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Communication

Concise Total Synthesis of (−)-Bipolarolide D

Shengling Sun,[#] Qi Wei,[#] Yufei Liu, and Zhaohong Lu*

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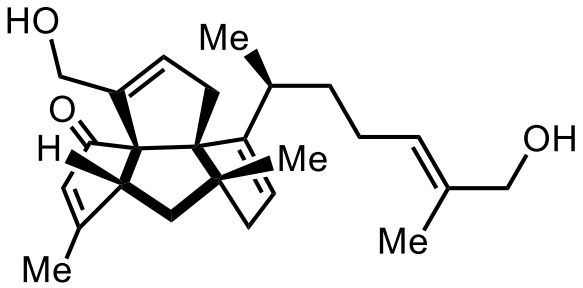
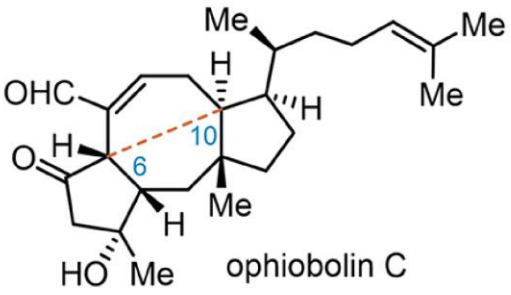
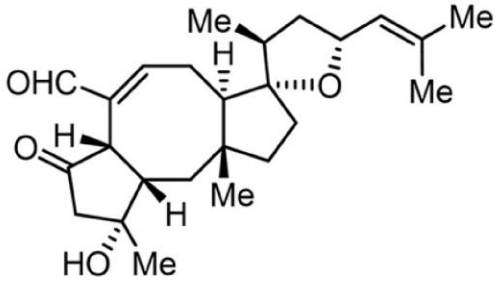


bipolarolide D (**1**)

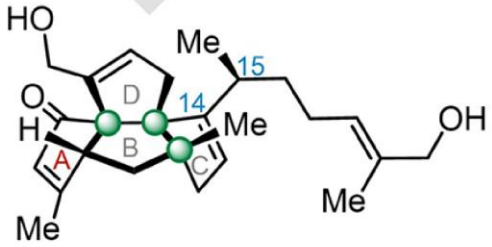


ophiobolin C



ophiobolin A

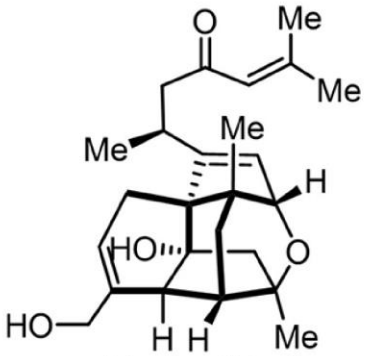
biosynthesis
C6-C10 formation



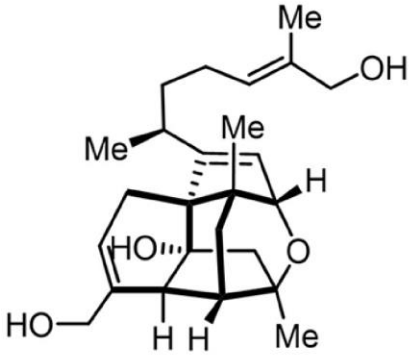
bipolarolide D (**1**)

Structure features:

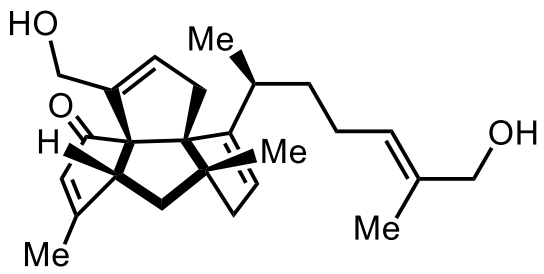
- unprecedented 5/5/5/5 fused ring
- 3 contiguous quaternary centers (green, 2 tricyclic bridgehead quaternary centers)
- A/B/C rings on the convex surface
- fully functionalized A-ring
- attached chiral side chain



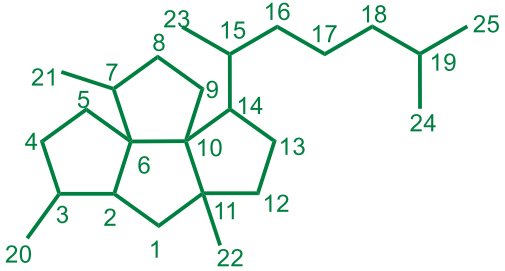
bipolarolide A



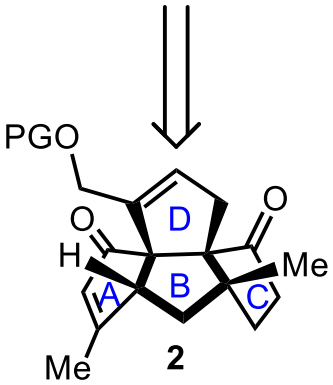
bipolarolide B



bipolarolide D (**1**)

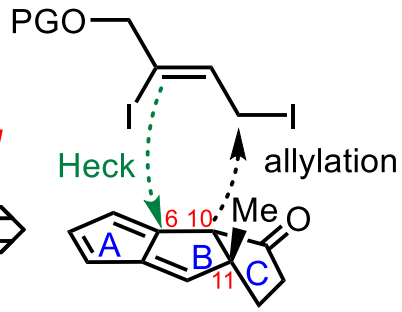


core skeleton and carbon numbering



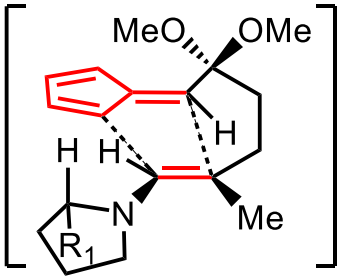
2

pentafulvene-involved Heck cyclization

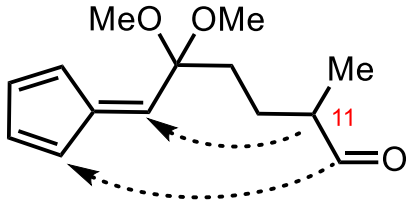


3

enantioselective pentafulvene [6+2]



chiral enamine intermediate (**5**)



