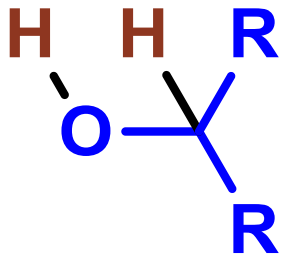
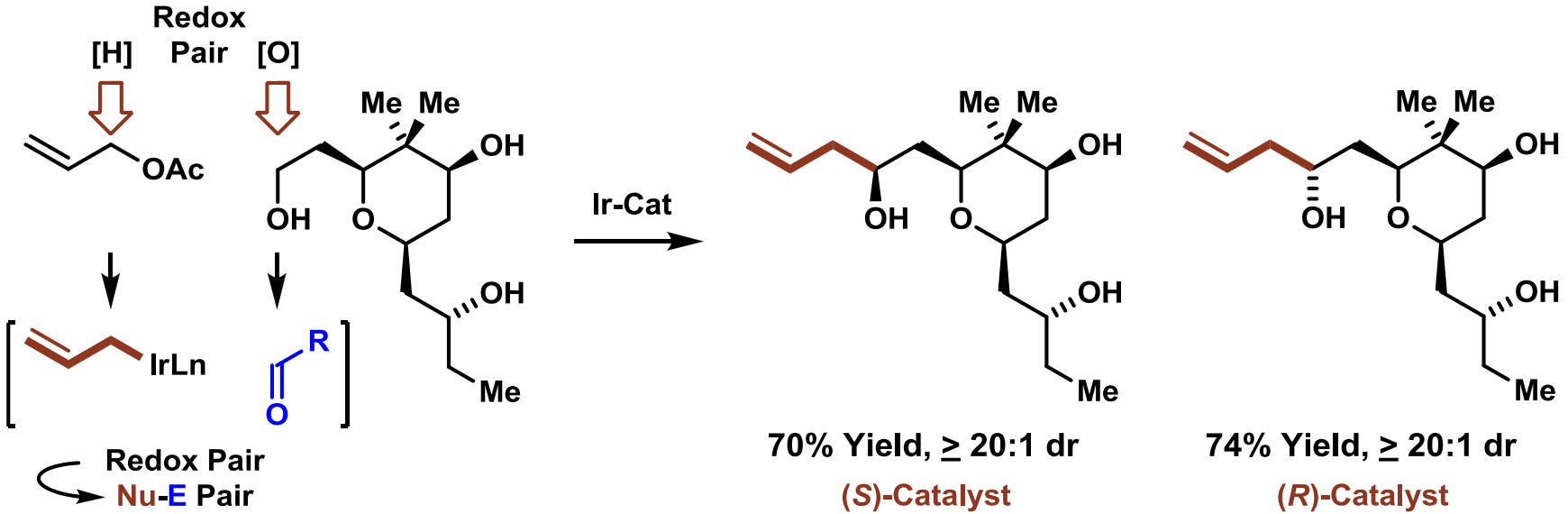
Hydrogen Mediated C-C Bond Formation

Professor Michael J. Krische *University of Texas at Austin*

H–H

IASOC 2016
September 25-30, 2016



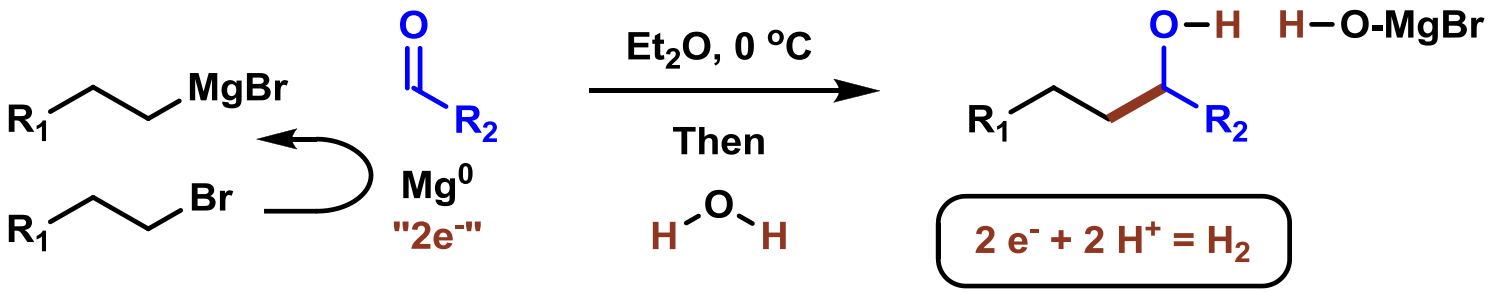


70% Yield, ≥ 20:1 dr
(*S*)-Catalyst

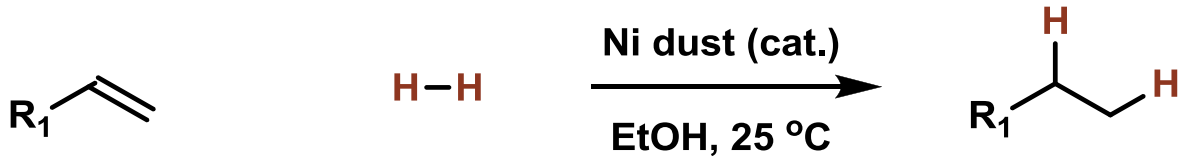
74% Yield, ≥ 20:1 dr
(*R*)-Catalyst

1912

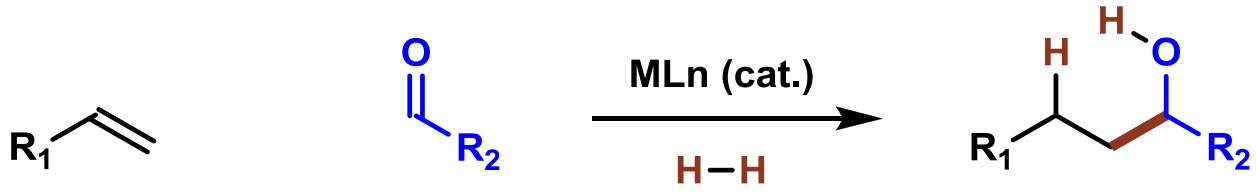
Victor Grignard, C. R. Acad. Sci. 1900, 130, 1322.



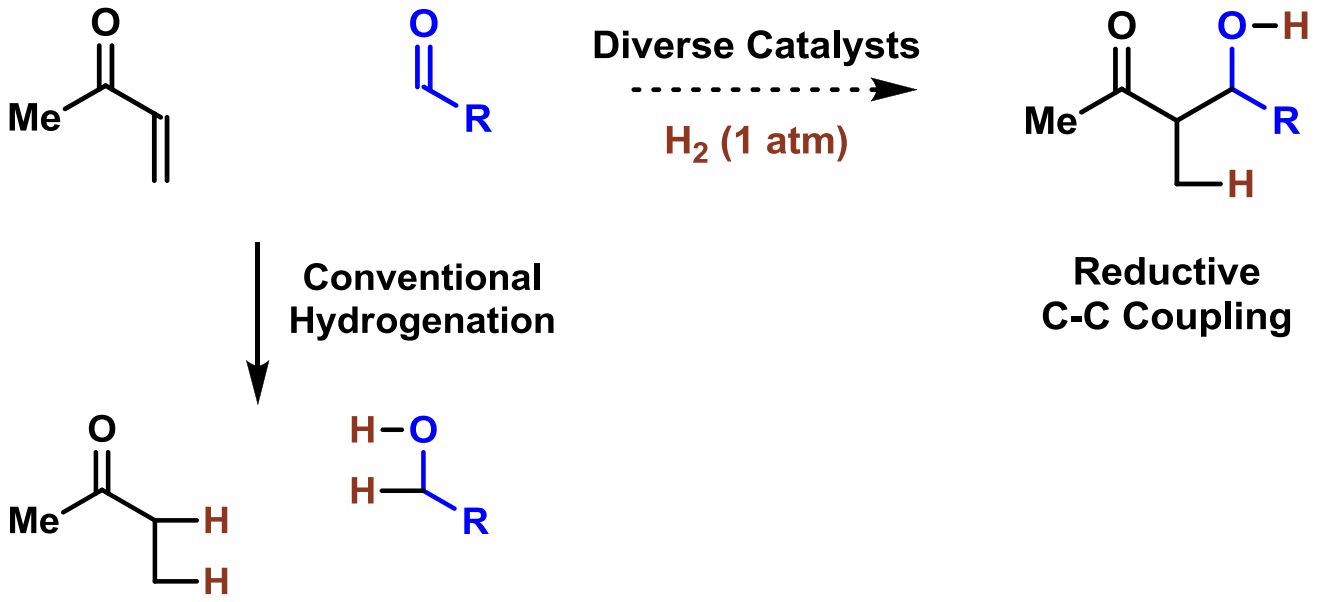
Paul Sabatier, C. R. Acad. Sci. 1896, 1240.



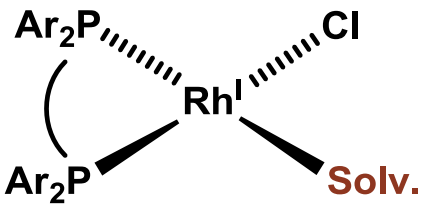
Hydrogen-Mediated Carbonyl Addition



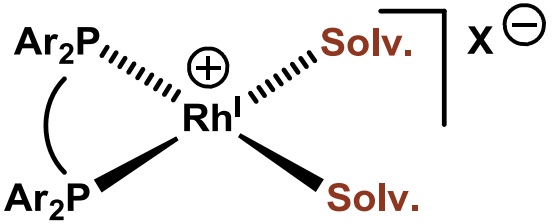
Hydrogenation: > 10% of GMP Reactions



Halpern *Science* 1982, *217* 401
Inorg. Chim. Acta 1998, *270*, 285

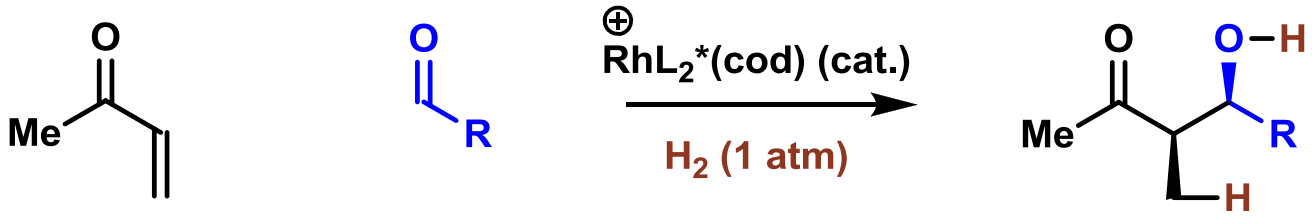


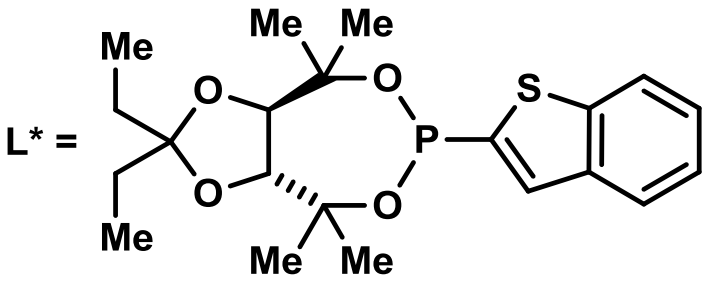
Neutral Rhodium(I) Complex
H_2-Activation - FAST
Open Coordination Sites - ONE

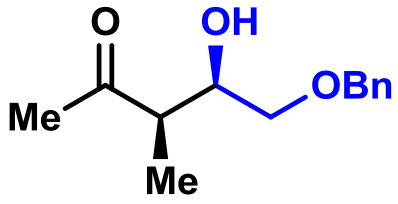


Cationic Rhodium(I) Complex
H_2-Activation - SLOW
Open Coordination Sites - TWO

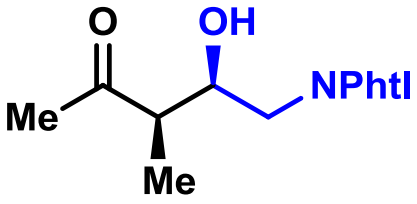
J. Am. Chem. Soc. 2008, 2747



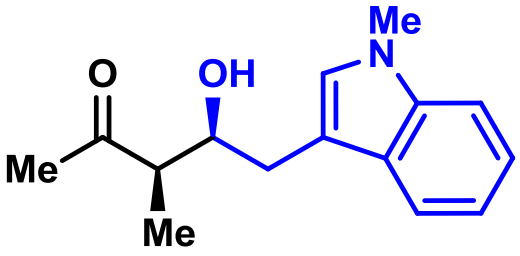




87% Yield, 25:1 dr
91% ee

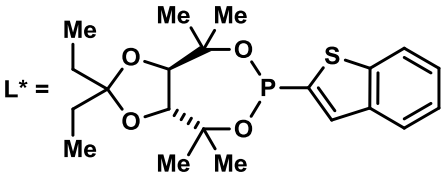


92% Yield, 50:1 dr
96% ee

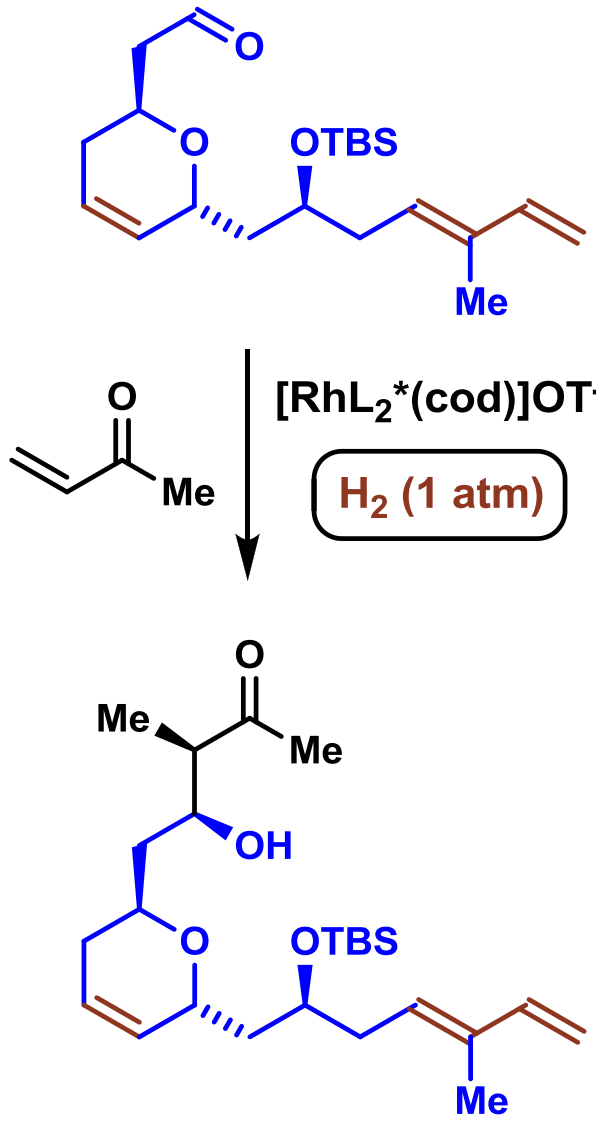


92% Yield, 50:1 dr
96% ee

<u>Reviews</u>: *Angew. Chem. Int. Ed.* 2009, *48*, 34; *Top. Organomet. Chem.* 2011, *43*, 107.

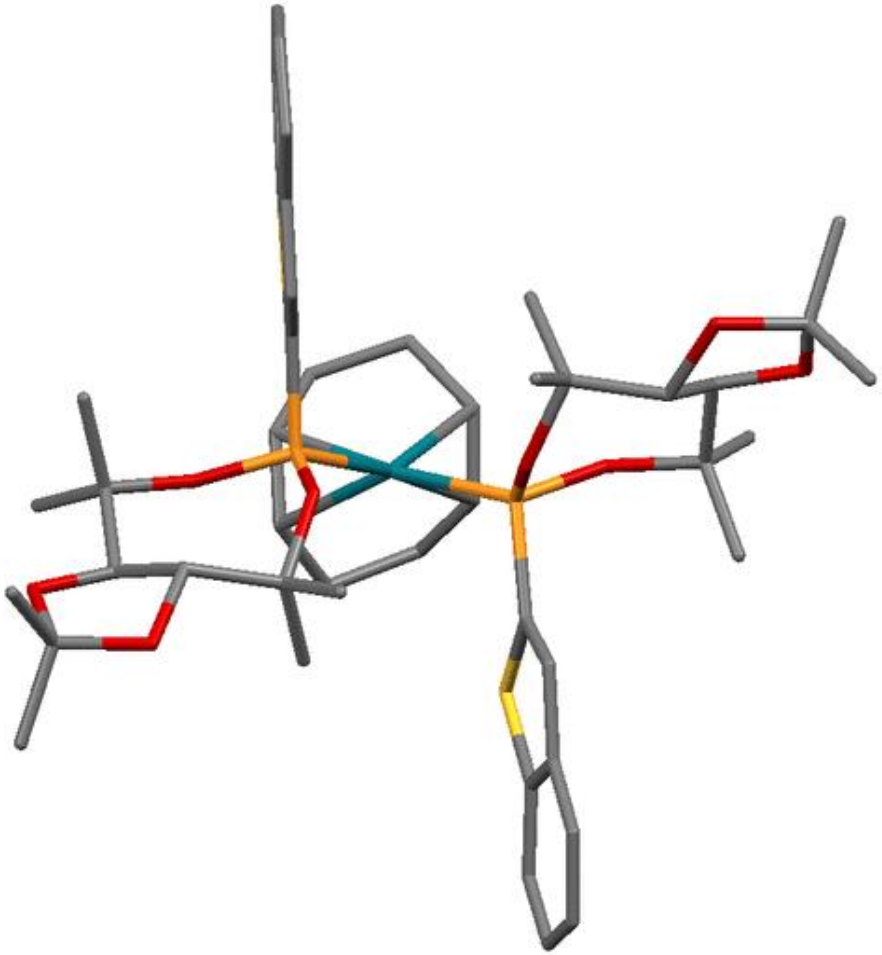


Swinholide A

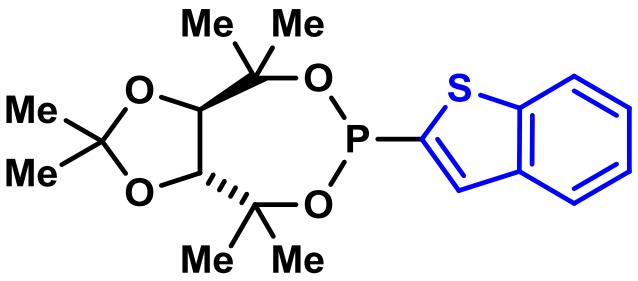


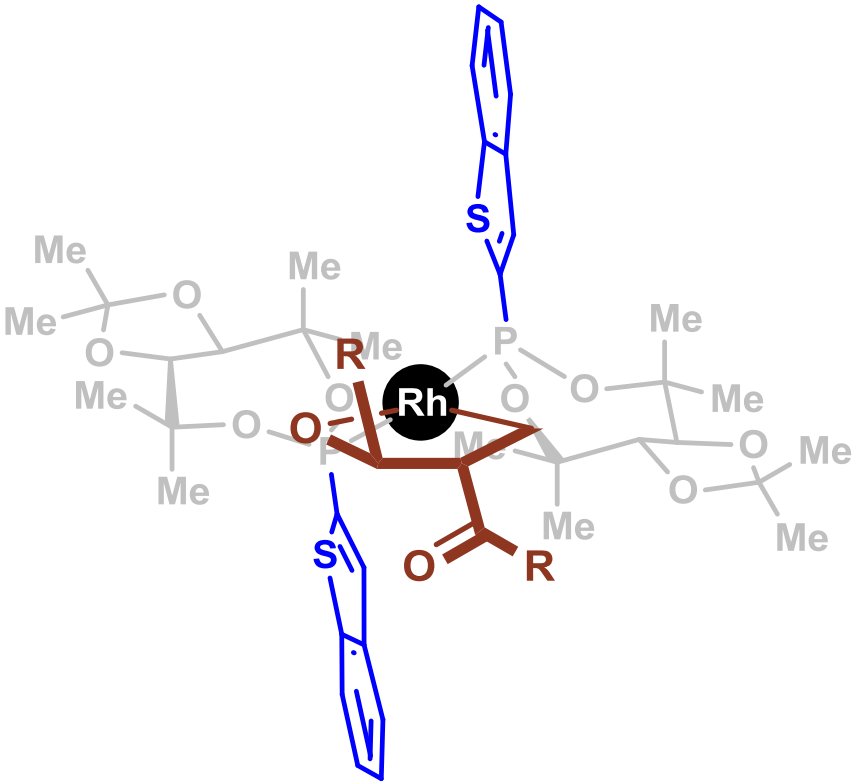
69% Yield, 7:1 dr

X-Ray Crystal Structure
RhL_2*(cod)



