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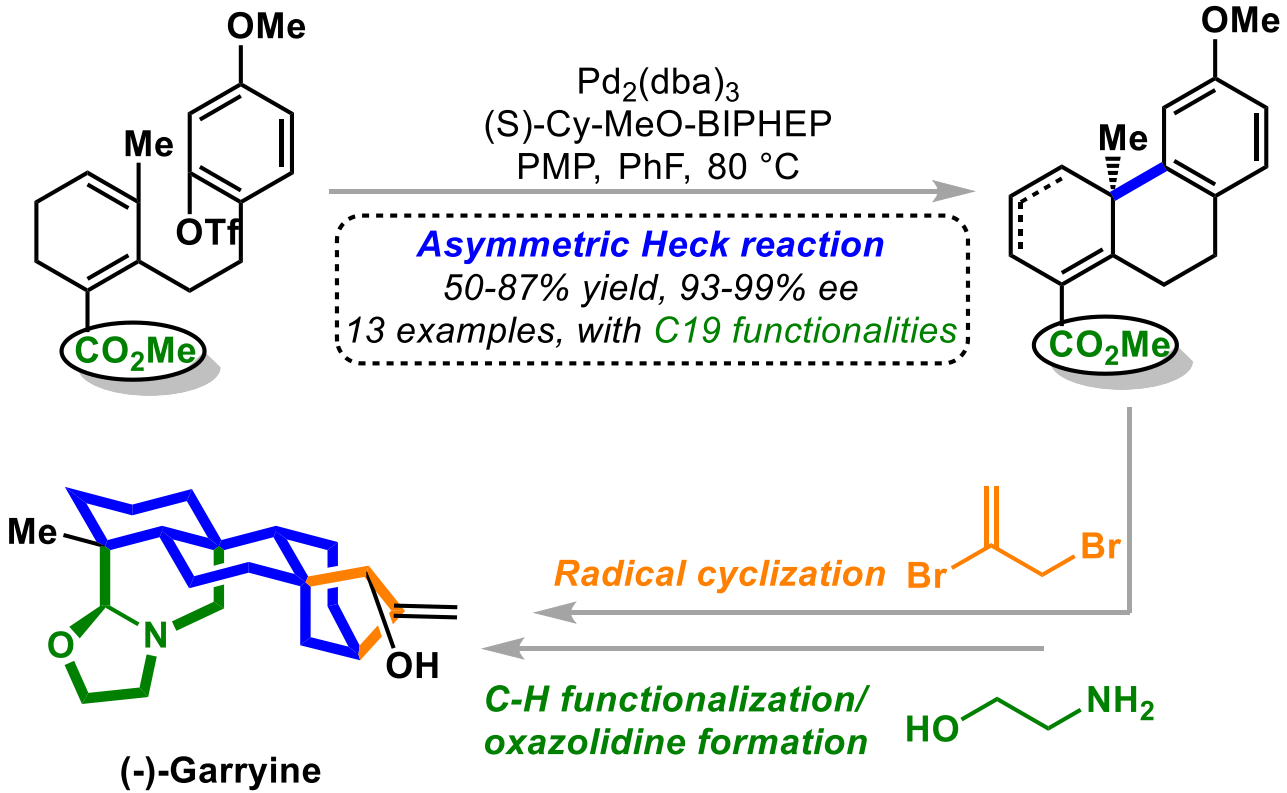
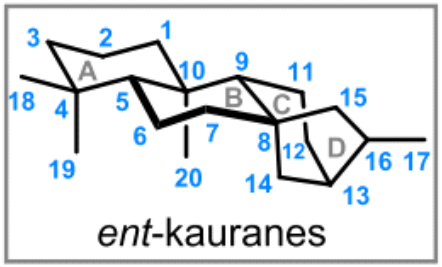
Article

Catalytic Asymmetric Total Synthesis of (−) Garryine via an Enantioselective Heck Reaction

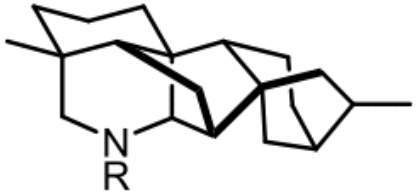


J. Am. Chem. Soc., **2024**, *146*, 1081.

A) Skeletons of *ent*-kaurane diterpenoids and related alkaloids



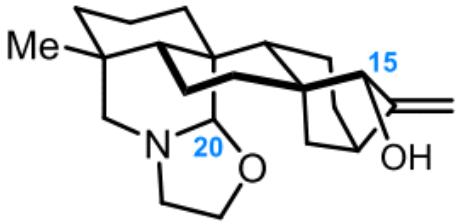
ent-kauranes



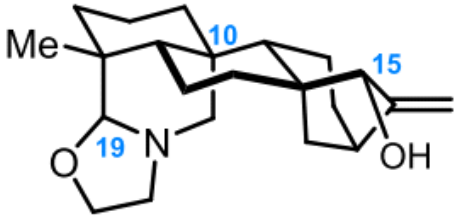
napelline-type alkaloids

veatchine-type alkaloids

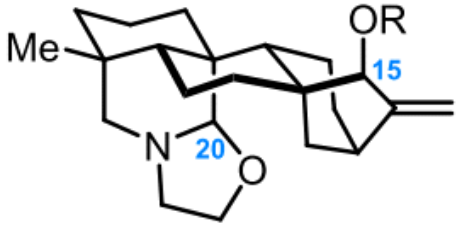
B) Representative members of the veatchine-type alkaloids



veatchine (**1**)



