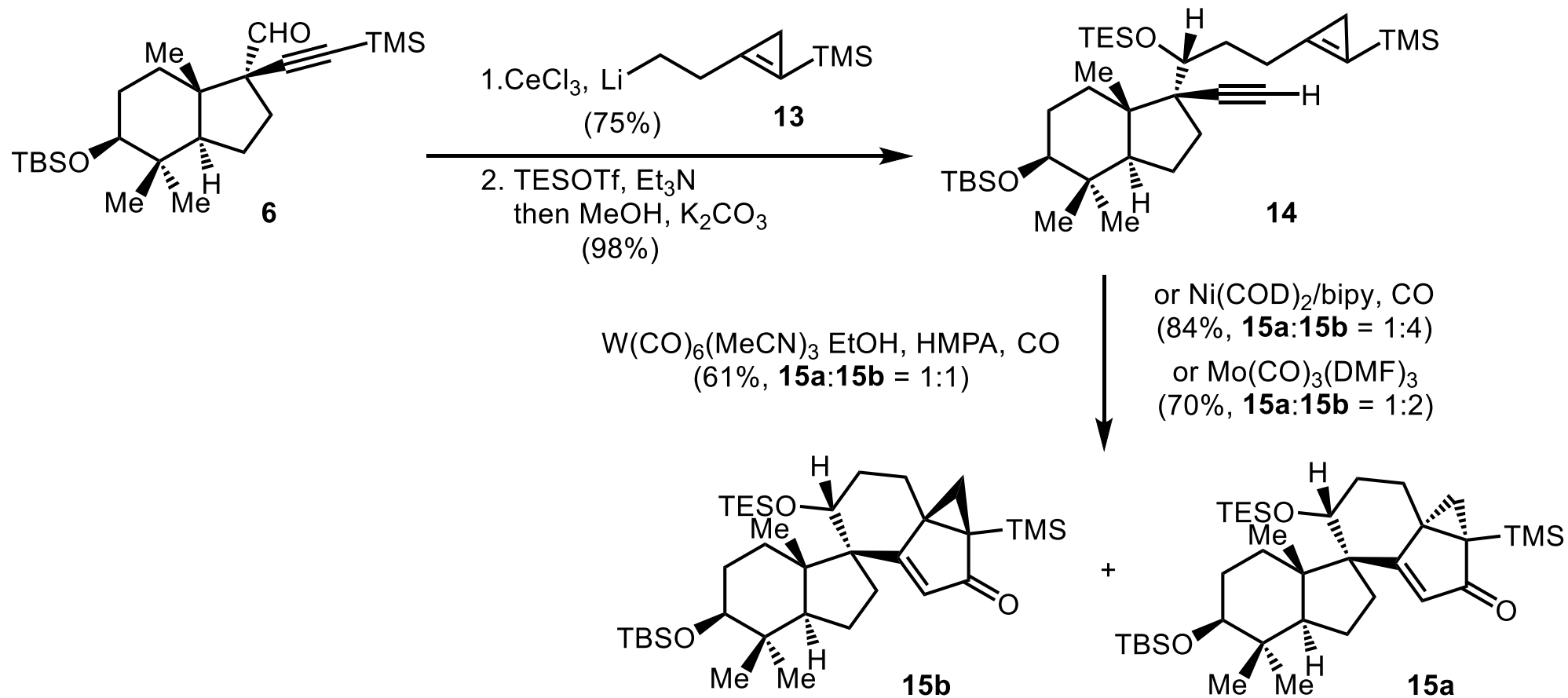
The mechanism of the *Pauson-Khand reaction* has not been fully elucidated. However, based on the regio- and stereochemical outcome in a large number of examples, a reasonable hypothesis has been inferred.



