

Total Synthesis of (+)-Aberrarone

Yang Wang, Yongjian Su, and Yanxing Jia*

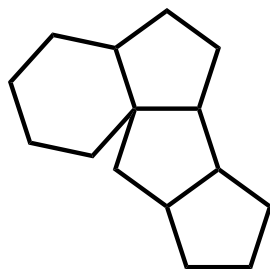


Cite This: *J. Am. Chem. Soc.* 2023, 145, 9459–9463

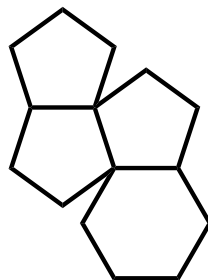


Read Online

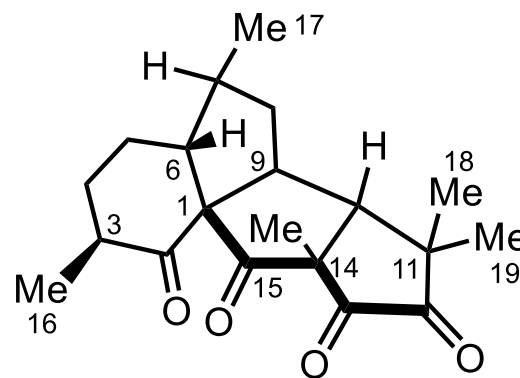
Background



A



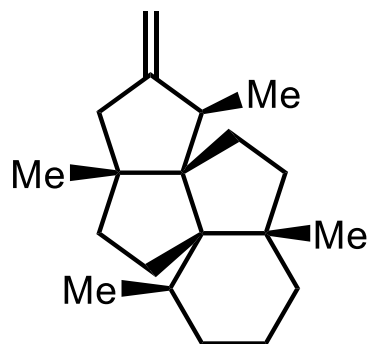
B



(+)-aberrarone (1)

Carreira (2022)
15 steps

This work
12 steps
**(Protecting-
group-free)**



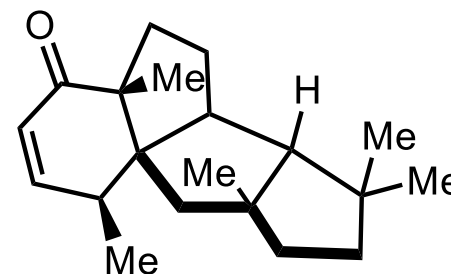
(+)-waihoensene (3)

Lee (2017)
21 steps (racemic)

Yang (2020)
15 steps

Snyder (2020)
17 steps

Gaich (2021)
19 steps



(-)-conidiogenone (2)

Tu (2016)
24 steps

Snyder (2019)
13 steps

Zhai (2020)
14 steps

Lee (2023)
17 steps

Ring Closure

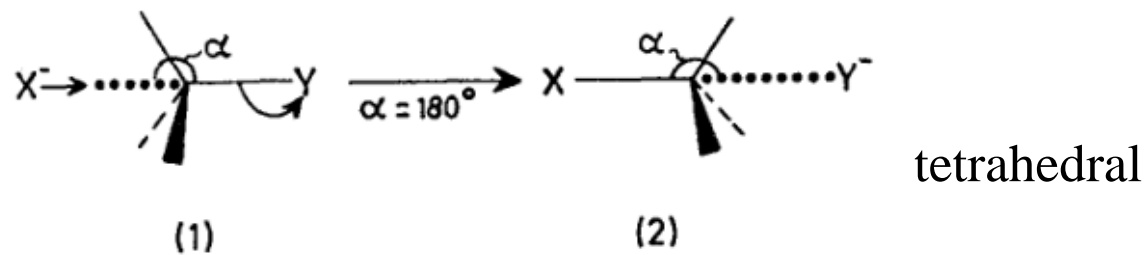


FIGURE 1: *Tet.*



SCHEME 1

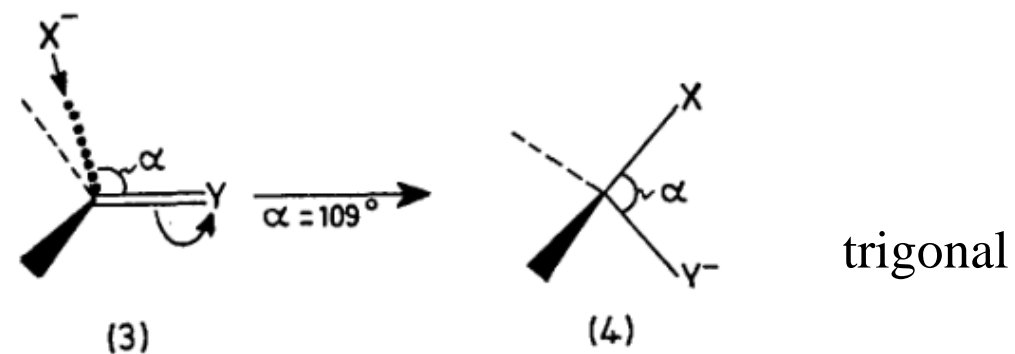


FIGURE 2: *Trig.*

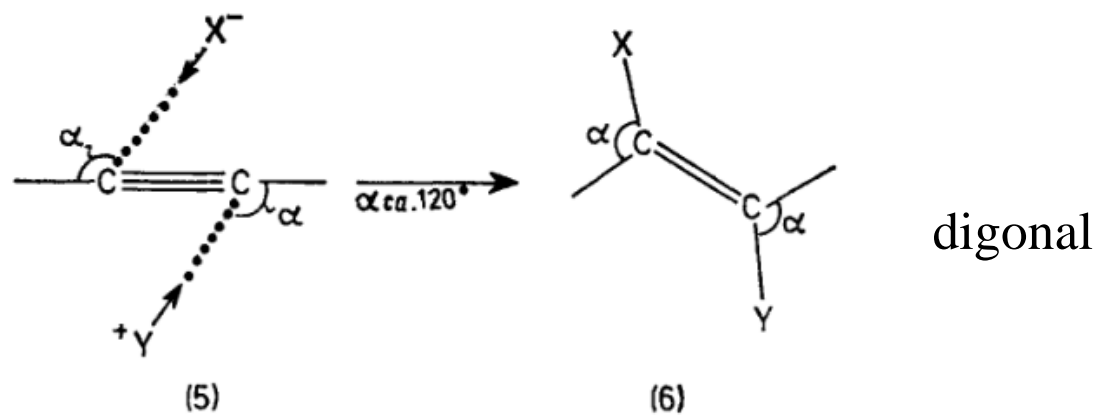


FIGURE 3: *Dig.*

Baldwin's Rules

The Rules are as follows:—

Rule 1: Tetrahedral Systems: Scheme 2.

(a) 3 to 7-*Exo-Tet* are all favoured¹ processes with many literature precedents;²

(b) 5 to 6-*Endo-Tet* are disfavoured.³

Rule 2: Trigonal Systems: Scheme 3.

(a) 3 to 7-*Exo-Trig* are all favoured processes with many literature precedents;⁴

(b) 3 to 5-*Endo-Trig* are disfavoured;⁵ 6 to 7-*Endo-Trig* are favoured.

Rule 3: Digonal Systems: Scheme 4.

(a) 3 to 4-*Exo-Dig* are disfavoured processes; 5 to 7-*Exo-Dig* are favoured;⁶

(b) 3 to 7-*Endo-Dig* are favoured.⁷

favoured:

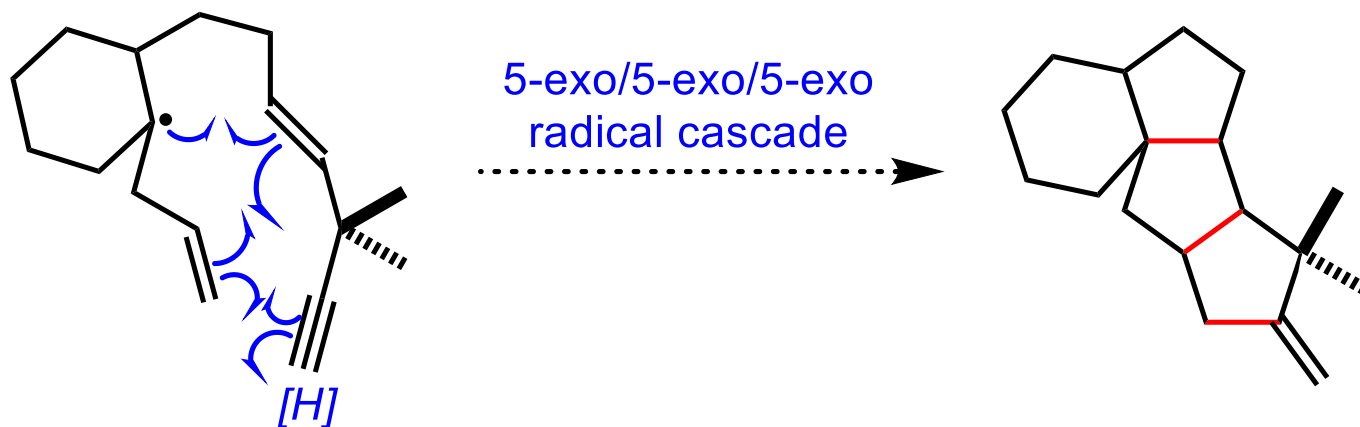
5-exo-tet

5-exo-trig

5-exo-dig

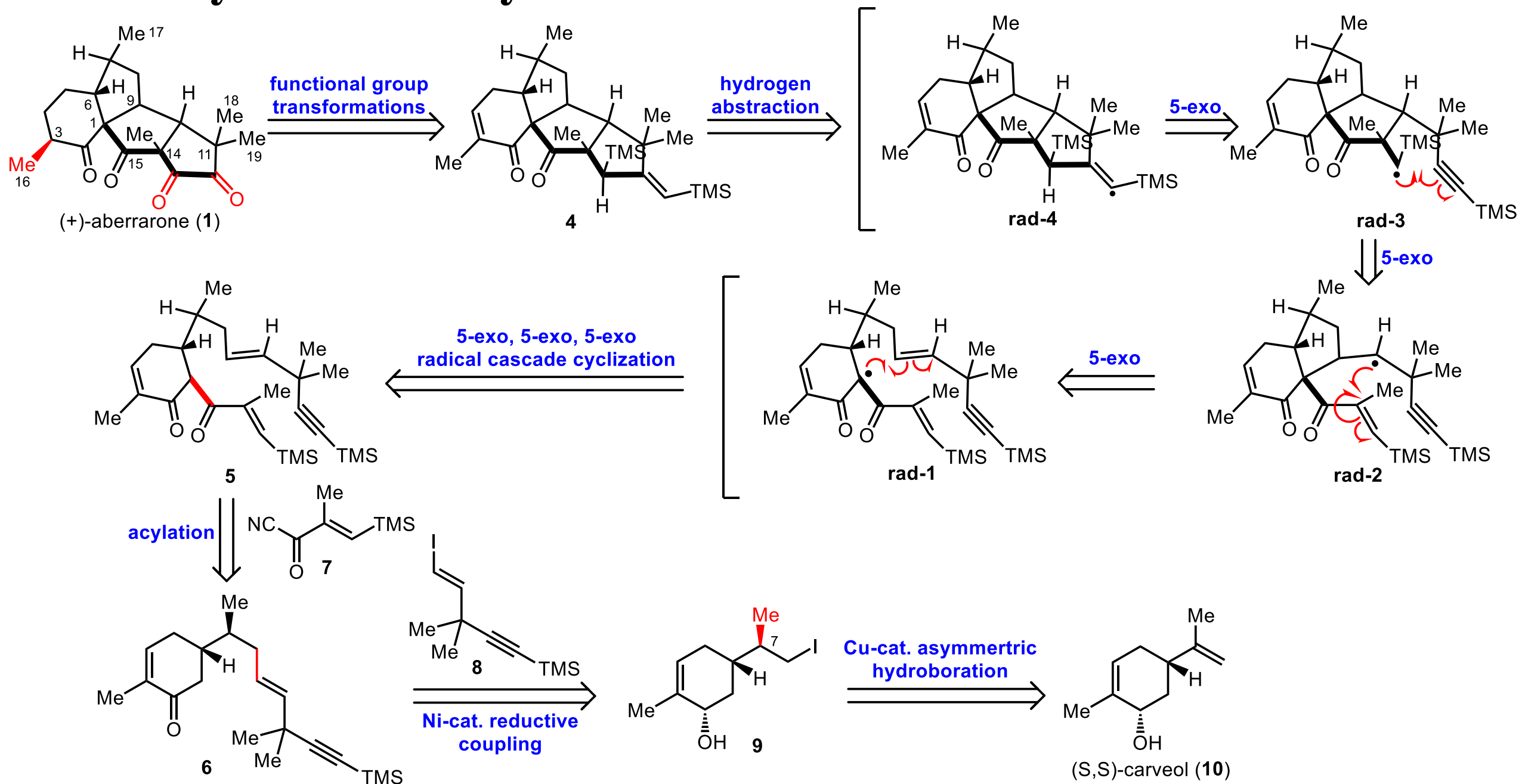
5-endo-dig

Radical Cascade Cyclization Strategy:



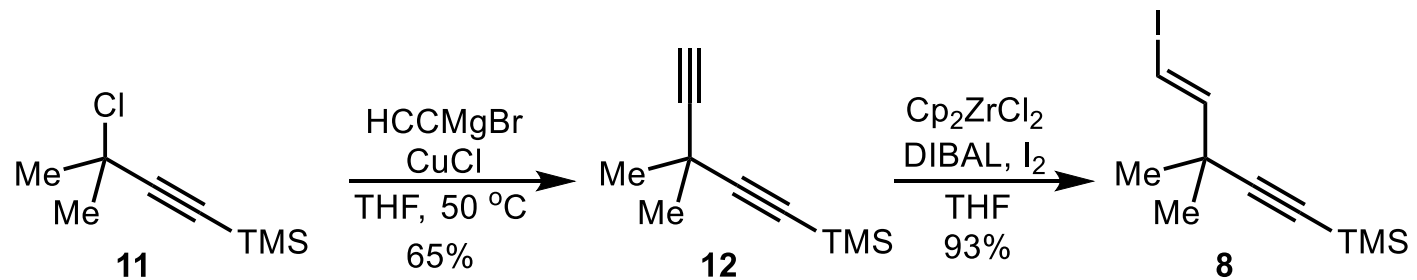
- * **one** step
- * **three** C-C bonds
- * **three** rings
- * **four** stereocenters

Retrosynthetic Analysis

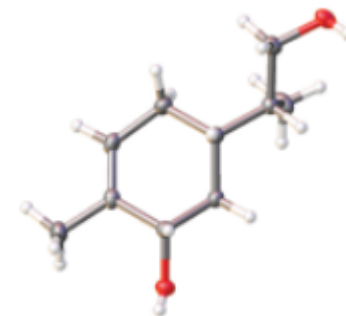
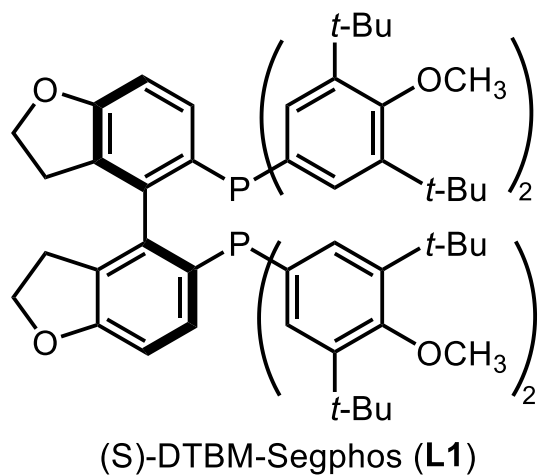
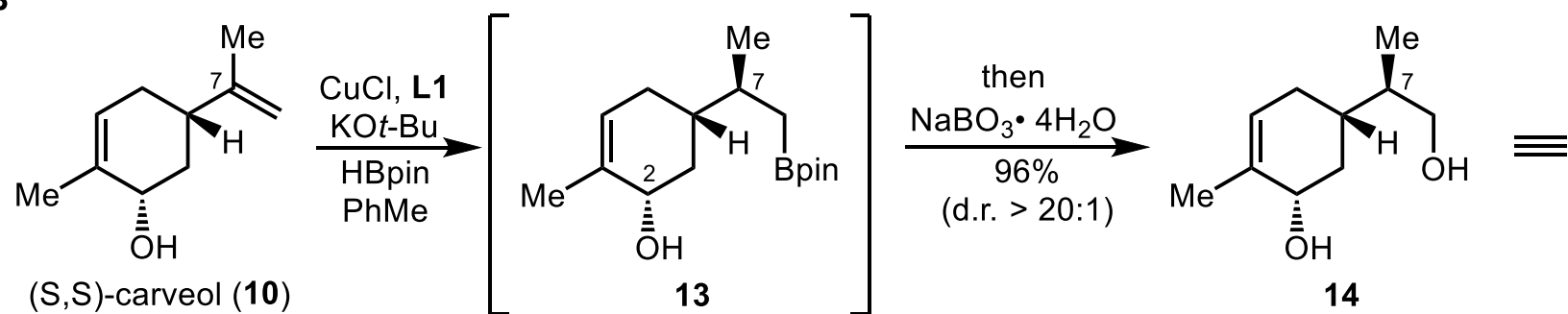


Preparation of Alkenyl Iodide 8 and Alkyl Iodide 9

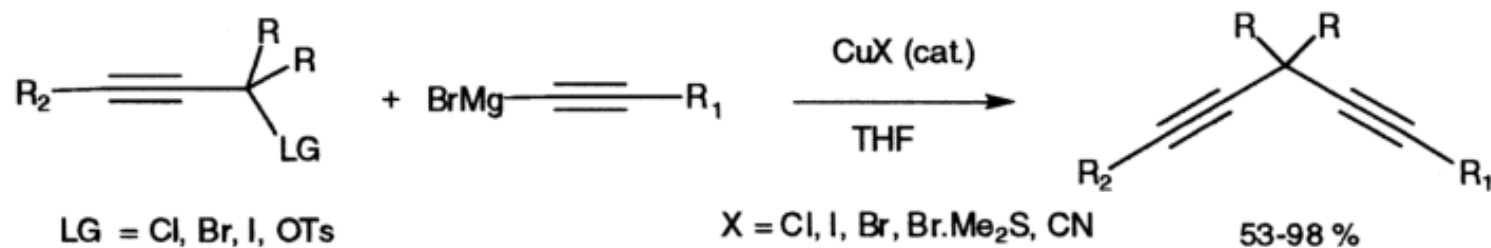
A



B

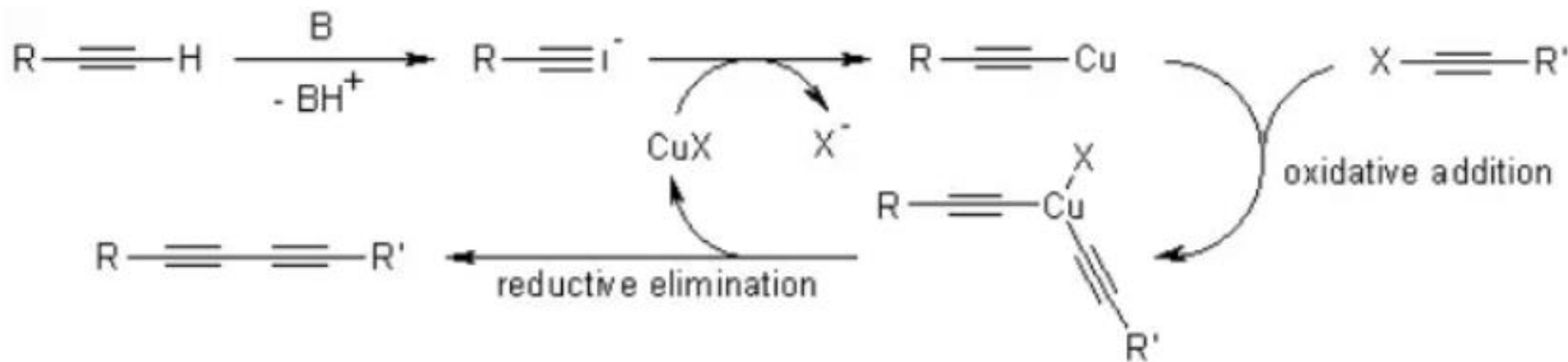


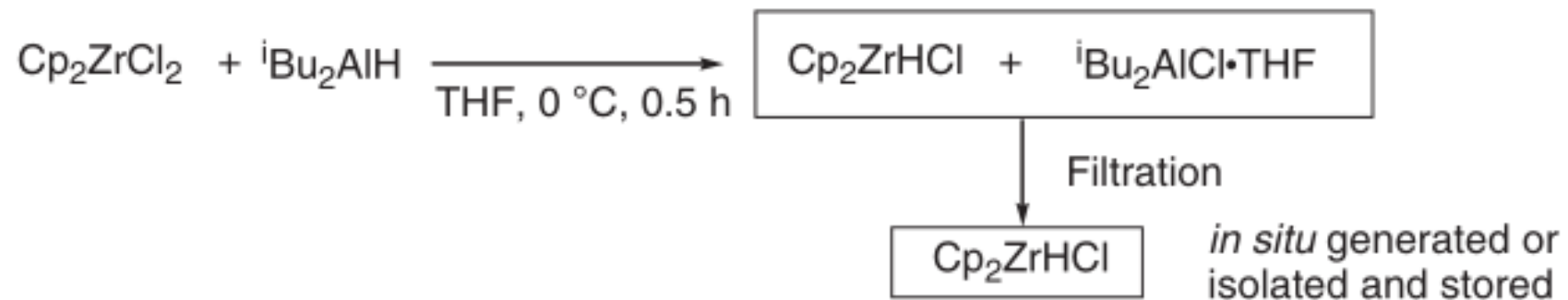
1,4-Diynes from alkynyl/propargyl coupling reactions :



J. Org. Chem., 2003, 670, 151.

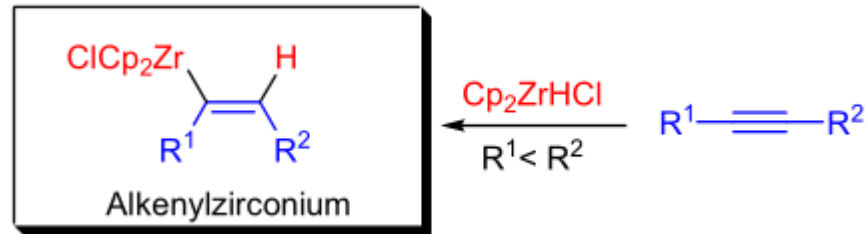
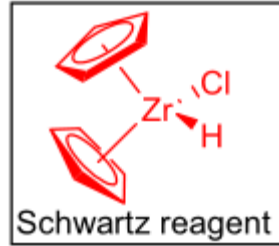
Cadiot-Chodkiewicz Coupling Reaction



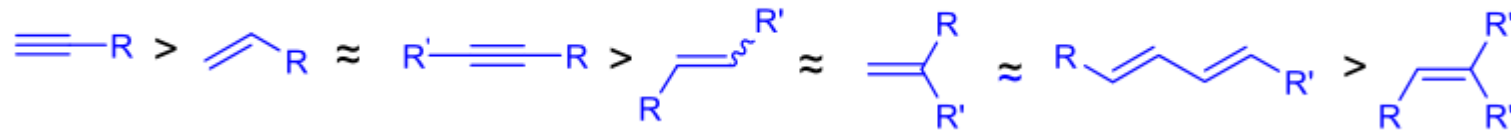


Org. Lett., **2006**, *8*, 3675.

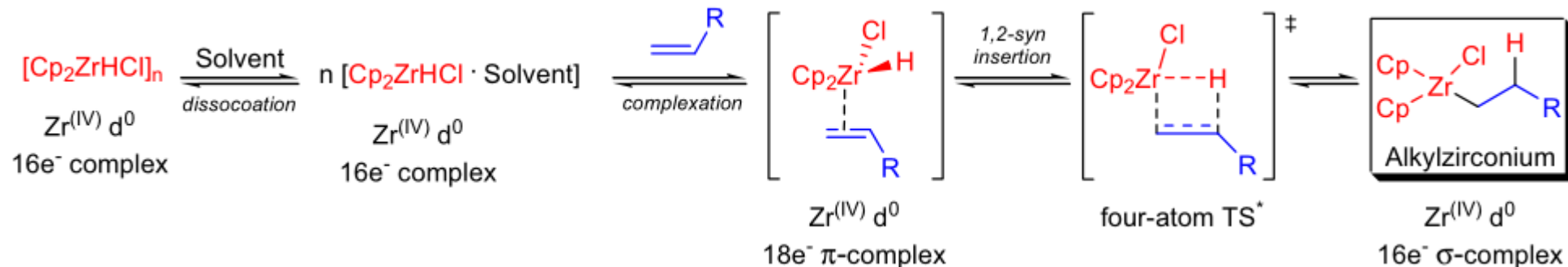
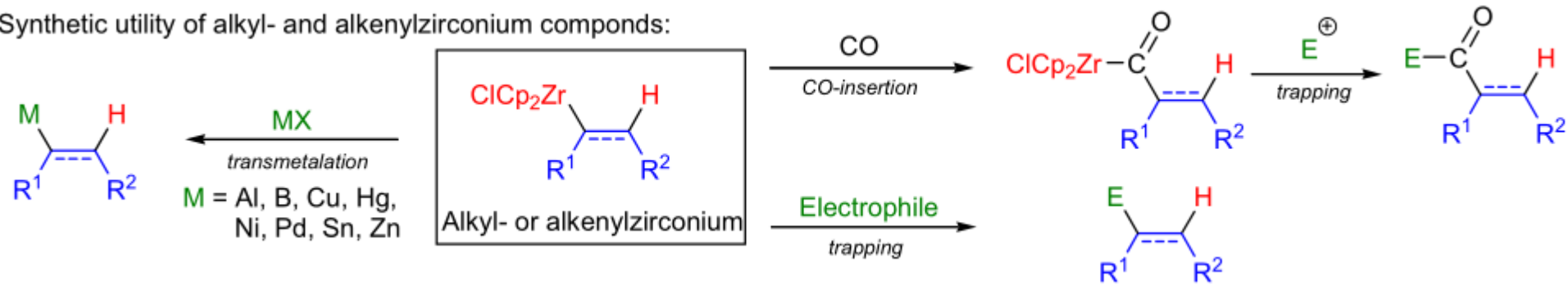
Schwartz Hydrozirconation



Order of reactivity in hydrozirconation reactions:



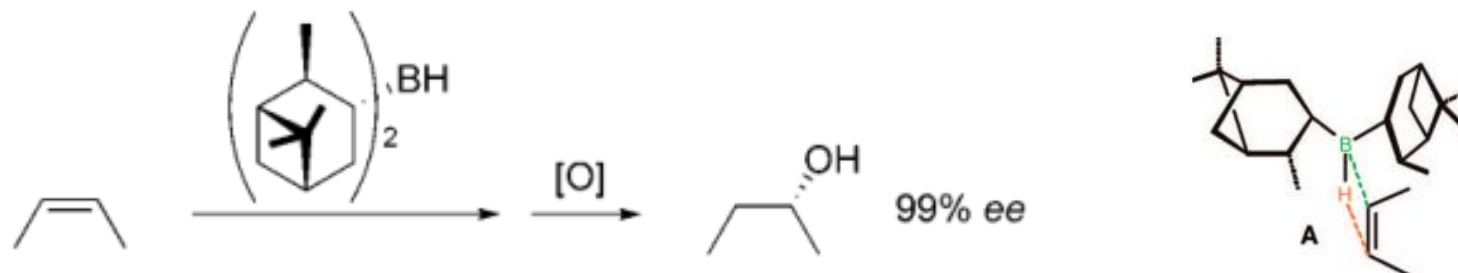
Synthetic utility of alkyl- and alkenylzirconium compounds:



Enantioselective Hydroboration Reaction

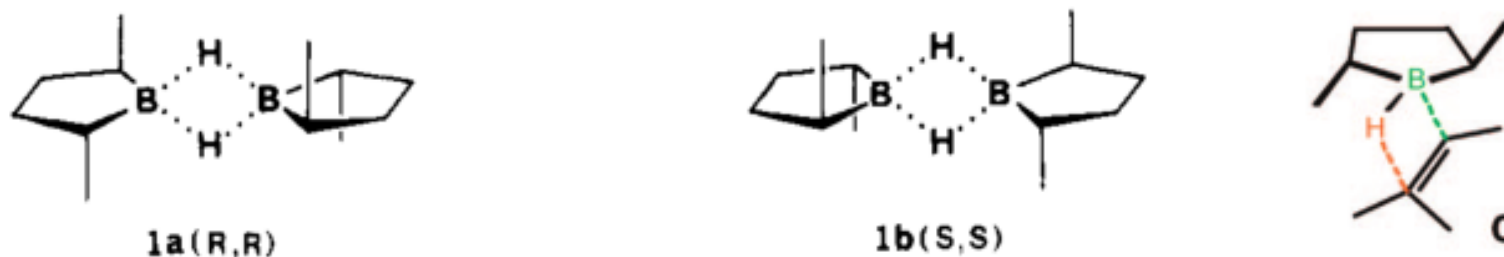
I. chiral organoborane reagents

Brown



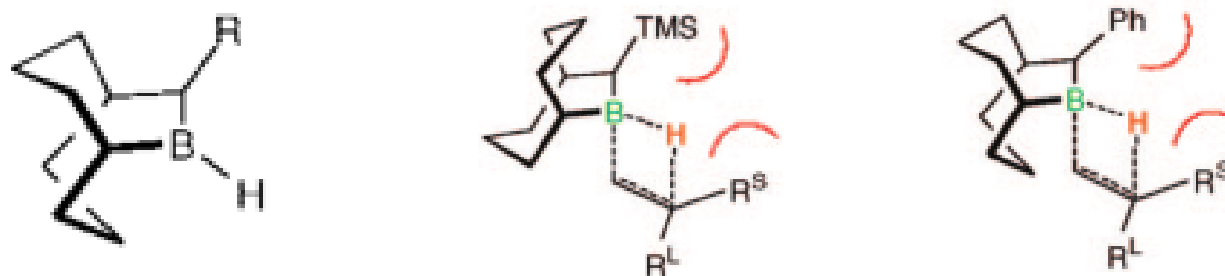
J. Am. Chem. Soc., **1961**, 83, 486.

Masamune



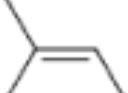
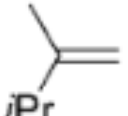
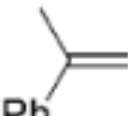


J. Am. Chem. Soc., **1985**, 107, 4549.

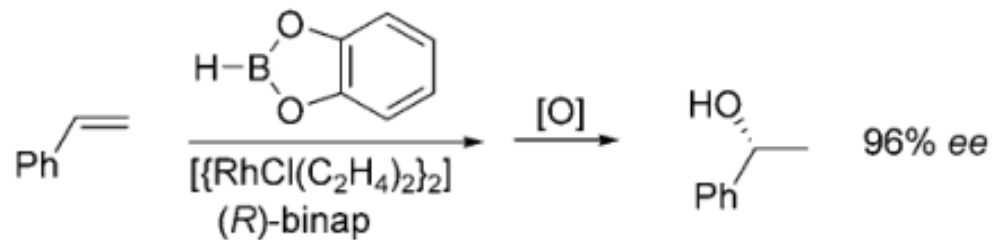
Soderquist



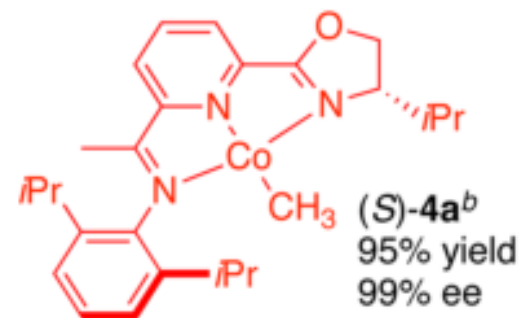
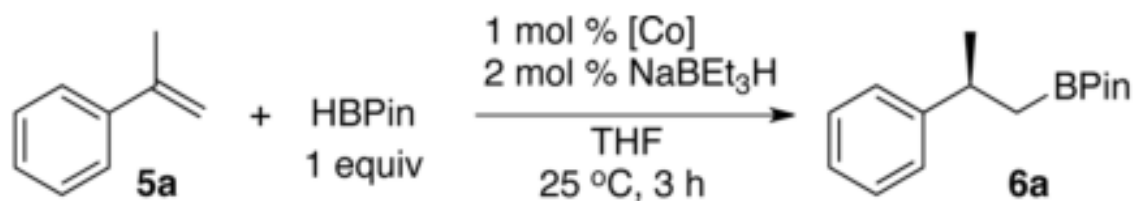
J. Am. Chem. Soc., **2008**, 130, 9218.

Alkene class	(<i>lpc</i>) ₂ BH	(<i>lpc</i>)BH ₂	DMB	5 a	5 b
	14	73	99.5	96	95
	99.1	24	97.6	32	84
	15	53	97.6	74	—
 <i>iPr</i>	32	—	1.5	38	52
 Ph	—	5	—	78	66

II. transition-metal-catalyzed systems

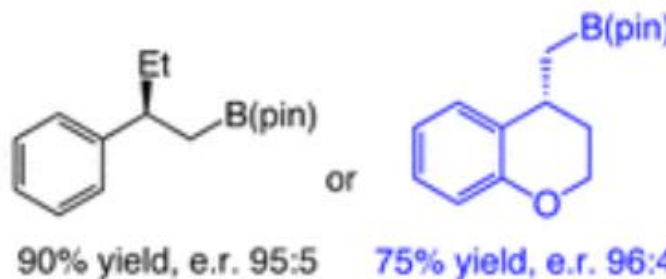
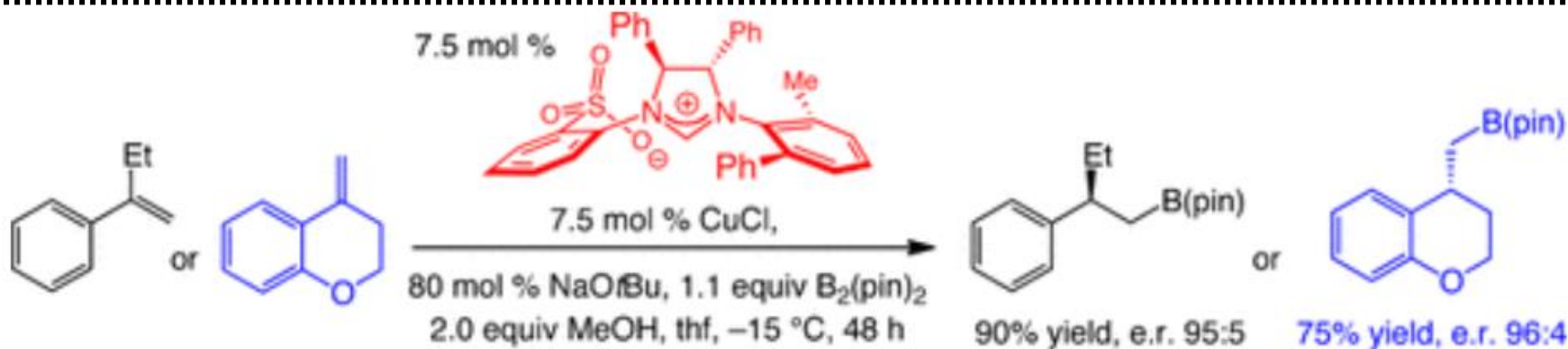


Angew. Chem. Int. Ed., **2009**, 48, 1896.



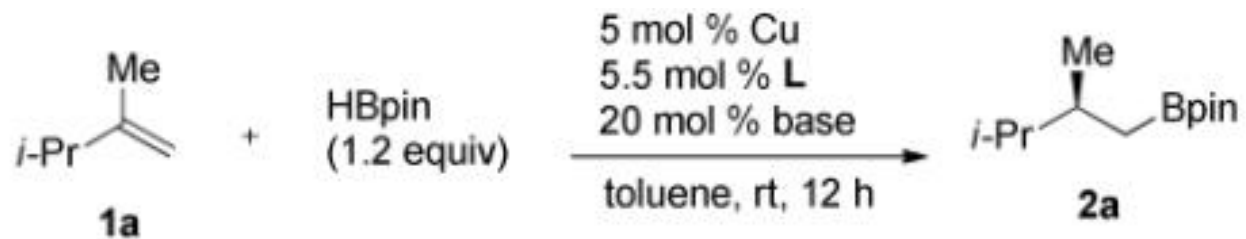
(S)-4a^b
95% yield
99% ee

J. Am. Chem. Soc., **2014**, 136, 15501.



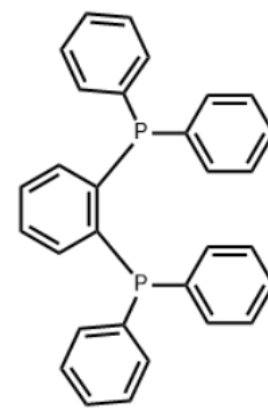
90% yield, e.r. 95:5 75% yield, e.r. 96:4

Angew. Chem. Int. Ed., **2011**, 50, 7079.

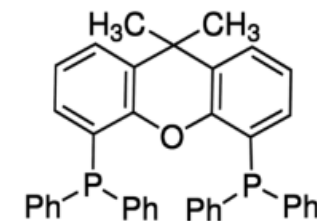


entry	[Cu]/ligand	base	yield (%) ^a	ee (%) ^b
1	CuCl/dppbz	NaO <i>t</i> -Bu	0	—
2	CuCl/xantphos	NaO <i>t</i> -Bu	0	—
3	IMesCuCl	NaO <i>t</i> -Bu	0	—
4	CuCl/L1	NaO <i>t</i> -Bu	0	—
5	CuCl/L2	NaO <i>t</i> -Bu	0	—
6	CuCl/L3	NaO <i>t</i> -Bu	0	—
7	CuCl/L4	NaO <i>t</i> -Bu	36	86
8	CuTC ^c /L4	—	0	—
9	CuTC/L4	KO <i>t</i> -Bu	18	87
10	CuCl/L4	KO <i>t</i> -Bu	94	87

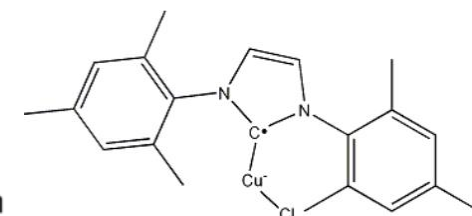
^aIsolated yield. ^bEe was determined by HPLC analysis. ^cCuTC = copper(I)-thiophene-2-carboxylate.



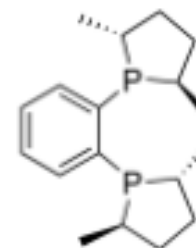
dppbz



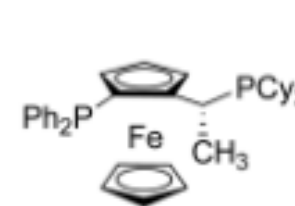
xantphos



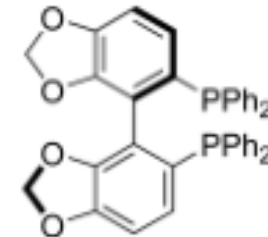
IMesCuCl



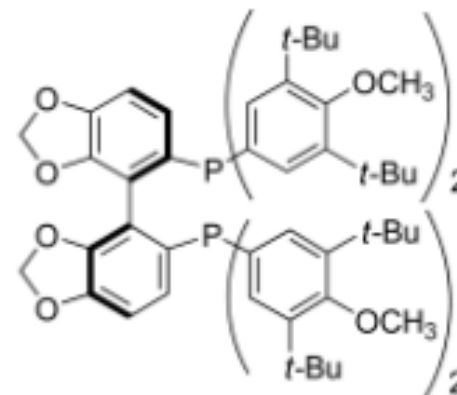
(*R,R*)-Me-Duphos (L1)



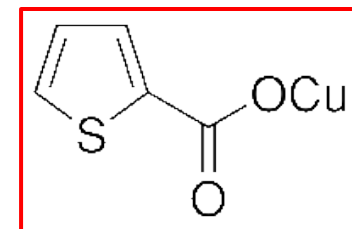
(*R,S*)-Josiphos (L2)



(*R*)-Segphos (L3)



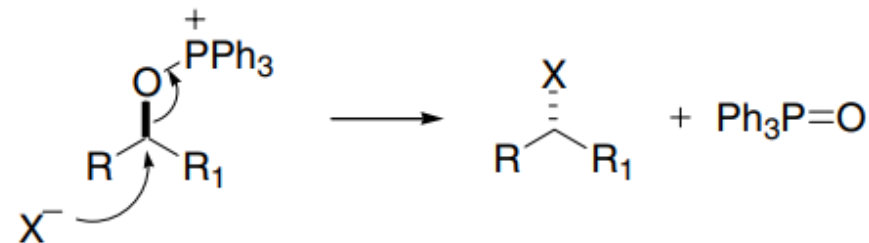
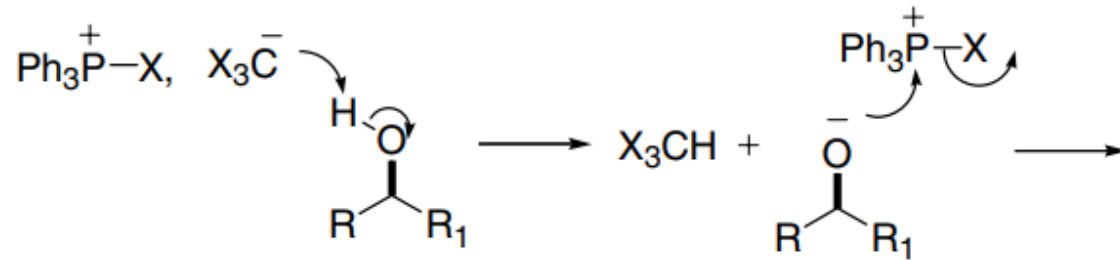
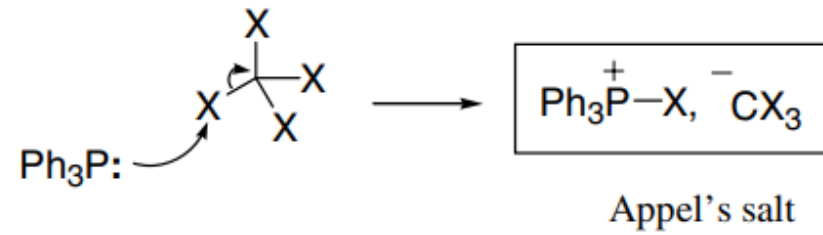
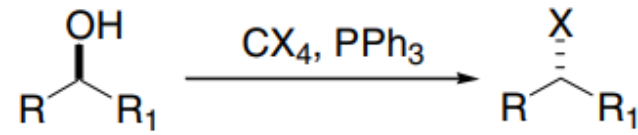
(*R*)-DTBM-Segphos (L4)



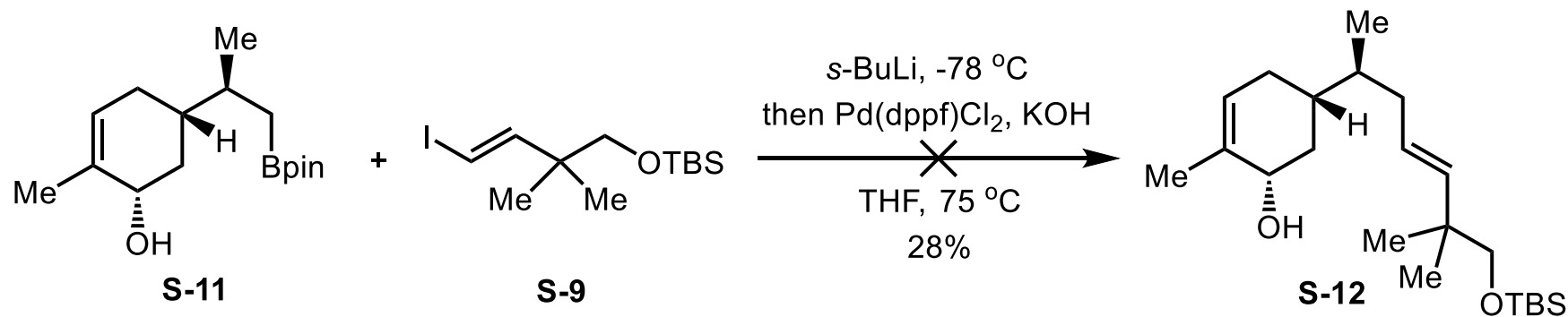
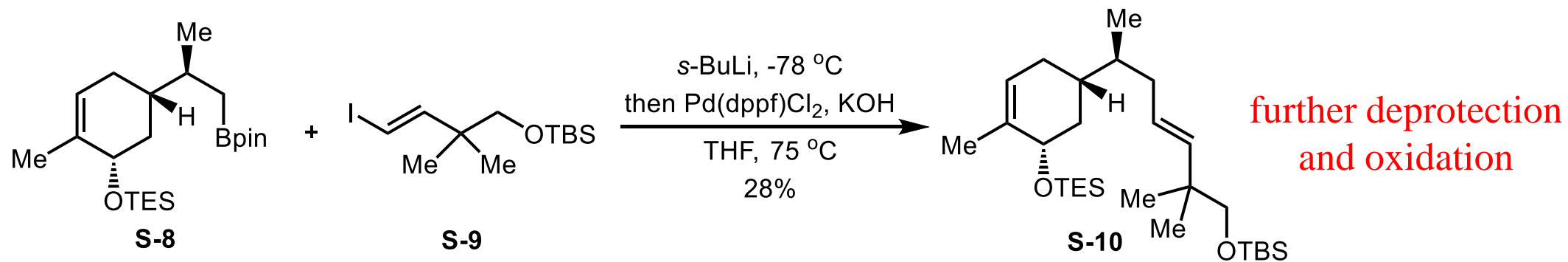
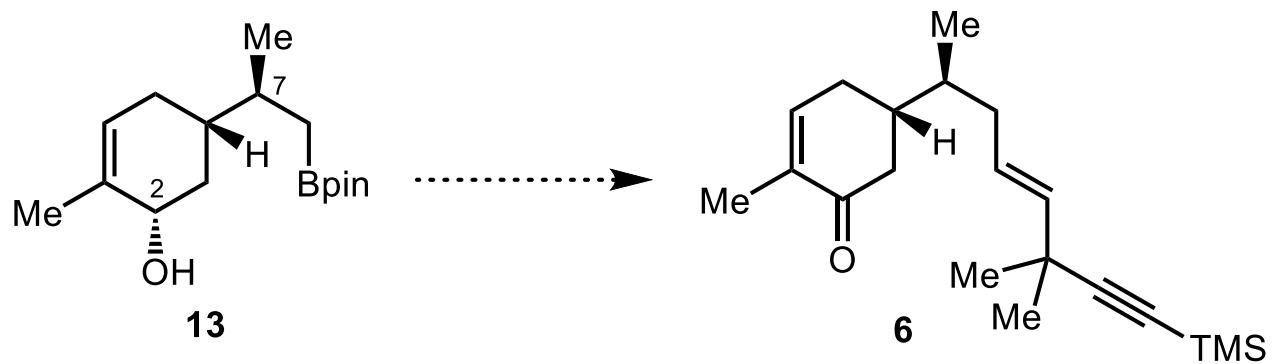
CuTC

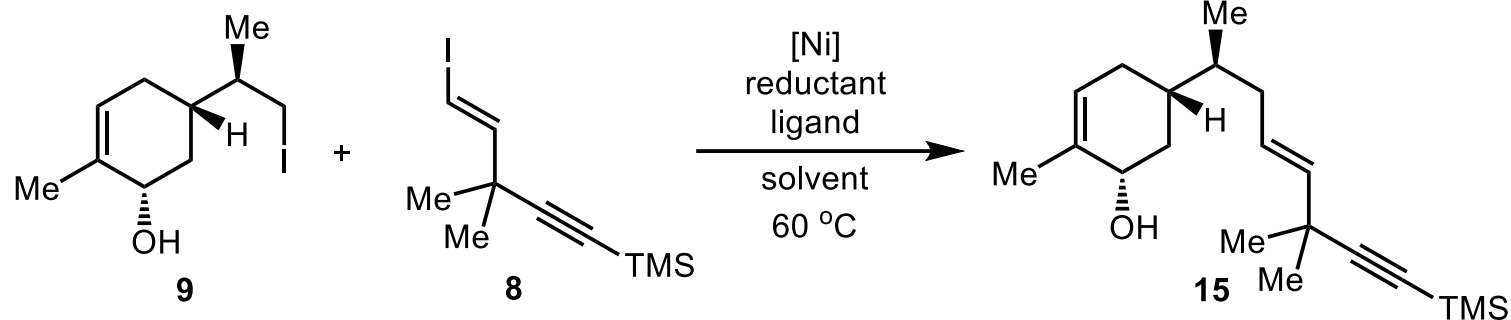
J. Am. Chem. Soc., 2017, 139, 13660.

Appel Reaction



Attempts to Suzuki reaction of 13 and C2-OH protected 13





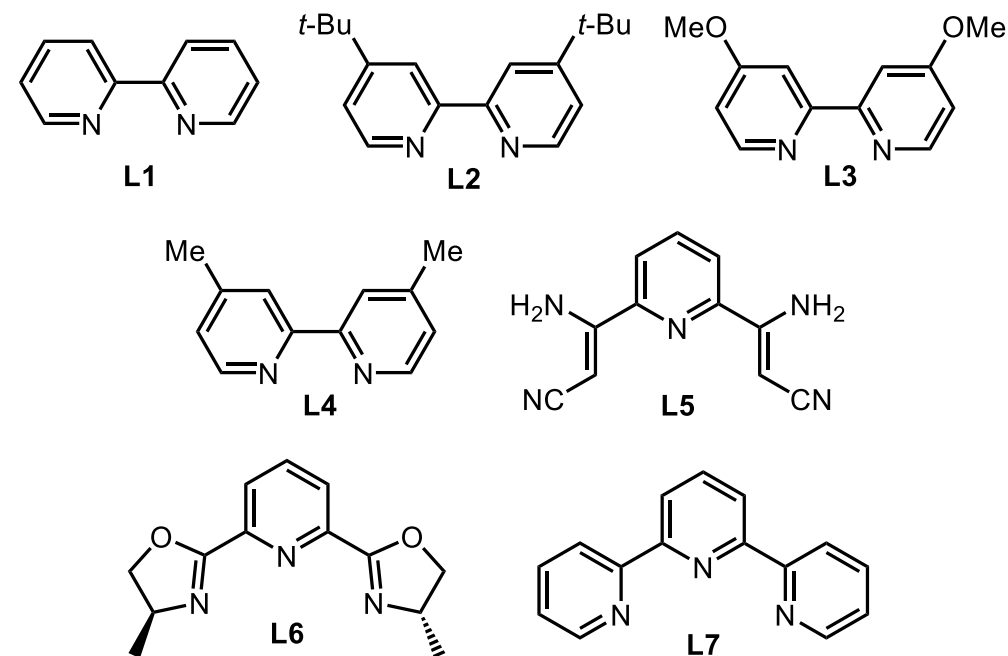
entry	[Ni]	ligand	reductant	solvent	yield ^b
1	NiI ₂	L1	Mn	DMF	40%
2	NiI ₂	L2	Mn	DMF	29%
3	NiI ₂	L3	Mn	DMF	27% ^c
4	NiI ₂	L4	Mn	DMF	33%
5	NiI ₂	L5	Mn	DMF	23%
6	NiI ₂	L6	Mn	DMF	54%
7	NiI ₂	L7	Mn	DMF	68% ^c
8	Ni(PHex ₃)Cl ₂	L7	Mn	DMF	35%
9	Ni(dppf)Cl ₂	L7	Mn	DMF	40%
10	Ni(acac) ₂	L7	Mn	DMF	44%
11	Ni(OAc) ₂	L7	Mn	DMF	38%
12	NiBr ₂	L7	Mn	DMF	38%
13	NiCl ₂	L7	Mn	DMF	36%
14	NiI ₂	L7	Zn	DMF	22%
15	NiI ₂	L7	Mn	DMA	38%
16	NiI ₂	L7	Mn	DMPU	21%
17 ^d	NiI ₂	L7	Mn	DMF	42%

^aReaction condition: 9 (2.00 equiv.), 8 (1.00 equiv.), NiX₂ (10.0 mol%), ligand (12.0 mol%), reductant (2.00 equiv.), solvent (0.100 M).

^bThe yield was determined by NMR with CH₂Br₂ as an internal standard.

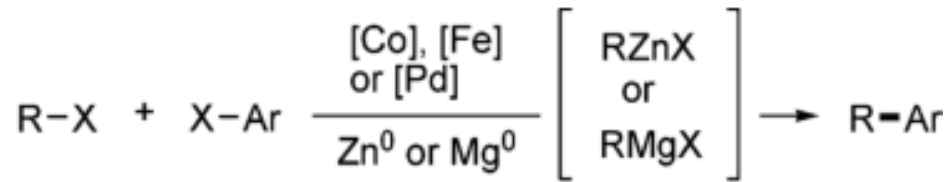
^cIsolated yield.

^d0.200 equiv. TMSCl was added

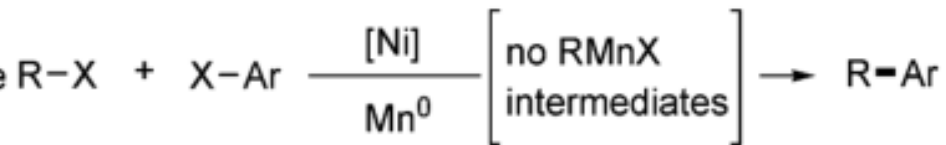


Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides

Prior Work:
in situ
Cross-Coupling

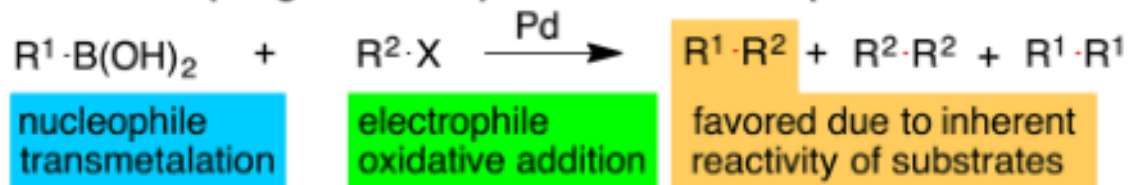


This Work:
Direct Reductive
Cross-Coupling

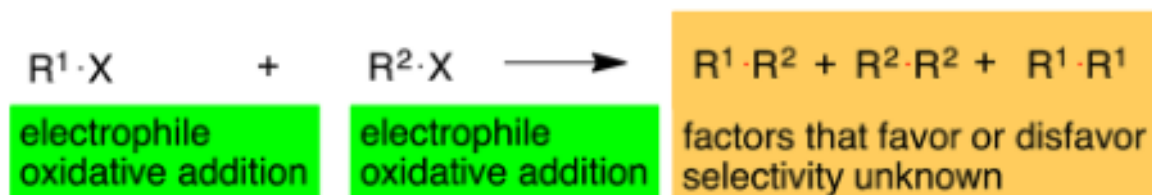


J. Am. Chem. Soc., **2010**, *132*, 920.

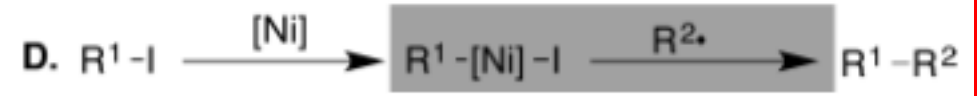
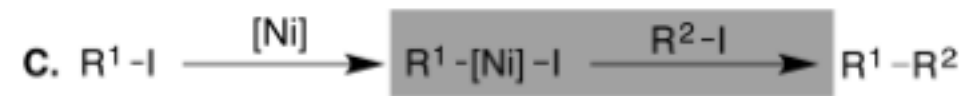
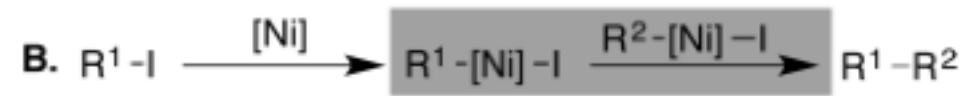
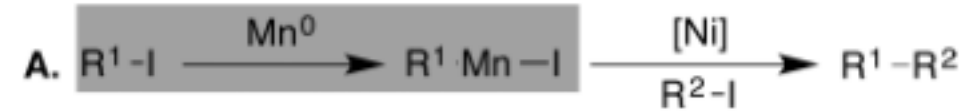
Cross-Coupling of Nucleophiles with Electrophiles



Cross-Electrophile Coupling – This Work



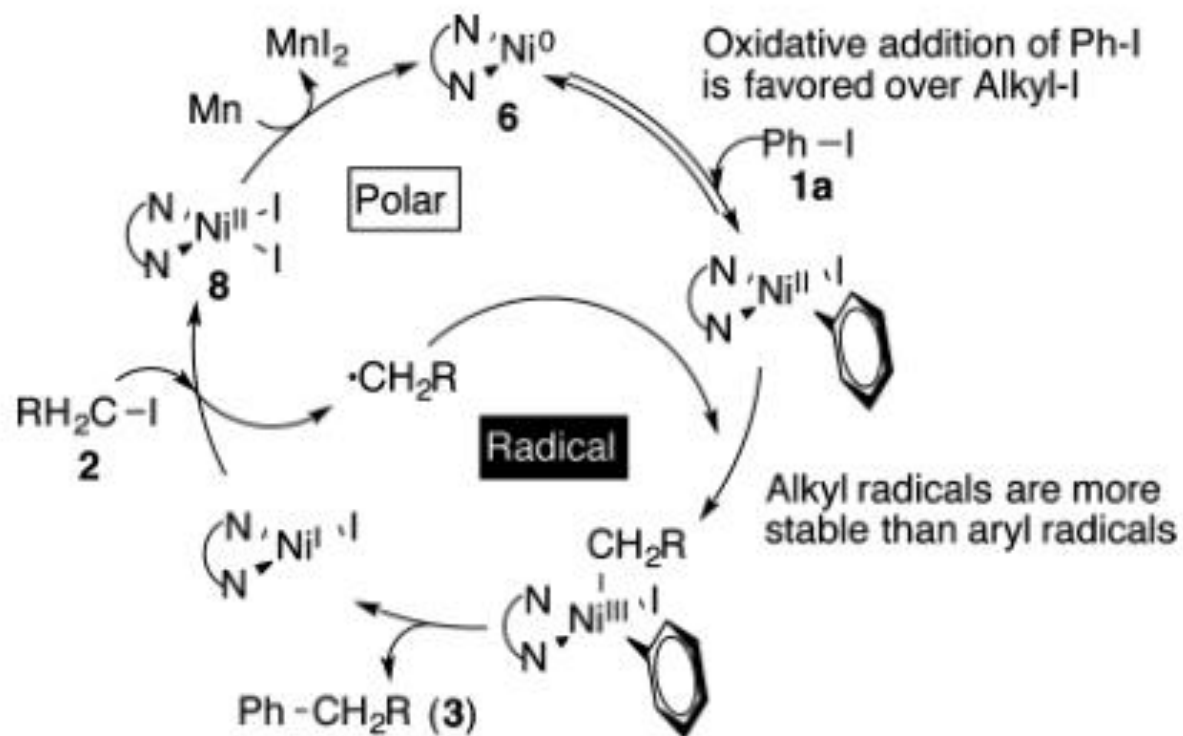
potential mechanisms for cross-electrophile coupling



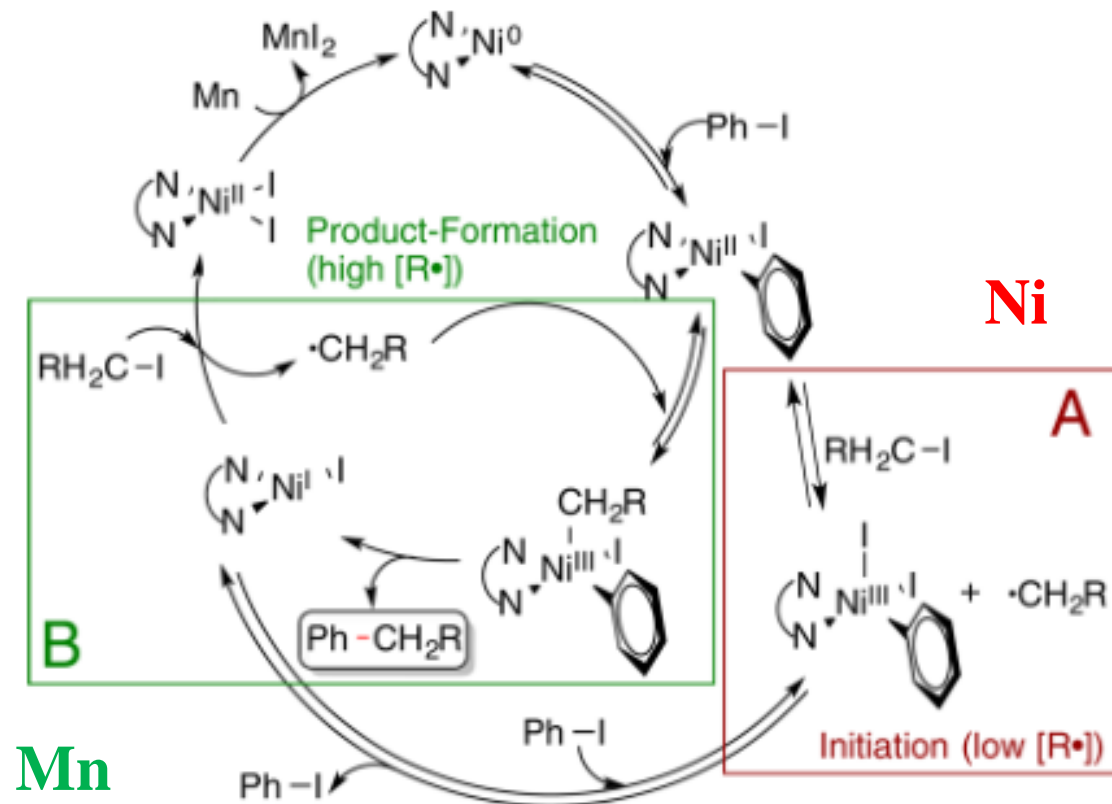
Potential mechanisms for cross-electrophile coupling:
(A) in situ formation of an organometallic reagent (R1MnI) followed by cross-coupling; (B) transmetalation between two organonickel species; (C) sequential oxidative additions at a single nickel center; and (D) radical chain reaction. R1 and R2 could be either alkyl or aryl.

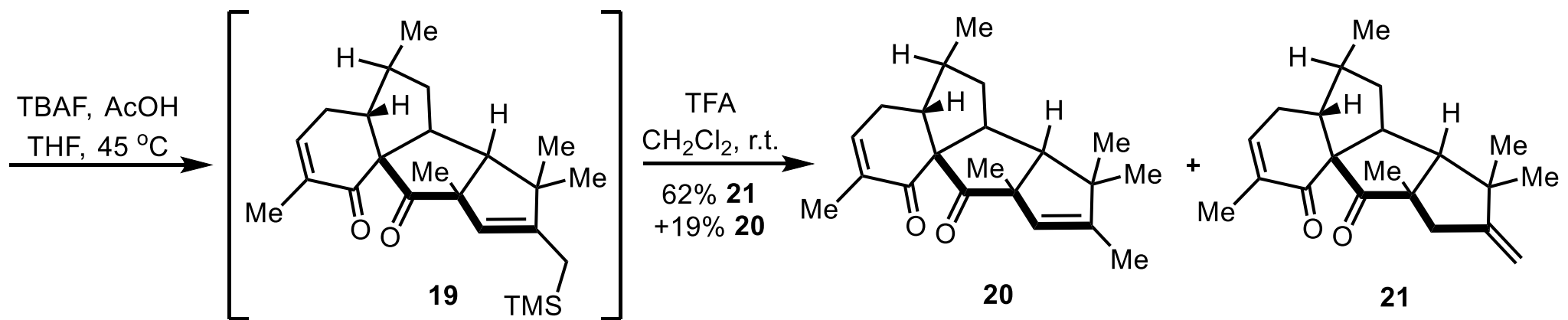
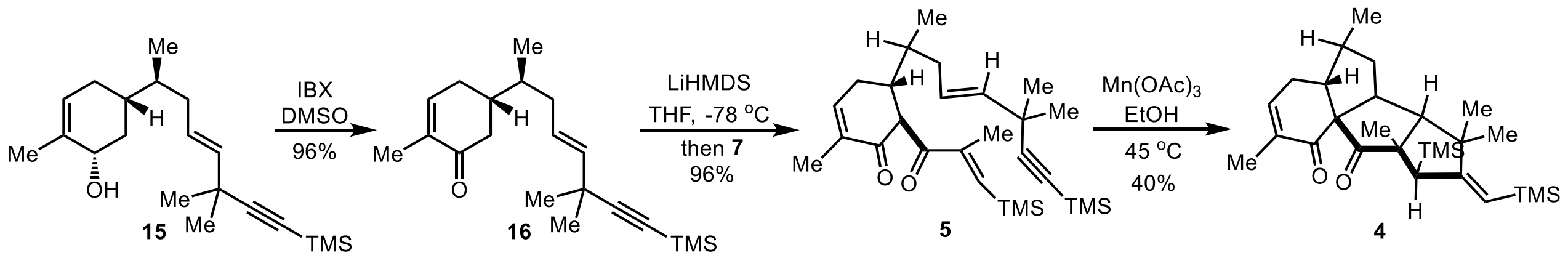
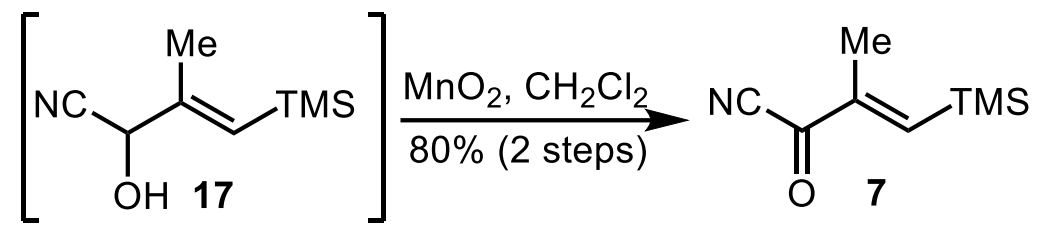
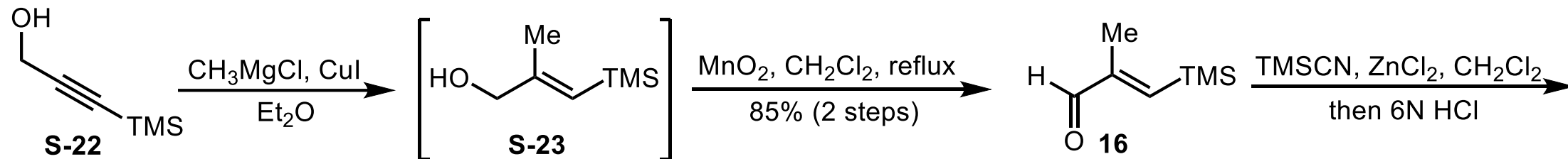
J. Am. Chem. Soc., **2013**, *135*, 16192.

Proposed Mechanism

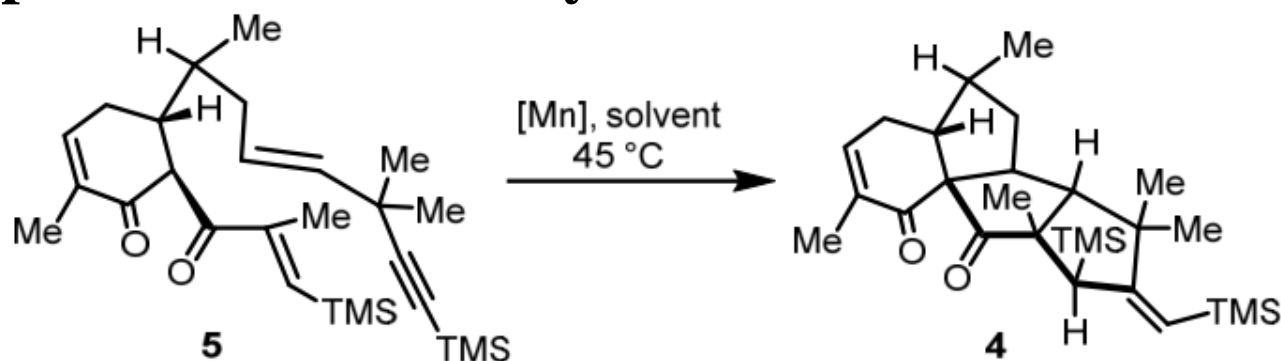


Hypothesis for Self-Initiation





Optimization of the key radical cascade reaction



entry	[Mn]	solvent	Temp.	concentration	yield ^a
1	Mn(OAc) ₃ ·2H ₂ O	EtOH	45 °C	0.03 M	40% ^b
2	Mn(OAc) ₃ ·2H ₂ O	CF ₃ CH ₂ OH	45 °C	0.03 M	N.R.
3	Mn(OAc) ₃ ·2H ₂ O	DMF	45 °C	0.03 M	28%
4	Mn(OAc) ₃ ·2H ₂ O	DCE	45 °C	0.03 M	N.R.
5	Mn(OAc) ₃ ·2H ₂ O	THF	45 °C	0.03 M	N.R.
6	Mn(OAc) ₃ ·2H ₂ O	DMSO	45 °C	0.03 M	0%
7	Mn(OAc) ₃ ·2H ₂ O	MeCN	45 °C	0.03 M	N.R.
8	Mn(OAc) ₃ ·2H ₂ O	MeOH	45 °C	0.03 M	7%
9	Mn(OAc) ₃ ·2H ₂ O	AcOH	45 °C	0.03 M	0%
10	Mn(OAc) ₃ ·2H ₂ O	<i>i</i> -PrOH	45 °C	0.03 M	15%
11	Mn(OAc) ₃ ·2H ₂ O	<i>i</i> -PrOH/EtOH	45 °C	0.03 M	31%

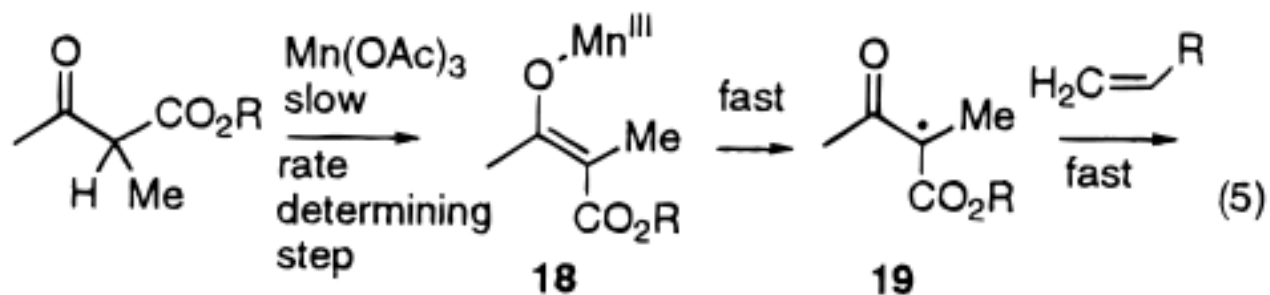
12	Mn(OAc) ₃ ·2H ₂ O	<i>s</i> -BuOH	45 °C	0.03 M	17%
13	Mn(OAc) ₃ ·2H ₂ O	1,4-dioxane	45 °C	0.03 M	7%
14	Mn(OAc) ₃ ·2H ₂ O	DME	45 °C	0.03 M	10%
15	Mn(OAc) ₃ ·2H ₂ O	EtOH	30 °C	0.03 M	N.R.
16	Mn(OAc) ₃ ·2H ₂ O	EtOH	60 °C	0.03 M	38%
17	Mn(OAc) ₃ ·2H ₂ O	EtOH	45 °C	0.1 M	24%
18	Mn(OAc) ₃ ·2H ₂ O	EtOH	45 °C	0.015 M	25%
19	Mn(acac) ₃	EtOH	45 °C	0.03 M	22%
20	Mn(dmp) ₃	EtOH	45 °C	0.03 M	5%
21	MnF ₃	EtOH	45 °C	0.03 M	N.R.
22 ^c	Mn(OAc) ₃ ·2H ₂ O	DCE	125 °C	0.03 M	0%

^aThe yield is determined by NMR with CH₂Br₂ as an internal standard.

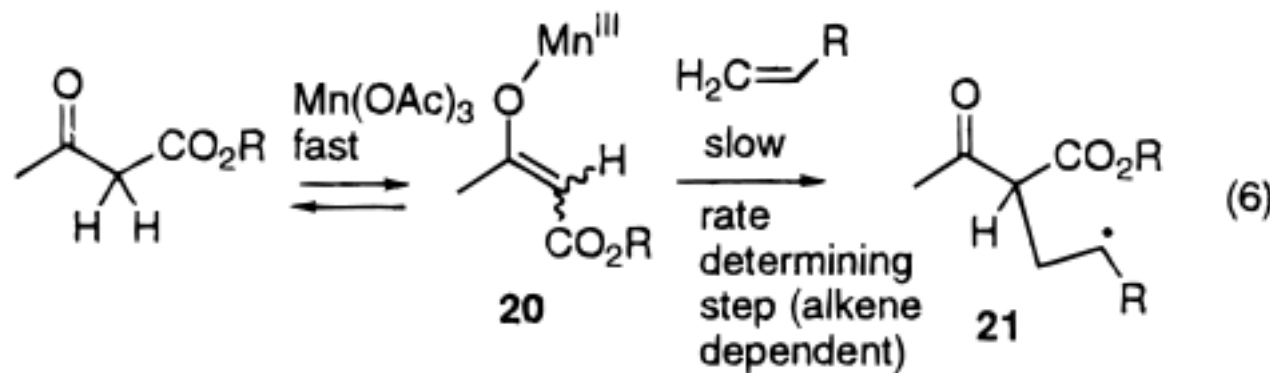
^bIsolated yield.

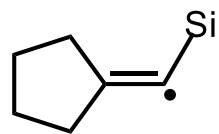
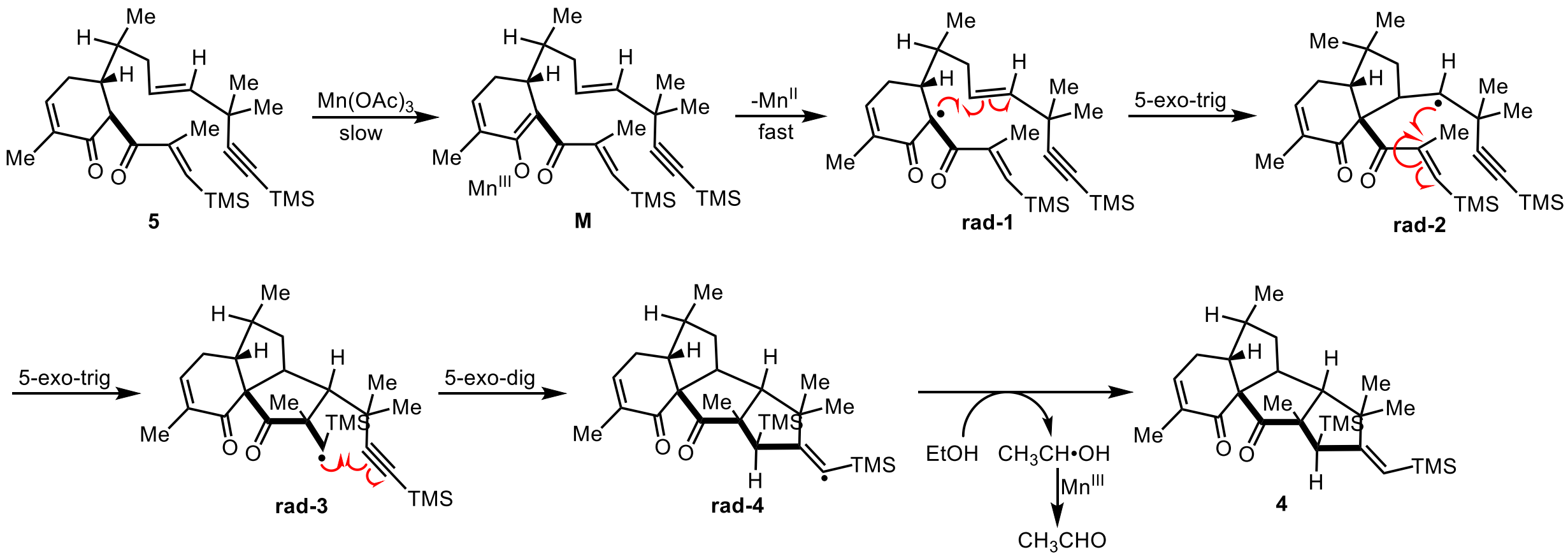
^cMicrowave (100 W, 125 °C)

Manganese(III)-Based Oxidative Free-Radical Cyclizations

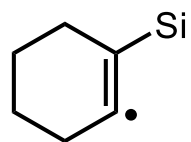


1. Acidity of the α -proton
2. Stability of the radical





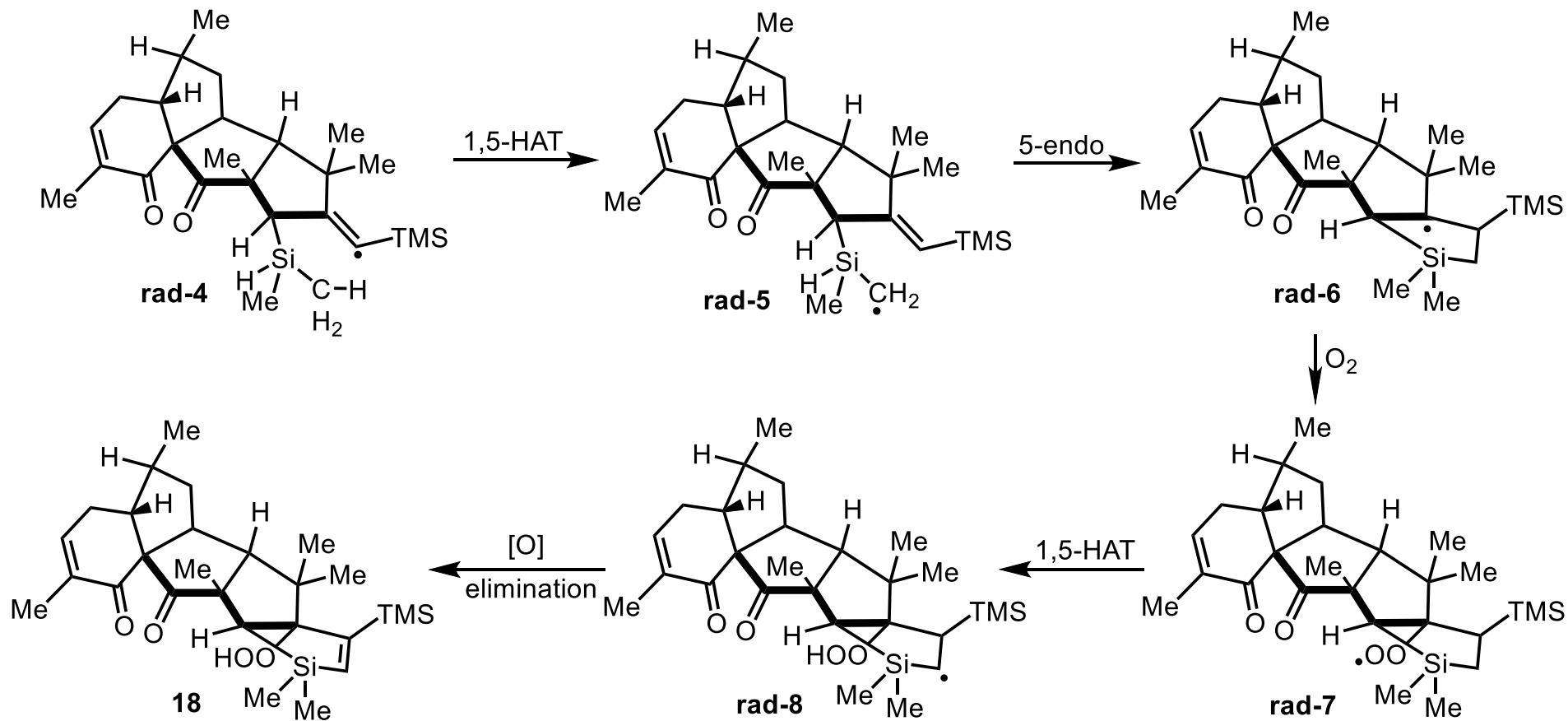
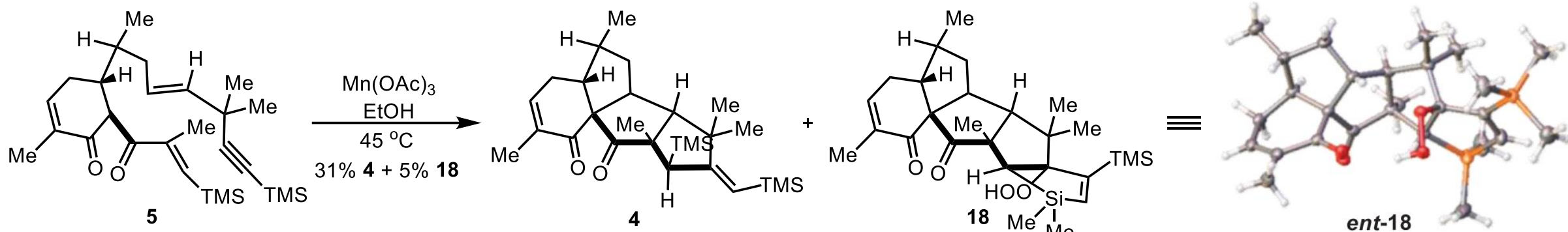
5-exo

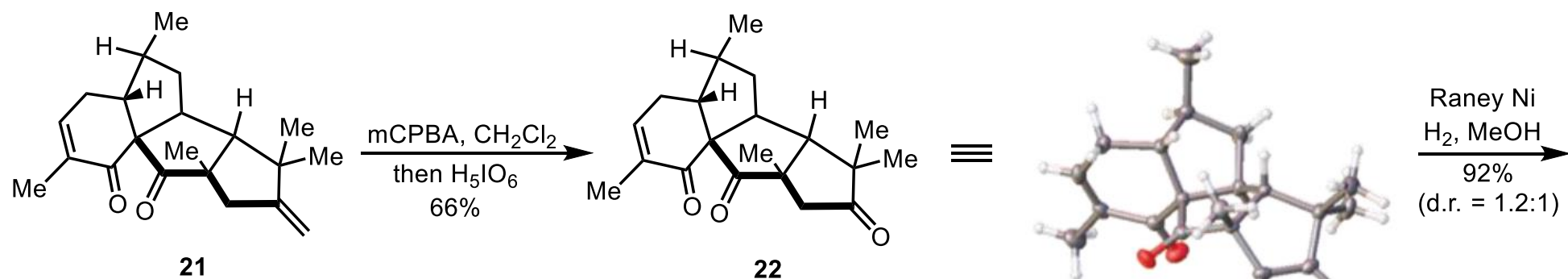


6-endo

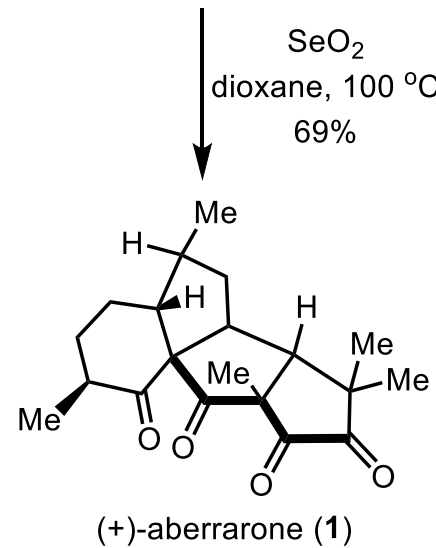
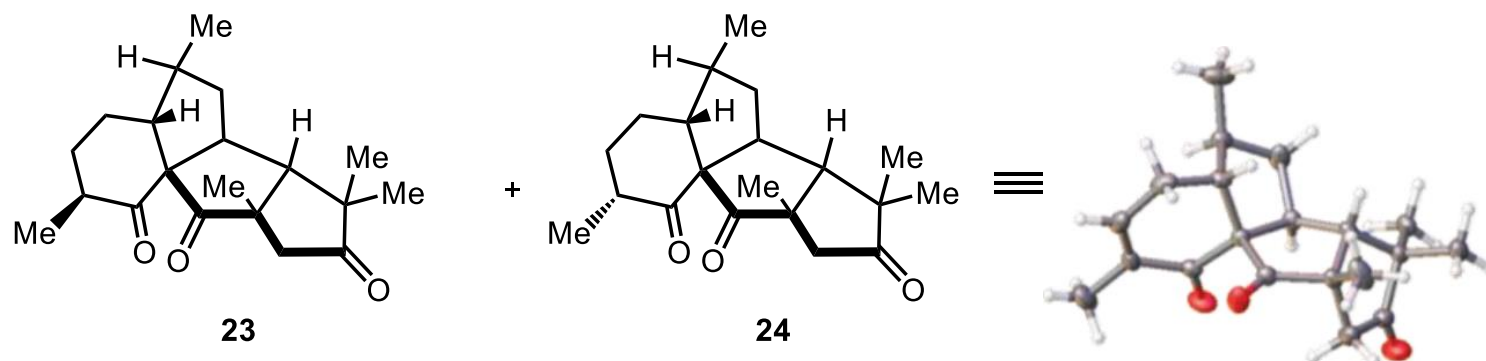
Si的 α -效应

a trace amount of O₂ in system :



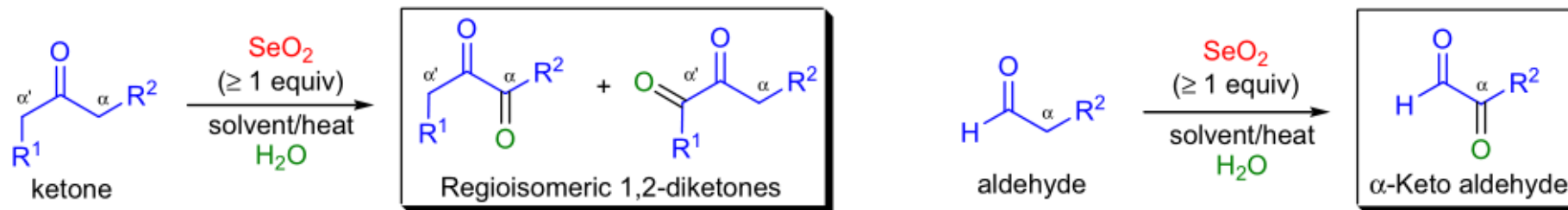


Raney Ni
H₂, MeOH
92%
(d.r. = 1.2:1)

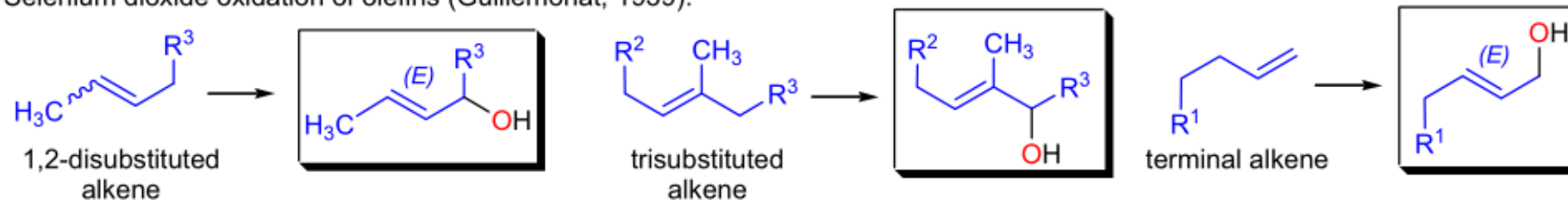


Riley Selenium Dioxide Oxidation

Selenium dioxide oxidation of ketones and aldehydes (Riley, 1932):

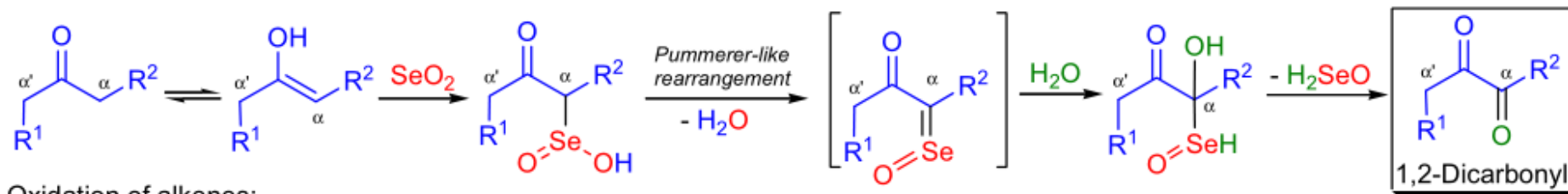


Selenium dioxide oxidation of olefins (Guillemonat, 1939):



Mechanism: ²⁴⁻⁴¹

Oxidation of carbonyl compounds:



Oxidation of alkenes:

