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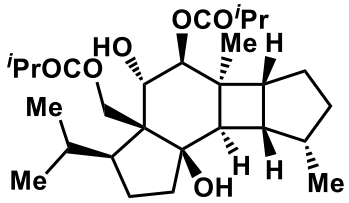
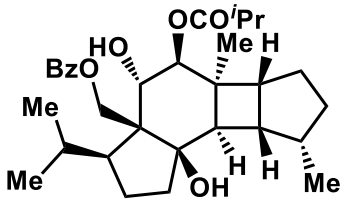
Total Synthesis

Divergent Total Syntheses of (+)-Vulgarisins A–E

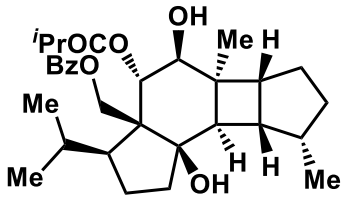
*Kaixiang Xu, Shan Mu, Huijuanzi Rao, Jialei Hu, and Hanfeng Ding**



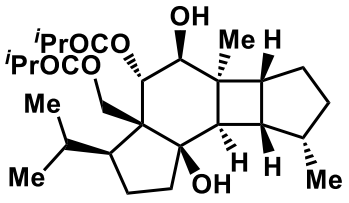
(+)-vulgarisin A (1)



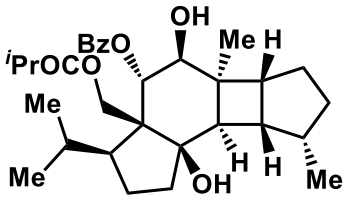
(+)-vulgarisin B (2)



(+)-vulgarisin C (3)

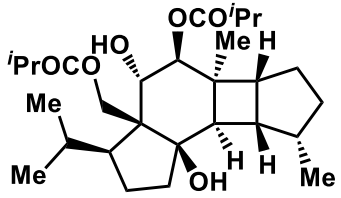


(+)-vulgarisin D (4)

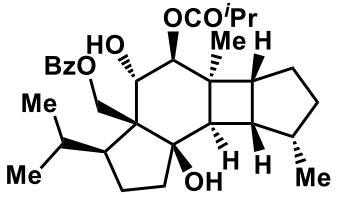


(+)-vulgarisin E (5)

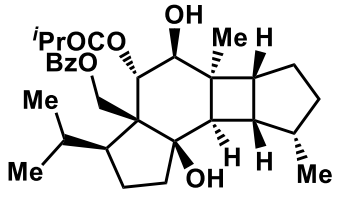
DOI: 10.1002/anie.202303668.



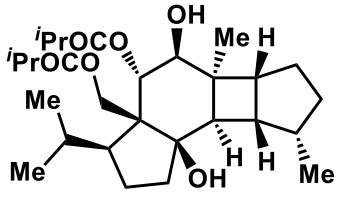
(+)-vulgarisin A (1)



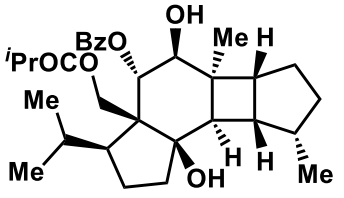
(+)-vulgarisin B (2)



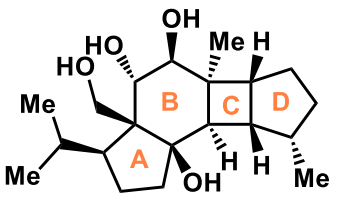
(+)-vulgarisin C (3)



(+)-vulgarisin D (4)

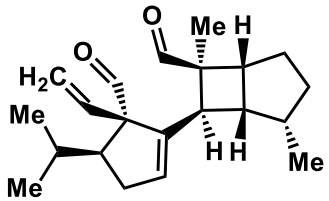


(+)-vulgarisin E (5)



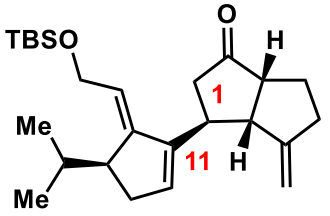
6 [common int.]

stereocontrolled
pinacol cyclization



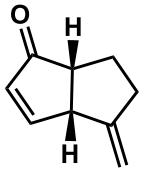
7

Wolff
ring contraction



8

reductive
Heck



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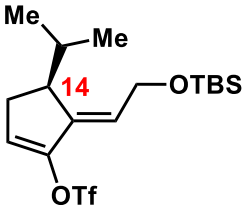

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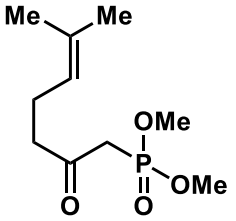
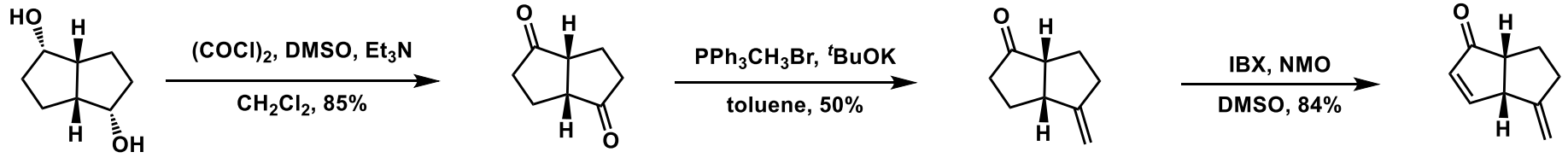
CAIMCP



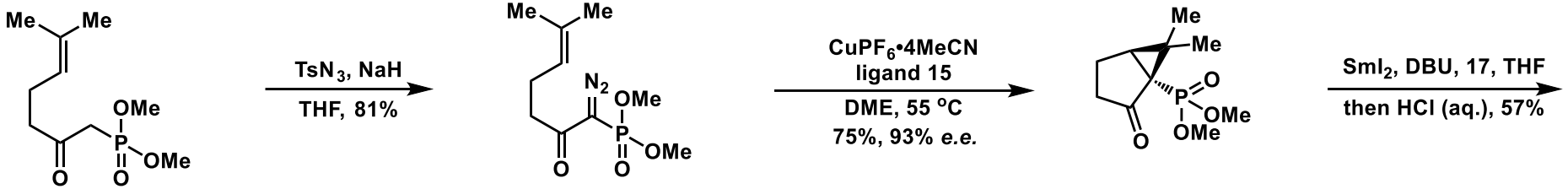
11

A.

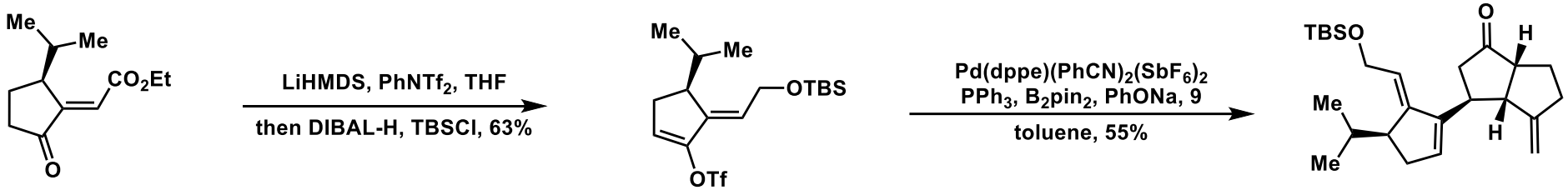


(+)-12, > 99% *e.e.* | 13, > 99% *e.e.* | S-1 | 9

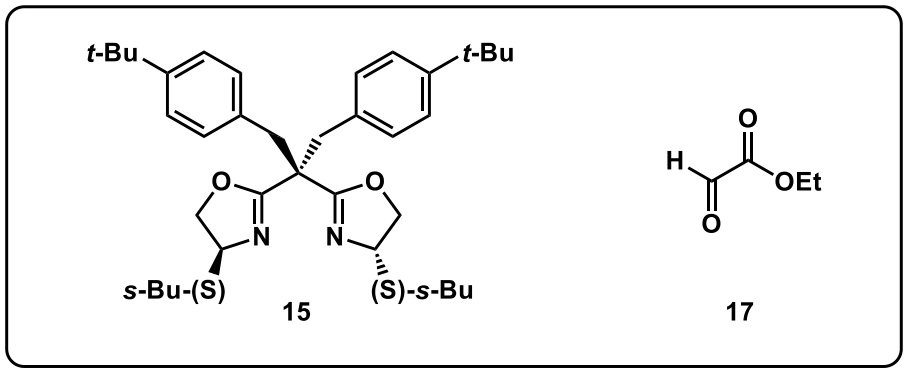
B.



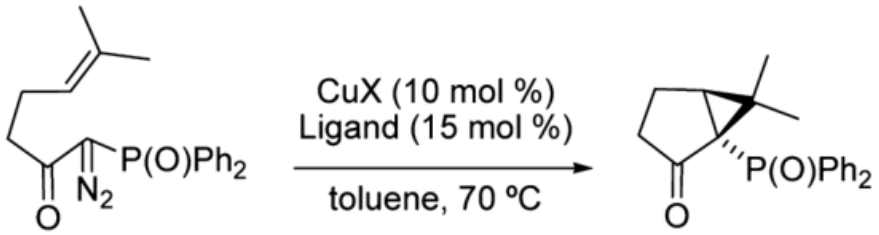
11 | 14 | 16



E-(18) | 10 | 8



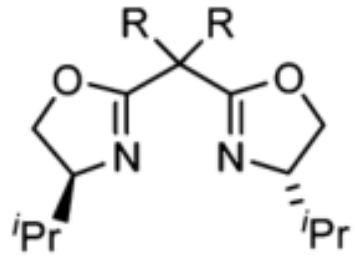
15 | 17



12 **13**

entry	ligand	CuX	time (h)	yield[a] (%)	ee[b] (%)
1	**8a**	CuOTf[c]	1.5	43	63
2	**8b**	CuOTf[c]	16	37	73
3	**8c**	CuOTf[c]	4	90	75
4	**8d**	CuOTf[c]	4	59	86
5	**8e**	CuOTf[c]	3	51	75
6	**8f**	CuOTf[c]	19	43	81
7	**8g**	CuOTf[c]	5	44	84
8	**8h**	CuOTf[c]	30	64	84
9	**8d**	$CuBF_4$[d]	12	79	**91**

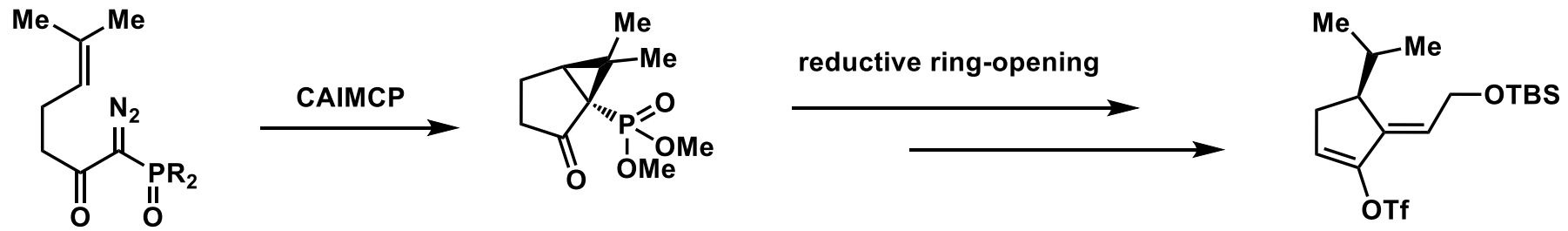
[a] Isolated yields. [b] ee determined by HPLC. For conditions, see the Supporting Information. [c] $(CuOTf)_2 \cdot$ toluene was used. [d] $CuBF_4 \cdot 4MeCN$ was used.



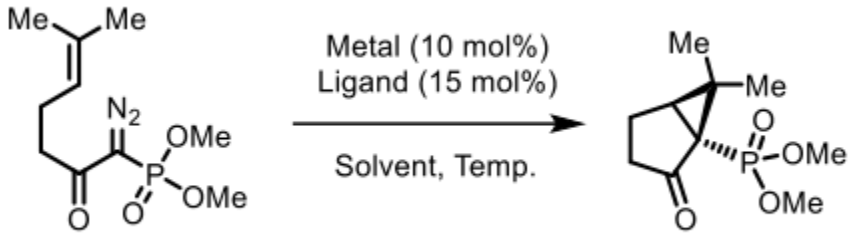
8a (R = Me)
8b (R = Et)
8c (R = isobutyl)
8d (R = Bn)
8e (R = 2-MeBn)
8f (R = 3-MeBn)
8g (R = 4-MeBn)
8h (R = 3,5-(^{t}Bu)$_2$Bn)

Org. Lett., **2013**, *15*, 1004.

Strategy:



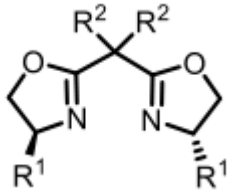
11 **16** **10**



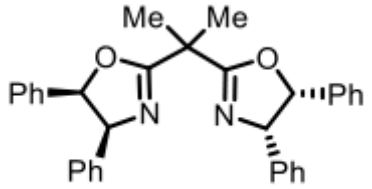
14 **16**

Entry	Metal	Ligand	Solvent	Temp. (°C)	Yield (%), ee (%)
1	CuBF4·4MeCN	L1	toluene	80	53, 65
2	CuBF4·4MeCN	L17	toluene	80	74, 81
3	CuBF4·4MeCN	L17	toluene	55	75, 84
4	CuBF4·4MeCN	L17	DME	55	75, 88
5	CuPF6·4MeCN	L17	DME	55	83, 91
6*	CuPF6·4MeCN	L17	DME	55	75, 93

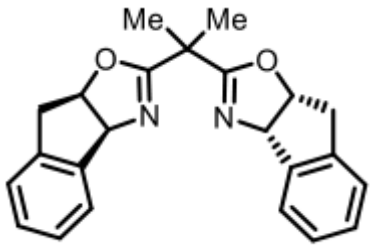
*** Decagram scale (c = 0.4 M).**



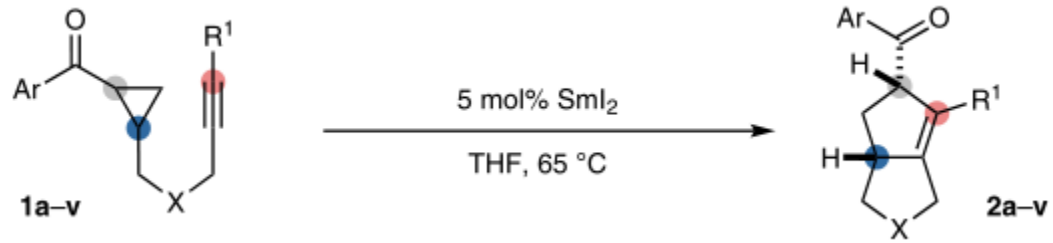
L1: R^1 = *i*-Pr, R^2 = Bn
L2: R^1 = *i*-Pr, R^2 = 2-MeBn
L3: R^1 = *i*-Pr, R^2 = 3-MeBn
L4: R^1 = *i*-Pr, R^2 = 4-MeBn
L5: R^1 = *i*-Pr, R^2 = 4-*t*-BuBn
L6: R^1 = *i*-Pr, R^2 = 4-BrBn
L7: R^1 = *i*-Pr, R^2 = 4-IBn
L8: R^1 = *i*-Pr, R^2 = 4-PhBn
L9: R^1 = *i*-Pr, R^2 = 3,5-$(Me)_2$Bn
L10: R^1 = *i*-Pr, R^2 = 3,5-$(t\text{-}Bu)_2$Bn
L11: R^1 = *i*-Pr, R^2 = Et
L12: R^1 = *i*-Pr, R^2 = *s*-Bu
L13: R^1 = Me, R^2 = Bn
L14: R^1 = *t*-Bu, R^2 = Bn
L15: R^1 = (*S*)-*s*-Bu, R^2 = Bn
L16: R^1 = (*S*)-*s*-Bu, R^2 = 4-MeBn
L17: R^1 = (*S*)-*s*-Bu, R^2 = 4-*t*-BuBn
L18: R^1 = (*S*)-*s*-Bu, R^2 =3,5-$(t\text{-}Bu)_2$Bn

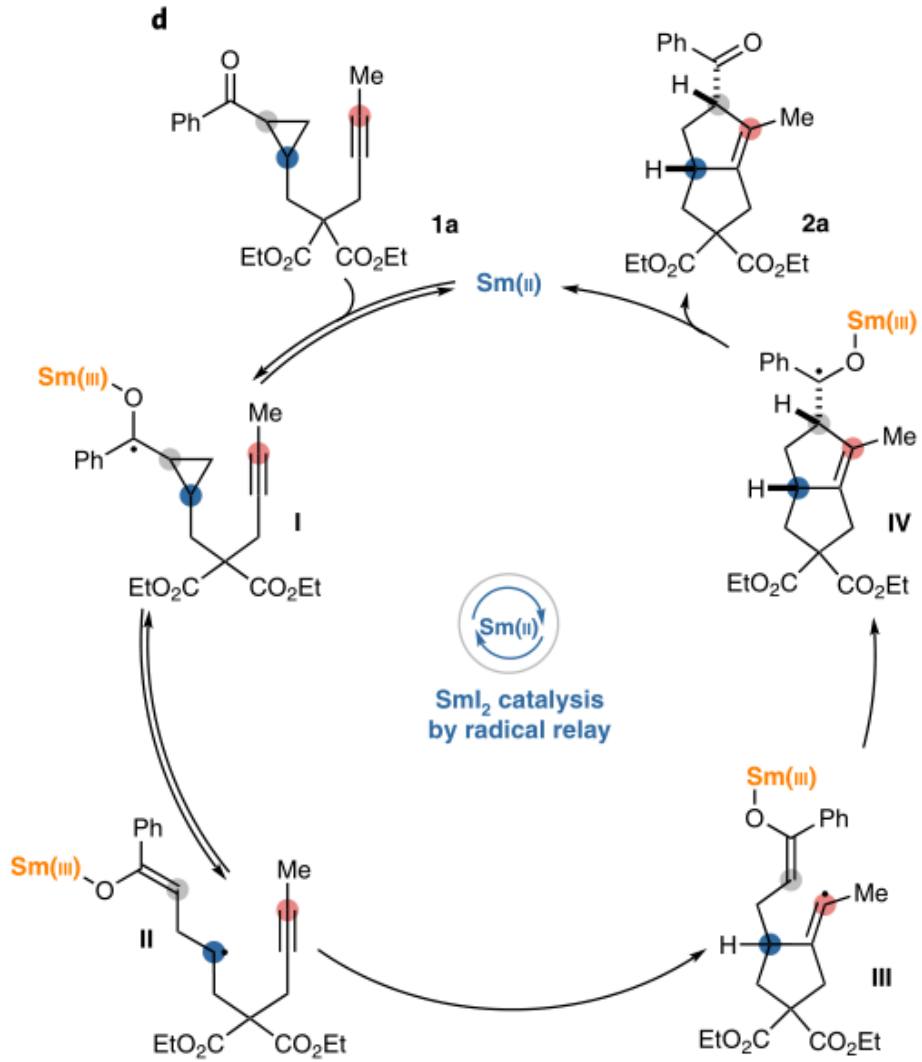


L19

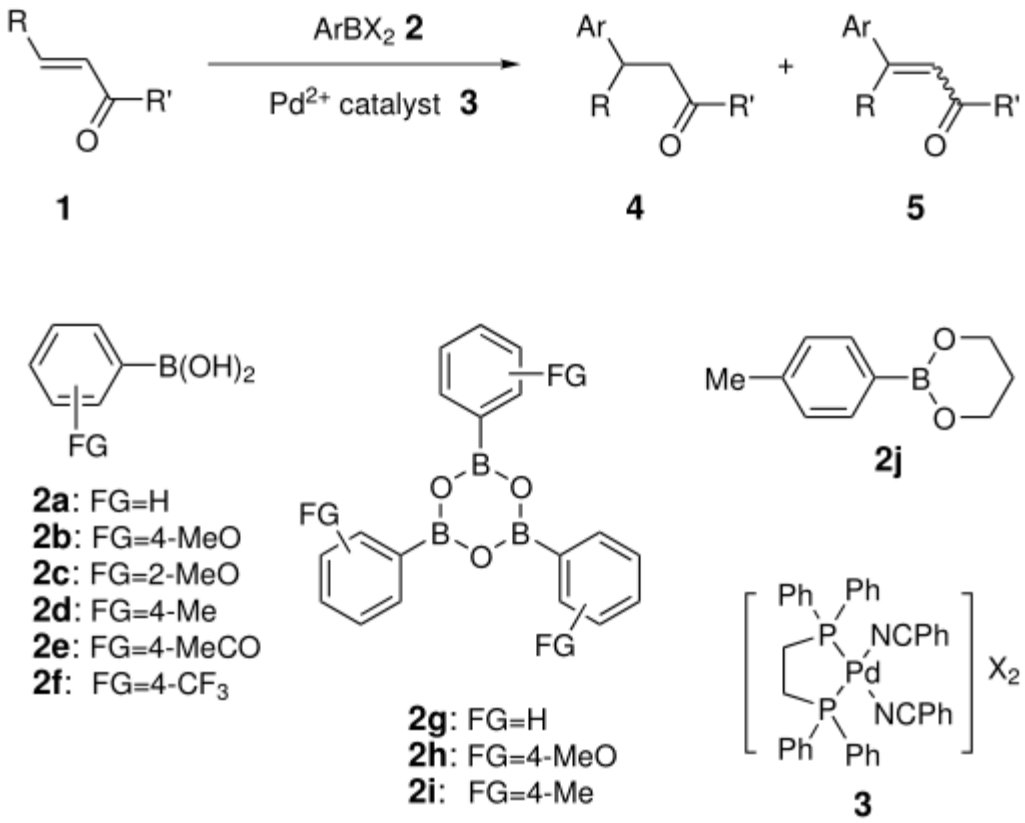


L20

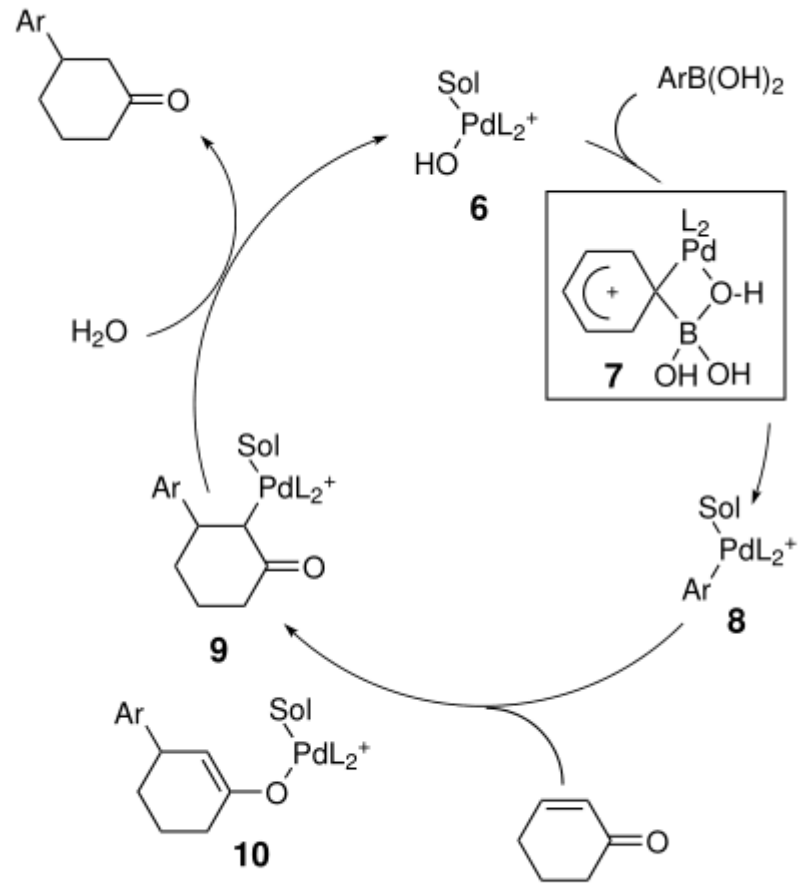




Nature. Catalysis, **2019**, *2*, 211.

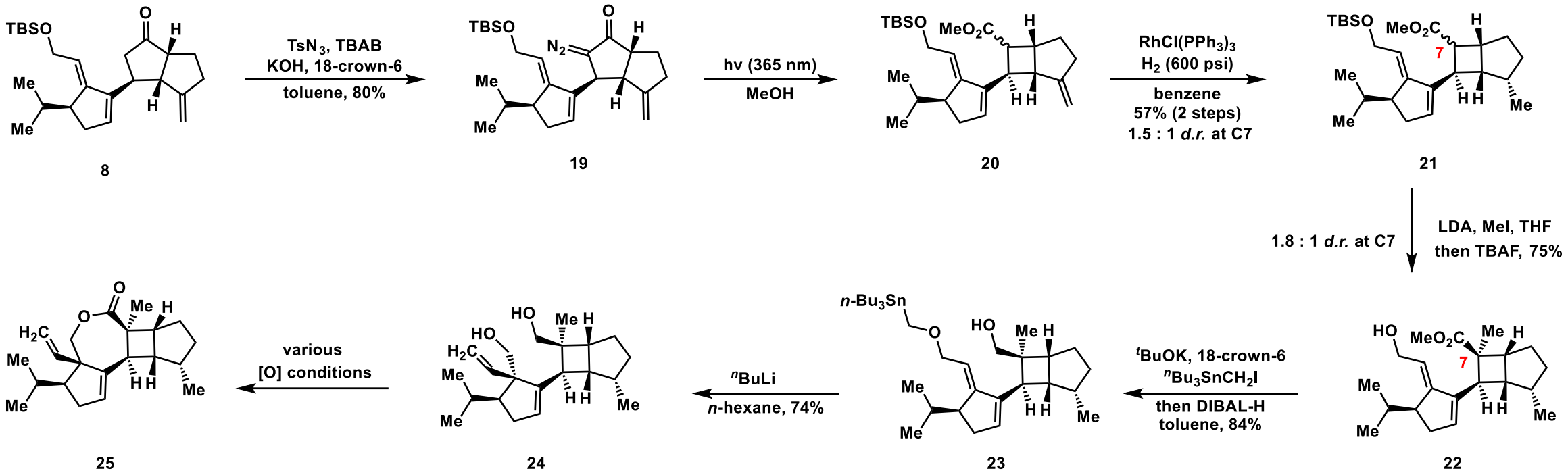


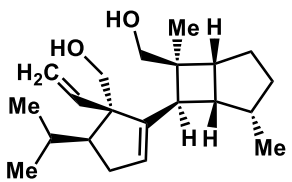
Scheme 1. Palladium(II)-catalyzed 1,4-addition of aryl boron compounds to α,β-unsaturated carbonyl compounds.



Scheme 2. Proposed catalytic cycle. Sol = solvent molecule.

Angew. Chem. Int. Ed., **2003**, *42*, 2768.

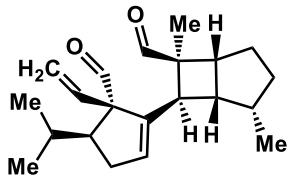

TBSO
O
H
Me
Me
H
8
TsN3, TBAB
KOH, 18-crown-6
toluene, 80%
TBSO
N2
O
H
Me
Me
H
19
hv (365 nm)
MeOH
TBSO
MeO2C
H
Me
Me
H H
20
RhCl(PPh3)3
H2 (600 psi)
benzene
57% (2 steps)
1.5 : 1 d.r. at C7
TBSO
MeO2C
H
7
Me
Me
H H
Me
21
1.8 : 1 d.r. at C7
LDA, MeI, THF
then TBAF, 75%
HO
MeO2C
Me H
7
Me
Me
H H
Me
22
tBuOK, 18-crown-6
nBu3SnCH2I
then DIBAL-H
toluene, 84%
n-Bu3Sn
O
HO
Me H
Me
Me
H H
Me
23
nBuLi
n-hexane, 74%
HO
HO
Me H
H2C
Me
Me
H H
Me
24
various
[O] conditions
O
O
Me H
H2C
Me
Me
H H
Me
25



24

$(COCl)_2$, DMSO, Et_3N

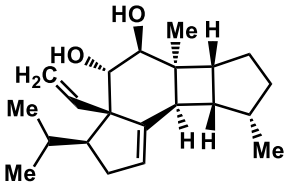
CH_2Cl_2, 90%



7

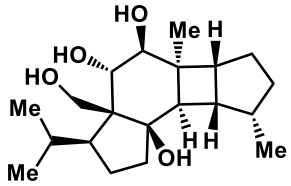
SmI_2

tetraglyme, 65%



26

1. $Mn(acac)_2$, PPh_3
$PhSiH_3$, O_2
2. O_3, then $NaBH_4$
77% (2 steps)



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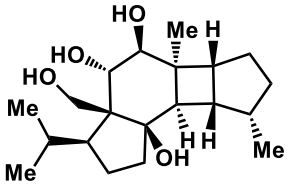
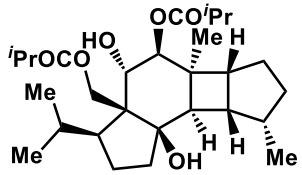


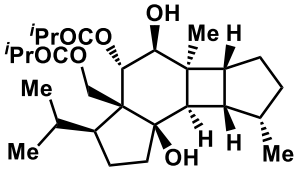
6

IBCl, Py, DMAP



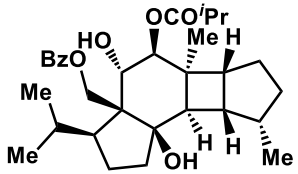
(+)-vulgarisin A (1, 47%)

+



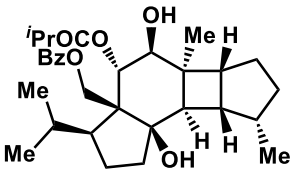
(+)-vulgarisin D (4, 25%)

BzCl, Py, DMAP
then IBCl



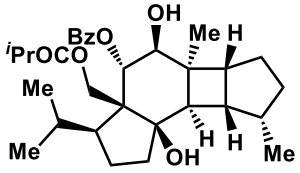
(+)-vulgarisin B (2, 43%)

+



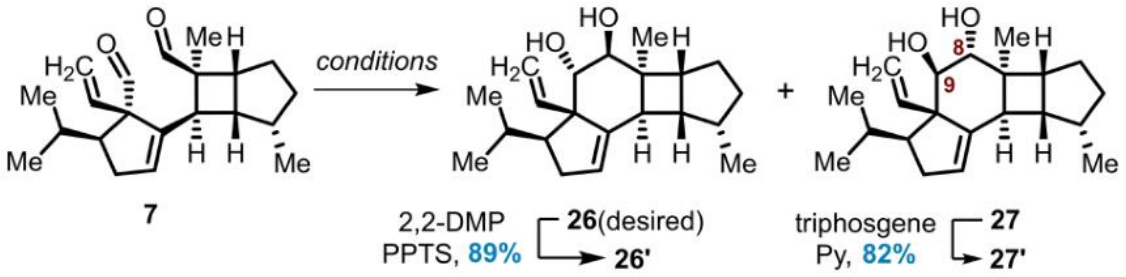
(+)-vulgarisin C (3, 12%)

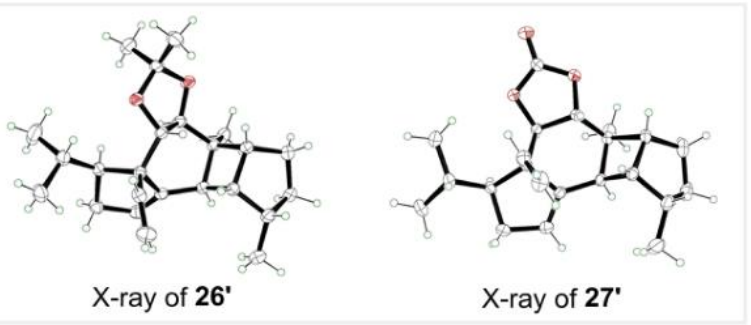
+

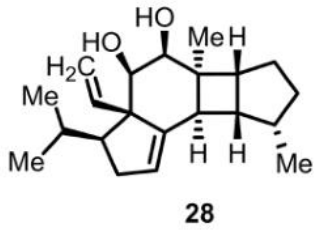


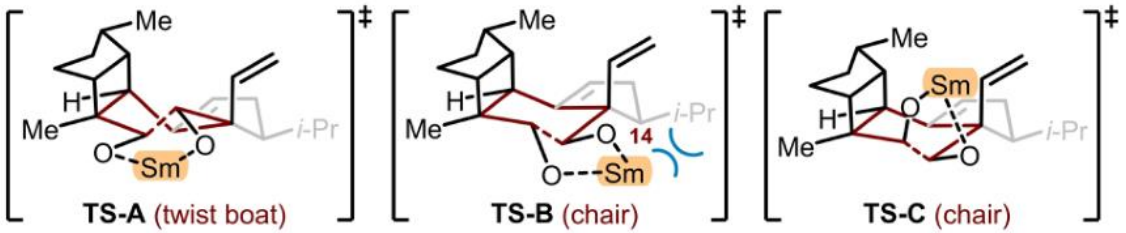
(+)-vulgarisin E (5, 11%)

Table 1: Optimization on the Pinacol Cyclizations of **7**.[a]



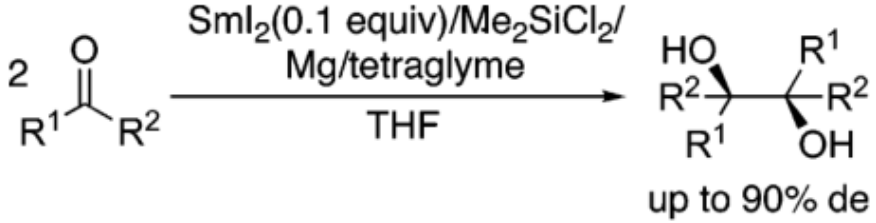




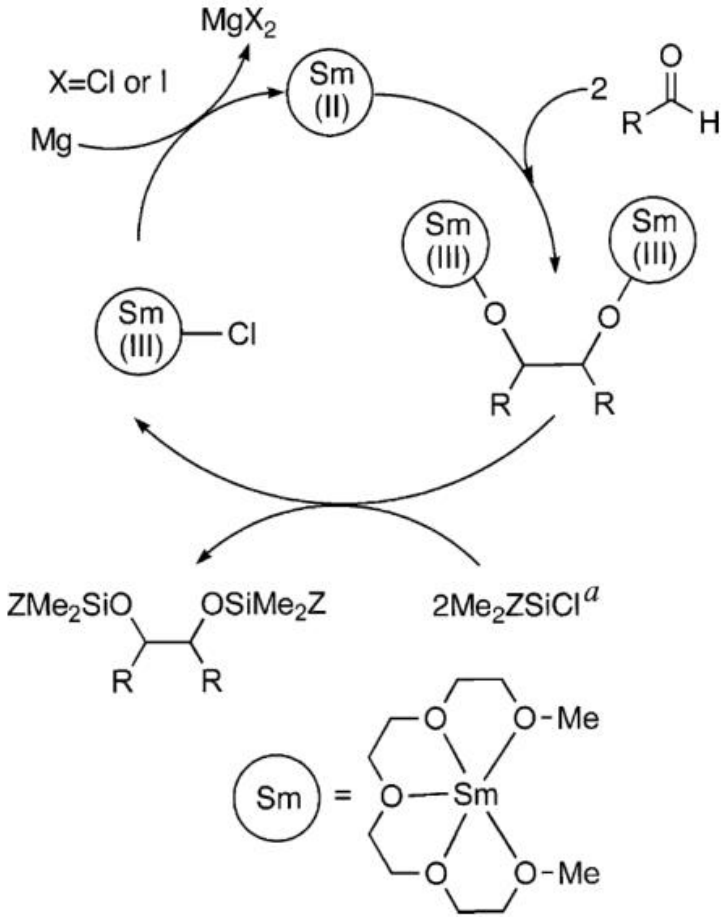


Entry	Conditions	Yield[%][b]		
		26	**27**	**28**
1	$TiCl_4$, Zn, r.t.	9	43	12
2	$VCl_3(THF)_3$, Zn, 0 °C	4	6	5
3[c]	*n*-Bu_3SnH, AIBN, 80 °C	0	0	0
4	SmI_2, −40 °C **TS-C**	14	0	57
5	SmI_2, 0 °C **TS-B**	10	30	21
6	SmI_2, 50 °C	16	55	0
7	SmI_2, −20 °C **TS-A**	33	24	11
8	SmI_2, (*R*,*R*)-*i*-Pr-pybox, −20 °C	13	58	10
9	SmI_2, 2,2′:6′,2″-terpyridine, −20 °C	43	16	15
10	SmI_2, (*S*)-BINAP, −20 °C	44	36	0
11	SmI_2, 18-crown-6, −20 °C	47	29	7
12	SmI_2, 15-crown-5, −20 °C	51	30	8
13	SmI_2, tetraglyme, −20 °C	68(65)[d]	15(13)[d]	6(9)[d]

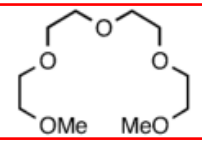
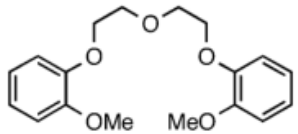
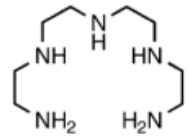
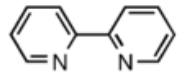
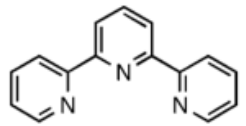
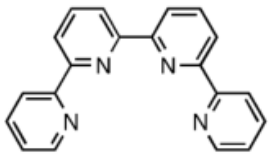
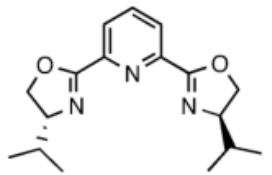
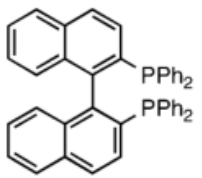
[a] Reaction conditions: **7** (0.1 mmol), low-valent metal (3.0 equiv) and reductant or additive (6.0 equiv) in THF (c = 0.025 M) at indicated temperature. [b] Isolated yields. [c] *n*-Bu_3SnH (1.5 equiv), AIBN (0.1 equiv) in toluene (c = 0.025 M). [d] Yield based on 1.0 mmol scale. AIBN = 2,2′-azobis(2-methylpropionitrile), BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, 2,2-DMP = 2,2-dimethoxypropane, *i*-Pr-pybox = 2,6-bis[4-isopropyl-2-oxazolin-2-yl]pyridine, PPTS = pyridinium 4-toluenesulfonate.



Scheme 1. SmI_2-Catalyzed Pinacol Coupling Reaction



[a] Me_2ZSiCl is Me_2SiCl_2 or Me_3SiCl.

entry	L	conversion/%	±/meso	byproduct/%
1	none	80	50/50	
2			15/85	
3		>99	43/57	<1
4[b]		>90	35/65	<1
5[b]		>90	47/53	15
6		>90	34/66	15
7		>90	38/62	15
8[b]		>99	28/72	<1
9		>99	35/65	<1

Org. Lett., **2005**, *7*, 1919.