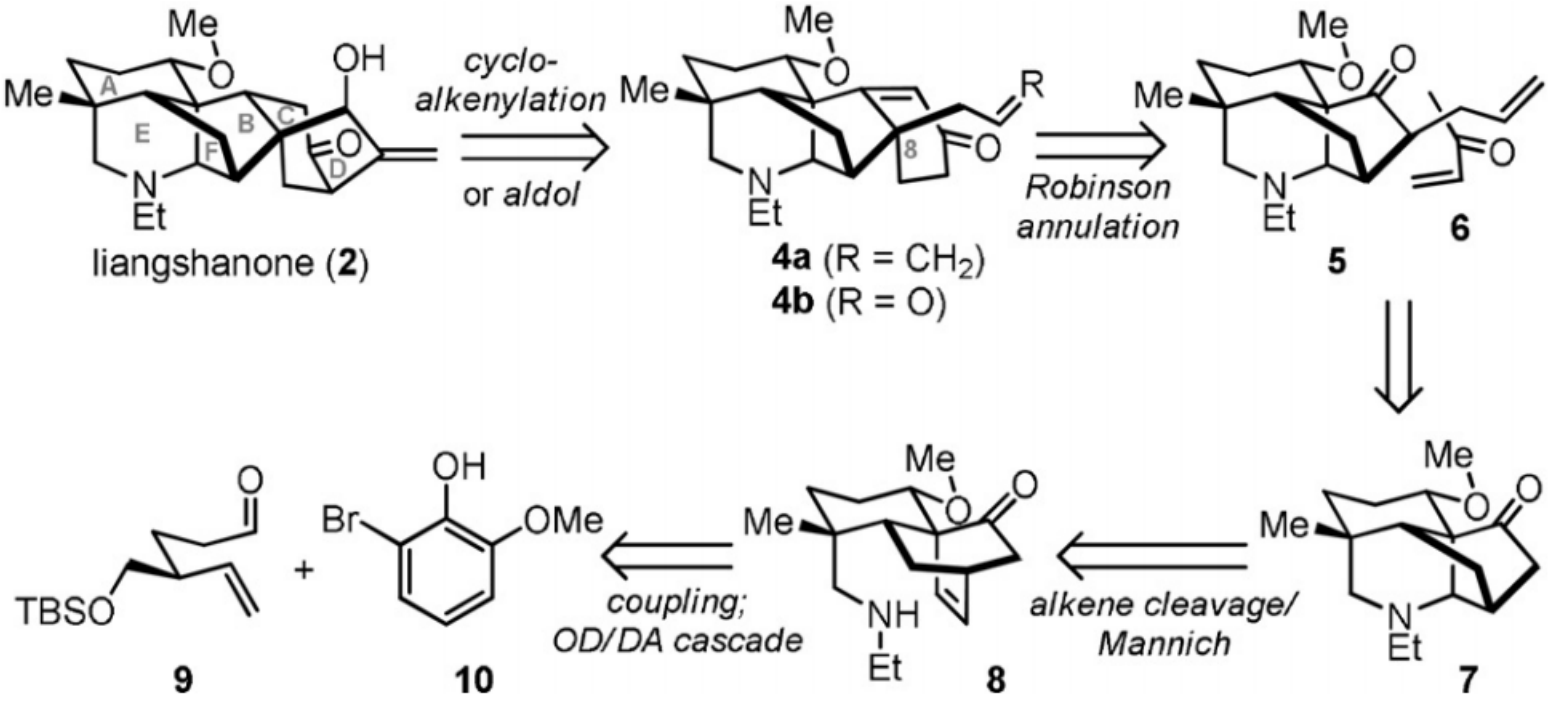
garryine (**2**)



ovatine (**3**, R = Ac)
garryfoline (**4**, R = H)

