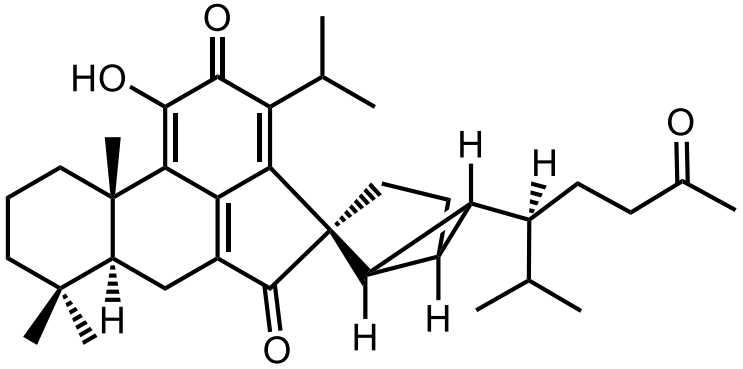
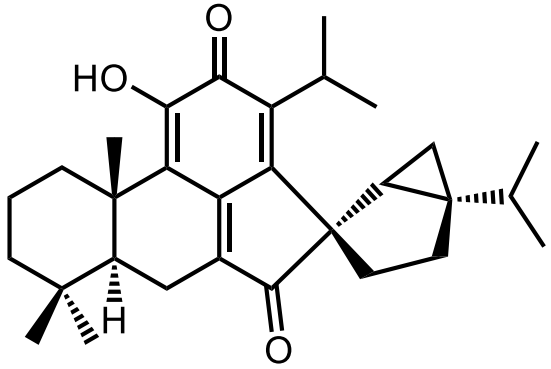
# Total Synthesis of Cryptotrione

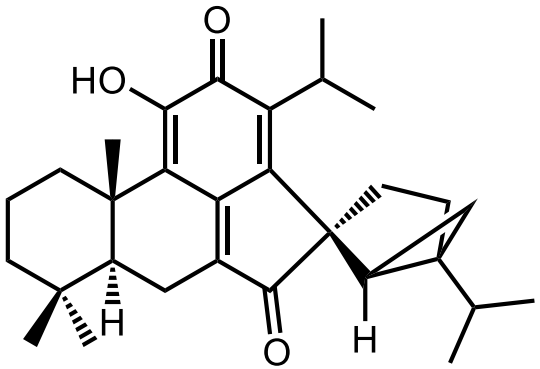
Mao-Yun Lyu, Zhuliang Zhong, Vanessa Kar-Yan Lo, Henry N. C. Wong,* Xiao-Shui Peng *



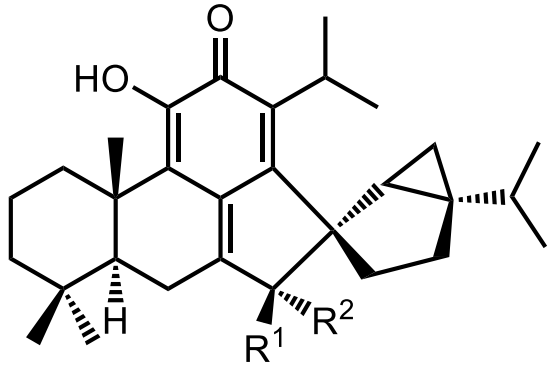

cryptotrione(**1**)




chamaecydin(**2**)

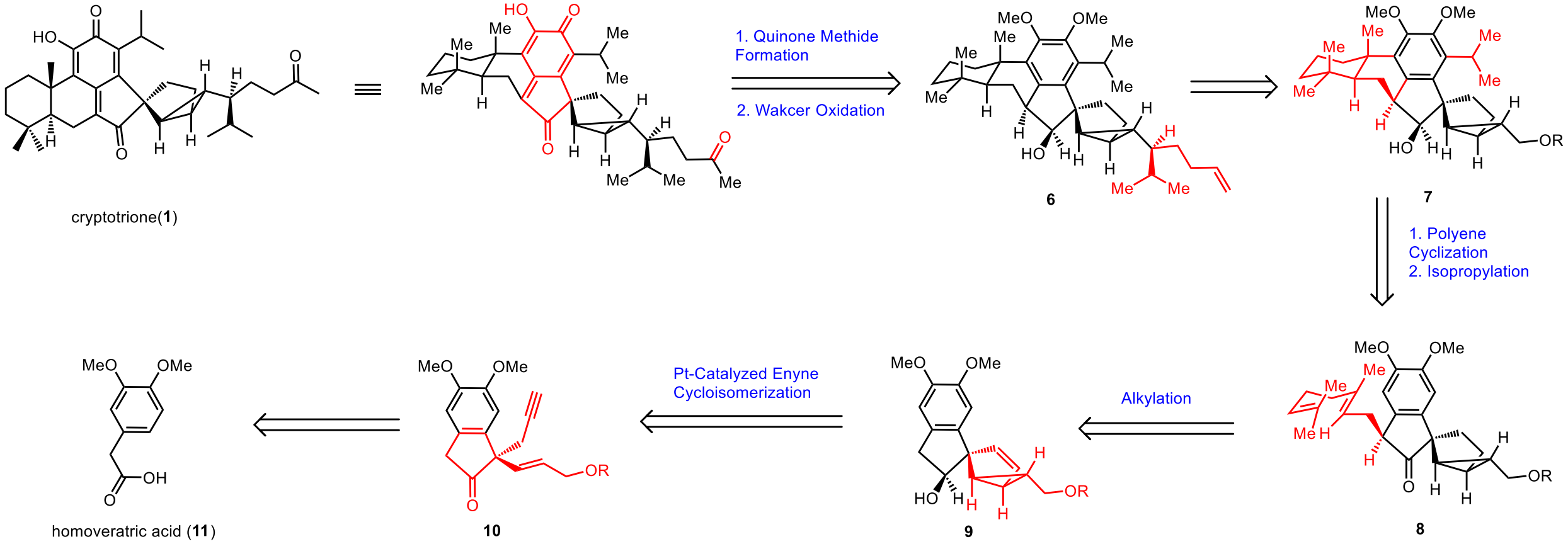


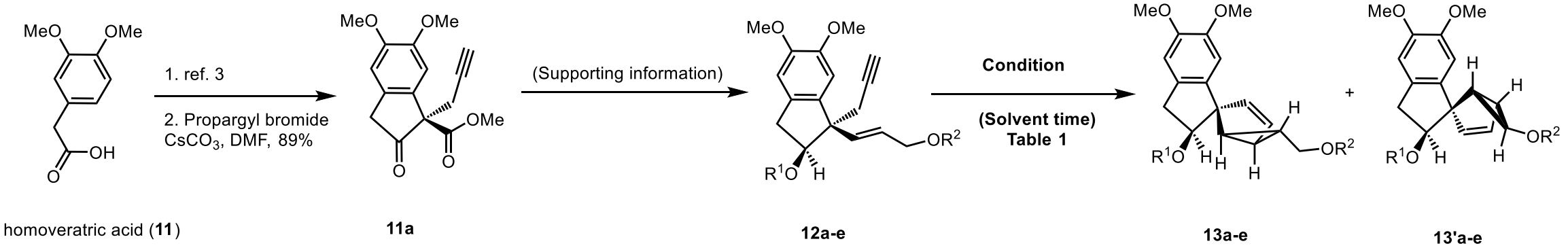

isochamaecydin(**3**)




cryptoquinonemethide D (**4**) $R^1$=OH, $R^2$=H
cryptoquinonemethide E (**5**) $R^1$=H, $R^2$=OH