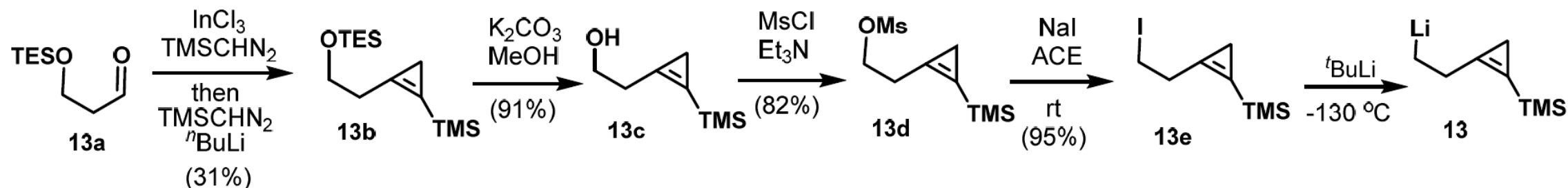




Entry	Additive	Equiv	Solvent	Temperature	Atmosphere	Result
1	-	-	tol.	110 °C	CO	9a+9b
2	celite	3.0 wt.	tol.	110 °C	CO	9a+9b
3	celite	3.0 wt.	tol.	95 °C	CO	8
4	4Å MS	3.0 wt.	tol.	95 to 110 °C	CO	9a+9b
5	CyNH ₂	3.0	tol.	85 °C	CO	8
6	TMTU	6.0	tol.	95 °C	CO	8
7	NMO	3.0	tol.	85 °C	CO	8
8	NMO	3.0	tol.	110 °C	CO	9a
9	4Å MS, TMANO	3.0 wt., 3.0	tol.	95 °C	CO	8
10	TMANO	3.0	THF	60 °C	CO	8
11	<i>n</i> BuSMe	3.0	tol.	95 °C	CO	8+9a
12	-	-	tol.	95 to 110 °C	N ₂	9a
13	-	-	tol.	125 °C	CO (20 atm)	8

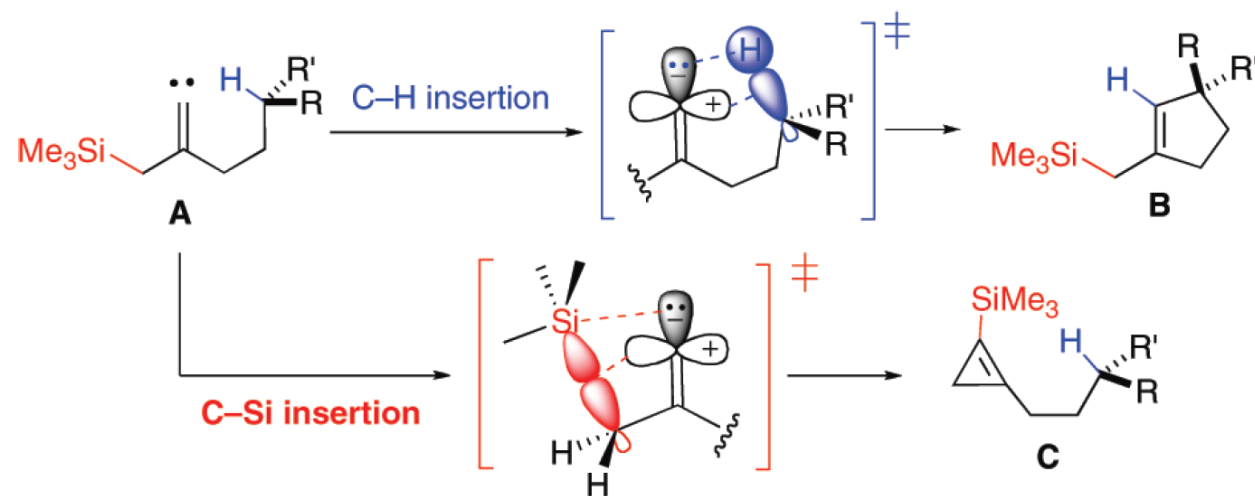
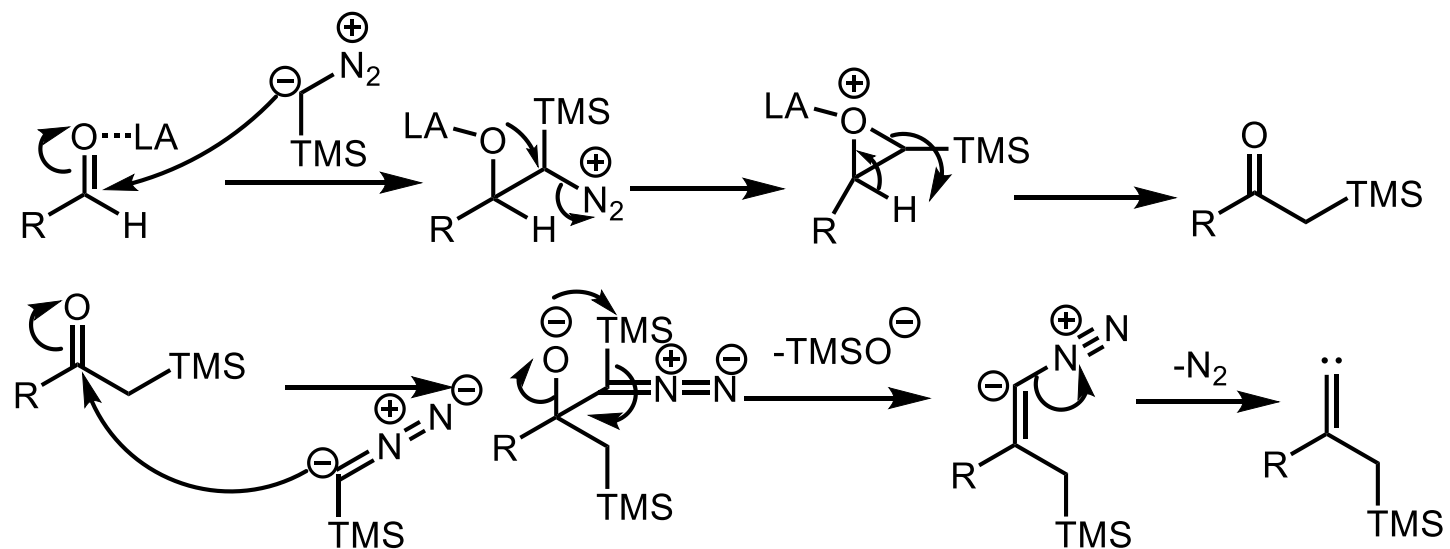


