Multifaceted Cobalt: Mechanistic paradigms

OUTLINE

1. **Introduction**
2. **Co-catalyzed cross-coupling reactions**
3. **Co-mediated/catalyzed transformations of epoxides, alkyl and acyl halides**
4. **Reductive Coupling**
5. **Cobalt-carbene radical transformations**
6. **Cycloisomerization reactions**
7. **Cyclotrimerization reactions**
8. **C—H activation**
9. **Hydroacylation**
10. **Oxidation reactions**
11. **Hydride transfer reactions**

NOT INCLUDED

1. **HAT (see Mr. Bingham GM, 2018)**
2. **Pauson-Khand (see Mr. Bingham GM, 2017)**
3. **Nicholas reaction**
4. **Heterogeneous catalysis**
5. **Chemistry of vitamin B_{12}**

REFERENCES

"3d Transition Metals for C–H Activation" Ackermann, *Chem. Rev.* **2019,** 2192
"Hydride Transfer Reactions Catalyzed by Cobalt Complexes", Liu, *Chem. Rev*. **2019**, 2876
"Cobalt-Catalyzed Cross-Coupling Reactions", Cahiez, *Chem. Rev*. **2010**, 1435
"Cobalt-Mediated [2 + 2 + 2] Cycloaddition", Gandon in "Transition-Metal-Mediated Aromatic Ring Construction" John Wiley & Sons, Ltd
"Enantioselective Cobalt-Catalyzed Transformations", Pellissier, *Chem. Rev*. **2014**, 2775
"Methods Utilizing First-Row Transition Metals in Natural Product Total Synthesis" Newhouse, *Chem. Rev*. **2017**, 11680

Kobold

(German) goblin, evil spirit

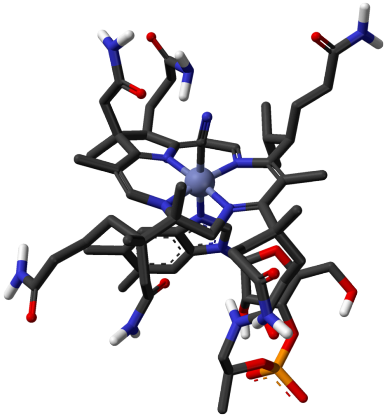
Cobalt have been used as blue dye for > 4000 years
As an element discovered in 1735

Carrolite
$CuCo_2S_4$

Erythrite
$Co_3(AsO_4)_2{\bullet}8H_2O$

Cobalt blue
$CoAl_2O_4$

Oxiadtion states: (–1) – (+3)
The most stable: +2, +3
$Co_3^+ + e^- \rightarrow Co_2^+$ E = +1.82 eV – strong oxidant



Cobalt is essential trace metal (only 2–5 mg of B_{12})

The only naturally occuring organometalic compound

Co-enzyme of isomerases, methyltransferases, dehalogenases

Dorothy Hodgkin (Nobel Prize 1964) – pioneer in protein crystallography elucidated structure of vitamin B_{12} as well as insulin and penicillin by X-Ray.

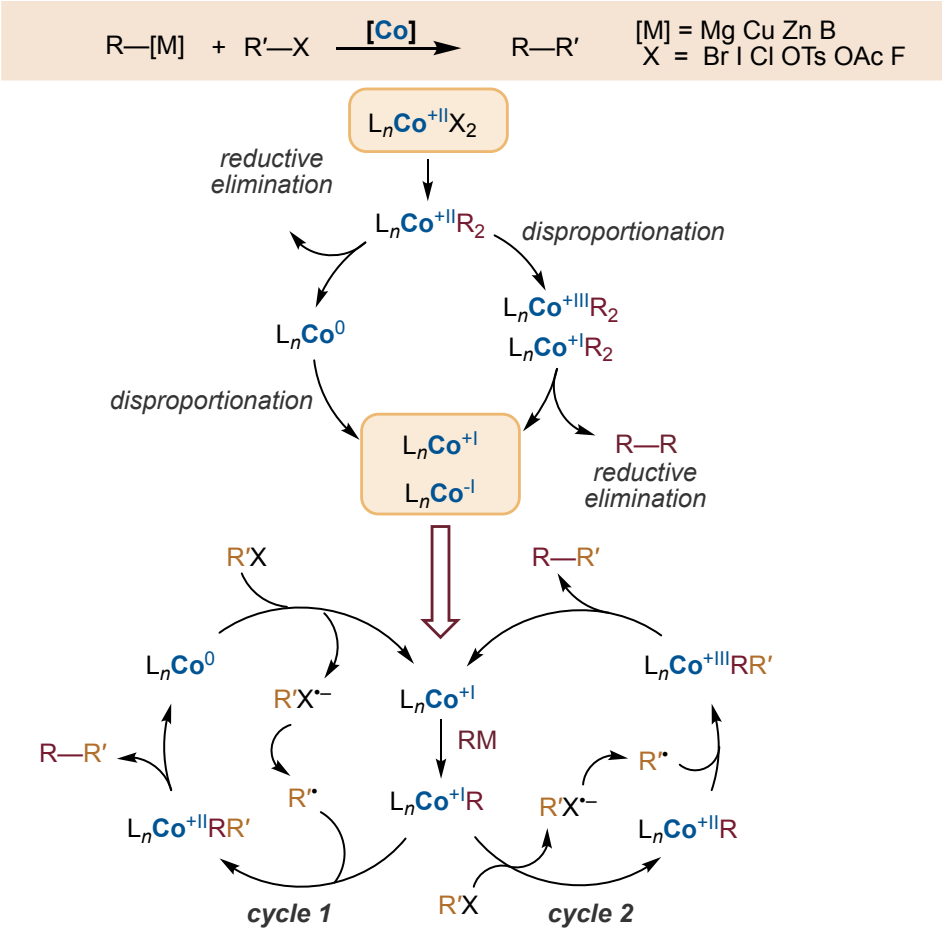
Cobalt mine production (2017)

1. DR Kongo 64,000 tonnes
2. Russia 5,600 tonnes
12. USA 650 tonnes

Applicaitions:
Catalyst for Fisher–Tropsch process
Hydroformylation of alkenes
Radioactive ^{60}Co is strong gamma ray source: cancer treatment, food & blood irradiation, etc.
Co/Cr/Mo alloy (Vitallium) – prosthetic parts
Co/Al/Ni/Fe alloy (Alnoci) – permanent magnet
Co/Pt alloy – jewelry suitable for fine casting

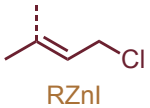
Multifaceted Cobalt: Mechanistic paradigms

CROSS-COUPLING



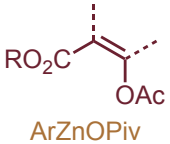
Chem. Eur. J., **2019**, 5912

Selected Examples



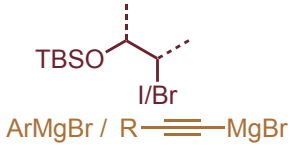
$CoBr_2$ (10 mol %)
S_N2 selectivity
no isomerization

ACIE **1996**, 1700



$CoBr_2$ (5 mol %)
bpy (5 mol %)

ACIE **2018**, 11436



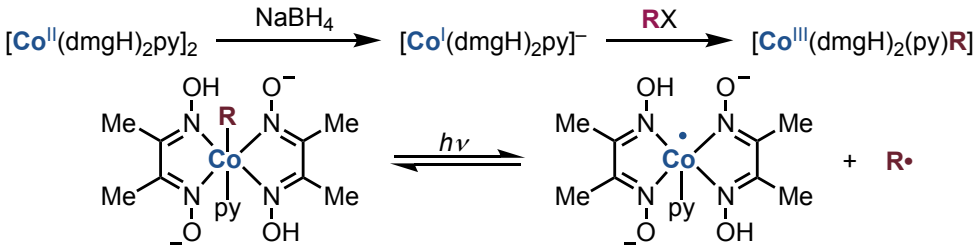
$CoCl_2$•LiCl (0.85 equiv.)
TMEDA (30 mol %)

OL **2014**, 6500
OL **2016**, 4778

$[CoCl_2(dppp)]$
(10 mol %)

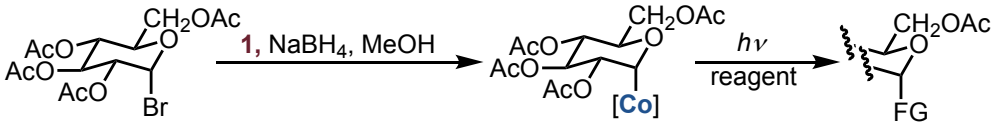
ACIE **2002**, 4137

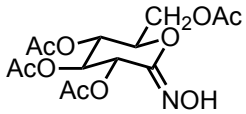
HALIDES AND EPOXIDES AS RADICAL PRECURSORS