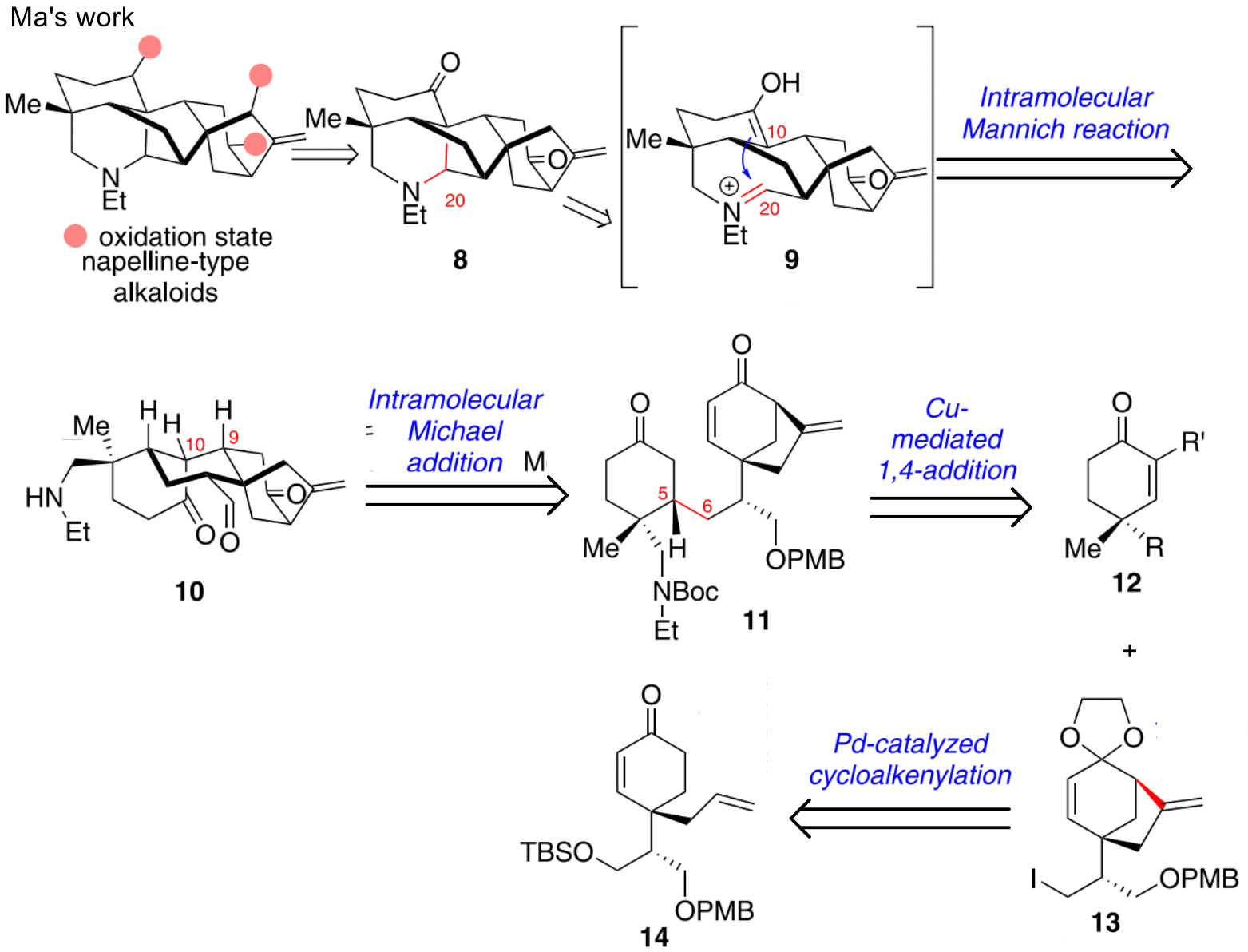
Retrosynthetic analysis of liangshanone (**2**).

Qin's work



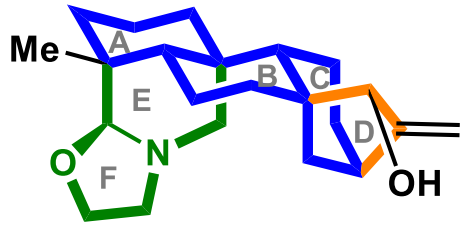
Angew. Chem. Int. Ed., **2020**, *59*, 23609.

Retrosynthetic Analysis of the Napelline-Type Alkaloid



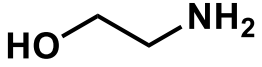
J. Am. Chem. Soc., **2022**, *144*, 15355.

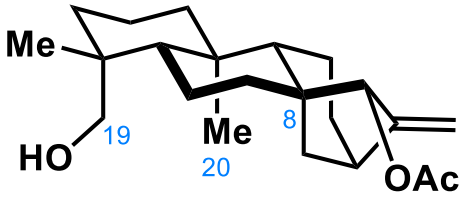
Retrosynthetic Analysis of Garryine (**2**)



garryine (**2**)

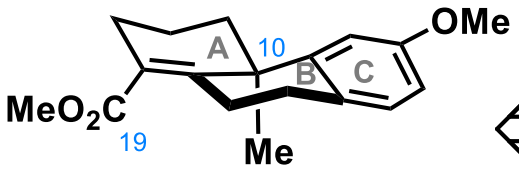
C-H functionalization/ oxazolidine formation