# Retrosynthetic Analysis of Cryptotrione (1).



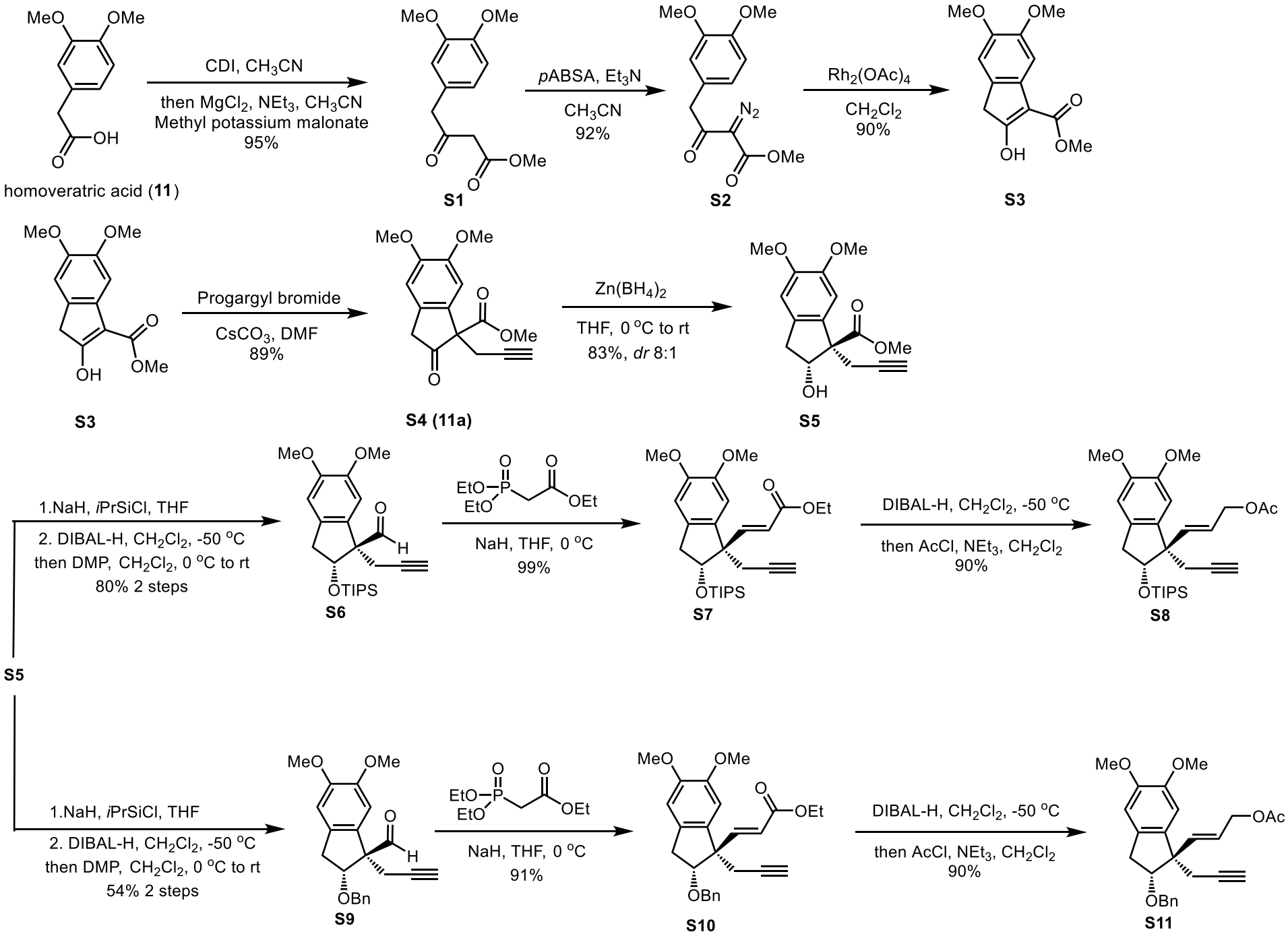


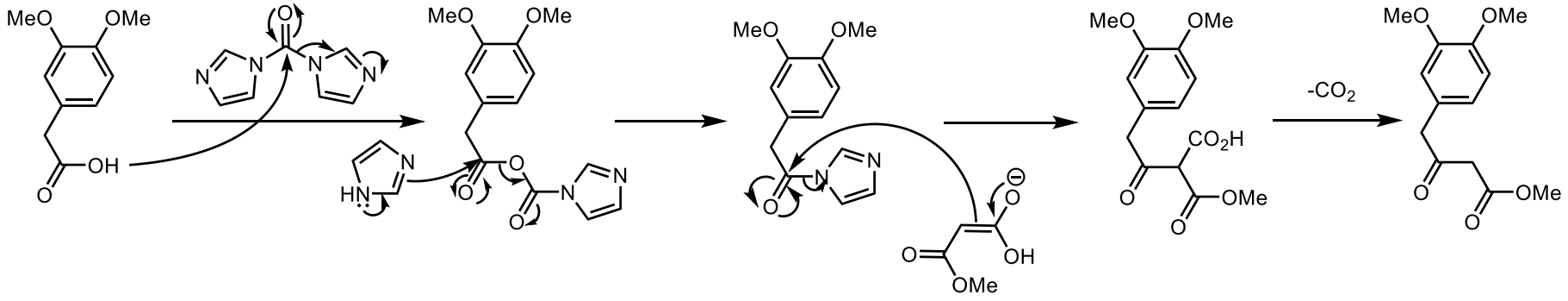

12a: $R^1$=*i*$Pr_3Si$, $R^2$=Ac; 12b: $R^1$=TBS, $R^2$=Ac; 12c: $R^1$=Bn, $R^2$=Ac;
12d: $R^1$=Me, $R^2$=Ac; 12e: $R^1$=*i*$Pr_3Si$, $R^2$=Piv

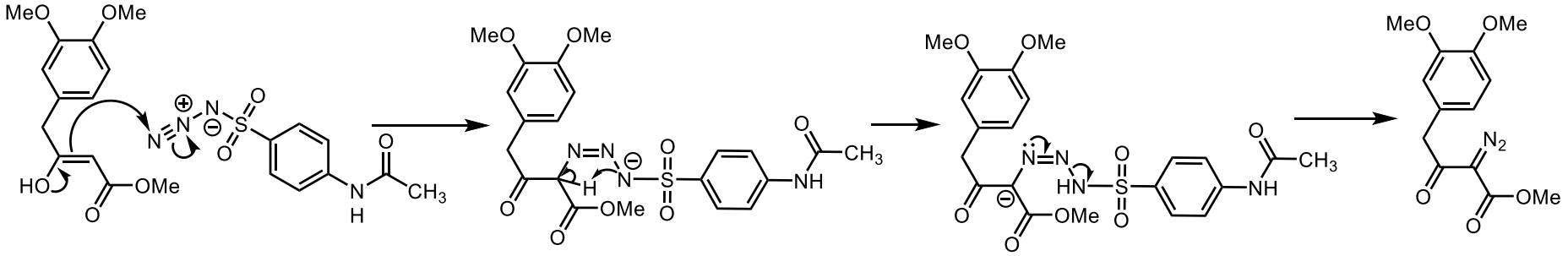
**Table 1.** Optimization of 1,5-Enyne Cycloisomerization[a].

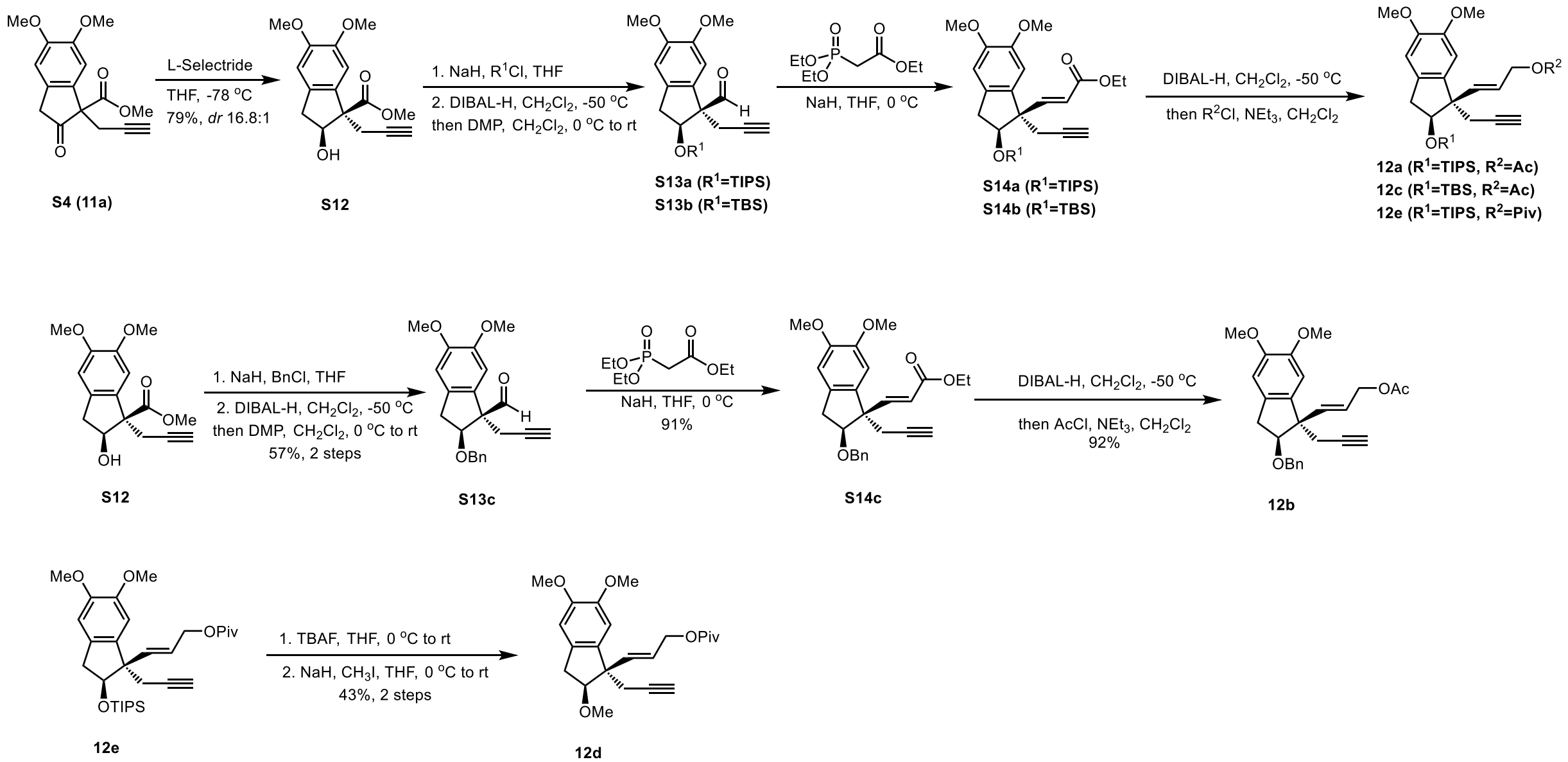
| Entry | Enyne | Catalyst (mol%) | Solvent | Ratio[b] (13:13') | t(h) | Yield[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **12a** | $Ph_3PAuSbF_6$ | $CH_2Cl_2$ | – | 0.5 | 0 |
| 2 | **12a** | $PtCl_2$ (20) | Toluene | >30:1 | 18 | 44 |
| 3 | **12b** | $PtCl_2$ (20) | Toluene | >30:1 | 18 | 32 |
| 4 | **12c** | $PtCl_2$ (20) | Toluene | >30:1 | 18 | 30 |
| 5 | **12d** | $PtCl_2$ (20) | Toluene | 12:1 | 6 | 20 |
| 6 | **12e** | $PtCl_2$ (20) | Toluene | >30:1 | 18 | 47 |
| 7 | **12e** | $PtCl_4$ (10) | Dioxane | >30:1 | 4 | 75 |
| 8[d] | **12e** | $PtCl_4$ (10) | Dioxane | >86:1 | 7 | 71 |

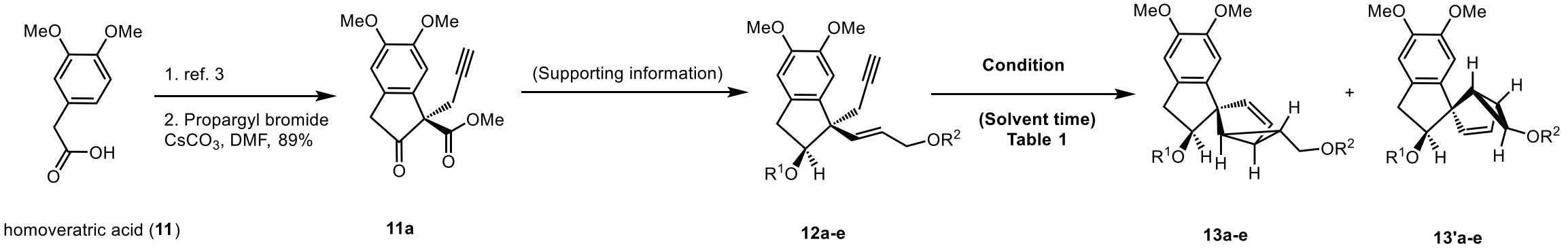
[a] Standard conditions: **12** (0.05 mmol) and platinum catalyst in solvent (5 mL) at 100 °C under argon. [b] *dr* ratio determined by $^1$H NMR spectra after global deprotection of **13** and **13'**. [c] Isolated yield. [d] 15g scale at 115 °C.


homoveratric acid (11)
CDI, CH3CN
then MgCl2, NEt3, CH3CN
Methyl potassium malonate
95%
S1
pABSA, Et3N
CH3CN
92%
S2
Rh2(OAc)4
CH2Cl2
90%
S3
Progargyl bromide
CsCO3, DMF
89%
S4 (11a)
Zn(BH4)2
THF, 0 °C to rt
83%, dr 8:1
S5
1.NaH, iPrSiCl, THF
2. DIBAL-H, CH2Cl2, -50 °C
then DMP, CH2Cl2, 0 °C to rt
80% 2 steps
S6
NaH, THF, 0 °C
99%
S7
DIBAL-H, CH2Cl2, -50 °C
then AcCl, NEt3, CH2Cl2
90%
S8
1.NaH, iPrSiCl, THF
2. DIBAL-H, CH2Cl2, -50 °C
then DMP, CH2Cl2, 0 °C to rt
54% 2 steps
S9
NaH, THF, 0 °C
91%
S10
DIBAL-H, CH2Cl2, -50 °C
then AcCl, NEt3, CH2Cl2
90%
S11


MeO
OMe
OH
O
N
HN
CO2H
OMe
-CO2


MeO
OMe
HO
OMe
N
H
CH3
NH
HN
N2


L-Selectride
THF, -78 °C
79%, dr 16.8:1
1. NaH, R1Cl, THF
2. DIBAL-H, CH2Cl2, -50 °C
then DMP, CH2Cl2, 0 °C to rt
NaH, THF, 0 °C
DIBAL-H, CH2Cl2, -50 °C
then R2Cl, NEt3, CH2Cl2
1. NaH, BnCl, THF
2. DIBAL-H, CH2Cl2, -50 °C
then DMP, CH2Cl2, 0 °C to rt
57%, 2 steps
NaH, THF, 0 °C
91%
DIBAL-H, CH2Cl2, -50 °C
then AcCl, NEt3, CH2Cl2
92%
1. TBAF, THF, 0 °C to rt
2. NaH, CH3I, THF, 0 °C to rt
43%, 2 steps
S4 (11a)
S12
S13a (R1=TIPS)
S13b (R1=TBS)
S14a (R1=TIPS)
S14b (R1=TBS)
12a (R1=TIPS, R2=Ac)
12c (R1=TBS, R2=Ac)
12e (R1=TIPS, R2=Piv)
S12
S13c
S14c
12b
12e
12d

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| 5 | **12d** | $PtCl_2$ (20) | Toluene | 12:1 | 6 | 20 |
| 5 | **12d** | $PtCl_2$ (20) | Toluene | 12:1 | 6 | 20 |
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| 7 | **12e** | $PtCl_4$ (10) | Dioxane | >30:1 | 4 | 75 |
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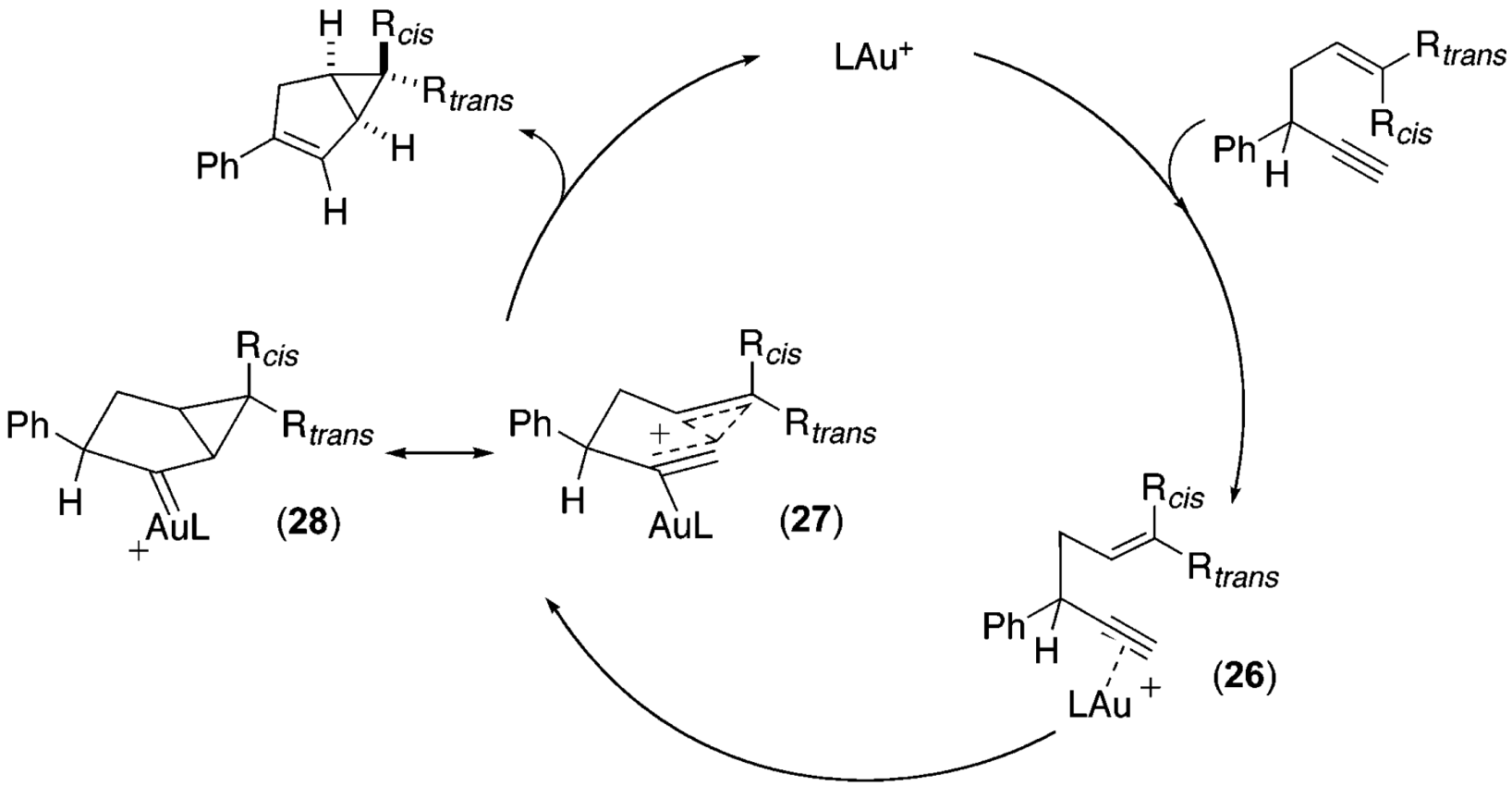
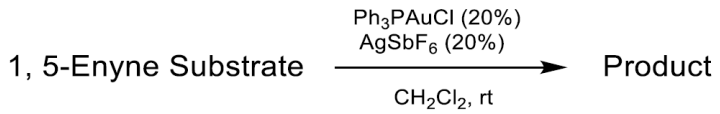
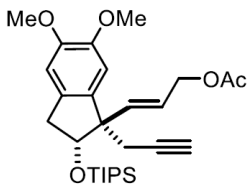
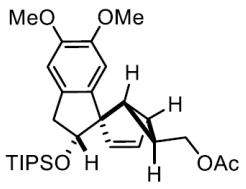
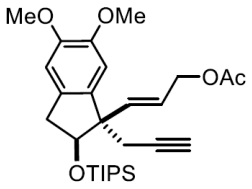
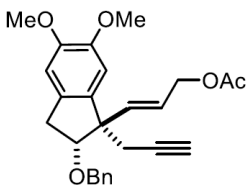
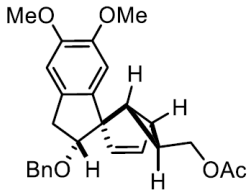
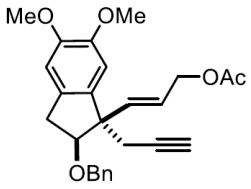
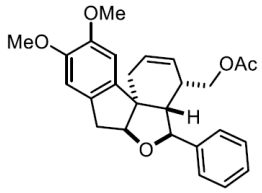
***Scheme 1.*** Mechanistic Proposal for Au(I)-Catalyzed Cycloisomerization



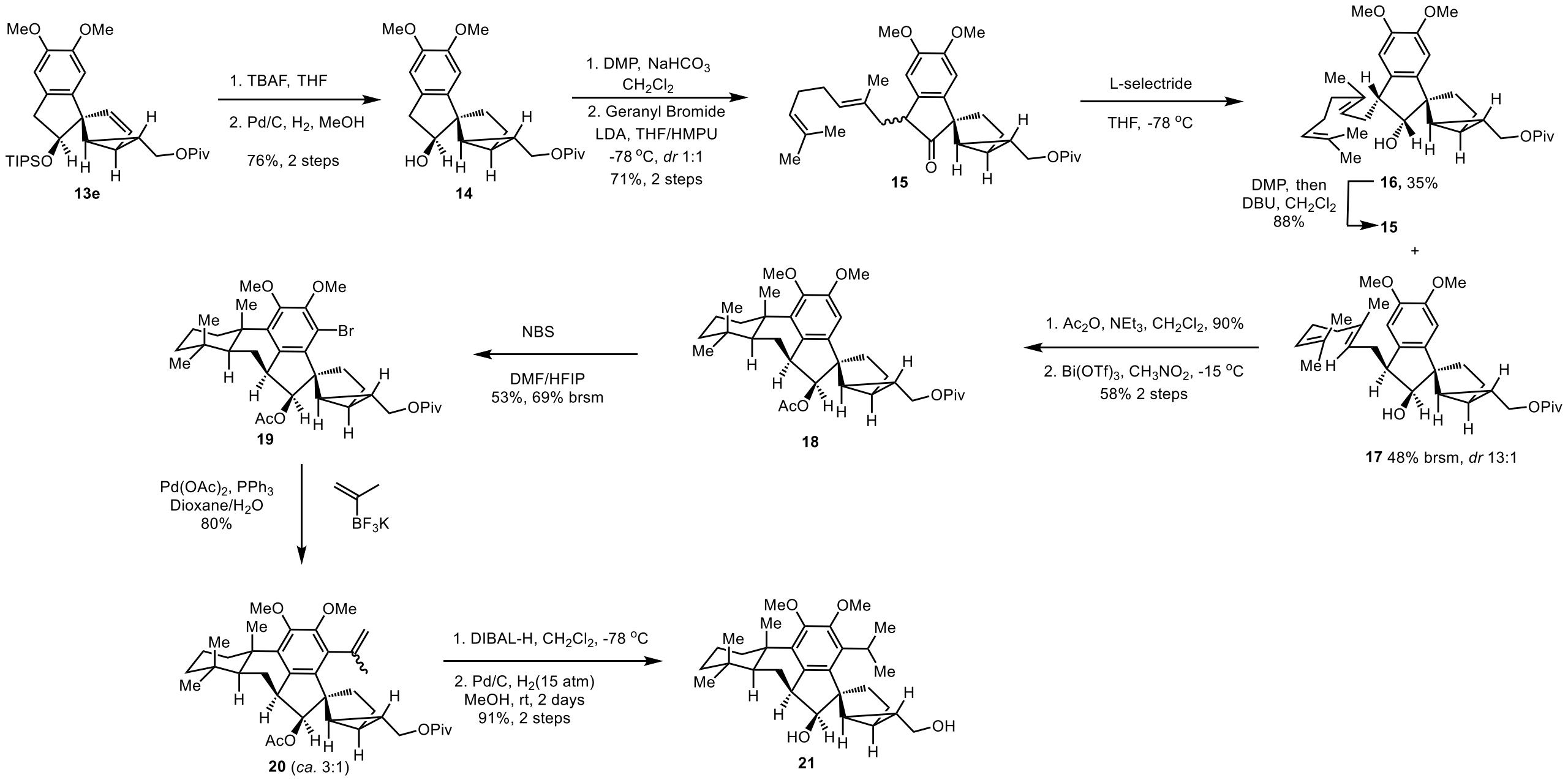

*J. AM. CHEM. SOC.* **2004**, 126, 10858-10859

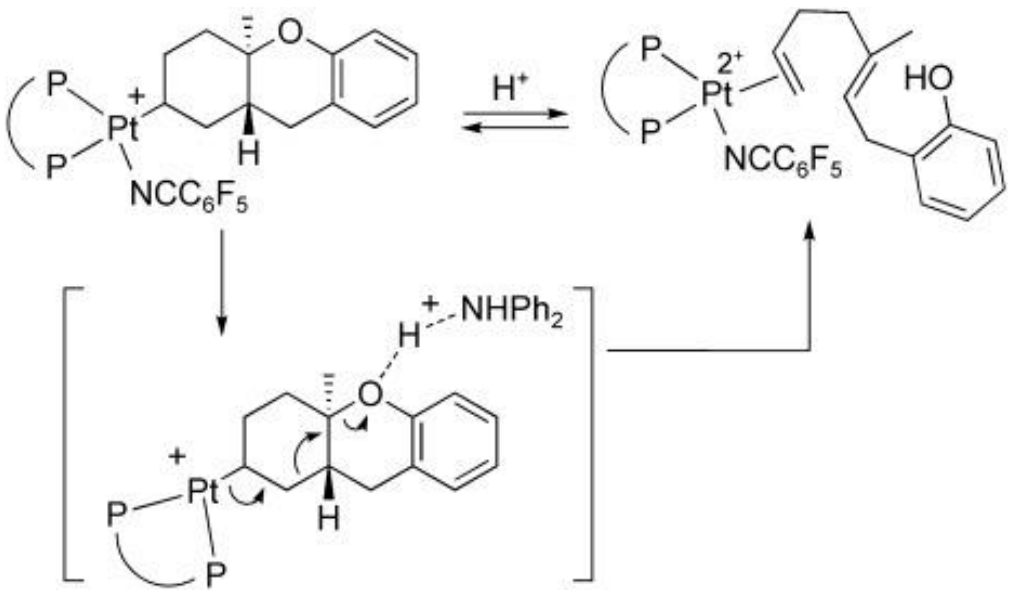
**Table S2. Results of gold catalyzed 1, 5-enyne cycloisomerization reactions**[a]



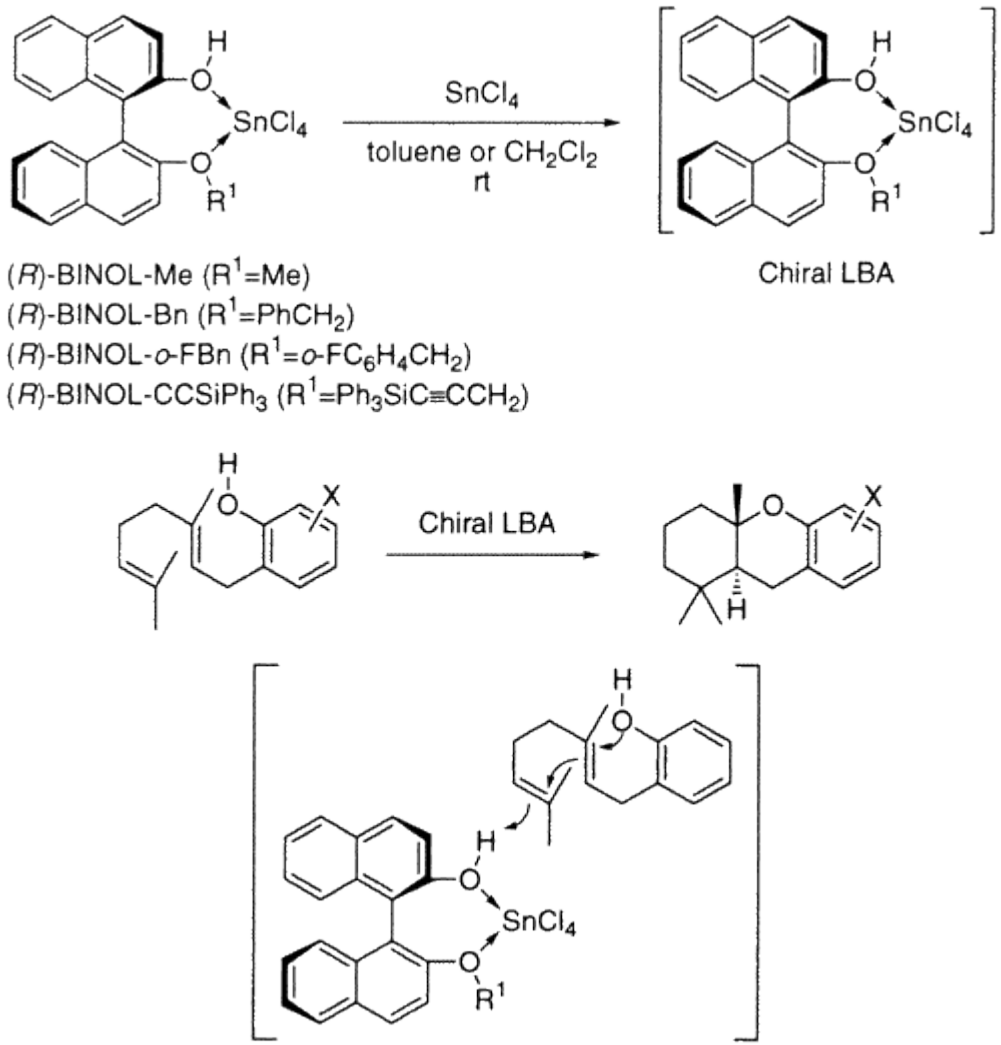

| Entry | Substrate | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  **S8** |  **[X-Ray]** **S15** | 46 |
| 2 |  **12a** | Decomposed | 0 |
| 4 |  **S11** |  **S16** | 27 |
| 5[c] |  **12b** |  **S17** | 30 |

a. Standard conditions: 1, 5-enyne substrate (0.1 mmol), $Ph_3PAuCl$ (0.02 mmol), $AgSbF_6$ (0.017 mmol), $CH_2Cl_2$ (4 mL), 23 °C, the reaction was monitored by TLC, and normally finished in 15 minutes. b. Isolated yields. c. For further details, see ref. 2.

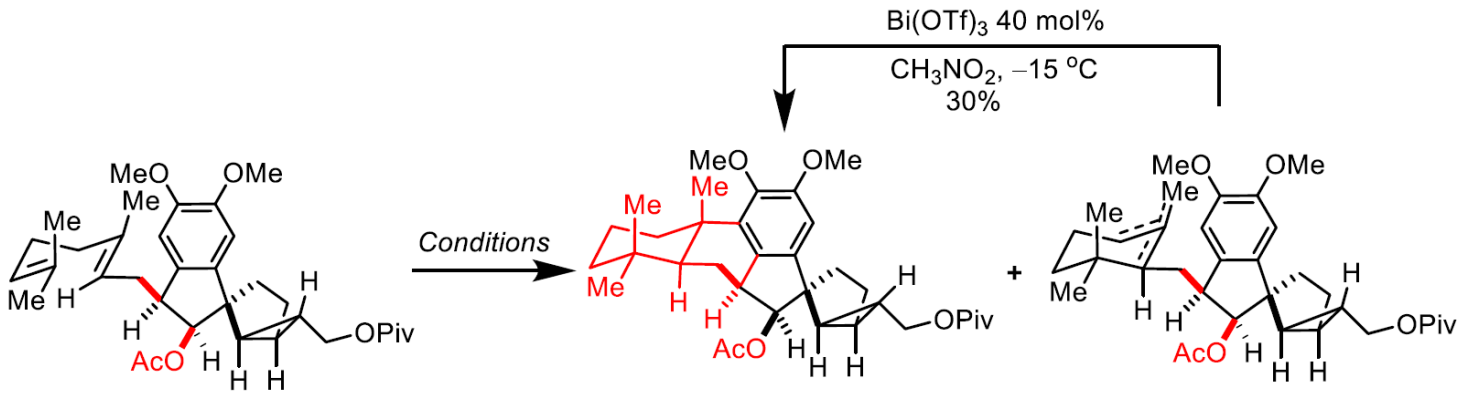

13e
1. TBAF, THF
2. Pd/C, H2, MeOH
76%, 2 steps
14
1. DMP, NaHCO3
CH2Cl2
2. Geranyl Bromide
LDA, THF/HMPU
-78 °C, dr 1:1
71%, 2 steps
15
L-selectride
THF, -78 °C
16, 35%
DMP, then
DBU, CH2Cl2
88%
15
+
17 48% brsm, dr 13:1
1. Ac2O, NEt3, CH2Cl2, 90%
2. Bi(OTf)3, CH3NO2, -15 °C
58% 2 steps
18
NBS
DMF/HFIP
53%, 69% brsm
19
Pd(OAc)2, PPh3
Dioxane/H2O
80%
BF3K
20 (ca. 3:1)
1. DIBAL-H, CH2Cl2, -78 °C
2. Pd/C, H2(15 atm)
MeOH, rt, 2 days
91%, 2 steps
21



