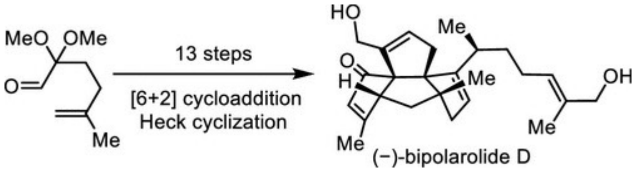
Concise Total Synthesis of (–)-Bipolarolide D

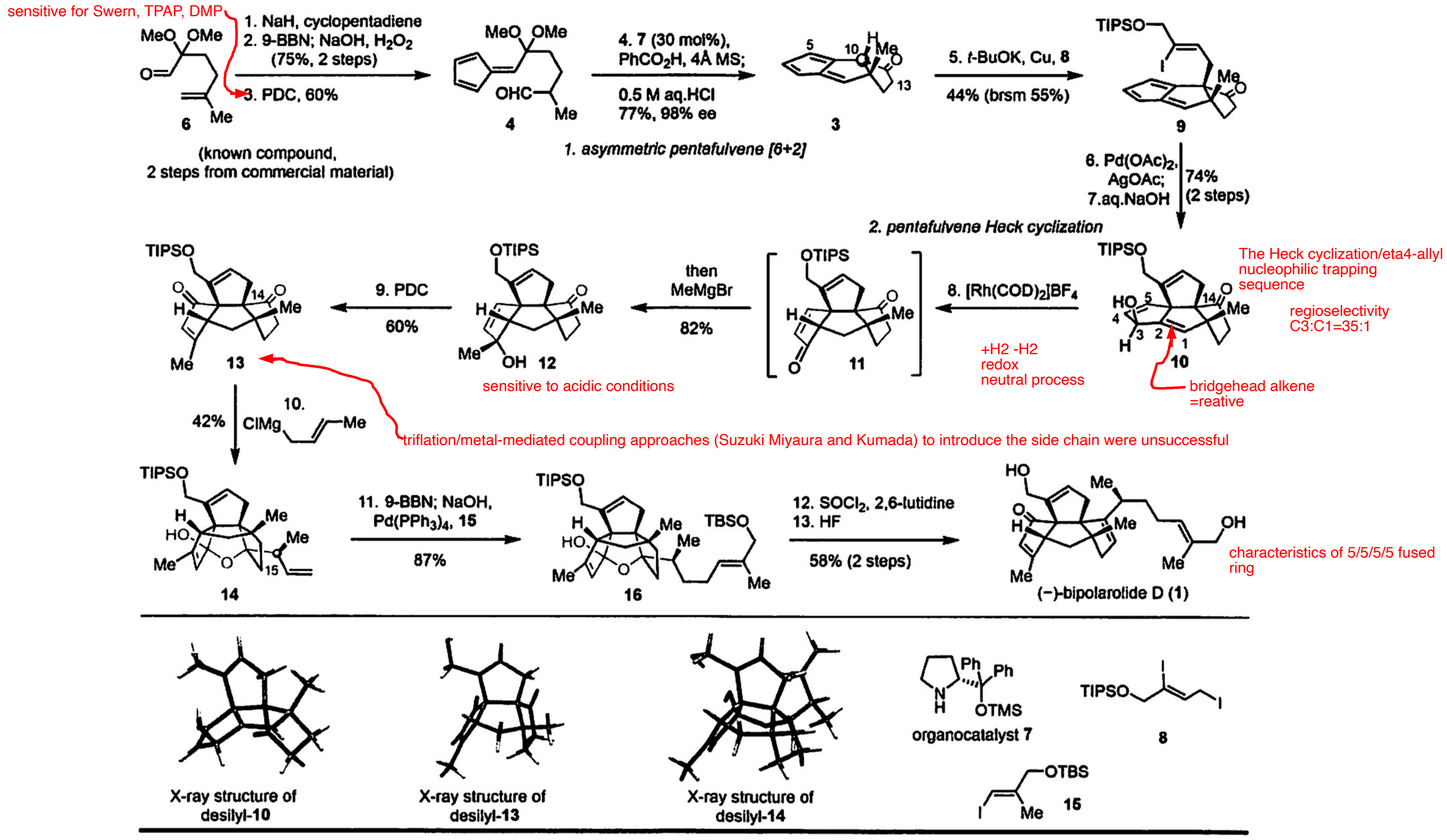
Shengling Sun, Qi Wei, Yufei Liu, and Zhaohong Lu*

Cite this: J. Am. Chem. Soc. 2024, 146, 21, 14427–14432

utilizing fulvenes as versatile synthons



Scheme 1. Total Synthesis of Bipolarolide D



sensitive for Swern, TPAP, DMP

The Heck cyclization/eta4-allyl nucleophilic trapping sequence

regioselectivity C3:C1=35:1

bridgehead alkene =reative

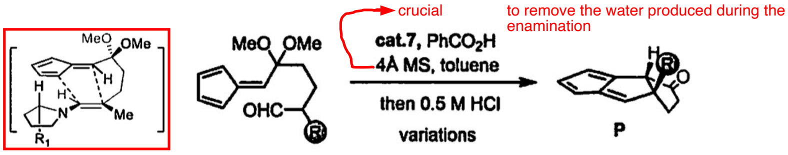
+H2 -H2 redox neutral process

sensitive to acidic conditions

triflation/metal-mediated coupling approaches (Suzuki Miyaura and Kumada) to introduce the side chain were unsuccessful

characteristics of 5/5/5/5 fused ring

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



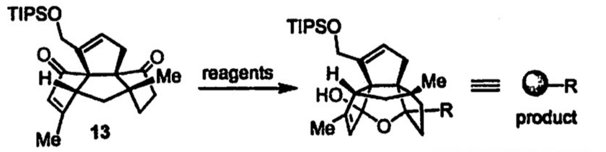
crucial

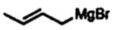
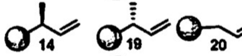
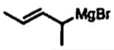
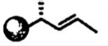
to remove the water produced during the enamination

Entry	Ⓡ=	cat. 7	PhCO₂H	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	CH₂CH₂OBn	30 mol%	15 mol%	-30°C	3a	76%	97%

the flexibility of this asymmetric [6+2]

Table 3. Installation of Different Side Chains through Nucleophilic Addition Reaction

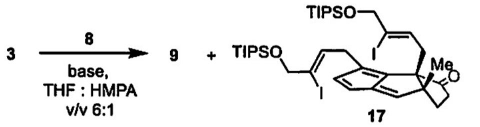


Entry	reagents	product	yield (%)
1	MeMgBr	●–Me **18**	0
2	MeLi	●–Me **18**	81
3	 MgBr	 **14** **19** **20**	42 : 22 :18
4	 MgBr	 **21**	90

metathesis with ethene → 19

allylmetallates (Mg, Li) often exhibit high reactivity even toward sterically hindered carbonyl groups with excellent stereoselectivity.

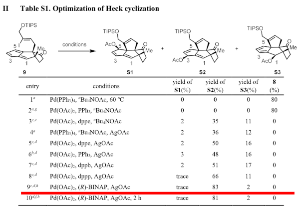
Table 2. Optimization of Allylation Conditions to Establish the Second Quaternary Carbon Center



decomposition under strongly basic conditions

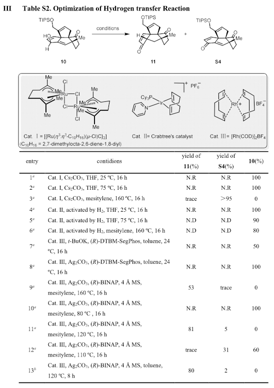
Entry	Variations	yield (%) 9	17	recovery 3 (%)
1	LDA	<5	0	0
2	MeONa	21	15	10
3	t-BuOK	25	20	12
4	t-BuOK, t-BuOH	33	16	15
5	t-BuOK (1.7 eq), t-BuOH, Cu powder	44	23	20

reduced the decomposition



II Table S1. Optimization of Heck cyclization

entry	conditions	yield of S1(%)	yield of S2(%)	yield of S3(%)	8 (%)
1[a]	Pd(PPh₃)₄, ⁿBu₄NOAc, 60 °C	0	0	0	80
2[a,g]	Pd(OAc)₂, PPh₃, ⁿBu₄NOAc	0	0	0	80
3[c,e]	Pd(OAc)₂, dppe, ⁿBu₄NOAc	2	35	11	0
4[a]	Pd(PPh₃)₄, ⁿBu₄NOAc, AgOAc	2	36	12	0
5[c,d]	Pd(OAc)₂, dppe, AgOAc	2	50	16	0
6[b,d]	Pd(OAc)₂, PPh₃, 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



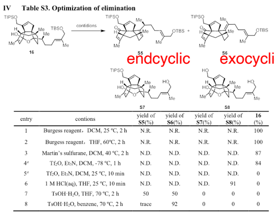
III Table S2. Optimization of Hydrogen transfer Reaction

Cat. Ⅰ = [{Ru(η³:η³-C₁₀H₁₆)(μ-Cl)C}₂] (C₁₀H₁₆ = 2,7-dimethylocta-2,6-diene-1,8-diyl)

Cat. Ⅱ= Crabtree's catalyst

Cat. Ⅲ= [Rh(COD)]₂BF₄

entry	contidions	yield of 11(%)	yield of S4(%)	10(%)
1[a]	Cat. I, Cs₂CO₃, THF, 25 ºC, 16 h	N.R	N.R	100
2[a]	Cat. I, Cs₂CO₃, THF, 75 ºC, 16 h	N.R	N.R	100
3[a]	Cat. I, Cs₂CO₃, mesitylene, 160 ºC, 16 h	trace	>95	0
4[a]	Cat. II, activated by H₂, THF, 25 ºC, 16 h	N.R	N.R	100
5[a]	Cat. II, activated by H₂, THF, 75 ºC, 16 h	N.D	N.D	90
6[a]	Cat. II, activated by H₂, 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, Ag₂CO₃, (R)-DTBM-SegPhos, toluene, 24 ºC, 16 h	N.R	N.R	100
9[a]	Cat. III, Ag₂CO₃, (R)-BINAP, 4 Å MS, mesitylene, 160 ºC, 16 h	53	trace	0
10[a]	Cat. III, Ag₂CO₃, (R)-BINAP, 4 Å MS, mesitylene, 80 ºC , 16 h	N.R	N.R	100
11[a]	Cat. III, Ag₂CO₃, (R)-BINAP, 4 Å MS, mesitylene, 120 ºC, 16 h	81	5	0
12[a]	Cat. III, Ag₂CO₃, (R)-BINAP, 4 Å MS, mesitylene, 110 ºC, 16 h	trace	31	60
13[b]	Cat. III, Ag₂CO₃, (R)-BINAP, 4 Å MS, toluene, 120 ºC, 8 h	80	2	0

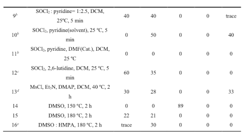


IV Table S3. Optimization of elimination

endcyclic

exocyclic

entry	contions	yield of S5(%)	yield of S6(%)	yield of S7(%)	yield of S8(%)	16 (%)
1	Burgess reagent，DCM, 25 ºC, 2 h	N.R.	N.R.	N.R.	N.R.	100
2	Burgess reagent，THF, 60ºC, 2 h	N.R.	N.R.	N.R.	N.R.	100
3	Martin's sulfurane, DCM, 40 ºC, 2 h	N.D.	N.D.	N.D.	N.D.	87
4[a]	Tf₂O, Et₃N, DCM, -78 ºC, 1 h	N.D.	N.D.	N.D.	N.D.	84
5[a]	Tf₂O, Et₃N, DCM, 25 ºC, 10 min	N.D.	N.D.	N.D.	N.D.	0
6	1 M HCl(aq), THF, 25 ºC, 10 min	N.D.	N.D.	N.D.	91	0
7	TsOH·H₂O, THF, 70 ºC, 2 h	50	50	0	0	0
8	TsOH·H₂O, benzene, 70 ºC, 2 h	trace	92	0	0	0



9[b]	SOCl₂ : pyridine= 1:2.5, DCM, 25ºC, 5 min	40	40	0	0	trace
10[b]	SOCl₂, pyridine(solvent), 25 ºC, 5 min	0	50	0	0	40
11[b]	SOCl₂, pyridine, DMF(Cat.), DCM, 25 ºC	0	0	0	0	0
12[c]	SOCl₂, 2,6-lutidine, DCM, 25 ºC, 5 min	60	35	0	0	0
13[d]	MsCl, Et₃N, DMAP, DCM, 40 ºC, 2 h	30	28	0	0	33
14	DMSO, 150 ºC, 2 h	0	0	89	0	0
15	DMSO, 180 ºC, 2 h	22	21	0	0	0
16[e]	DMSO : HMPA, 180 ºC, 2 h	trace	30	0	0	0