Synthetic route of lithium reagent **13**:

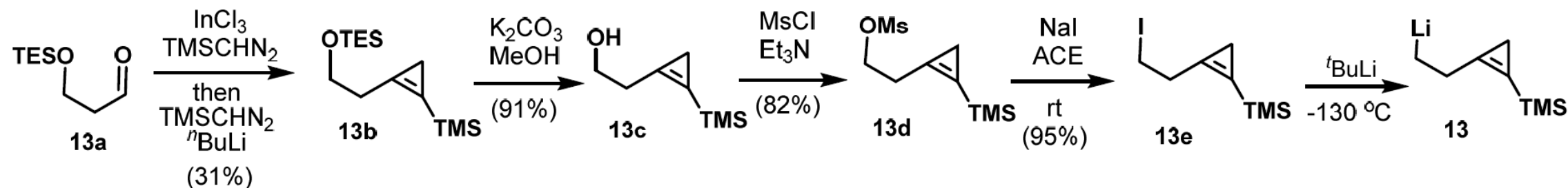


Compound **13b** was synthesized following slightly modified published methods.⁶ To a solution of compound **13a** (35.0 g, 186 mmol, 1.0 equiv) and TMSCHN₂ (112 mL, 2 M in hexane, 223 mmol, 1.2 equiv) in a mixed solvent of dry DCM and Et₂O = 1:1, 200 mL) was added InCl₃ with released bubble, and the reaction temperature was maintained at 25 °C using a water bath, and reaction was stirred at 25 °C for 1 h. The solvent and excess amount of trimethylsilyldiazomethane were removed under vacuum, and the crude α -TMS ketone was used in the next step without purification.

To a cooled (-78 °C) solution of TMS diazomethane (112 mL, 2 M in hexane, 223 mmol, 1.2 equiv) in THF (400 mL) was added *n*BuLi (93.0 mL, 2.5 M in hexane, 233 mmol, 1.25 equiv) in a dropwise manner under N₂ atmosphere, and the mixture was stirred at -78 °C for 30 minutes. To this solution was added a solution of the α -TMS ketone made above in THF (100 mL) in a dropwise manner, and the reaction mixture was stirred at -78 °C for 20 minutes. The reaction mixture was warmed up to room temperature and then quenched by addition of a saturated solution of NH₄Cl (30 mL), and then dried over anhydrous MgSO₄ directly. The mixture was filtered off through a short silica gel plug (washed with petroleum ether, 3 \times 200 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by a flash chromatography on silica gel (petroleum ether/DCM = 150:1) to give the desired product **13b** (15.6 g, 31%) as a light yellowish oil.

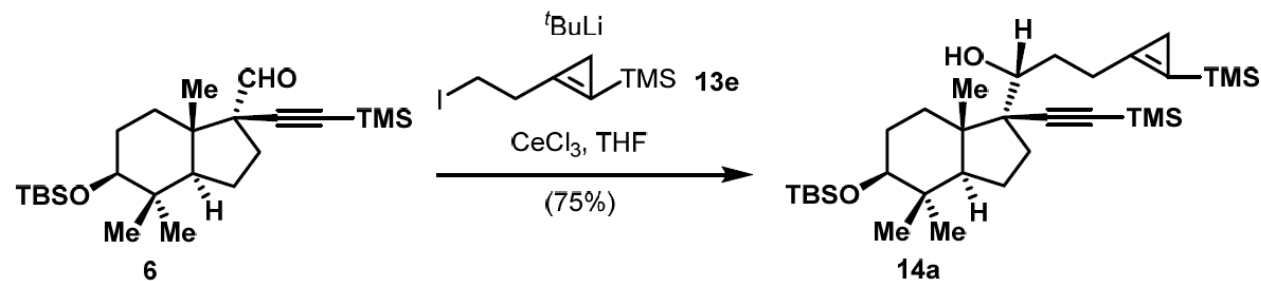


Synthetic route of lithium reagent **13**:



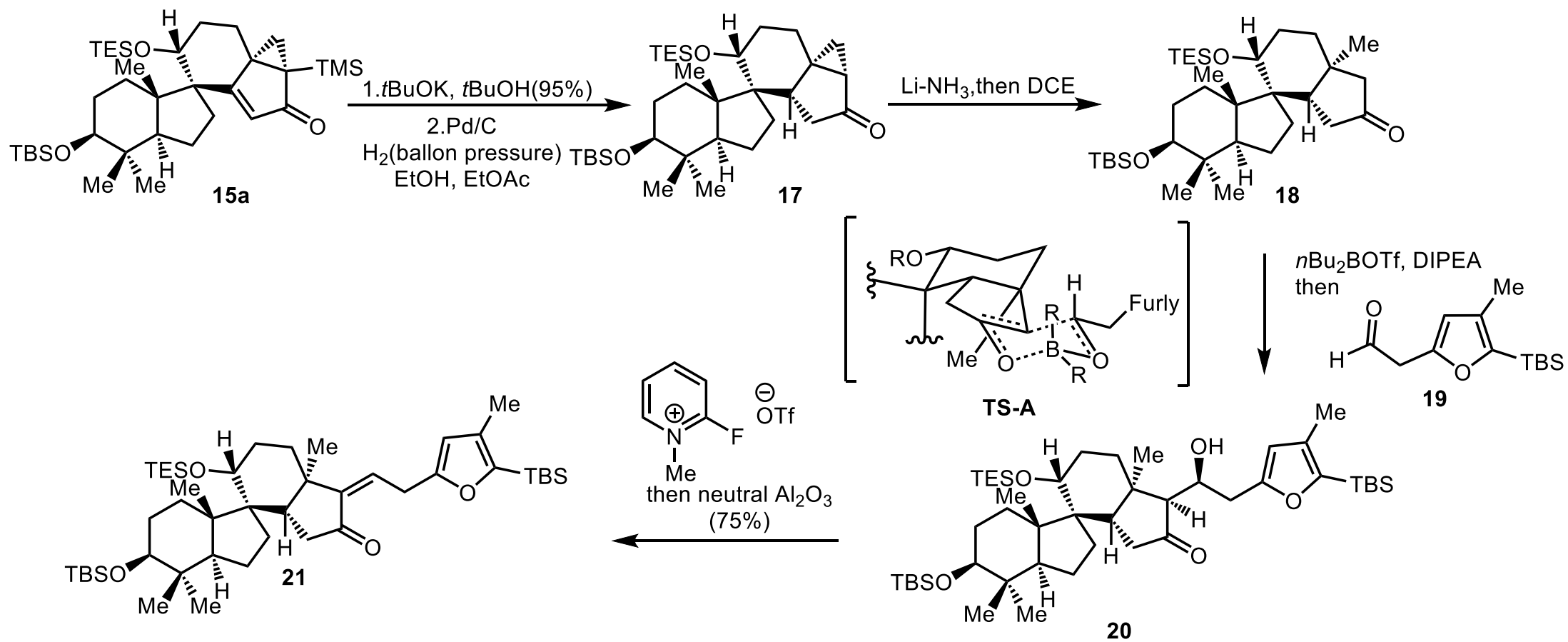
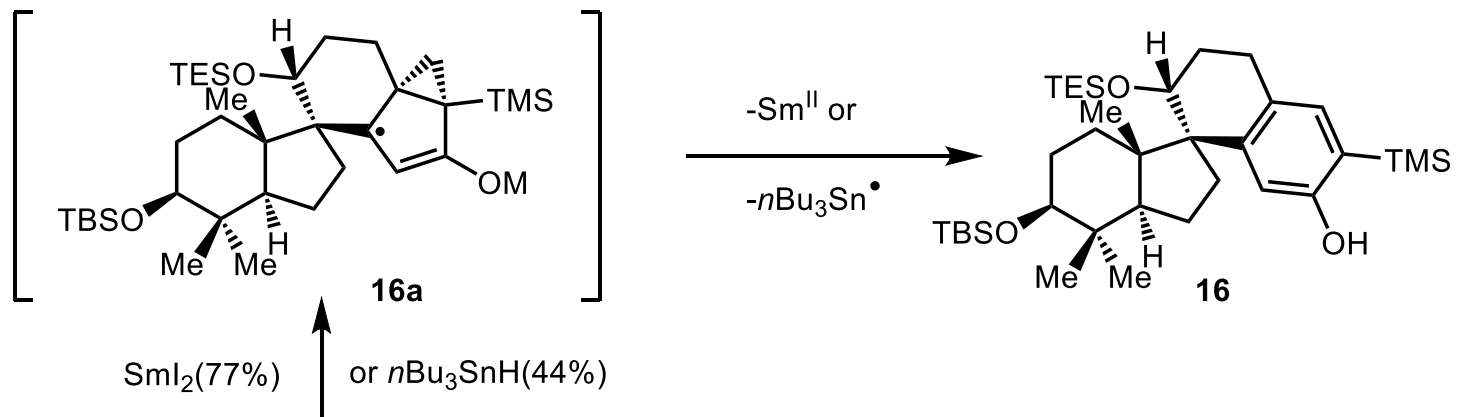
Note: alkyl lithium reagent **13** was freshly prepared according to the following procedure: ^tBuLi (22.0 mL, 1.25 M in pentane, 27.5 mmol, 2.6 equiv) was slowly added along flask wall to the solution of compound **13e** (3.66 g, 13.8 mmol, 1.3 equiv) in dry pentane (30 mL) and Et₂O (30 mL) mixed solvent at -130 °C. The resultant light yellow solution was stirred at -130 °C for 1h, and then transferred to -78 °C bath directly and stirred for 20 min to form an off-white suspension, and then re-cooled to -130 °C.

Synthesis of compound 14a:

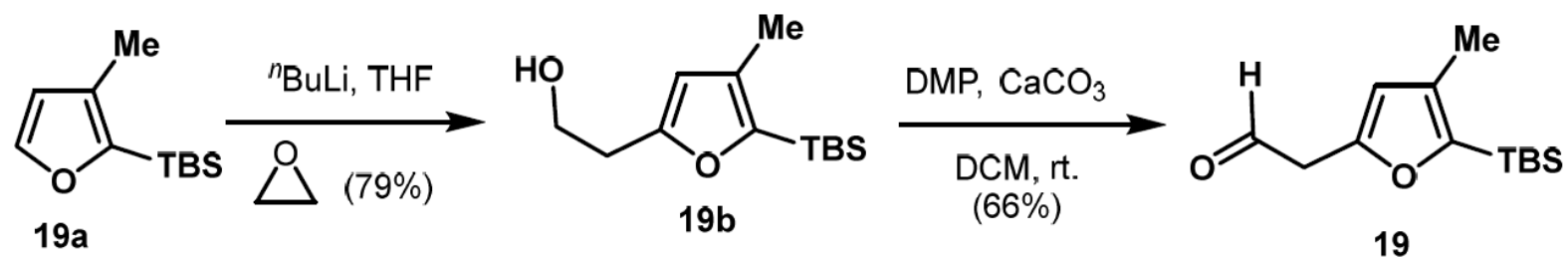


To a round bottom flask equipped with a stirring bar was added CeCl_3 (3.39 g, 13.8 mmol, 1.3 equiv), and the flask was heated to 160 °C under vacuum for 1.5 h. After cooling back to 0 °C, a solution of THF (34 mL) was added to the above flask, and the resultant mixture was stirred at room temperature for 10 h. To this solution was added a solution of compound **6** (4.45 g, 10.6 mmol, 1.0 equiv) in THF (20 mL), and the mixture with white suspension was stirred at room temperature for 2 h.

To the suspension of the CeCl_3 -complex compound **6** was added the freshly prepared alkyl lithium **13** (stored at -130 °C) at -98 °C via a cannula (diameter = 2.0 mm, wrapped with tissue) as fast as possible, and the resultant mixture was stirred with gradually warming up to -60 °C over 2.5 h. The reaction mixture was quenched by addition of a saturated solution of Seignette salt (50 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by a flash chromatography on silica gel (petroleum ether/DCM = 10:1 to 3:1) to give product **14a** (4.46 g, 75%) as viscous colorless gel.

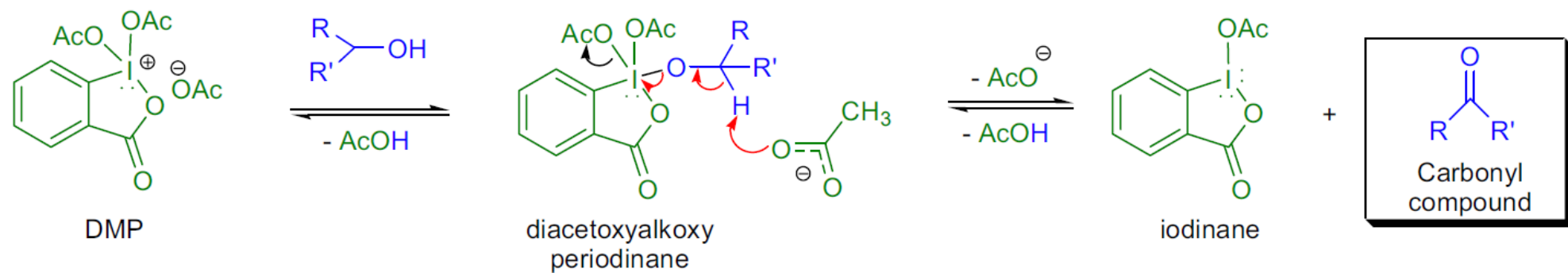
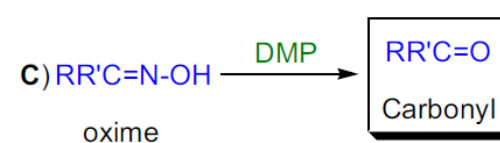
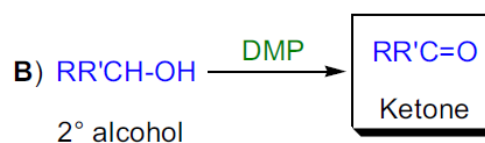
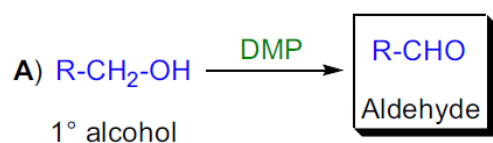
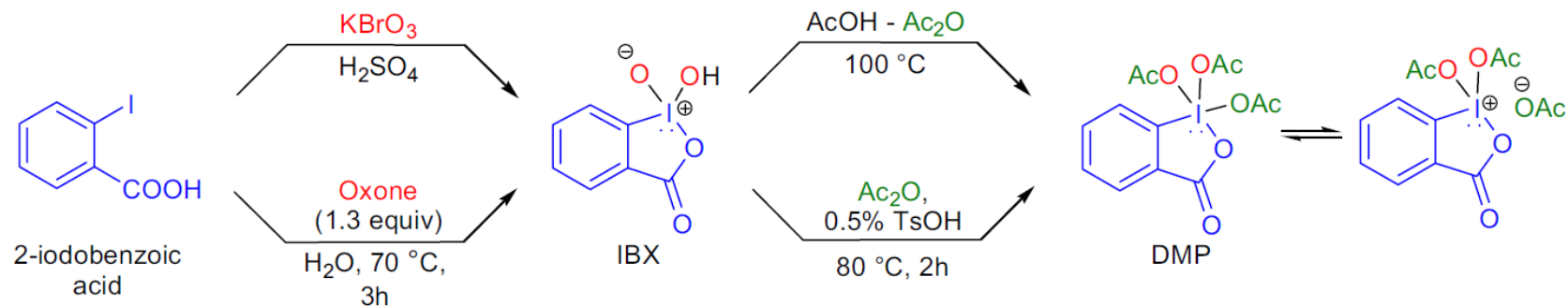


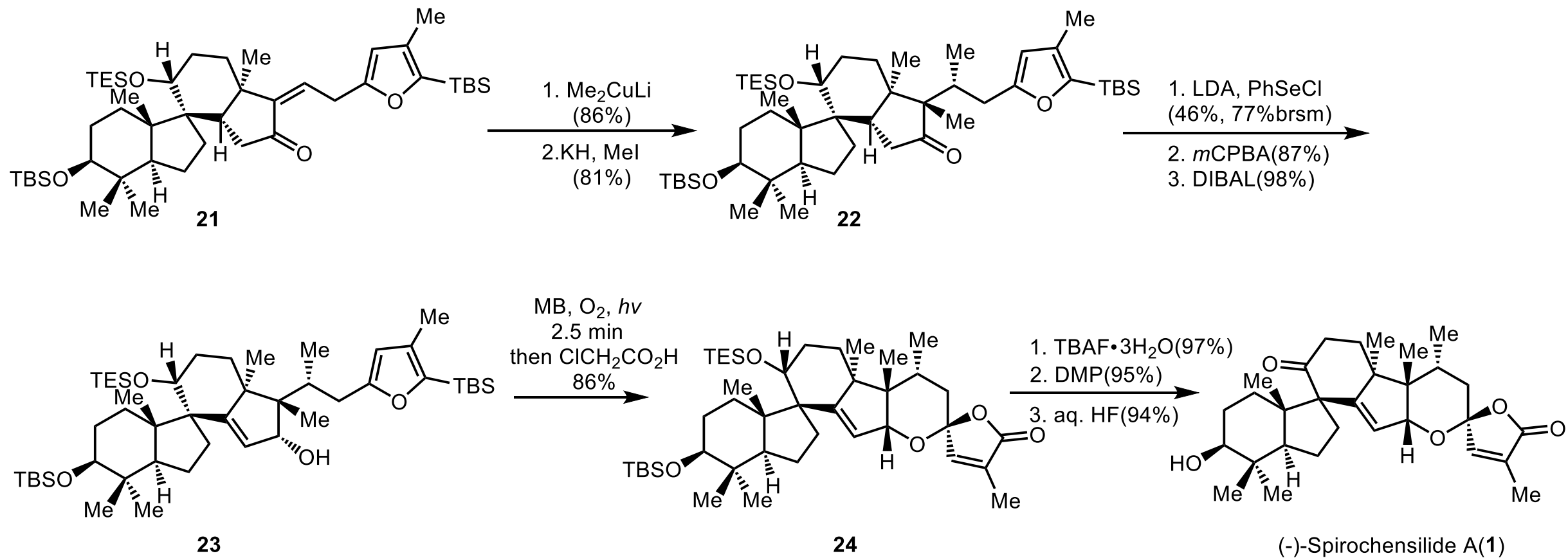
Synthetic route of furyl acetaldehyde 19:



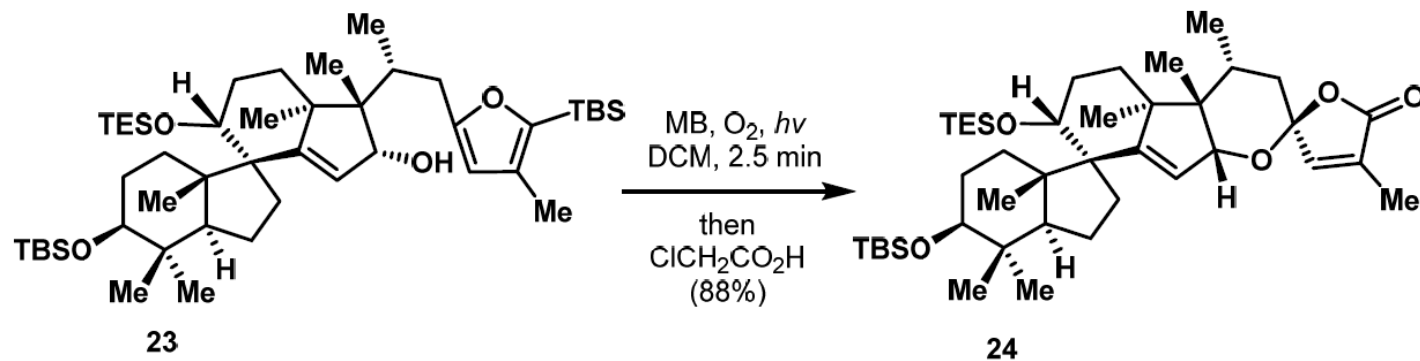
DESS-MARTIN OXIDATION

(References are on page 574)