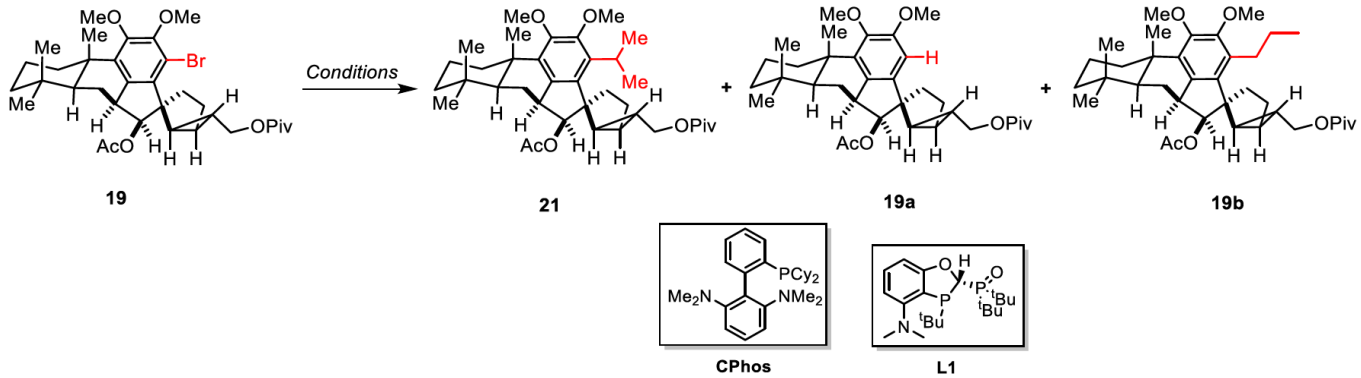

*J. Am. Chem. Soc.* **2002**, 124, 14, 3647–3655




*Angew. Chem. Int. Ed*. **2008,** 47, 6011 –6014

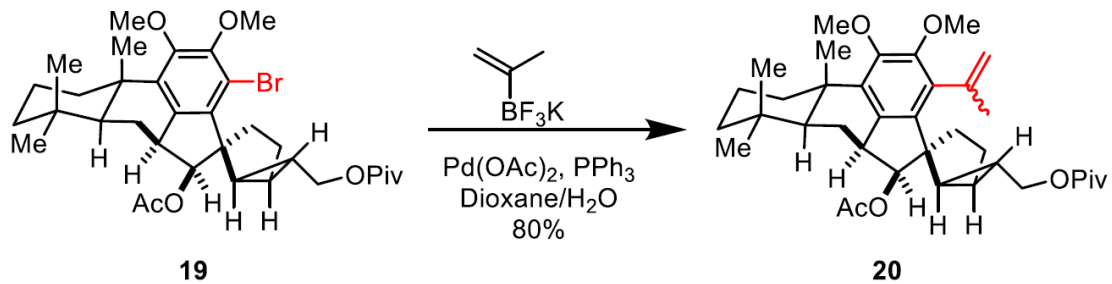


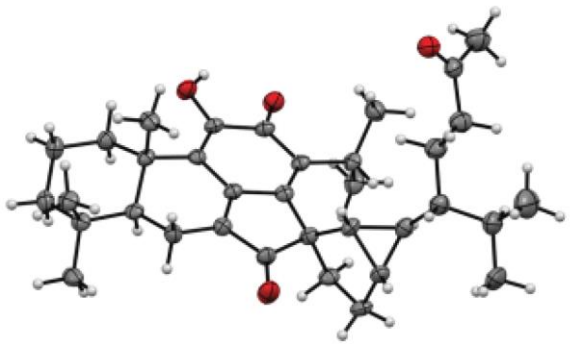

| Entry | LA (mol%) | Solvent | T (°C) | Isolated Yield (%) | |
|---|---|---|---|---|---|
| | | | | **18** | **18a** |
| 1 | $BF_3{\cdot}OEt$ (15) | $MeNO_2$ | –20 | 35 | 15 |
| 2 | $Sc(OTf)_3$ (10) | $MeNO_2$ | 0 to rt | <10 | 60 |
| 3 | $RuCl_3.xH_2O$ (5)<br>AgOTf (10) | $ClCH_2CH_2Cl$ | rt to 50 | 15 | 70 |
| 4 | $Bi(OTf)_3$ (10) | $MeNO_2$ | 0 to 80 | 18 | 65 |
| 5 | $Bi(OTf)_3$ (20) | $MeNO_2$ | 0 | 25 | 40 |
| 6 | $Bi(OTf)_3$ (40) | $MeNO_2$ | –15 | 58 | 15 |



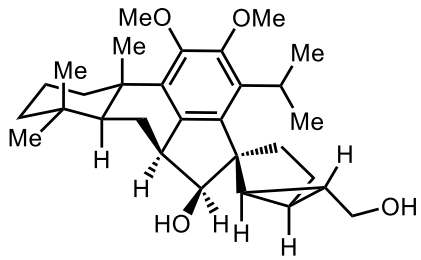

| Entry | Conditions | Yield (%)[a] | | | |
|---|---|---|---|---|---|
| | | **19** | **19a** | **19b** | **21** |
| 1[b] | *i*PrZnCl, CPhos, $Pd(OAc)_2$, THF, rt, 24 h | 0 | 30 | 50 | 0 |
| 2[c] | *i*PrB(OH)$_2$, [Pd(1-phenylallyl)Cl]$_2$, $K_3PO_4 \cdot H_2O$, L1, toluene, 100°C, 18 h | 50 | 22 | 0 | 0 |
| 3[d] | Potassium isopropyltrifluoroborate, $K_2CO_3$, $Pd(OAc)_2$, $PPh_3$, dioxane/$H_2O$ (9:1), reflux, 12 h | 55 | 18 | 0 | 0 |

a. yield determined by $^1$H NMR, b. ref 3, c. ref 4, d. ref 5.



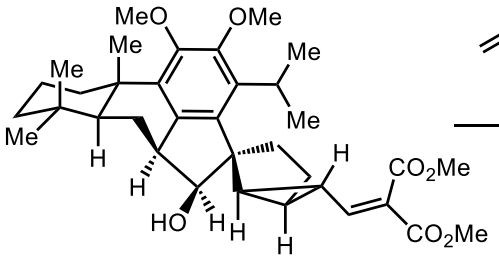


X-ray of **25**



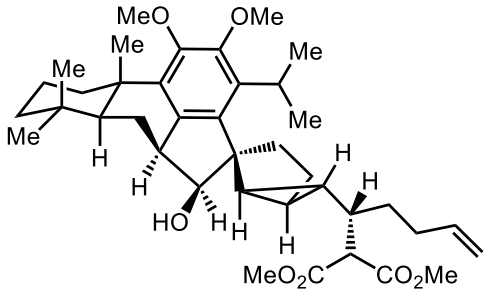
**21**

1. PIDA, TEMPO, $CH_2Cl_2$, rt, 92%
2. L-Proline
Methyl malonate
DMSO,40 °C, 80 °C



**22**

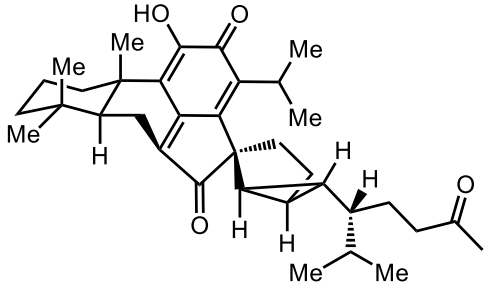
**22a** (10 eq)
$Li_2CuCl_4$(2 eq)
THF, -78 °C
85%, dr>20:1



**24**

1. LAH, THF, rt; TsCl, $Et_3N$, $CH_2Cl_2$, rt
2. $NaBH_4$, DMSO, 80 °C
3. NaH, EtSH, DMF
4. $PdCl_2$, CuCl, $O_2$(1 atm) DMF/$H_2O$

21%, 4 steps

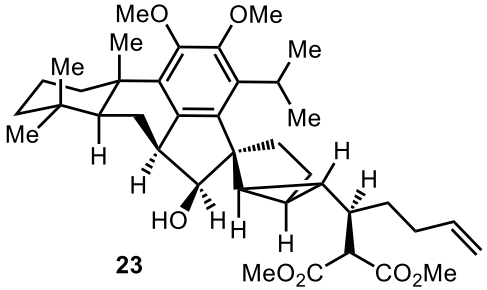


7-epi-cryptotrione(**25**)

MgBr (**22a**, 20 eq)

$Li_2CuCl_4$ (2 eq)

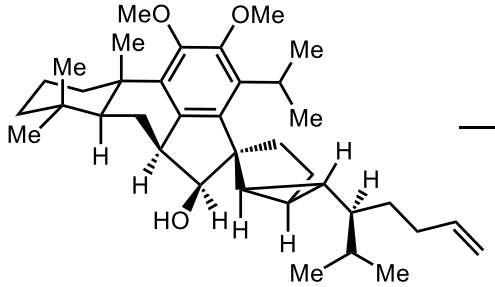
THF, -78 °C
80%, dr>20:1



**23**

1. LAH, THF, rt, 70%
2. TsCl, $Et_3N$, $CH_2Cl_2$, rt
3. $NaBH_4$, DMSO, 80 °C

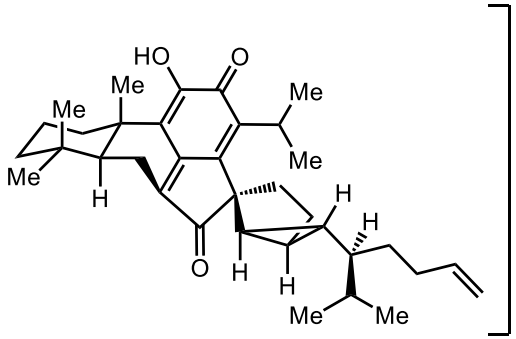
44%, 2 steps



**6**

NaH, EtSH

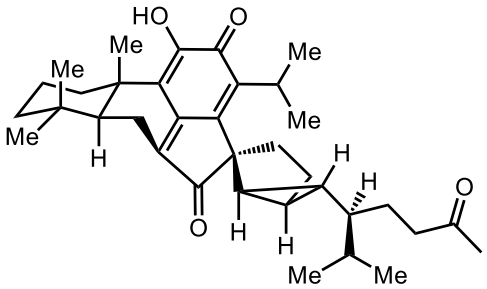
DMF, 140 °C
then $MnO_2$, rt



**6a**

$PdCl_2$, CuCl
$O_2$(1 atm)