RhL_2*(cod)

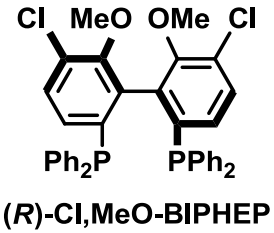




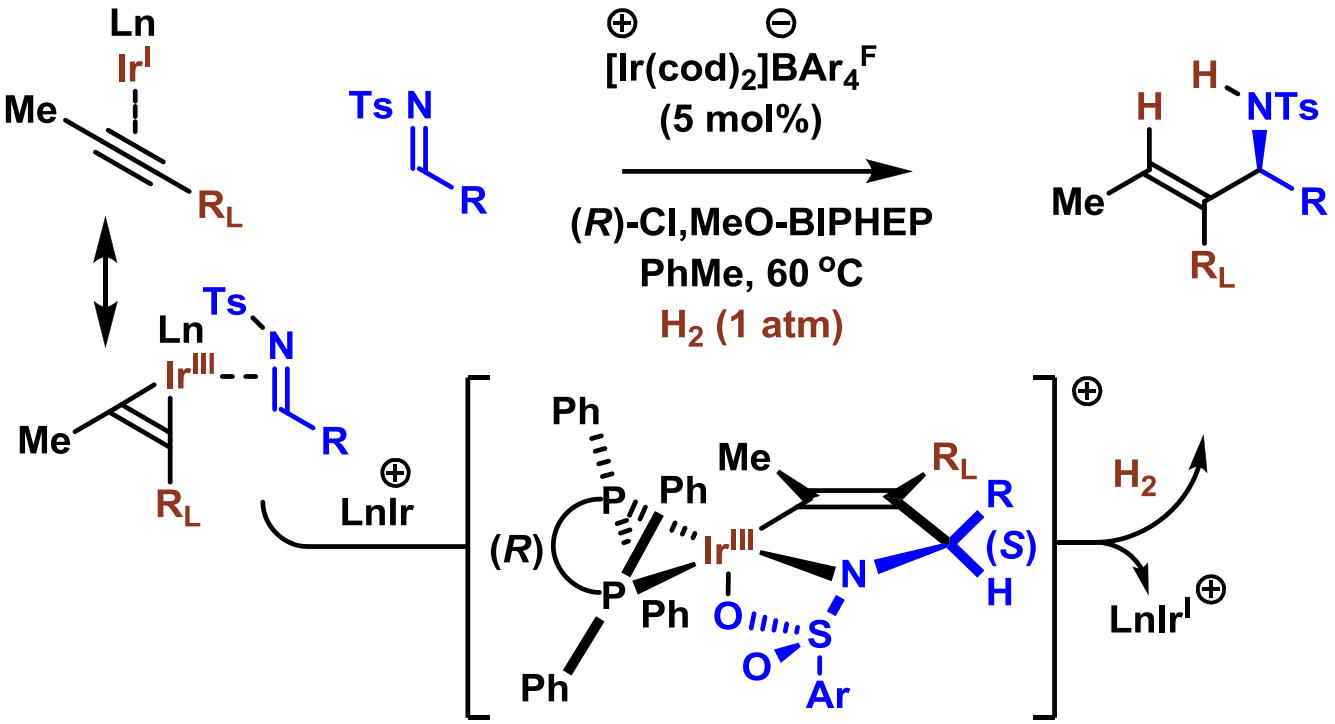
***JACS* 2008, 2747**

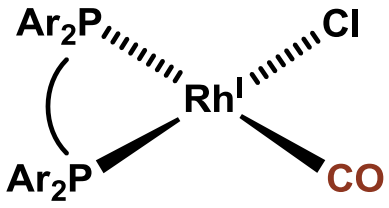
Front View (COD Omitted)

JACS 2007, 12644.

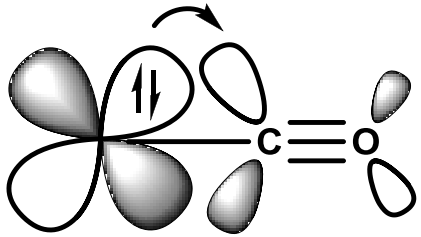


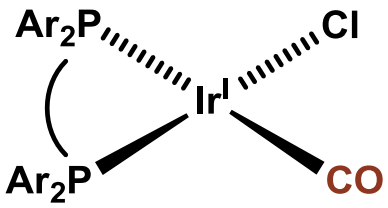
(*R*)-Cl,MeO-BIPHEP





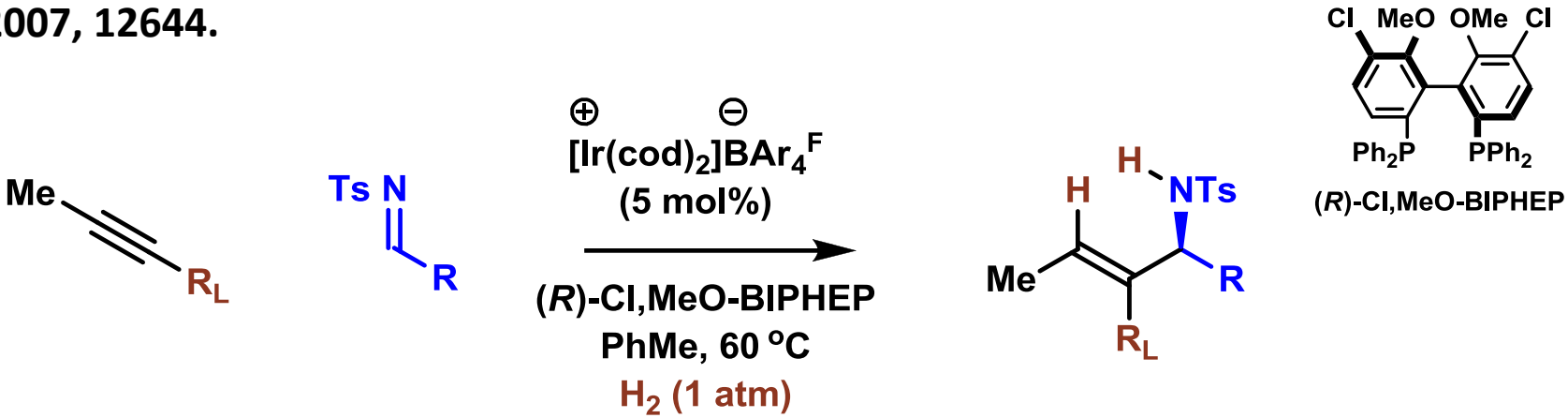
υ_{CO} = 1980 cm^{-1}

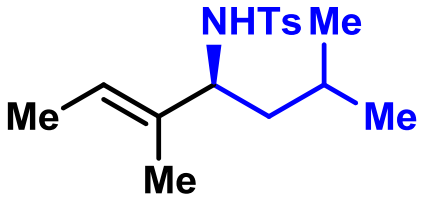




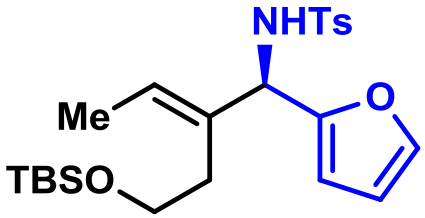
υ_{CO} = 1965 cm^{-1}

JACS 2007, 12644.

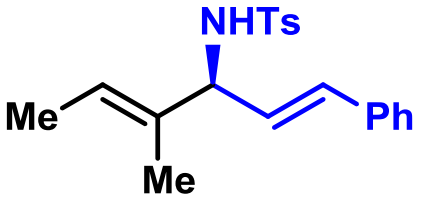




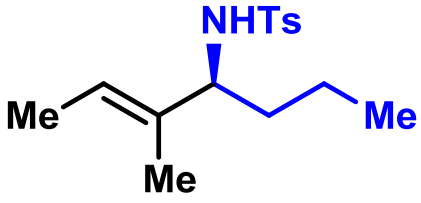
70% Yield, 99% ee



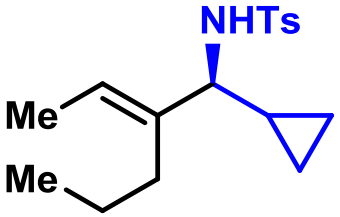
69% Yield, 98% ee
10:1 rr



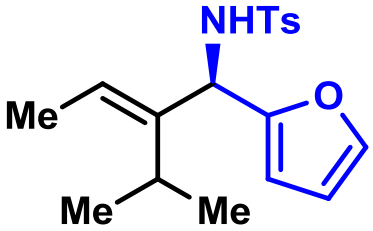
76% Yield, 99% ee



74% Yield, 98% ee

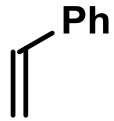


65% Yield, 99% ee
10:1 rr

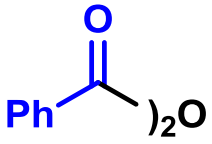


80% Yield, 97% ee
>20:1 rr

Angew. Chem. Int. Ed. 2006, 6885

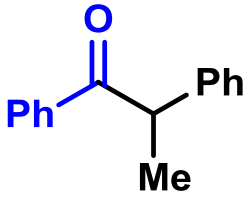


Styrene
81 M Tons / Year
8 cents / mole



$\oplus$ $\ominus$
$Rh(cod)_2BAr_4^F$ (2 mol%)
Ph_3As (4.4 mol%)

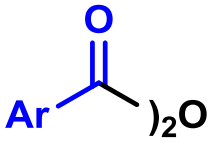
i-Pr_2NEt (200 mol%)
65 °C, H_2 (1 atm)



93% Yield
>99:1 Branched

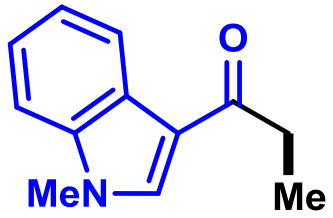
$H_2C{=}CH_2$

Ethylene
115 M Tons / Year
2 cents / mole

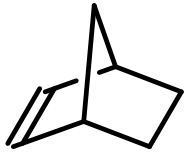


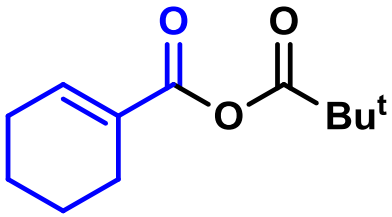
As Above

H_2 (1 atm)



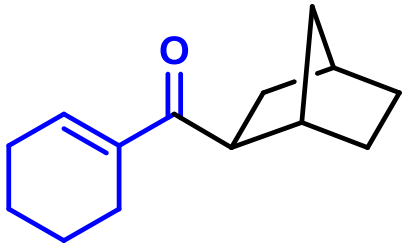
63% Yield



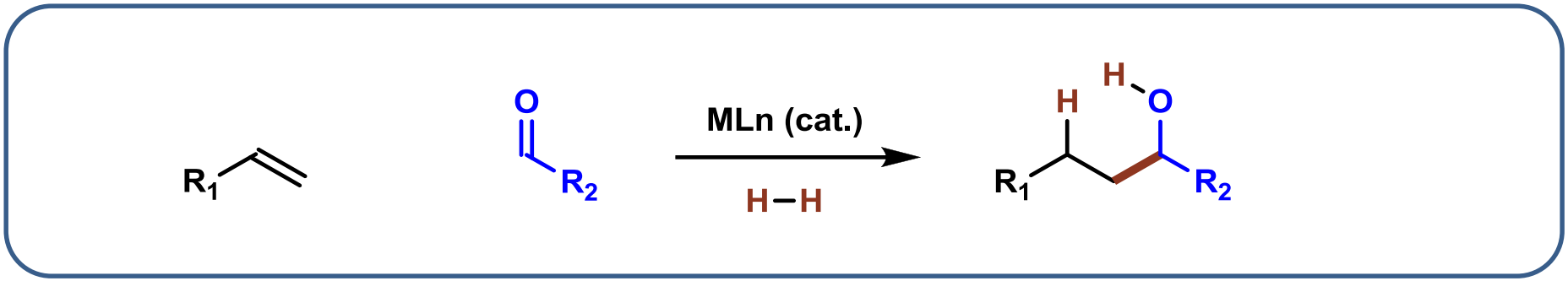


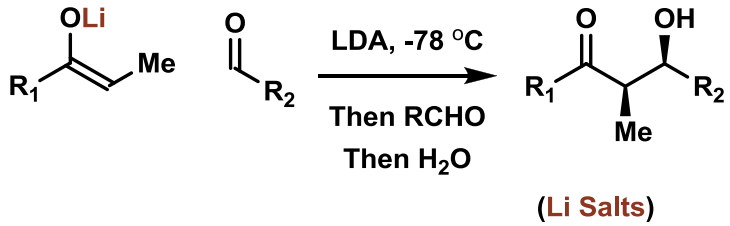
As Above

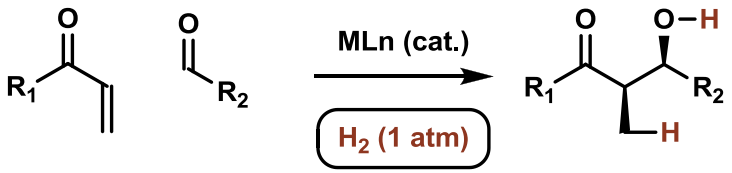
H_2 (1 atm)

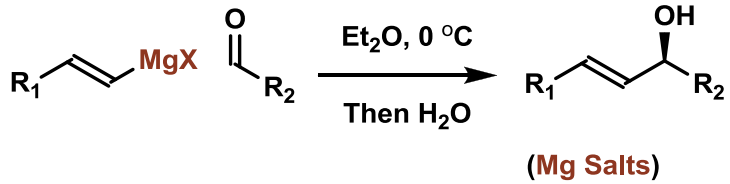


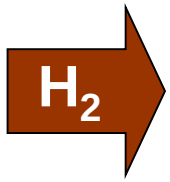
86% Yield

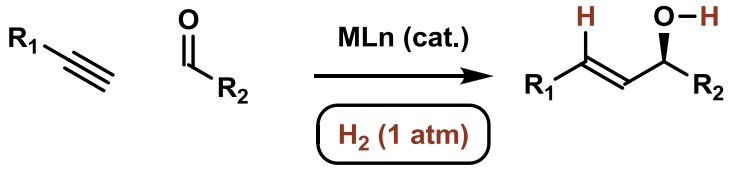

R1
O
R2
MLn (cat.)
H–H
H
H
O
R1
R2

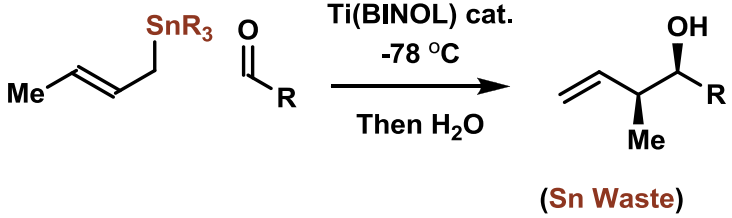

OLi
Me
R1
O
R2
LDA, -78 °C
Then RCHO
Then H2O
O
OH
R1
R2
Me
(Li Salts)

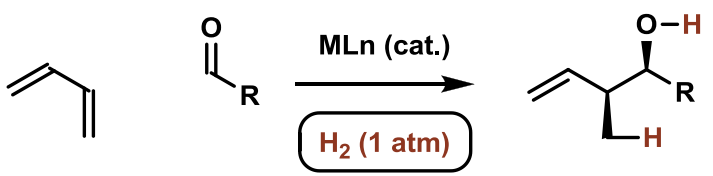

R1
O
R2
MLn (cat.)
H2 (1 atm)
O
O–H
R1
R2
H

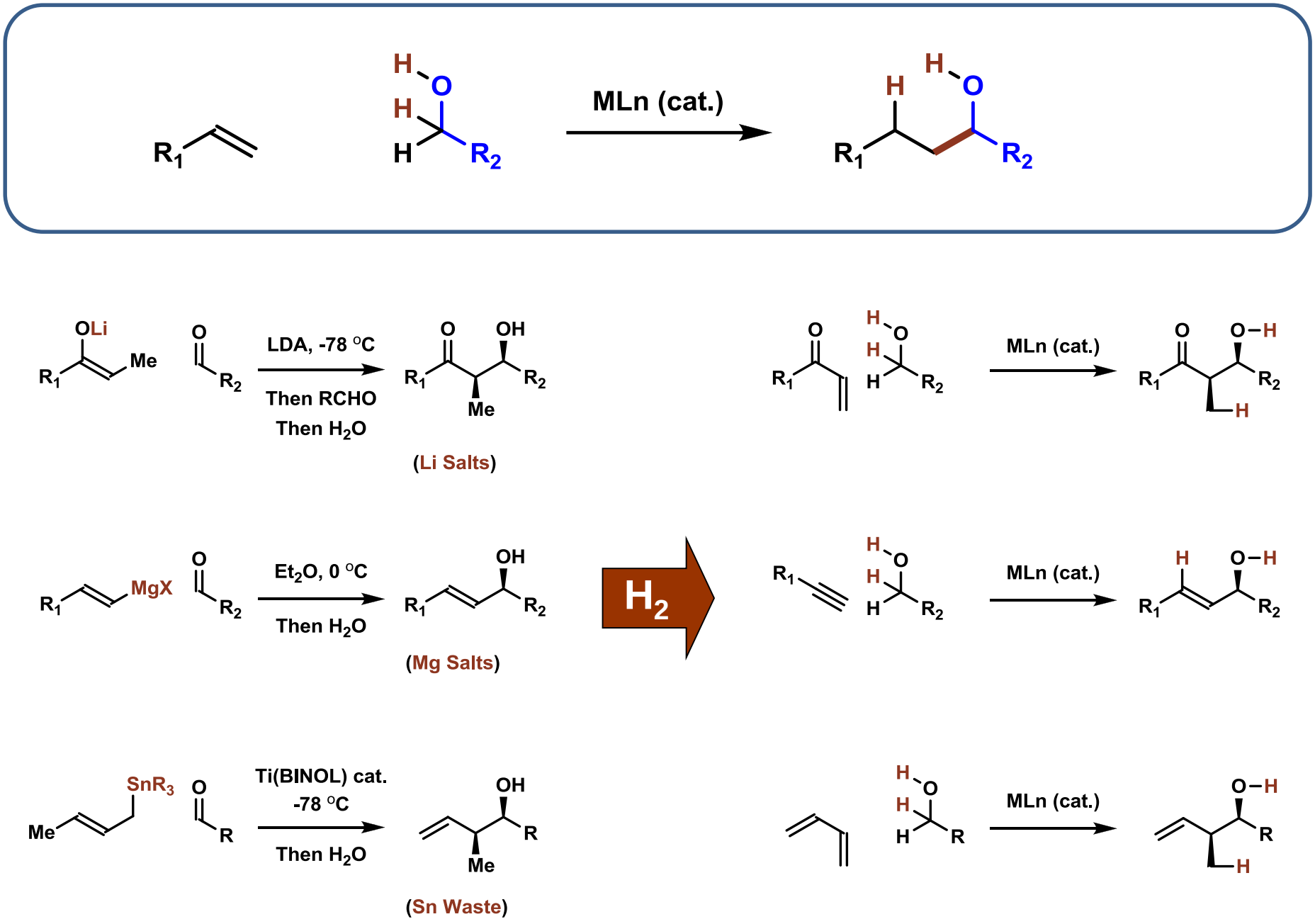

MgX
R1
O
R2
Et2O, 0 °C
Then H2O
OH
R1
R2
(Mg Salts)


