

Cobalt in Organic Synthesis



Respect Cobalt!

Zhongxing Huang
February 20th, 2013

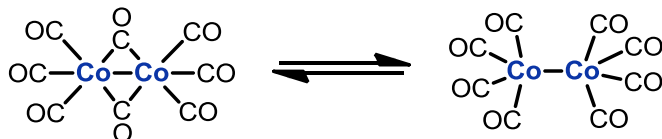
About Cobalt

• Uses of cobalt

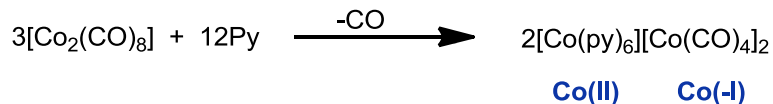
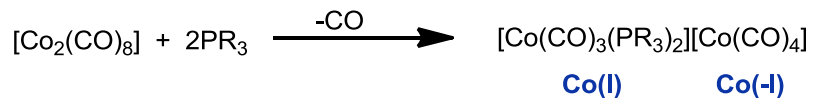
- Dyes (glass, pottery, china)
- Magnetic material (along with iron and nickel)
- Co-60 as gamma ray source

• Common organocobalt complexes

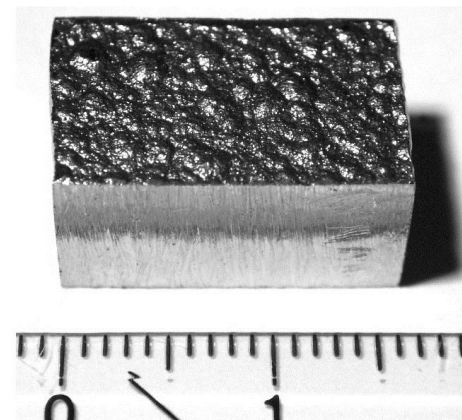
- $\text{Co}_2(\text{CO})_8$



- Sensitive to air and temperature
- Polymerize under high temperature
- Stabilized by CO atmosphere/pressure



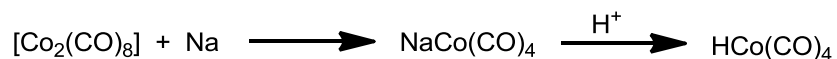
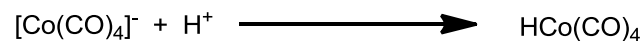
- Disproportionation under Lewis bases



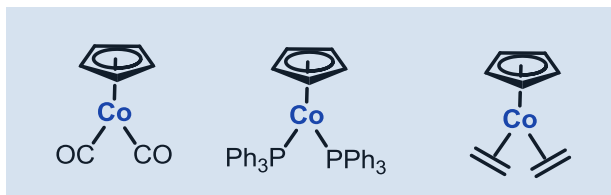
- **Common organocobalt complexes**

- $\text{HCo}(\text{CO})_4$

- sensitive to air and **very sensitive** to temperature
- Precatalyst in many carbonylation reaction



- $\text{Co}(\text{I})$

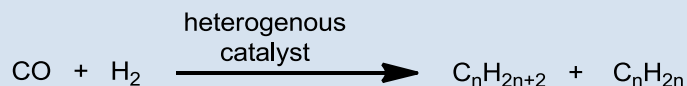
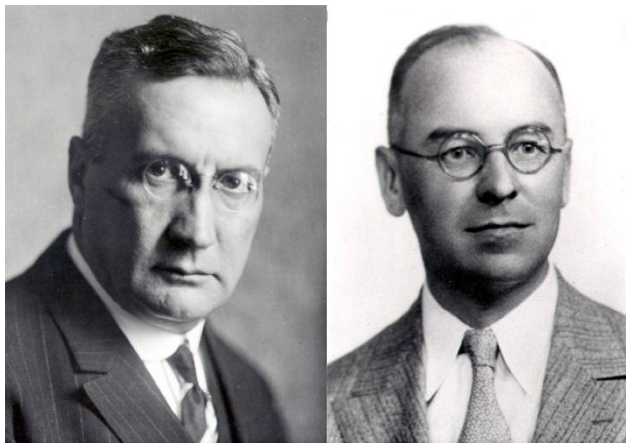


- CpCo(I) 14e: dienophile, crucial for cyclization
- High temperature to dissociate for vac. sites

- $\text{Co}(\text{II})$ and $\text{Co}(\text{III})$

- CoX_2 , $\text{Co}(\text{acac})_2$, $\text{Co}(\text{acac})_3$
- Thermodynamically stable compounds
- In-situ reduced to active intermediate

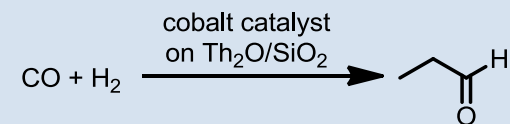
- Fisher-Tropsch reaction**



- Otto Roelen's contribution**



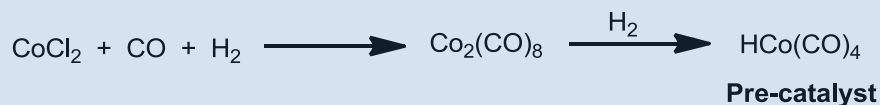
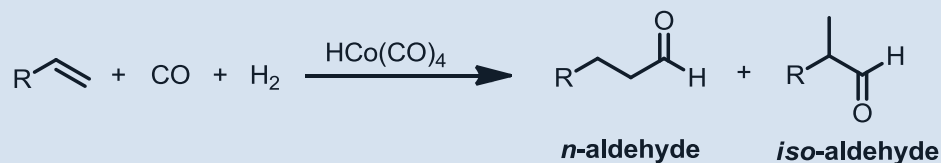
serendipitous discovery:



- cobalt is able to transform ethylene to propanal
- reaction can occur in organic phase

The Birth of Homogeneous Catalysis

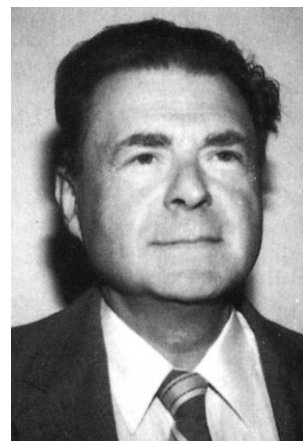
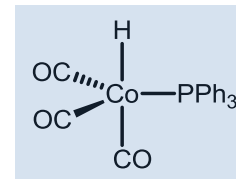
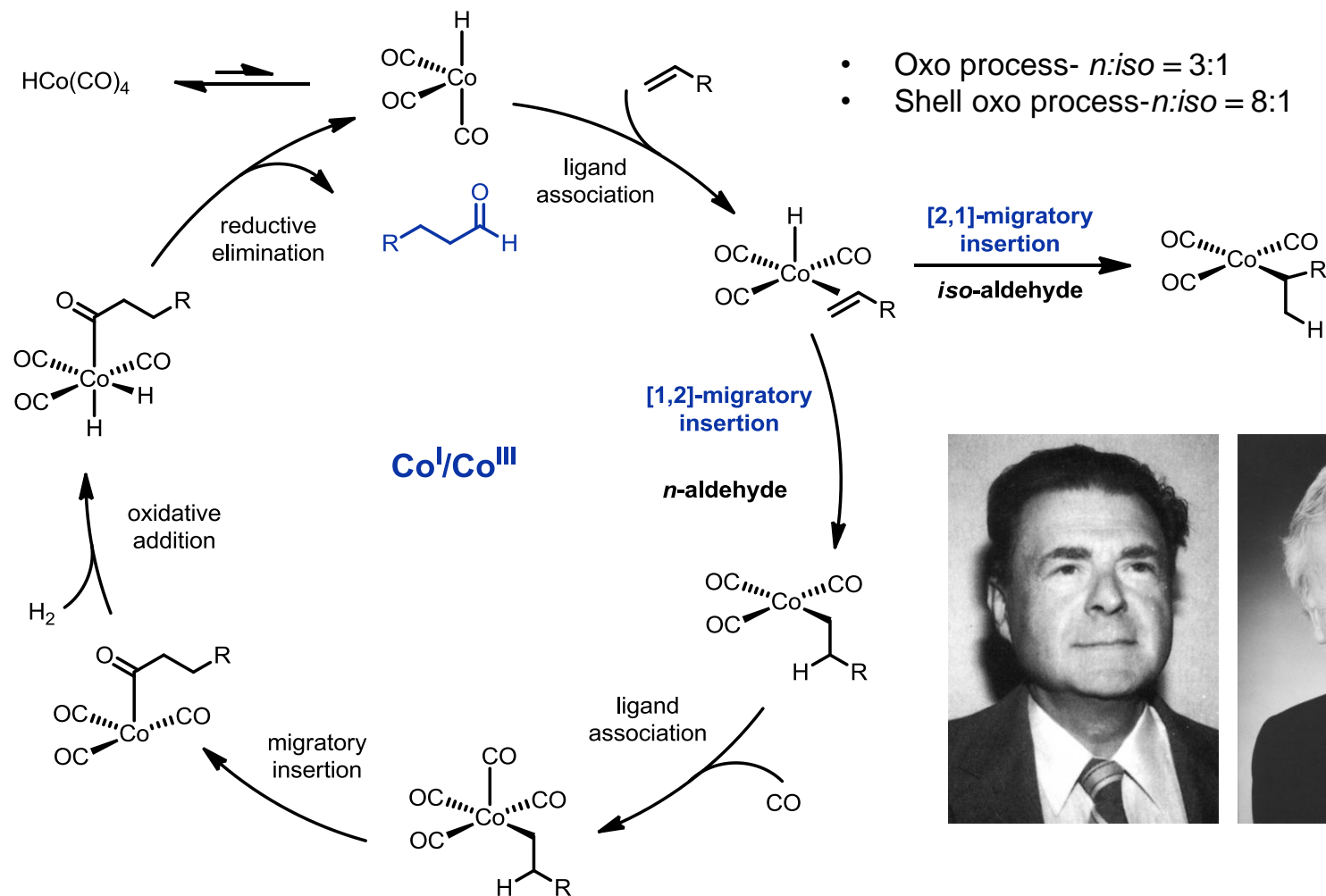
- Oxo Process – 1st Generation Cobalt Catalyst**



- Self-generating and activating catalyst
- Limitation: decomposition, *n:iso*, separation
- Replaced by Rh catalyst later
- World production 10⁶ ton/year (w/ Rh)

Cobalt-Catalyzed Hydroformylation

Catalytic cycle

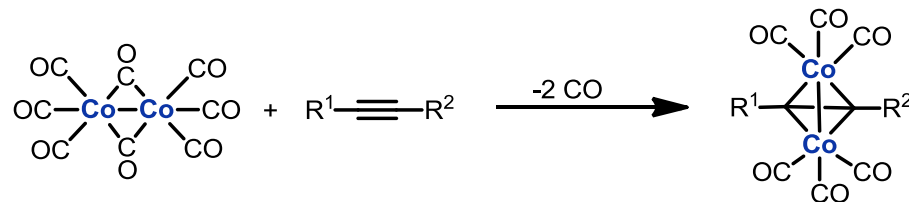


- ***Reactions based on acetylenehexacarbonyl dicobalt complex***
 - *Nicholas reaction*
 - *Pauson-Khand reaction*
- ***Cobalt-mediated/catalyzed cyclization***
- ***Cobalt-catalyzed coupling reaction***
- ***Cobalt-catalyzed C-H activation***

- **Reactions based on acetylenehexacarbonyl dicobalt complex**
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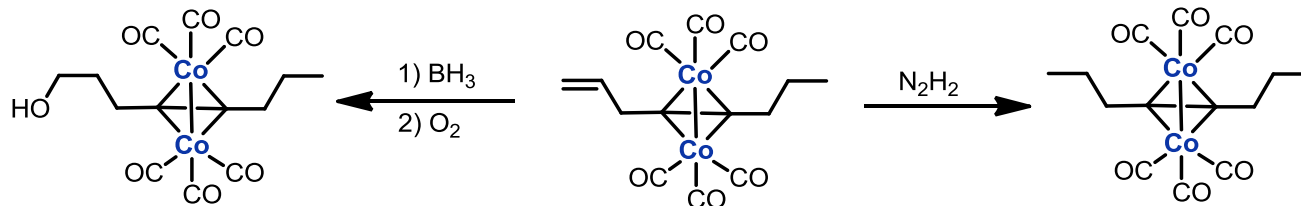
Reactions based on acetylenehexacarbonyl dicobalt complex

• Reaction of cobalt carbonyl and alkyne

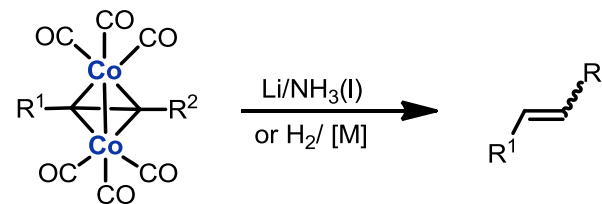


- Typically high yields
- Proceed at ambient temperature
- Stable product (some can be isolated with column)

• Protecting groups for alkynes

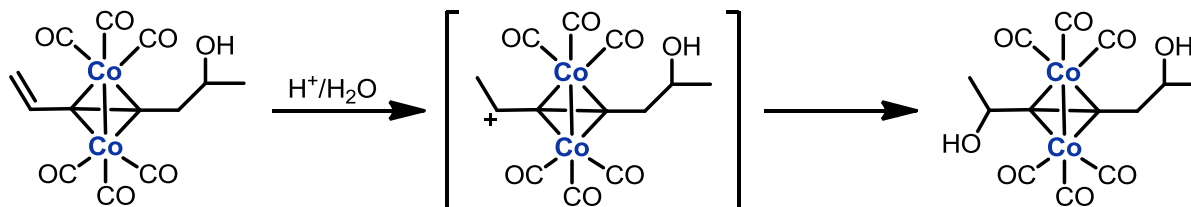


- Generally stable in acidic conditions
- Sensitive to base
- unstable in catalytic hydrogenation
- Removed by mild oxidation (Fe³⁺, Ce⁴⁺)

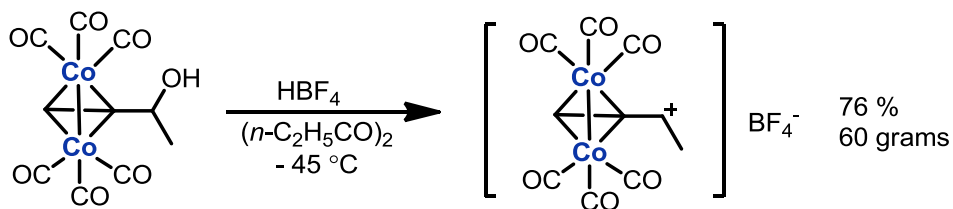


Reactions based on acetylenehexacarbonyl dicobalt complex

- Nicholas reaction**



- High stability of propargylic carbocation discovered during hydration of **X**

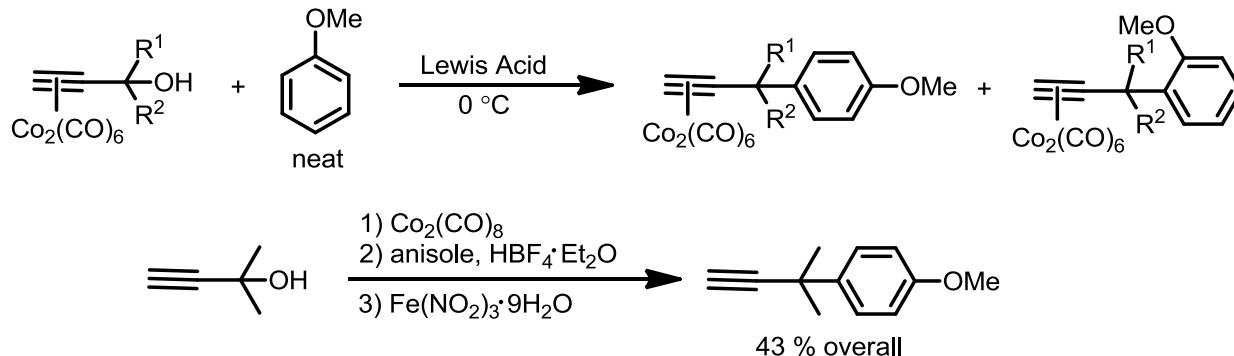


- Stable in dry air, stored indefinitely under N_2
- Positive charge highly delocalized
- Comparable stability with Ar_3C^+

Reactions based on acetylenehexacarbonyl dicobalt complex

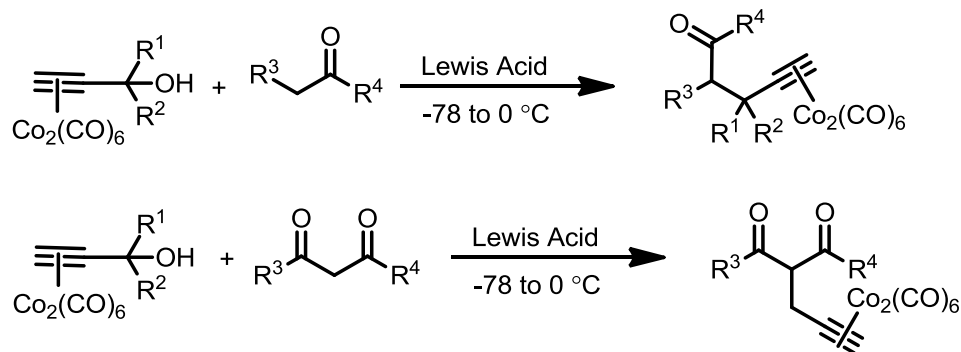
• **Nicholas reaction - protected propargylic cation as synthon**

- With electron-rich arenes



- Substrates including anisole, phenol, *N,N*-dimethylbenzene, etc.
- Selectivity controlled by steric hindrance of cation

- With ketone and enol ether

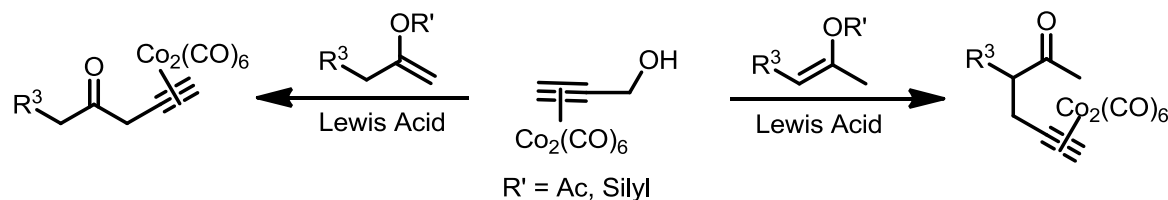


- Via enol intermediate, react with more substituted α -position-**thermodynamic control**

Reactions based on acetylenehexacarbonyl dicobalt complex

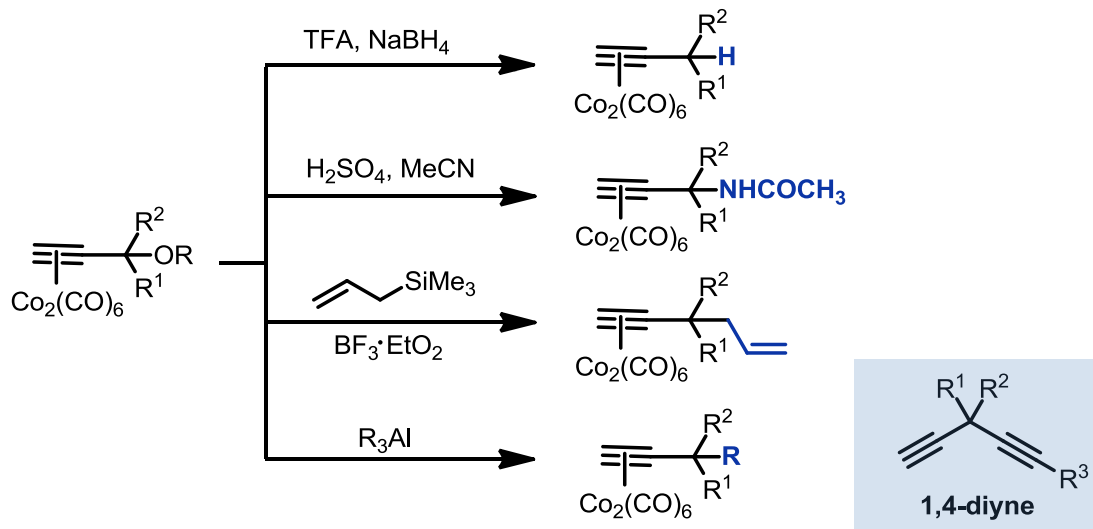
- **Nicholas reaction - protected propargylic cation as synthon**

- With ketone and enol ether



- Pre-prepared enol ether: 1) stoichiometric amount 2) high selectivity

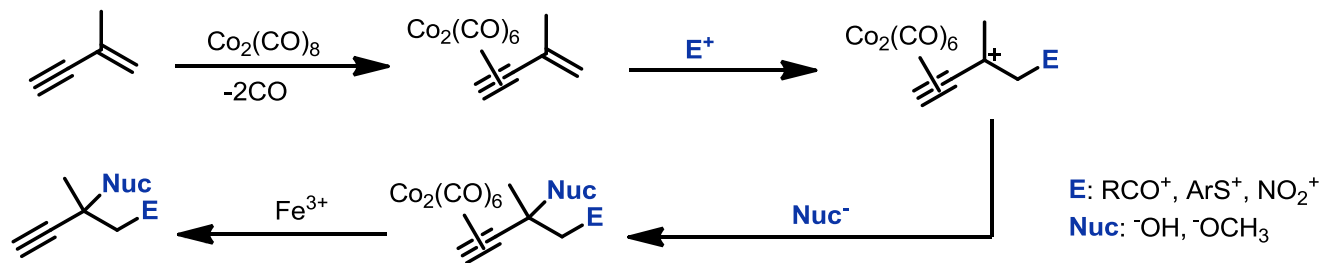
- With other nucleophiles



Reactions based on acetylenehexacarbonyl dicobalt complex

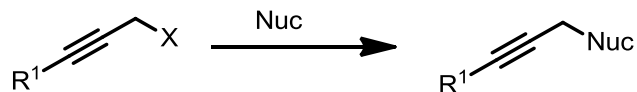
• *Nicholas reaction - protected propargylic cation as synthon*

- Conjugate enyne



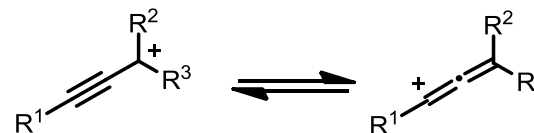
- Difunctionalization of alkene in conjugate enyne

• *Advantages of cobalt-stabilized propargylic cation*



Reaction with propargylic halide ($\text{S}_{\text{N}}2$):

- Fast reaction due to little hindrance
- Multi-substituted product



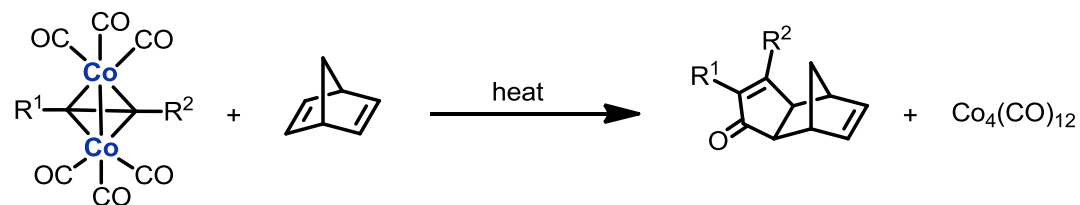
Unprotected propargylic cation ($\text{S}_{\text{N}}1$):

- Not stable cation
- Elimination reaction
- Allene byproduct
- Not electrophilic enough

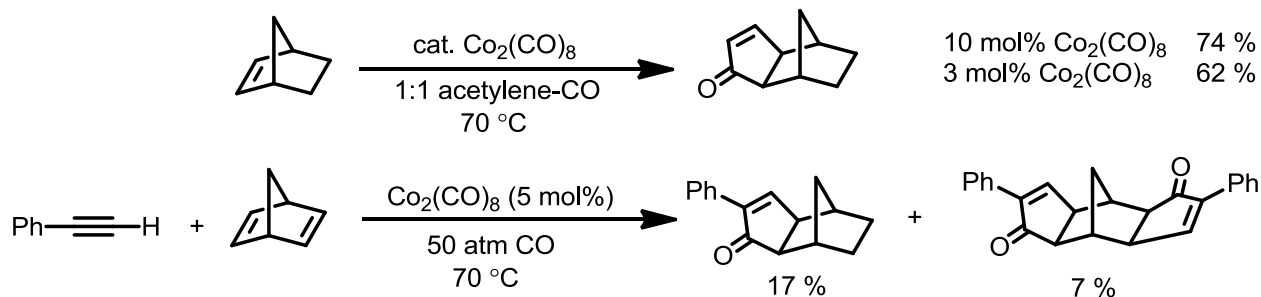
Reactions based on acetylenehexacarbonyl dicobalt complex

• Pauson-Khand reaction

- First discovered in 1973



- Formal [2+2+1] cyclization
 - High selectivity for alkyne: R¹>R²
- Initial concepts about catalytic reaction



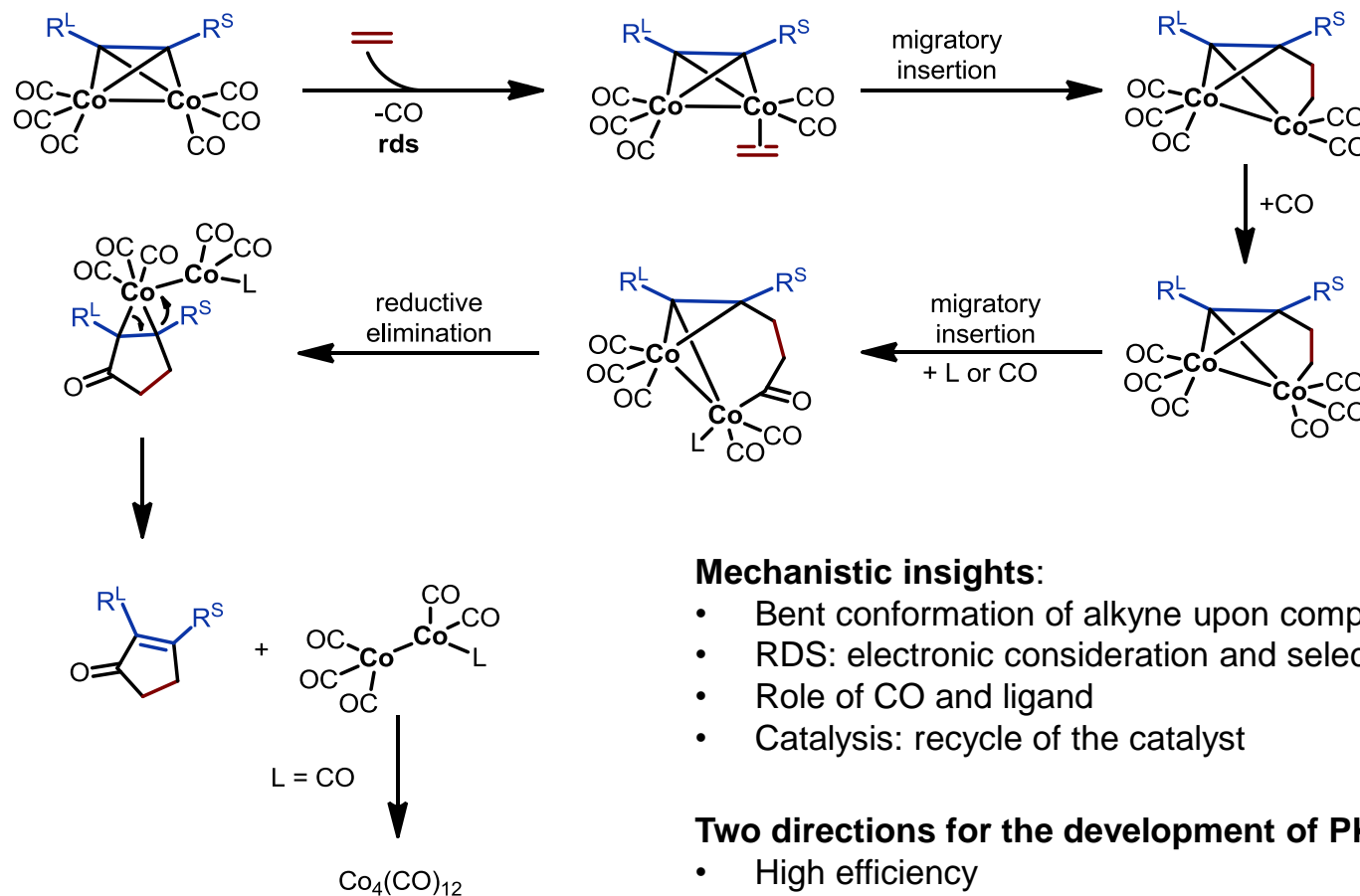
Problems:

- Typically a stoichiometric reaction
- Harsh conditions for alkenes except strained olefins and ethylene
- Internal alkyne and trisubstituted olefins are unreactive
- Low selectivity for olefin cyclization partner

Khand, I. U.; Knox, G. R.; Pauson, W. E. W. *J. Chem. Soc. Chem. Commun.* **1971**, 36

Khand, I. U.; Knox, G. R.; Pauson, W. E. W.; Foreman, M. I. *Chem. Soc. Chem., Perkin Trans. 1* **1973**, 977

• Pauson-Khand reaction-proposed mechanism



Mechanistic insights:

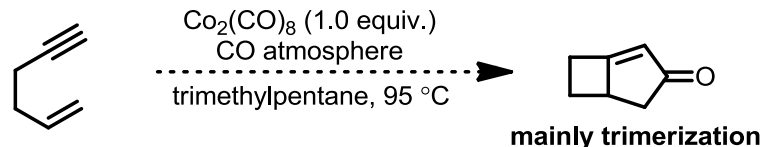
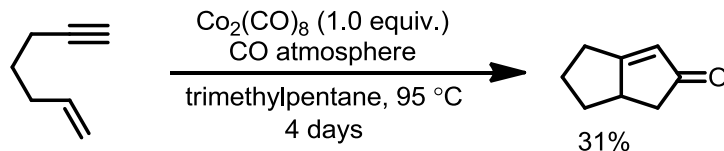
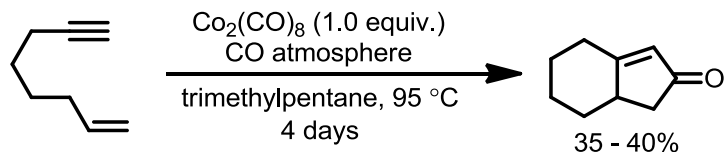
- Bent conformation of alkyne upon complexing
- RDS: electronic consideration and selectivity
- Role of CO and ligand
- Catalysis: recycle of the catalyst

Two directions for the development of PKR:

- High efficiency
- Catalytic amount of cobalt

Reactions based on acetylenehexacarbonyl dicobalt complex

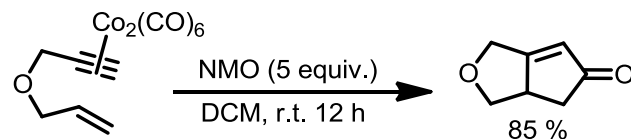
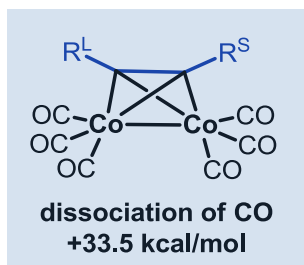
Intramolecular Pauson-Khand reaction



- Unactivated olefin can participate
- No regioselectivity problem for olefin
- Useful synthesis of bicyclic moieties

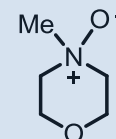
Additives for Pauson-Khand reaction

- N-oxide



- Oxidation of CO on Co to release a vacant site
- Greatly-optimized conditions (temp., time)
- Decomposition of Co-alkyne w/o alkene

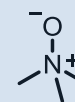
Schreiber:



NMO

N-methylmorpholine
-N-oxide

Jeong:



TMANO

Trimethylamine
N-oxide

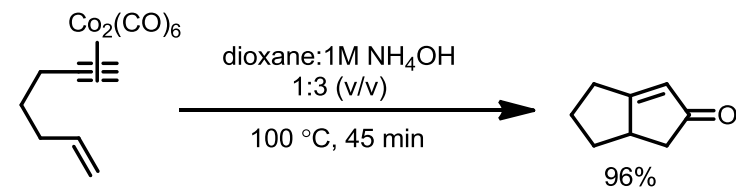
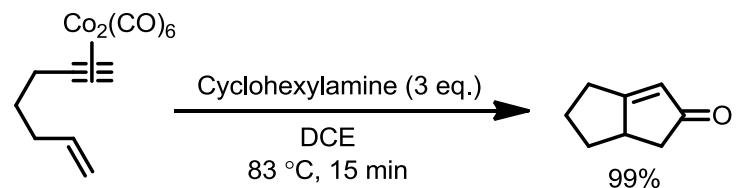
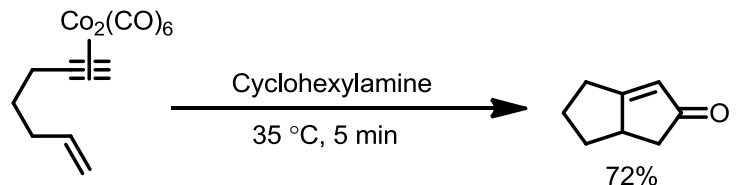
Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436

Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289

Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett.* **1991**, 204

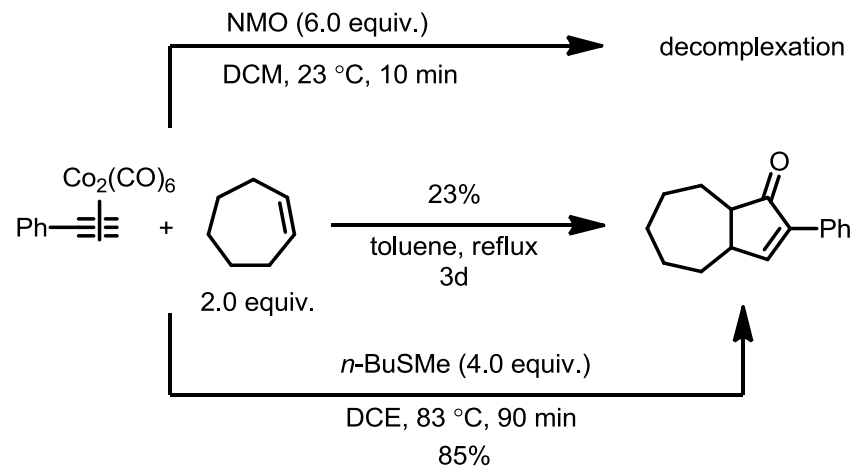
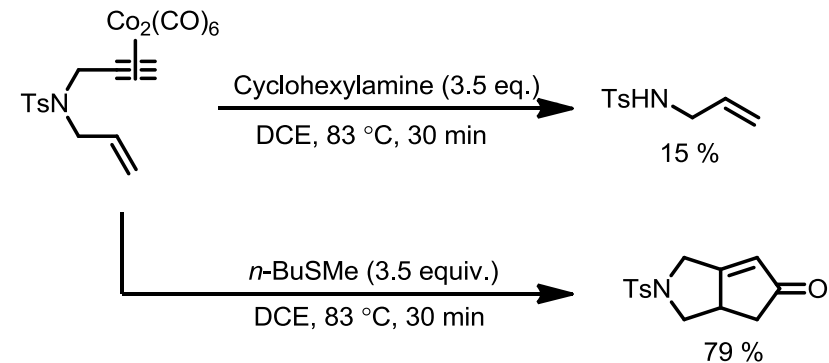
• Additives for Pauson-Khand reaction

• Amine



- Control confirmed the role of NH_3
- *Cheapest and most convenient promoter*

• Sulfide



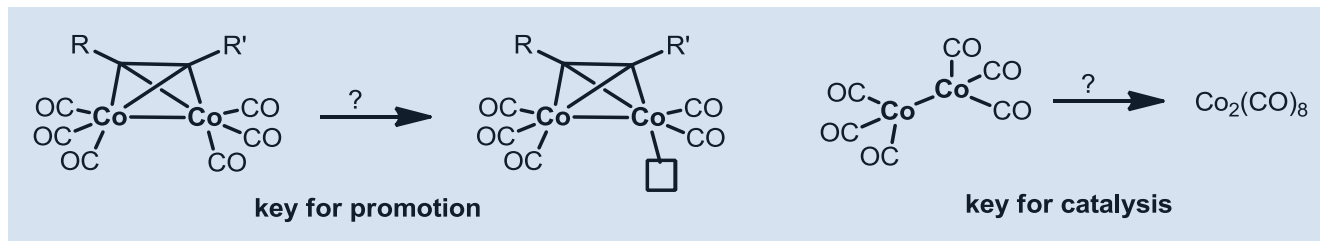
Reactions based on acetylenehexacarbonyl dicobalt complex

- **Additives for Pauson-Khand reaction**

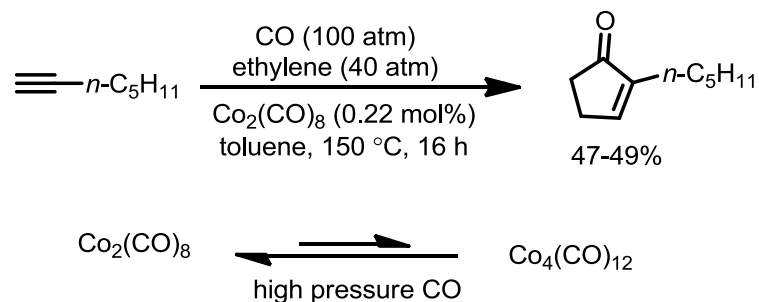
- Other promotions
 - Silica gel and molecular sieves
 - Photochemical induction

- **Catalytic Pauson-Khand reaction**

- Different setting points



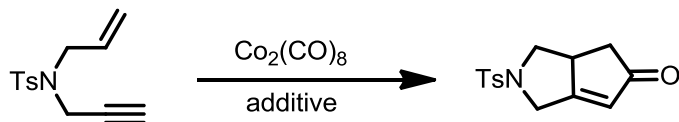
- **A straightforward solution**



Simonian, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, 27, 1245
Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Org. Lett.* **1999**, 1, 1187
Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, 118, 2285
Rautenstrauch, V.; Megard, P.; Conesa, J.; Kuster, W. *Angew. Chem. Int. Ed.* **1990**, 29, 1413

Catalytic Pauson-Khand reaction

- Additive

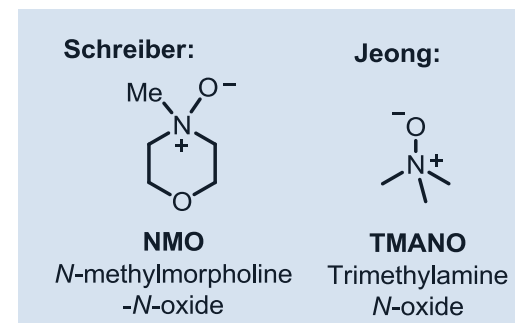


Entry	Co ₂ (CO) ₈ (mol%)	Additive (mol%)	Solvent	T (°C)	p(CO) (atm)	yield (%)
1	7.5	none	DME	60	1	86
2	10	none	DME	70	1	63
3	5	P(OPh) ₃ (20)	DME	120	3	94
4	3	DME (12)	Toluene	120	7	84
5	10	CyNH ₂ (20)	DME	70	1	89
6	5	Bu ₃ PS (30)	Benzene	70	1	87
7	10	TMTU (60)	Benzene	70	1	95

- In all cases, CO atmosphere is indispensable
- Non-oxidative additives are best
- Reaction conditions are quite specific

- Two criteria for additive

- Stabilize unsat. Co
- Create vacant site

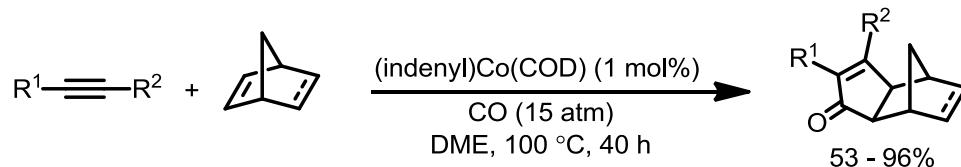


- N-oxide is detrimental in catalytic reaction**

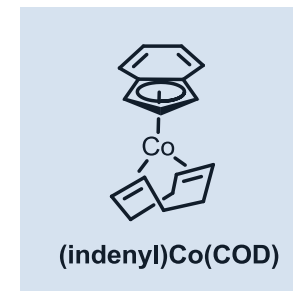
- High purity of cobalt carbonyl is critical**

- Catalytic Pauson-Khand reaction with other Co source**

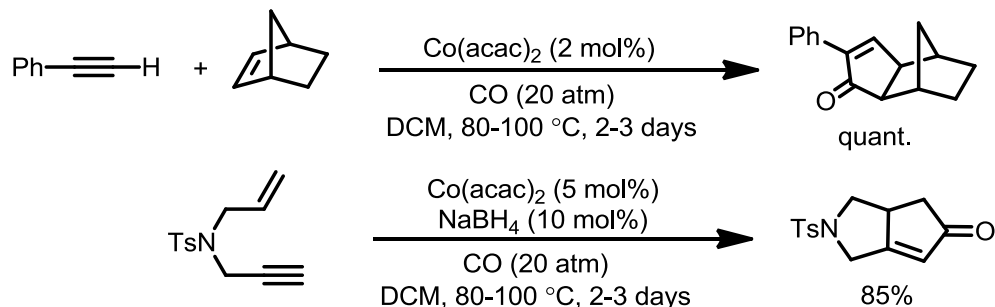
- (indenyl)Co(COD)*



- Indenyl group is indispensable
- Unactive olefin not working



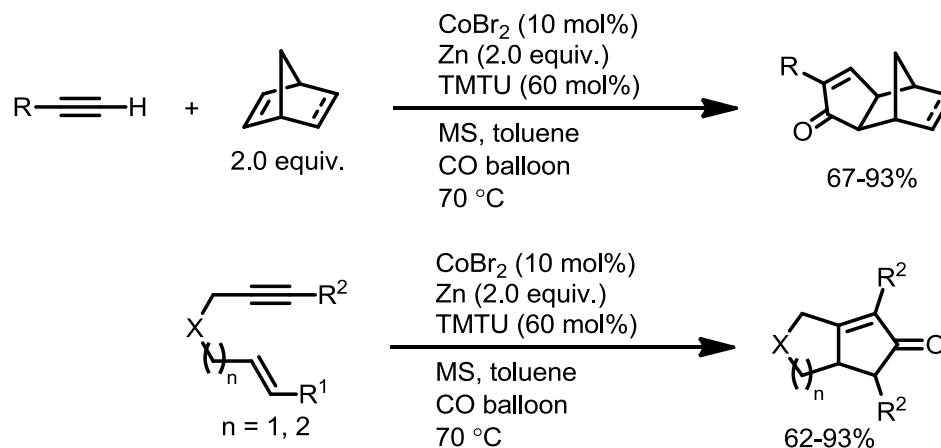
- Co(acac)₂* with *NaBH₄*



- CoCl_2 , $\text{CoCl}(\text{PPh}_3)_3$, $\text{CpCo}(\text{CO})_2$ showed marginal reactivity
- $\text{Co}_2(\text{CO})_6$ -alkyne complex was isolated in the reaction

- **Catalytic Pauson-Khand reaction with other Co source**

- $\text{CoBr}_2/\text{Zn}/\text{TMTU}$



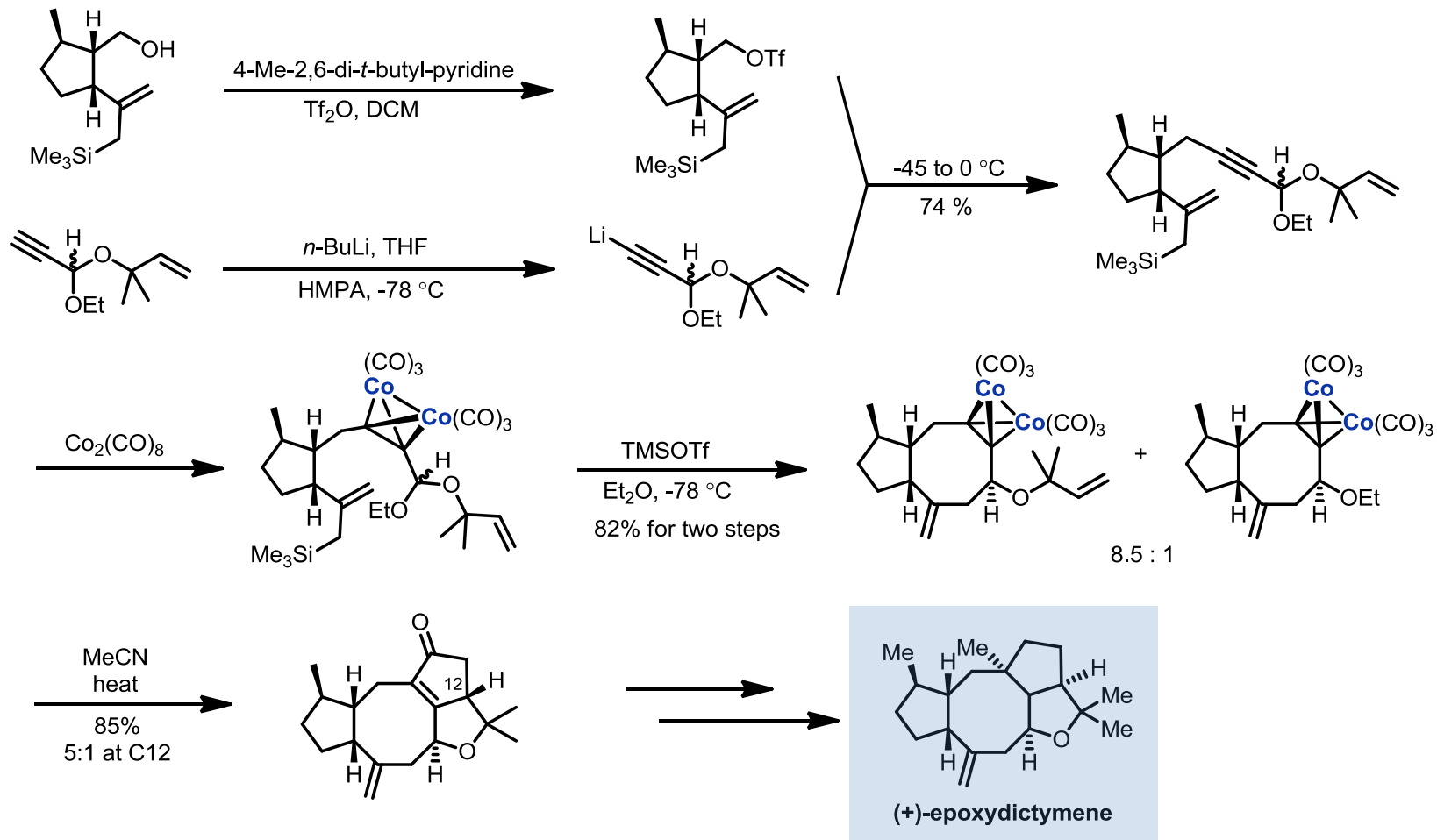
- **Summary of Pauson-Khand reaction**

- Superior reaction to synthesize cyclopentenone
- Intramolecular reaction more reliable and useful
- Intermolecular: limitation of substrate scope
- Catalytic: fine-tuning of conditions needed, specific condition

Reactions based on acetylenehexacarbonyl dicobalt complex

Application of Nicholas and Pauson-Khand reaction

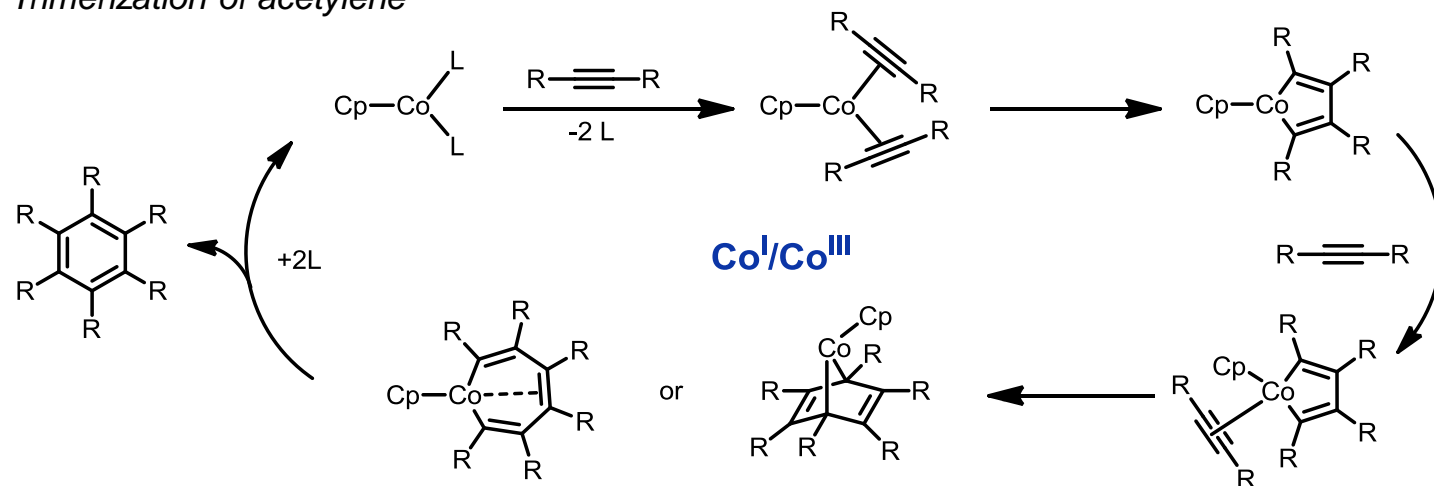
- Cobalt-mediated total synthesis of (+)-Epoxydictymene



- *Reactions based on acetylenehexacarbonyl dicobalt complex*
 - *Pauson-Khand reaction*
 - *Nicholas reaction*
- ***Cobalt-mediated/catalyzed cyclization***
- *Cobalt-catalyzed coupling reaction*
- *Cobalt-catalyzed C-H activation*

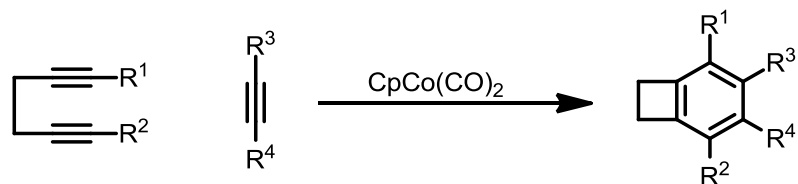
- **[2+2+2] Cycloaddition**

- *Trimerization of acetylene*



- Co catalyst can be employed in catalytic amount
- Symmetric internal alkyne works best
- Alkyne with bulky silyl groups failed to trimerize

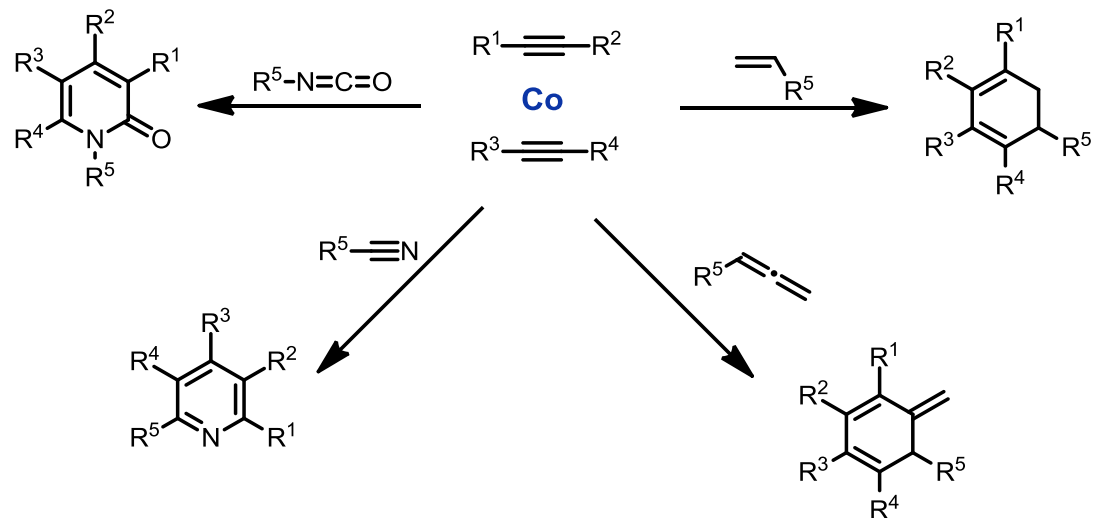
- *Elegant modification*



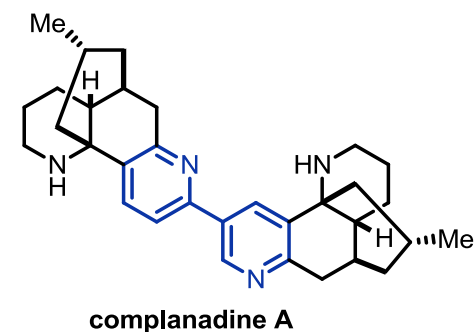
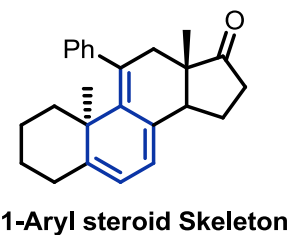
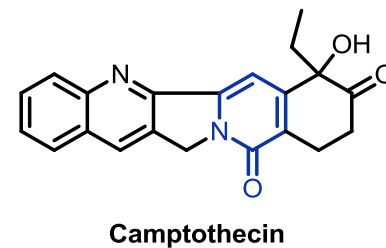
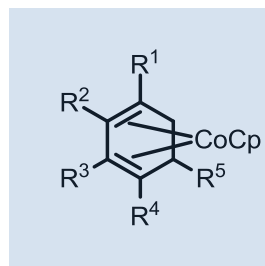
- $\text{R}^3 \text{ R}^4$: bulky group, usually silyl
- Various fused ring systems

• [2+2+2] Cycloaddition

- Versatile methodology



- Often stoichiometric Co is necessary
- Nitriles and cyanates are less likely to trimerize
- Total-synthesis-directed development



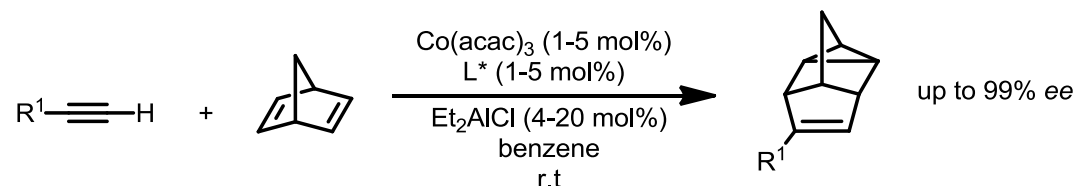
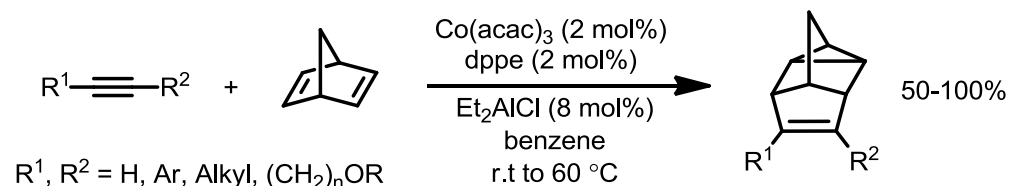
Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991

Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 3937

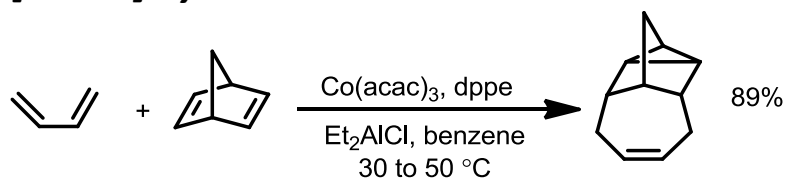
Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924

Cobalt-Mediated/Catalyzed Cycloaddition

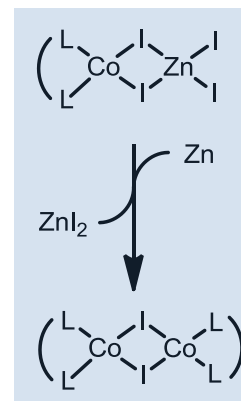
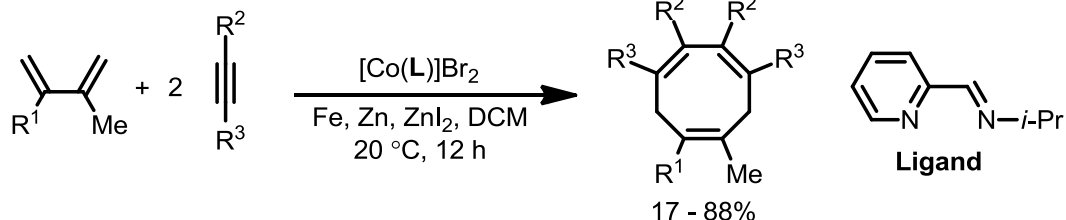
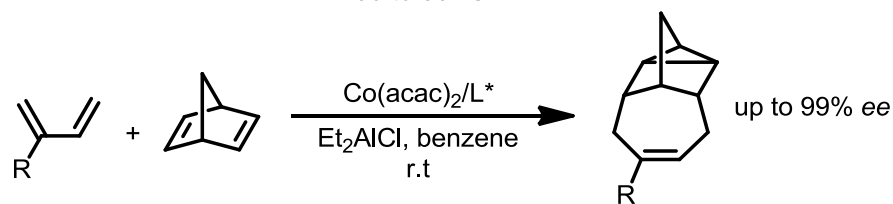
• [2+2+2] Homo-Diels-Alder cycloaddition



• [4+2+2] Cycloaddition



- Usually done by Ni(0), Rh, Fe and Ru
- Substrates expanded to electron-neutral alkynes
- Different roles of nbd as in PKR

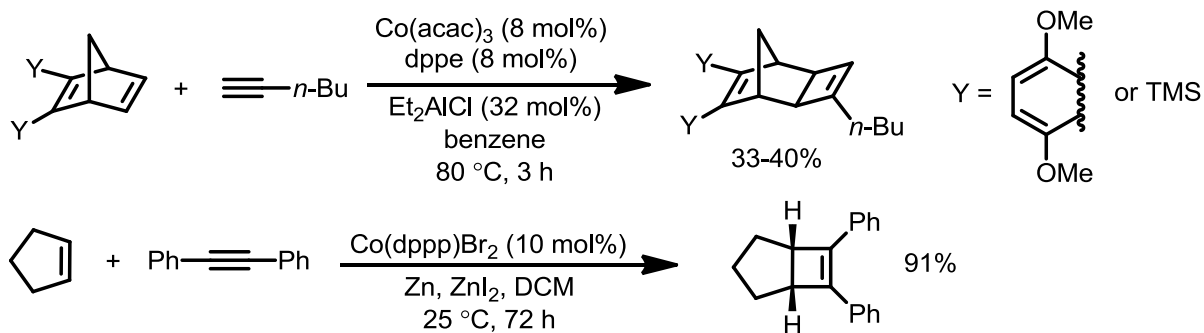


Lyons, J. E.; Myers, H. K.; Schneider, A. *J. Chem. Soc. Chem. Commun.* **1978**, 636

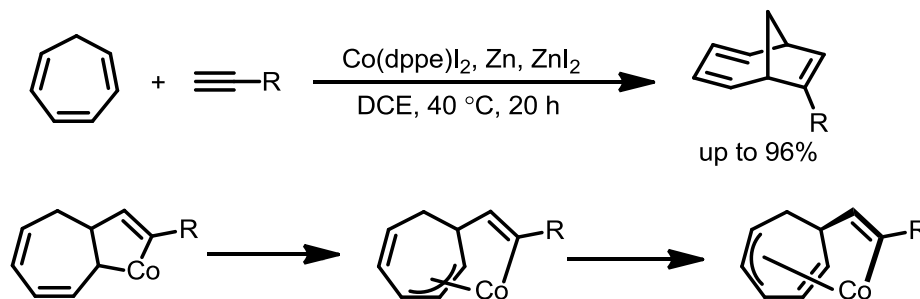
Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, 112, 5627

Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, 117, 6863

• [2+2] Cycloaddition

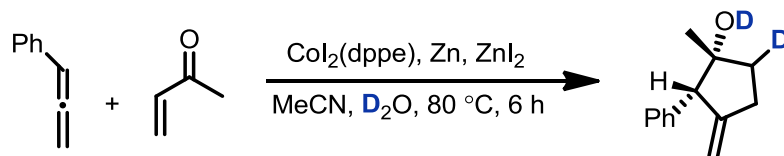
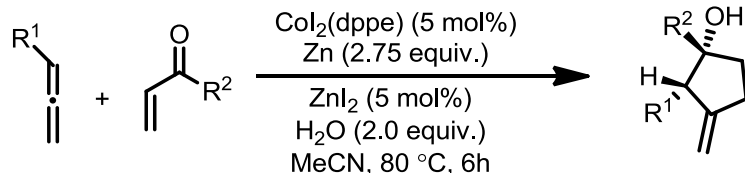


• [6+2] Cycloaddition



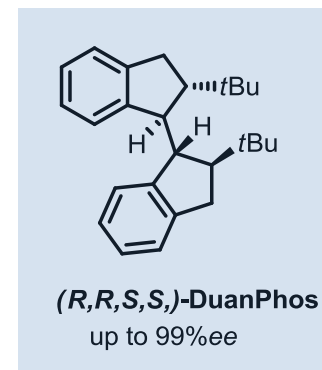
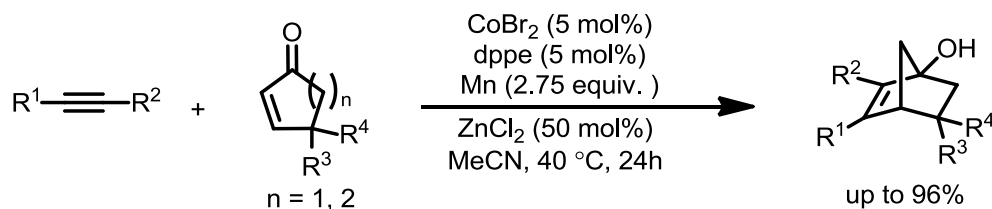
• [3+2] Cycloaddition

- With allenes and enones



- High diastereoselective
- Co(I)/Co(III)-catalytic cycle
- Crucial role of ZnI₂

- With alkynes and cyclic enones



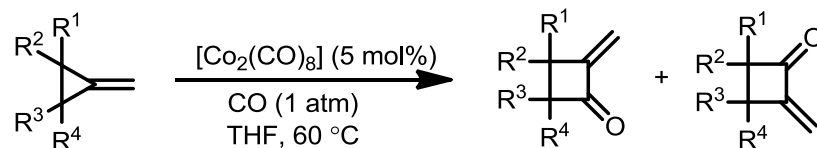
- Derivatives of nickel-catalyzed reductive cyclization (Ni(0)/Et₃SiH)
- Not as versatile as nickel chemistry (substrate scope)

Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166

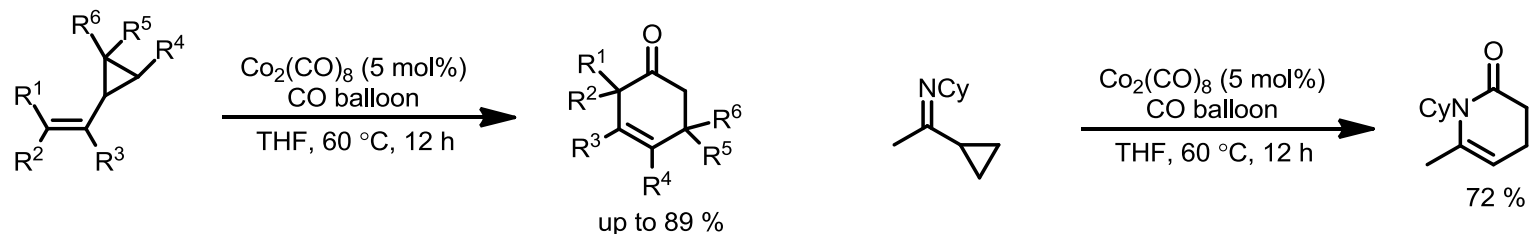
Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 10592

Cobalt-Mediated/Catalyzed Cycloaddition

• [3+1] Cycloaddition

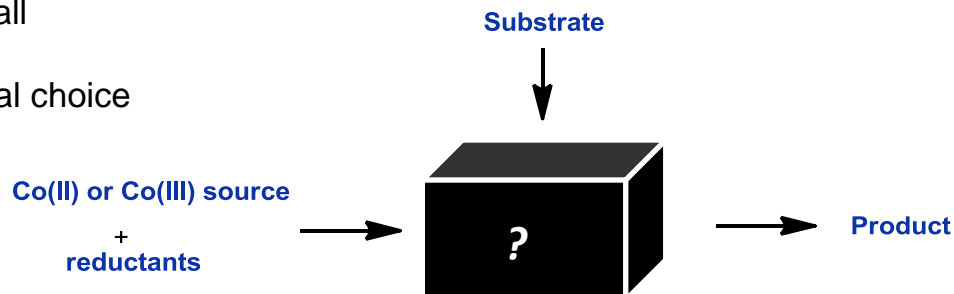


• [5+1] Cycloaddition



• Summary of Cobalt-Mediated/Catalyzed Cycloaddition

- Trimerization is the most useful among all
- However, high temperature is needed
- Competitive field-cobalt is not the optimal choice
- Little solid evidence of intermediate

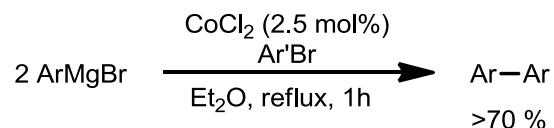


Kurahashi, T.; de Meijere, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7881
Kurahashi, T.; de Meijere, A. *Synlett.* **2005**, *17*, 2619

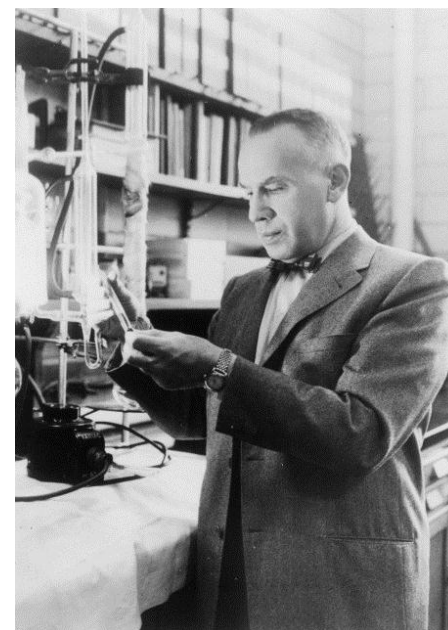
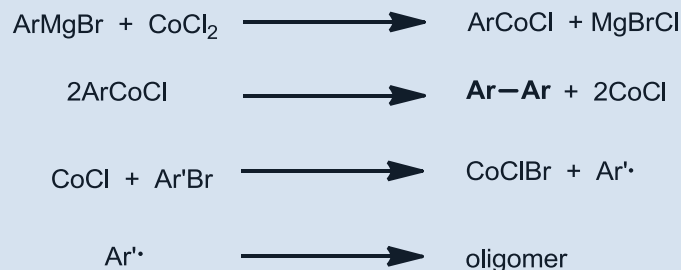
- *Reactions based on acetylenehexacarbonyl dicobalt complex*
 - *Pauson-Khand reaction*
 - *Nicholas reaction*
- *Cobalt-mediated/catalyzed cyclization*
- ***Cobalt-catalyzed coupling reaction***
- *Cobalt-catalyzed C-H activation*

Cobalt-Catalyzed Coupling Reaction

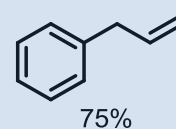
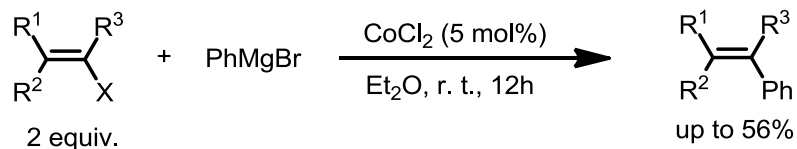
- Homo-coupling of Grignard Reagent**



- **First metal-catalyzed homo-coupling of Grignard reagent**
- Stoichiometric amount of oxidant (~1.0 equiv)



- Cross-coupling of Grignard Reagent with vinyl halide**



- 30 years before Kumada coupling
- Replaced by Pd, Ni, Co for 30 years.

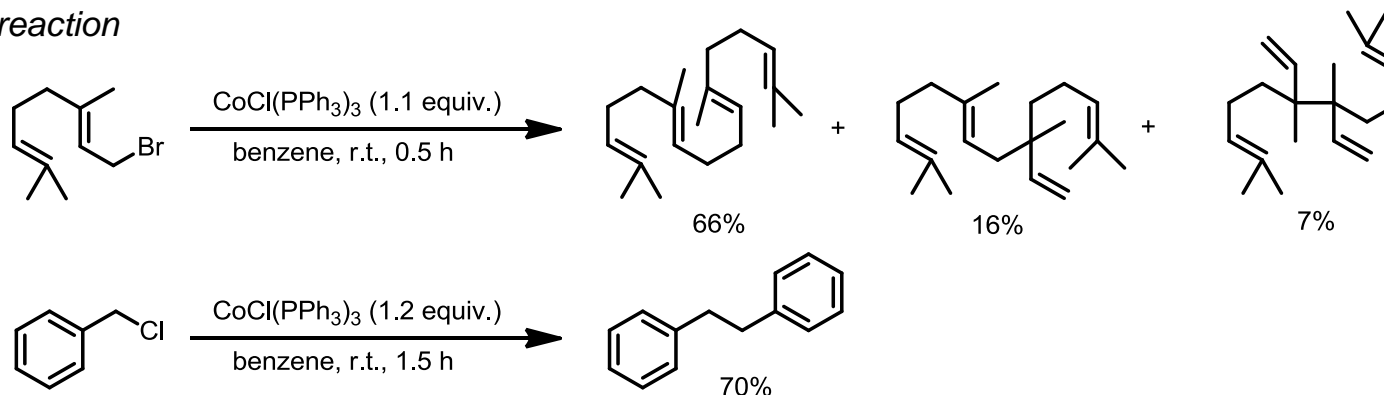
Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, 63, 2316

Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, 65, 504

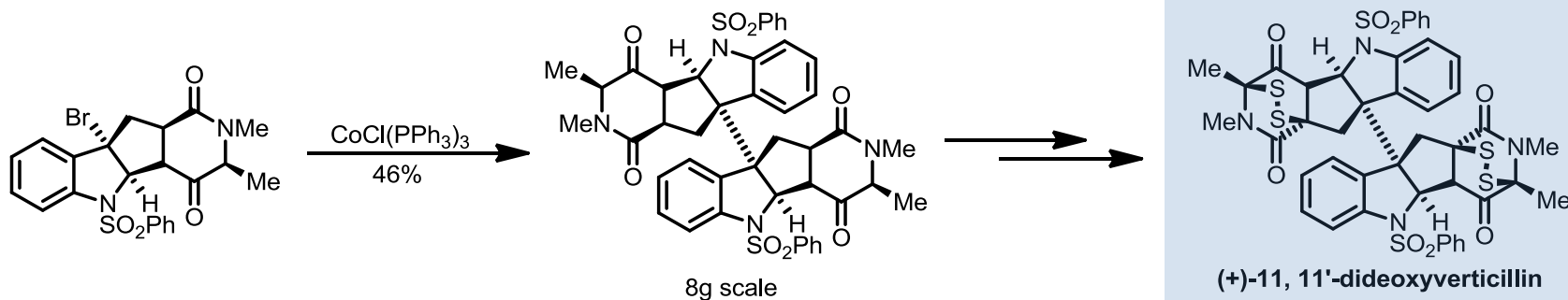
Cobalt-Catalyzed Coupling Reaction

- **Radical dimerization**

- *Early reaction*



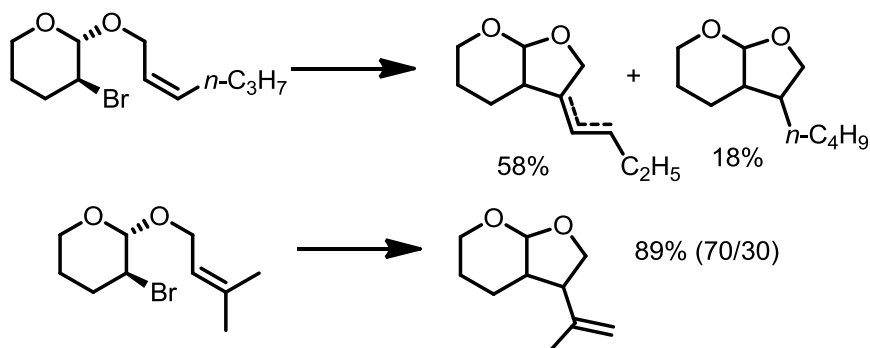
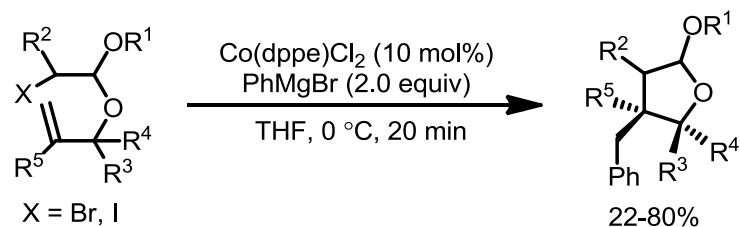
- *Application in total synthesis*



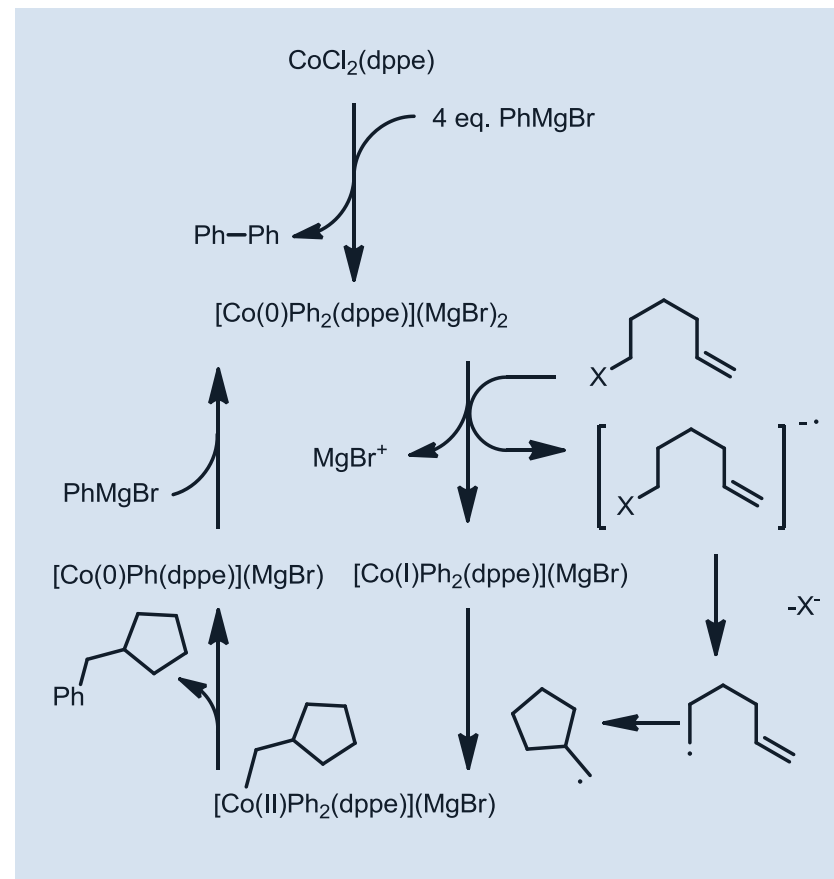
Momose, D.; Iguchi, K.; Sugiyama, T.; Yamada, Y. *Tetrahedron Lett.* **1983**, 24, 921
Yamada, Y.; Momose, D. *Chem. Lett.* **1981**, 1277
Kim, J.; Ashenurst, J. A.; Movassaghi, M. *Science* **2009**, 324, 238

Cobalt-Catalyzed Coupling Reaction

- Revived in the field of sp^3 halide coupling
 - Tandem radical cyclization and coupling

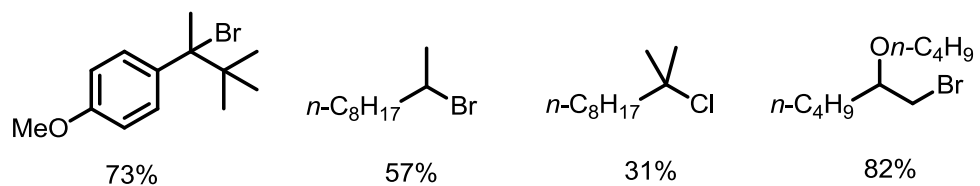
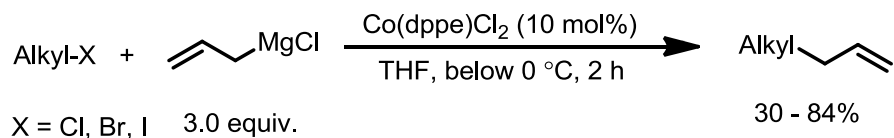


- Less than 4eq. GR didn't work for stoichiometric rxn
- Different reactivity of internal alkene

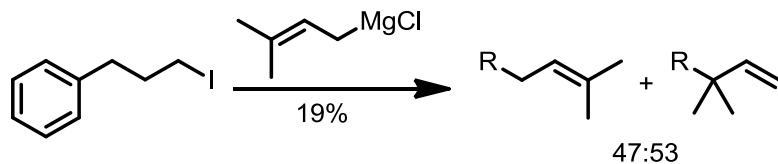


Cobalt-Catalyzed Coupling Reaction

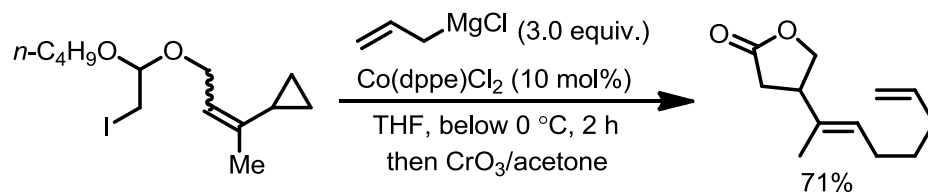
- Revived in the field of sp^3 halide coupling
 - Allylation of alkyl halide- sp^3 - sp^3 coupling



- Unsymmetric allyl Grignard reagent



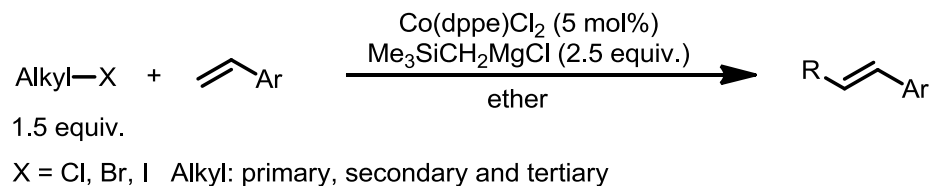
- Radical clock



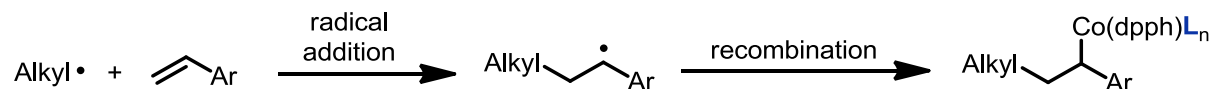
Cobalt-Catalyzed Coupling Reaction

- Revived in the field of sp^3 halide coupling

- Heck-type reaction of alkyl halides



- Key for success



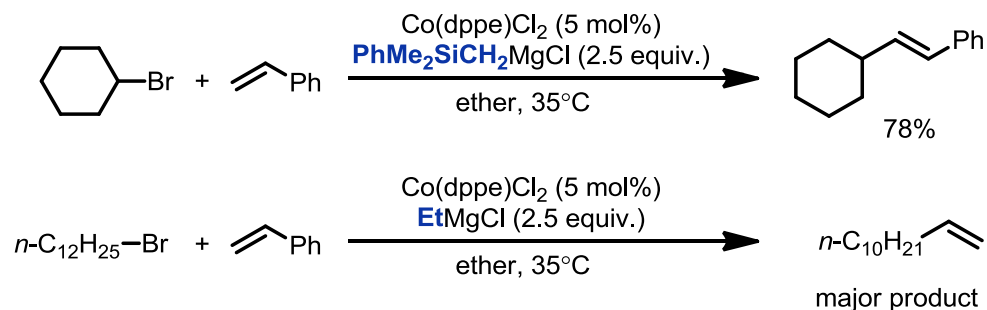
- Selection of L

L = Aryl, reductive elimination

L = Alkyl w/o β -H, Heck type

L = Alkyl w/ β -H, selectivity issue

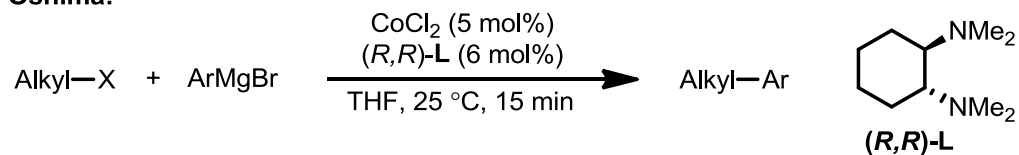
- Reaction with other alkyl Grignard reagents



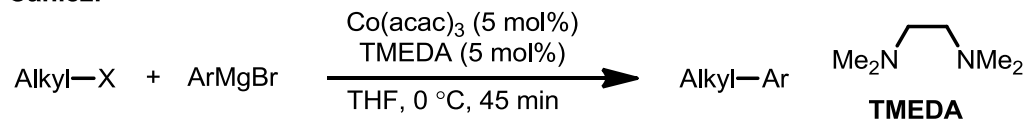
Cobalt-Catalyzed Coupling Reaction

- **Revived in the field of sp^3 halide coupling**
 - Cross-coupling of alkyl halide and Grignard reagent

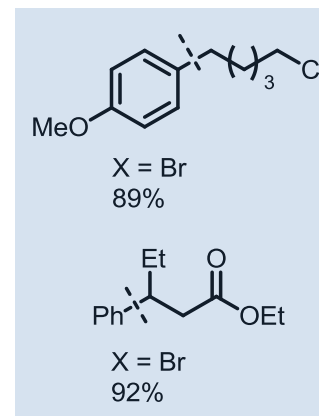
Oshima:



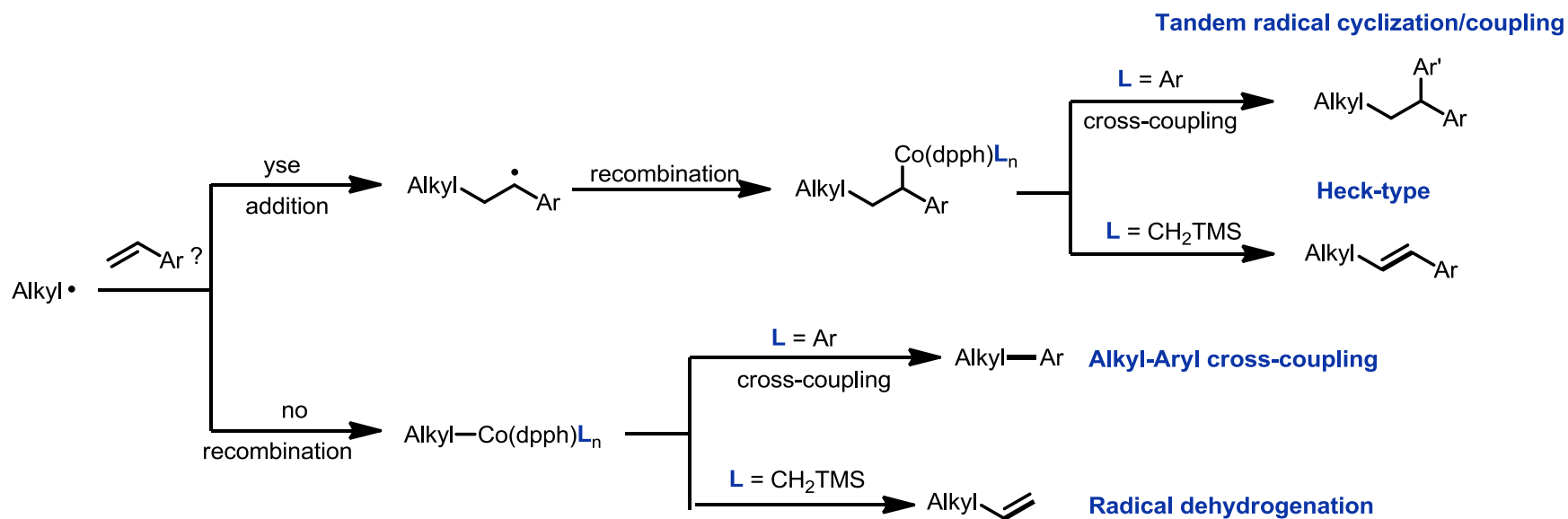
Cahiez:



Alkyl: primary, secondary



- Summary of cobalt-catalyzed coupling**

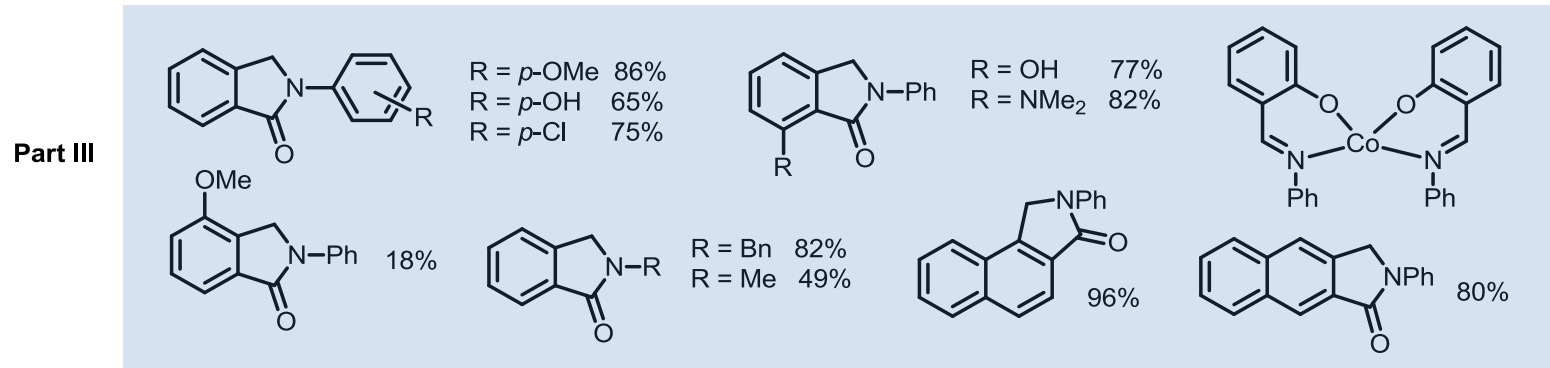
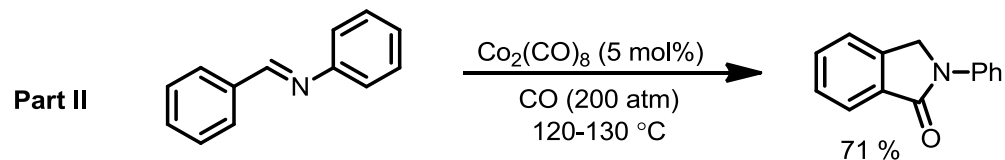
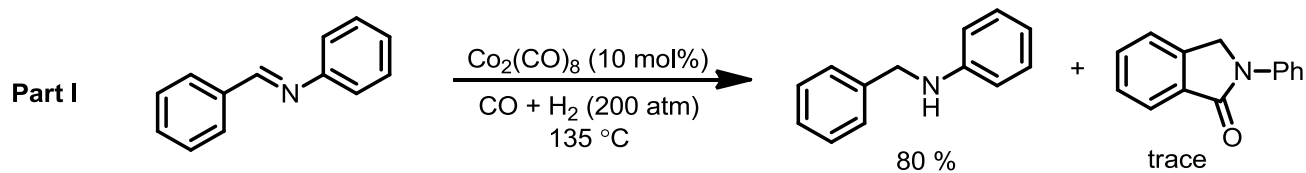


- Good choice to do coupling with alkyl halide
- Complimentary to palladium coupling reaction
- Not as systematic and versatile as nickel-catalyzed coupling (G. C. Fu's work)

- *Reactions based on acetylenehexacarbonyl dicobalt complex*
 - *Pauson-Khand reaction*
 - *Nicholas reaction*
- *Cobalt-mediated/catalyzed cyclization*
- *Cobalt-catalyzed coupling reaction*
- ***Cobalt-catalyzed C-H activation***

- **First report-C-H activation of Schiff base and azobenzene**

Horie

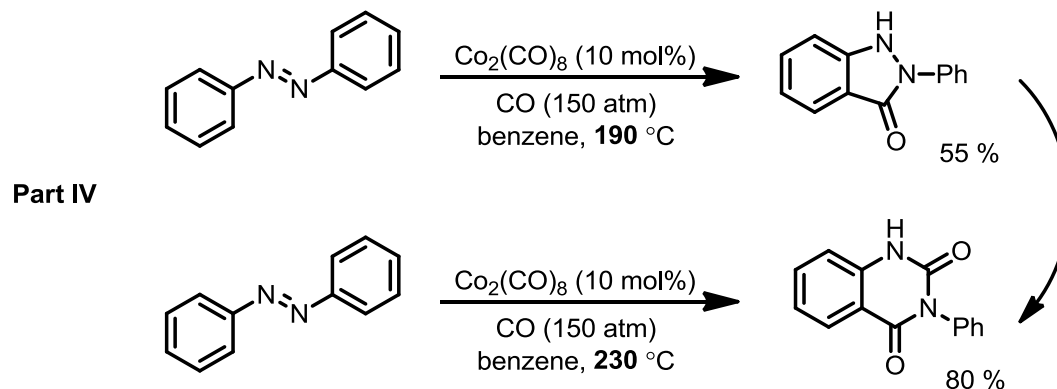


- Serendipitous discovery
- Chelation-assisted C-H activation

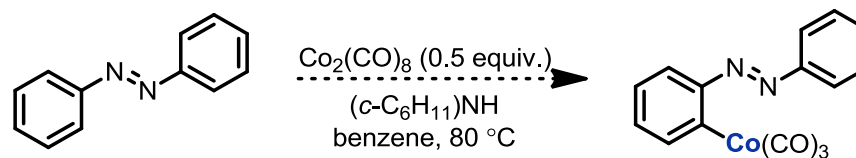
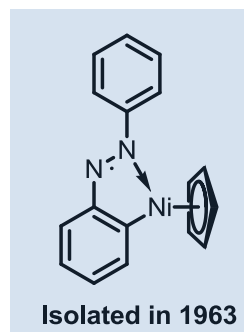
Cobalt-Catalyzed C-H Activation

- **C-H activation of azobenzene**

- C-H and N-N bond tandem activation



- Mechanistic study by Heck

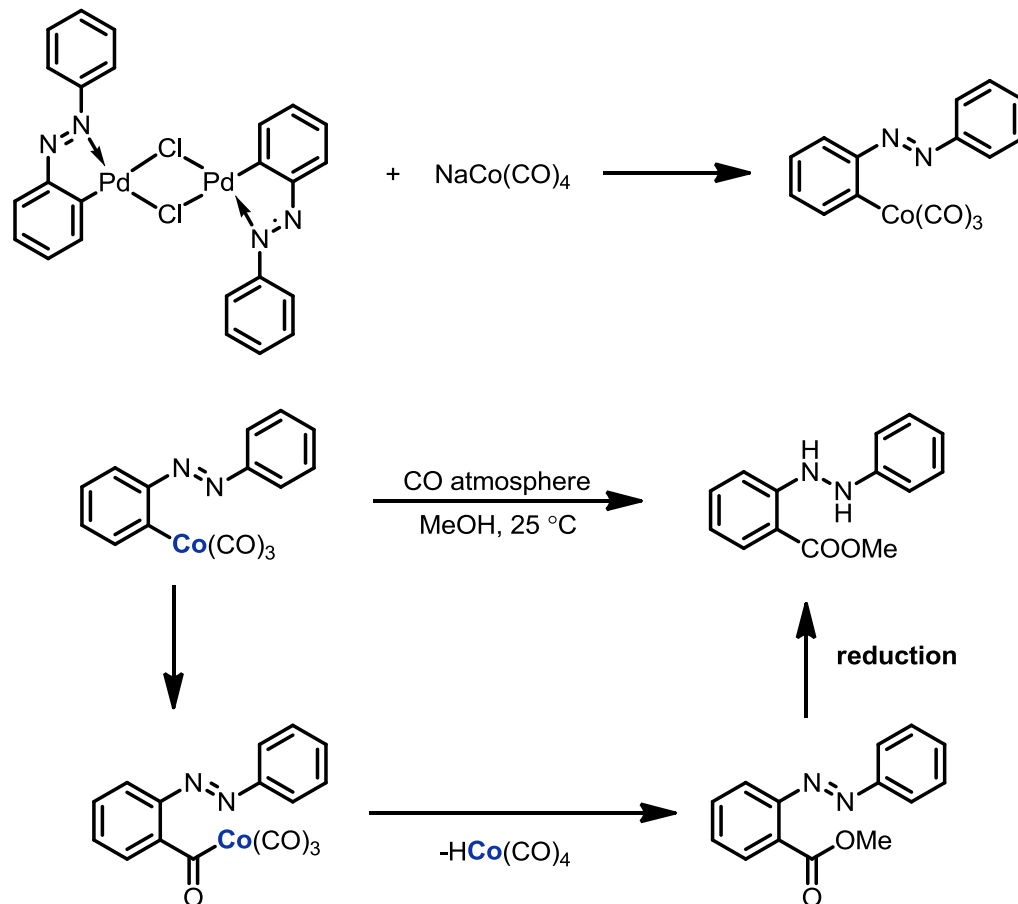


- No additional CO
- Reaction of the proton acceptor with $\text{Co}_2(\text{CO})_8$

Cobalt-Catalyzed C-H Activation

- **C-H activation of azobenzene**

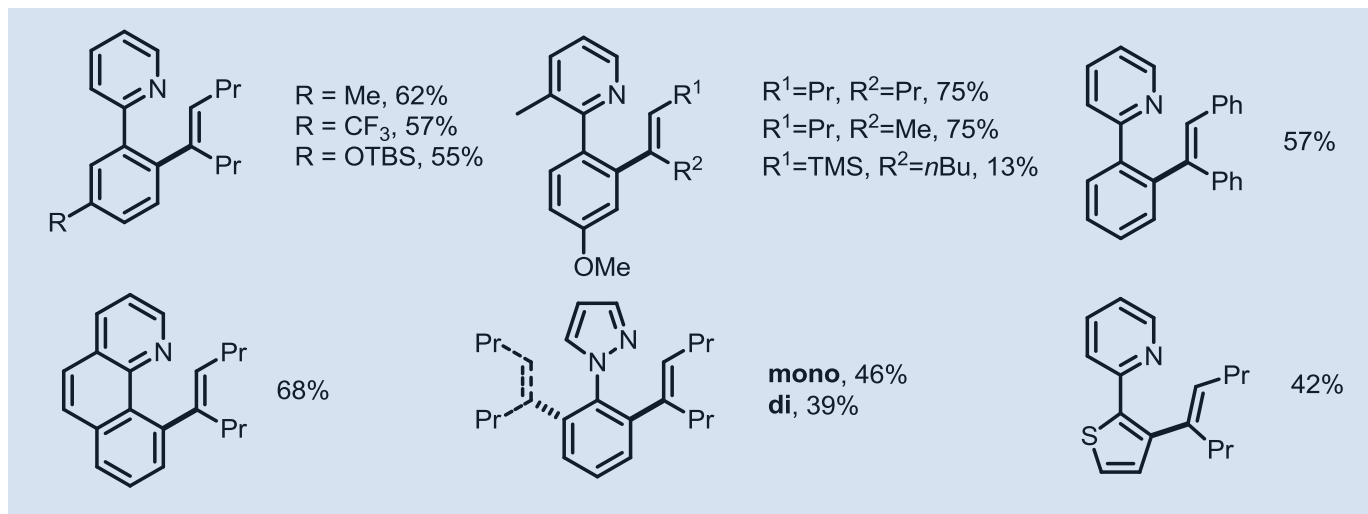
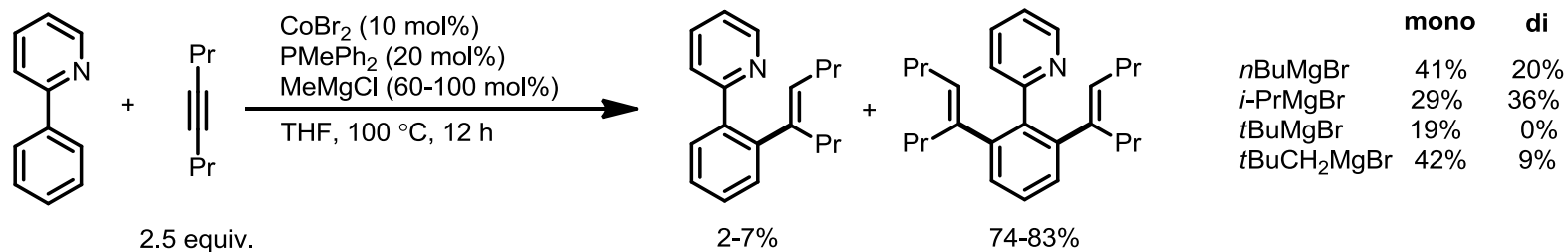
- Mechanistic study by Heck



Cobalt-Catalyzed C-H Activation

• Sp^2 C-H activation

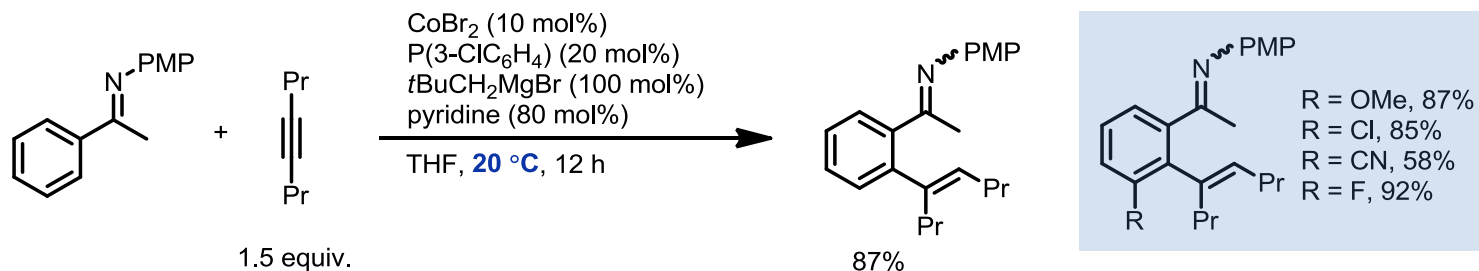
• Hydroarylation of alkyne



- Similar strategy used for iron-catalyzed C-H activation before
- Intermolecular KIE experiment: no H/D crossover, $k_H/k_D=2.1$

- Sp^2 C-H activation

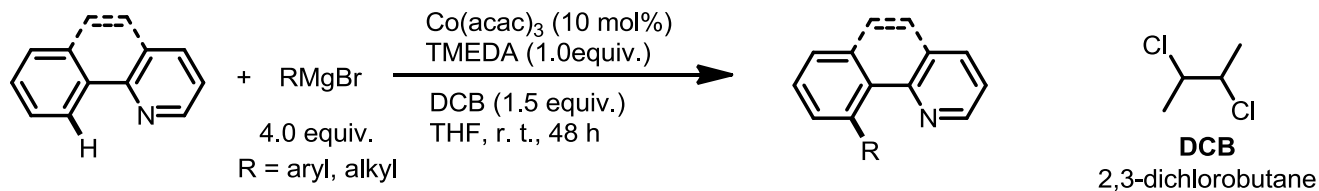
- Imine-directed



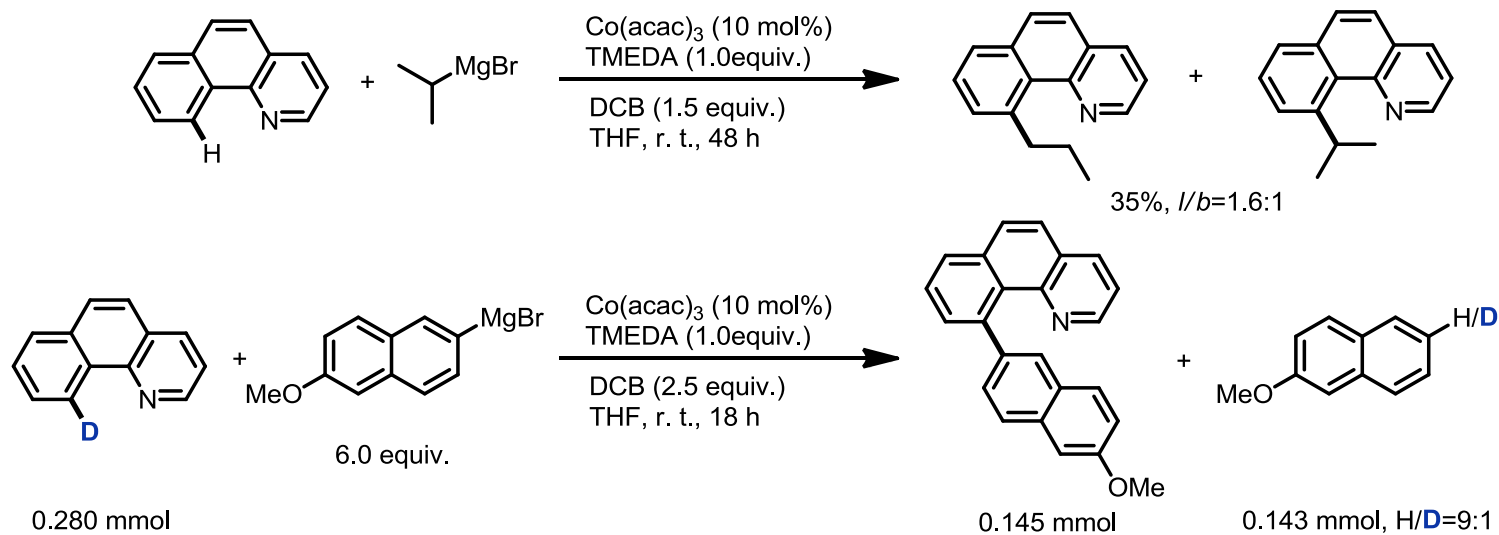
- Vital role of grignard reagent
- Low-temp C-H activation: high tolerance of FG, like CN
- Interesting secondary directing effect

- Sp² C-H activation**

- Coupling with Grignard reagent



- Mechanistic study

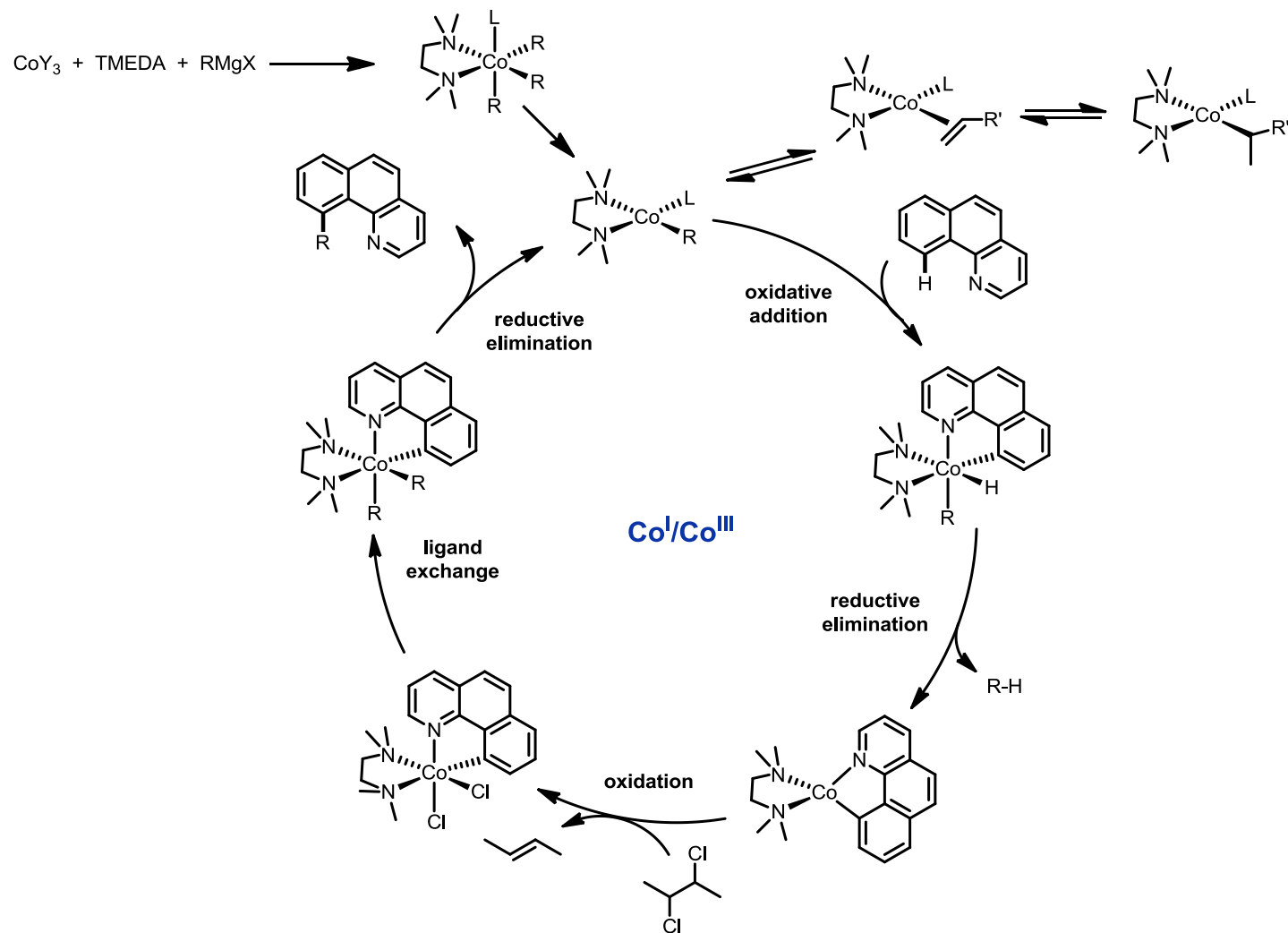


- Intermolecular KIE: $k_H/k_D=1.04$

Cobalt-Catalyzed C-H Activation

- **Sp² C-H activation**

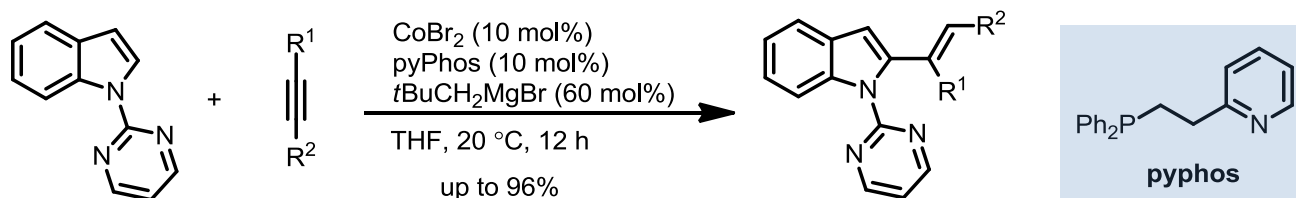
- *Mechanistic study*



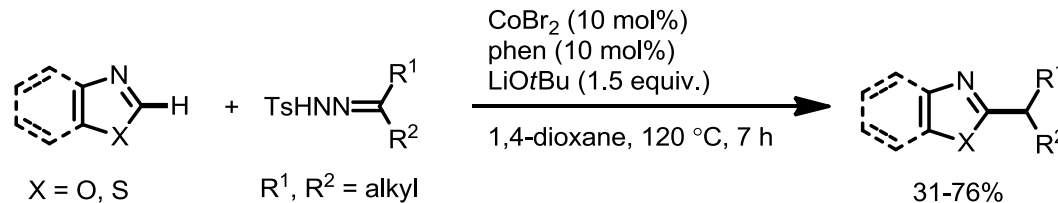
Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109

- **Sp² C-H activation**

- C2-alkenylation of indole



- Alkylation of azole



- C-H functionalization instead of C-H activation
- Complementary to previous Cu(I) chemistry

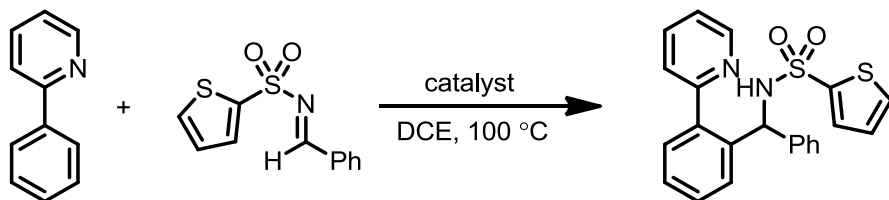
Ding, Z.-H.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4698

Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 775

Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296

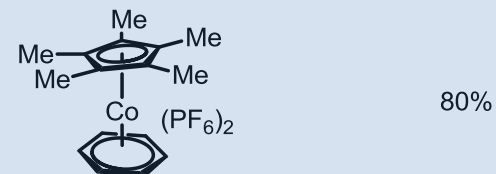
- Sp² C-H activation**

- With Co(III) complex



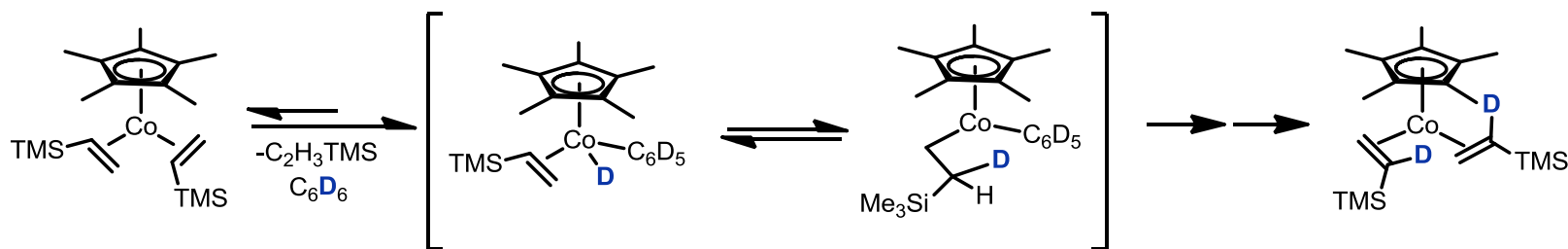
- Can react with imine and Michael acceptor
- Stable and easily available catalyst
- No additive needed for the reaction

[Cp*CoCl₂]₂ (5 mol%) 0%
 [Cp*CoCl₂]₂ (5 mol%)/AgPF₆ (20 mol%) 48%



- Hydroacylation with Co(I)**

- Discovery of C-H activation at Co(I) center

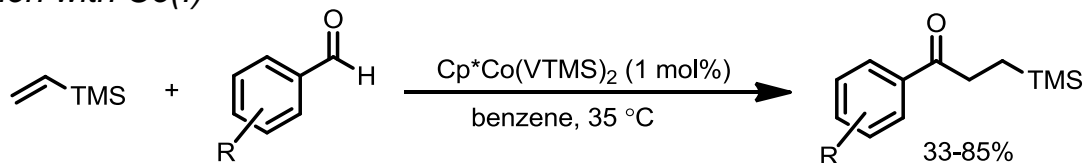


Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207
 Lenges, C. P.; Brookhart, M.; Grant, B. E. *J. Organomet. Chem.* **1997**, *528*, 199

Cobalt-Catalyzed C-H Activation

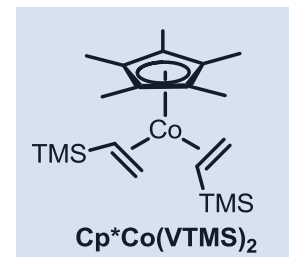
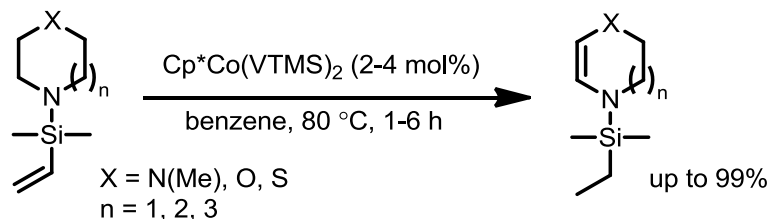
- ***Sp² C-H activation***

- *Hydroacylation with Co(I)*



- Works well for olefin with bulky silyl groups
- Intramolecular hydroacylation available

- ***Sp³ C-H activation***



- Vinyl group as directing group and hydrogen acceptor
- Milder condition compared to previous rhodium version

- ***Summary of cobalt-catalyzed C-H activation***

- Almost no novel reaction type
- Whatever C-H activation Co does, it does mildly

Lenges, C. P.; White, P. S.; Brookhart, M. J. *Am. Chem. Soc.* **1998**, *120*, 6965
Bolig, A. D.; Brookhart, M. J. *Am. Chem. Soc.* **2007**, *129*, 14544

- ***'Traditional' chemistry***
 - Co opens up various areas of organometallic chemistry
 - Usually replaced later by other transition-metals, Rh, Pd, Ru..
- ***'Novel' chemistry***
 - Almost no novel reactions discovered by using cobalt nowadays
 - Co is impressively versatile to replace other metals in developed reactions
- ***Co₂(CO)₈***
 - Stoichiometric reactions are reliable and efficient
 - Catalytic reactions rely on fine tuning of conditions
 - Readily converted to other oxidation states
 - Very good catalyst for carbonylation
- ***Co(II)/Co(III) + reductant***
 - Highly reactive species, milder reaction condition
 - Radical and cobalt-mediated transformation in one rxn
 - Usually Co(I)/Co(III) catalytic cycle
- ***Topics not covered today***
 - Carbonylation
 - Oxidation and reduction
 - Salen-Co chemistry