DMF/$H_2O$
40%



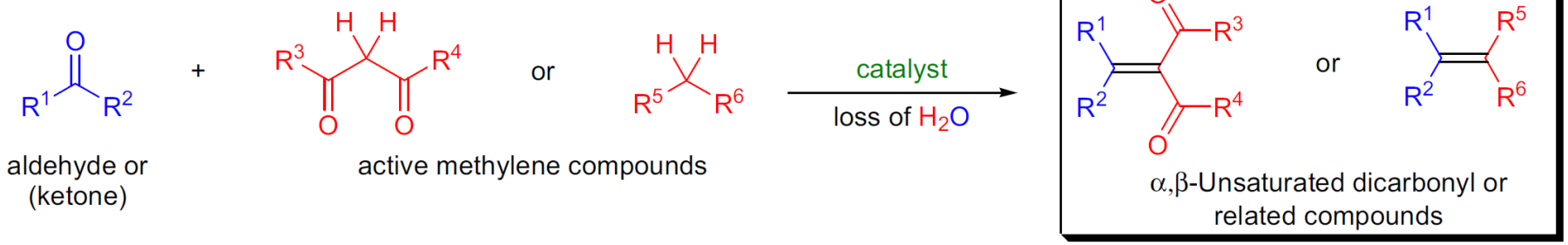
cryptotrione(**1**)

# KNOEVENAGEL CONDENSATION

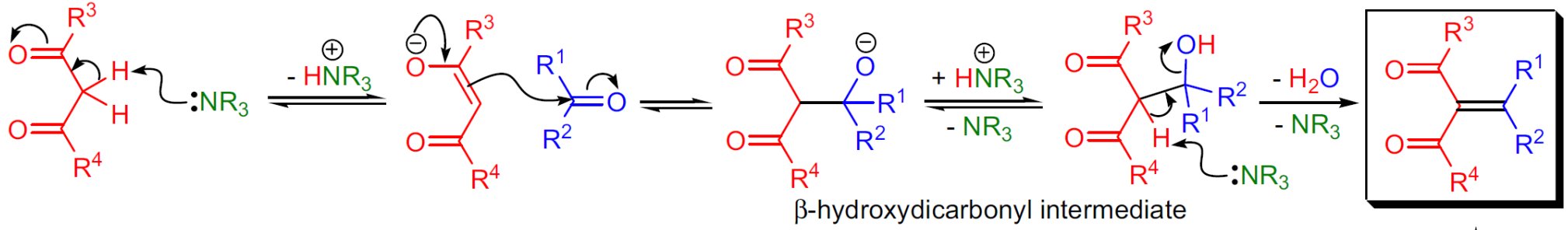
(References are on page 613)

## Importance:

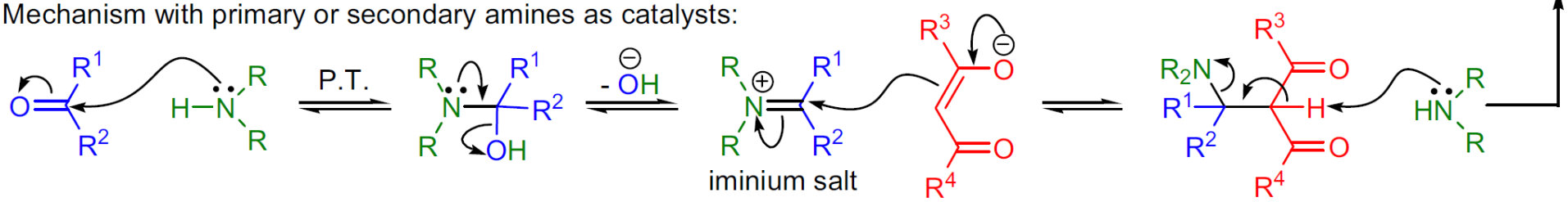
Knoevenagel condensation:




Hann-Lapworth mechanism with tertiary amines as catalysts:

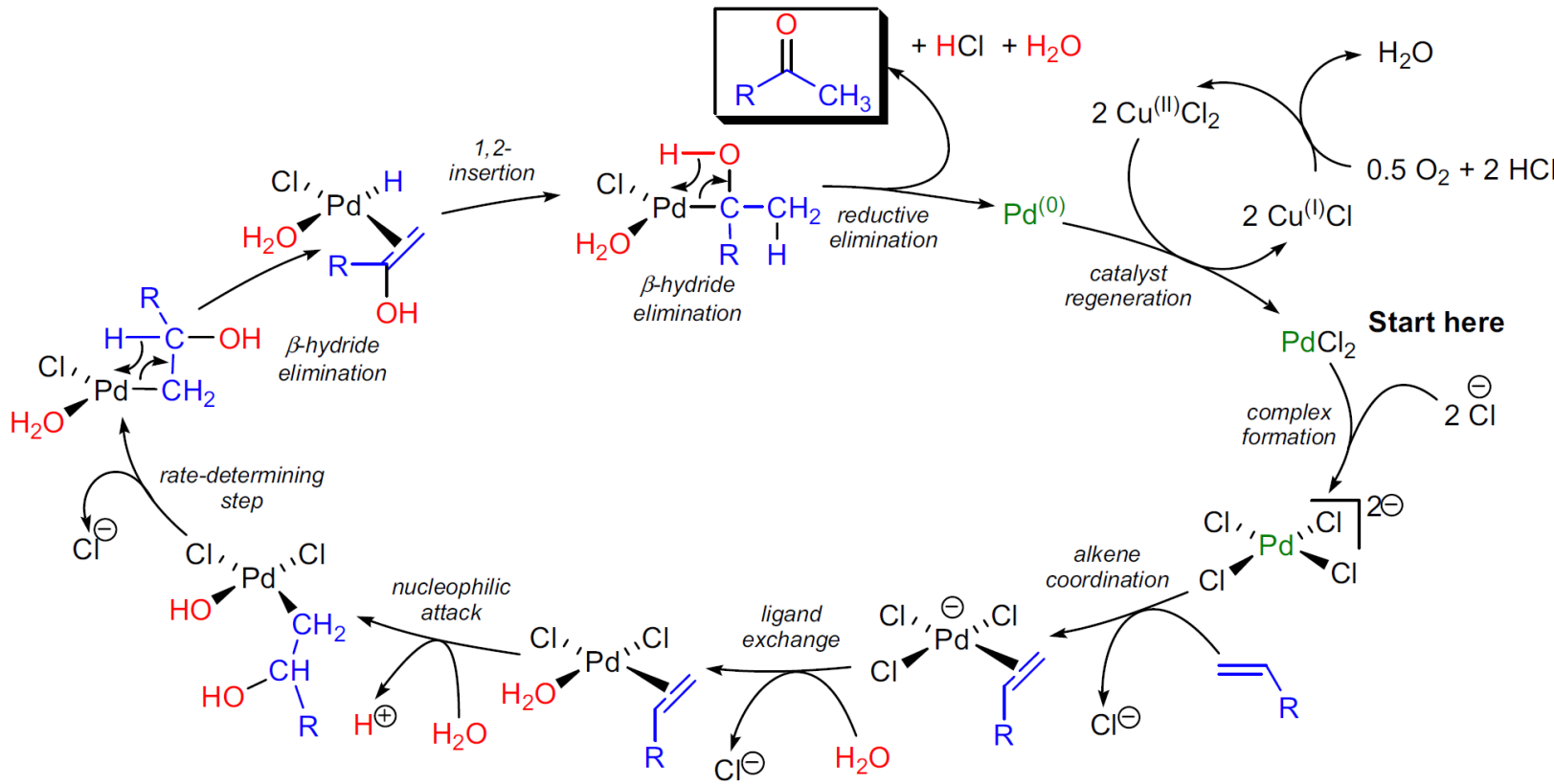



Mechanism with primary or secondary amines as catalysts:



# WACKER OXIDATION

(References are on page 702)

Wacker oxidation:

$R^1$ = alkyl, substituted alkyl; $R^2$ = alkyl, aryl, O-alkyl