H2


R1
O
R2
MLn (cat.)
H2 (1 atm)
H
O–H
R1
R2


SnR3
Me
O
R
Ti(BINOL) cat.
-78 °C
Then H2O
OH
R
Me
(Sn Waste)

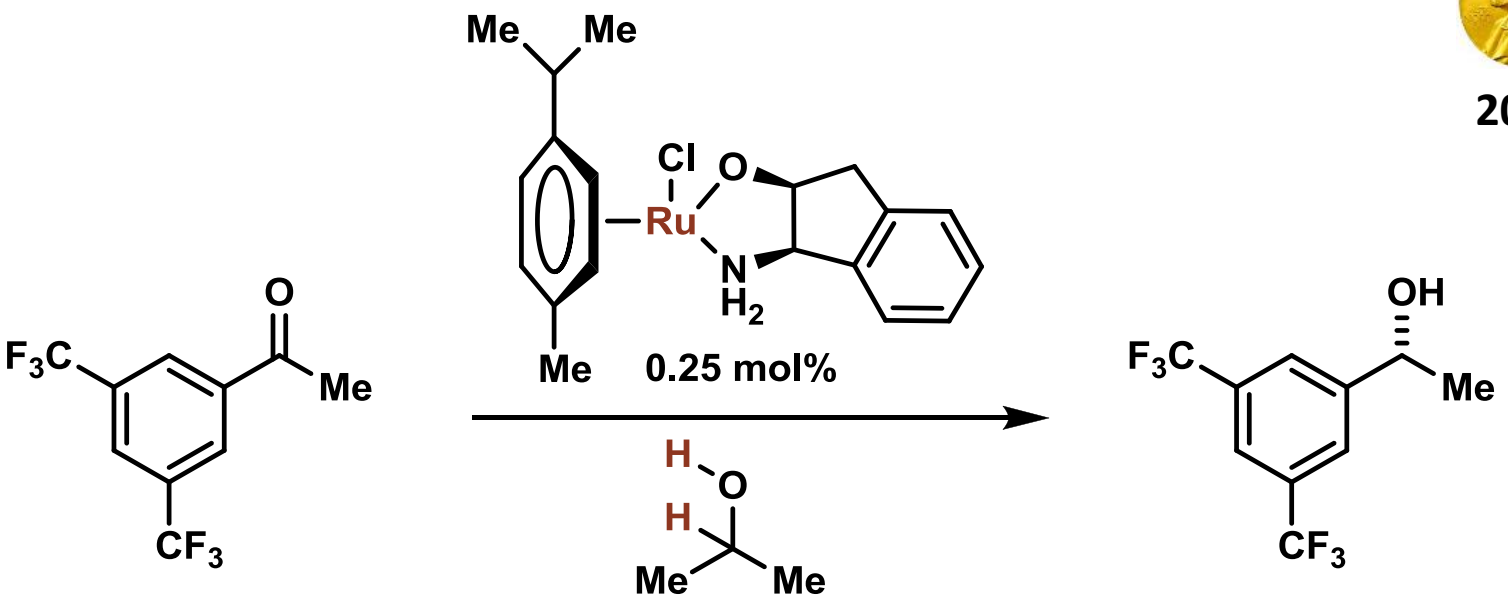

O
R
MLn (cat.)
H2 (1 atm)
O–H
R
H


MLn (cat.)
OLi
Me
LDA, -78 °C
Then RCHO
Then H2O
(Li Salts)
MLn (cat.)
MgX
Et2O, 0 °C
Then H2O
(Mg Salts)
H2
MLn (cat.)
SnR3
Me
Ti(BINOL) cat.
-78 °C
Then H2O
(Sn Waste)
MLn (cat.)

Tetrahedron Asymm. 2003, 3581
Merck Process

Noyori *JACS* 1980, 7932
JACS 1995, 7562

2001



90 Kg Scale

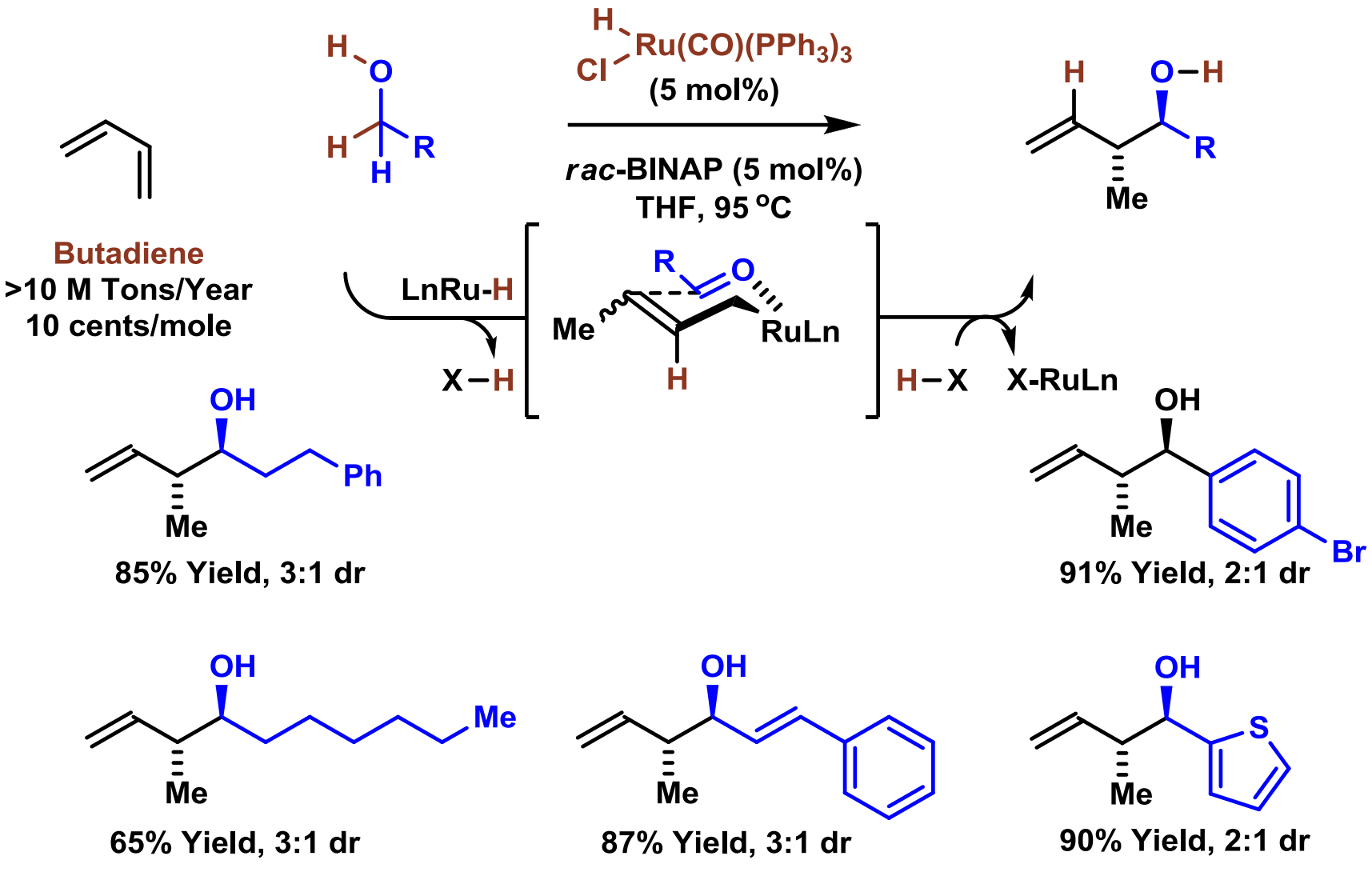
Solvent

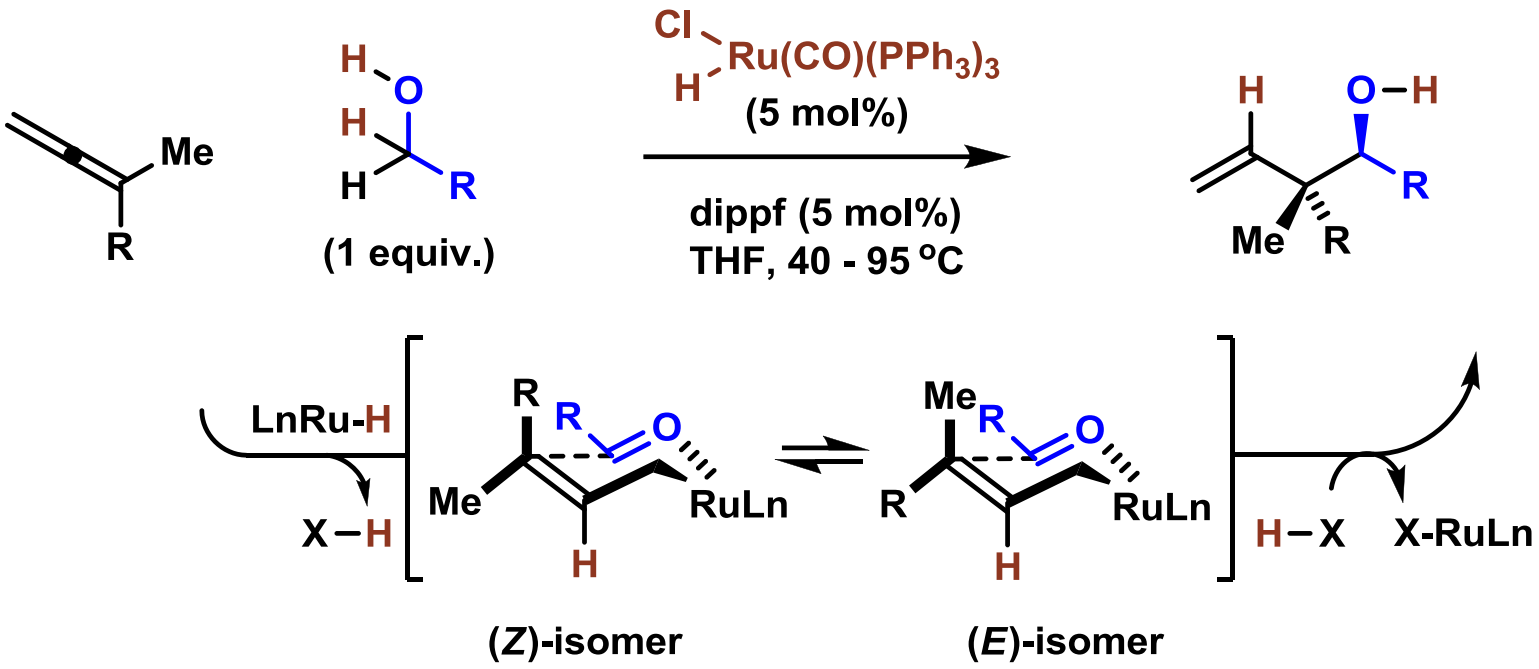
87% Yield, 90% ee

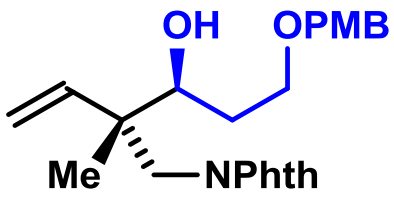
*Metal Price 01/2014-01/2015**	Pt	Pd	Rh	Ir	Ru
$$ / Ounce	1,381	809	1,175	555	64
$$ / Mole	9,503	3,037	4,265	3,763	228

http://www.platinum.matthey.com

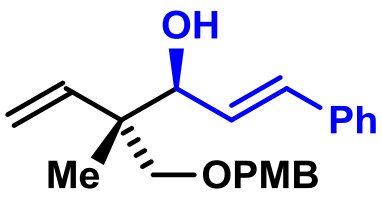
JACS 2008, 6338; *JACS* 2008, 14120.



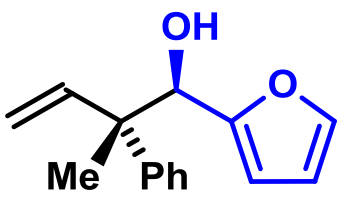




72% Yield
>20:1 dr

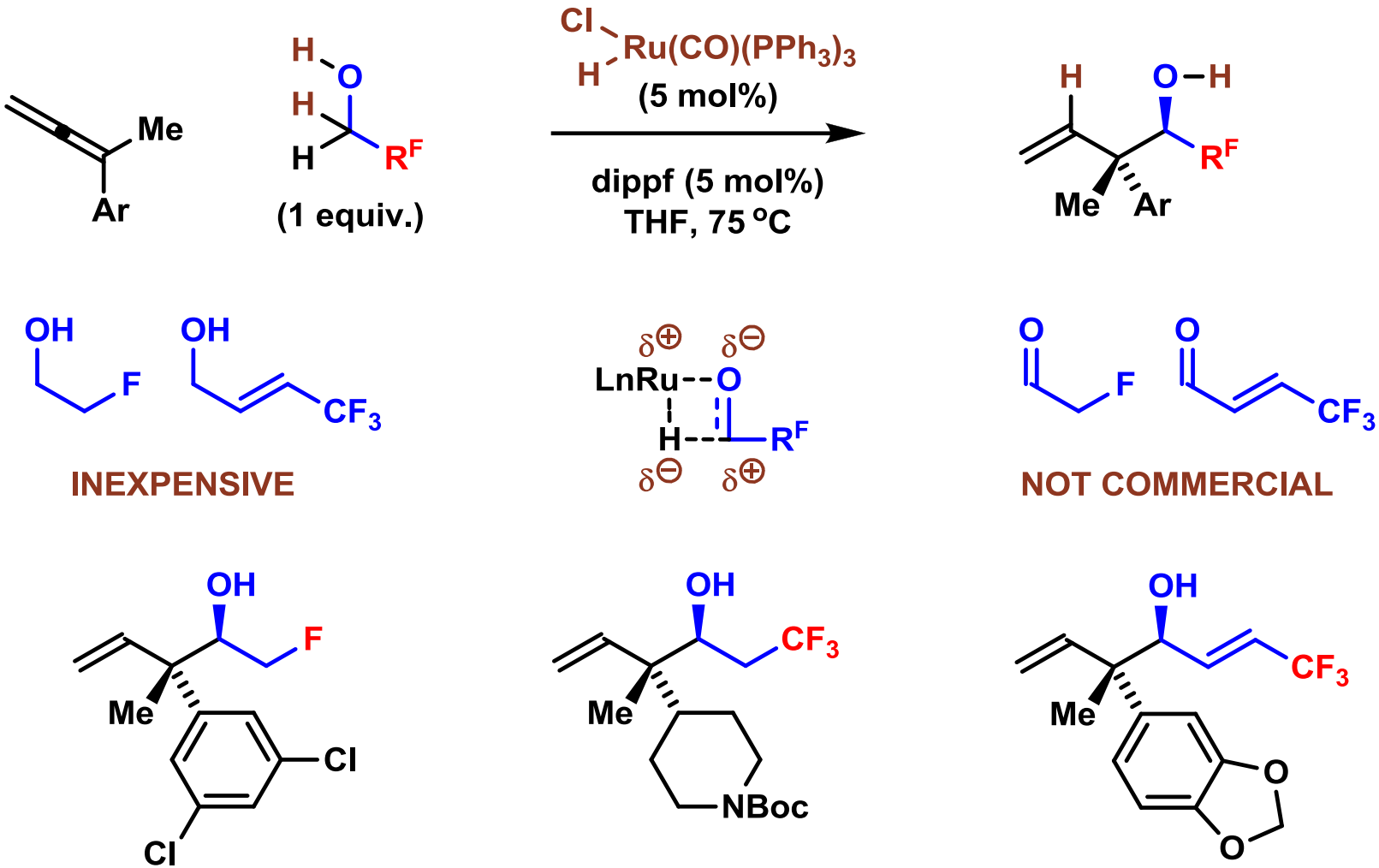


94% Yield
14:1 dr



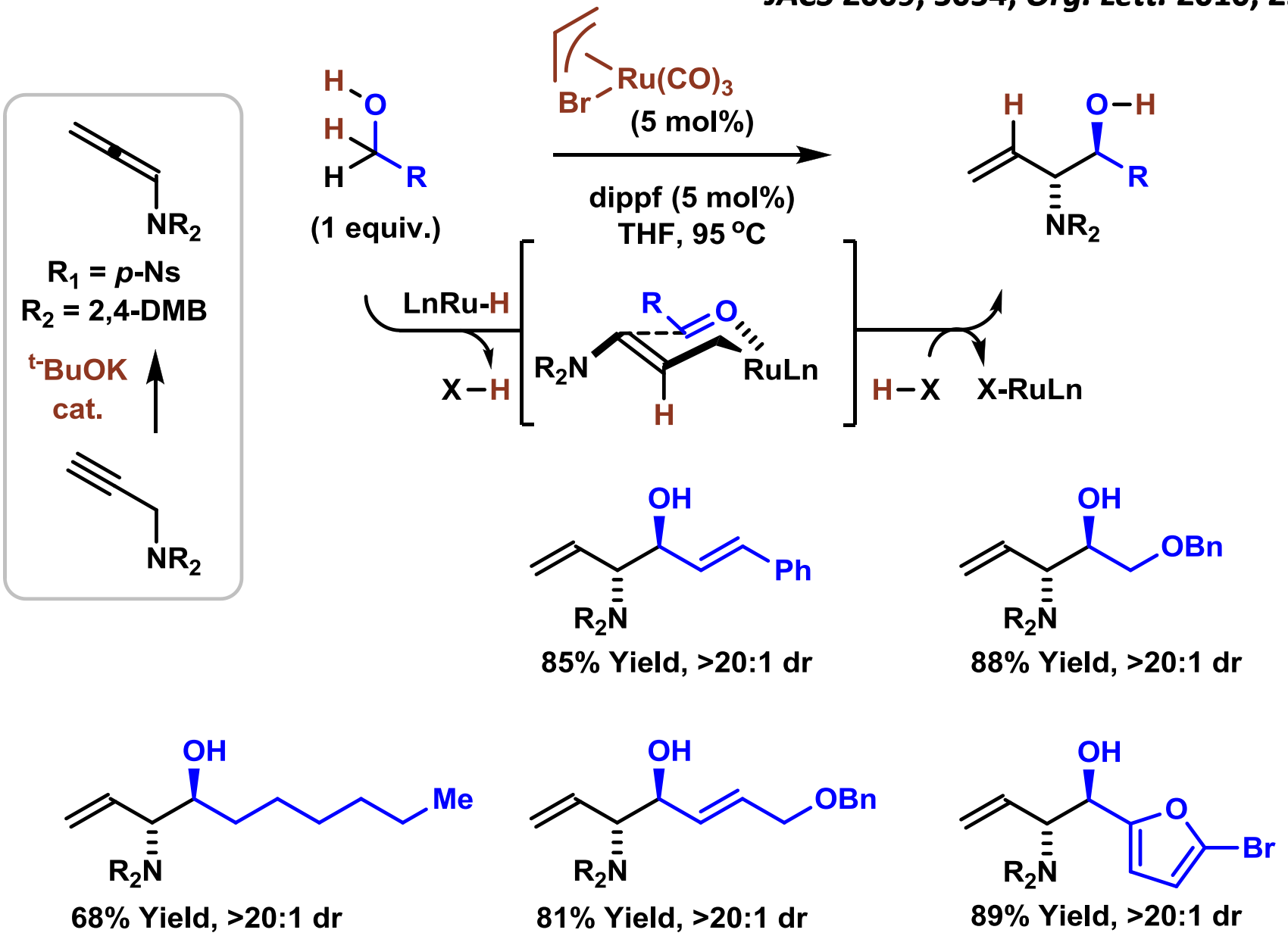
97% Yield
10:1 dr

JACS 2007, 15134; *JACS* 2011, 1141

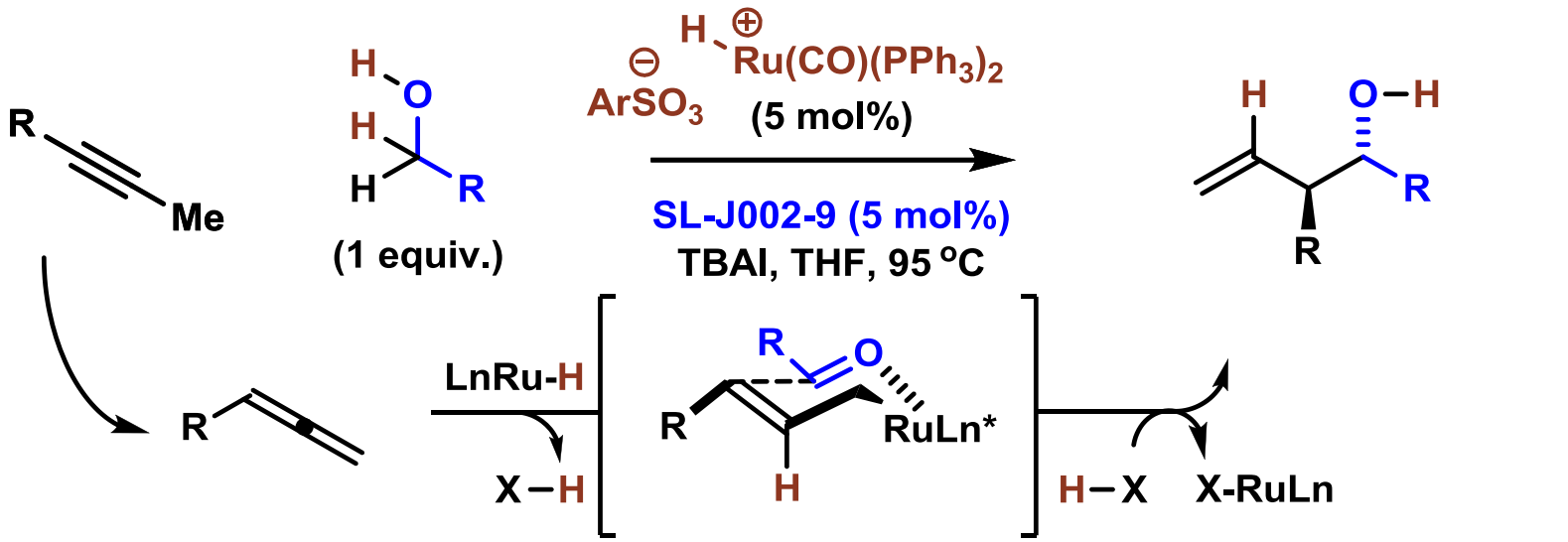


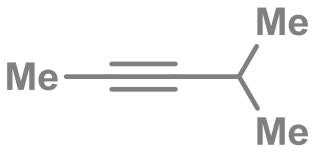
ACIE 2015, 5465

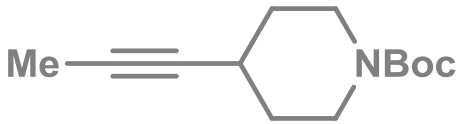
JACS 2009, 5054; *Org. Lett.* 2010, 2514.

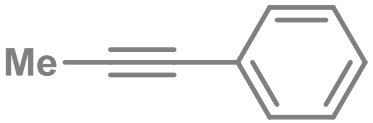


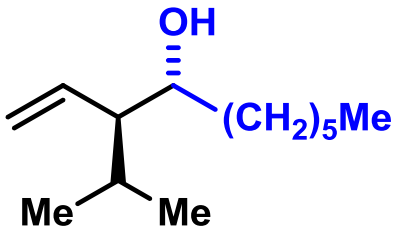
JACS 2015, 3161





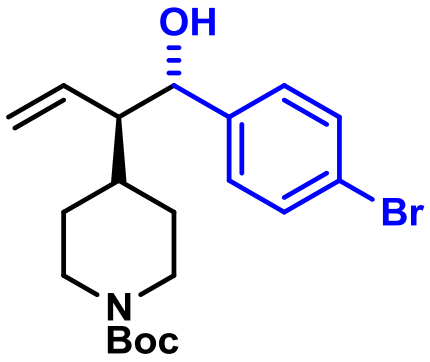






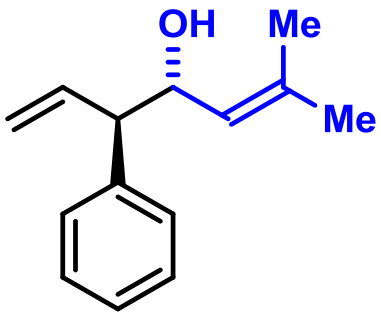
72% Yield, >20:1 dr

93% ee



65% Yield, >20:1 dr

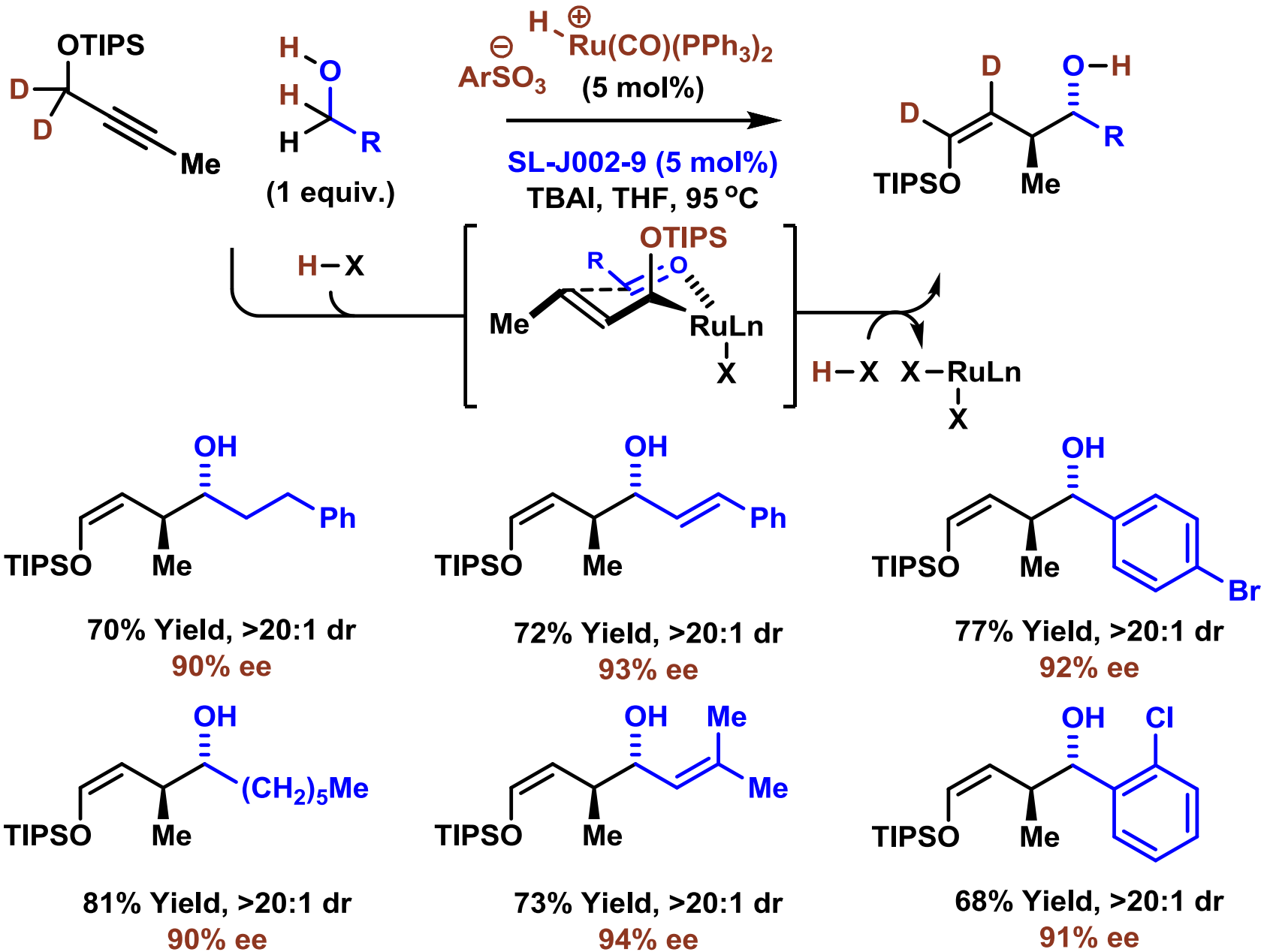
90% ee



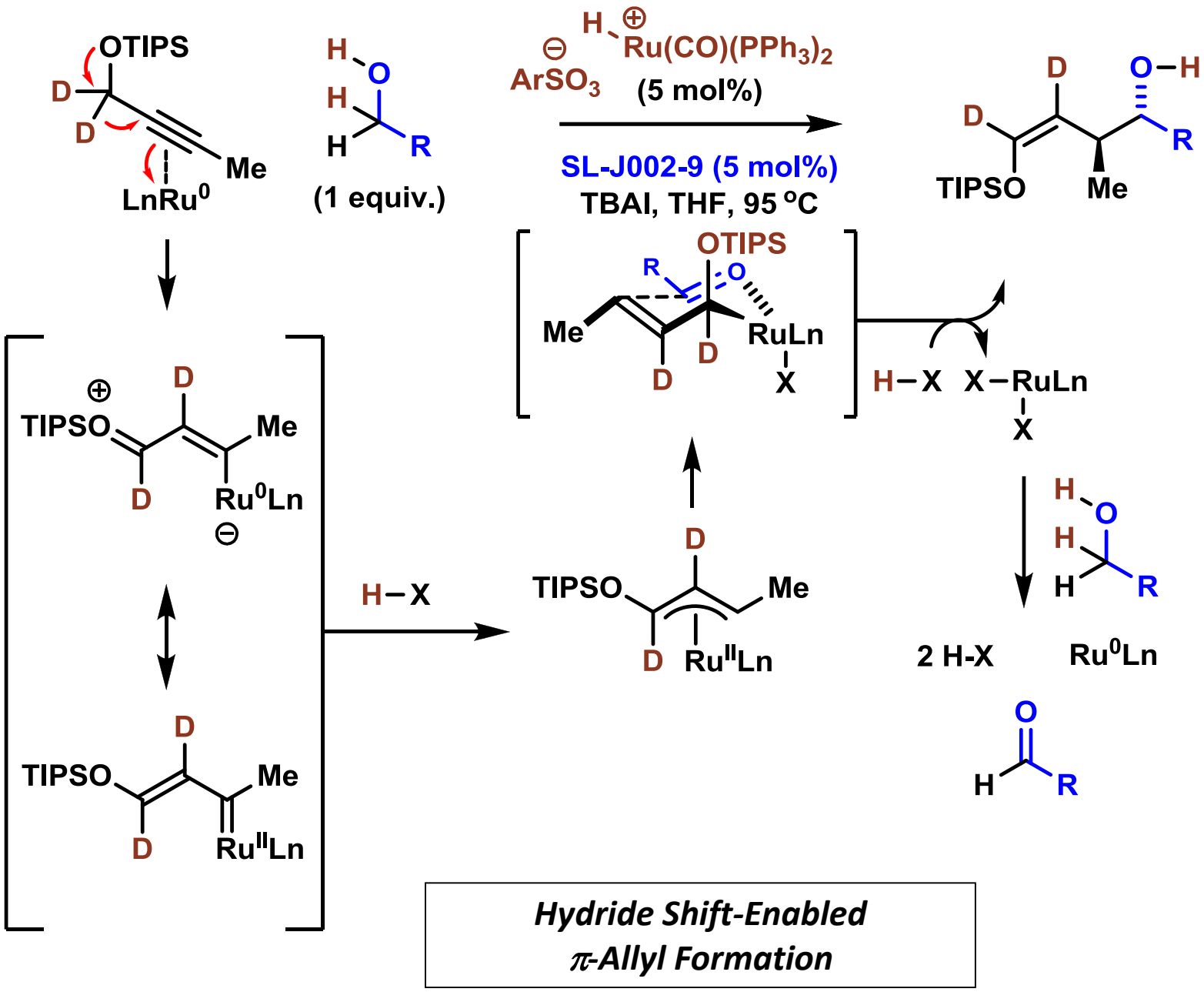
90% Yield, >20:1 dr

92% ee

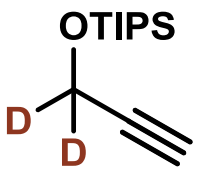
JACS 2015, 13066

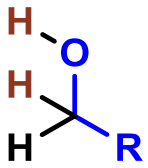


JACS 2015, 13066



Hydride Shift-Enabled π-Allyl Formation

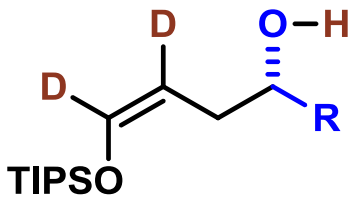


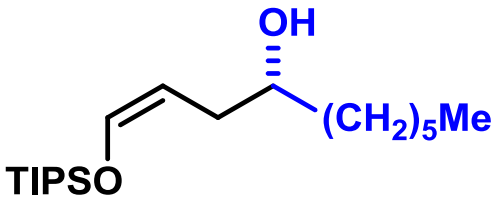


(1 equiv.)

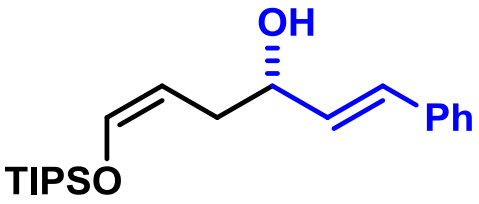
$[Ir(cod)Cl]_2$ (2.5 mol%)
(*R*)-H_8-BINAP (5 mol%)

Ph_3CCO_2H (5 mol%)
Bu_4NI (10 mol%)
PhMe (1 M), 95 °C

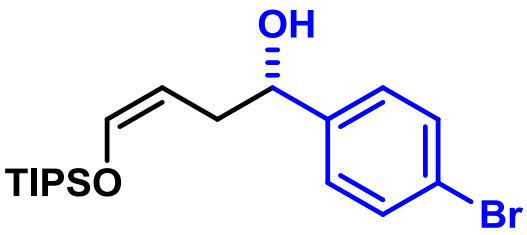




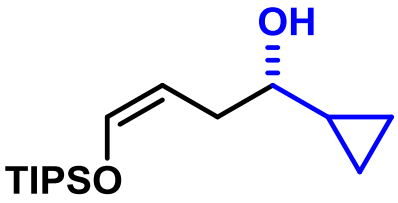
70% Yield, 90% ee
>20:1 (*Z*:*E*)



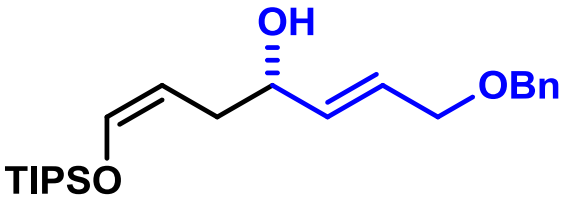
78% Yield, 94% ee
>20:1 (*Z*:*E*)



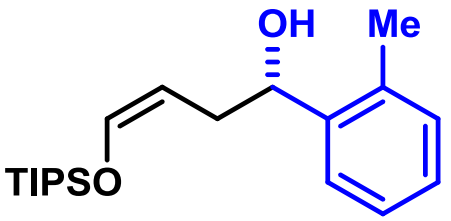
86% Yield, 91% ee
>20:1 (*Z*:*E*)



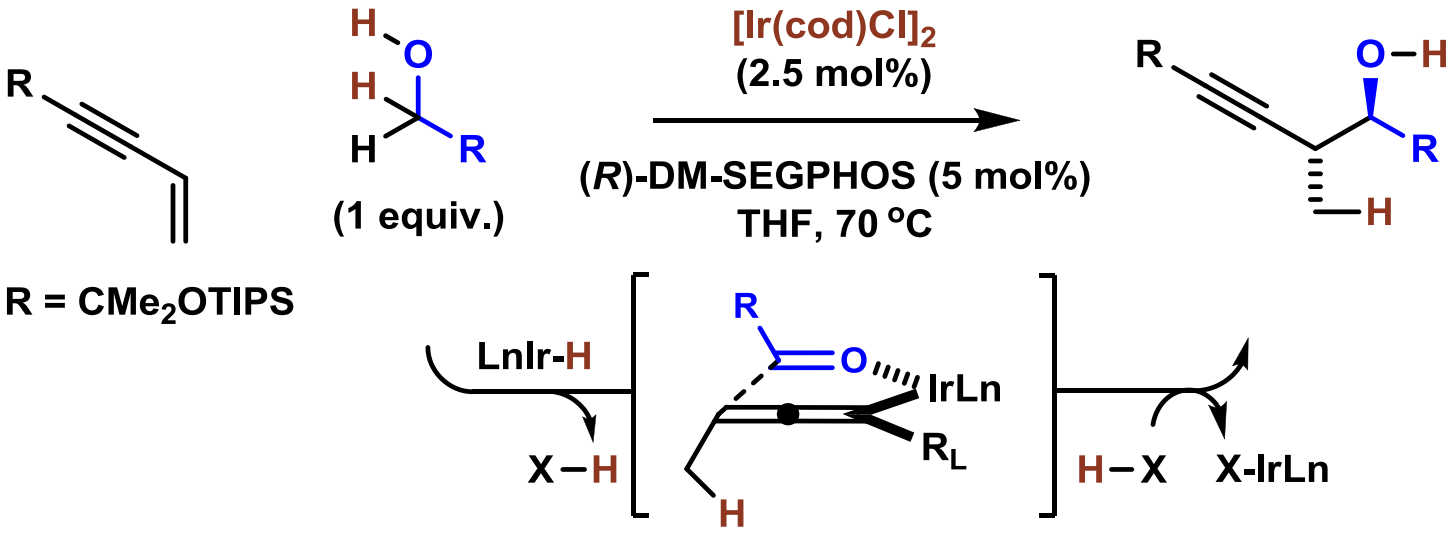
68% Yield, 95% ee
>20:1 (*Z*:*E*)