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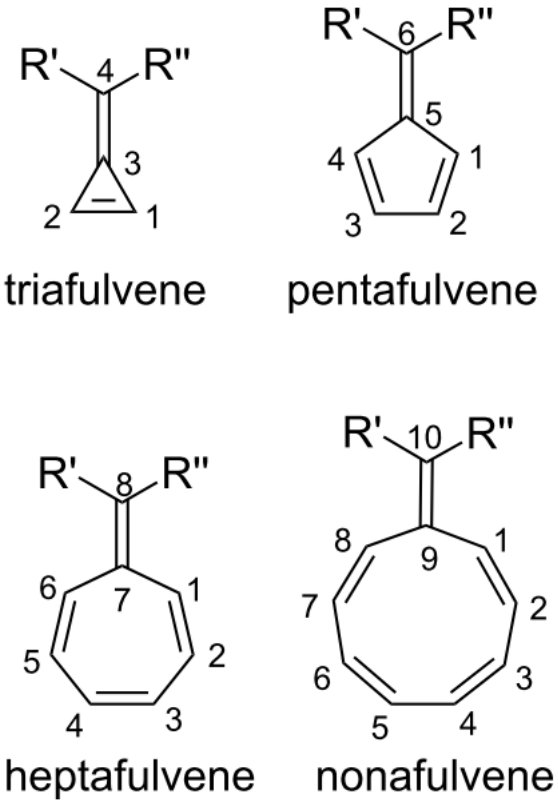
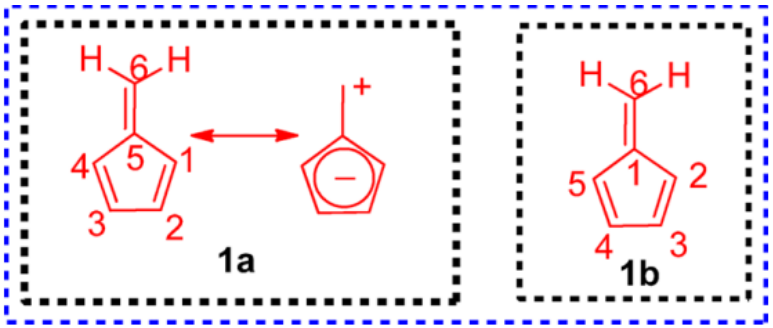
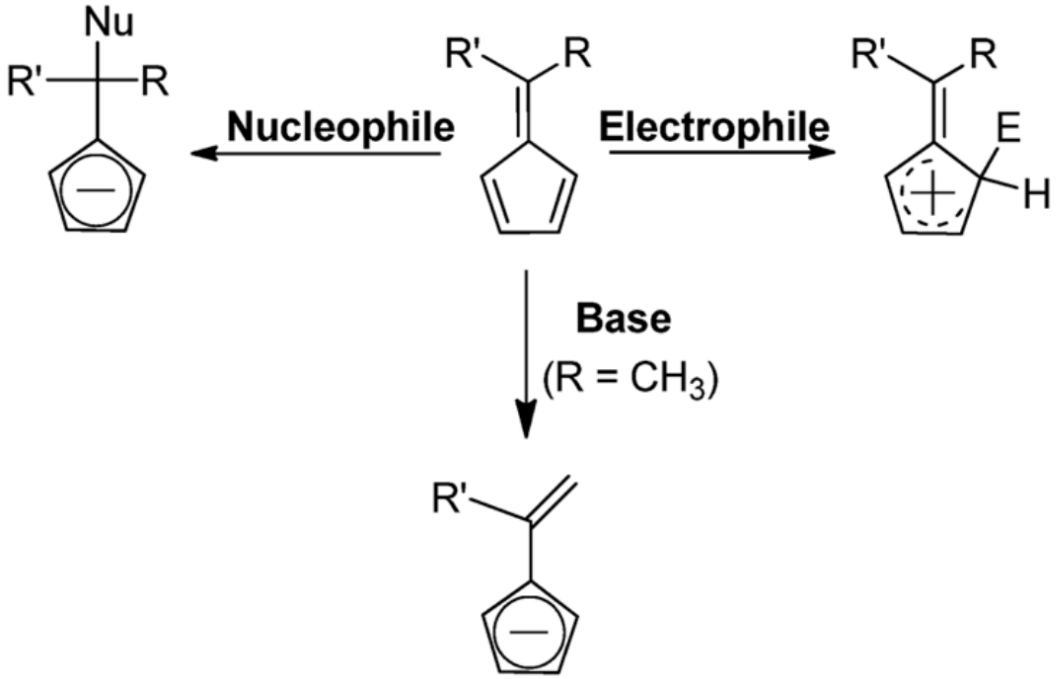
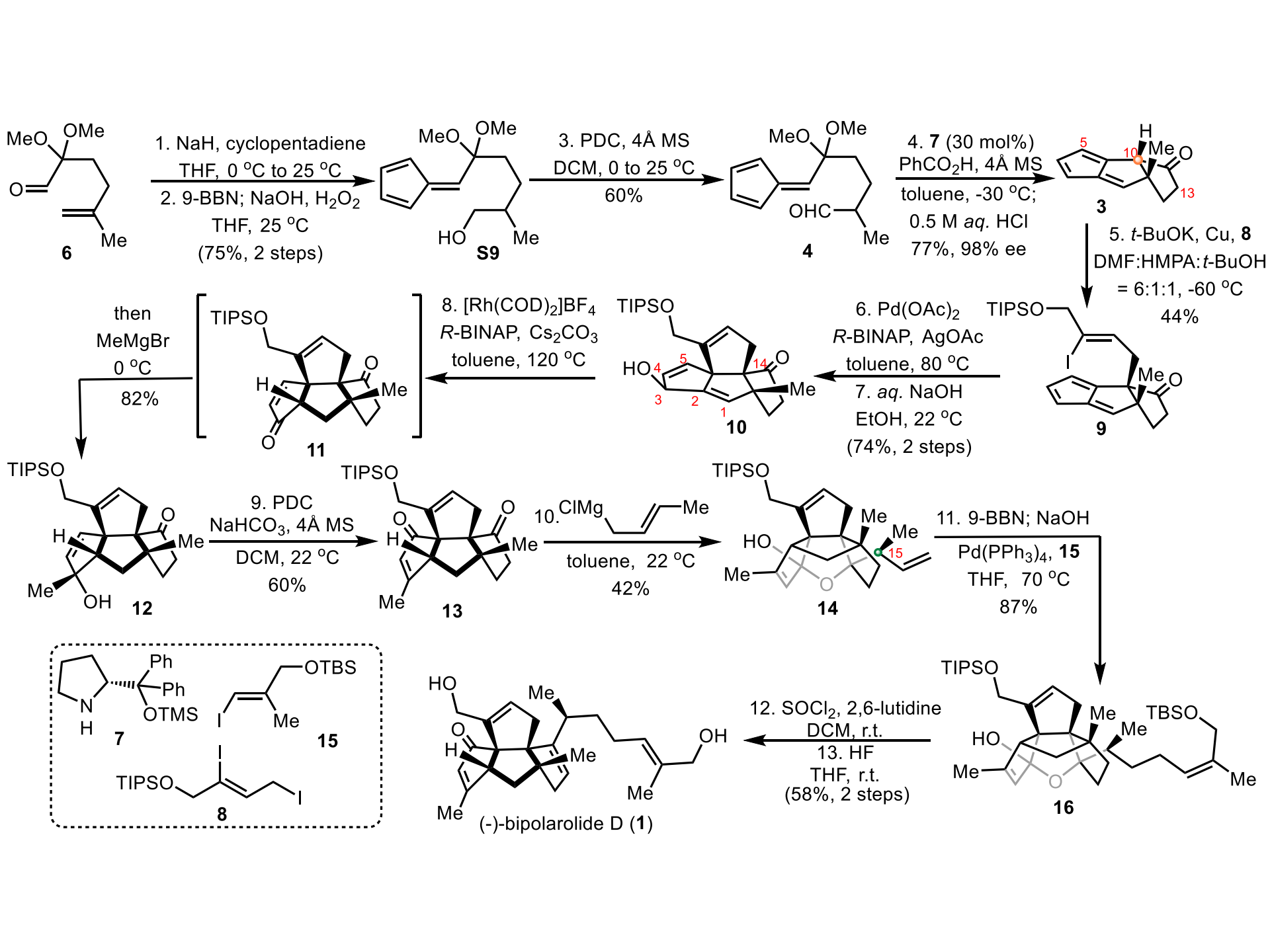


