

Transition-Metal-Catalyzed Laboratory-Scale Carbon–Carbon Bond-Forming Reactions of Ethylene

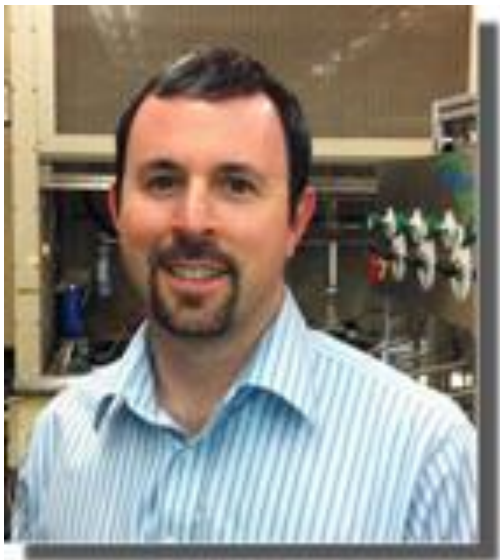
*Vaneet Saini, Benjamin J. Stokes, and Matthew S. Sigman**

Reporter: Huan Sun

Supervisor: Prof. Huang

2013-10-28

Angew. Chem. Int. Ed. **2013**, 52, 11206–11220.



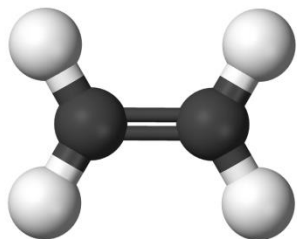
Matthew S. Sigman

- **1992**, B.S. Sonoma State University
- **1996**, Ph.D. Washington State University (with Prof. Bruce Eaton)
- **1997-1999**, NIH postdoctoral fellow, Harvard University (with Prof. Eric Jacobsen)
- **1999**, University of Utah

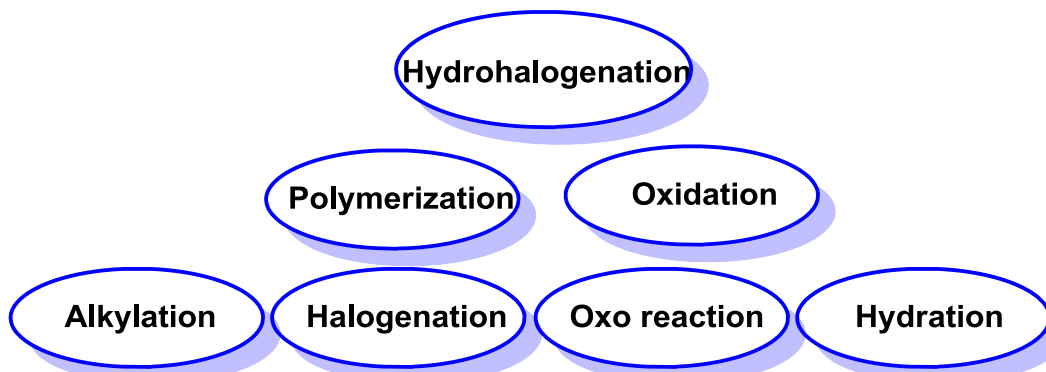
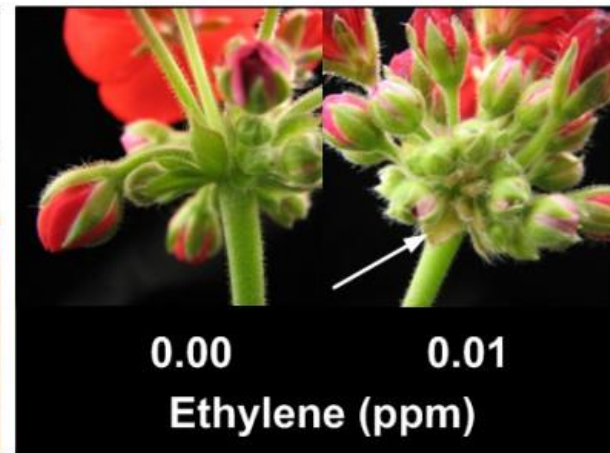
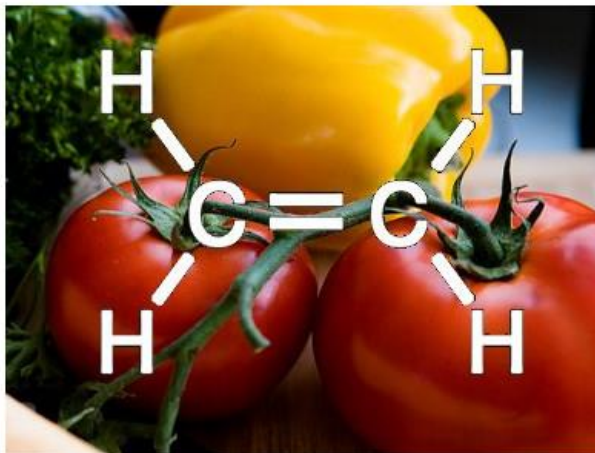
Research interests

- Pd-catalyzed alkene oxidations
- Enantioselective Heck-type reactions: enantioselective catalysis and ligand design
- Novel Diarylmethines as Lead Compounds for Breast Cancer Therapy
- Stereoselective C-H Functionalization

Ethylene



- colorless flammable gas with a faint "sweet and musky" odor when pure
- the simplest alkene
- the simplest unsaturated hydrocarbon after acetylene
- more than 140 million tons of ethylene are produced annually



Absent ethylene

apprehensions about working with gas-phase reactants

Attractive ethylene

- ◆ *abundance of this two-carbon building block*
 - ◆ *functionalization reactions of alkanes (methane and ethane in particular) are challenging*
 - ◆ *the simplest, readily functionalized hydrocarbon synthon*
-

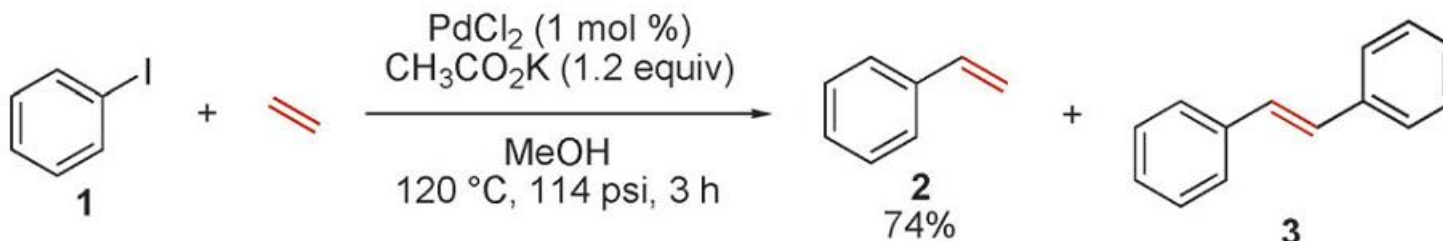
Contents:

- ✓ **Mizoroki-Heck-Type Reactions**
- ✓ **Multicomponent Coupling Reactions**
- ✓ **Hydrovinylation Reactions**
- ✓ **Directed C-H Functionalization Reactions**
- ✓ **Olefin Metathesis Reactions**
- ✓ **Nonmetathetic Ethylene**

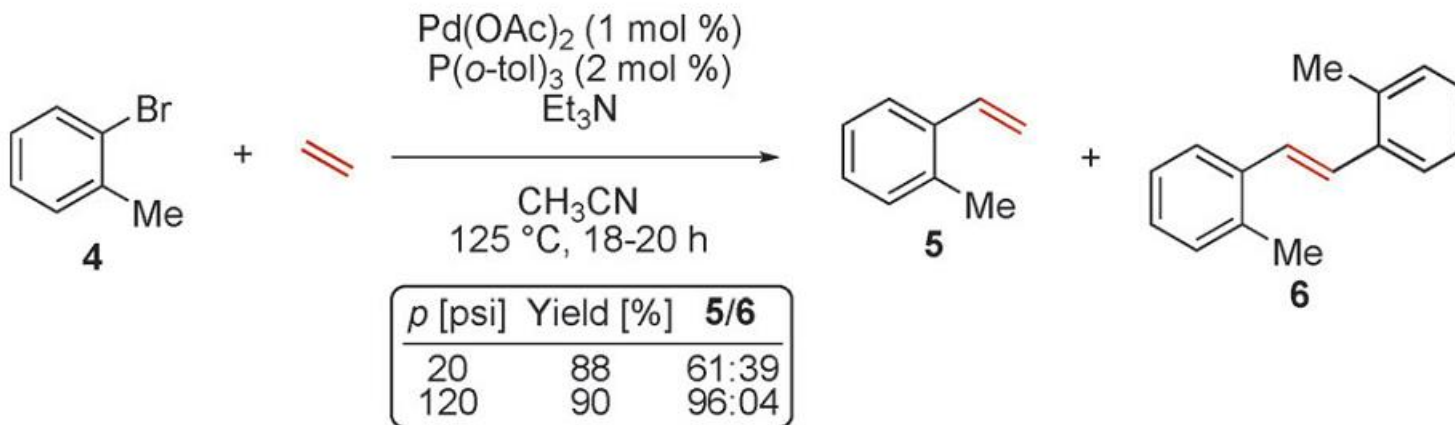
Mizoroki-Heck-Type Reactions of Ethylene

Palladium-catalyzed Mizoroki-Heck reactions using aryl electrophiles

a) Mizoroki Protocol (1971):



b) Heck Protocol (1978):

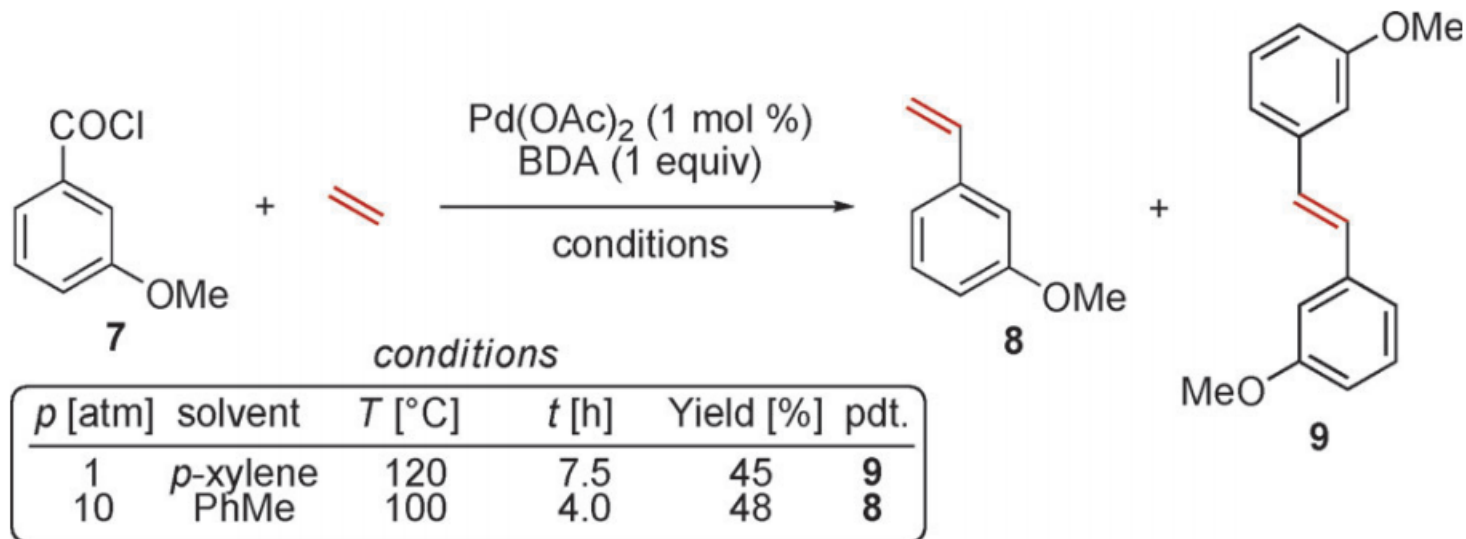


Reaction efficiency: reduction of catalyst load and pressure of ethylene

Optimization: DMF/H₂O as the solvent

1. *Bull. Chem. Soc. Jpn.* **1971**, 44, 581. 2. *J. Org. Chem.* **1978**, 43, 2454.
3. *Organometallics* **1994**, 13, 2405. 4. *J. Mol. Catal. A* **1995**, 97, 73.

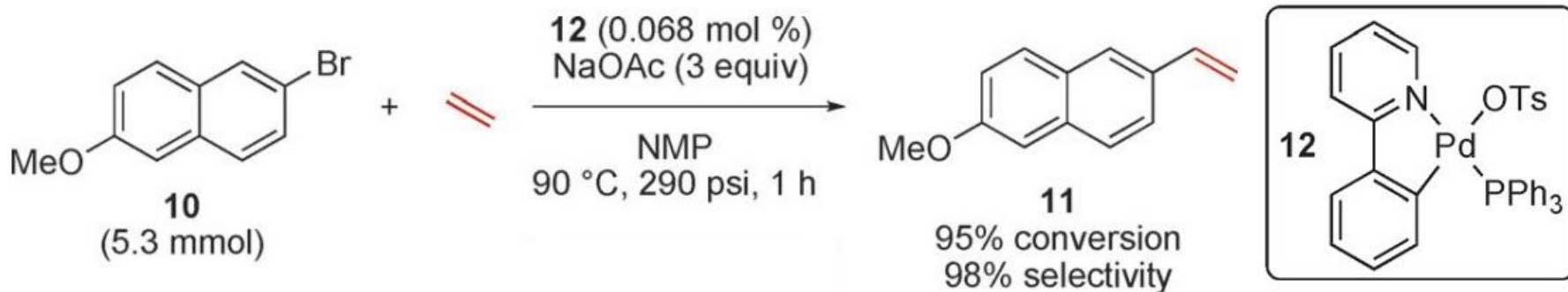
Decarbonylative Mizoroki-Heck reactions using **benzoyl chlorides** as electrophiles



selectivity based on the **pressure of ethylene**

J. Organomet. Chem. **1983**, 247, 117.

The **C,N-palladacycle**-catalyzed Mizoroki-Heck arylation



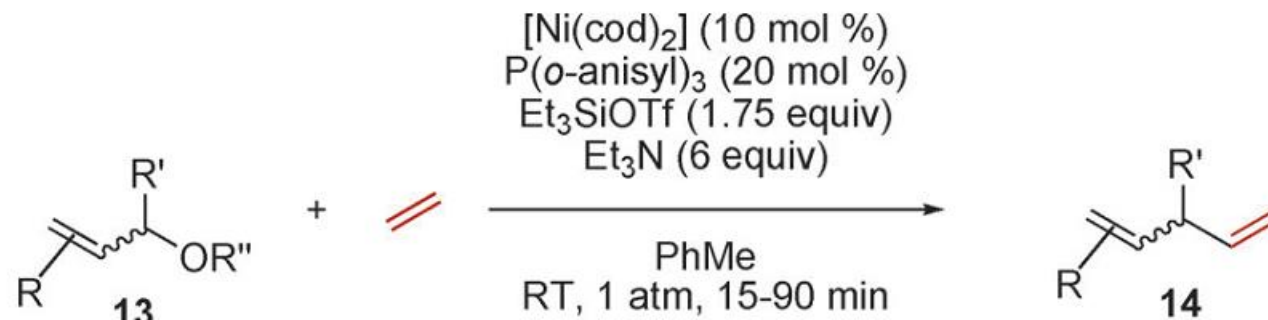
thermal stability VS product polymerization

1. *J. Organomet. Chem.* **2009**, 694, 683. 2. *Tetrahedron* **2010**, 66, 1102.

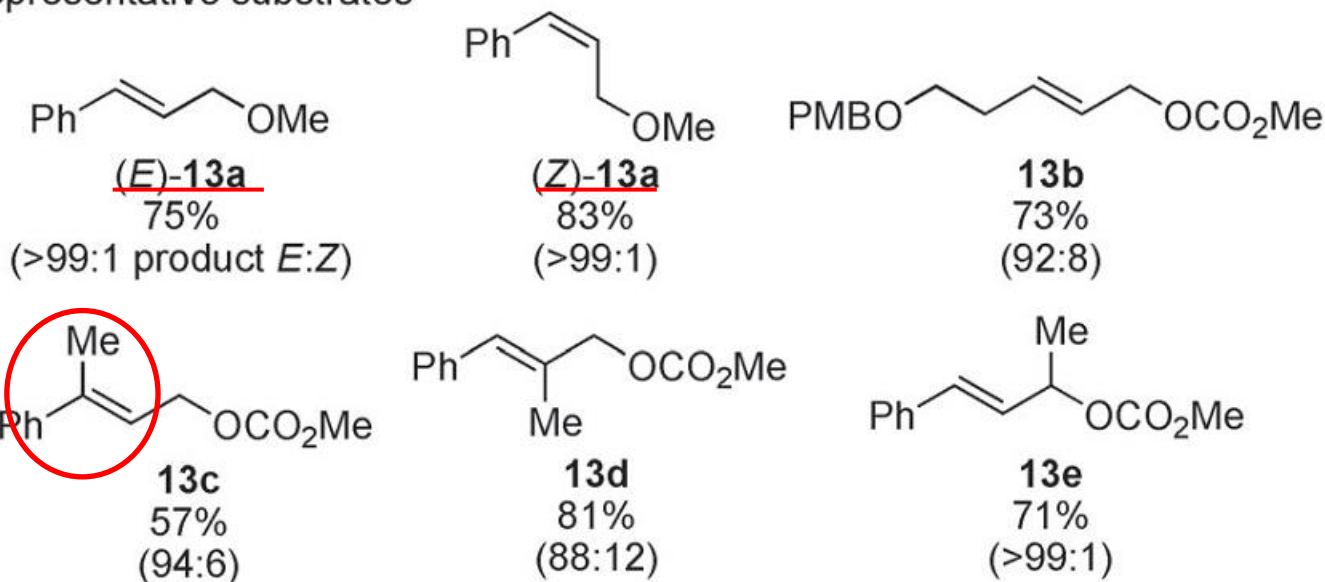
Palladium-catalyzed Mizoroki-Heck reactions: **not found widespread**

- ◆ *Always using aryl halides as electrophiles*
- ◆ *High operating pressure and temperature*
- ◆ *Polymerization of the desired products*

Nickel-catalyzed Mizoroki-Heck-Type reactions using *allylic electrophiles*

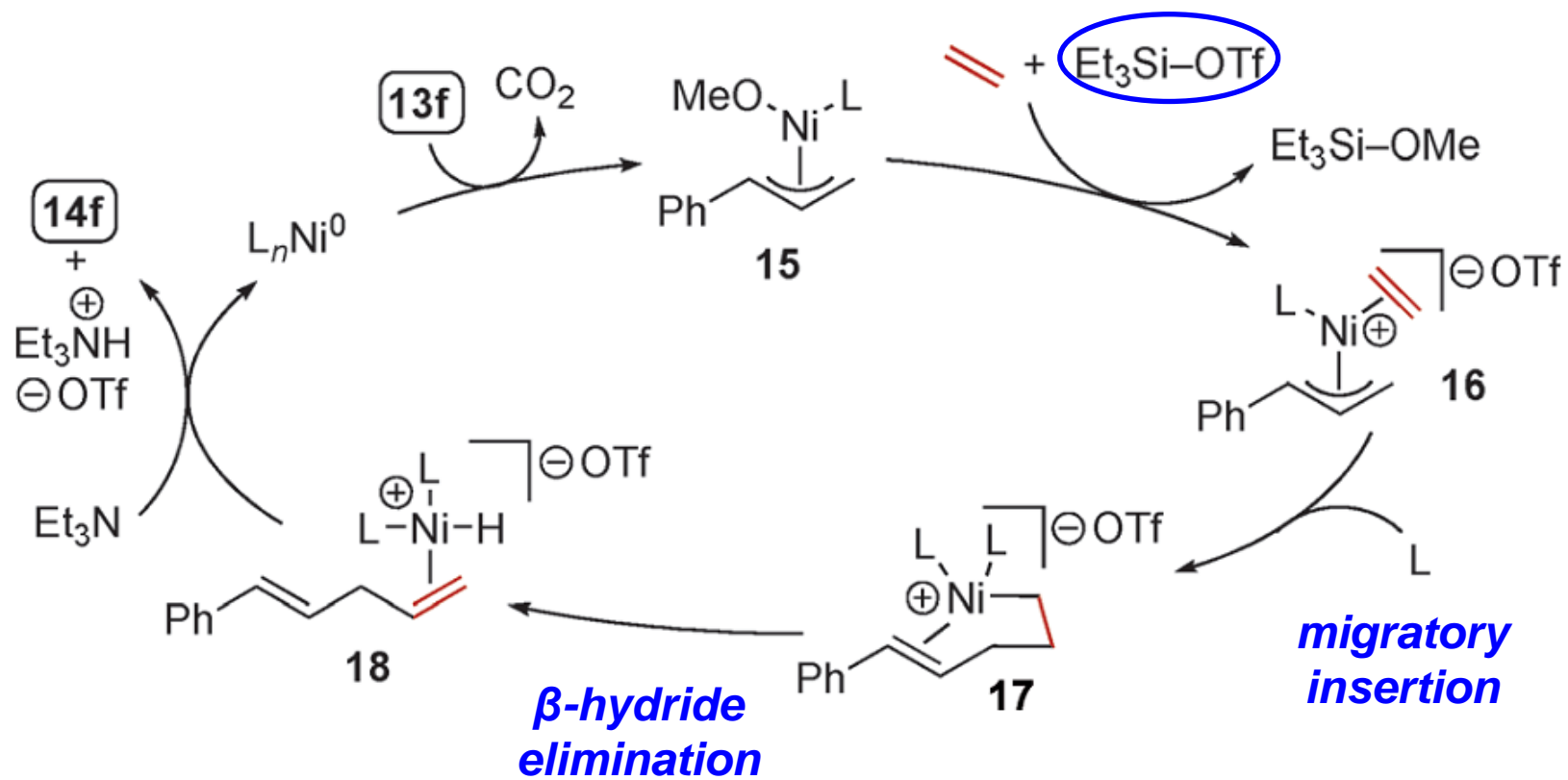


Representative substrates

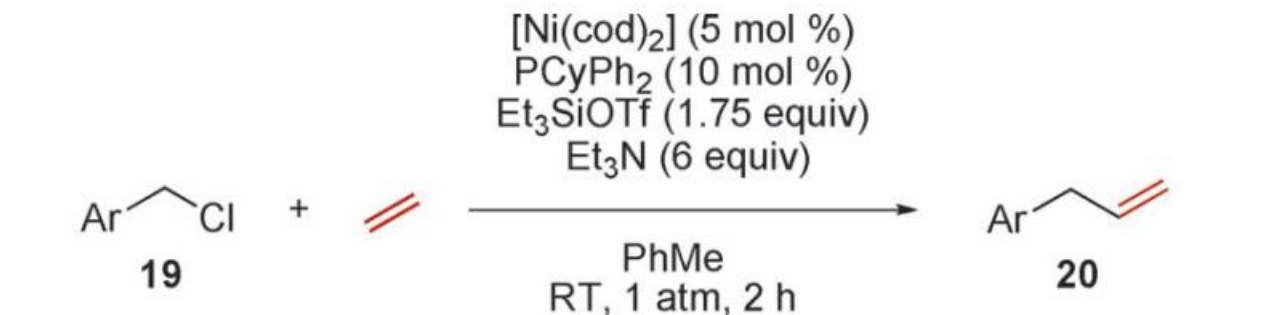


J. Am. Chem. Soc. **2010**, 132, 6880.

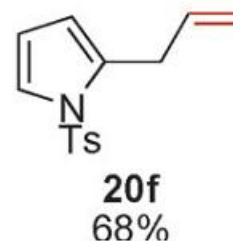
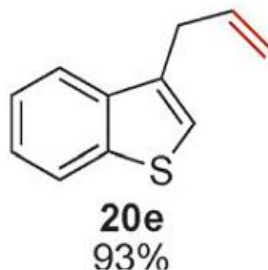
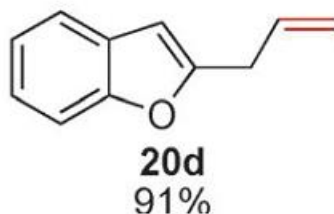
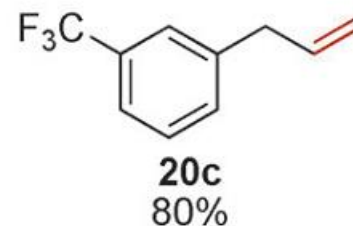
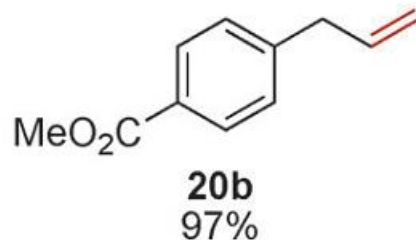
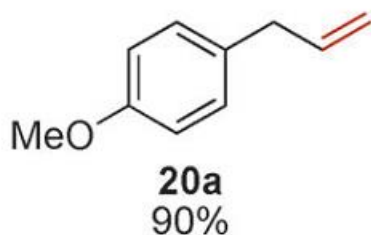
Proposed mechanism



Nickel-catalyzed Mizoroki-Heck-Type reactions using *benzylic electrophiles*



Representative reaction scope



J. Am. Chem. Soc. **2011**, 133, 19020.

- Limited to **allylic** and **benzylic** electrophiles, **stabilize nickel/alkyl** intermediates
- Kinetic resolution reactions using suitable chiral ligand

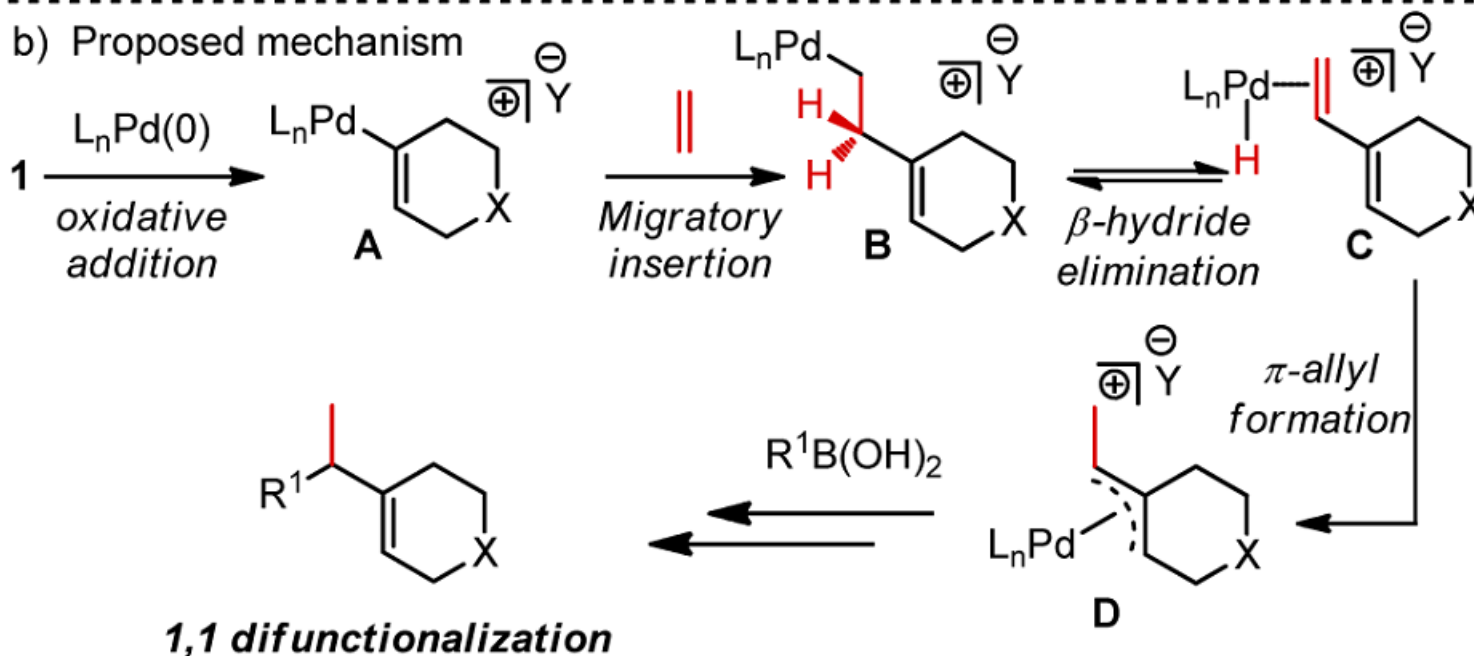
Multicomponent Coupling Reactions of Ethylene

Palladium-catalyzed three-component *reductive 1,1-difunctionalization*

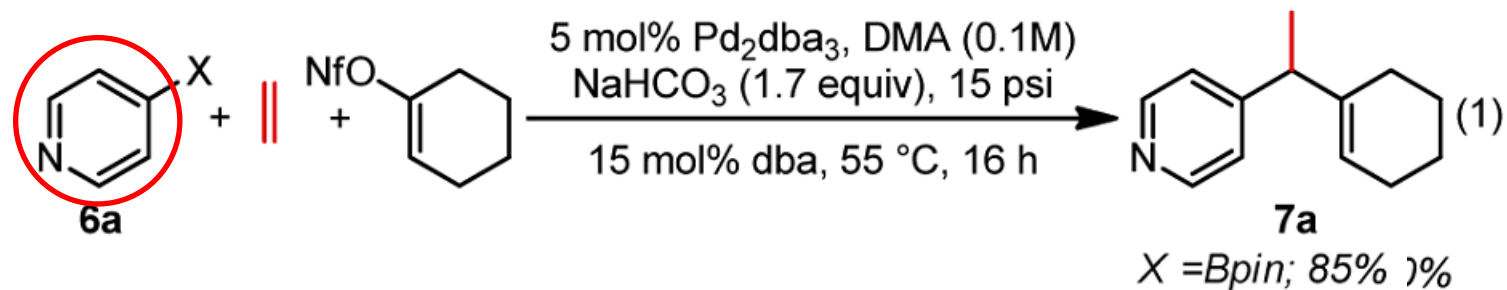
a) Pd catalyzed 1,1 vinylarylation of ethylene



b) Proposed mechanism

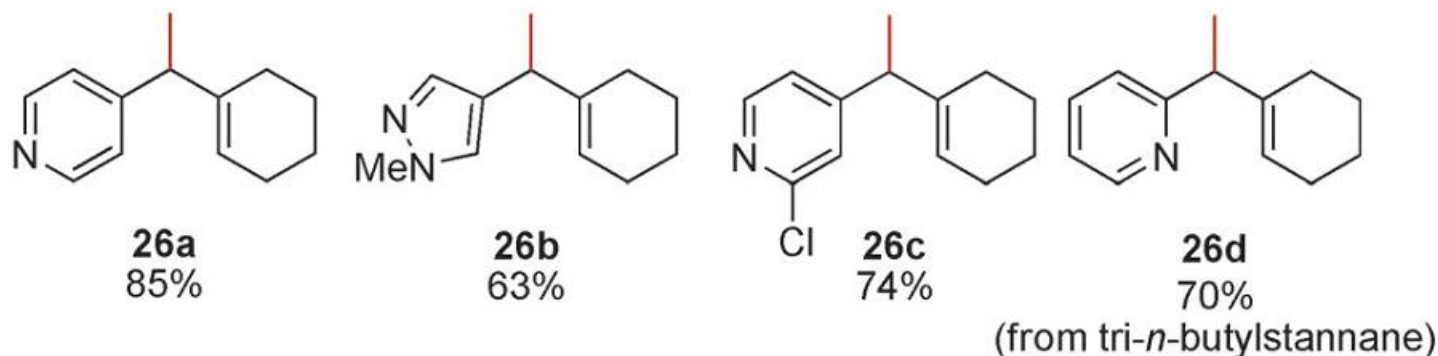


Using *heteroaromatic transmetalating reagents*



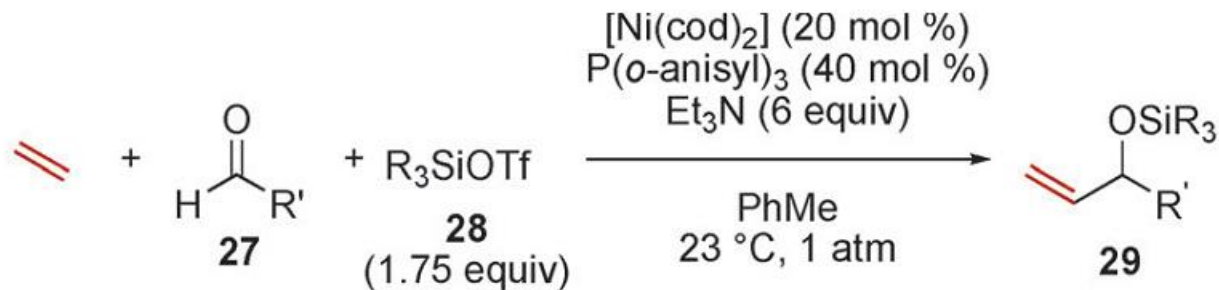
1. Lewis basicity, 2. slow rate of transmetallation, 3. propensity to decompose by protodeborylation

Representative product scope

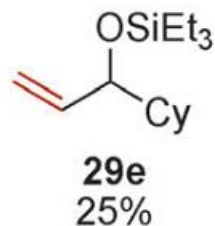
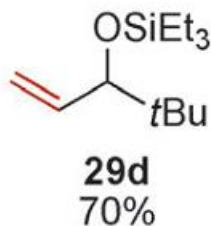
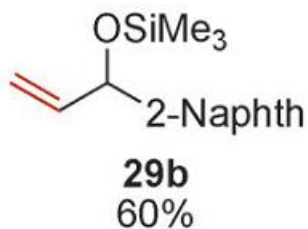
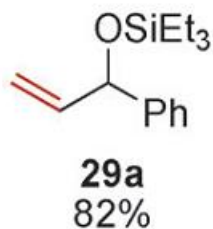


1. *Angew. Chem. Int. Ed.* **2012**, 51, 2667.
2. *J. Am. Chem. Soc.* **1964**, 86, 2666.
3. *J. Am. Chem. Soc.* **2012**, 134, 11372.

Nickel-catalyzed: synthesis of *allyl silyl ether*

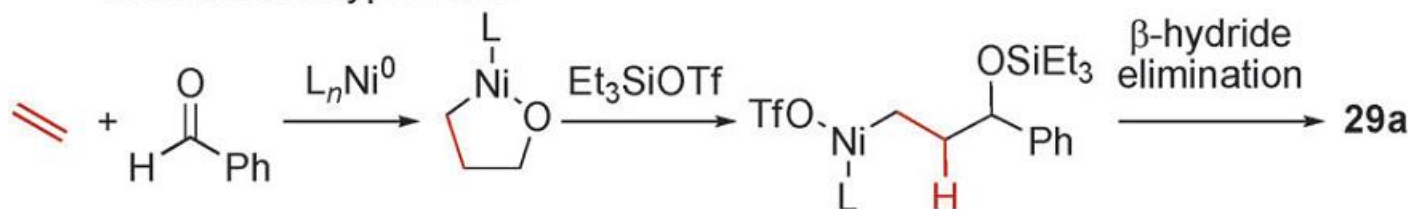


Representative examples



***catalyst loading
enantioselective***

Mechanistic hypothesis



Main obstacle

- two alkenes are reacting with each other **resulting in a chain-elongated alkene** which must **not be accepted by the catalyst** as starting material
- **oligomerisation** or **polymerisation** process



the choice of starting materials is crucial



styrene derivatives with ethene

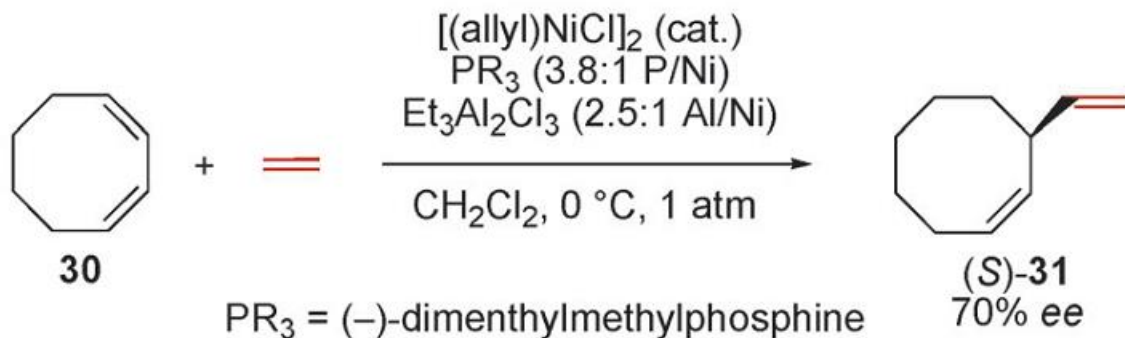
the **electronic nature** or the **steric hindrance of the double bonds** are significantly altered so that **oligomerisation reactions are prevented**

Metal: *Ni*, *Pd*, Co, Pt, Ir, Ru, Fe, etc.

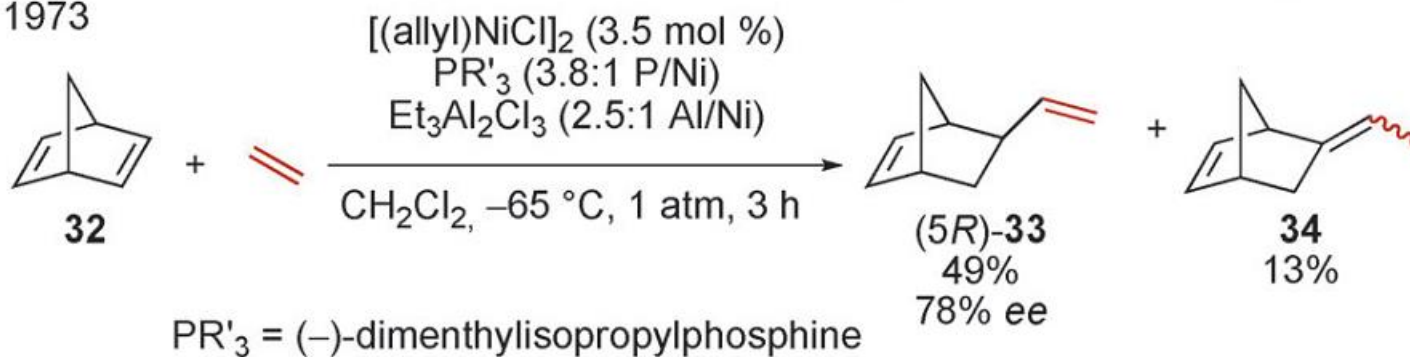
Chiral ligand: **bidentate** BINAP, phosphoramidite, amino-phosphane phosphinites, **monodentate** NHC ligands or P-chiral ligands.

Nickel-catalyzed

a) 1972



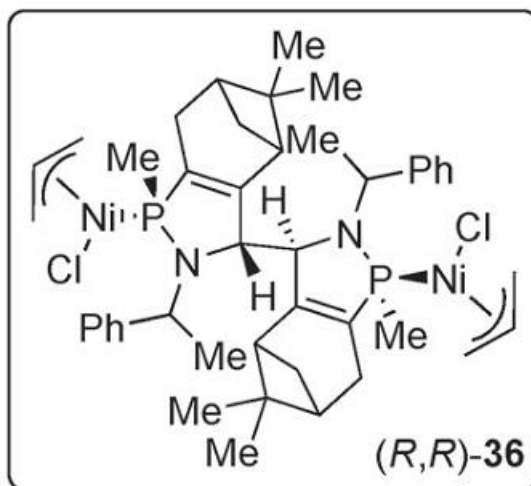
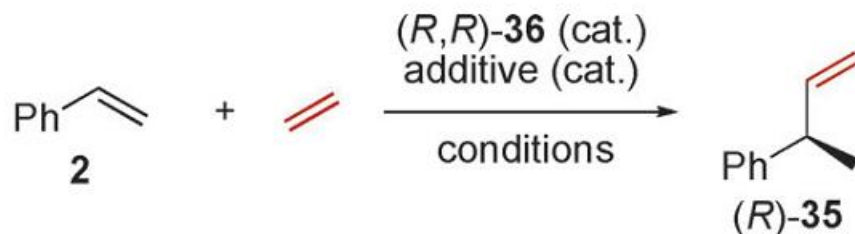
b) 1973



1. *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 1023.

2. *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 954.

Pinene-derived azaphospholene ligand

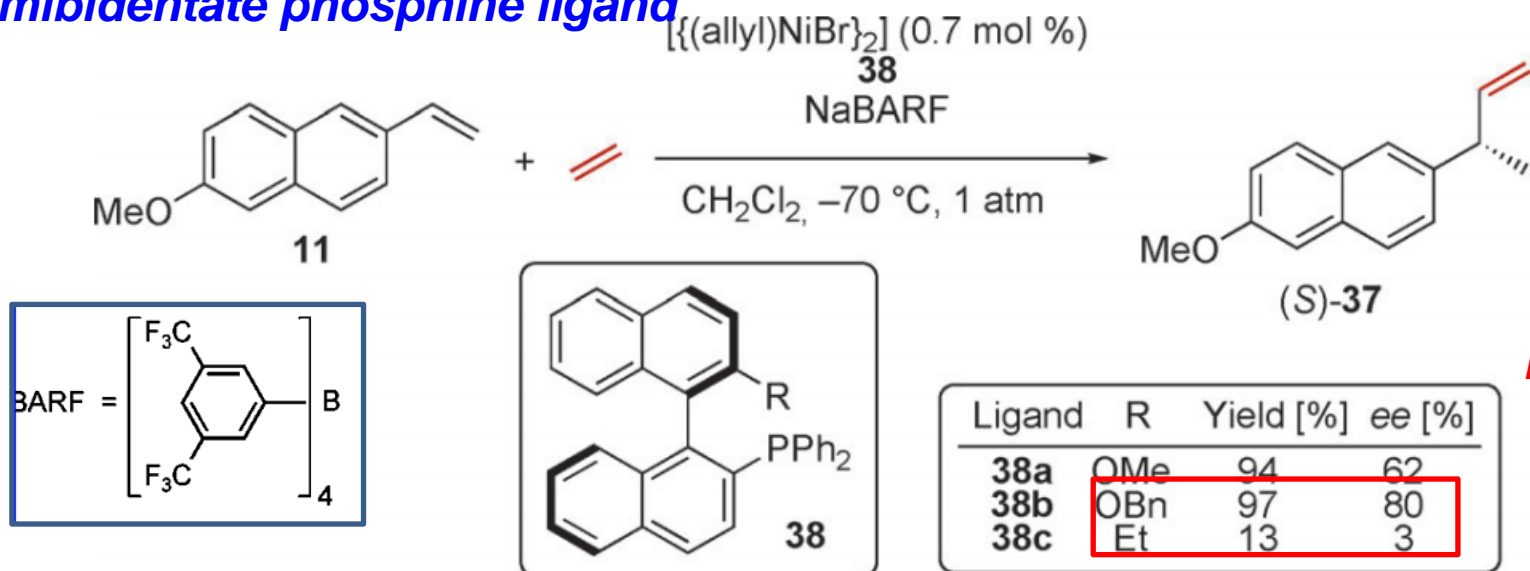


conditions

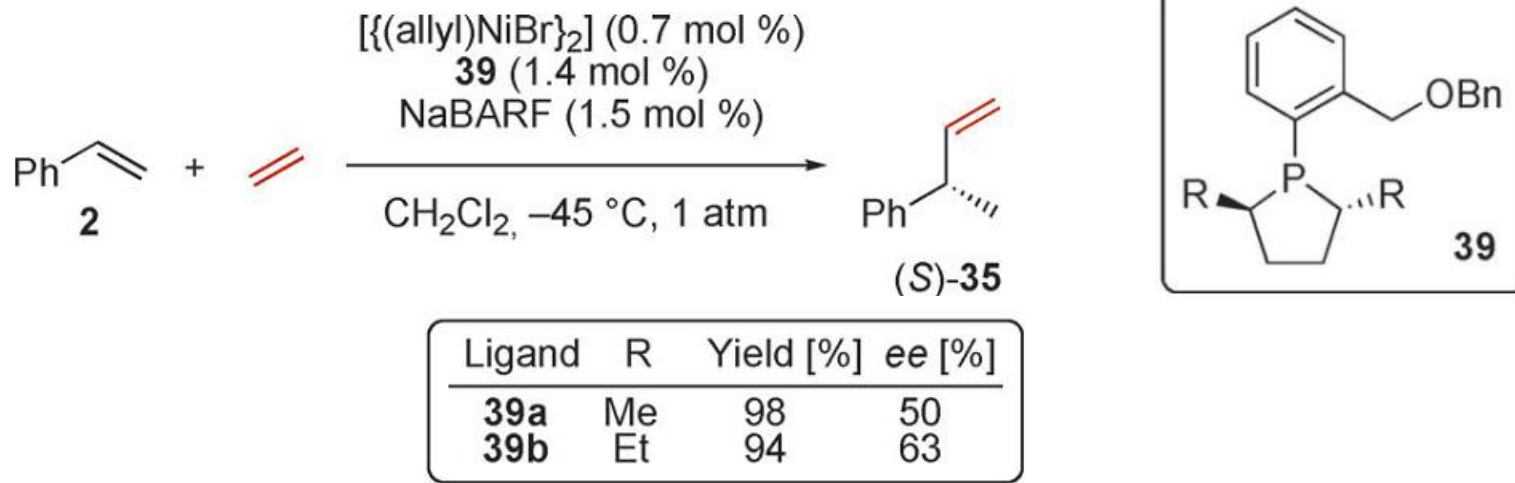
	Additive	Solvent	T [°C]	p [atm]	t [h]	Yield [%]	ee [%]
Wilke: ^[29]	$\text{Et}_3\text{Al}_2\text{Cl}_3$	CH_2Cl_2	-60	1	2.5	97	93
Leitner: ^[30]	NaBARF	$\text{CO}_2(\text{sc})$	1	73	0.5	89	86

1. US Patent, 4912274, **1990**.
2. *Chem. Commun.* **1999**, 1583.

Hemibidentate phosphine ligand



Lewis-basic
functional
group

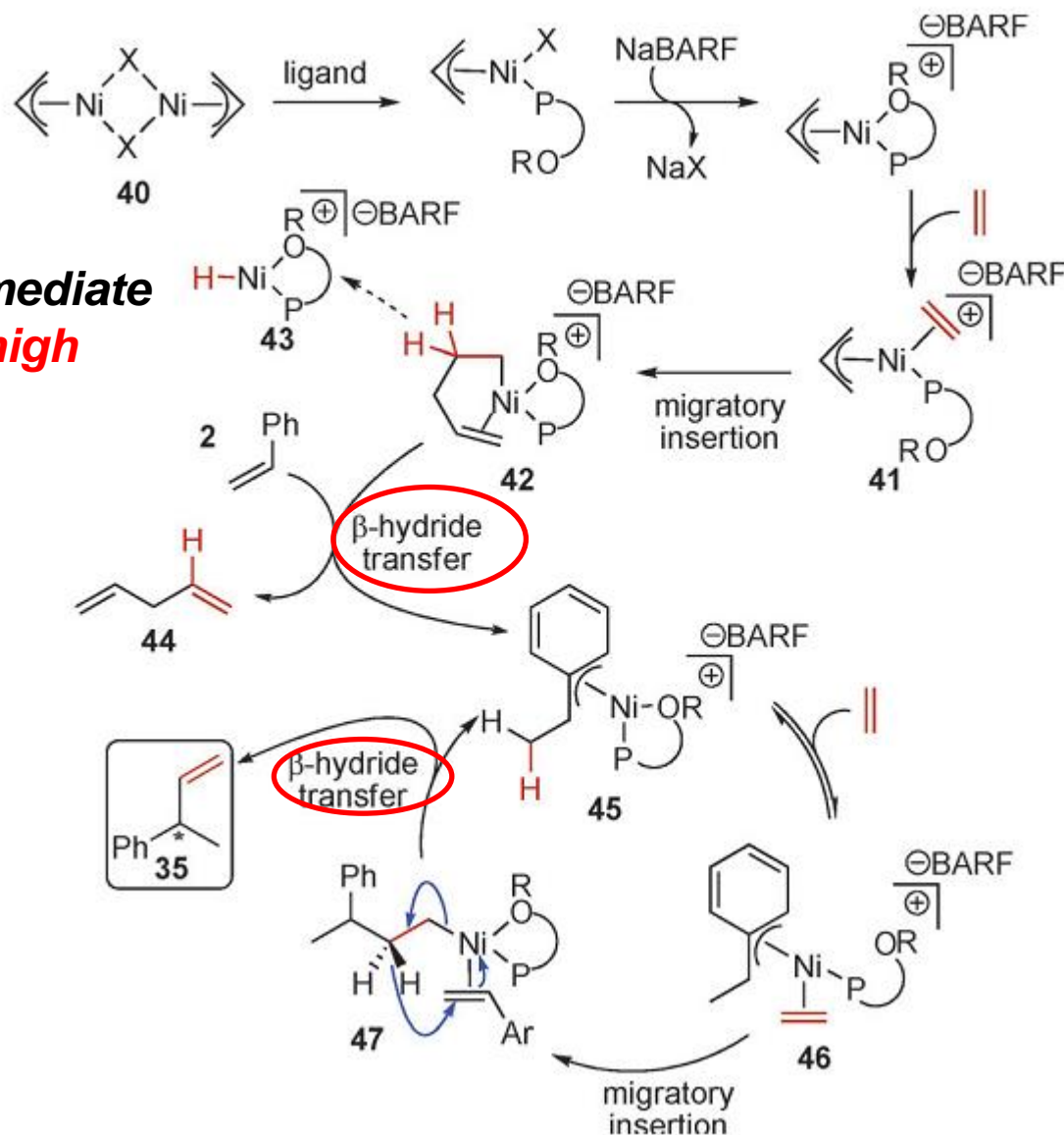


1. *J. Org. Chem.* **1993**, 58, 1945.
2. *Organometallics* **2009**, 28, 3552.
3. *J. Am. Chem. Soc.* **1999**, 121, 9899.

Proposed mechanism

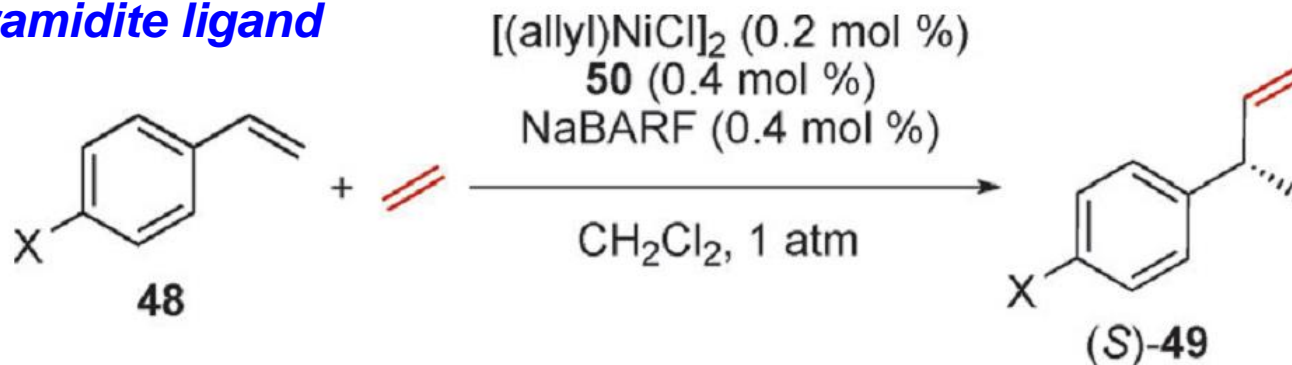
No Ni-H intermediate
TS energy is high

multiple ligand exchanges

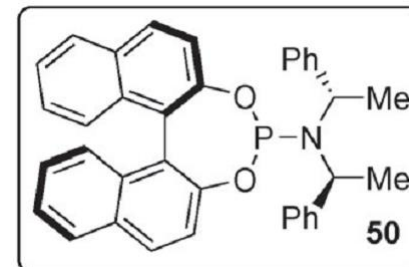
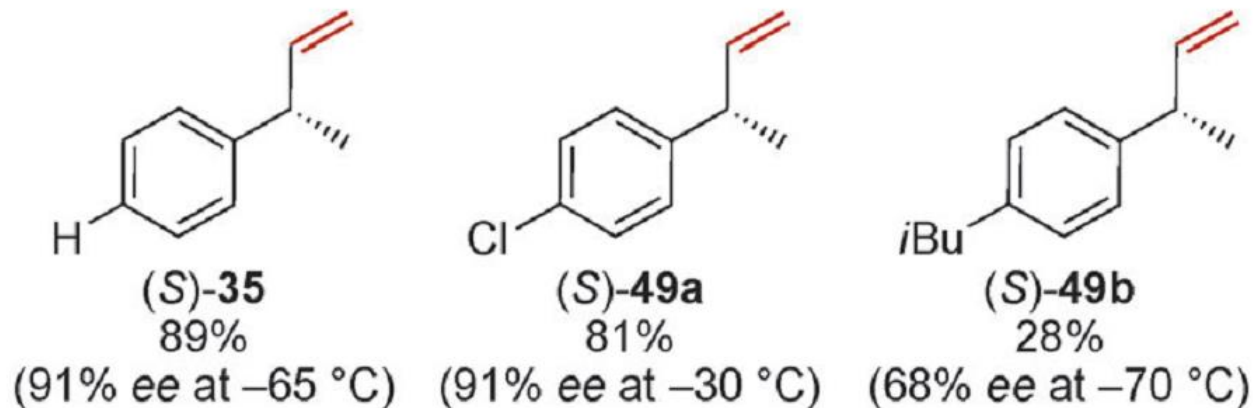


Organometallics **2009**, 28, 3552.

Phoramidite ligand



Representative products



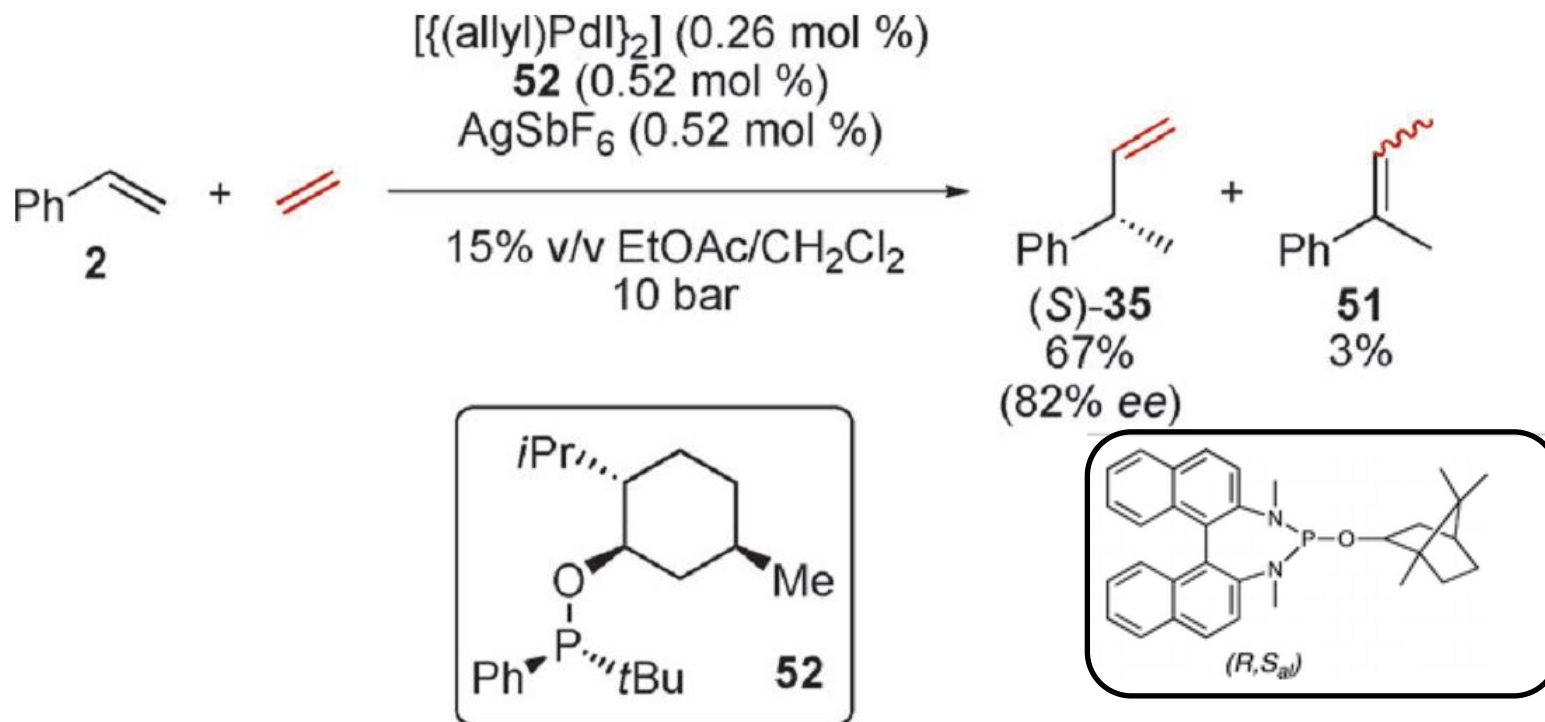
**modular
fashion**

J. Am. Chem. Soc. **2002**, 124, 736.

Ni-catalyzed:

enantioselective synthesis of many other **biologically active compounds**, such as trikentrin, various pyrrolidinoindolines, and pseudopterosins

Pd-catalyzed, chiral phosphonite ligand

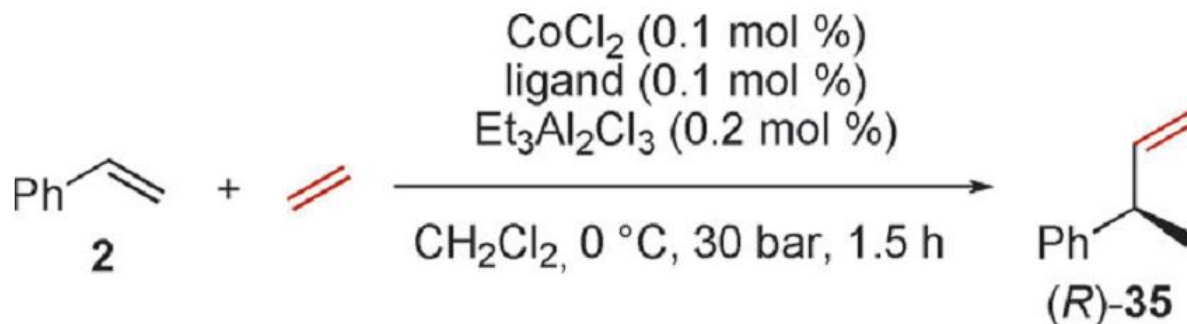


up to 90% ee

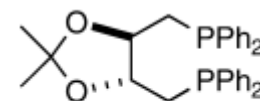
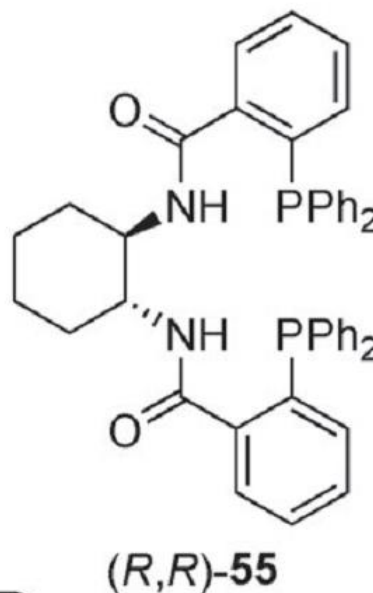
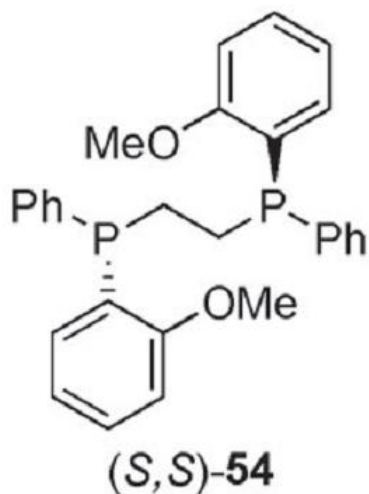
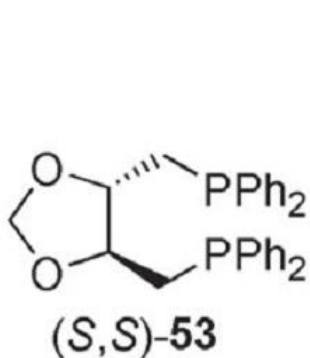
EA: act as a ligand to prevent agglomeration of Pd
PF₆, SbF₆: poorly coordinating counteranions, minimize alkene isomerization

1. *J. Organomet. Chem.* **1998**, 552, 187.
2. *Organometallics* **2011**, 30, 115.

Co-catalyzed



Representative ligands

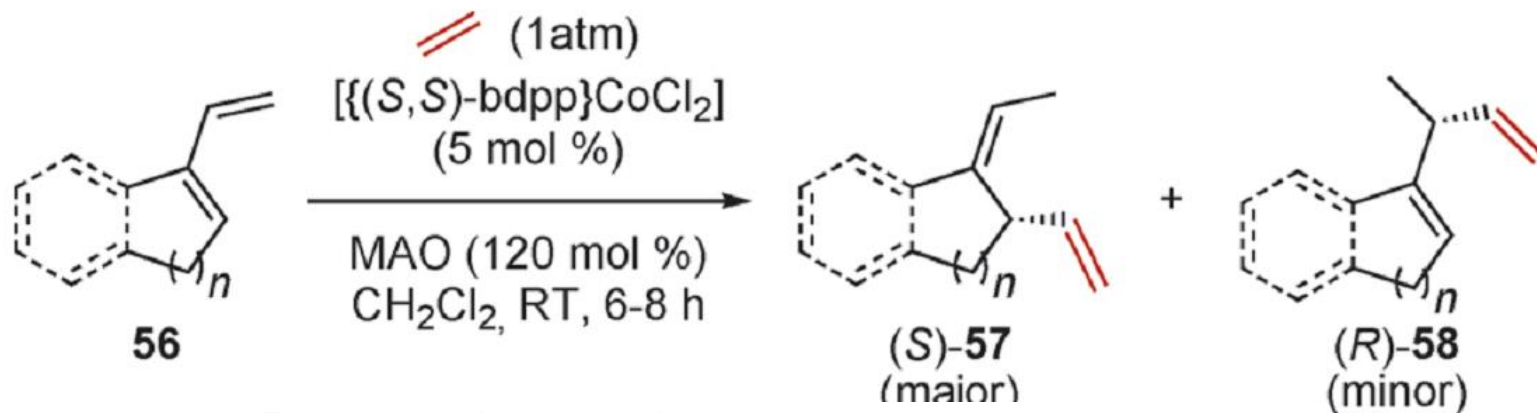


14 (RR)-DIOP

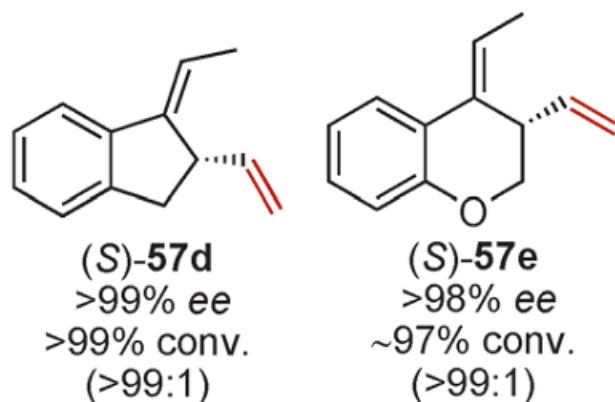
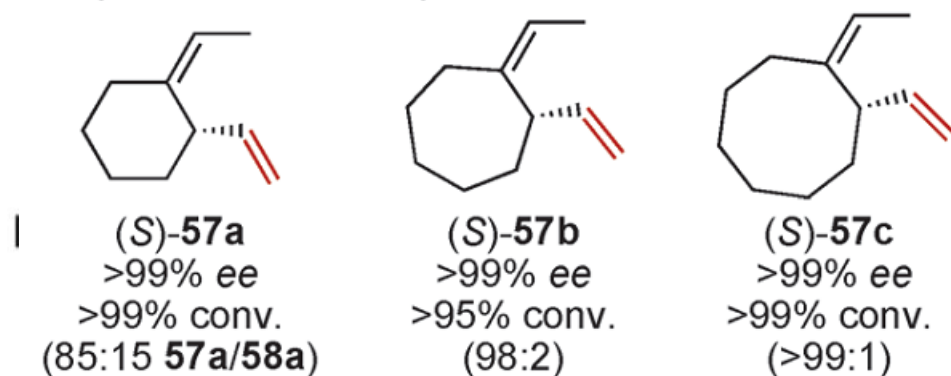
Up to 95% ee

Ligand	Conv. [%]	ee [%]
(S,S)-53	8	14
(S,S)-54	30	26
(R,R)-55	74	47

1. *Adv. Synth. Catal.* **2009**, 351, 2199.
2. *J. Am. Chem. Soc.* **2006**, 128, 7414.
3. *J. Am. Chem. Soc.* **2010**, 132, 3295.

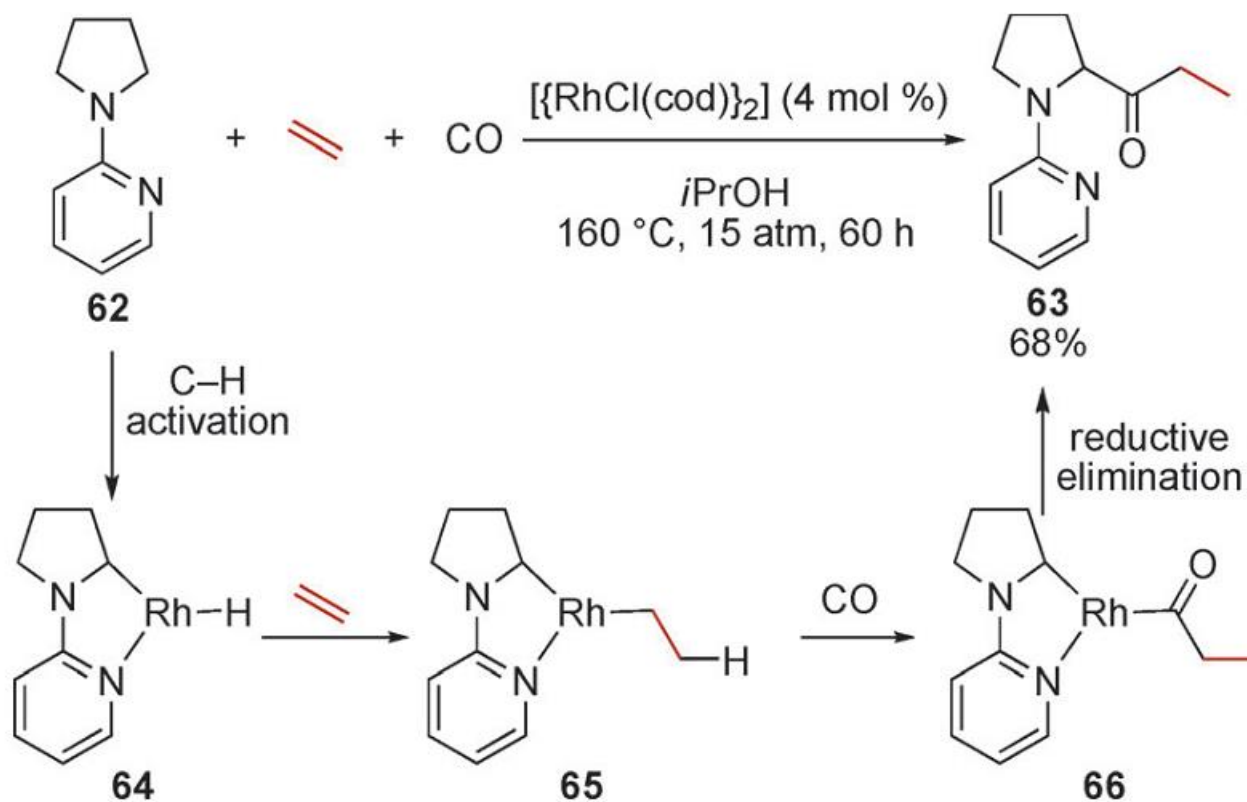
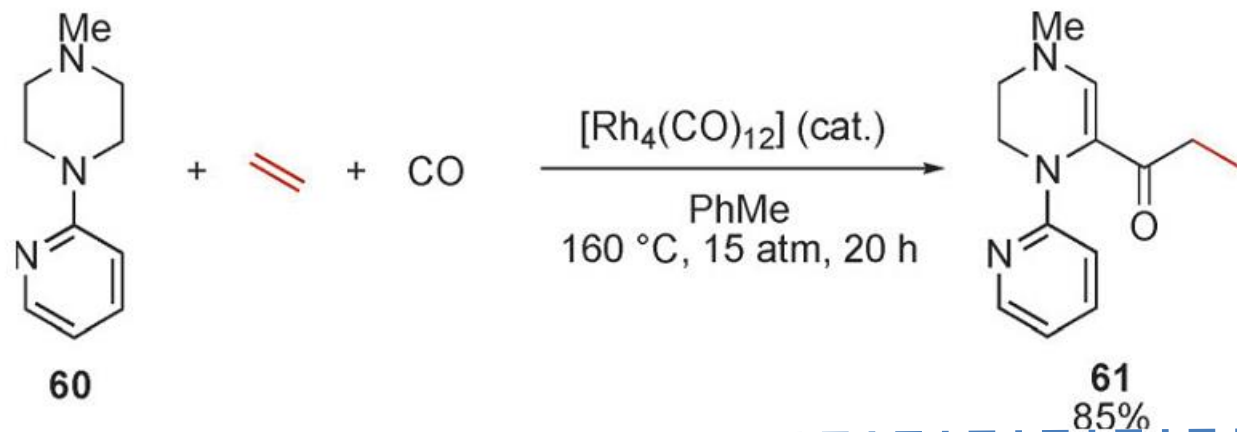


Representative examples

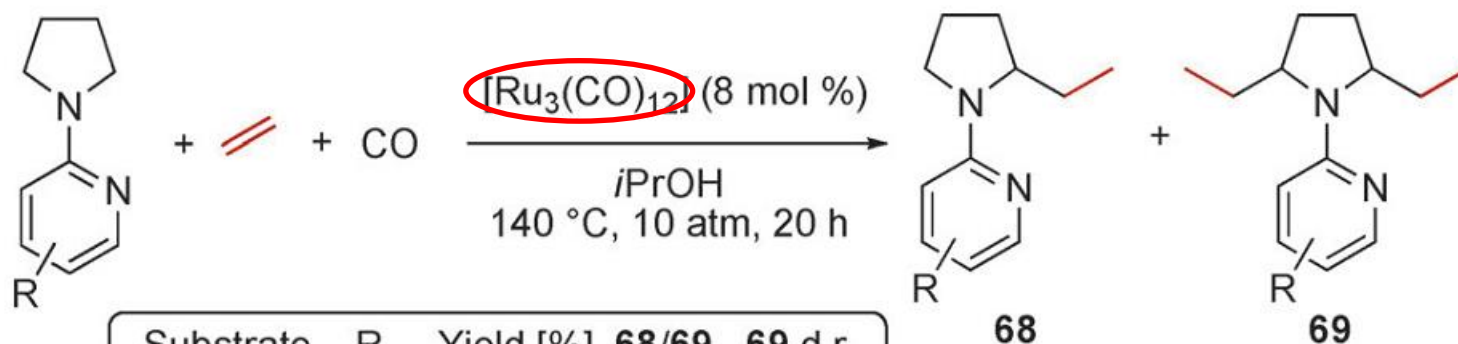


**Metal-alkyl intermediate
(Π -allyl or Π -benzyl)**

Pyridine-Directed C-H Functionalization Reactions

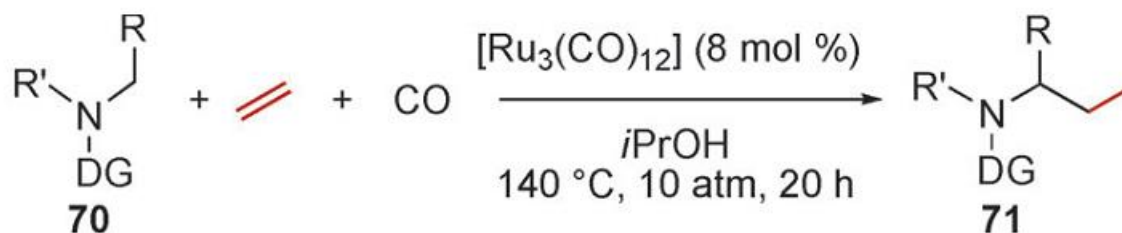


Ethylation

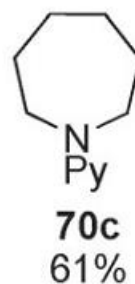
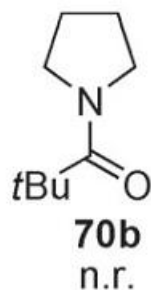
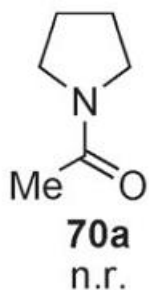


Substrate	R	Yield [%]	68/69	69 d.r.
62	H	92	0:100	54:46
67a	6-Me	50	78:22	52:48
67b	4-CO ₂ Me	n.r.	n.a.	n.a.

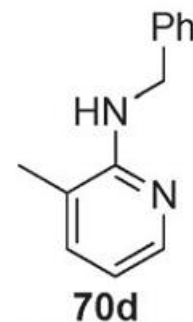
**Reductive elimination
from ethylene insertion**



Representative substrates



(77:23 mono/diethylation)
(52:48 d.r.)

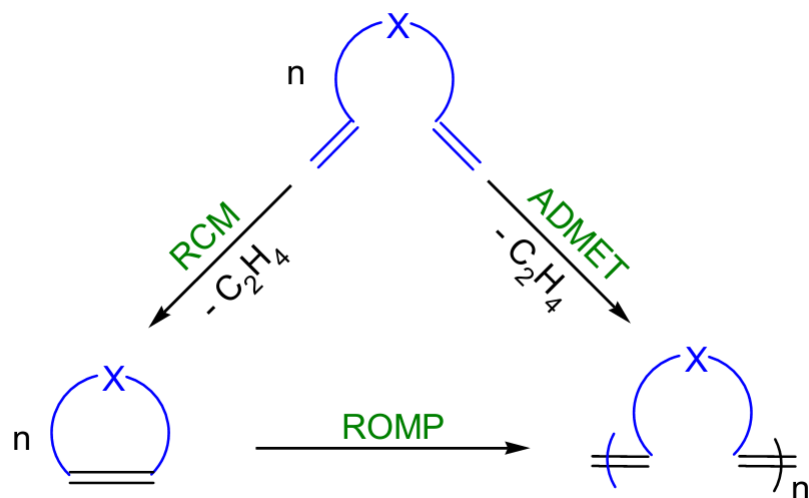


82% (40 h)
(CO not used)

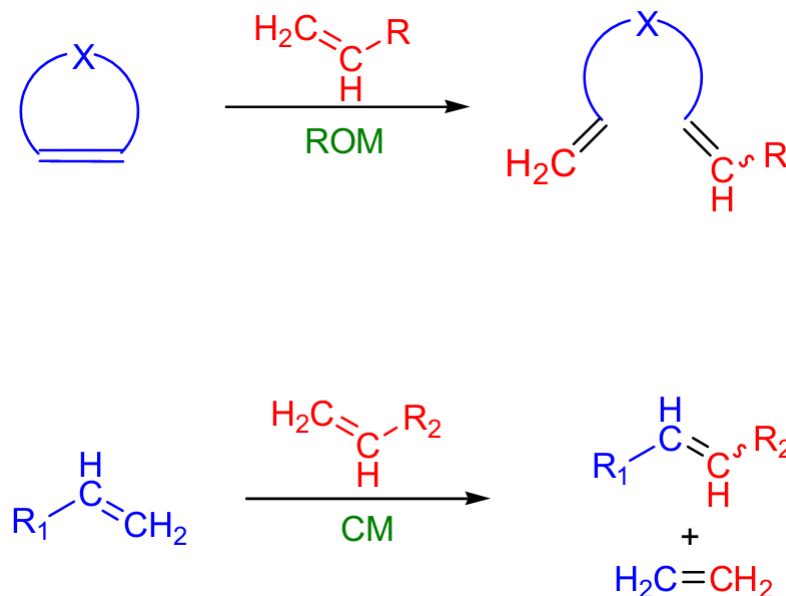
Limited acyclic N-Pyridyl amines

Olefin Metathesis Reactions

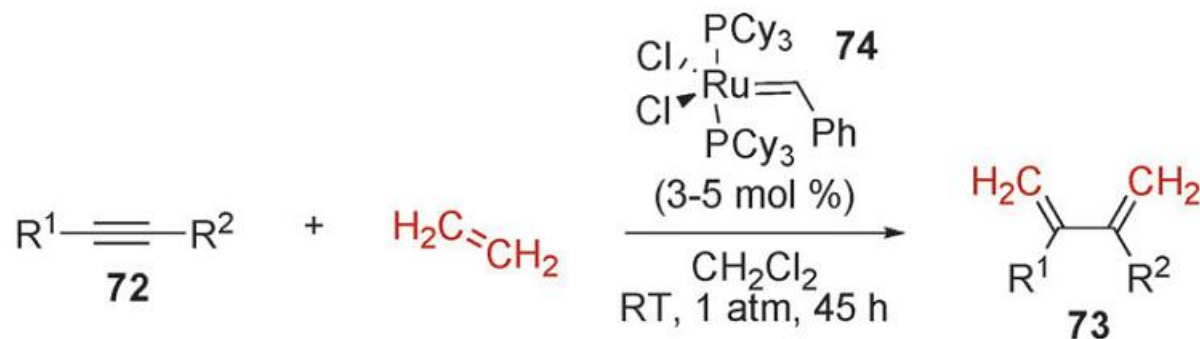
As a byproduct



As a reactant

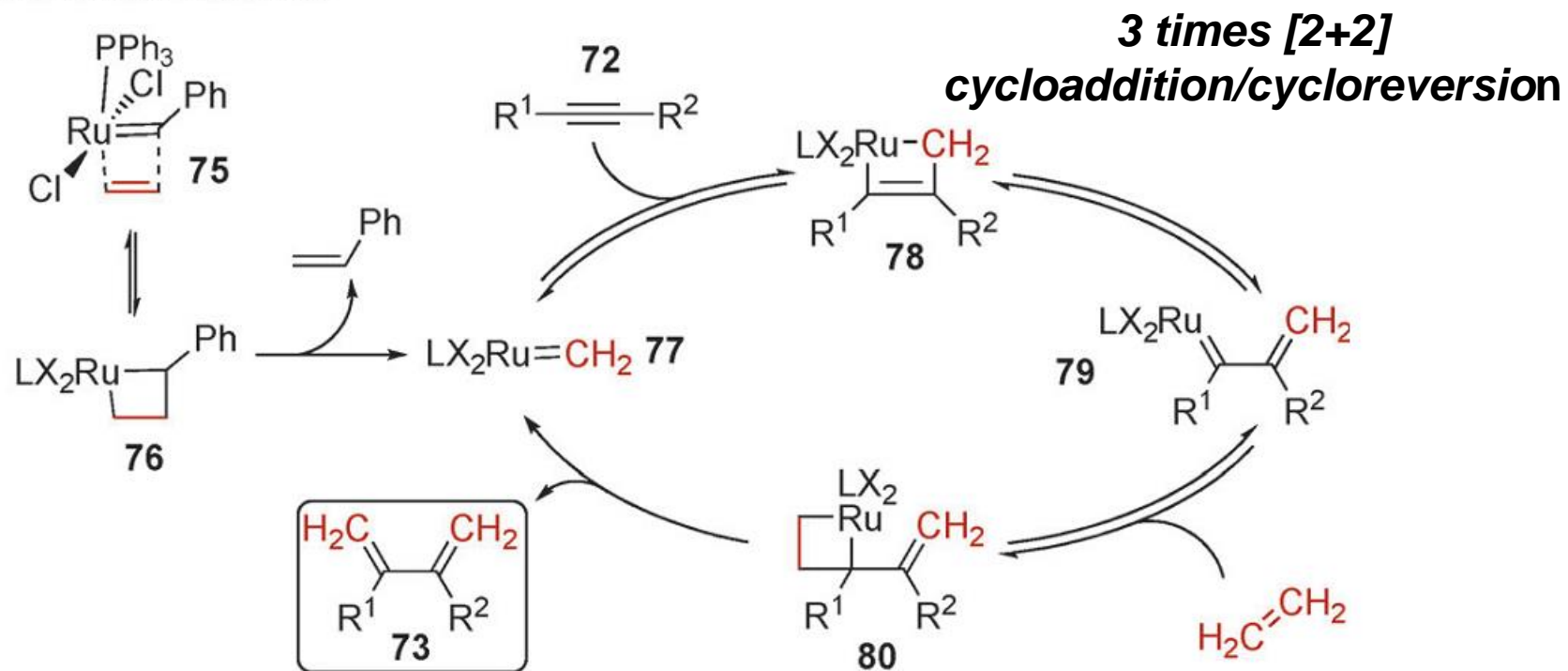


Intermolecular enyne metathesis

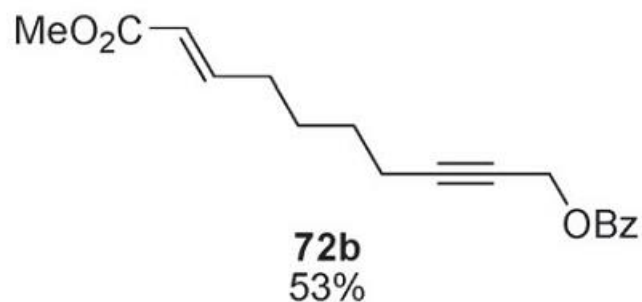
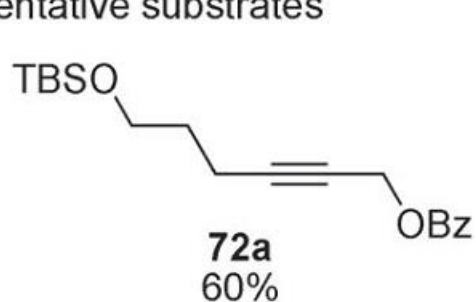


J. Am. Chem. Soc. **1997**, 119, 12388.

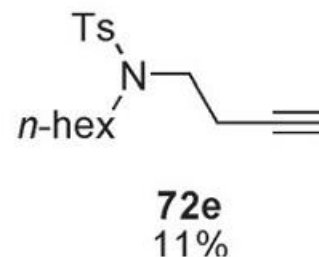
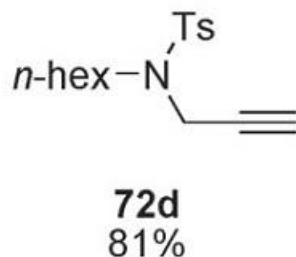
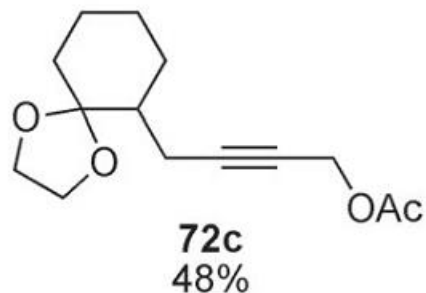
Mechanistic rationale



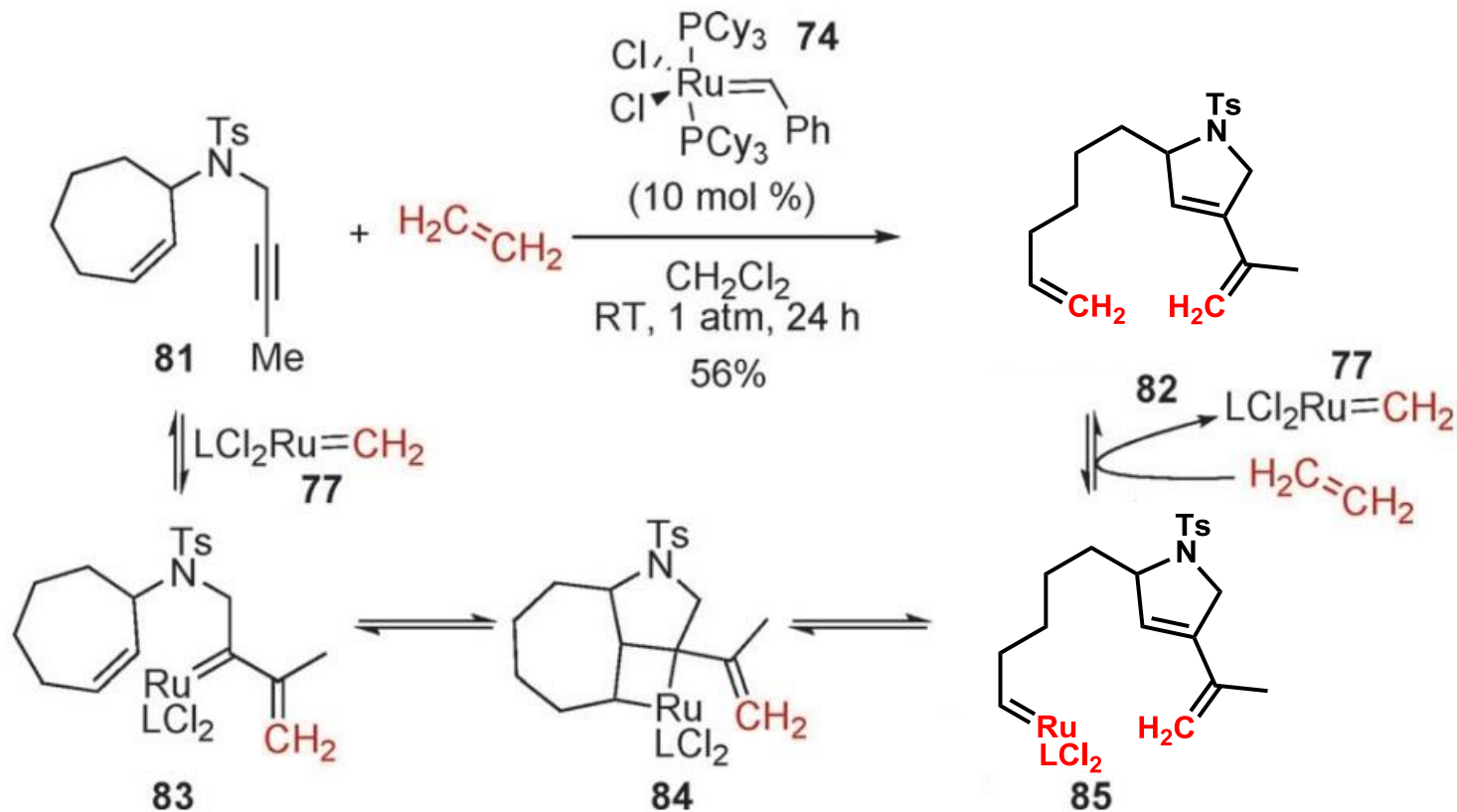
Representative substrates



Coordination of N with Ru, prevent cycloreversion to 79



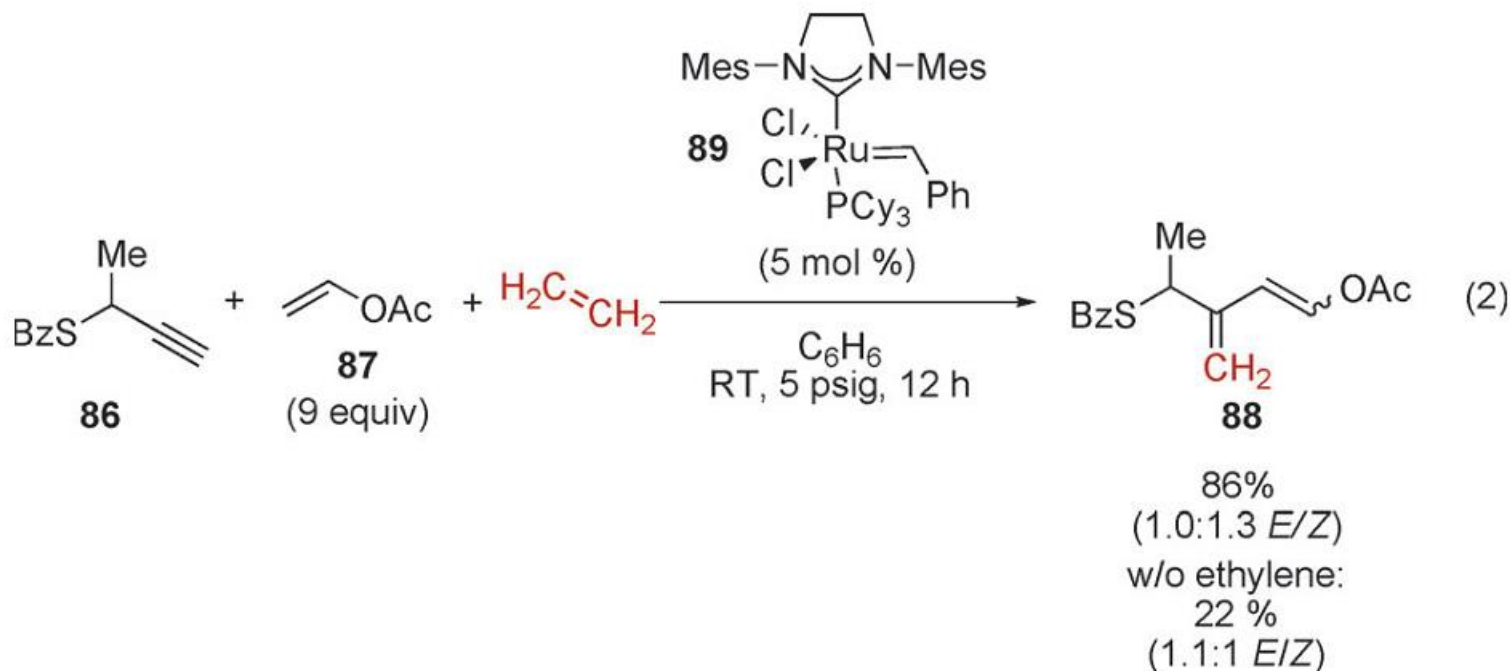
Tandem ring-closing/ring-opening



Org. Lett. **2001**, 3, 1161.

Under Ar: only substrate polymerization

Ethylene-promoted intermolecular alkyne-ene cross-metathesis reactions

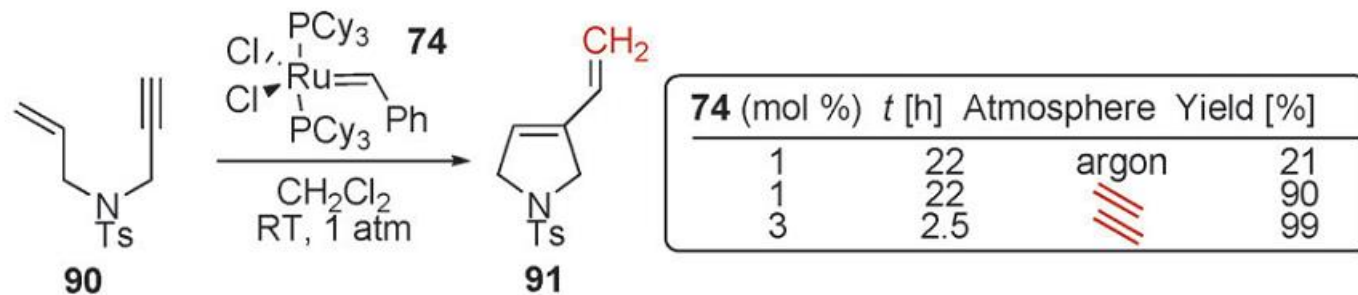


Active species: $[\text{LCl}_2\text{Ru}=\text{CH}_2]$ or $[\text{LCl}_2\text{Ru}=\text{CHOAc}]$?

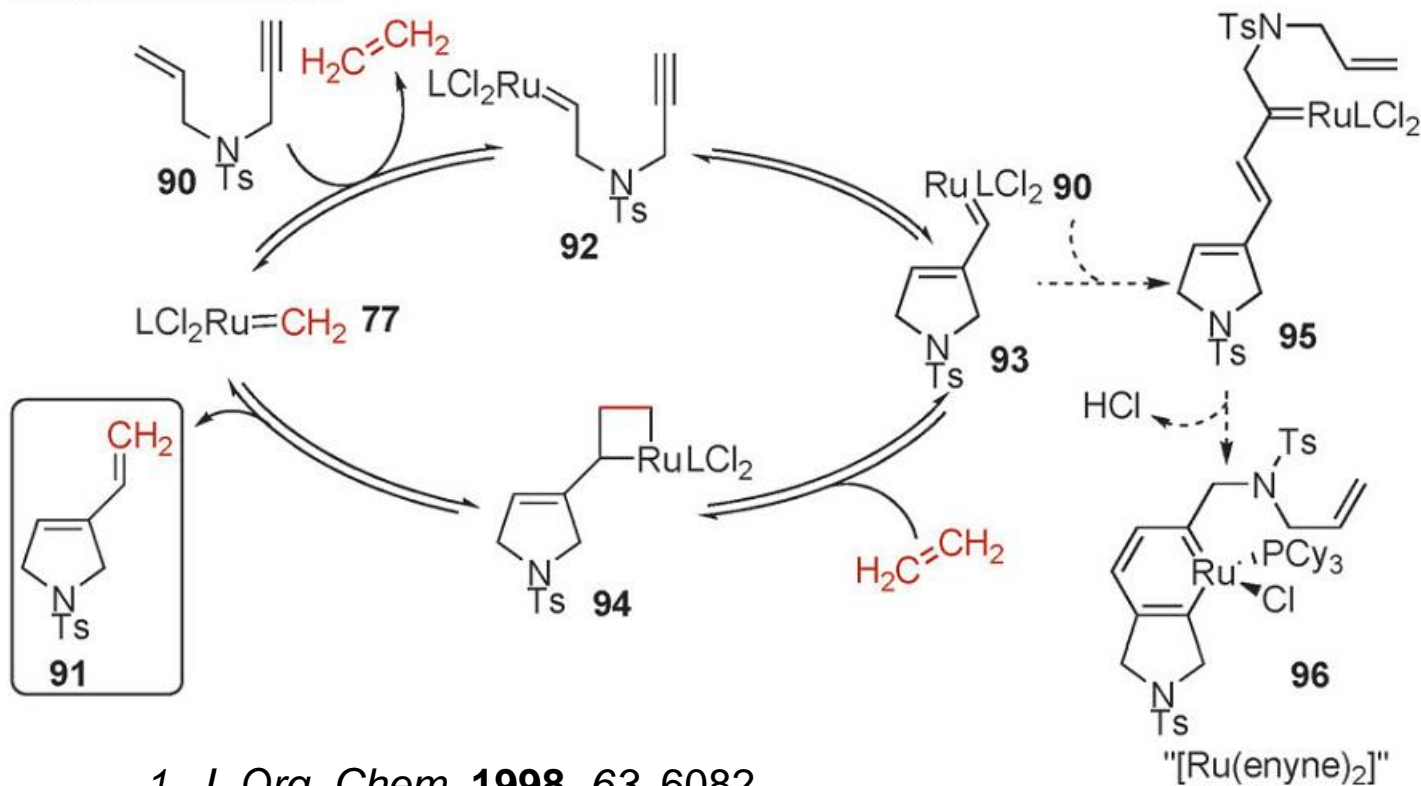
Multiple reaction mechanisms may be operating simultaneously

Org. Lett. **2003**, 5, 3819.

Ethylene in Intramolecular ring-closing enyne metathesis reactions

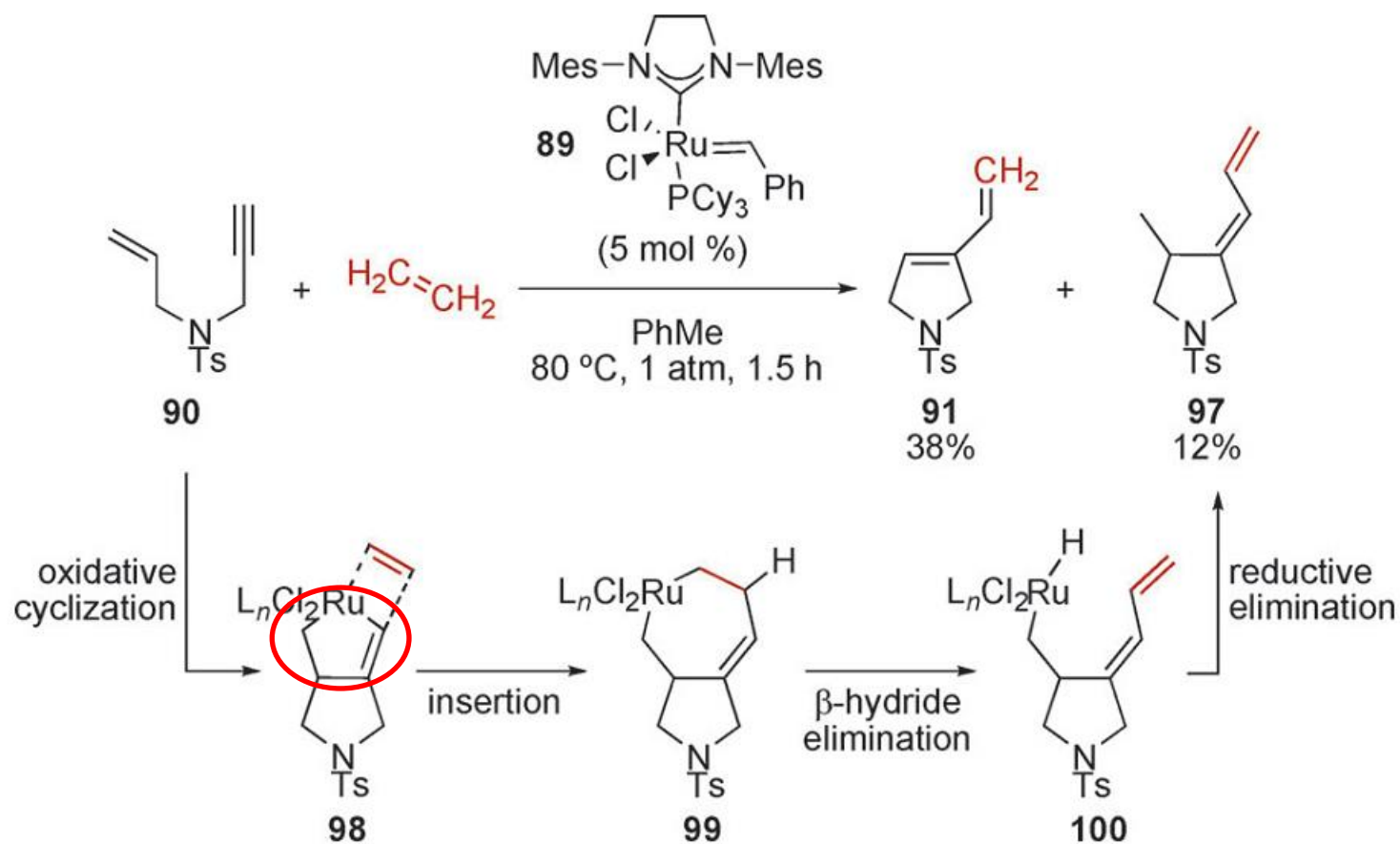


Mechanistic rationale



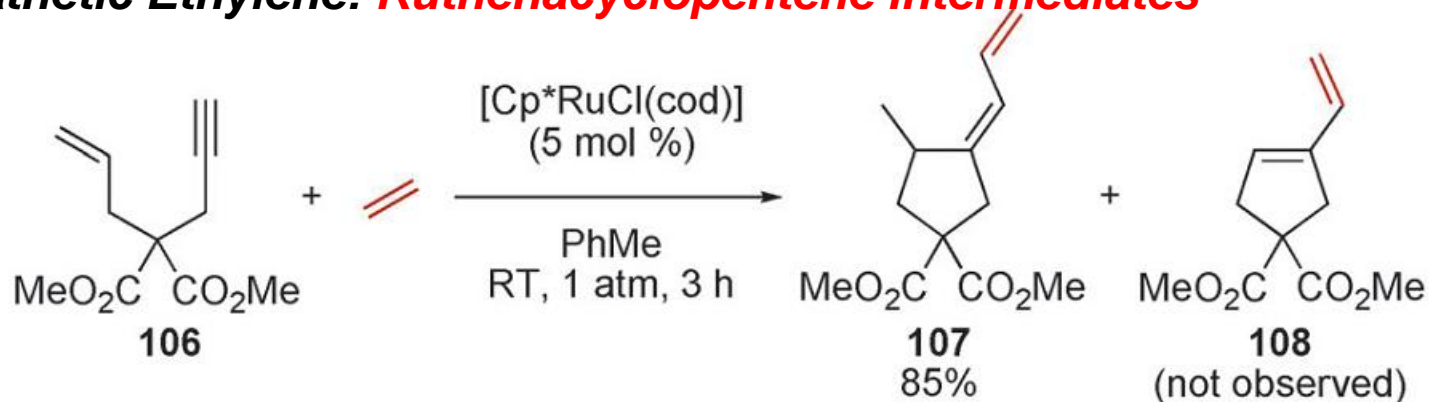
1. *J. Org. Chem.* **1998**, 63, 6082.
2. *J. Am. Chem. Soc.* **2011**, 133, 15918.

Grubbs' second-generation catalyst

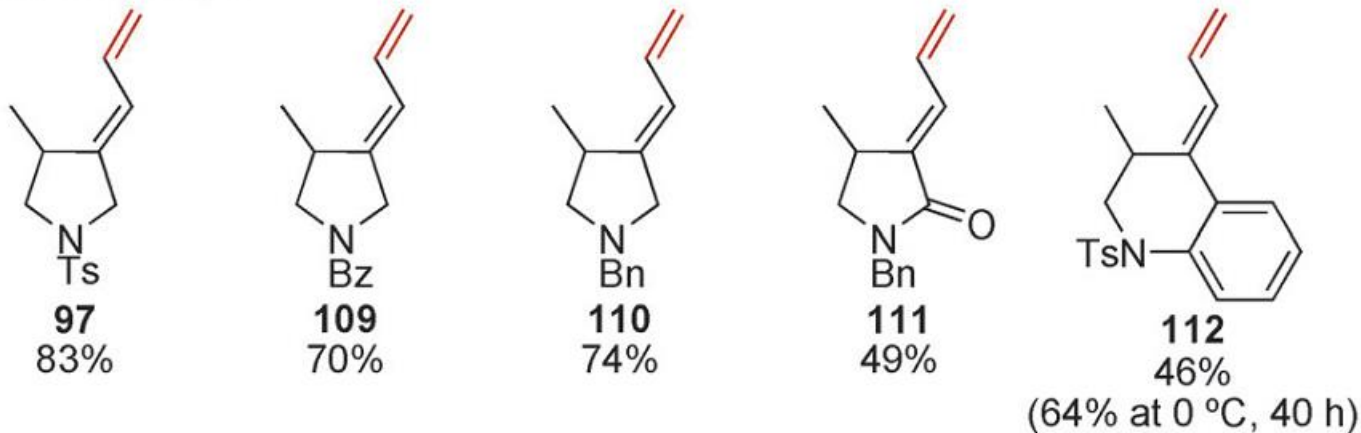


1. *Organometallics* **2008**, 27, 6313.
2. *J. Am. Chem. Soc.* **2003**, 125, 5606.

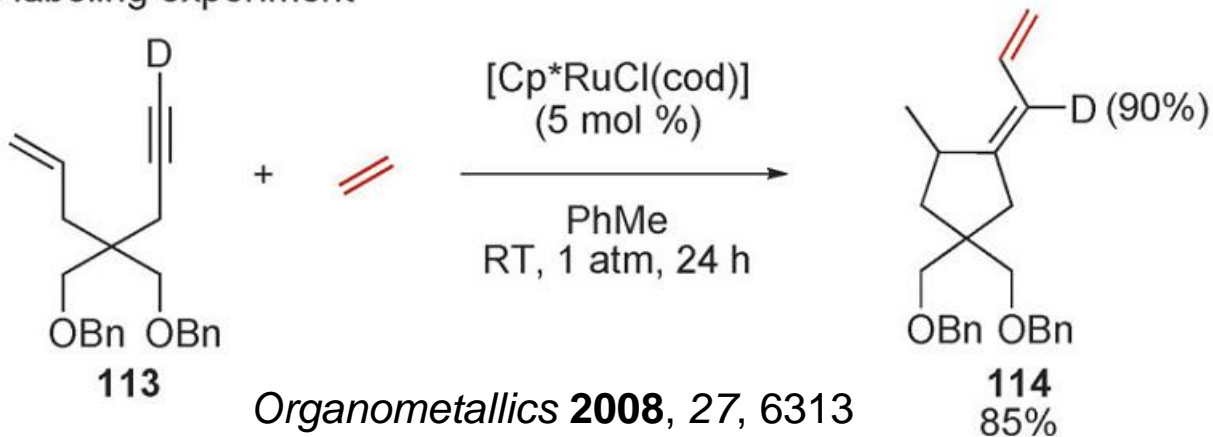
Nonmetathetic Ethylene: *Ruthenacyclopentene Intermediates*

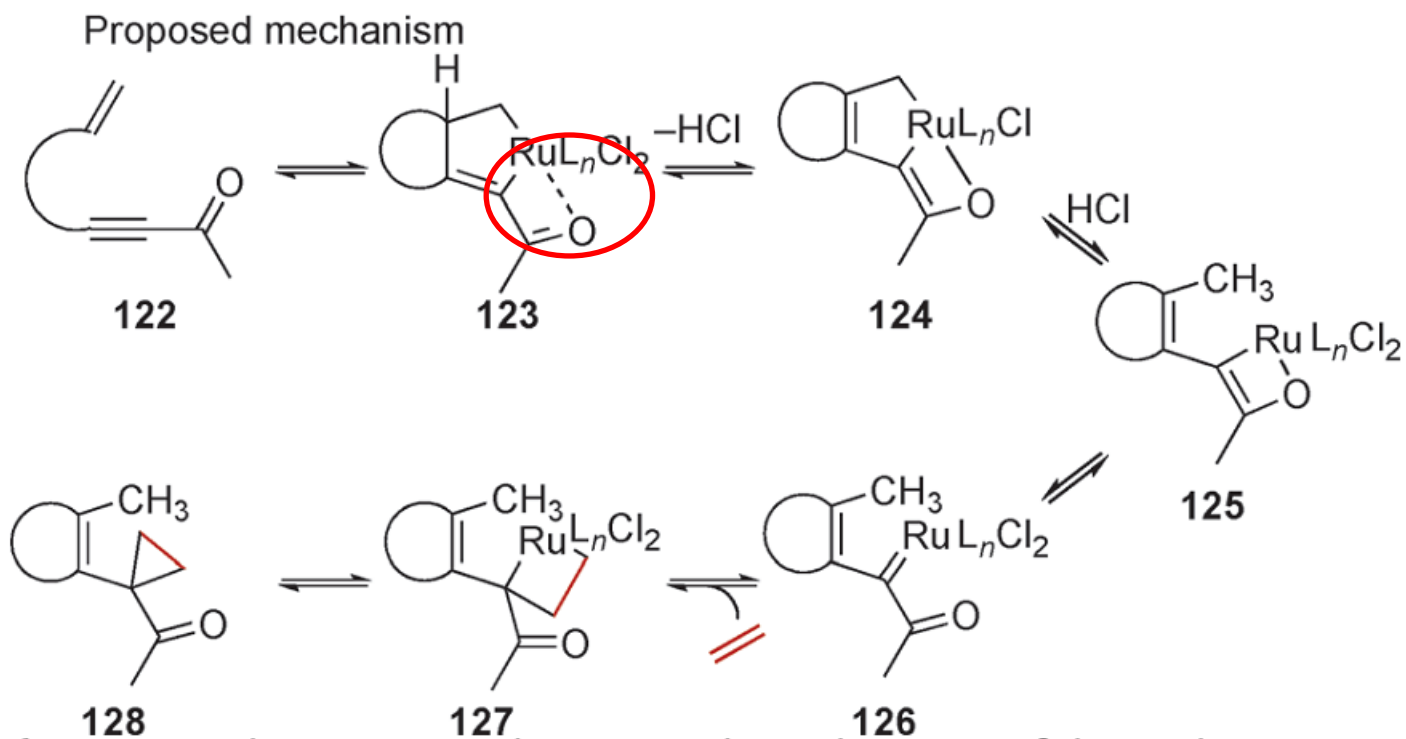
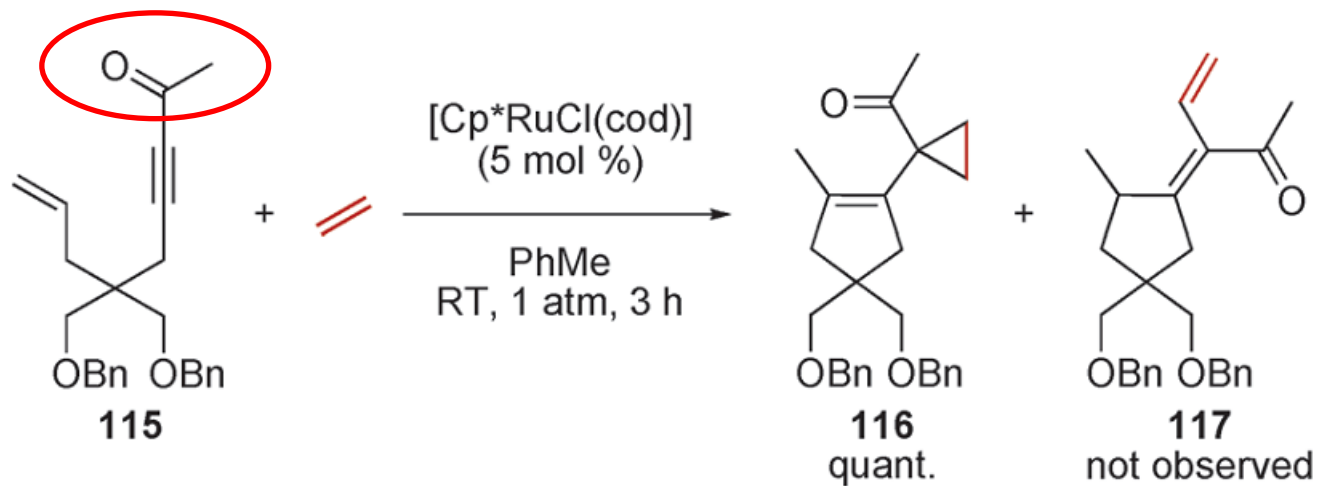


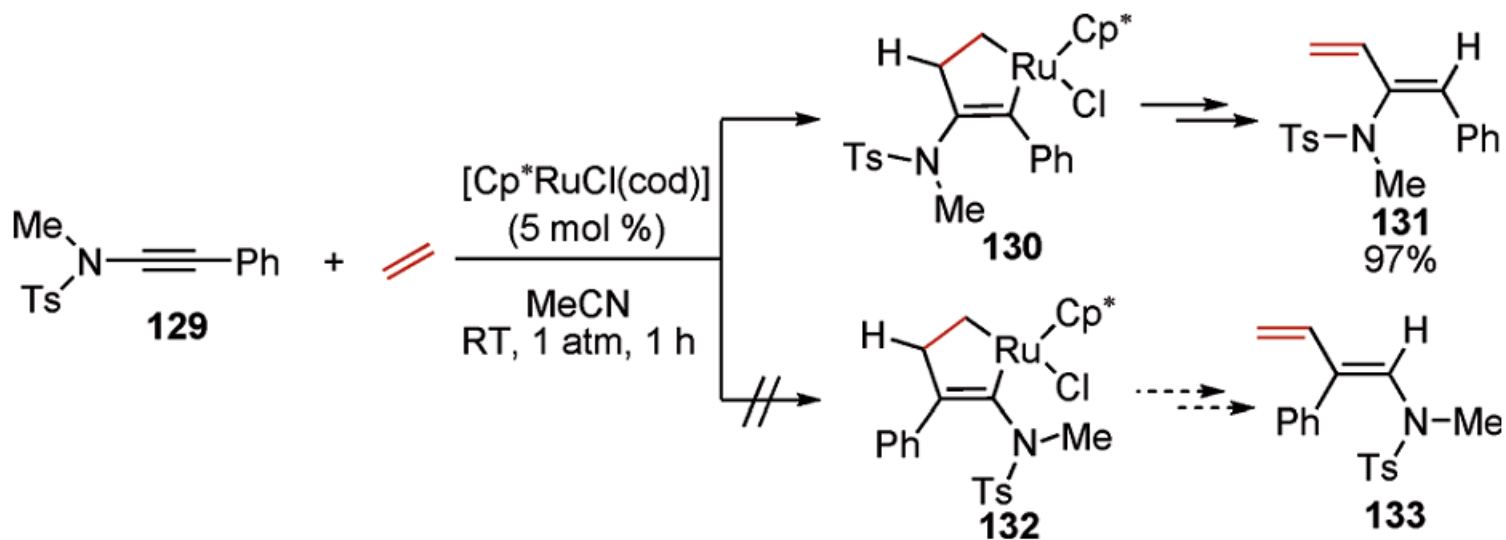
Additional scope



Isotopic labeling experiment







React with relatively electrophilic β -carbon atom

Summary

- **Mizoroki-Heck-Type Reactions**

- ✓ *High temperature and pressure, limited electrophiles*

- **Multicomponent Coupling Reactions**

- ✓ *Limited substrates, high catalyst loading, no enantioselectivity*

- **Hydrovinylation Reactions**

- ✓ *Moderated ee, isomerization, oligomerization*

- **Directed C-H Functionalization Reactions**

- ✓ *Limited example, no functional handle, potential asymmetric ethylation*

- **Olefin Metathesis Reactions**

- ✓ *Well-developed, minimization of competing metathesis reaction*

- **Nonmetathetic Ethylene**

- ✓ *Oxidative ruthenacyclopentene step*

Early in its evolution!

Thank you for your attention!

Application