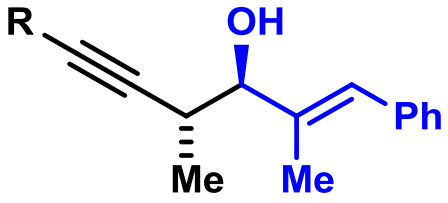


75% Yield, 92% ee
>20:1 (*Z*:*E*)

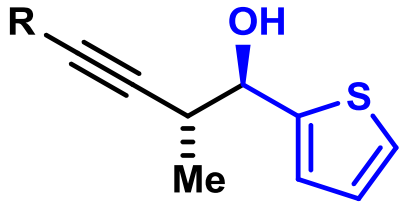


85% Yield, 95% ee
>20:1 (*Z*:*E*)

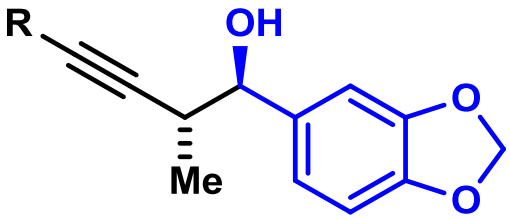




62% Yield, 32:1 dr
90% ee

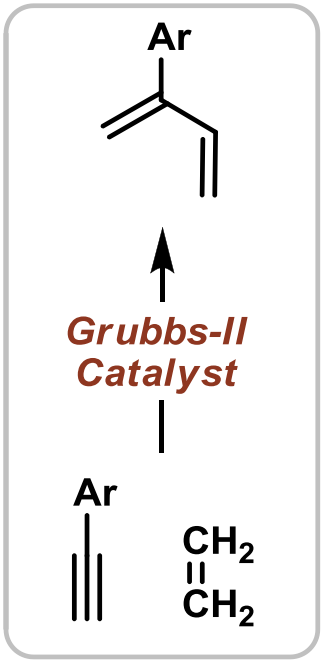


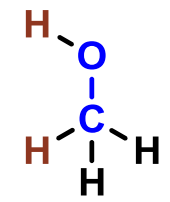
81% Yield, 29:1 dr
95% ee



77% Yield, 18:1 dr
92% ee

Angew. Chem. Int. Ed. 2012, 2972

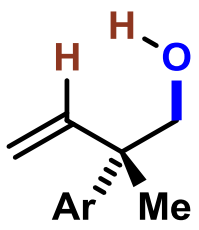


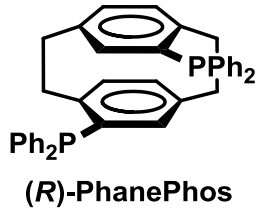


(Solvent)

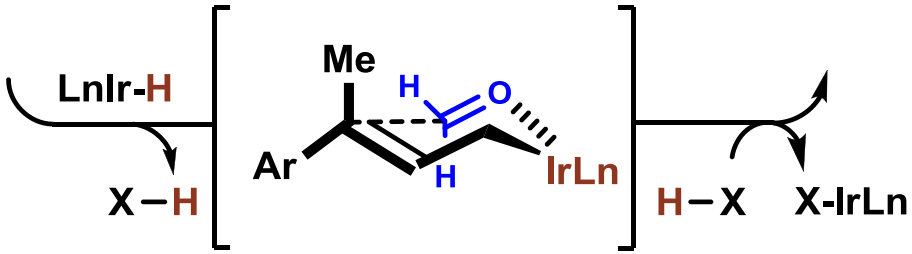
$[Ir(cod)Cl]_2$ (2.5 mol%)
(*R*)-Phanphos (5 mol%)

Acetone-MeOH
95 °C

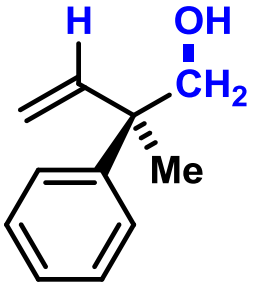




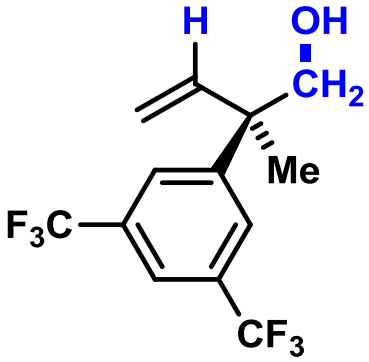
(*R*)-PhanePhos



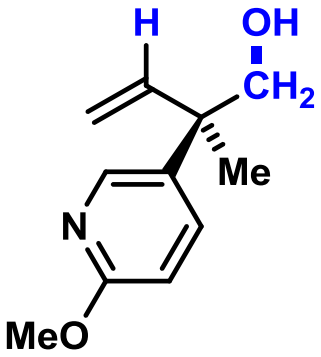
Methanol: 36 Million Tons (2014)



65% Yield
94% ee

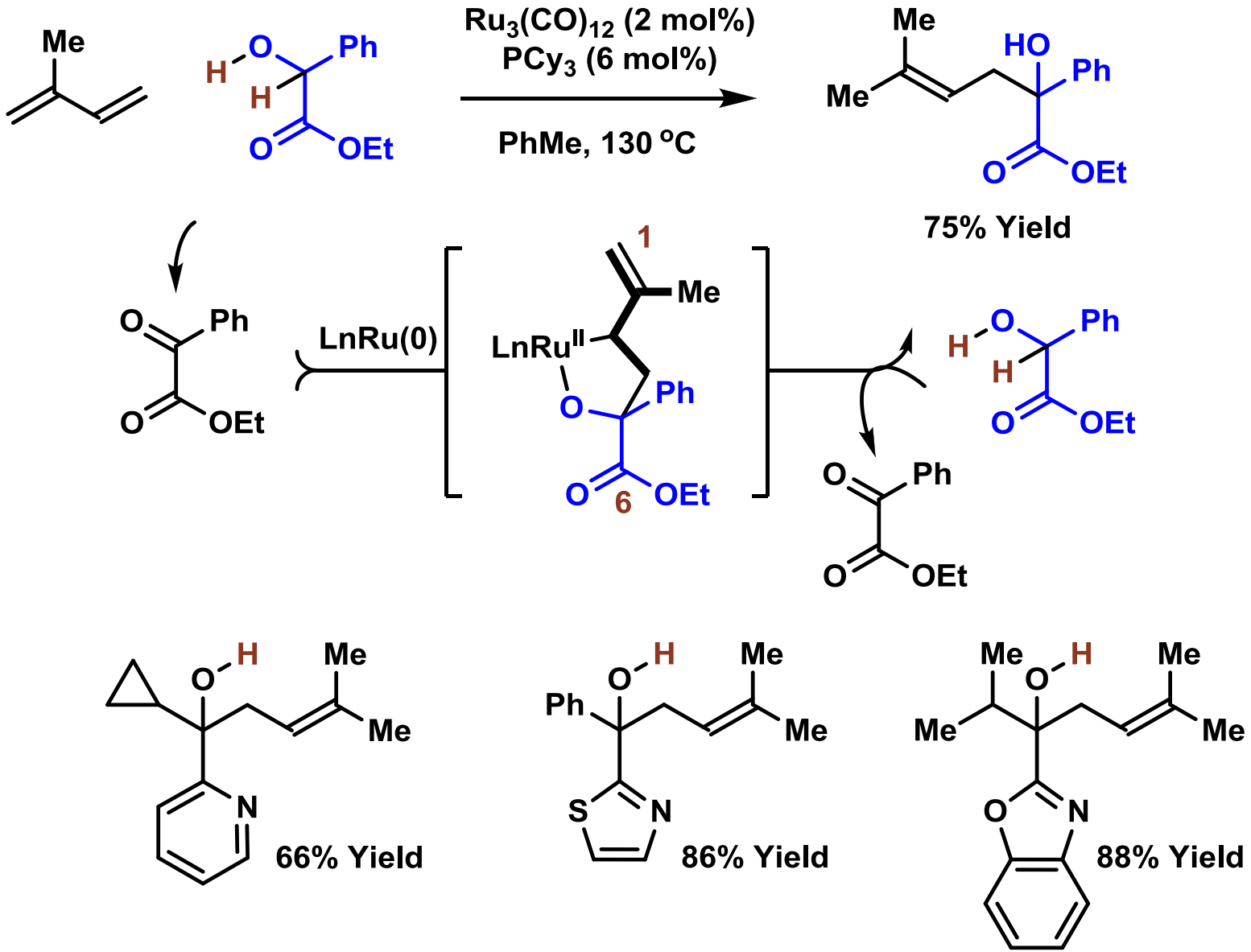


68% Yield
91% ee

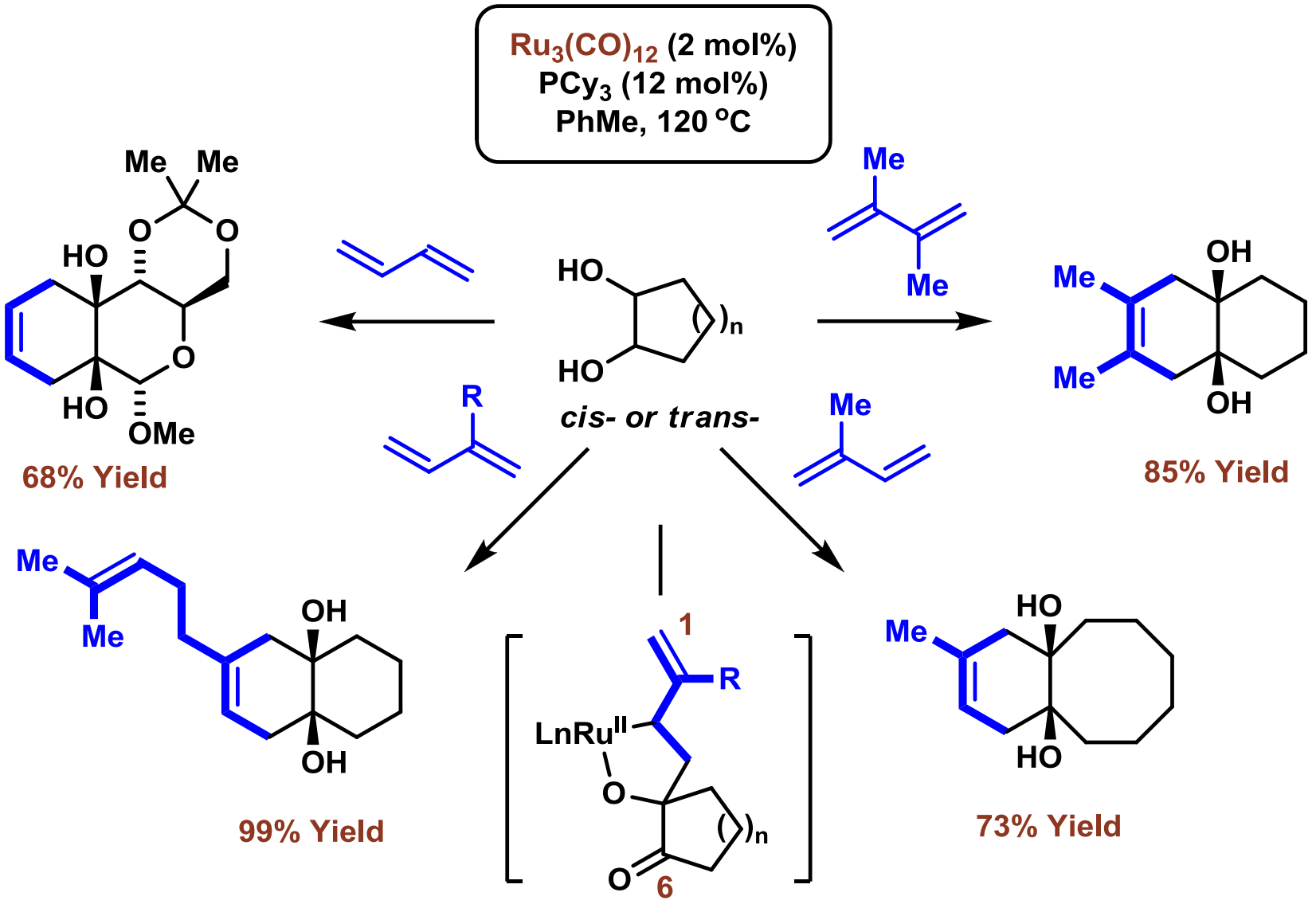


72% Yield
93% ee

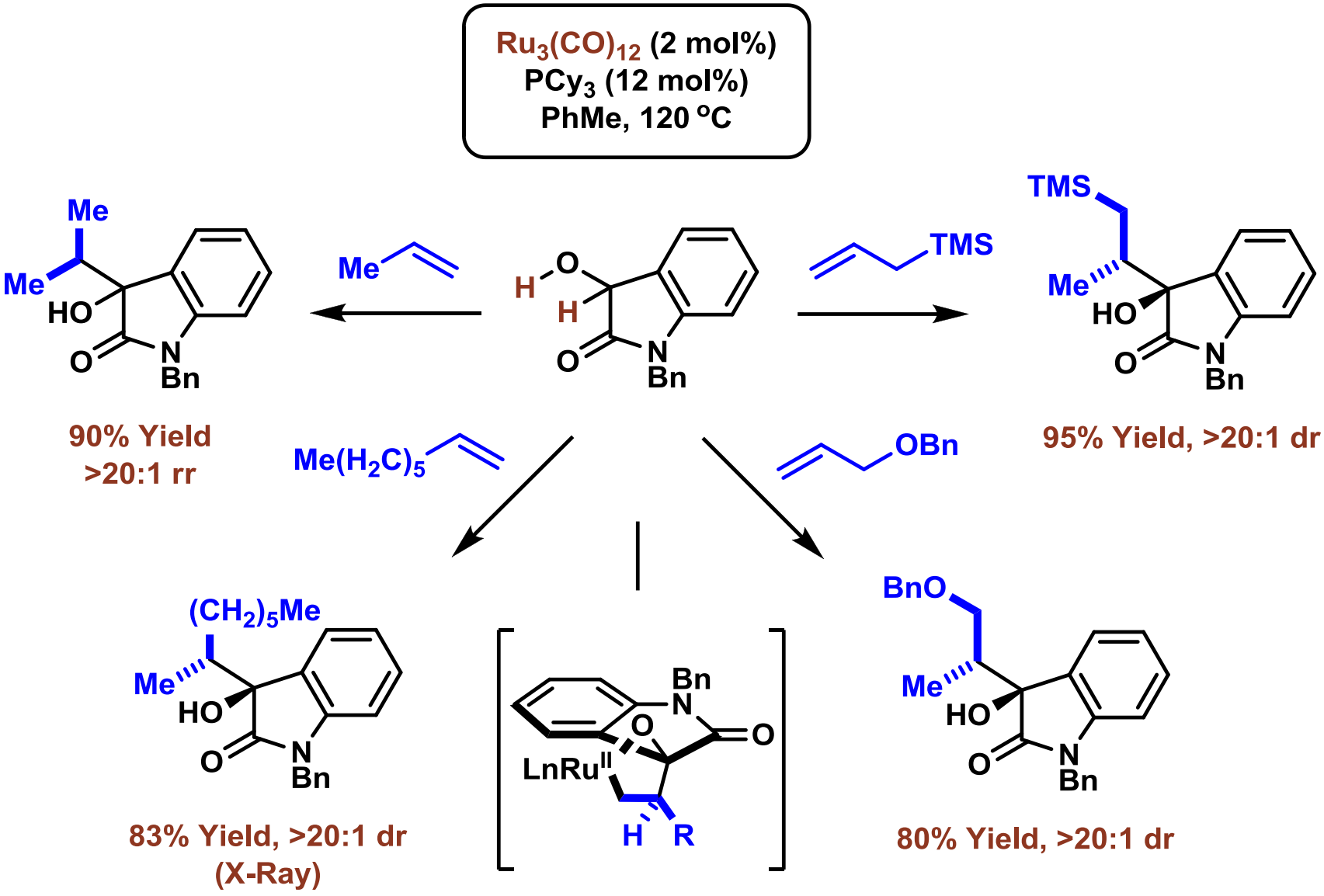
Nature Chem. 2011, 287; Submitted for Publication, 2016



JACS 2012, 15700; *JACS* 2013, 16320.

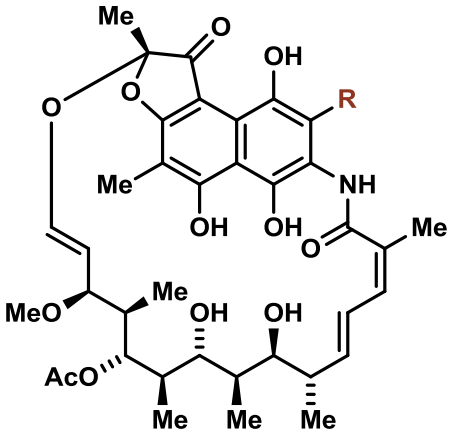


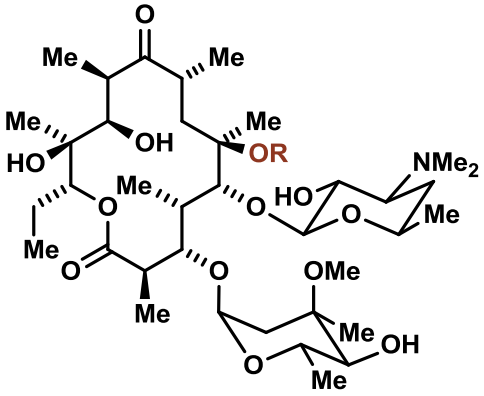
JACS 2012, 15700; *JACS* 2013, 16320; *ChemComm* 2014, 7545

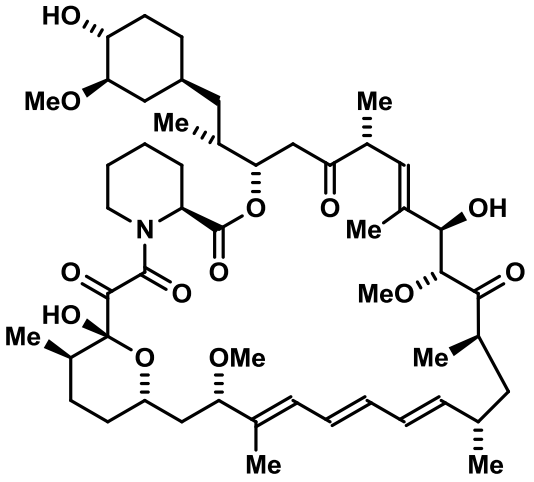


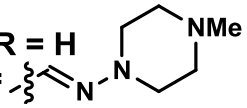
Angew. Chem. Int. Ed. 2013, 8428

Polyketide Natural Products: Commercial Medicines From Soil Bacteria (FDA Approved)







Rifamycin SV, R = H
Rifampicin, R = 

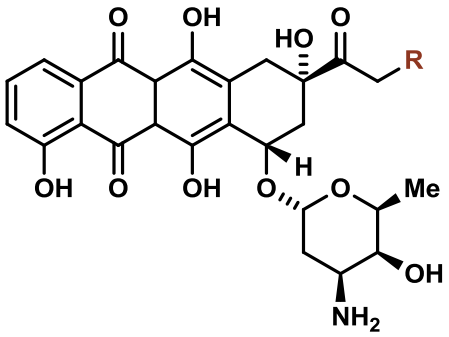
Tuberculosis and AIDS-Associated Mycobacterial Infections

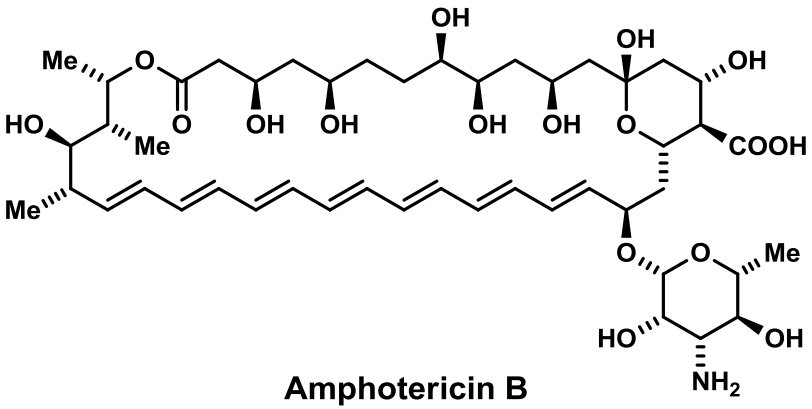
Erythromycin A, R = OH
Clarithromycin, R = OMe

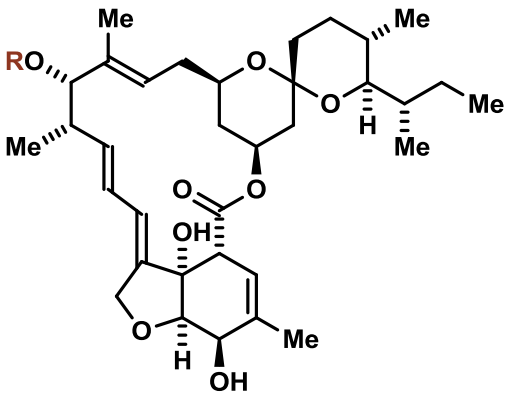
Bacterial Infection

Rapamycin (Sirolimus)

Immunosuppressant Used to Prevent Rejection in Organ Transplants







Daunorubicin, X = H
Doxorubicin, X = OH

Diverse Cancers

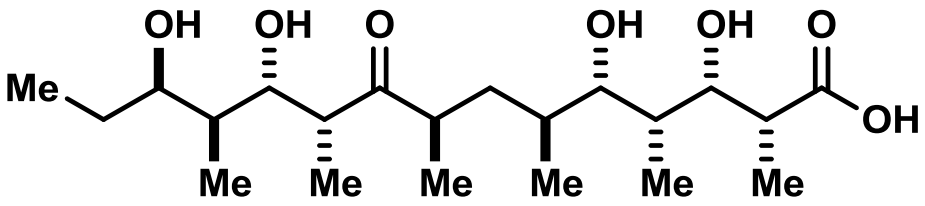
Amphotericin B

Fungal Infection

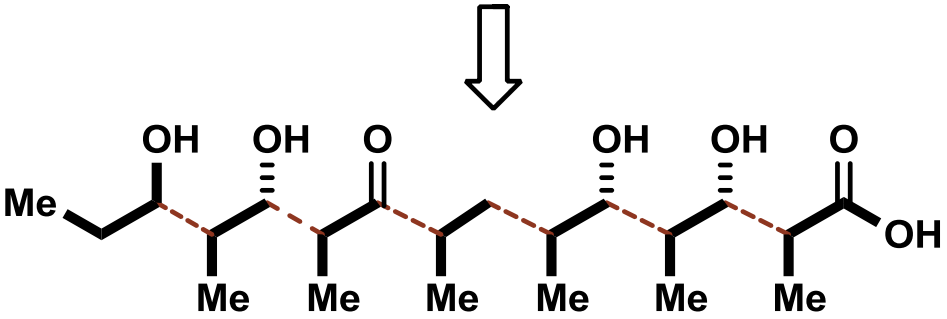
Ivermectin B_{1a}
R = Disaccharide

Antiparasitic

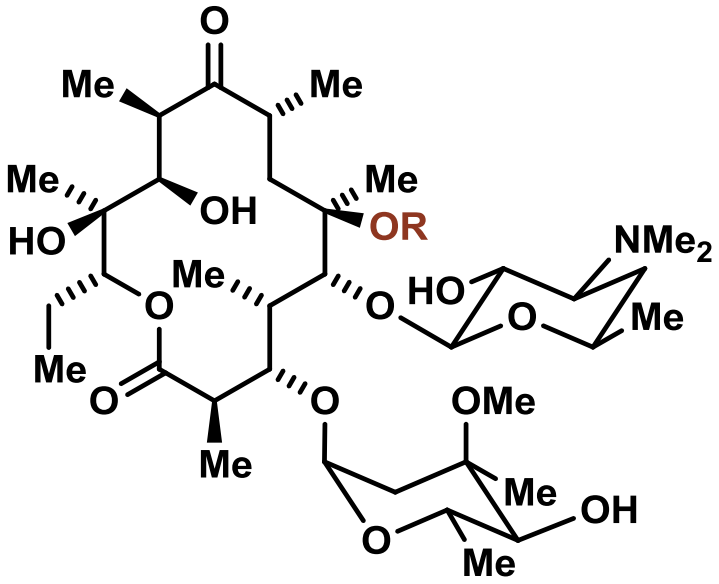
Polyketide Natural Products: Commercial Medicines From Soil Bacteria (FDA Approved)



Erythromycin A Seco Acid



7 Priopionate Subunits

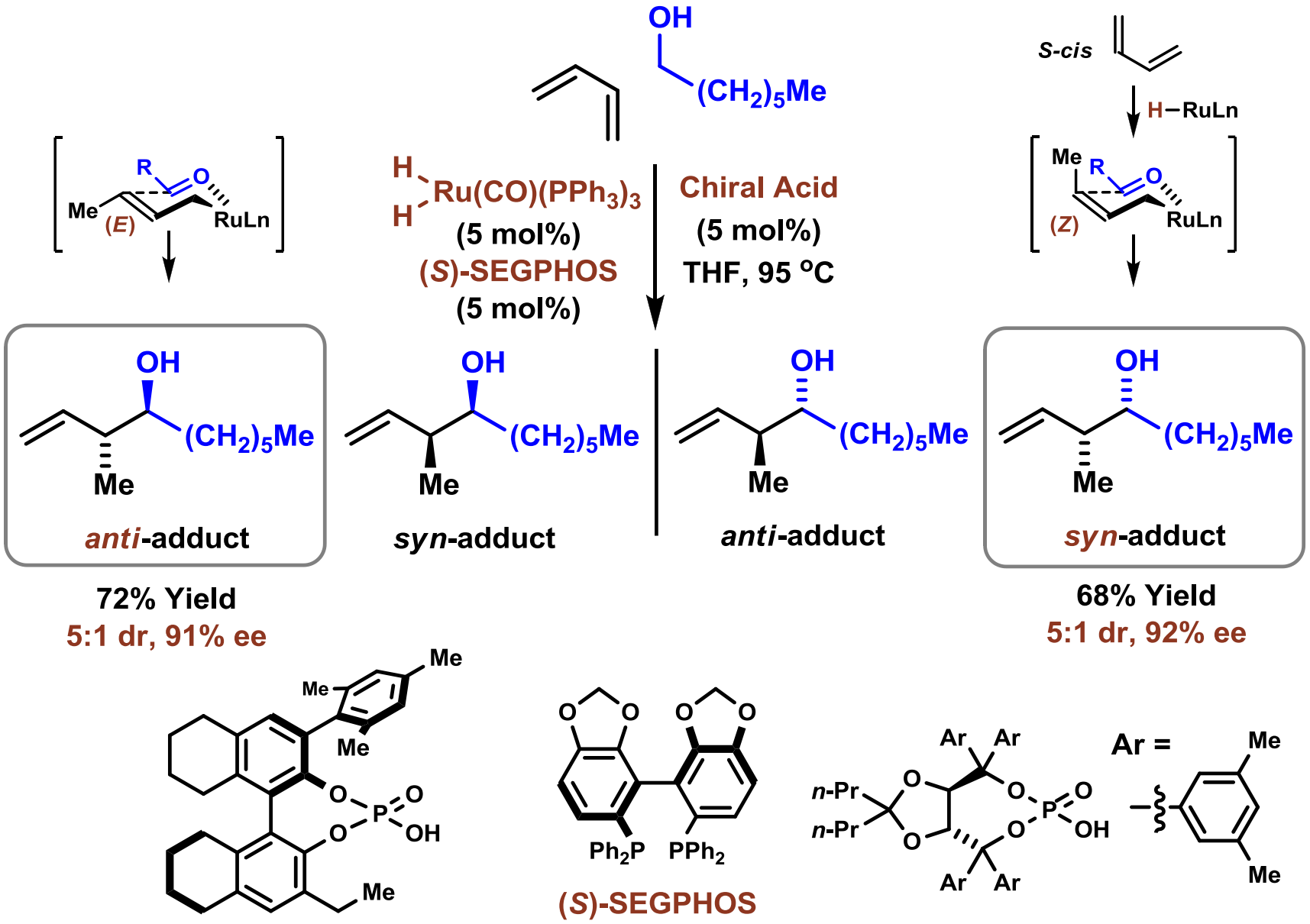


Erythromycin A, R = OH
Clarithromycin, R = OMe

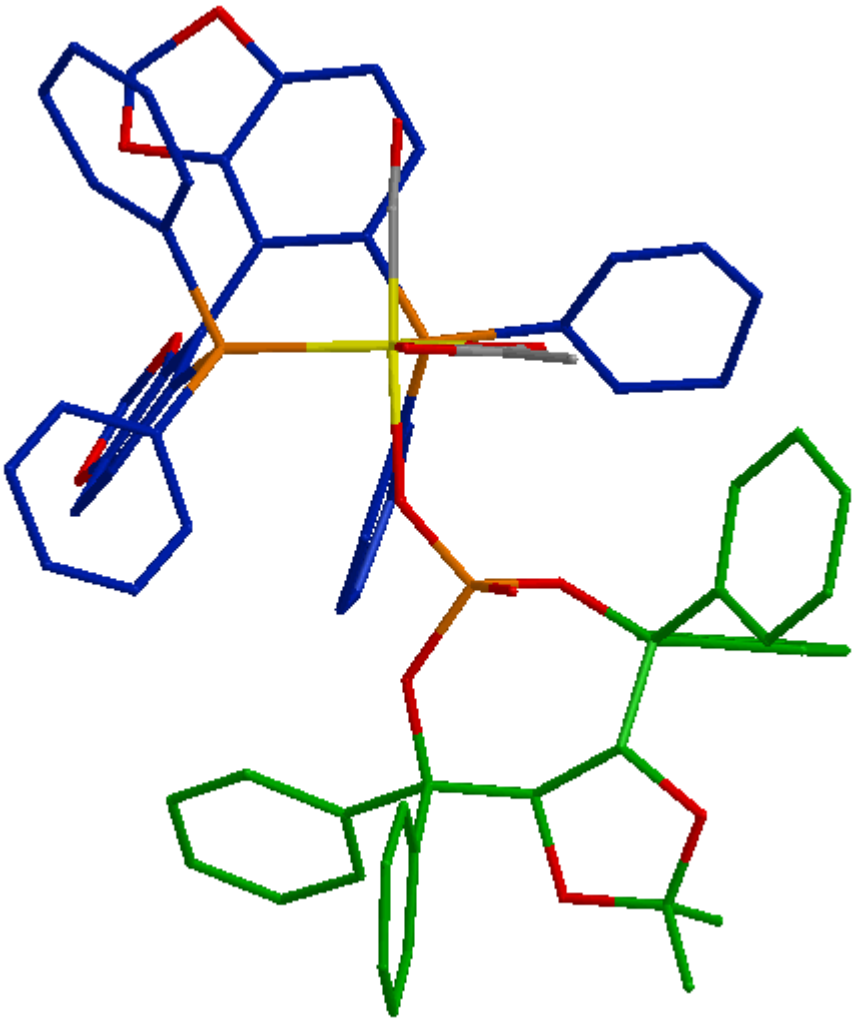
Bacterial Infection
Eli Lilly, 1952

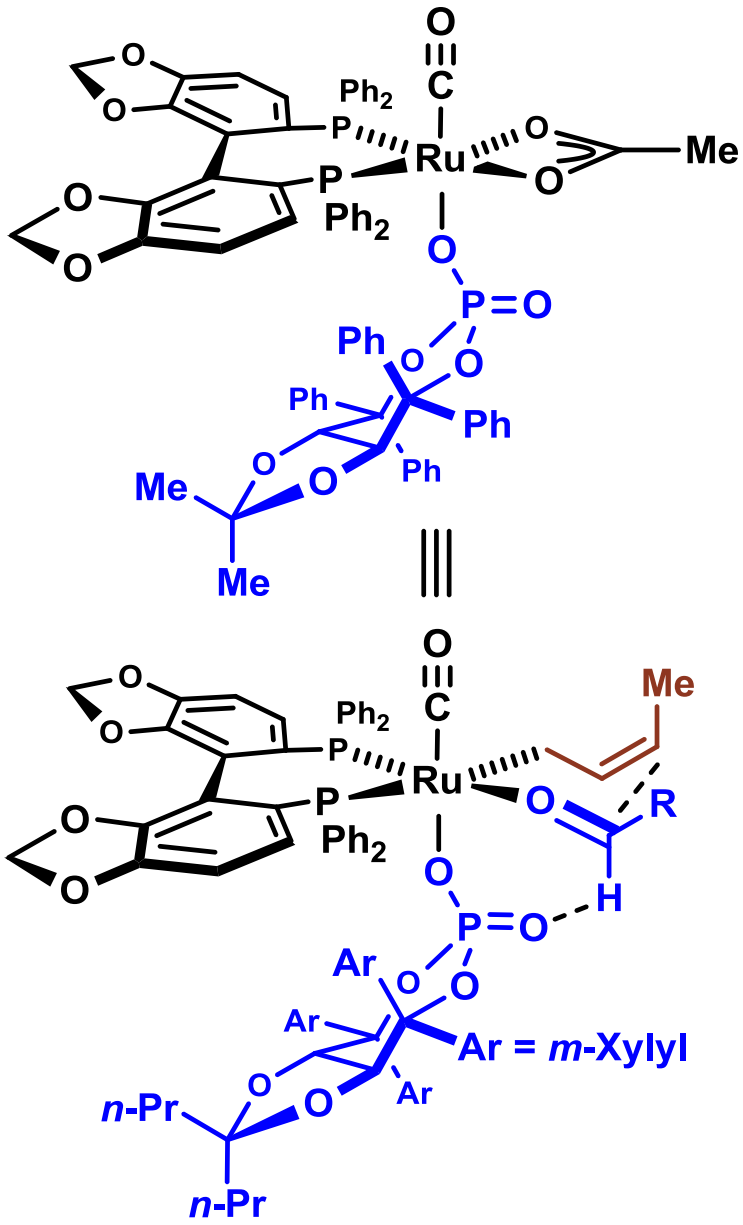
Review: *Nat. Prod. Rep.* 2014, *31*, 504

Science 2012, *336*, 324; *JACS* 2012, 20628; Computation - Houk *JACS* 2015, 8838.

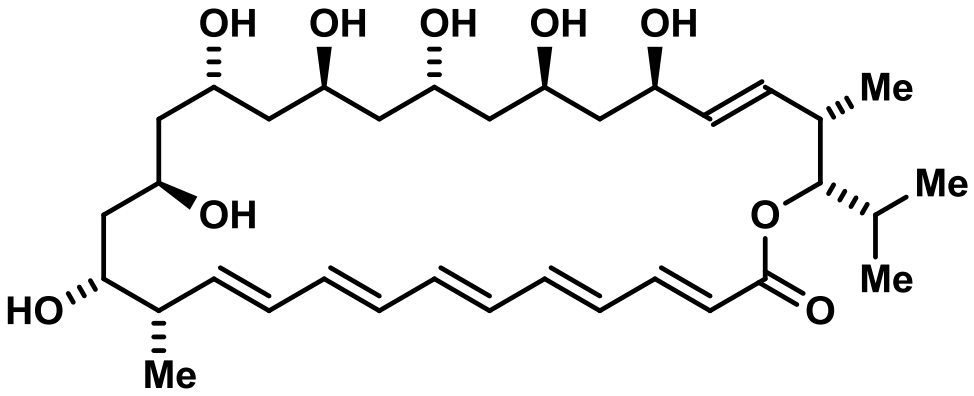


X-Ray Crystal Structure





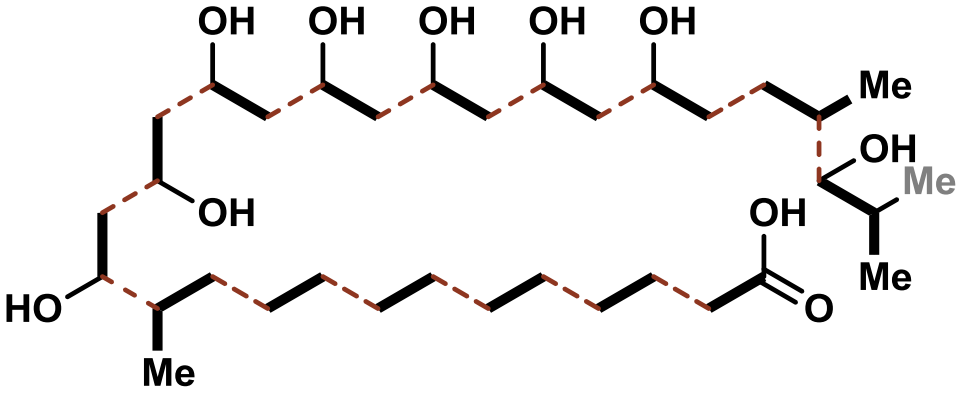
Science 2012, *336*, 324; *JACS* 2012, 20628; Computation - Houk *JACS* 2015, 8838.



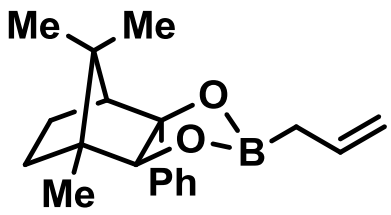
Roxaticin - An Oxopolyene Macrolide

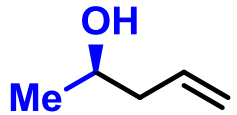
12 Acetate Subunits

3 Priopionate Subunits



Hoffmann *Angew. Chem.* 1978, 822

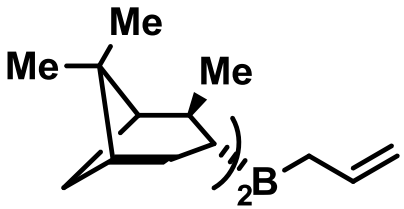


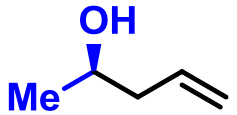


86% Yield

86% ee

Brown *JACS* 1983, 2092

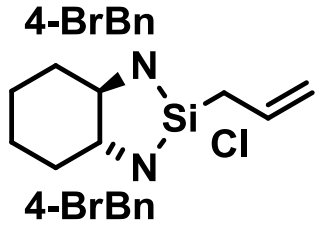


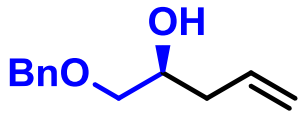


74% Yield

93% ee

Leighton *Org. Lett.* 2004, 4375





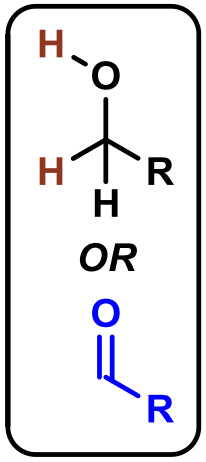
82% Yield

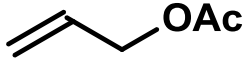
96% ee

<u>Henry Ford</u>: "If I'd asked people what they wanted, they would've said a faster horse."

JACS 2008, 6340

JACS 2008, 14891





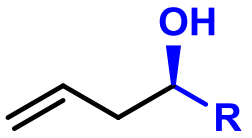
$[Ir(cod)Cl]_2$ (2.5 mol%)

(*R*)-Cl,MeO-BIPHEP (5 mol%)

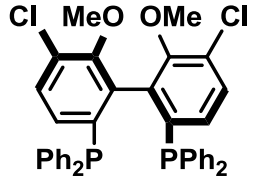
Cs_2CO_3 (20 mol%)

m-NO_2BzOH (10 mol%)

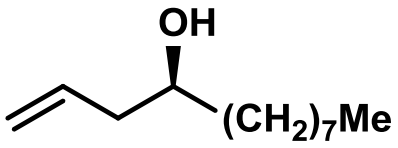
THF, 100 °C

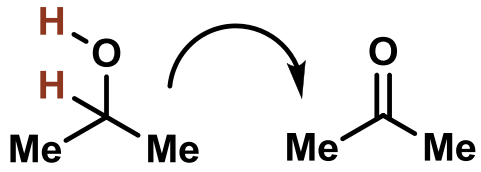


(HOAc)

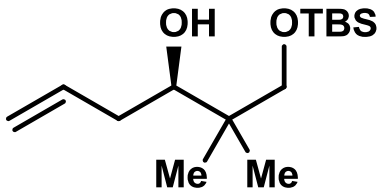


(*R*)-Cl,MeO-BIPHEP



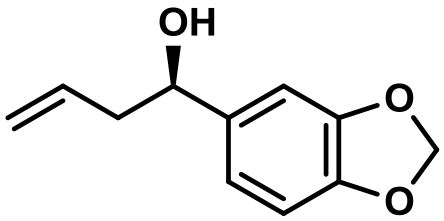


(for RCHO couplings)



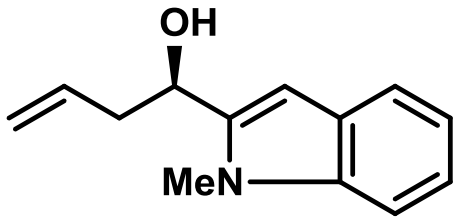
78% Yield, 95% ee — *alcohol* — 80% Yield, 93% ee

77% Yield, 97% ee — *aldehyde* — 81% Yield, 94% ee



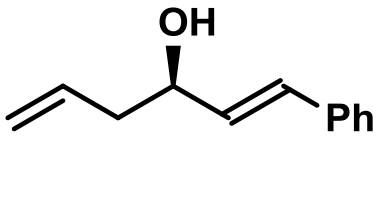
76% Yield, 91% ee

81% Yield, 93% ee



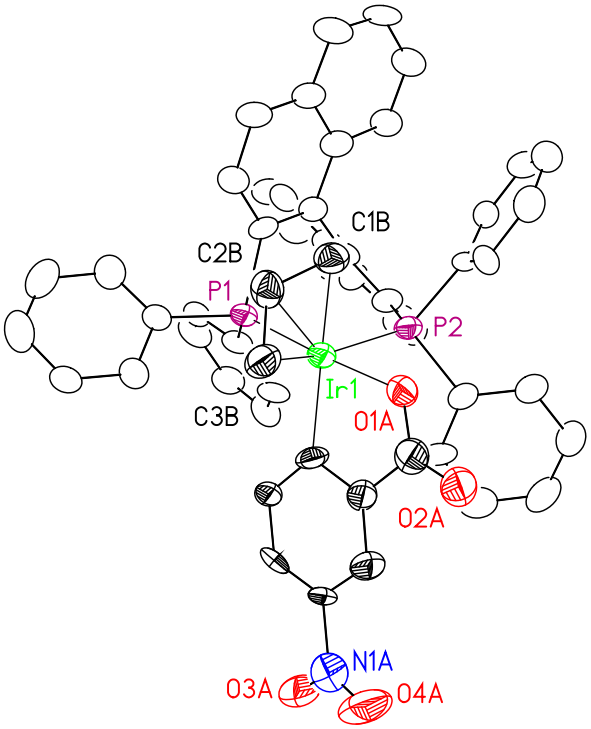
85% Yield, 90% ee

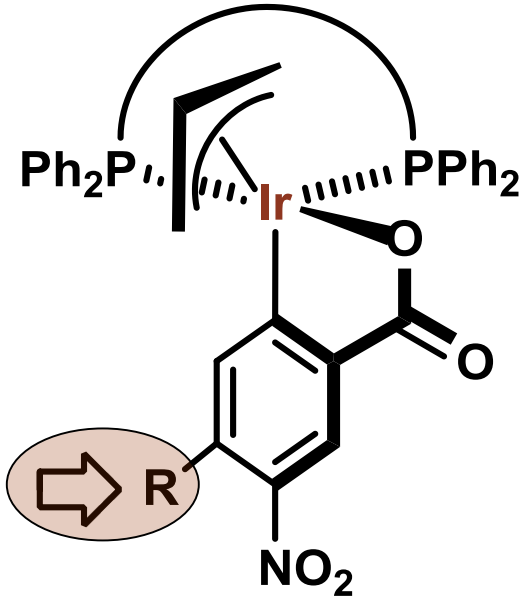
89% Yield, 94% ee



72% Yield, 91% ee

73% Yield, 94% ee

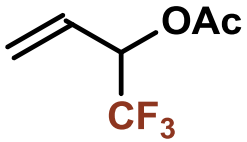


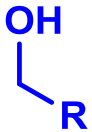


JACS 2008, 6340
JACS 2008, 14891

SiO_2 Column Purified

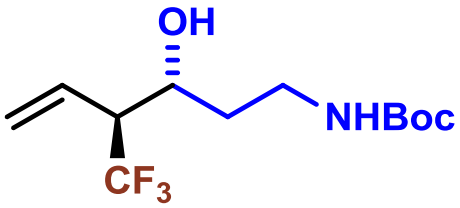
ACIE 2011, 4173





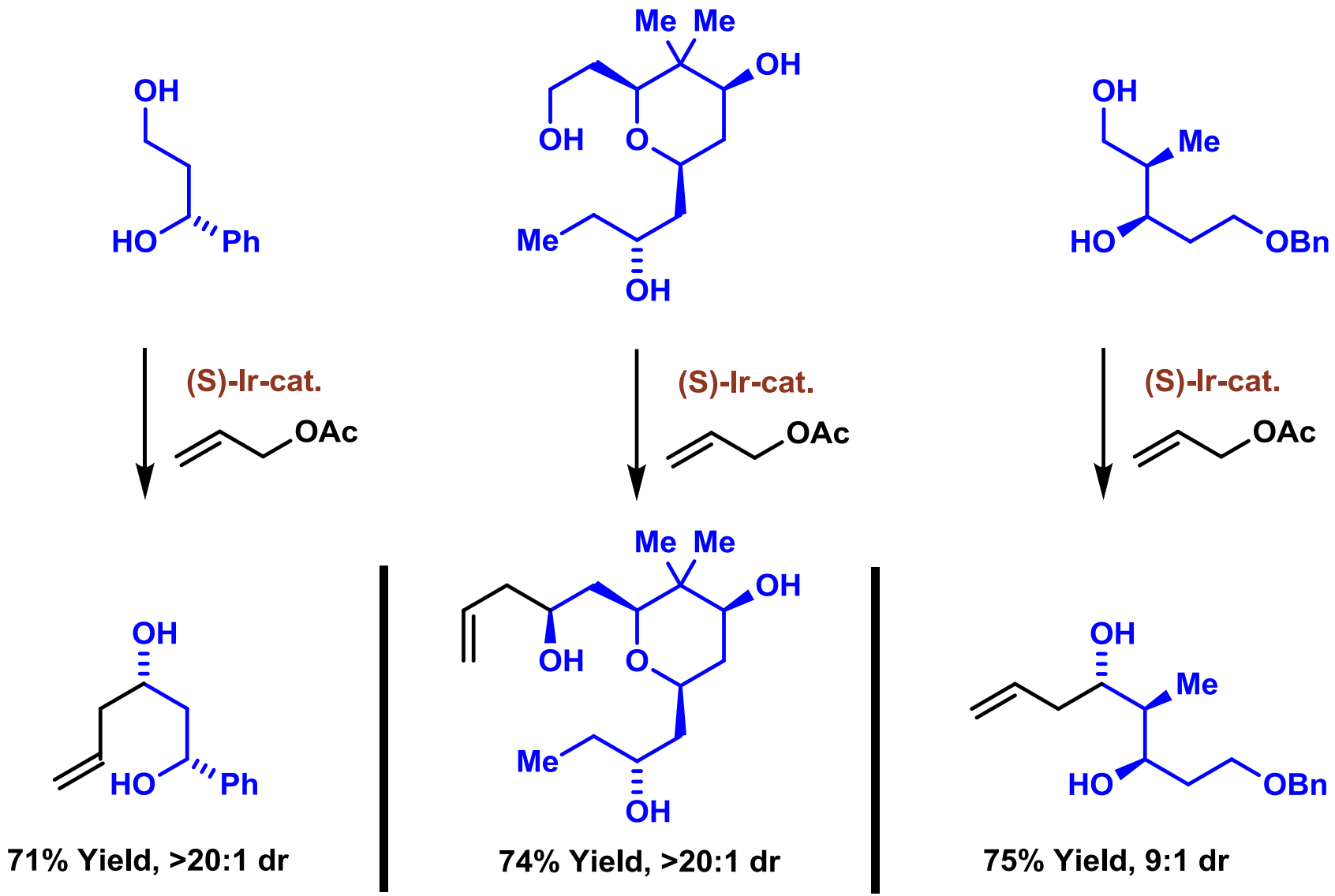
Preformed Ir-Catalyst
(5 mol%)

K_3PO_4 (50 mol%)
THF-H_2O, 60 °C

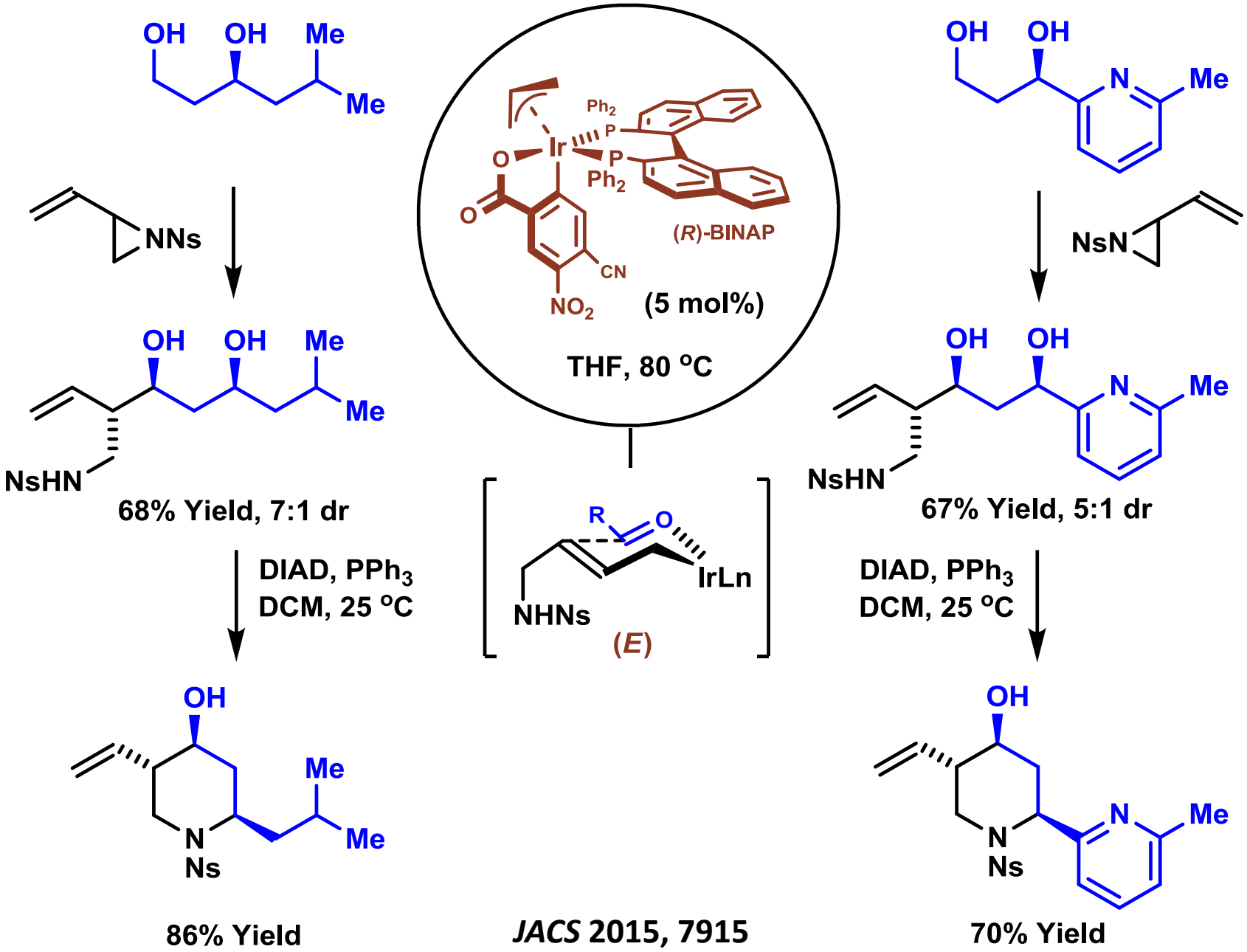


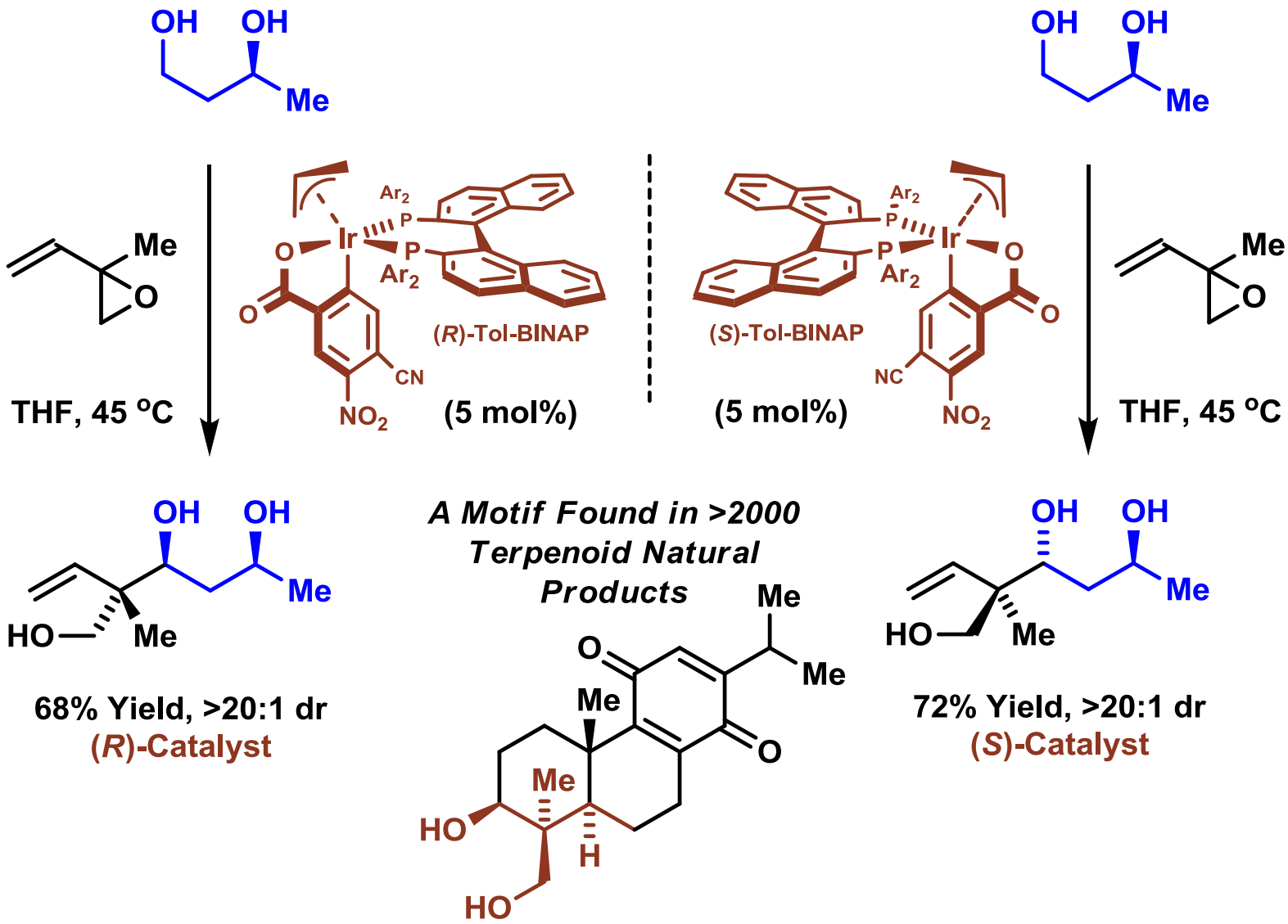
73% Yield
96% ee, > 20:1 dr

L = SEGPHOS, R = CN



Angew. Chem. Int. Ed. 2013, 3195; *Chem. Eur. J.* 2014, 13382.


OH
OH
Me
Me
NNs
OH
OH
Me
Me
NsHN
68% Yield, 7:1 dr
DIAD, PPh3
DCM, 25 °C
OH
Me
N
Ns
Me
86% Yield
Ph2
P
Ir
O
P
Ph2
O
(R)-BINAP
CN
NO2
(5 mol%)
THF, 80 °C
R
O
IrLn
NHNs
(E)
OH
OH
N
Me
NsN
OH
OH
N
Me
NsHN
67% Yield, 5:1 dr
DIAD, PPh3
DCM, 25 °C
OH
N
Me
N
Ns
70% Yield
JACS 2015, 7915

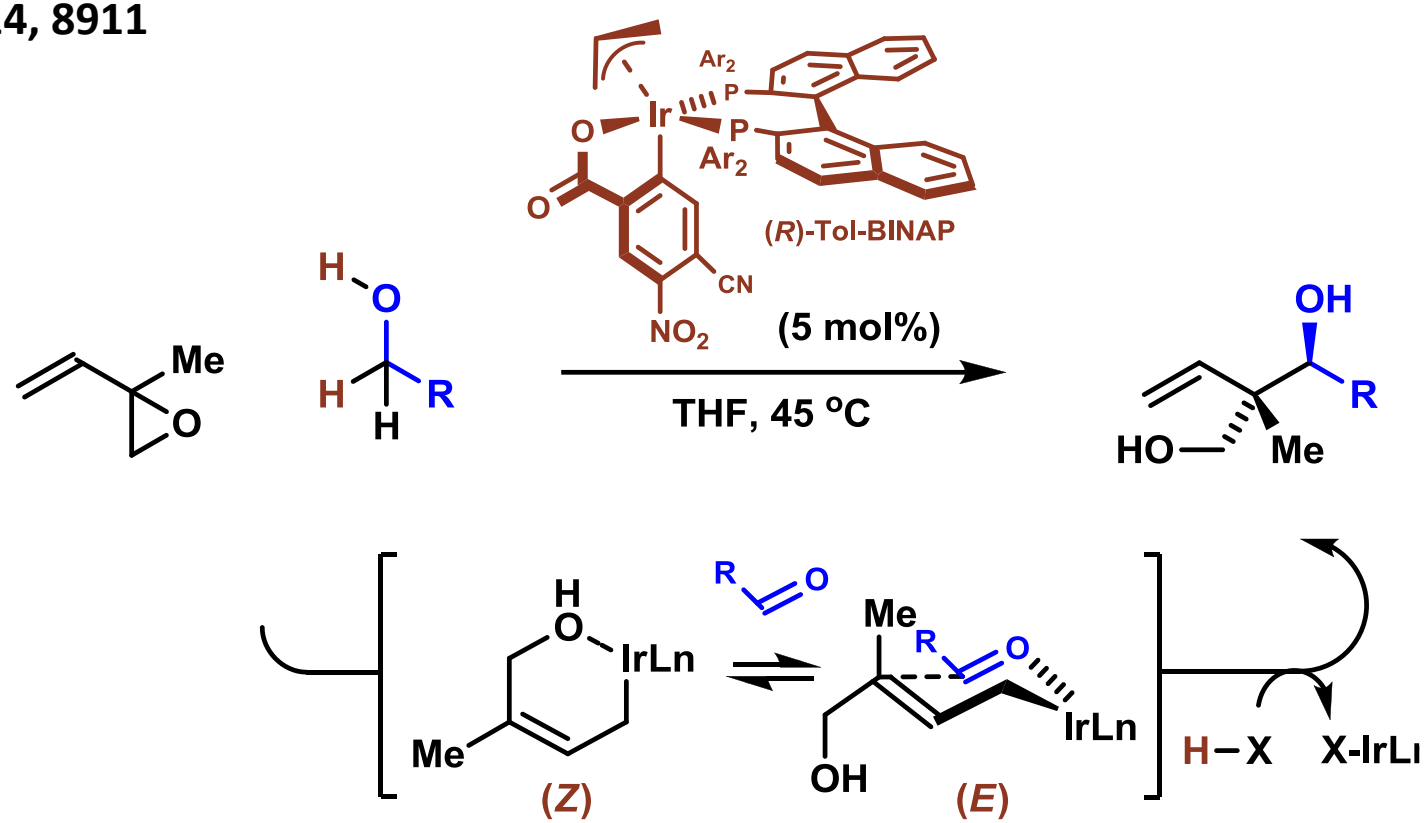


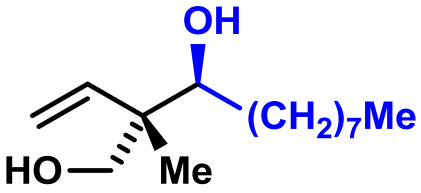
A Motif Found in >2000 Terpenoid Natural Products

Triptoquinone C
Previously 15-18 Steps
Now 7 Steps

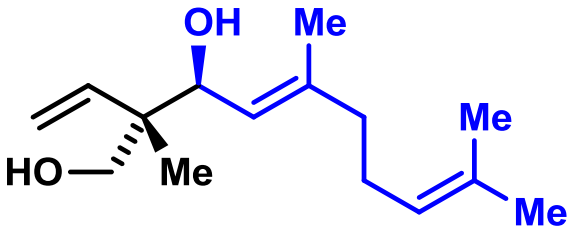
JACS* 2014, 8911; JACS 2016, *In Press

JACS 2014, 8911

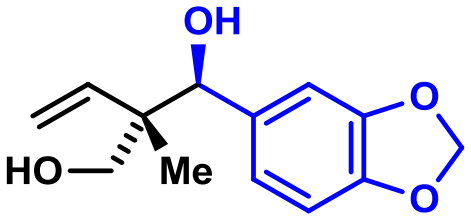




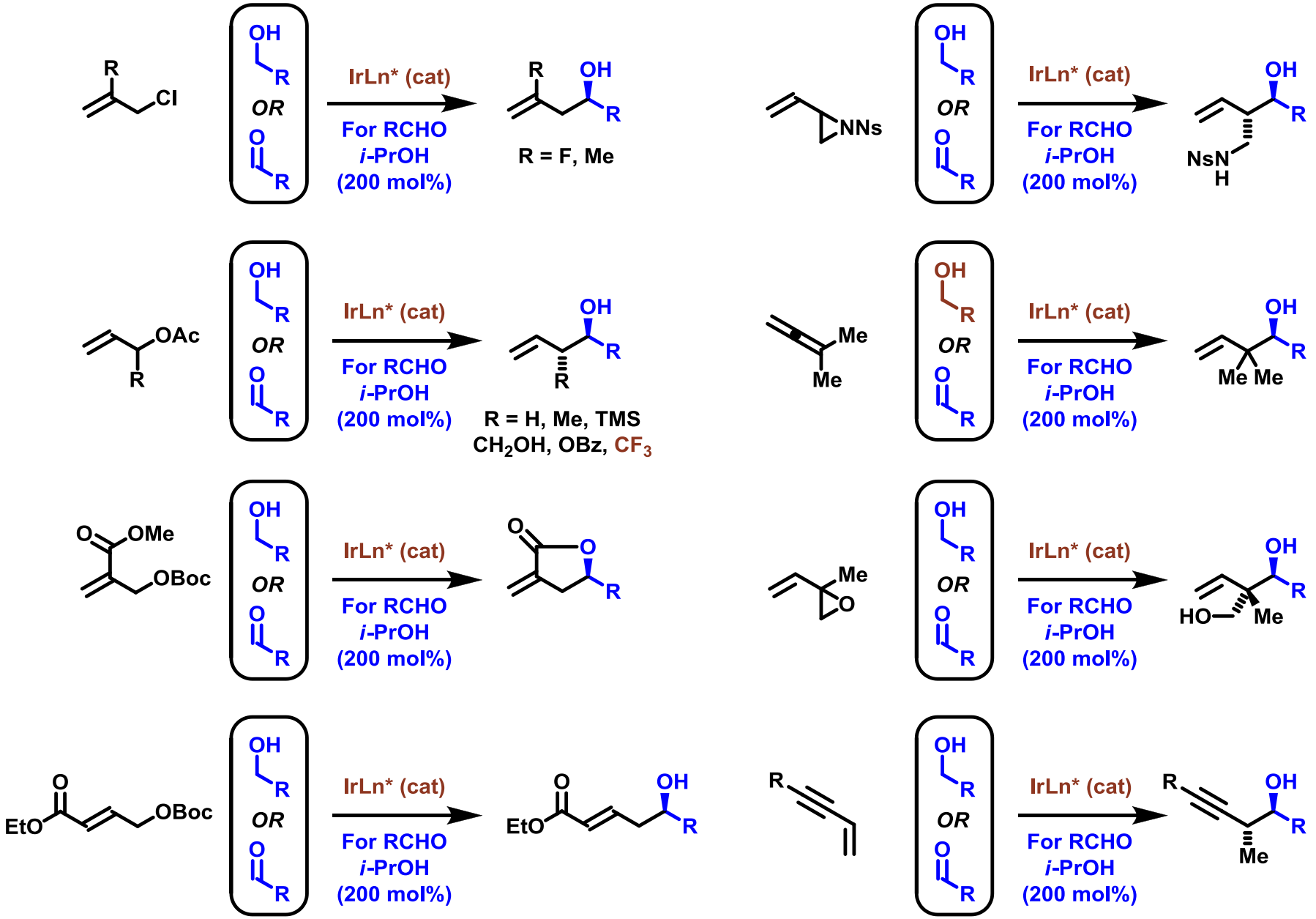
74% Yield, 40:1 dr
93% ee



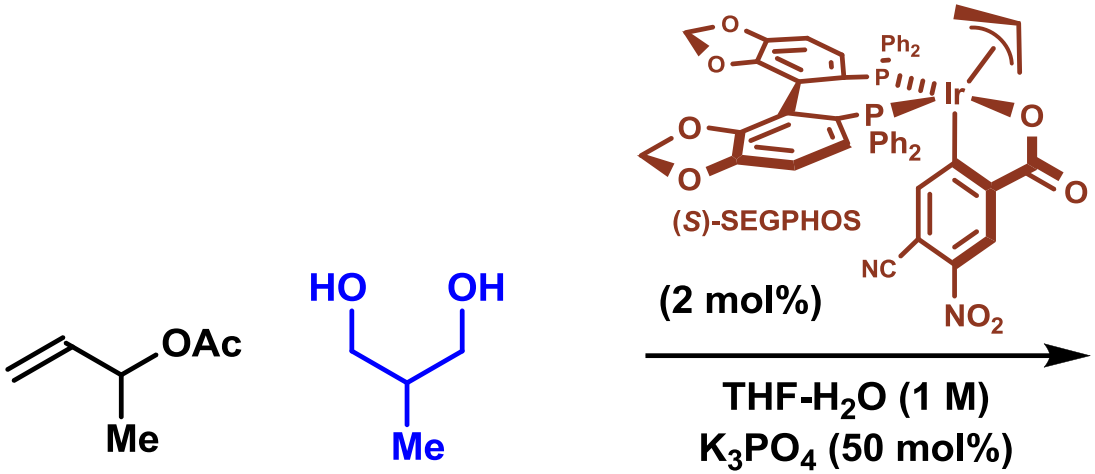
73% Yield, 30:1 dr
91% ee



89% Yield, 60:1 dr
94% ee

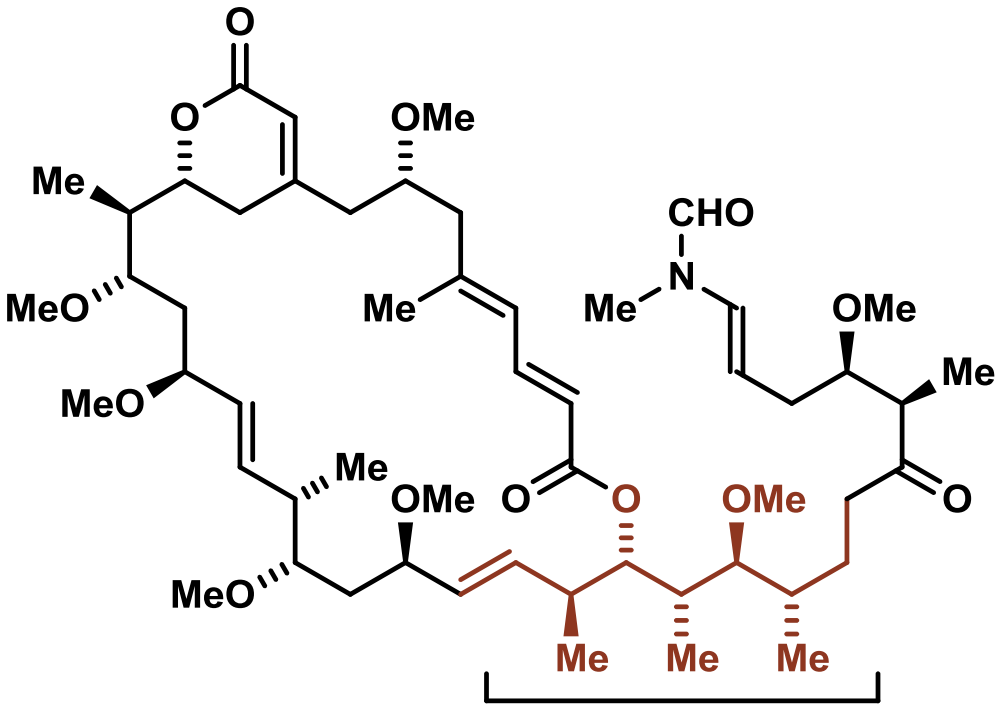

IrLn* (cat)
For RCHO
i-PrOH
(200 mol%)
R = F, Me
R = H, Me, TMS
CH2OH, OBz, CF3
Review: Angew. Chem. Int. Ed. 2014, 9142

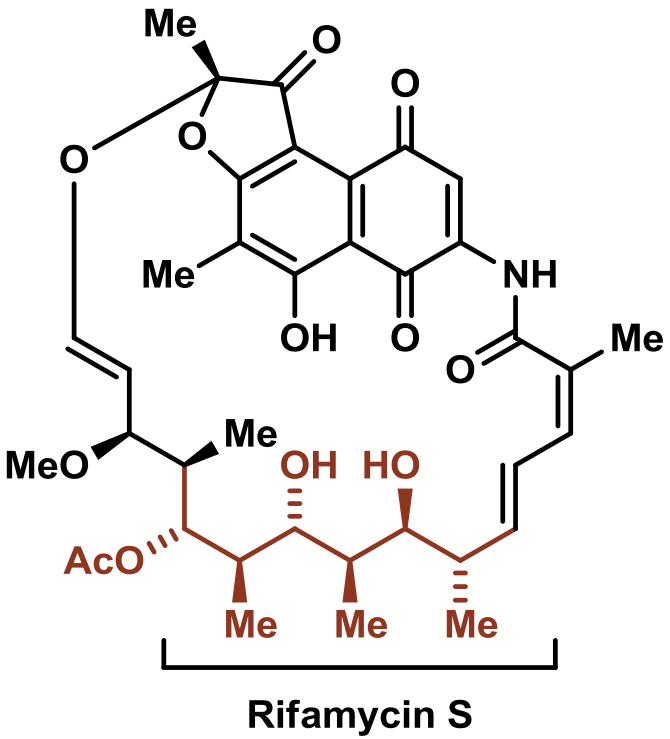
JACS 2011, 12795



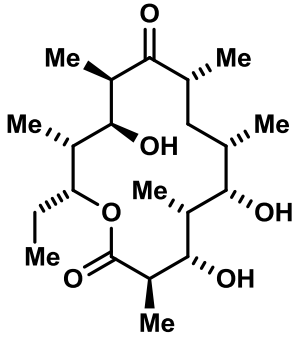
62% Yield, 6:1 dr

99% ee



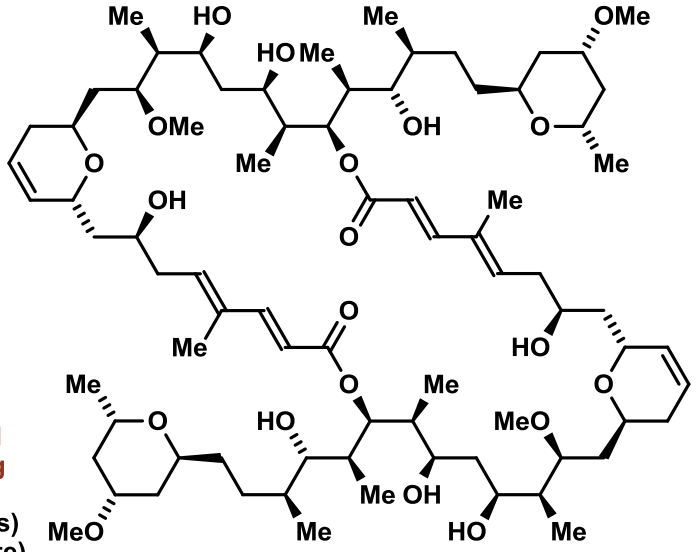


Review: *Nat. Prod. Rep.* 2014, 504; **Perspective**: *J. Am. Chem. Soc.* 2016, 5467.



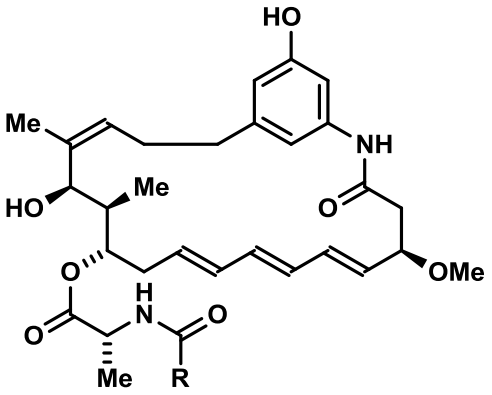
6-DEOXYERYTHRONOLIDE B
14 Steps (LLS), 3 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

26 Steps (Masamune), 23 Steps (Evans)
42 Steps (Danishefsky), 23 Steps (White)



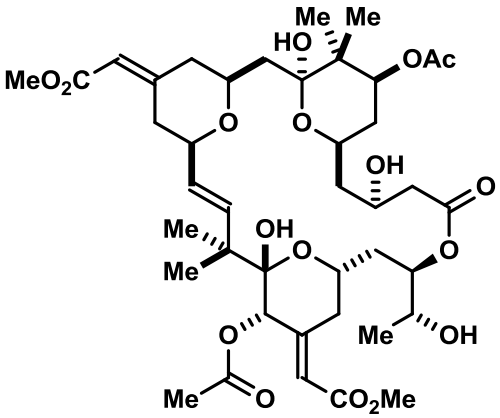
SWINHOLIDE A
15 Steps (LLS), 10 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

27 Steps (Paterson), 35 Steps (Nicolaou)



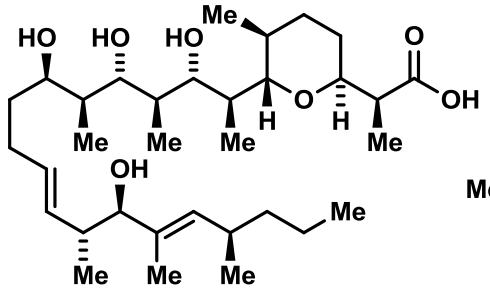
TRIENOMYCINS A and F
16 Steps (LLS), 3 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

30 Steps (Smith)



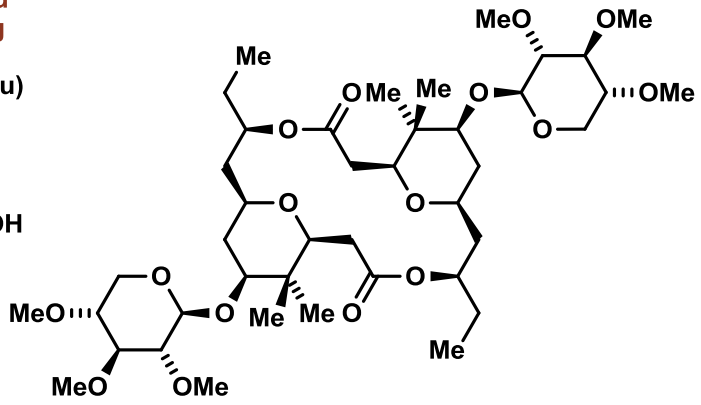
BRYOSTATIN 7
20 Steps (LLS), 5 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

41 Steps (Masamune), 43 Steps (Yamamura)
42 Steps (Evans), 31 Steps (Keck)
28 Steps (Trost), 25 Steps (Wender)



(+)-ZINCOPHORIN
13 Steps (LLS), 4 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

22 Steps (Leighton), 28 Steps (Cossy)
38 Steps (Miyashita), 35 Steps (Danishefsky)
49 Steps (Guindon)



CYANOLIDE A
6 Steps (LLS), 4 C-C Bonds Formed
via Hydrogen Mediated C-C Coupling

14 Steps (Hong), 17 Steps (Reddy)
14 Steps (She), 17 Steps (Pabbaraja)
12 Steps (Rychnovsky), 15 Steps (Jennings)