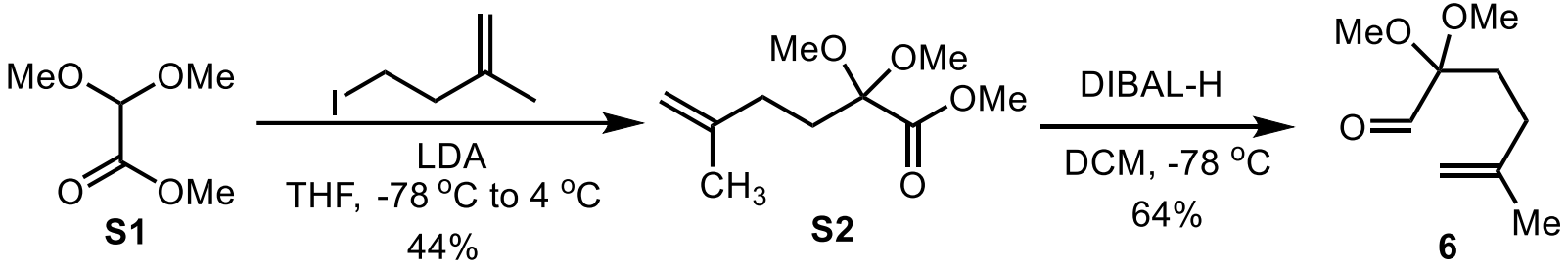
Beilstein J. Org. Chem., **2019**, *15*, 2113.
Chem. Rev., **2017**, *117*, 3930−3989.





Beilstein J. Org. Chem., **2019**, *15*, 2113.
Chem. Rev., **2017**, *117*, 3930.


1. NaH, cyclopentadiene
THF, 0 °C to 25 °C
2. 9-BBN; NaOH, H2O2
THF, 25 °C
(75%, 2 steps)
3. PDC, 4Å MS
DCM, 0 to 25 °C
60%
4. 7 (30 mol%)
PhCO2H, 4Å MS
toluene, -30 °C;
0.5 M aq. HCl
77%, 98% ee
5. t-BuOK, Cu, 8
DMF:HMPA:t-BuOH
= 6:1:1, -60 °C
44%
6. Pd(OAc)2
R-BINAP, AgOAc
toluene, 80 °C
7. aq. NaOH
EtOH, 22 °C
(74%, 2 steps)
8. [Rh(COD)2]BF4
R-BINAP, Cs2CO3
toluene, 120 °C
then
MeMgBr
0 °C
82%
9. PDC
NaHCO3, 4Å MS
DCM, 22 °C
60%
10.
toluene, 22 °C
42%
11. 9-BBN; NaOH
Pd(PPh3)4, 15
THF, 70 °C
87%
12. SOCl2, 2,6-lutidine
DCM, r.t.
13. HF
THF, r.t.
(58%, 2 steps)
6
S9
4
3
9
10
11
12
13
14
16
7
15
8
(-)-bipolarolide D (1)


MeO
OMe
O
OMe
S1
I
LDA
THF, -78 °C to 4 °C
44%
MeO
OMe
OMe
CH3
O
S2
DIBAL-H
DCM, -78 °C
64%
MeO
OMe
O
Me
6

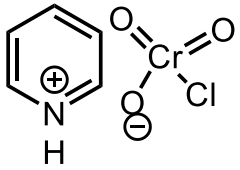
Jones 试剂：CrO_3 in H_2SO_4

能氧化仲醇成相应的酮，而不影响分子中存在的双键或叁键；也可氧化烯丙醇（伯醇）成醛
伯醇氧化成羧酸 （如果要使产物停留在醛的阶段，需要在无水条件下反应）
对于不耐强酸条件的底物来说是不适用的

Collins 试剂 ：CrO_3·Py

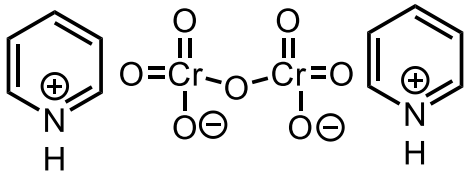
Collins试剂可以将伯醇氧化成醛，仲醇氧化成酮。因为吡啶是碱性的，
对酸不稳定的醇来说是一种很好的氧化剂，反应一般在二氯甲烷中进行
不影响分子中存在的双键或叁键
该试剂不稳定，易吸潮，难保存，要求无水条件，试剂要过量（5倍量以上）

PCC：



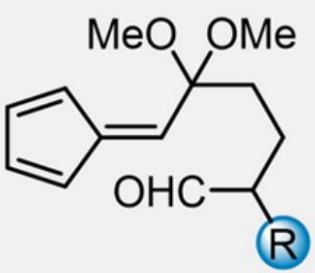
PCC显示一定的酸性，带有对酸敏感基团的底物需要加乙酸钠作为缓冲试剂
氧化伯醇/仲醇，不发生过度氧化
在反应中加入分子筛可以提高反应的速率
PCC可以与烯丙基叔醇发生氧化重排生成α,β-不饱和醛

PDC:



温和型中性氧化剂
与PCC比较，氧化能力较弱但却没有酸性
与MnO_2比较，不仅氧化能力较强，而且制备方便
氧化性受溶剂影响较大，在DMF溶液中，PDC将脂肪族伯醇氧化成相应的羧酸
在DCM中，PDC可以将伯醇、仲醇、苄醇和烯丙基醇稳定地氧化成为相应的醛酮化合物
在反应中加入分子筛可以提高反应的速率
PDC可以与烯丙基叔醇发生氧化重排生成α,β-不饱和醛

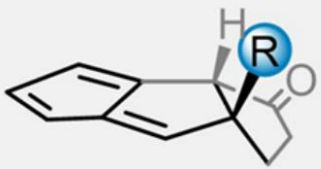
Table 1. Investigations of Asymmetric [6+2] Cycloaddition



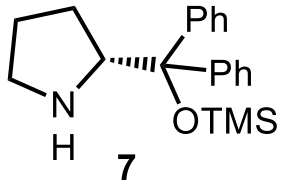
cat.7, $PhCO_2H$
4Å MS, toluene

then 0.5 M HCl

variations

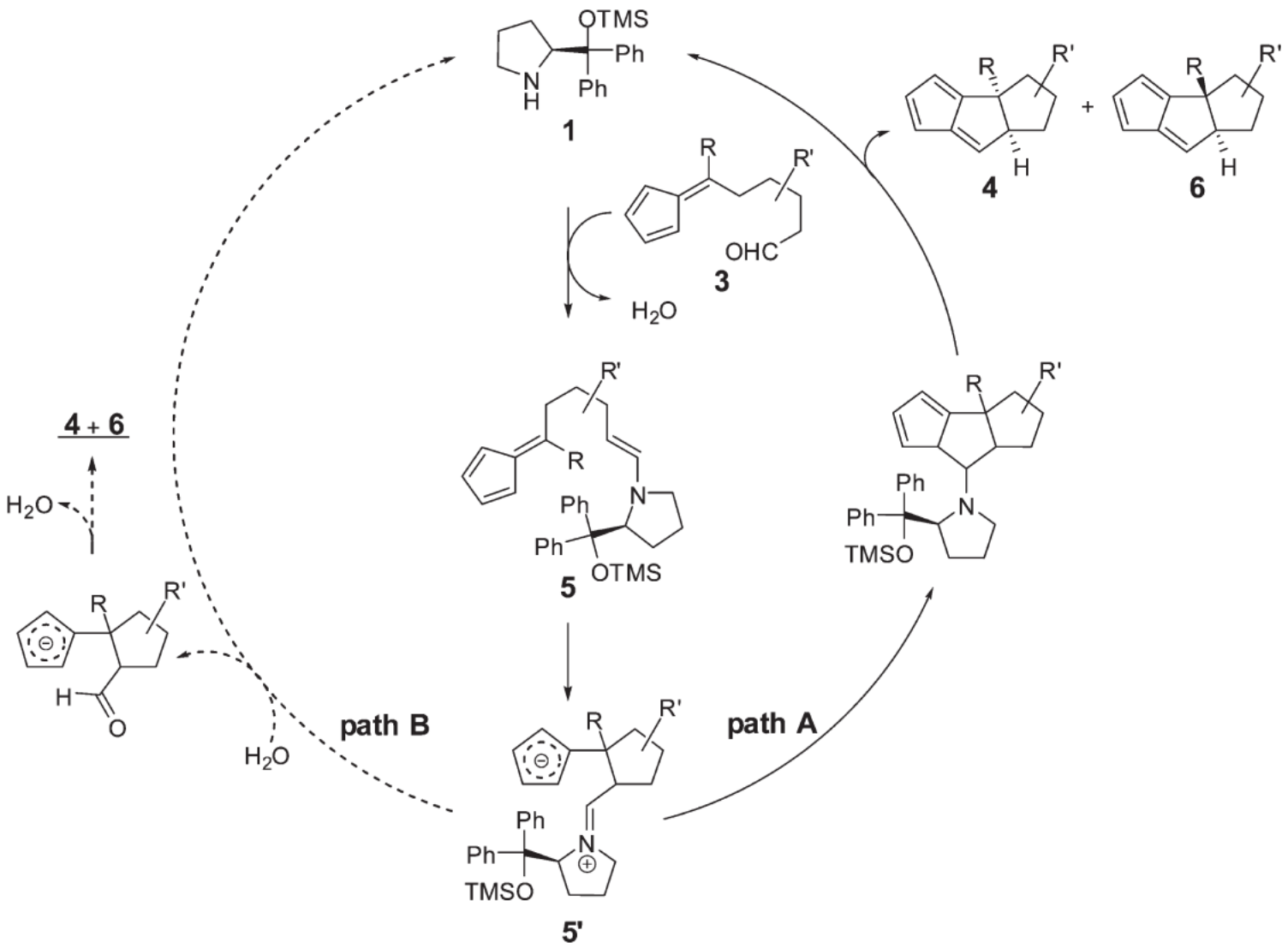


P



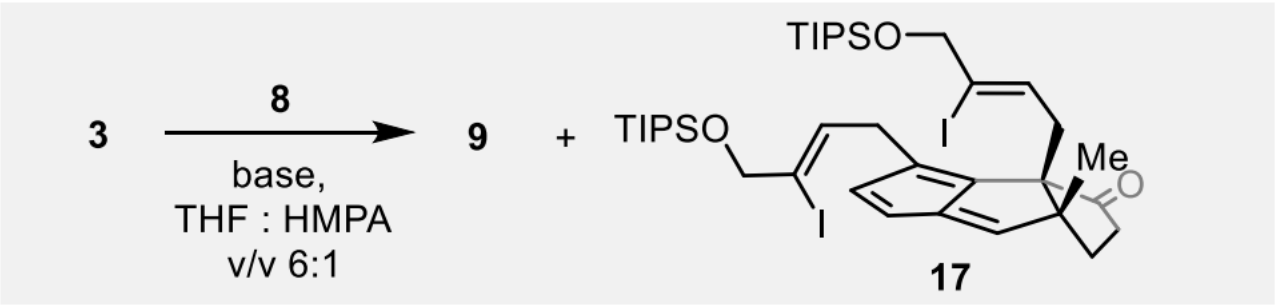
7

Entry	R=	cat. 7	$PhCO_2H$	*T*	P	yield	ee
1	Me	10 mol%	20 mol%	rt	**3**	75%	86%
2	Me	10 mol%	20 mol%	-30°C	**3**	17%	93%
3	Me	20 mol%	20 mol%	-30°C	**3**	30%	98%
4	Me	30 mol%	15 mol%	-30°C	**3**	77%	98%
5	Me	30 mol%	20 mol%	-30°C	**3**	75%	98%
6	Me	30 mol%	30 mol%	-30°C	**3**	47%	98%
7	CH_2CH_2OBn	30 mol%	15 mol%	-30°C	**3a**	76%	97%



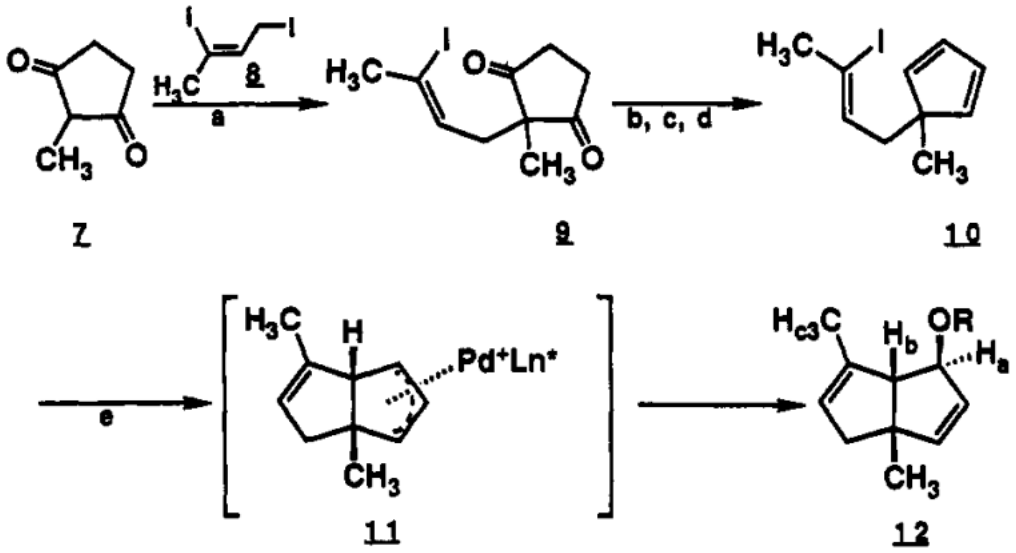
J. Am. Chem. Soc., **2011**, *133*, 20175.

Table 2. Optimization of Allylation Conditions to Establish the Second Quaternary Carbon Center



Entry	Variations	yield (%) **9**	**17**	recovery **3** (%)
1	LDA	<5	0	0
2	MeONa	21	15	10
3	*t*-BuOK	25	20	12
4	*t*-BuOK, *t*-BuOH	33	16	15
5	*t*-BuOK (1.7 eq), *t*-BuOH, Cu powder	44	23	20

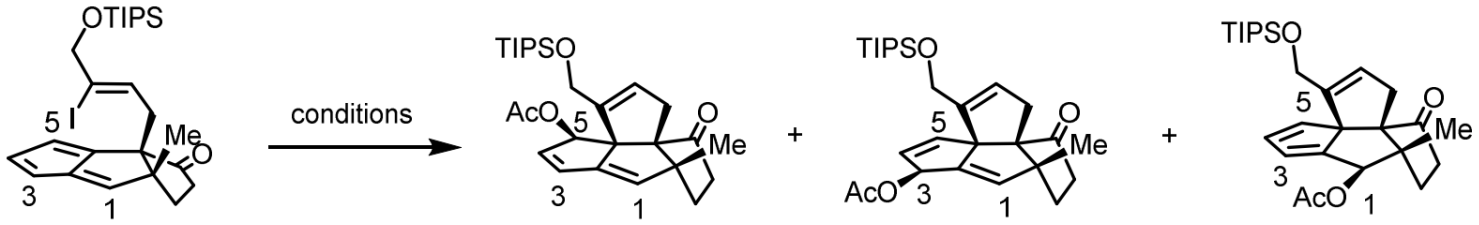
Scheme I[a]



[a] (a) Bu_4NOH, dioxane, H_2O (74%); (b) $NaBH_4$ (100%); (c) TsCl, DMAP, pyridine (96%); (d)[15] Al_2O_3, $ClCH_2CH_2Cl$ (86%); (e) $[Pd(allyl)Cl]_2$, (*R*,*R*)-CHIRAPHOS, Bu_4NOAc, toluene (61%).

J. Org. Chem., **1991**, *56*, 4093.

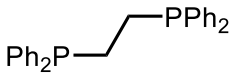
II Table S1. Optimization of Heck cyclization



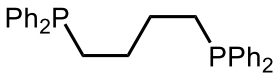
9 **S1** **S2** **S3**

entry	conditions	yield of **S1**(%)	yield of **S2**(%)	yield of **S3**(%)	**8** (%)
1[a]	$Pd(PPh_3)_4$, $^nBu_4NOAc$, 60 °C	0	0	0	80
2[a,g]	$Pd(OAc)_2$, PPh_3, $^nBu_4NOAc$	0	0	0	80
3[c,e]	$Pd(OAc)_2$, dppe, $^nBu_4NOAc$	2	35	11	0
4[a]	$Pd(PPh_3)_4$, $^nBu_4NOAc$, AgOAc	2	36	12	0
5[c,d]	$Pd(OAc)_2$, dppe, AgOAc	2	50	16	0
6[b,d]	$Pd(OAc)_2$, PPh_3, AgOAc	3	48	16	0
7[c,d]	$Pd(OAc)_2$, dppb, AgOAc	2	51	17	0
8[c,d]	$Pd(OAc)_2$, dppp, AgOAc	trace	66	11	0
9[c,d,h]	$Pd(OAc)_2$, (*R*)-BINAP, AgOAc	trace	83	2	0
10[d,f,h]	$Pd(OAc)_2$, (*R*)-BINAP, AgOAc, 2 h	trace	81	2	0

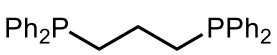
dppe



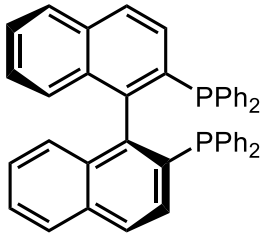
dppb



dppp

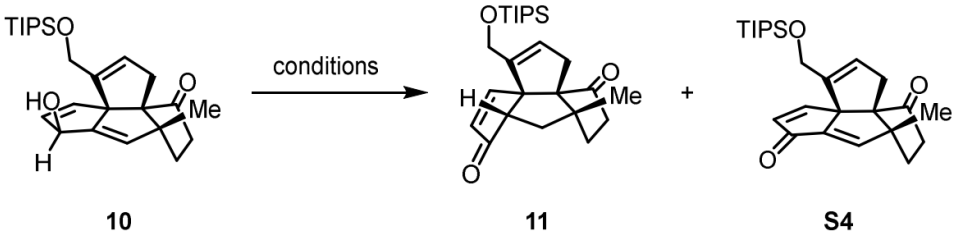


R-BINAP



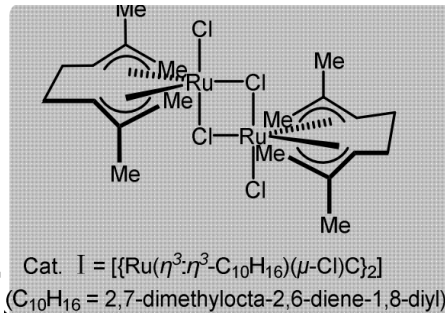
a. MeCN : THF = 4:1; b. 1.0 equiv $Pd(OAc)_2$, 2.0 equiv Ligand; c. 1.0 equiv $Pd(OAc)_2$, 1.0 equiv Ligand; d. toluene as solvent; e. MeCN as solvent; f. 5.0 mol% $Pd(OAc)_2$, 5.0 mol% Ligand; g. 1.0 equiv $Pd(OAc)_2$, 4.0 equiv Ligand; h. S2 :S3 = 35 :1; Unless otherwise noted, all reactions were complete at 80 °C, all reactions were complete in 0.5 h. dppe, ethylenebis(diphenylphosphine); dppb, 1,4-Bis(diphenylphosphino)butane; dppp, 1,3-Bis(diphenylphosphino)propane. Isolated yield.

III Table S2. Optimization of Hydrogen transfer Reaction

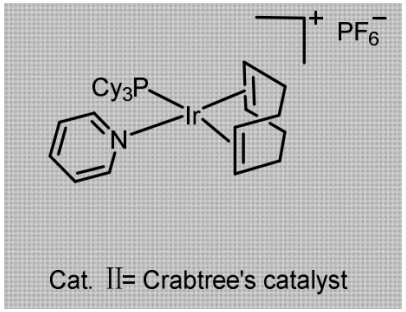


10 **11** **S4**

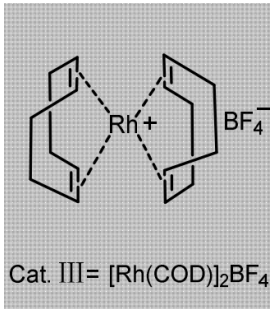
entry	contidions	yield of **11**(%)	yield of **S4**(%)	**10**(%)
1[a]	Cat. I, Cs_2CO_3, THF, 25 ºC, 16 h	N.R	N.R	100
2[a]	Cat. I, Cs_2CO_3, THF, 75 ºC, 16 h	N.R	N.R	100
3[a]	Cat. I, Cs_2CO_3, mesitylene, 160 ºC, 16 h	trace	>95	0
4[a]	Cat. II, activated by H_2, THF, 25 ºC, 16 h	N.R	N.R	100
5[a]	Cat. II, activated by H_2, THF, 75 ºC, 16 h	N.D	N.D	90
6[a]	Cat. II, activated by H_2, mesitylene, 160 ºC, 16 h	N.D	N.D	80
7[a]	Cat. III, *t*-BuOK, (*R*)-DTBM-SegPhos, toluene, 24 ºC, 16 h	N.R	N.R	50
8[a]	Cat. III, Ag_2CO_3, (*R*)-DTBM-SegPhos, toluene, 24 ºC, 16 h	N.R	N.R	100
9[a]	Cat. III, Ag_2CO_3, (*R*)-BINAP, 4 Å MS, mesitylene, 160 ºC, 16 h	53	trace	0
17[b]	Cat. III, Et_3N, (*R*)-BINAP, 4 Å MS, toluene, 120 ºC, 2 h	40	20	20
18[b]	Cat. III, Cs_2CO_3, (*R*)-DTBM-SegPhos, 4 Å MS, toluene, 120 ºC, 2 h	50	26	25
19[c]	Cat. III, Cs_2CO_3, (*R*)-BINAP, 4 Å MS, toluene, 120 ºC, 2 h	91	trace	0



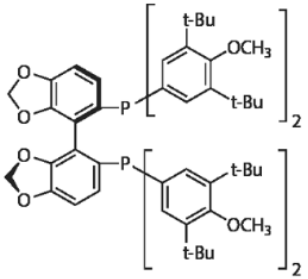
Cat. I = [{Ru(η^3:η^3-$C_{10}H_{16}$)(μ-Cl)C}$_2$] ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl)



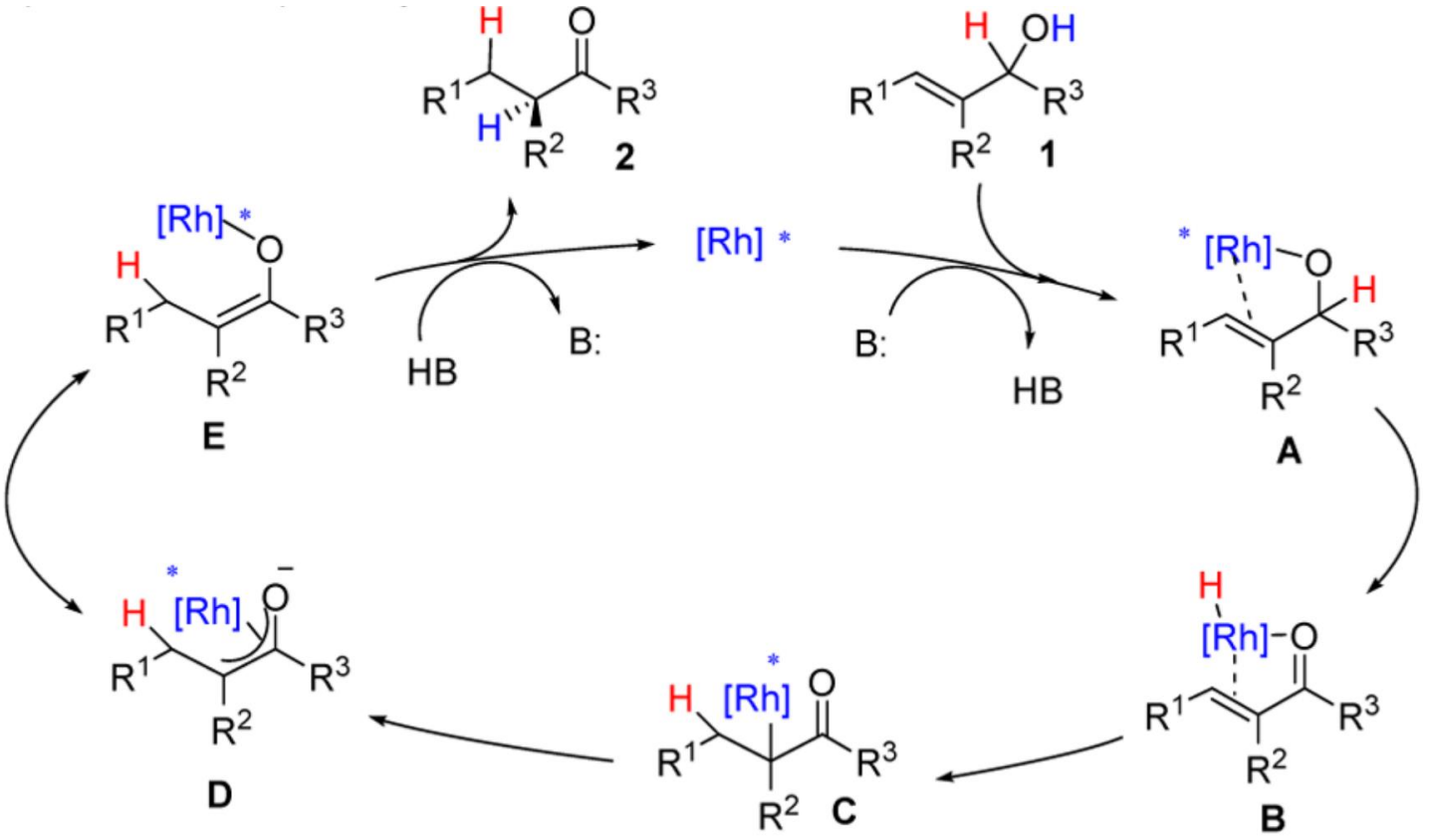
Cat. II= Crabtree's catalyst



Cat. III= $[Rh(COD)]_2BF_4$

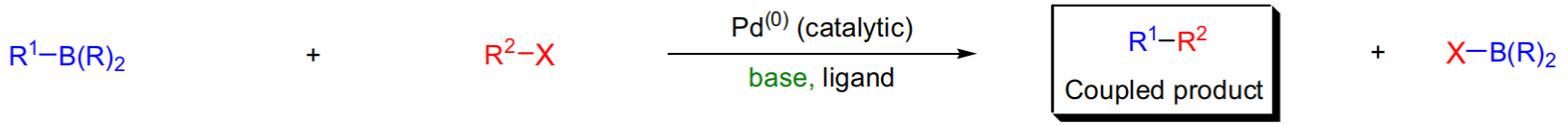


(*R*)-DTBM-SegPhos



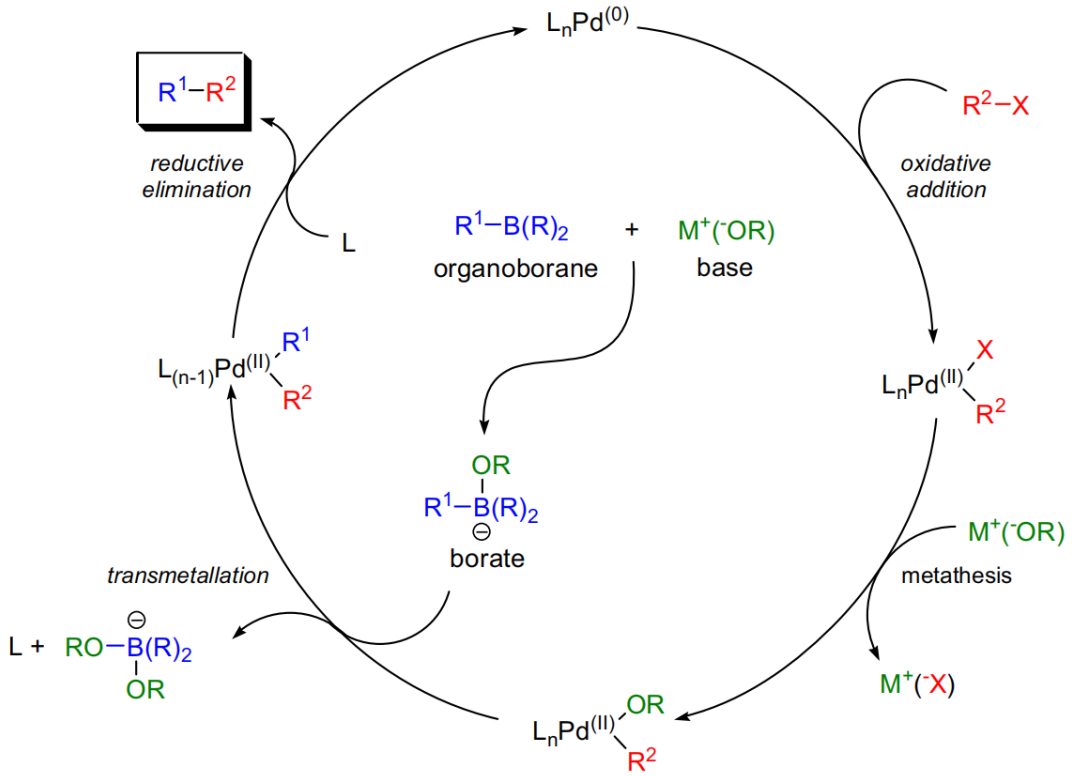
J. Am. Chem. Soc., **2017**, *139*, 3643.
Chem. Rev., **2003**, *103*, 27.