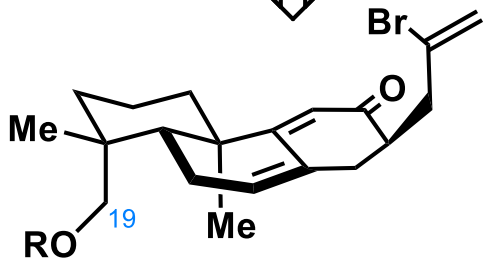
5

Radical cyclization



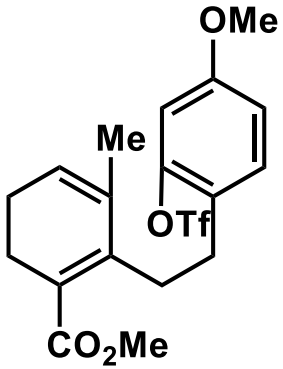
7

FG manipulations



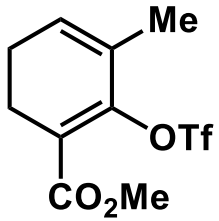
6

Asymmetric Heck reaction



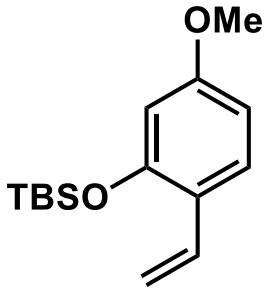
8

Fragment coupling



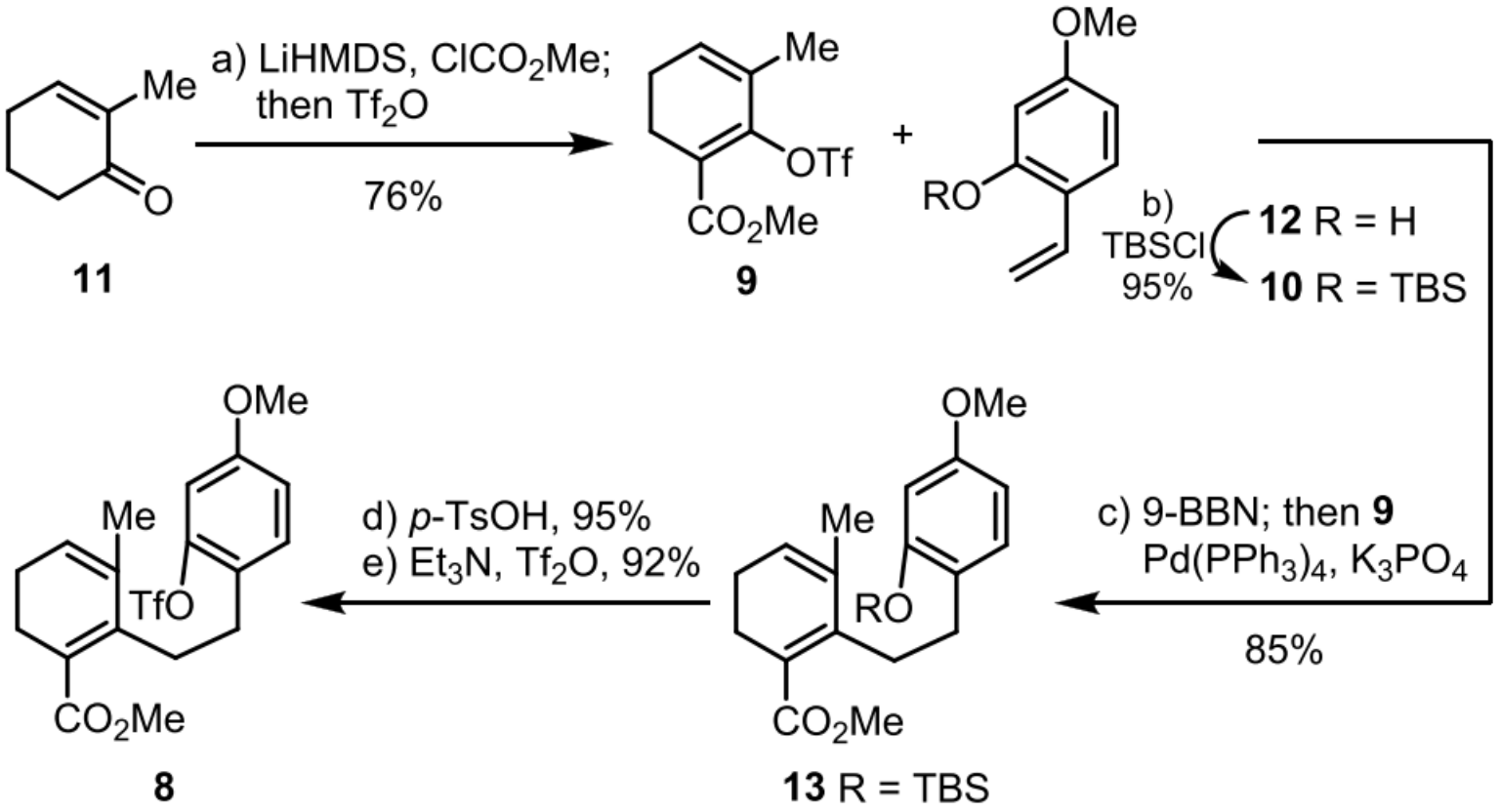
9

+

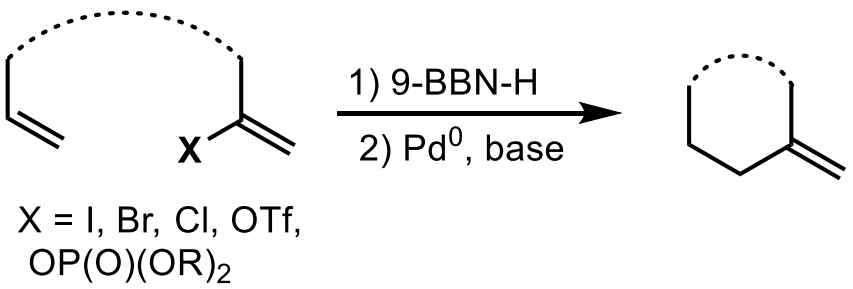


10

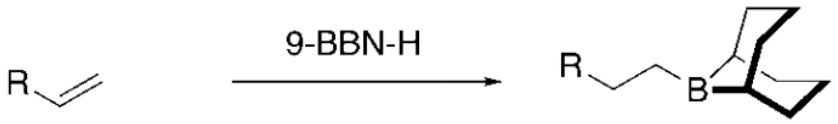
Preparation of Triflate **8**

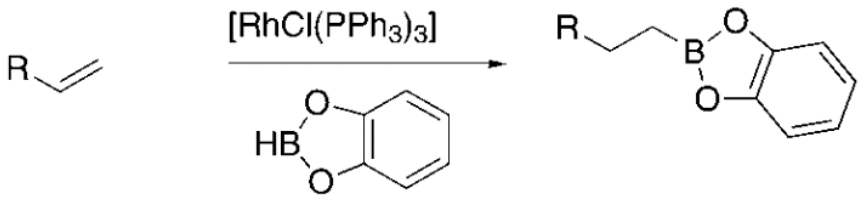


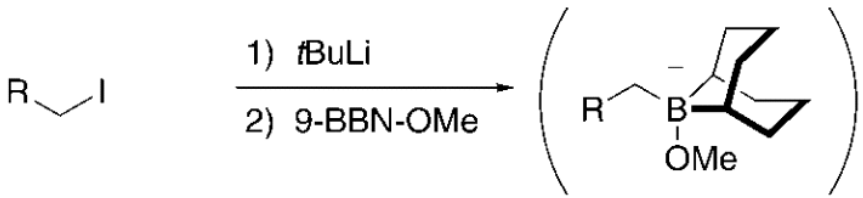
B-alkyl Suzuki–Miyaura coupling



X = I, Br, Cl, OTf, $OP(O)(OR)_2$



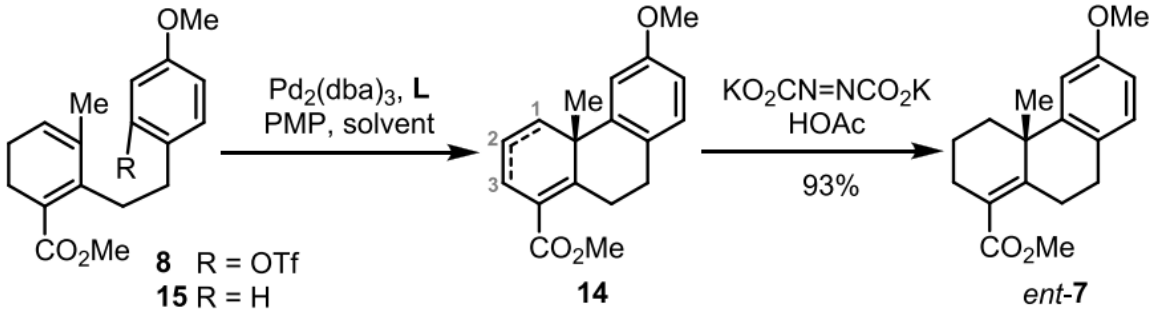




M = MgBr, Li

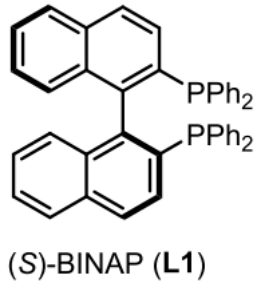
Angew. Chem. Int. Ed., **2001**, *40*, 4544.

Enantioselective Heck Reaction of **8**[a]

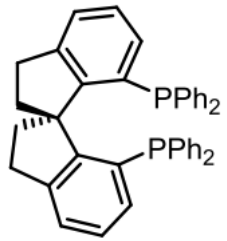


entry	L	solvent	T (°C)	conv. (%)[b]	yield (%)[b]	**14**/**15**[c]	ee (%)[d]
1	**L1**	PhMe	110	100	75	4:1	5
2	**L2**	PhMe	110	23	9	1:2.5	−10
3	**L3**	PhMe	110	20	5	1:3.2	16
4	**L4**	PhMe	110	0			
5	**L5**	PhMe	110	75	58	3:1	71
6	**L6**	PhMe	110	77	60	1.3:1	95
7[e]	**L6**	PhF	80	85	75	10:1	99
8[e,f]	**L6**	PhF	80	97	93	10:1	99

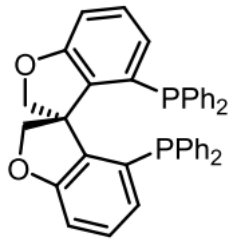
[a]Reactions were conducted using **8** (0.07 mmol), $Pd_2(dba)_3$ (5 mol%), L (20 mol %), PMP (5 equiv), and solvent (1.5 mL) at indicated temperature for 24 h.
[e]The reaction time was 60 h.
[f]Performed with 8 mol % $Pd_2(dba)_3$.



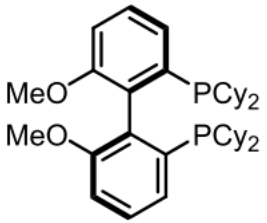
(*S*)-BINAP (**L1**)



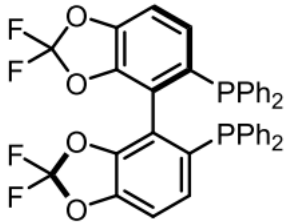
(*R*)-SDP (**L2**)



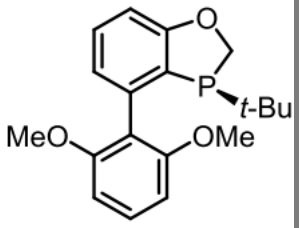
(*S*)-*O*-SDP (**L3**)



(*R*)-Cy-MeO-BIPHEP (**L6**)

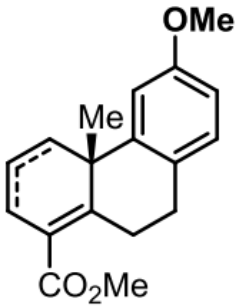


(*R*)-Difluorphos (**L5**)

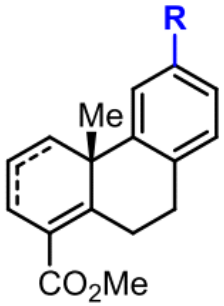


(*S*)-BI-DIME (**L4**)

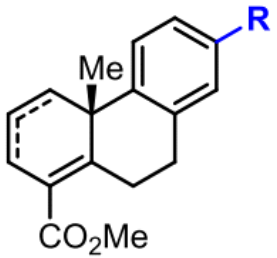
Substrate Scope of the Enantioselective Heck Reaction



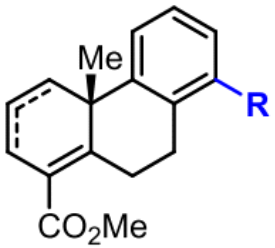
14, 85%, 99% ee



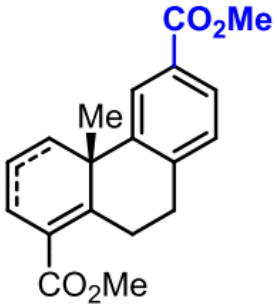
14a (R = H), 65%, 98% ee
14b (R = Me), 63%, 98% ee



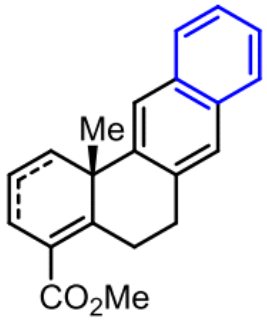
14c (R = OMe), 81%, 98% ee
14d (R = F), 67%, 99% ee



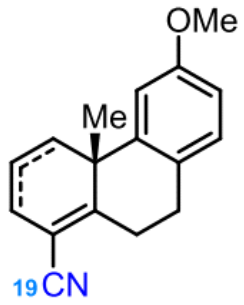
14e (R = OMe), 62%, 99% ee
14f (R = F), 87%, 99% ee



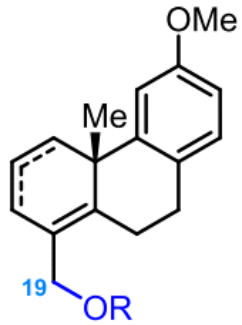
14g, 68%, 99% ee



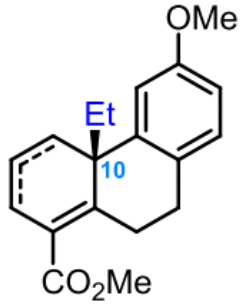
14h, 84%, 99% ee



14i[b], 50%, 99% ee

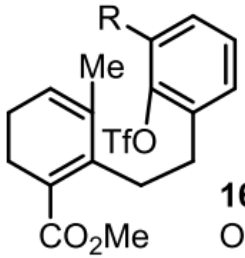


14j (R = MOM), 75%, 95% ee
14k (R = TBS), 60%, 99% ee

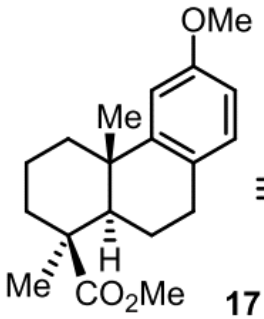


14l, 69%, 93% ee

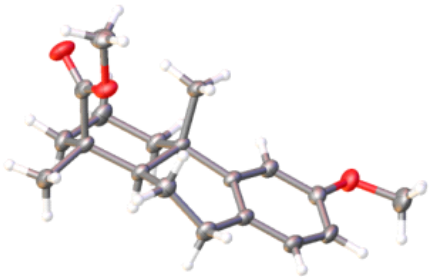
Unsuccessful substrates
(with *ortho*-substituents)



16 R = Me
OMe, or F

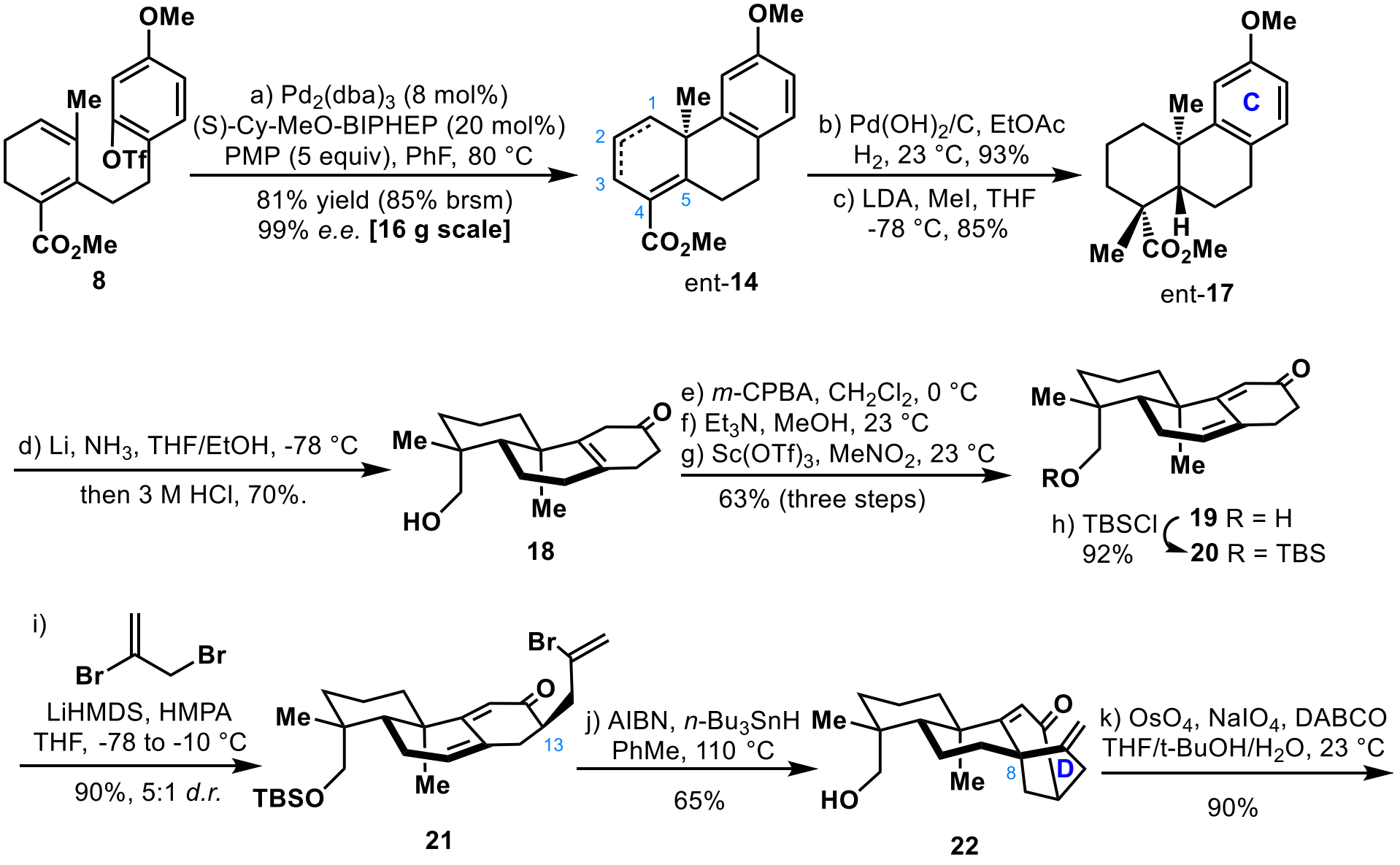


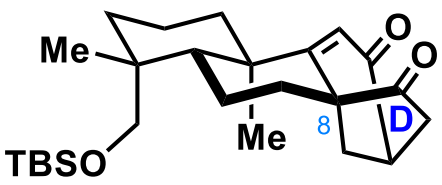
17
(2 steps from **14**)



[X-ray]

Total Synthesis of (−)-Garryine (**2**)

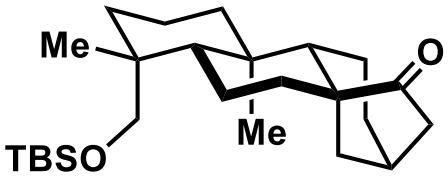




23

l) Lawesson's reagent
PhMe, 110 °C
m) Raney-Ni, EtOH, 23 °C
then Pd/C, H_2, 23 °C

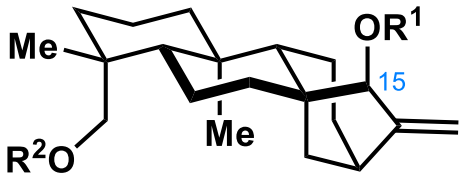
71% (two steps)



24

n) $Me_2NCH_2NMe_2$, Ac_2O
DMF, 95 °C, 80%

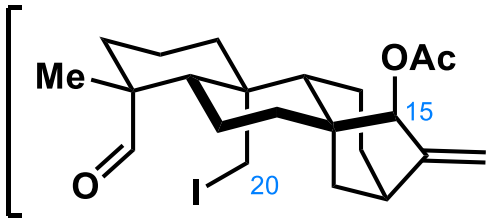
o) $NaBH(OMe)_3$
THF, - 40 °C, 87%



p) Ac_2O
q) p-TsOH
65% (2 steps)

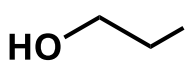
25 R^1 = H, R^2 = TBS
26 R^1 = Ac, R^2 = H

r) PIDA, I_2, *hv*
cyclohexane, 40 °C

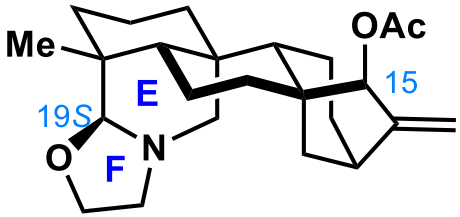


27

then



60 °C, 54%, 5:1 *d.r.*



28

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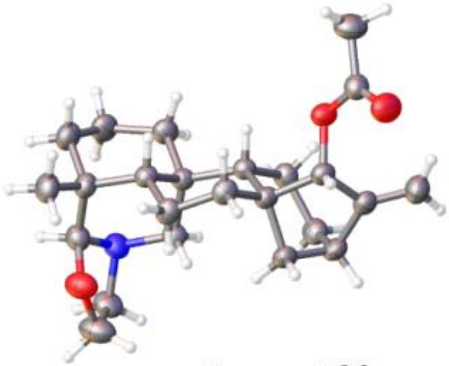
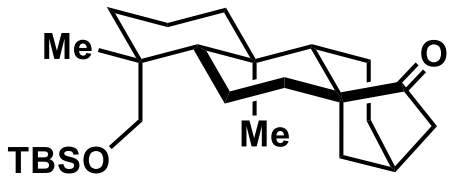


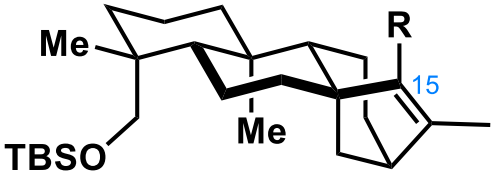
X-ray of **28**



24

s) LiHMDS, MeI
THF, -78 °C

then Comins reagent
-78 to 23 °C, 78%

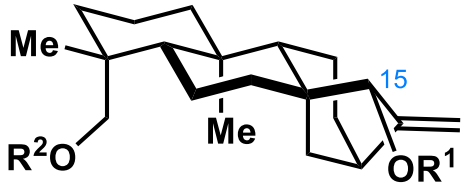


t) $Pd(OAc)_2$, Ph_3P
HCO_2H, 66%

29 R = OTf
30 R = H

u) TPP, $NaHCO_3$, O_2, *hv*
CH_3CN, 23 °C

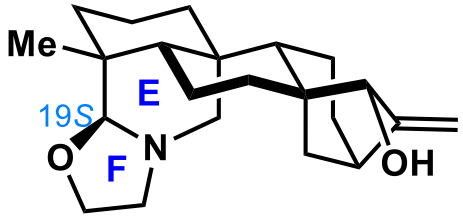
then Me_3P, 23 °C, 73%



x) PIDA, I_2, *hv*
cyclohexane, 40 °C
then ethanolamine, 60 °C

y) K_2CO_3, MeOH, 23 °C

55% (two steps)



(-)-garryine (**2**)

v) Ac_2O
w) *p*-TsOH
68% (2 steps)

31 R^1 = H, R^2 = TBS
5 R^1 = Ac, R^2 = H