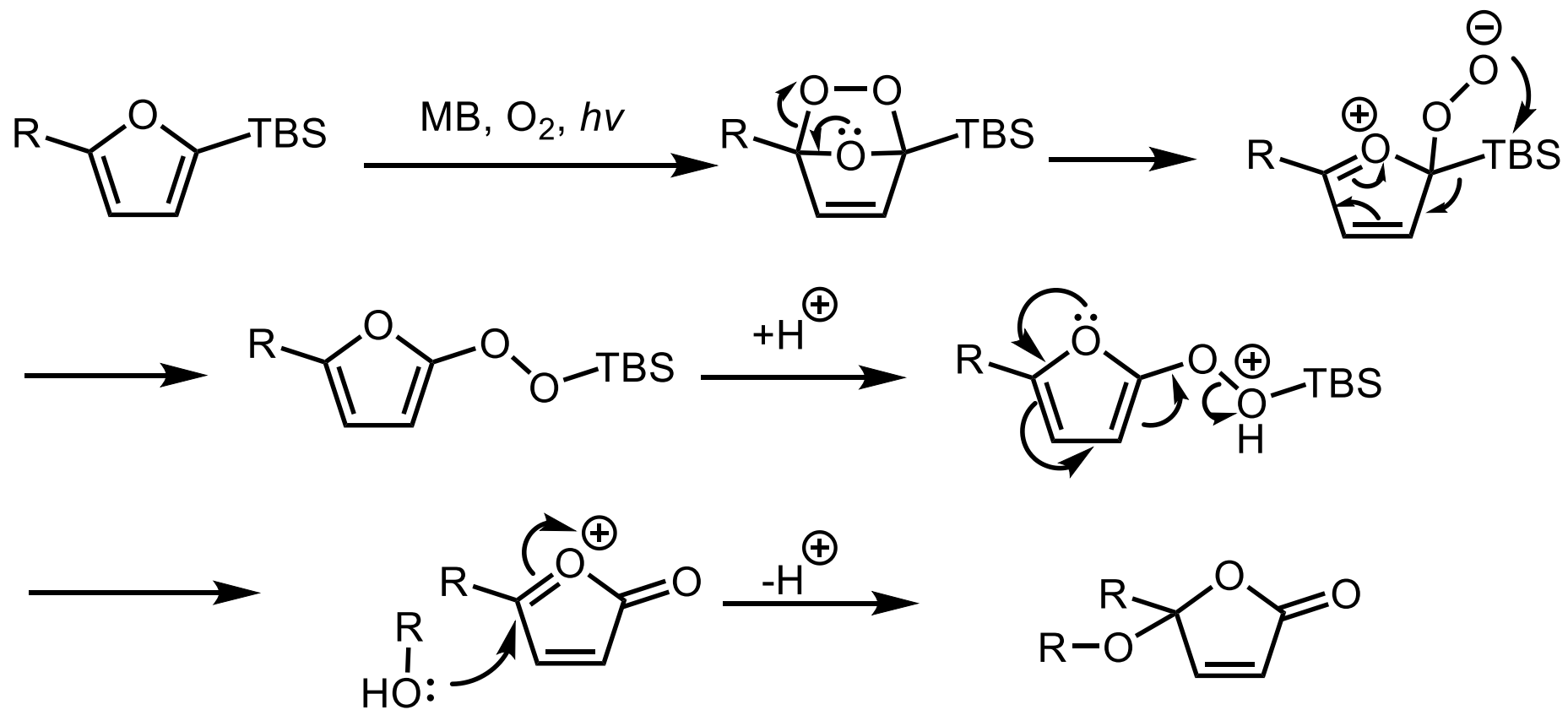




Synthesis of compound **24**:



Compound **23** (240 mg, 0.295 mmol, 1.0 equiv) was dissolved in DCM (15 mL), and the mixture was bubbled with O₂ at 0 °C for 10 min. To this solution was added a solution of methylene blue (MB) in a dropwise manner, and the resultant mixture was adjusted the concentration of MB to 10⁻⁴ M by colorimetric method. The reaction mixture was saturated with O₂ through bubbling with O₂ at 0 °C, and the resultant reaction mixture was irradiated with a 500 W tungsten lamp at 0 °C for 2.5 min (the completion of reaction was monitored by TLC). To this solution was added a solution of ClCH₂CO₂H (750 mg) and H₂O (0.75 mL) in MeCN (15 mL) at room temperature, and the mixture was stirred in dark for 1 h. The reaction mixture was quenched by addition of a saturated solution of NaHCO₃ (30 mL) and Na₂S₂O₃ (10 mL) at 0 °C, and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over Na₂SO₄, and solvent was removed under vacuum. The residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 125:1 to 100:1) to give product **24** (185 mg, 88%) as white solid.



Tetrahedron, 1967, 23, 2583-2599.