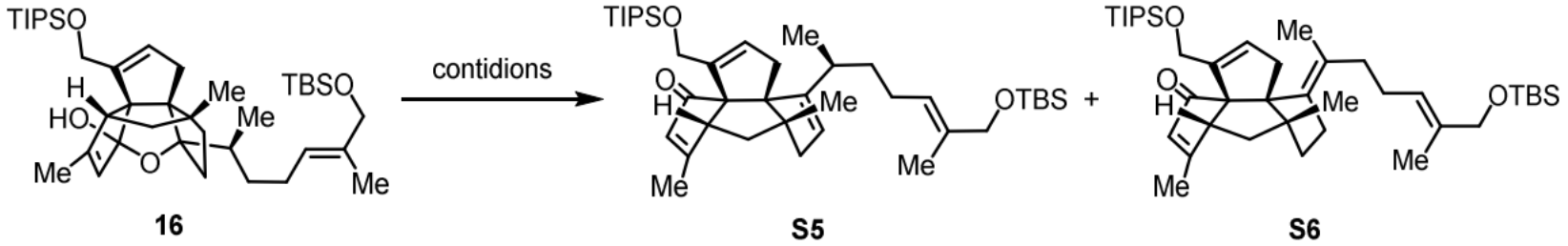
SUZUKI CROSS-COUPLING
(SUZUKI-MIYAURA CROSS-COUPLING)

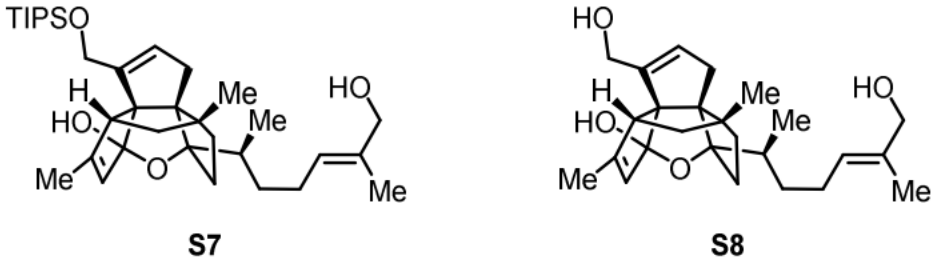


R^1 = alkyl, allyl, alkenyl, alkynyl, aryl; R = alkyl, OH, O-alkyl; R^2 = alkenyl, aryl, alkyl; X = Cl, Br,I, OTf, $OPO(OR)_2$ (enol phosphate);
base = Na_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3, K_2CO_3, TlOH, KF, CsF, Bu_4F, NaOH, $M^+(^-O\text{-alkyl})$

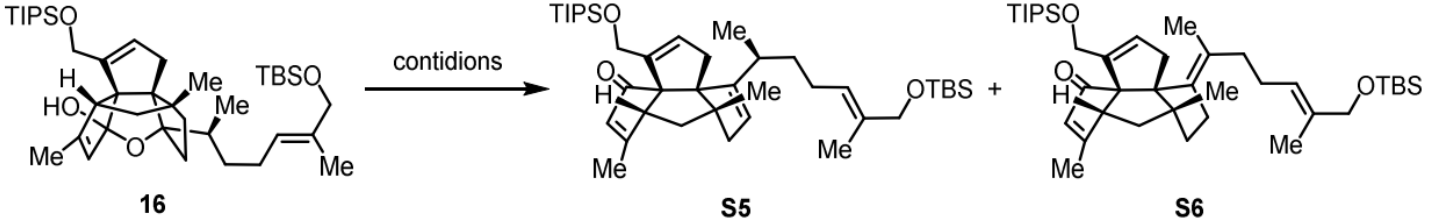
Mechanism:

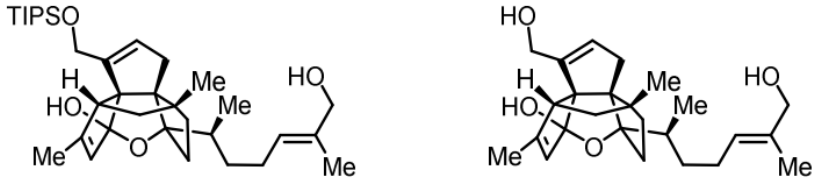






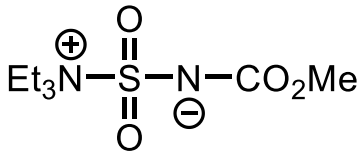
entry	contions	yield of **S5**(%)	yield of **S6**(%)	yield of **S7**(%)	yield of **S8**(%)	**16** (%)
1	Burgess reagent，DCM, 25 ℃, 2 h	N.R.	N.R.	N.R.	N.R.	100
2	Burgess reagent，THF, 60℃, 2 h	N.R.	N.R.	N.R.	N.R.	100
3	Martin's sulfurane, DCM, 40 ℃, 2 h	N.D.	N.D.	N.D.	N.D.	87
4[a]	Tf_2O, Et_3N, DCM, -78 ℃, 1 h	N.D.	N.D.	N.D.	N.D.	84
5[a]	Tf_2O, Et_3N, DCM, 25 ℃, 10 min	N.D.	N.D.	N.D.	N.D.	0
6	1 M HCl(aq), THF, 25 ℃, 10 min	N.D.	N.D.	N.D.	91	0
7	$TsOH·H_2O$, THF, 70 ℃, 2 h	50	50	0	0	0
8	$TsOH·H_2O$, benzene, 70 ℃, 2 h	trace	92	0	0	0