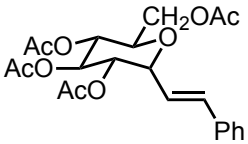
1: R = $Co(dmgH)_2py$
2: R = $SnPh_3$

Stochiometric reactions

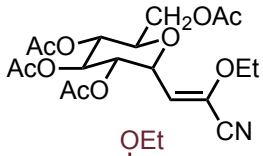


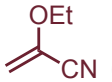


NO, 55%



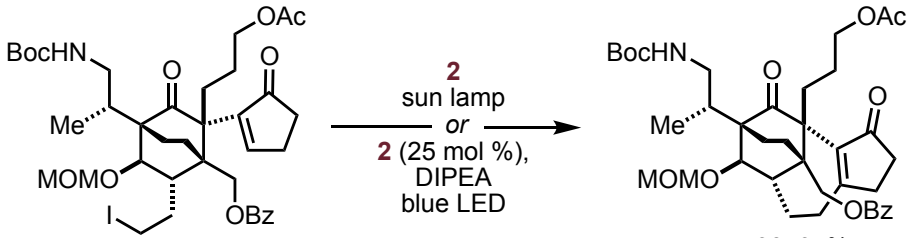
Ph 65%





68%

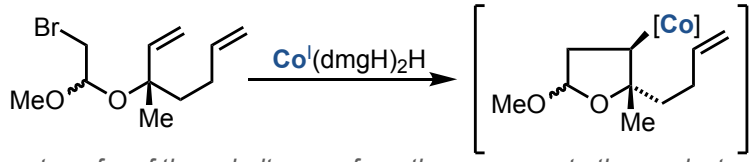
Giese, *Chem. Ber.* **1988**, 1807



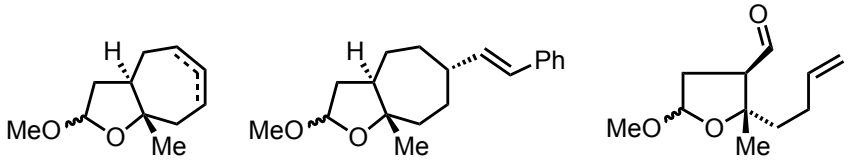
93–95%

Carreira, *ACIE* **2011**, 11501
Carreira, *ACIE* **2011**, 11125

Multifaceted Cobalt: Mechanistic paradigms



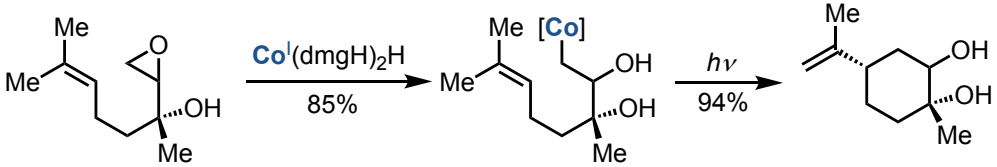
transfer of the cobalt group from the precursor to the product



hν, 58% | *hν*, styrene, 50% | *hν*, $^3O_2$, 30%

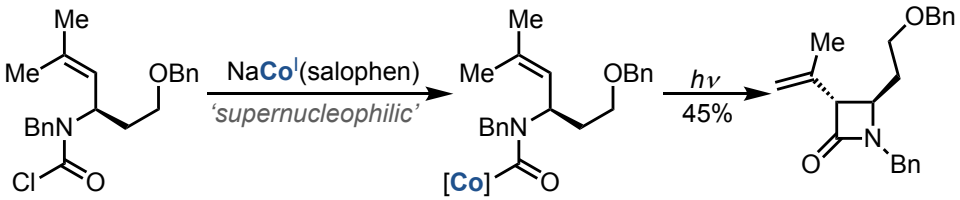
other trapping reagents: TEMPO, NO, SO_2, $(PhS)_2$, $(PhSe)_2$, MsCl, $BrCl_3C$, I_2

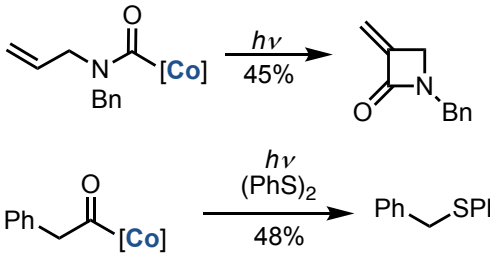
Pattenden, *Tetrahedron Lett.* **1992**, 2851



yellow powder
m.p. = 165 ºC

Pattenden, *Tetrahedron Lett.* **1991**, 243





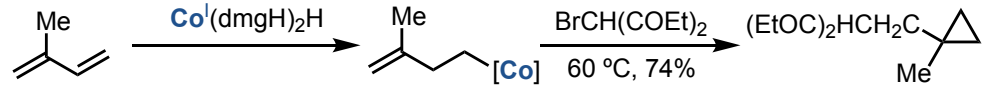
"…more flexible variant of the classical Hundsdiecker reaction and cobalt equivalent of the Barton radical decarboxylation"

Pattenden, *Tetrahedron Lett.* **1989**, 3229

S_H2

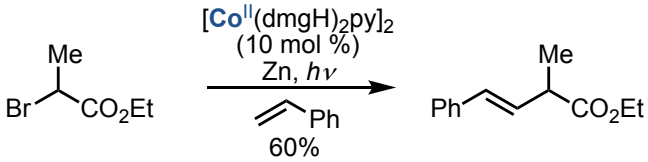
"Seldom postulated,rarely discussed, frequently discarded as improbable, but potentially of immense interest in organic chemistry"

$X^{\bullet} + RCH_2Y \longrightarrow RCH_2X + Y^{\bullet}$

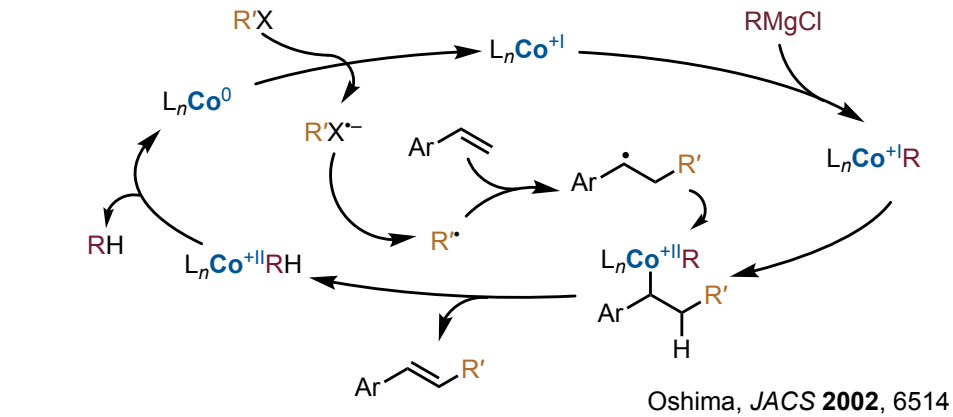


Johnson, *Acc. Chem. Res.* **1983**, 343

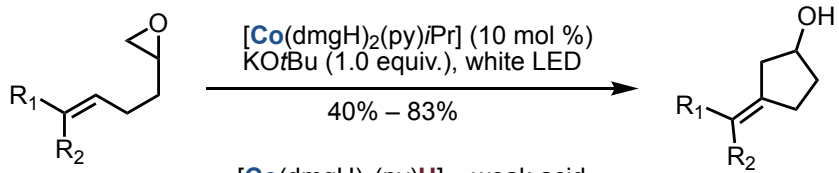
Catalytic reactions



Branchaud
Tetrahedron Lett. **1991**, 6273



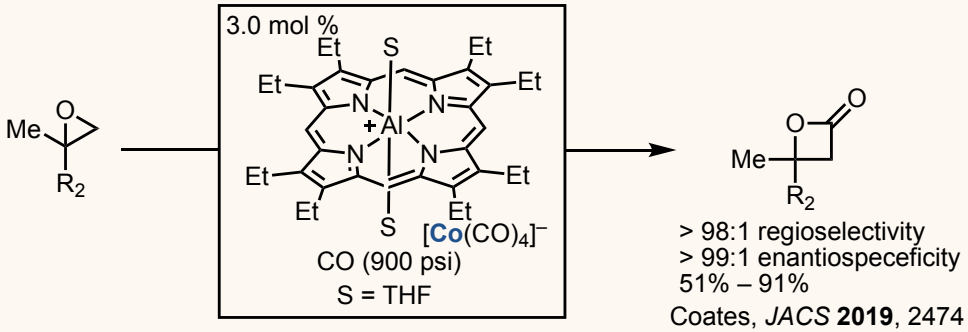
Oshima, *JACS* **2002**, 6514



[Co(dmgH)$_2$(py)H] – weak acid

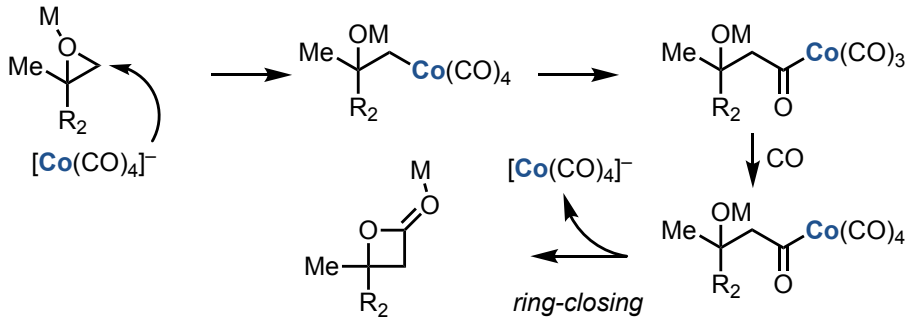
Morandi, *Chem. Commun.* **2016**, 9769

Multifaceted Cobalt: Mechanistic paradigms

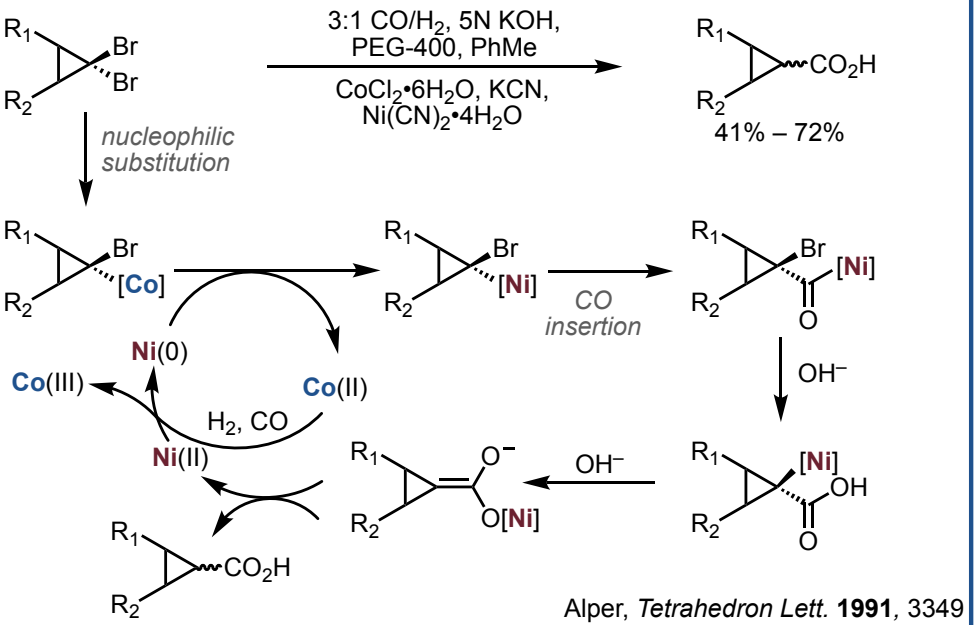


> 98:1 regioselectivity
> 99:1 enantiospeceficity
51% – 91%

Coates, *JACS* **2019**, 2474
Seminal work – Howard Alper



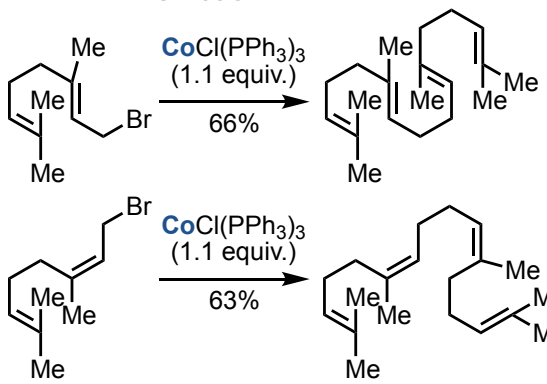
Transformative, paradigm-shifting, tool-box-expanding, unorthodox reactivity



Alper, *Tetrahedron Lett.* **1991**, 3349

REDUCTIVE COUPLING

Dimerization

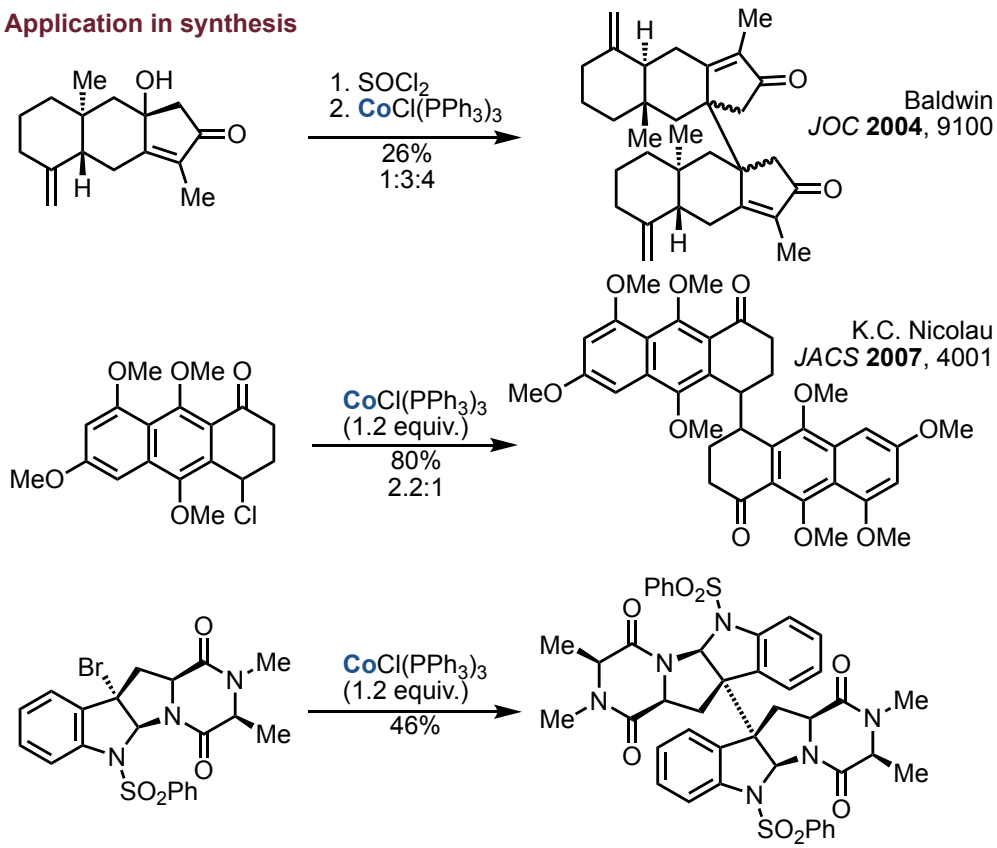


***CoCl(PPh$_3$)$_3$** mediates homodimerization of various halides under mild, non-basic conditions*

Retention of the olefin configuration in allylic bromides with S_N2 selectivity – rare selectivity in polyene synthesis

Yamada
Tetrahedron Lett. **1983**, 921

Application in synthesis



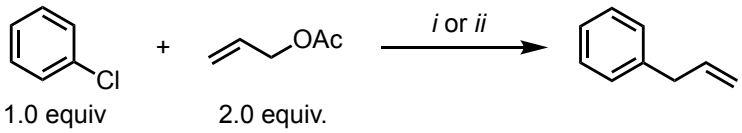
Baldwin
JOC **2004**, 9100

K.C. Nicolau
JACS **2007**, 4001

Movassaghi
Science **2010**, 238

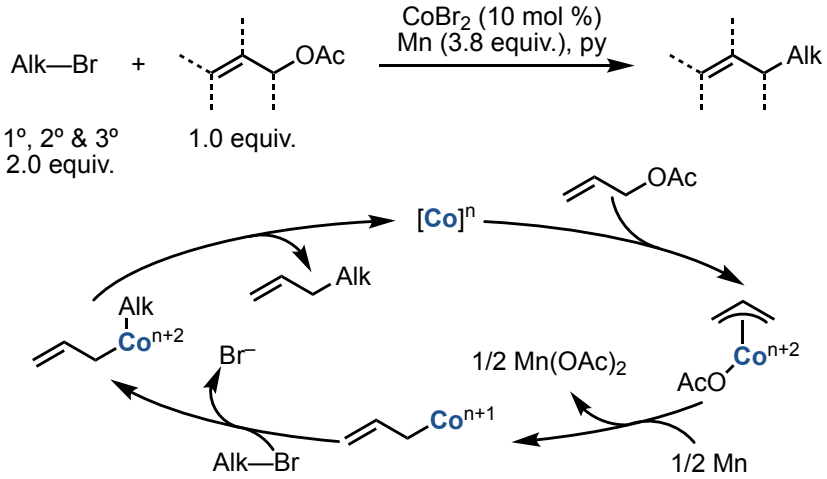
Multifaceted Cobalt: Mechanistic paradigms

Cross-coupling



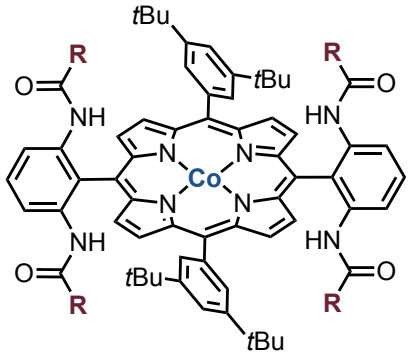
i : MeCN/py, **Co**Br_2 (40 mol %), Mn (10 equiv.), $FeBr_2$ (1 equiv.), 50 ºC
ii : MeCN/py, **Co**Br_2, Fe anode, stainless steel grid cathode, I = 0.2 A, 50 ºC

Gosmini, *Org. Lett.* **2003**, 1043

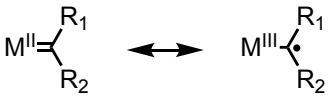


Gosmini, *ACIE* **2011**, 10402

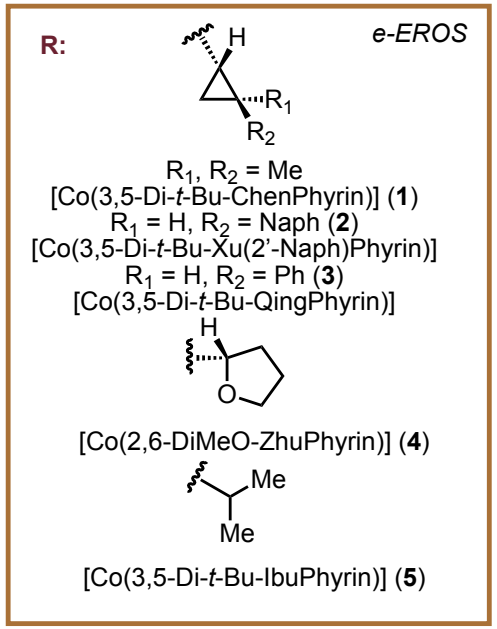
COBALT-CARBENE RADICAL TRANSFORMATIONS

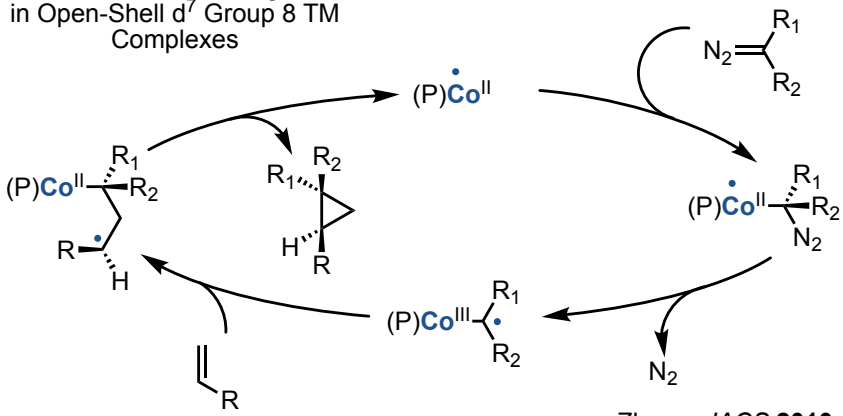


stable metalloradical
low spin $(d_{xy})^2(d_{xz,xy})^4(d_z^2)^1$



Redox Noninnocent Ligands
in Open-Shell d^7 Group 8 TM
Complexes





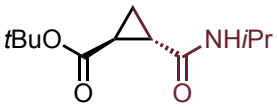
Zhang, *JACS* **2010**, 10891
JACS **2011**, 8518

"Different from the common electrophilic Fischer-type carbene intermediates, the new radical carbene intermediate is effectively an [Co(Por)]-supported carbon-based radical, which is capable of undergoing common radical reactions (such as radical addition and radical substitution) but is not "free", as its reactivity is well controlled by the electronic, steric, and chiral environments of the covalently attached [Co(Por)] element"

Multifaceted Cobalt: Mechanistic paradigms

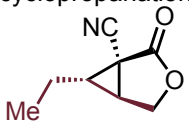
dimerization of diazocompound is not observed: olefin can be used as a limiting reagent

cyclopropanation of electron-deficient olefins



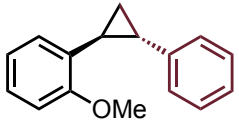
96%, 96% *ee*
1 mol % of **1**
JACS **2007**, 12074

intramolecular cyclopropanation



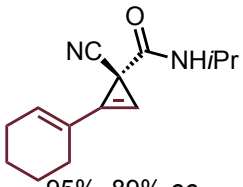
99%, 78% *ee*
2 mol % of **3**
JACS **2011**, 15292

cyclopropanation using hydrazones



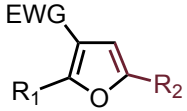
78%, 99% *ee*
Cs_2CO_3, 2 mol % of **2**
JACS **2017**, 1049

cyclopropenation



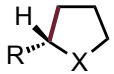
95%, 89% *ee*
1 mol % of **1**
JACS **2011**, 3304

synthesis of multisubstituted furanes very broad substrate scope



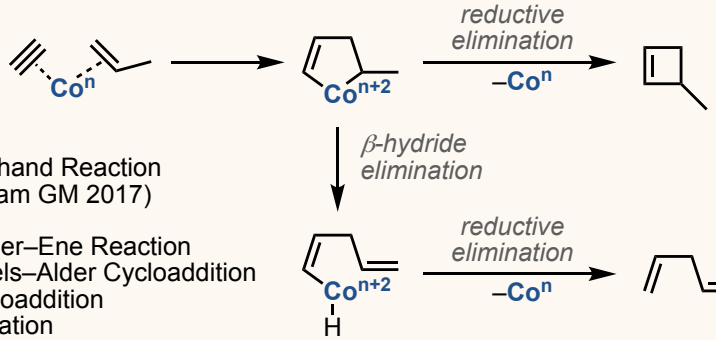
2 mol % of **5**
JACS **2012**, 19981

enantioselective C—H alkylation very broad substrate scope



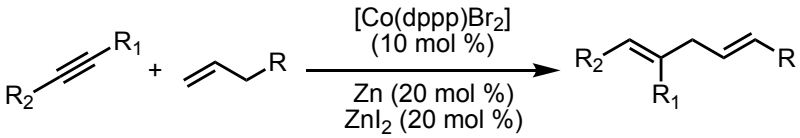
3 mol % of **4**
JACS **2018**, 4792

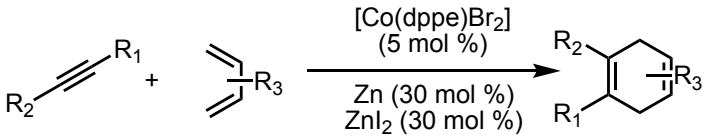
ALKYNE-ALKENE & DIENE-ALKENE COUPLING



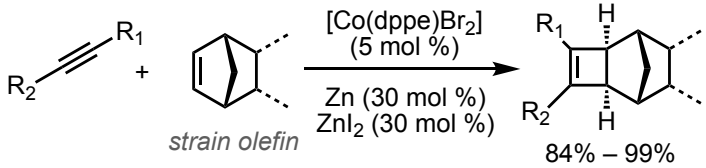
Pauson–Khand Reaction
(Mr. Bingham GM 2017)

Formal Alder–Ene Reaction
Formal Diels–Alder Cycloaddition
[2+2]–Cycloaddition
Hydrovinylation

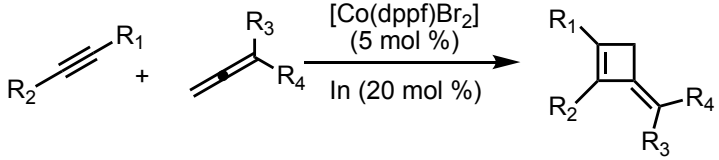




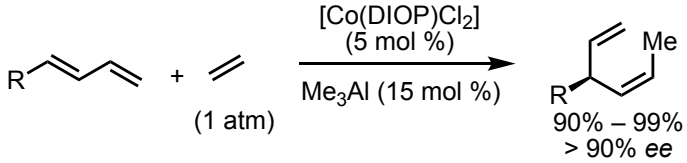
Hilt
ACIE **2007**, 8500
& references therein



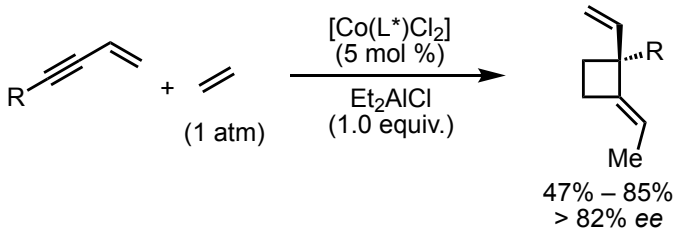
Hilt
ACIE **2008**, 6811
1 example with cyclopentene



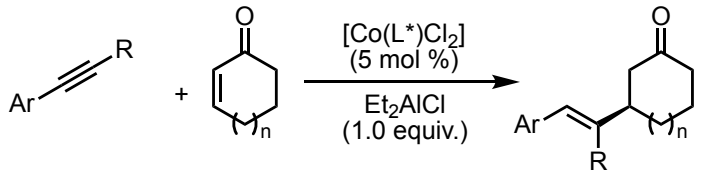
Yoshikai
ACIE **2019**, 2500



RajanBabu
JACS **2010**, 3295



RajanBabu
Science **2018**, 68

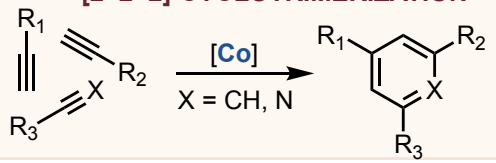


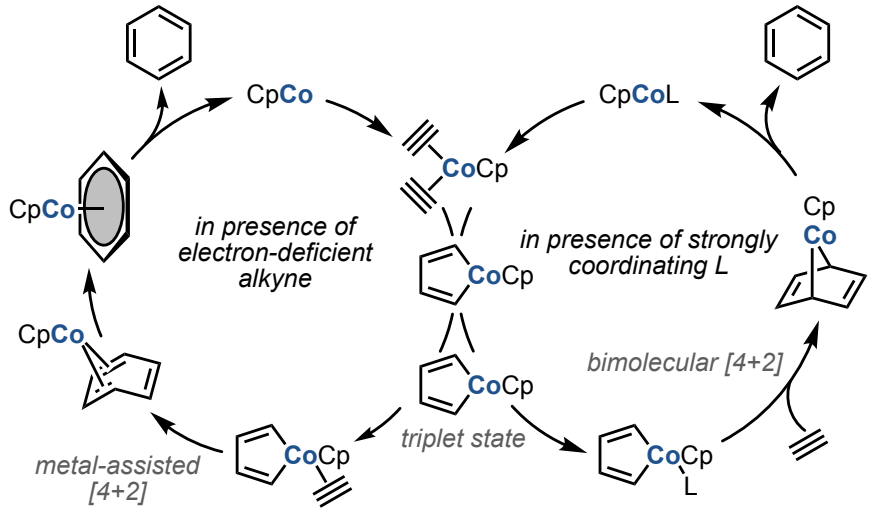
58% – 83%
85% – 96% *ee*

Cheng
JACS **2011**, 6942

Multifaceted Cobalt: Mechanistic paradigms

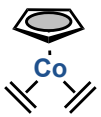
[2+2+2]-CYCLOTRIMERIZATION



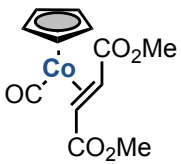


*17 different metals catalyze this transformation; however, **Co** is considered to be the most versatile and useful*

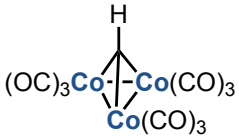
Catalysts



Classical catalyst
The most active
Heat is not required
Highly sensitive to oxygen

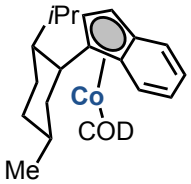


Gandon, *ACIE*, **2009**, 1810
Moisture- and air-stable
Crude solvents can be used



Sugihara
Chem. Comm. **2002**, 576
Moisture- and air-stable
Long shelf-life

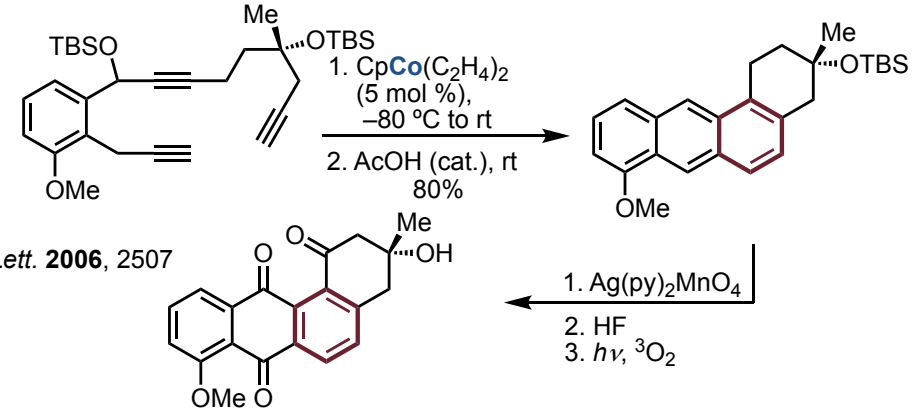
Recently user-friendly precatalytic mixtures were identified
$Co(dppe)I_2/Zn$
$CoCl_2$/IPr/Zn
$CoBr_2$(Cy-diimine)/Zn/ZnI_2
$CoCl_2 \cdot 6H_2O$/dipimp/Zn



Heller, *ACIE* **2004**, 3797
Enantioselective syntheis of biaryls

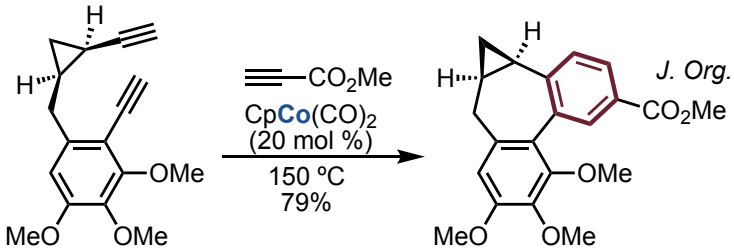
The major challenge is achieving high level of regioselectivity:
Use of stoichiometric metal complex
Tether components with cleavable Si-linker

Synthetic Applications



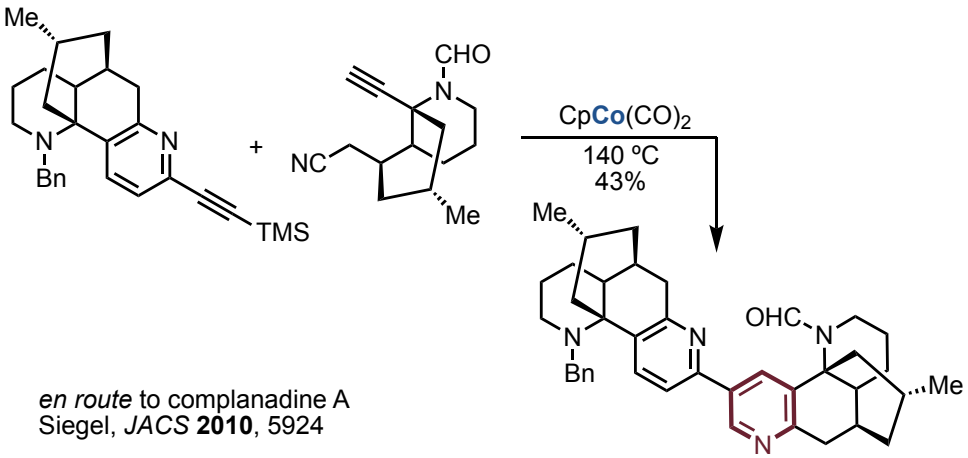
Groth
Org. Lett. **2006**, 2507

MM47755



Ramana
J. Org. Chem. **2016**, 3400

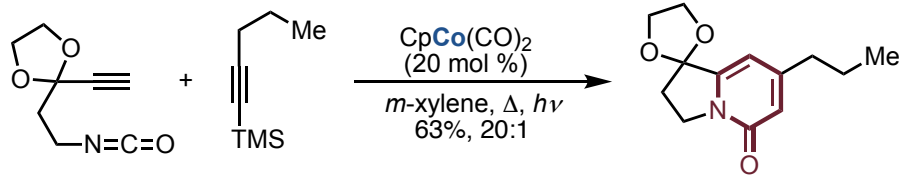
cyclopropylallocolchicinoid



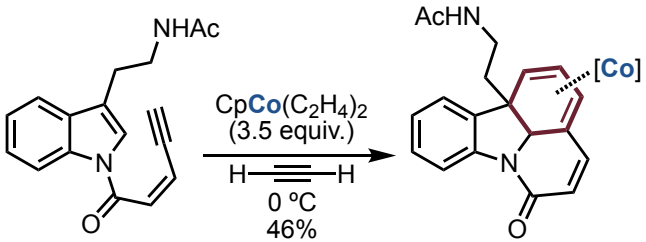
en route to complanadine A
Siegel, *JACS* **2010**, 5924

Multifaceted Cobalt: Mechanistic paradigms

en route to camptothecin
Vollhardt, *JACS* **1983**, 6991



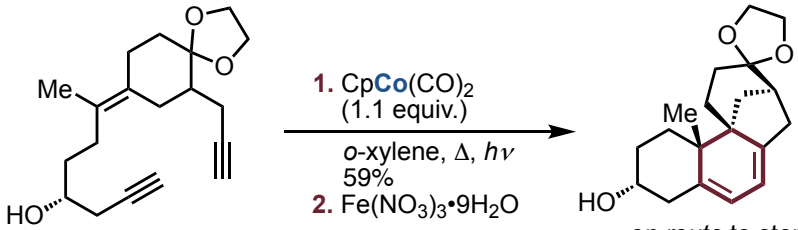
Enediyne [2+2+2] Cyclotrimerization



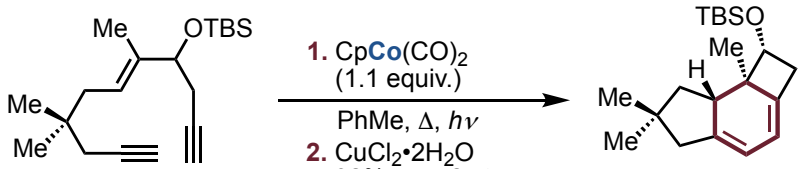
[Co] serves as protecting group for the following step

Catalytic method does not exist due to high affinity of TM to the 1,3-cyclohexyldienes as ligands

en route to strychnine (see Mr. Bingham GM 2018)
Vollhardt, *JACS* **2001**, 9324

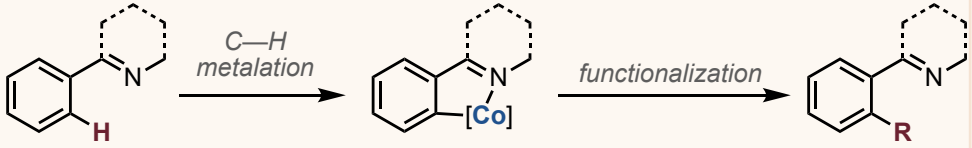


en route to stemodin
Vollhardt, *JACS* **1991**, 4006



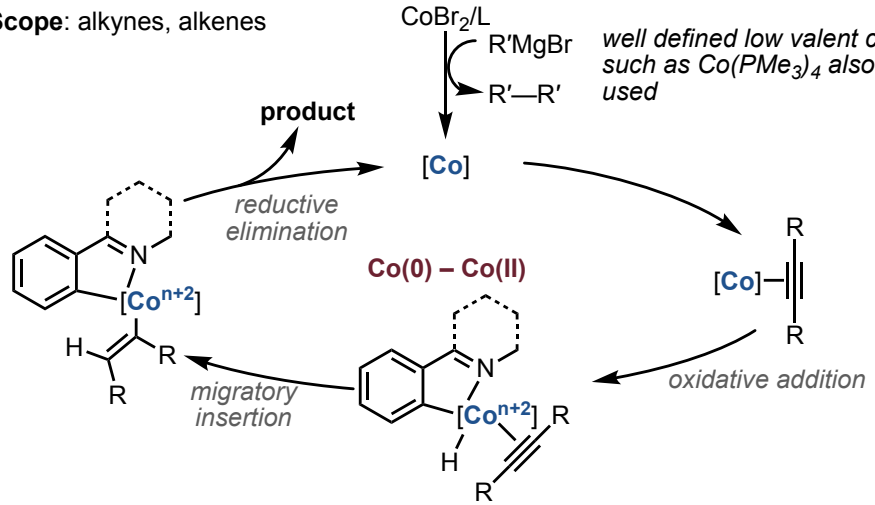
en route to illudol
Vollhardt, *JACS* **1991**, 381

C—H ACTIVATION

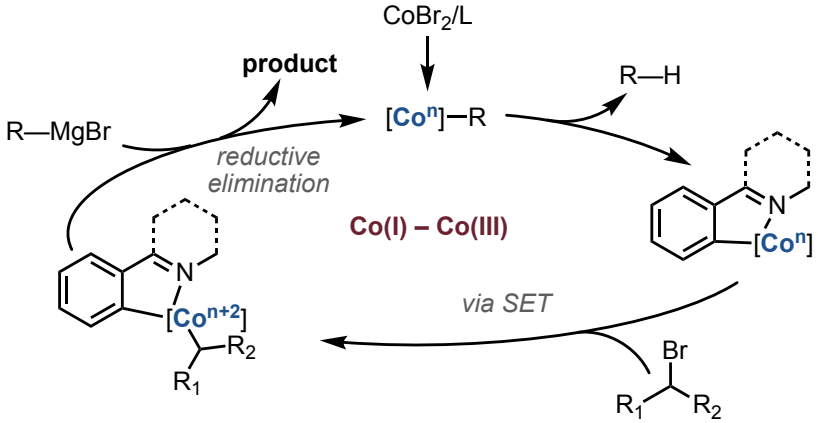


DG = ketimine, 2-pyridine, amide, etc.
No DG required for azoles, thiazoles, *N*-pyrimidyl indoles, *N*-pyrimidyl pyrroles,

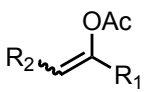
Scope: alkynes, alkenes



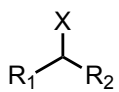
well defined low valent complex such as $Co(PMe_3)_4$ also can be used



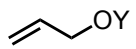
Multifaceted Cobalt: Mechanistic paradigms



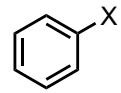
Alkenylation



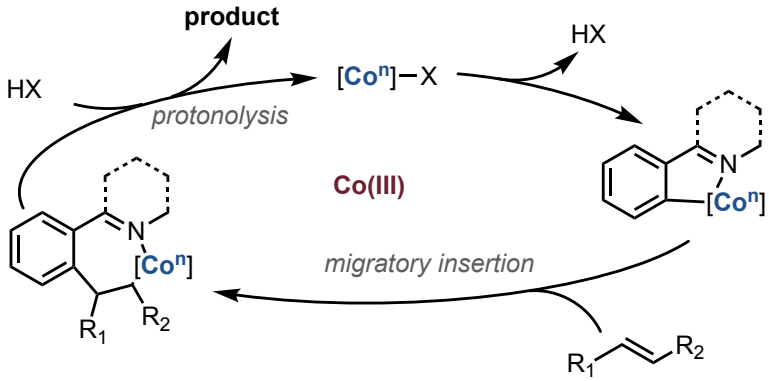
Alkylation
X = Cl, Br



Allylation

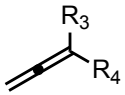


Arylation
X = Cl, $OC(O)NMe_2$
OSO_2NMe_2

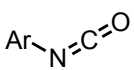


Ag(I) salts are common additives to abstract X^- and release H^+

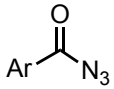
R = Alk, EWG
Alkylation

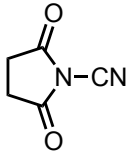


Alkenylation



Aminocarbonylation

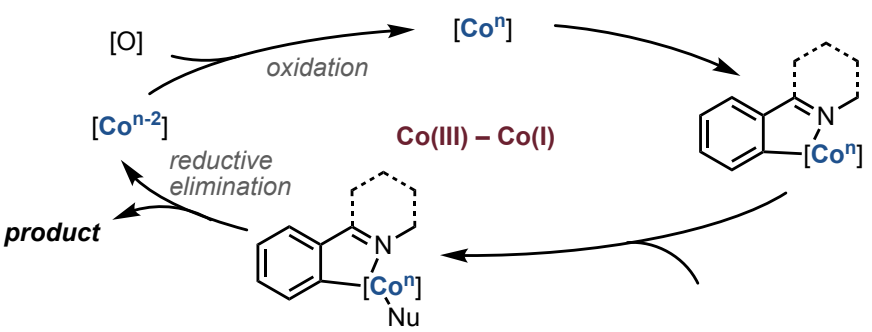




Cyanation

TsN_3, DPPA

Amination

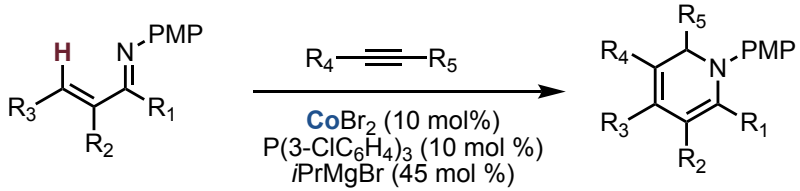


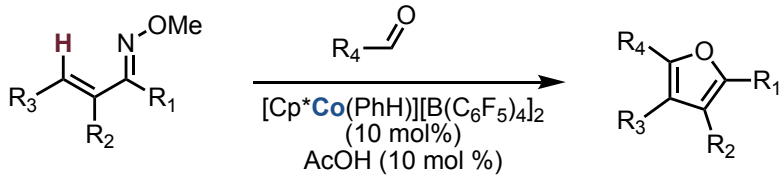
Oxidants: Ag^+, $K_2S_2O_8$, $Cu_2^+ + O_2$, peroxides, $Mn_3^+ + O_2$, electrochemical oxidation

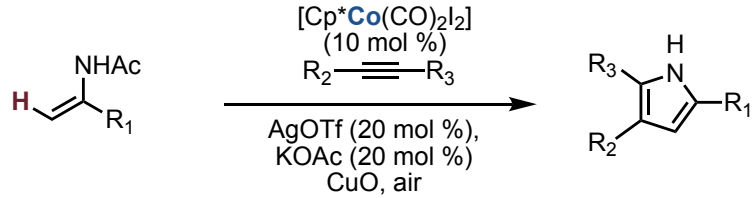
Nu^- : ROH, R_2NH, CO, *t*BuONO, RCO_2H, RSH

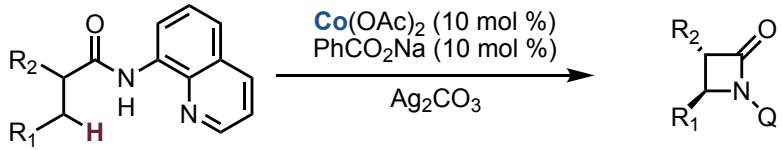
Ackermann, *Chem. Rev.* **2019**, 2192

Selected Examples

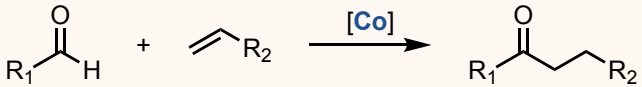




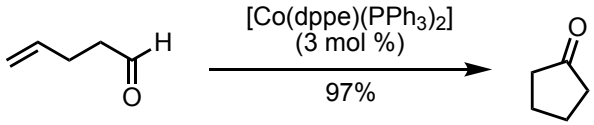




HYDROACYLATION

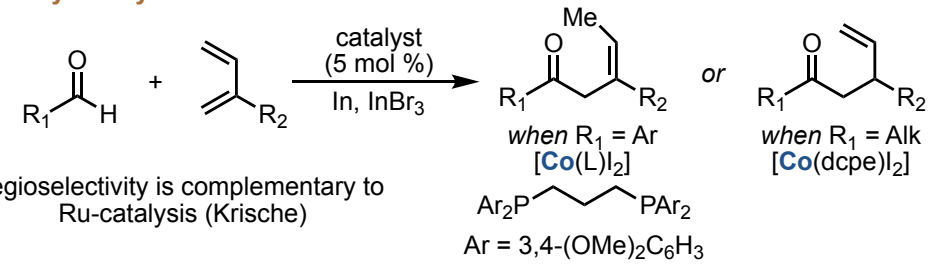


First report on intramolecular hydroacylation:
Vinogradov *J. Organomet. Chem.* **1988**, 123

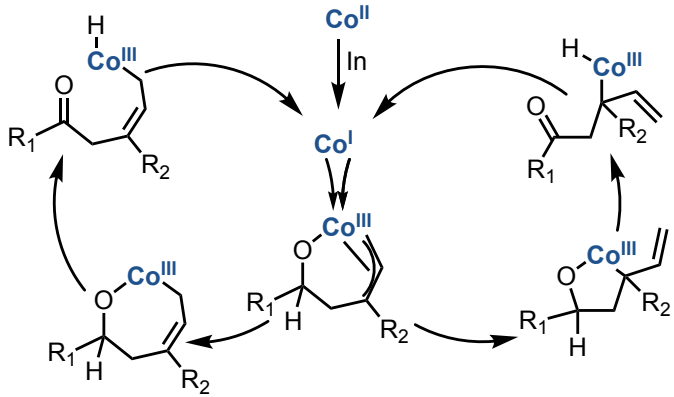


Multifaceted Cobalt: Mechanistic paradigms

Hydroacylation of Dienes



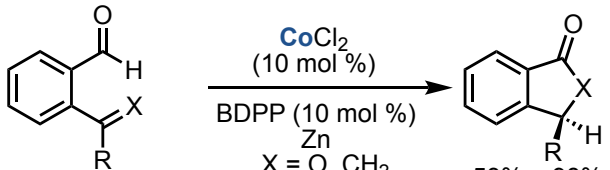
regioselectivity is complementary to Ru-catalysis (Krische)



reaction proceeds via
oxidative cyclization / β-hydride elimination / reductive elimination sequence

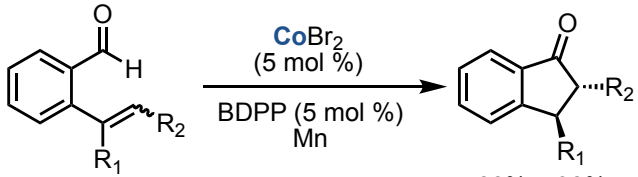
Dong, *JACS* **2014**, 3772

Enantioselective Hydroacylation



53% – 98%
81% – 97% *ee*

Yoshikai
JACS **2014**, 16748

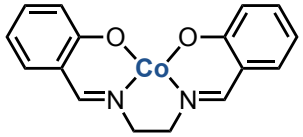


66% – 98%
63% – 97% *ee*

Yoshikai
ACIE **2017**, 2449

Mechanistic studies support
oxidative addition / migratory insertion / reductive elimination mechanism

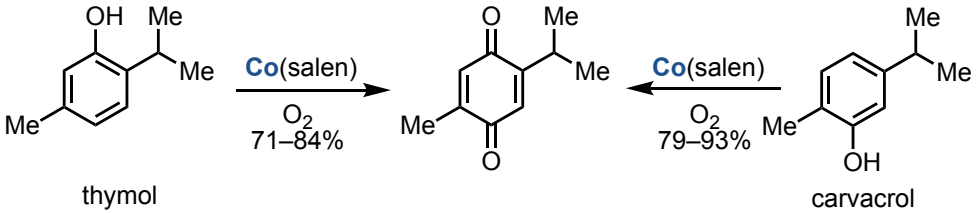
OXIDATIONS



Salcomine

Catalyst of choice for oxidation of *para*-unsubstituted phenols with molecular oxygen
Easy to handle, convenient workup
Gives better results than Fremy's salt

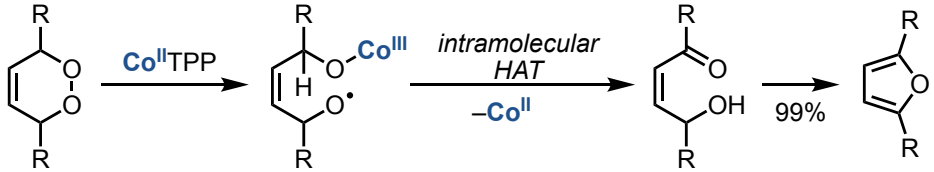
Synth. Commun. **1985**, 1033



thymol

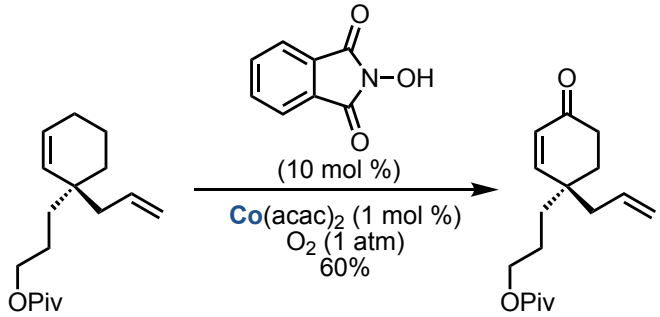
carvacrol

Rearrangement of endoperoxides



Foote, *J. Org. Chem.* **1989**, 3475

Allylic Oxidation (Ishii oxidation)



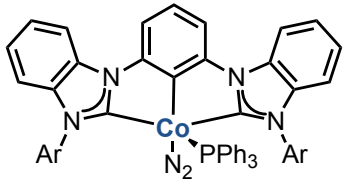
Ihara, *Org. Lett.* **2005**, 3929

Multifaceted Cobalt: Mechanistic paradigms

HYDRIDE TRANSFER REACTIONS

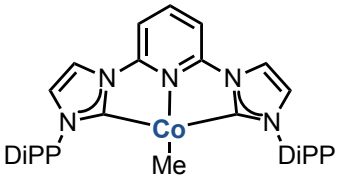
Hydrogenation

Original report:
Iguchi *Nippon Kagaku Kaishi* **1942**, 634
Very active area of research. Variety of catalysts have been developed within the last decade for hydrogenation of mono- and disubstituted olefins which are not covered here

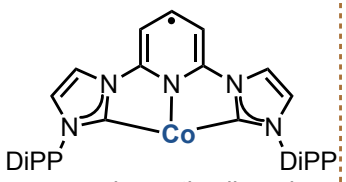


Fout, 2016

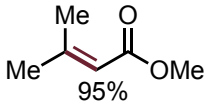
Hydrogenation of tri- and tetrasubstituted olefins



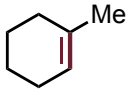
5 mol %, 4 atm H_2, 50 ºC
Chirik *JACS* **2013**, 13168



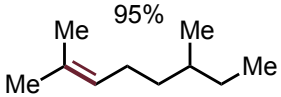
redox active ligand chelate radicals are likely catalytically active species



95%

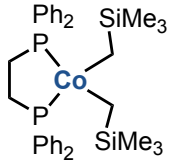


95%

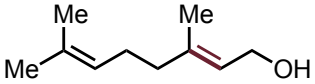


95%

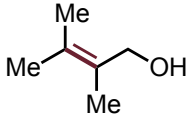
Hydroxyl-activation for Co-catalyzed hydrogenation



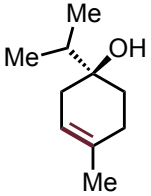
5 mol %, 4 atm H_2, 25 ºC
Chirik *JACS* **2014**, 13178



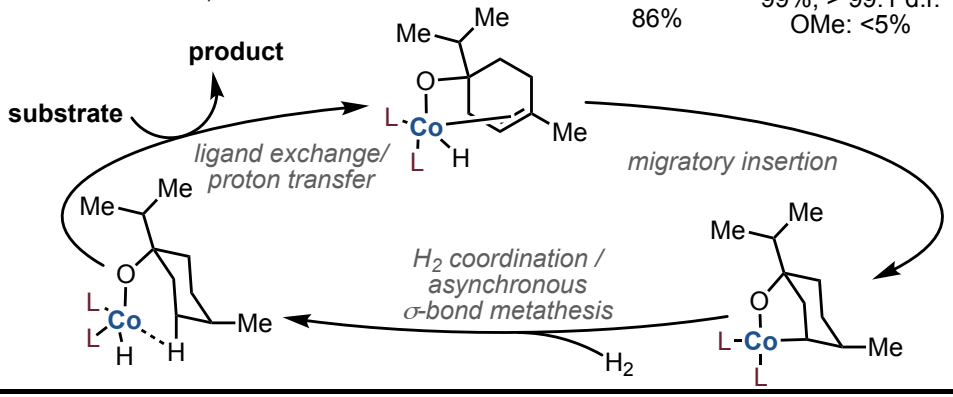
97%
OMe: <5%



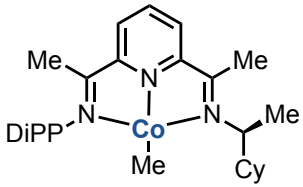
86%



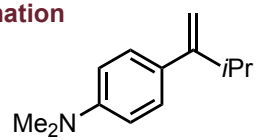
99%, > 99:1 d.r.
OMe: <5%



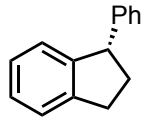
Enantioselective Hydrogenation



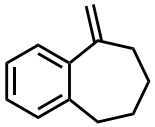
5 mol %, 4 atm H_2, 25 ºC
Chirik *JACS* **2016**, 3314



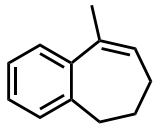
98%, 99% *ee*



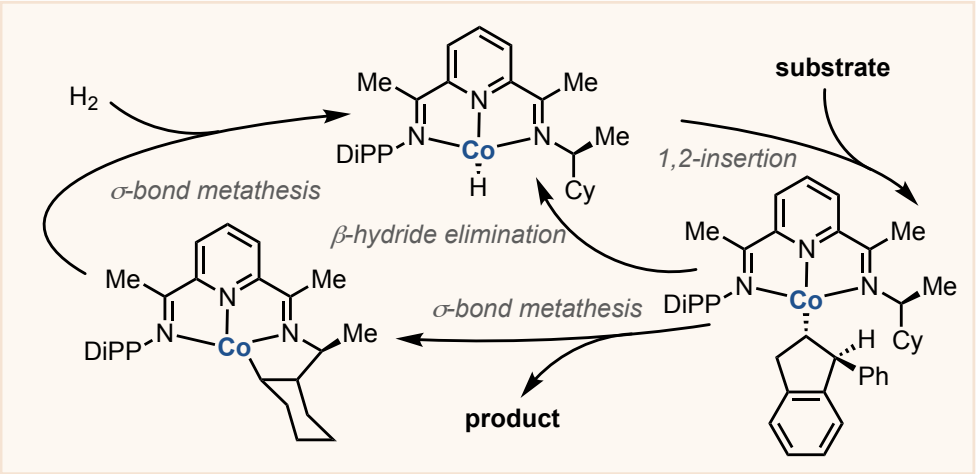
98%, 94% *ee*



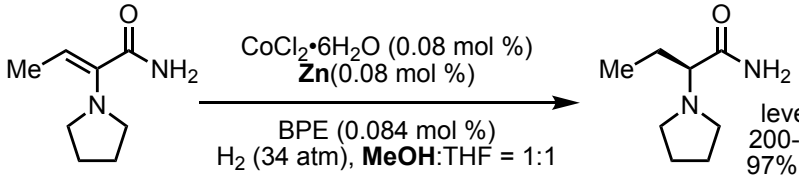
97%, 85% *ee* (*S*)-(–)

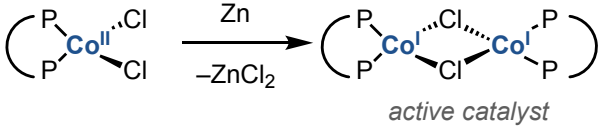


95%, 89% *ee* (*R*)-(+)



Zn/MeOH Protocol for Enantioselective Hydrogenation

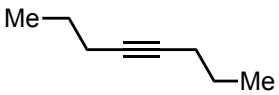




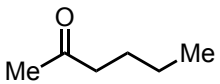
$LiCH_2TMS$ was previously used
More sensitive
Less compatible with majority of the ligands
Significant deactivation of the catalyst
Chirik, *Science* **2018**, 888

Multifaceted Cobalt: Mechanistic paradigms

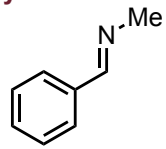
Other reducible functional groups under Co-catalysis



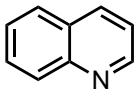
alkynes



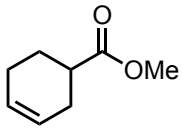
ketones



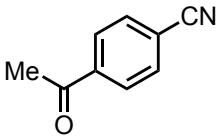
imines



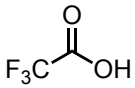
heterocycles



esters



nitriles



carboxylic acids
$CoBF_4 \cdot 6H_2O$, Triphos
de Bruin, *Science* **2016**, 298

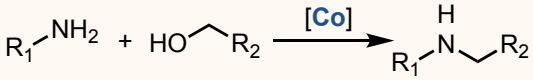
Transfer hydrogenation protocols have been developed

$NH_3 \cdot BH_3$ *i*PrOH $(EtO)_2SiMeH$

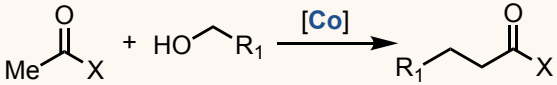
Dehydrogenation (Oxidation)

Hydrogen-Borrowing Reactions

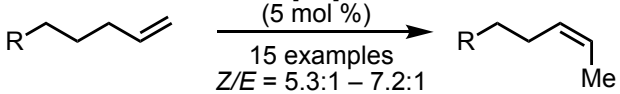
N-Alkylation



C-Alkylation

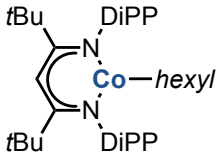


Isomerization

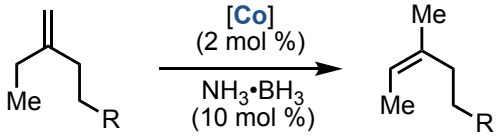


15 examples
Z/E = 5.3:1 – 7.2:1

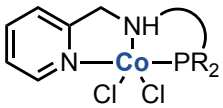
steric hinderence of the catzzalyst prevents further isomerization and β-hydride elimination towards E-isomer



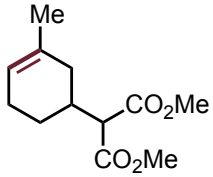
Weix & Holland
JACS **2014**, 945



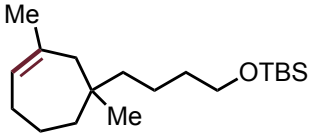
isomerization of 1,1-disubstituted olefins under kinetic control



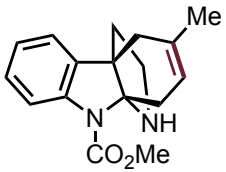
Jiao & Liu
JACS **2018**, 6873



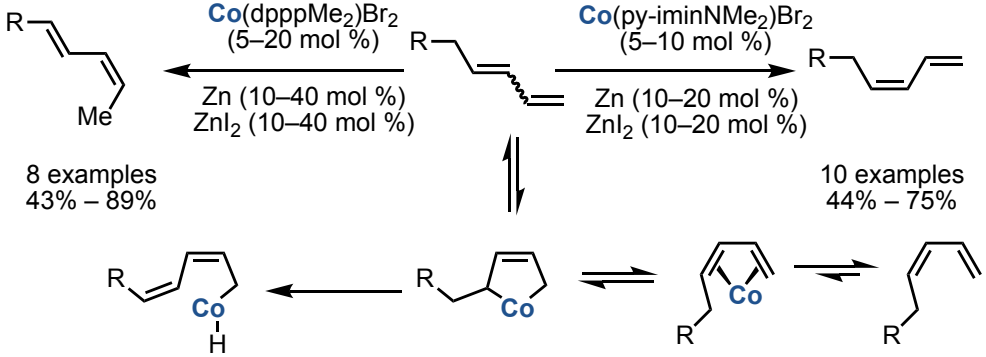
97% (10:1)
TsOH: 18% (2:1)



94% (> 99:1)

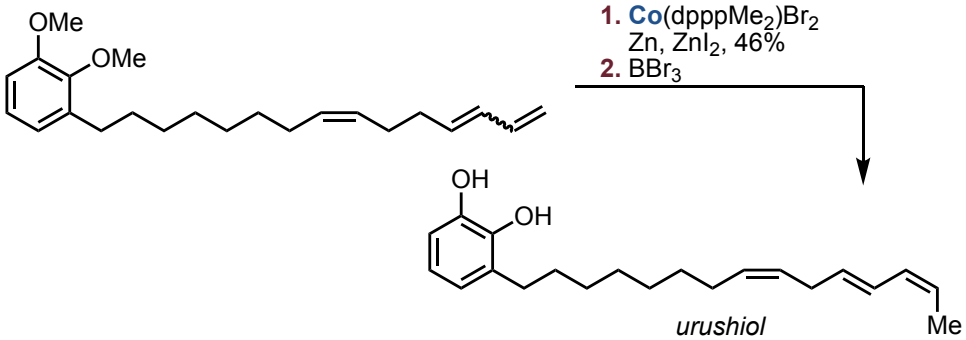


98% (18:1)
TsOH: 92% (1:2.2)
Jiao, *ACIE* **2016**, 8090



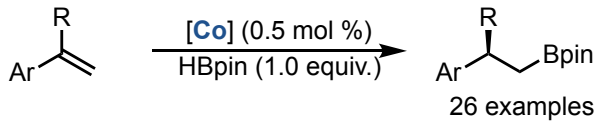
Hilt, *ACIE* **2012**, 1270

Synthesis of urushiol

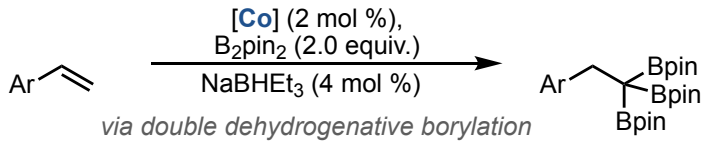


Multifaceted Cobalt: Mechanistic paradigms

Hydroboration



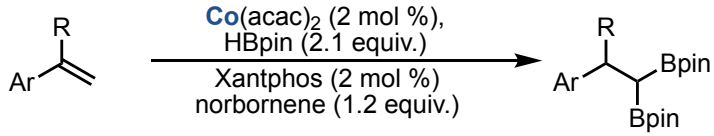
Huang, *JACS* **2014**, 15501



via double dehydrogenative borylation

24 examples
46% – 98%

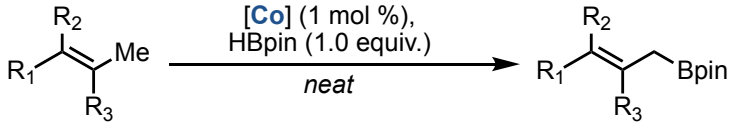
Huang
JACS **2015**, 15600



30 examples
25% – 87%

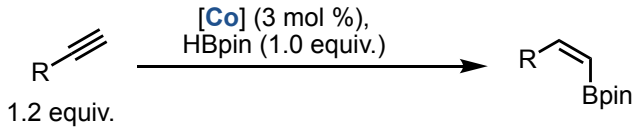
Ge
ACIE **2018**, 1654

norbornene as sacrificial olefin to access [Co]—Bpin
proceeds via valence tautomerization to the less hindered alkyl-Co species



7 examples
70% – 98%

Chirik
JACS **2013**, 19107



12 examples
41% – 91%

Chirik
JACS **2015**, 5855

C—H borylation followed by hydrogenation via sequential σ-bond metathesis

EXPRESS ADMIRATION FOR COBALT HERE