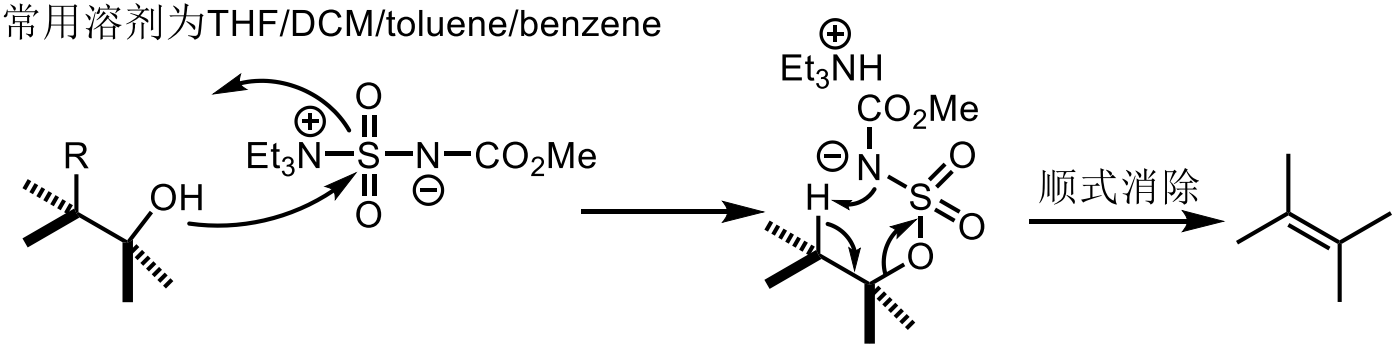


9[b]	$SOCl_2$: pyridine= 1:2.5, DCM, 25℃, 5 min	40	40	0	0	trace
10[b]	$SOCl_2$, pyridine(solvent), 25 ℃, 5 min	0	50	0	0	40
11[b]	$SOCl_2$, pyridine, DMF(Cat.), DCM, 25 ℃	0	0	0	0	0
12[c]	$SOCl_2$, 2,6-lutidine, DCM, 25 ℃, 5 min	60	35	0	0	0
13[d]	MsCl, Et_3N, DMAP, DCM, 40 ℃, 2 h	30	28	0	0	33
14	DMSO, 150 ℃, 2 h	0	0	89	0	0
15	DMSO, 180 ℃, 2 h	22	21	0	0	0
16[e]	DMSO : HMPA, 180 ℃, 2 h	trace	30	0	0	0

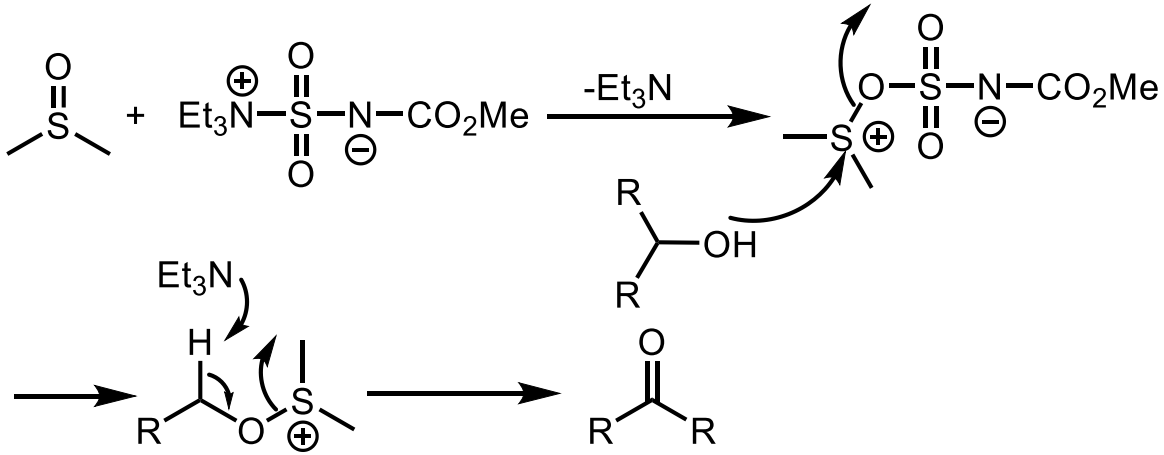
Reaction condition: a. Tf_2O : Et_3N = 1: 2; b. $SOCl_2$: pyridine = 1 : 2.5; c. $SOCl_2$: 2,6-lutidine = 1 : 2.5; d. MsCl : Et_3N = 1 : 2; e. DMSO : HMPA = 10 : 1; $SOCl_2$、pyridine、MsCl、Et_3N and 2,6-dimethylpyridine were distilled immediately before use . Determined by ^1H NMR analysis of the mixture. N.R.:no reaction; N.D.: not detected.

Burgess试剂: 

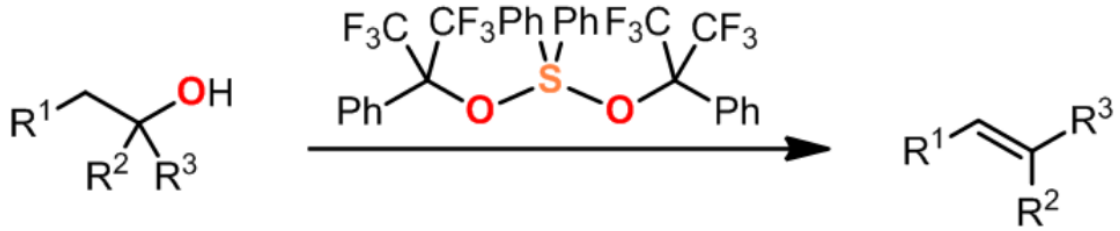
是非常有效的由仲醇和叔醇脱水制备烯烃的试剂
但一级醇反应效果不佳
常用溶剂为THF/DCM/toluene/benzene



若溶剂为DMSO，则将醇氧化为醛/酮

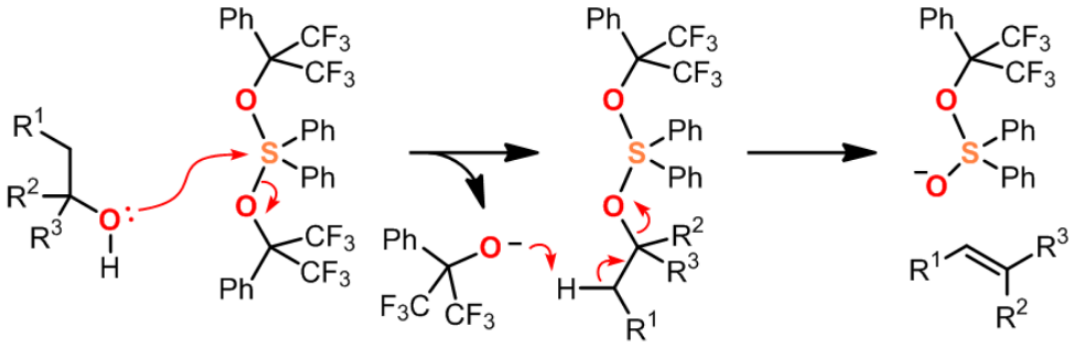


Martin试剂



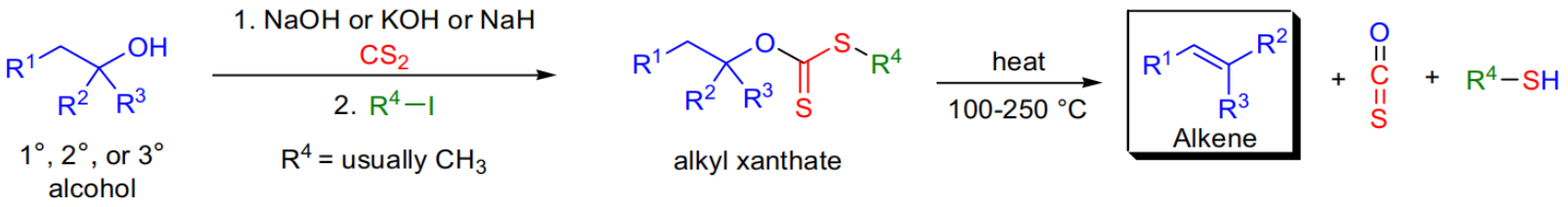
Martin试剂是一种已经商品化的试剂，它可以高效温和的将醇转化成对应的烯烃，即使在室温下也可快速发生反应。

反应机理



此类试剂还有一种替代：

Chugaev elimination reaction



1°醇的黄原酸酯对热较稳定，需要大于200 °C的高温才可发生裂解，而2°和3°醇的黄原酸酯远次之

Mechanism: