The Career of Michael J. Krische

Hui-Wen Shih

MacMillan Group Meeting

June 19, 2010

Career: A Summary

- B.S. Chemistry, University of California Berkeley — 1989
  Henry Rapoport
- Fulbright Fellow, Helsinki University — 1990
  Ari M. P. Koskinen
- PhD. Chemistry, Stanford University — 1996
  Barry M. Trost
- Postdoctoral Fellow, Universite Louis Pasteur — 1999
  Jean-Marie Lehn

University of Texas, Austin

Assistant Professor of Chemistry	1999
Professor of Chemistry	2004
Robert A. Welch Chair in Science	2007

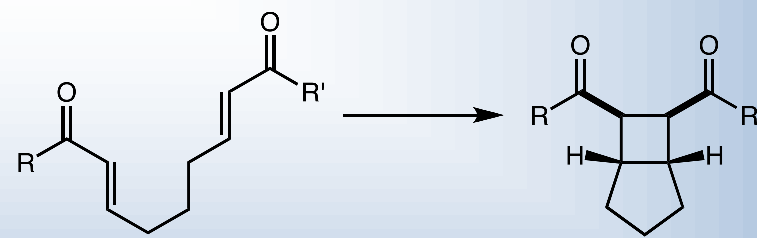
- **Selected Awards:** NSF CAREER, Camille Dreyfus Teacher-Scholar, ACS E.J. Corey, Presidental Green Chemistry Challenge, Tetrahedron Young Investigator...
- 96 primary literature publications as primary investigator

Research Areas

Catalytic Conjugate Addition-Electrophilic Trapping

seminal publication: *JACS* **2003**, *125*, 1110.

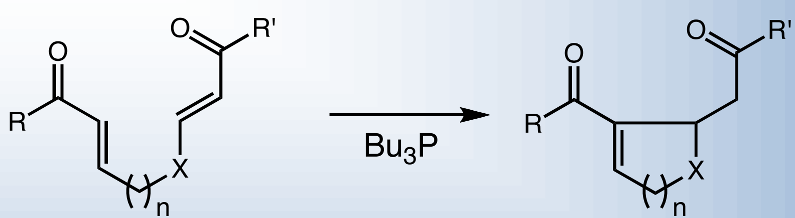
Metal-Catalyzed/Anion Radical [2+2] Cycloaddition



seminal publication: *JACS* **2001**, *123*, 6716.

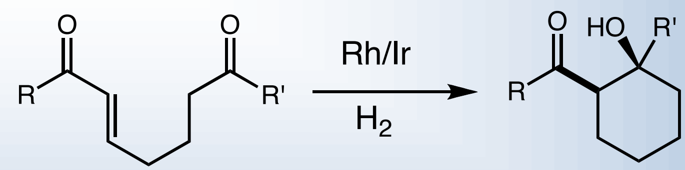
full article: *JACS* **2004**, *126*, 9448.

Nucleophilic Catalysis via Phosphine Conjugate Addn



seminal publication: *JACS* **2002**, *124*, 2402.

Hydrogen Mediated C-C Bond Formation



reviews: *Acc. Chem. Res.* **2004**, *37*, 653.
Acc. Chem. Res. **2007**, *40*, 1394.

Excludes: Supramolecular Chemistry — *JACS* **2000**, *122*, 5006.; *JACS* **2002**, *124*, 5074. (selected publications)

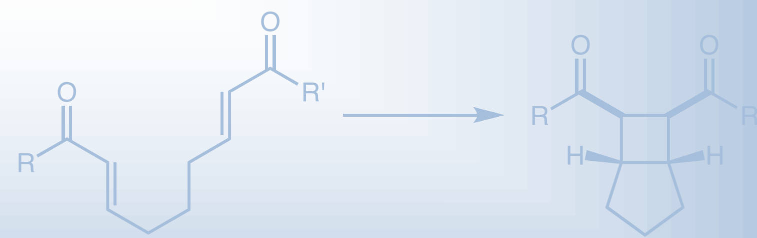
Transfer Hydrogenation — *ACIE* **2009**, *48*, 34. (review)

Research Areas

Catalytic Conjugate Addition-Electrophilic Trapping

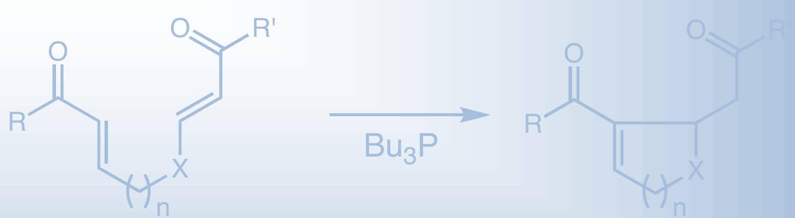
seminal publication: *JACS* **2003**, *125*, 1110.

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition



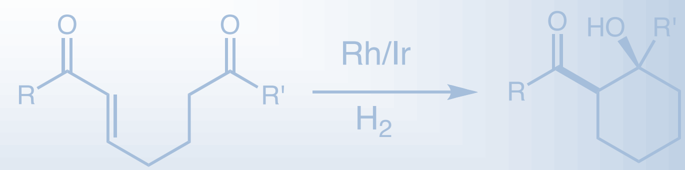
seminal publication: *JACS* **2001**, *123*, 6716.
full article: *JACS* **2004**, *126*, 9448.

Nucleophilic Catalysis via Phosphine Conjugate Addn



seminal publication: *JACS* **2002**, *124*, 2402.

Hydrogen Mediated C-C Bond Formation



reviews: *Acc. Chem. Res.* **2004**, *37*, 653.
Acc. Chem. Res. **2007**, *40*, 1394.

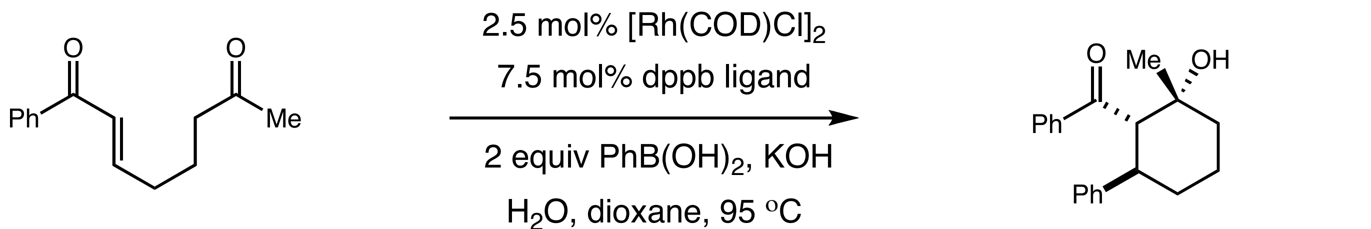
Excludes: Supramolecular Chemistry — *JACS* **2000**, *122*, 5006.; *JACS* **2002**, *124*, 5074. (selected publications)

Transfer Hydrogenation — *ACIE* **2009**, *48*, 34. (review)

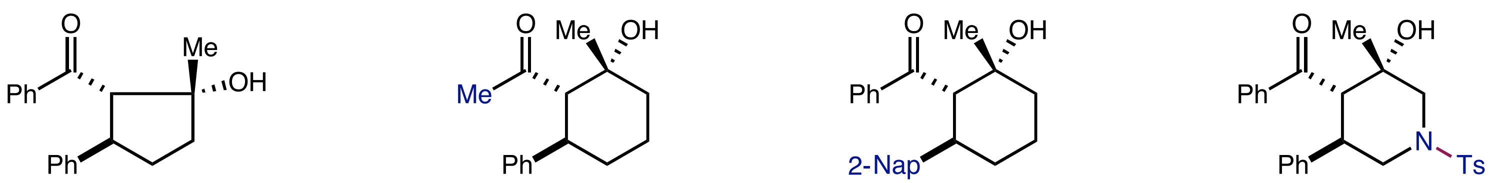
Catalytic Conjugate Addition-Electrophilic Trapping

Seminal Publication

- Rh-catalyzed tandem conjugate addition-aldol cyclization

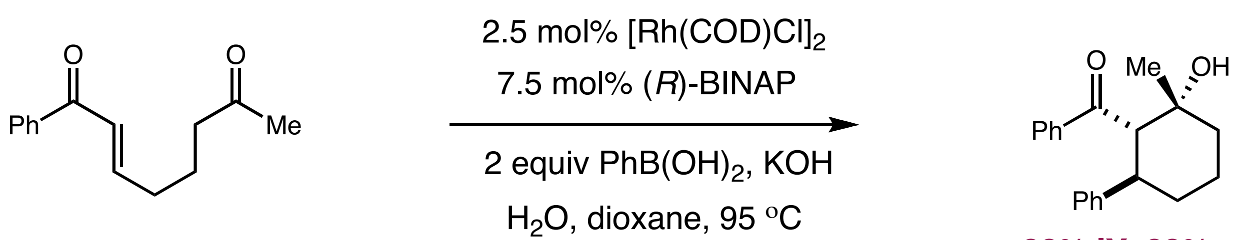


87% IY, single diastereomer



73% Y **45% Y** **70% Y** **84% Y**

- BINAP ligand induces enantioselectivity



88% IY, 88% ee

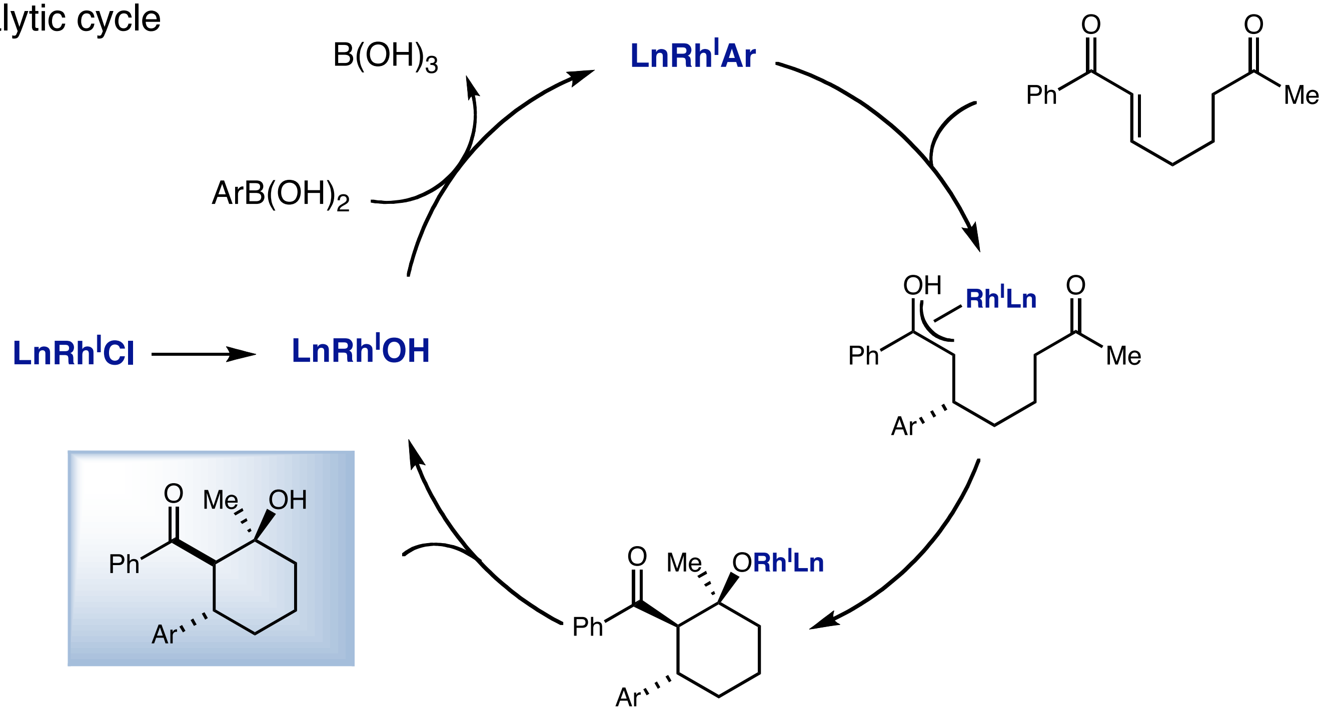
Scope: Aliphatic α,β-unsaturated ketones; 5 & 6 membered rings

J. Am. Chem. Soc. **2003**, *125*, 1110.

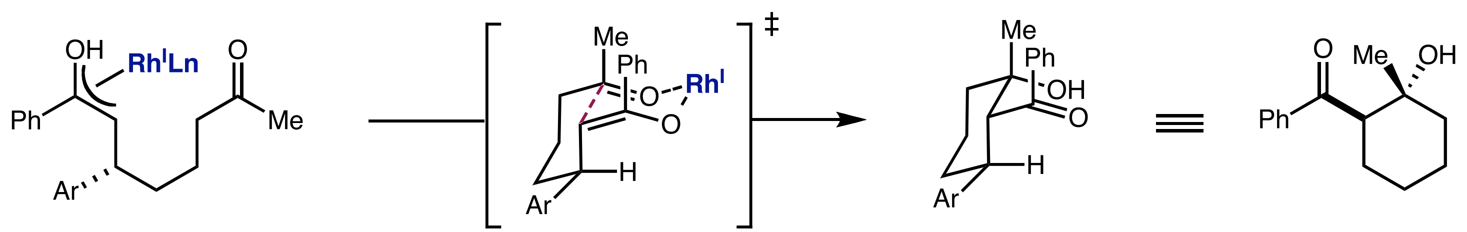
Catalytic Conjugate Addition-Electrophilic Trapping

Mechanism

- Catalytic cycle



- Zimmerman-Traxler transition state via Z-enolate

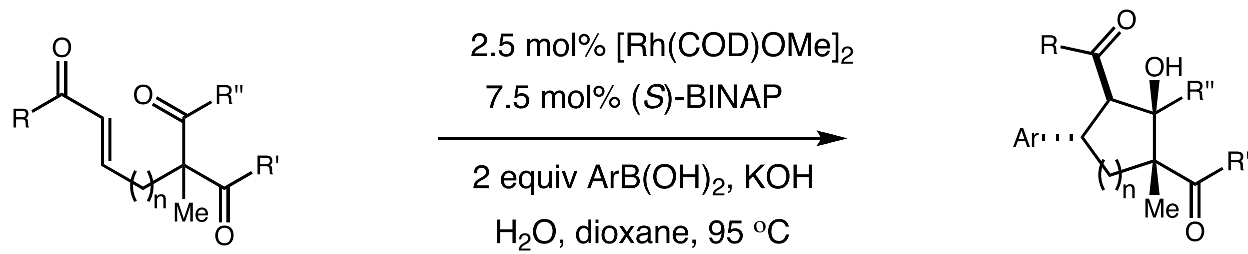


J. Am. Chem. Soc. **2003**, *125*, 1110.

Catalytic Conjugate Addition-Electrophilic Trapping

Improvements and Extensions

■ Rh-catalyzed tandem conjugate addition-aldol cyclization



65-87% Y, >99:1 de, 85-94% ee

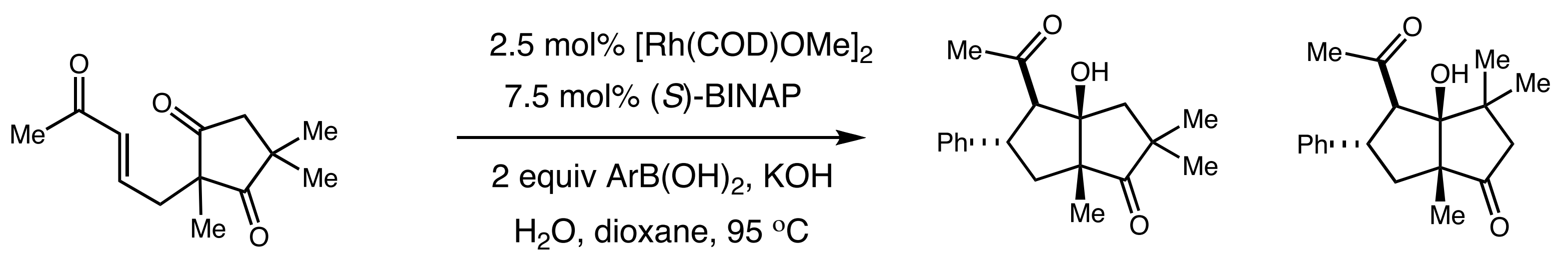
■ Improvements and extension of scope

[Rh(COD)OMe]$_2$ is more stable to oxidation

Electron rich and electron poor aryl boronic acids

Acyclic, cyclic 5- and 6-membered diones

■ Applied to dione desymmetrization via kinetic resolution



43% Y, >99:1 de
>99% ee

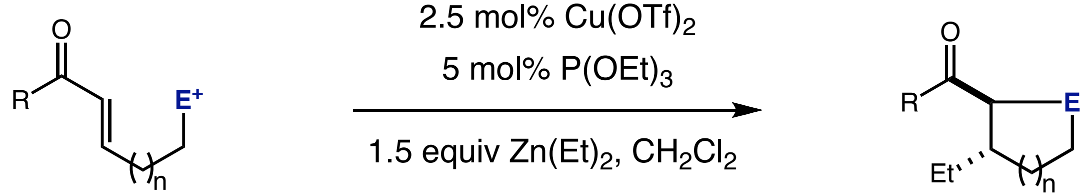
41% Y, >99:1 de
87% ee

Proc. Nat. Acad. Sci. U.S.A. **2004**, *101*, 5421

Catalytic Conjugate Addition-Electrophilic Trapping

Improvements and Extensions

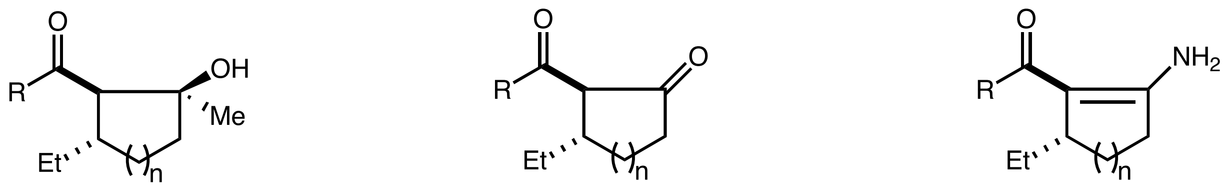
- Cu-catalyzed tandem conjugate addition-aldol cyclization



n=1,2

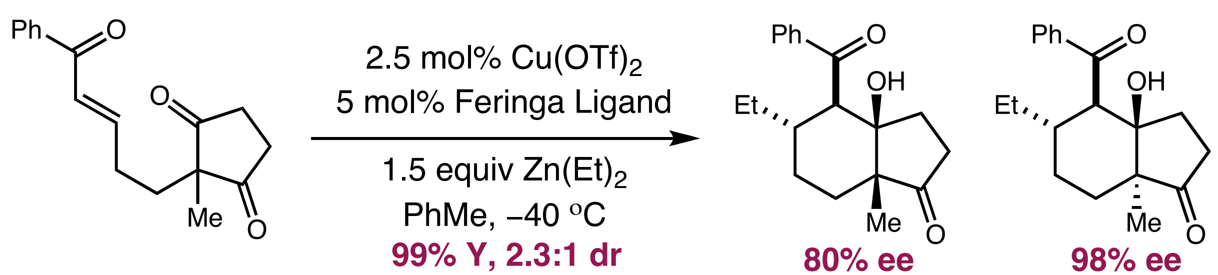
73-99% Y, 2:1 to >95:1 dr

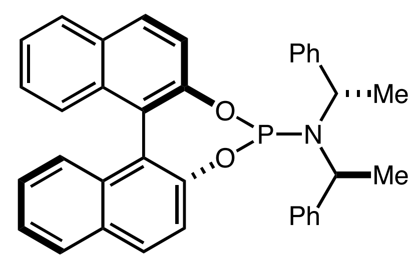
- Electrophiles



E^+ = ketone **E^+ = ester** **E^+ = nitrile**

- Enantioselective using Feringa phosphoramidite ligand



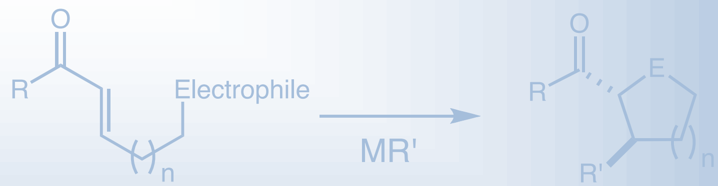


Feringa ligand

J. Am. Chem. Soc. **2004**, *126*, 4528.

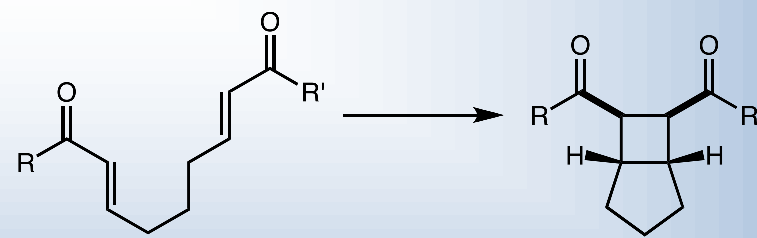
Research Areas

Catalytic Conjugate Addition-Electrophilic Trapping



seminal publication: *JACS* **2003**, *125*, 1110.

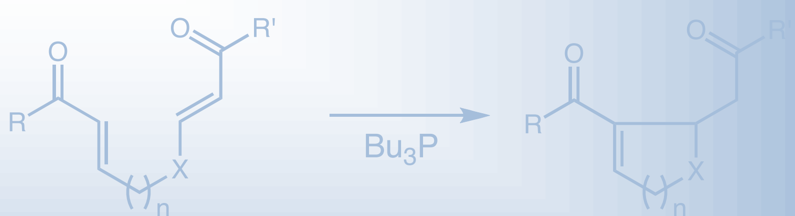
Metal-Catalyzed/Anion Radical [2+2] Cycloaddition



seminal publication: *JACS* **2001**, *123*, 6716.

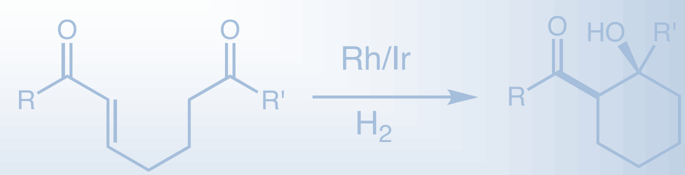
full article: *JACS* **2004**, *126*, 9448.

Nucleophilic Catalysis via Phosphine Conjugate Addn



seminal publication: *JACS* **2002**, *124*, 2402.

Hydrogen Mediated C-C Bond Formation



reviews: *Acc. Chem. Res.* **2004**, *37*, 653.
Acc. Chem. Res. **2007**, *40*, 1394.

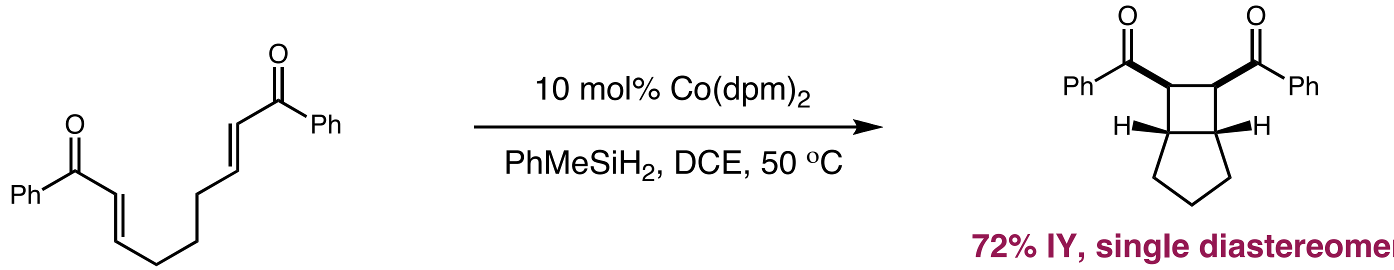
Excludes: Supramolecular Chemistry — *JACS* **2000**, *122*, 5006.; *JACS* **2002**, *124*, 5074. (selected publications)

Transfer Hydrogenation — *ACIE* **2009**, *48*, 34. (review)

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

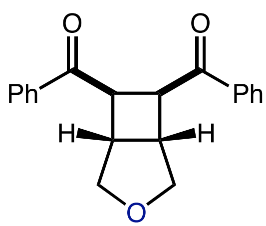
Seminal Publication

- Colbalt-mediated diastereoselective [2+2] cycloaddition

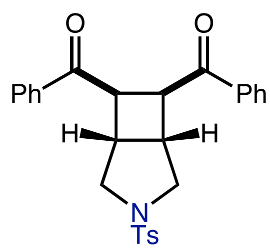


72% IY, single diastereomer

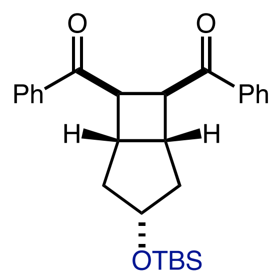
- Scope



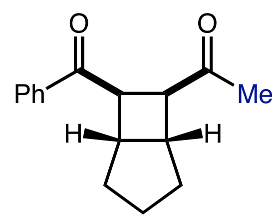
69% Y



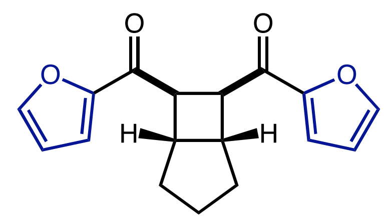
73% Y



65% Y



63% Y



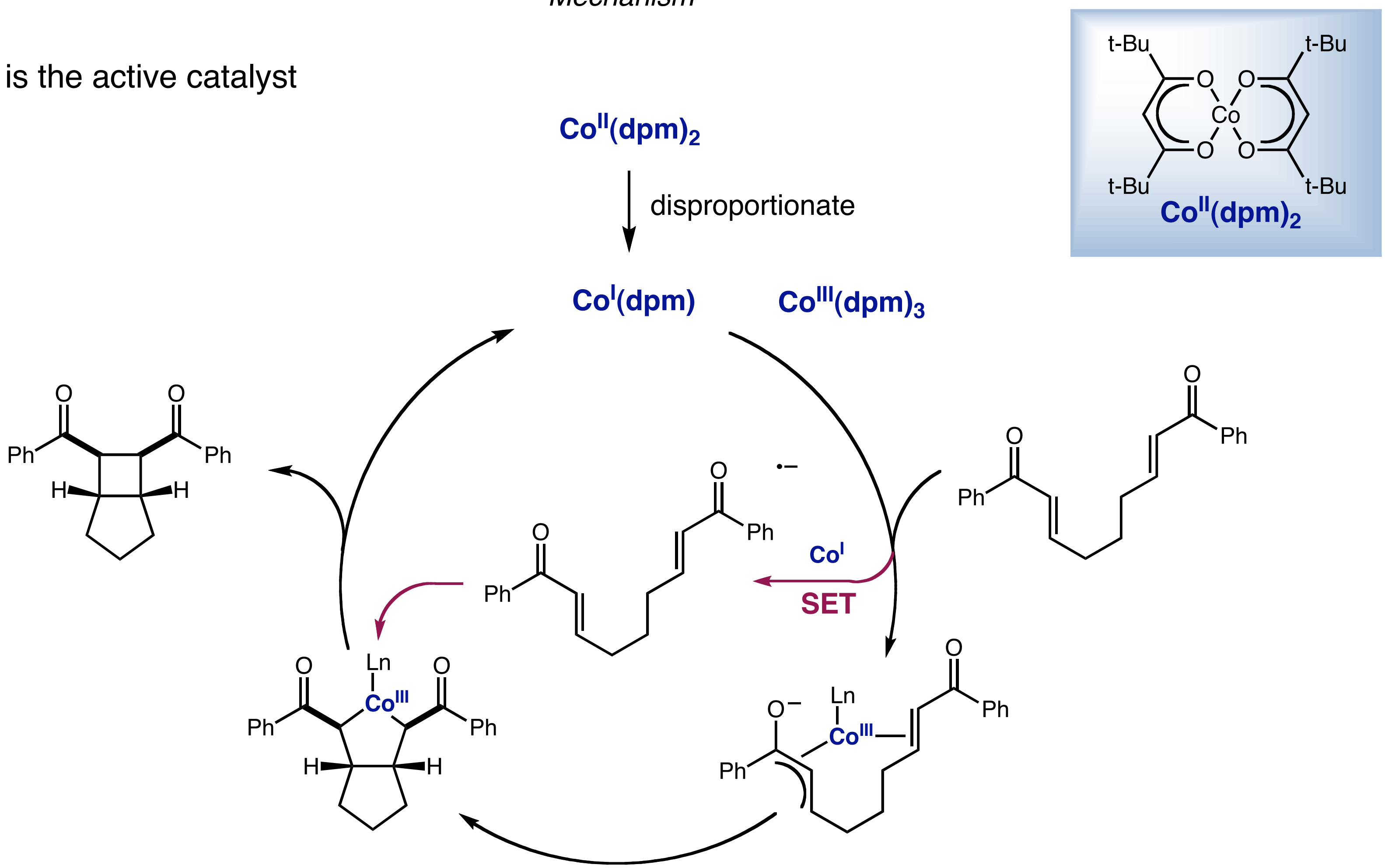
65% Y

J. Am. Chem. Soc. **2001**, *123*, 6716p.

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

Mechanism

- Co^{I} is the active catalyst

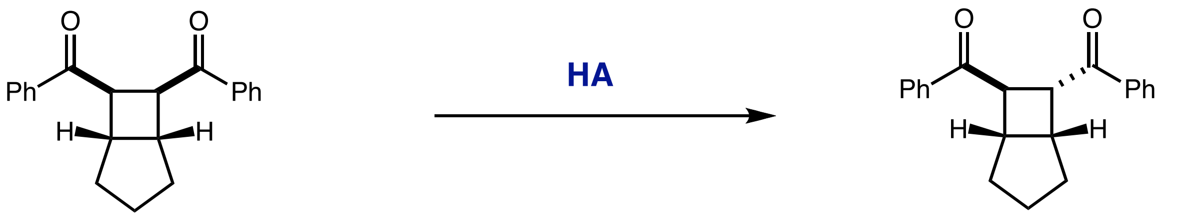


J. Am. Chem. Soc. **2002**, *124*, 9448.

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

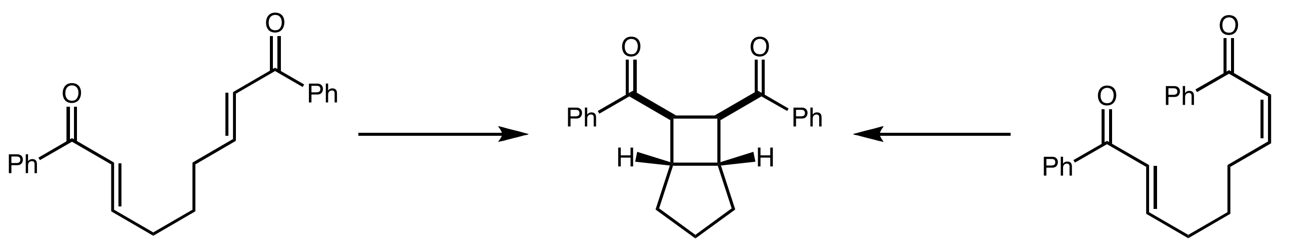
Some Observations

- Kinetic product is formed



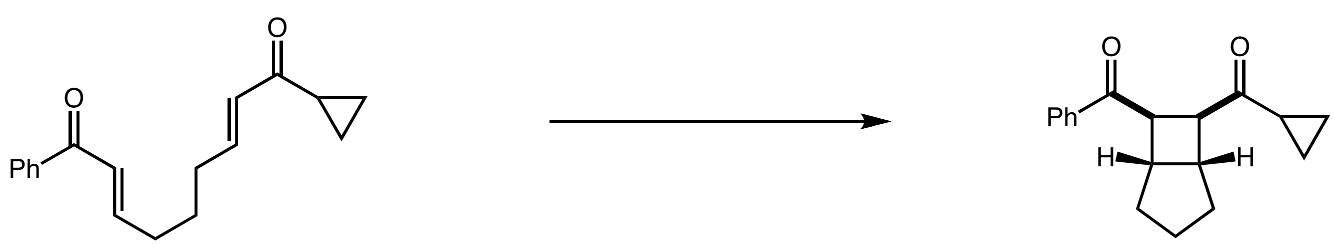
Co-cordination is involved

- E/Z isomers form same product



Co^{III}-enolates: rapid π-facial interconversion

- SET cyclopropane probe does not open

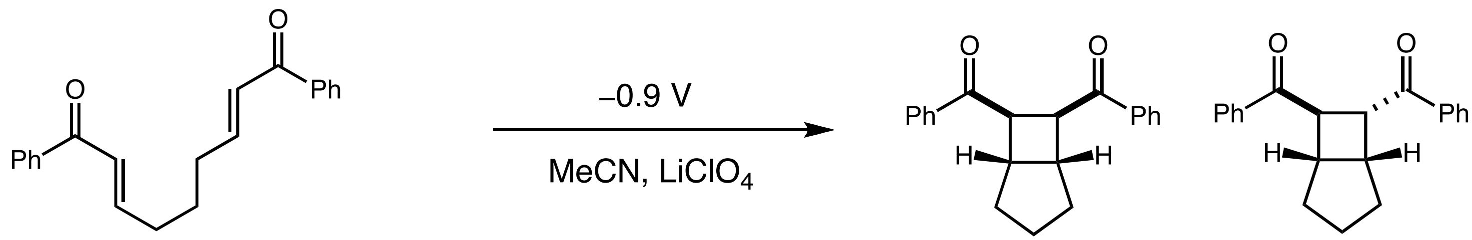


42% Y

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

Some Observations in Support of Radical Anion

- Cathodic reduction

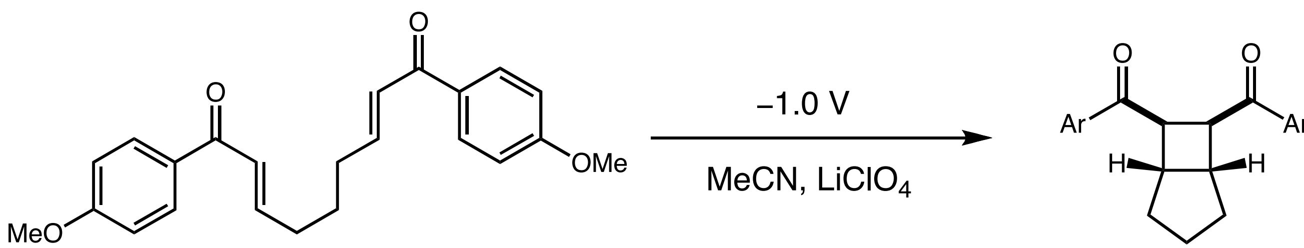


$E_{1/2}$ = –1.2 V

electron chain transfer

1:1.2

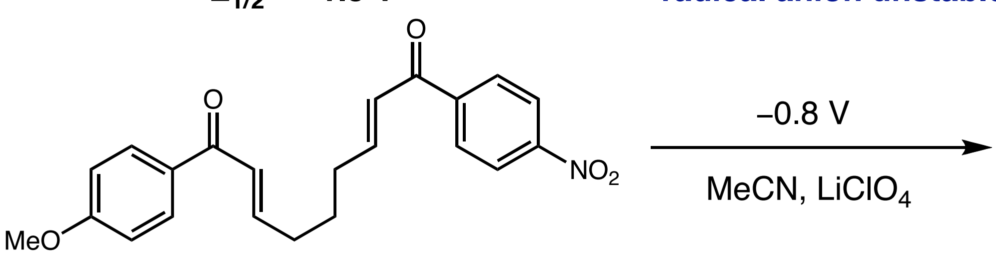
- Benzoyl is crucial for radical anion stabilization



dimer and oligomer products

$E_{1/2}$ = –1.3 V

radical anion unstable



dimer and oligomer products only

$E_{1/2}$ = –1.0 V

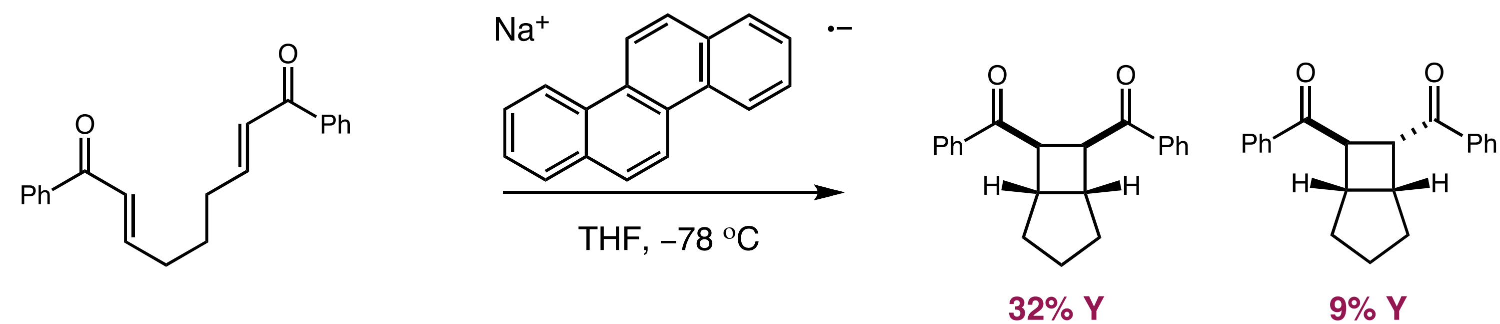
radical anion too stable = unreactive

Org. Lett. **2002**, *4*, 611.

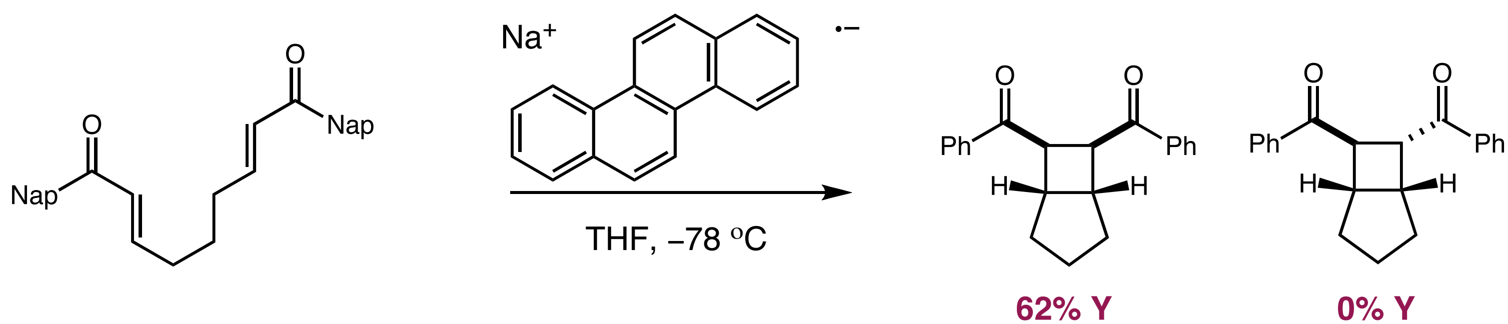
Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

Further Observations in Support of Radical Anion

- Chemical SET reduction



- Increasing radical delocalization improves desired reaction



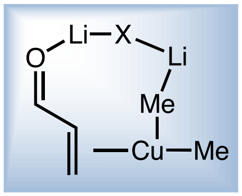
- Electrostatic interactions between Na and C=O result in cis-product
  - Not catalytic radical chain process

J. Am. Chem. Soc. **2004**, *126*, 1634.

Metal⁻Catalyzed/Anion Radical [2+2] Cycloaddition

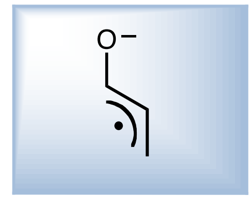
Using Products to Probe Mechanism

- Towards a mechanistic understanding of the Gilman Reagent

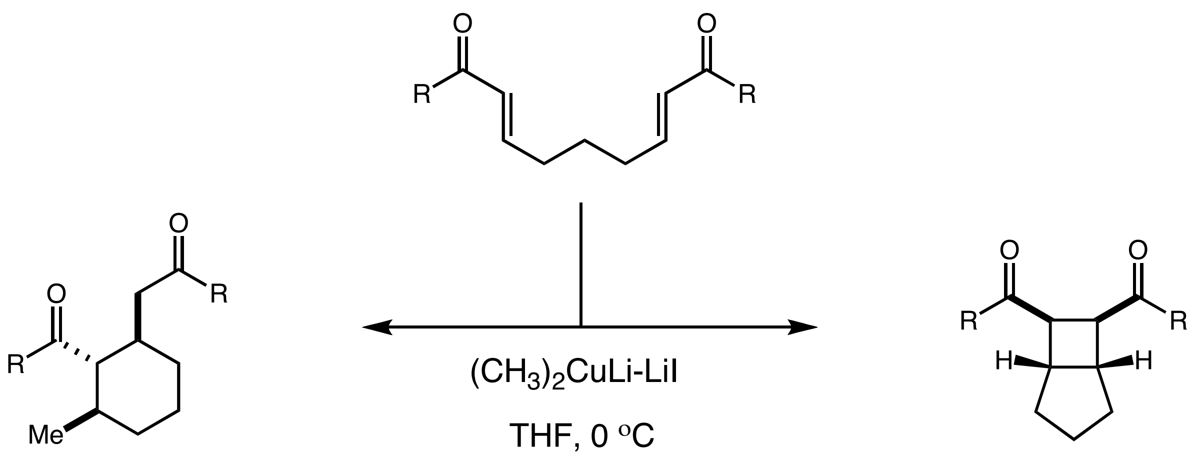


Cu complex followed by reductive elimination

$(CH_3)_2CuLi\text{-}LiI$



SET enone reduction



conjugate addition electrophile trapping product

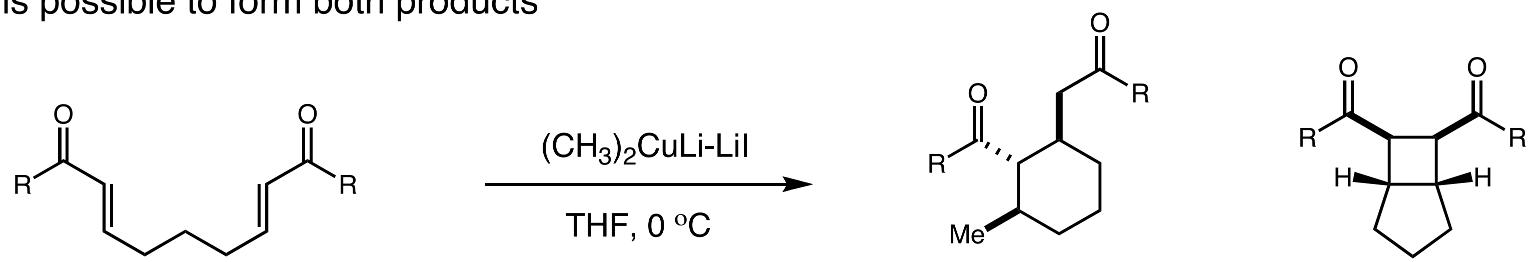
radical anion product

J. Org. Chem. **2004**, *69*, 7979.

Metal-Catalyzed/Anion Radical [2+2] Cycloaddition

Using Products to Probe Mechanism

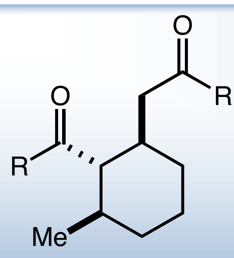
■ It is possible to form both products



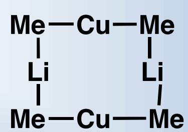
R=4-biphenyl

mol% $(CH_3)_2CuLi$	conjugate addition electrophile trapping product	radical anion product
100	**64**	**13**
200	**85**	**0**
25	**13**	**84**
25, slow addition	**0**	**91**

■ Kinetic studies show dependence on concentration



cyclic dimer

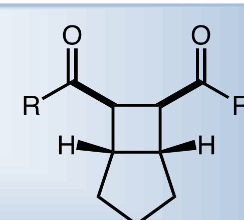


alkylating reagent

monomer

$(CH_3)_2CuLi$

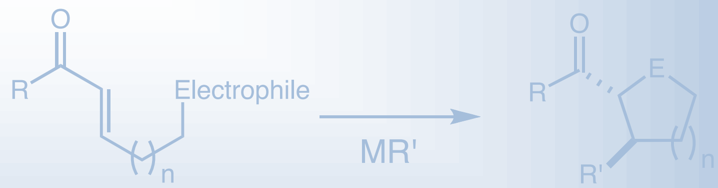
ET reagent



J. Org. Chem. **2004**, *69*, 7979.

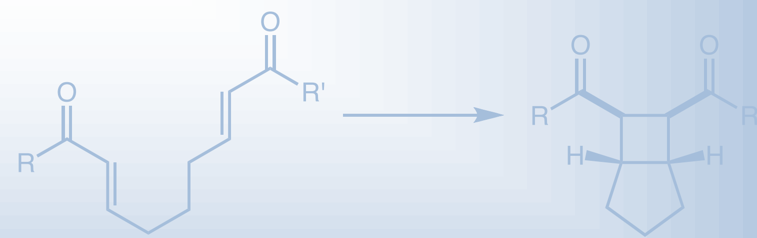
Research Areas

Catalytic Conjugate Addition-Electrophilic Trapping



seminal publication: *JACS* **2003**, *125*, 1110.

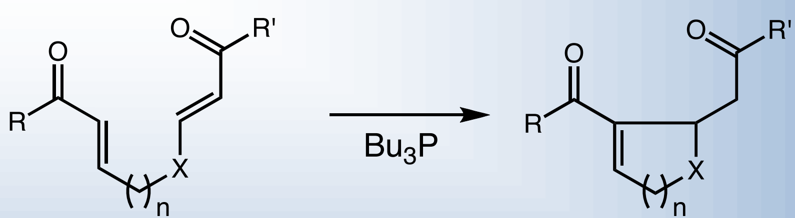
Metal-Catalyzed/Anion Radical [2+2] Cycloaddition



seminal publication: *JACS* **2001**, *123*, 6716.

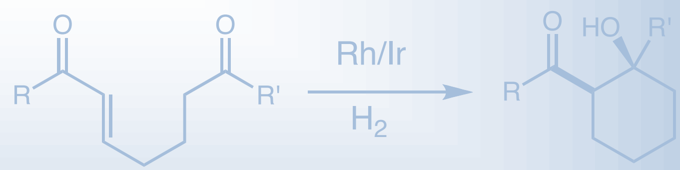
full article: *JACS* **2004**, *126*, 9448.

Nucleophilic Catalysis via Phosphine Conjugate Addn



seminal publication: *JACS* **2002**, *124*, 2402.

Hydrogen Mediated C-C Bond Formation



reviews: *Acc. Chem. Res.* **2004**, *37*, 653.

Acc. Chem. Res. **2007**, *40*, 1394.

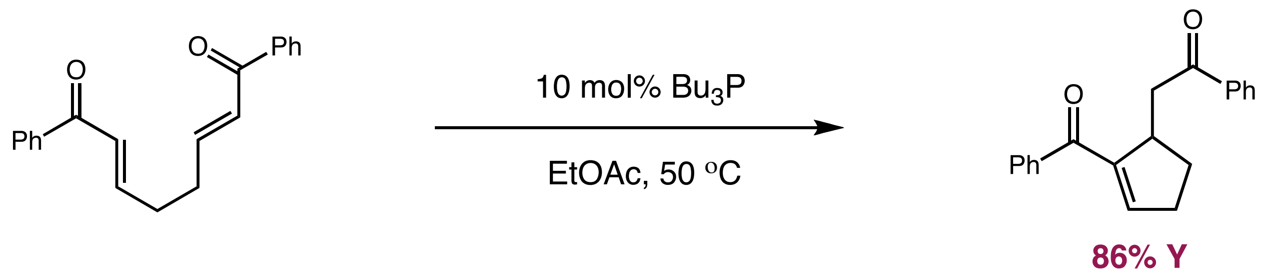
Excludes: Supramolecular Chemistry — *JACS* **2000**, *122*, 5006.; *JACS* **2002**, *124*, 5074. (selected publications)

Transfer Hydrogenation — *ACIE* **2009**, *48*, 34. (review)

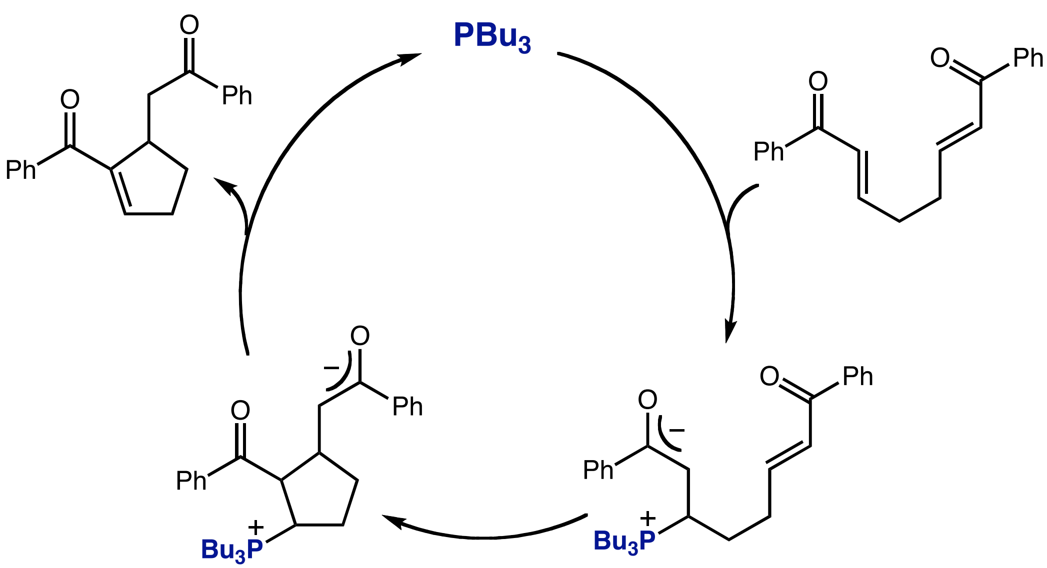
Nucleophilic Catalysis via Phosphine Conjugate Addition

Seminal Publication

■ Intramolecular Rauhut-Currier Reaction



■ Mechanism



■ Reaction is dependent on

Substrate electronics

more electrophilic enone preferred

Substrate sterics

less hindered enone preferred

Solvent polarity

more polar solvent improves reactivity

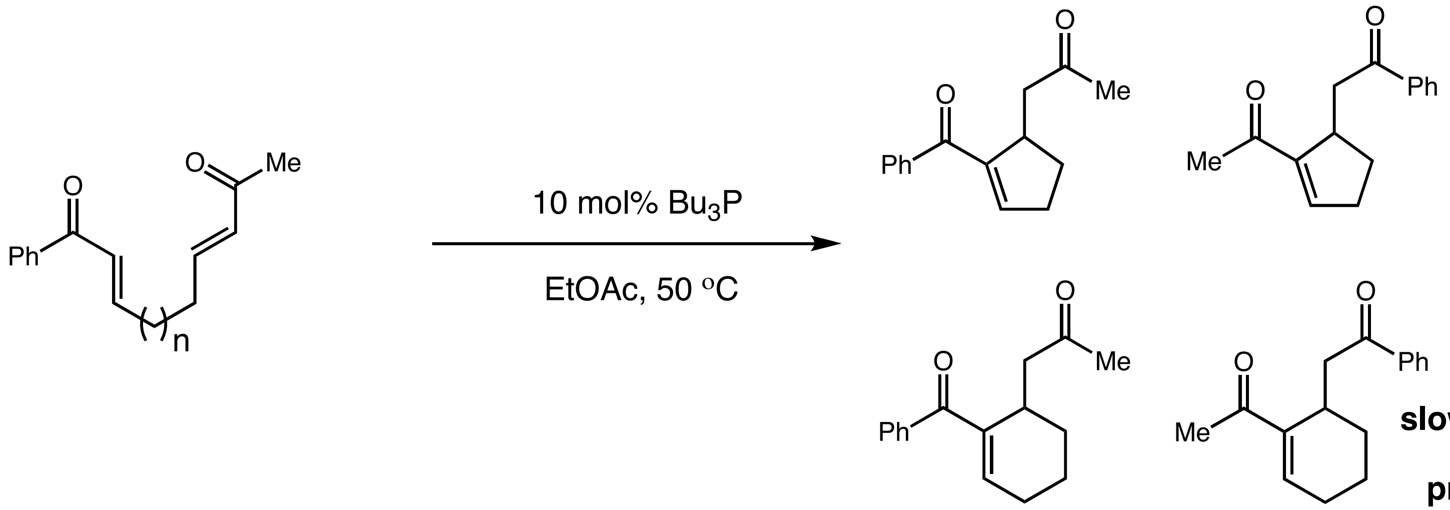
may lead to polymer products

J. Am. Chem. Soc. **2003**, *125*, 2402.

Nucleophilic Catalysis via Phosphine Conjugate Addition

Seminal Publication

- Electronic effects



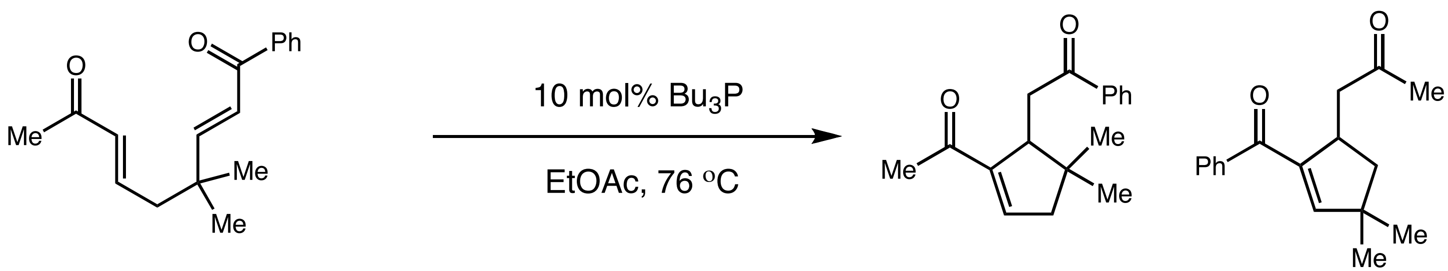
1:1

rapid cyclization

7:1

slower cyclization allows for preequilibrium

- Steric effects



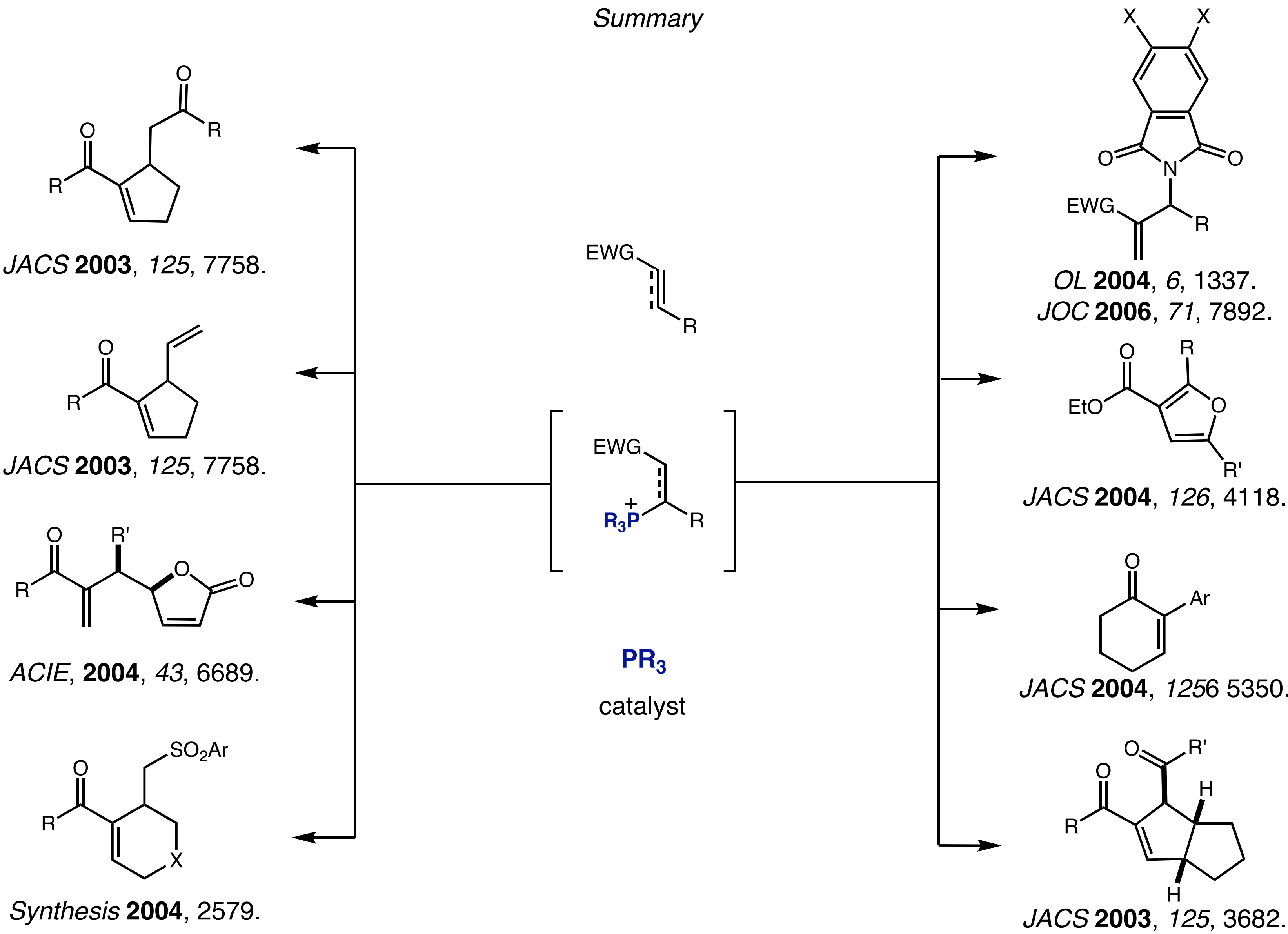
>95:5

rapid cyclization

J. Am. Chem. Soc. **2003**, *125*, 2402.

Nucleophilic Catalysis via Phosphine Conjugate Addition

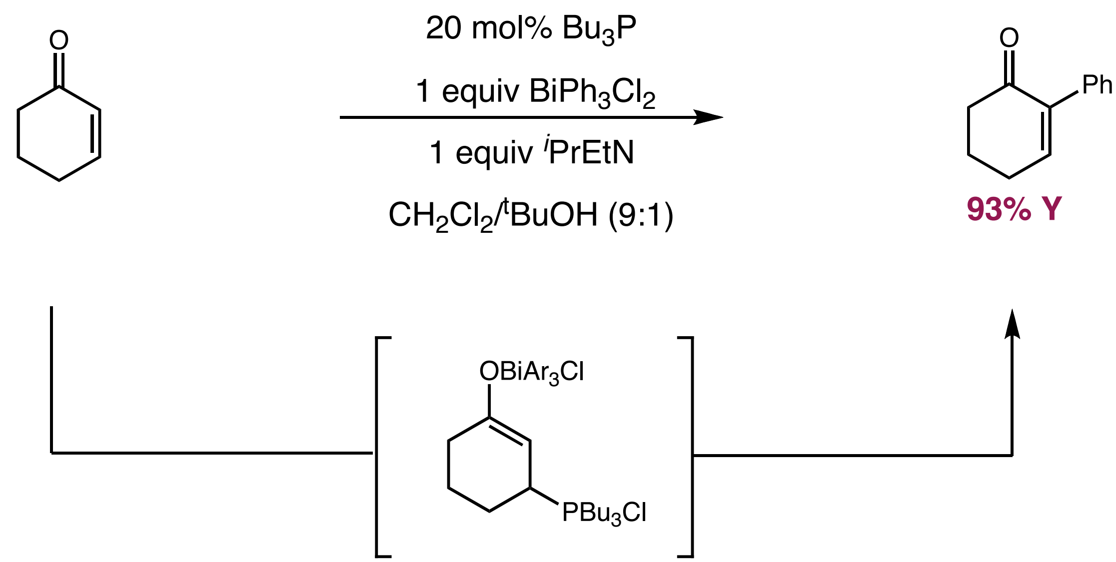
Summary



Nucleophilic Catalysis via Phosphine Conjugate Addition

Extensions

■ α-Arylation using hypervalent bismuth reagents



Substrates must be β-substituted

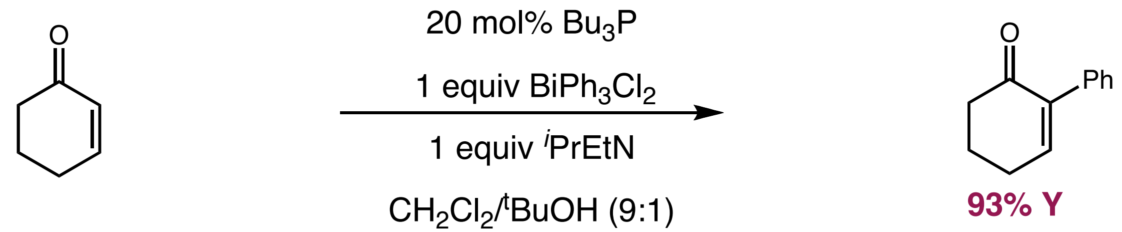
Acyclic enones perform poorly

J. Am. Chem. Soc. **2004**, *126*, 5350.

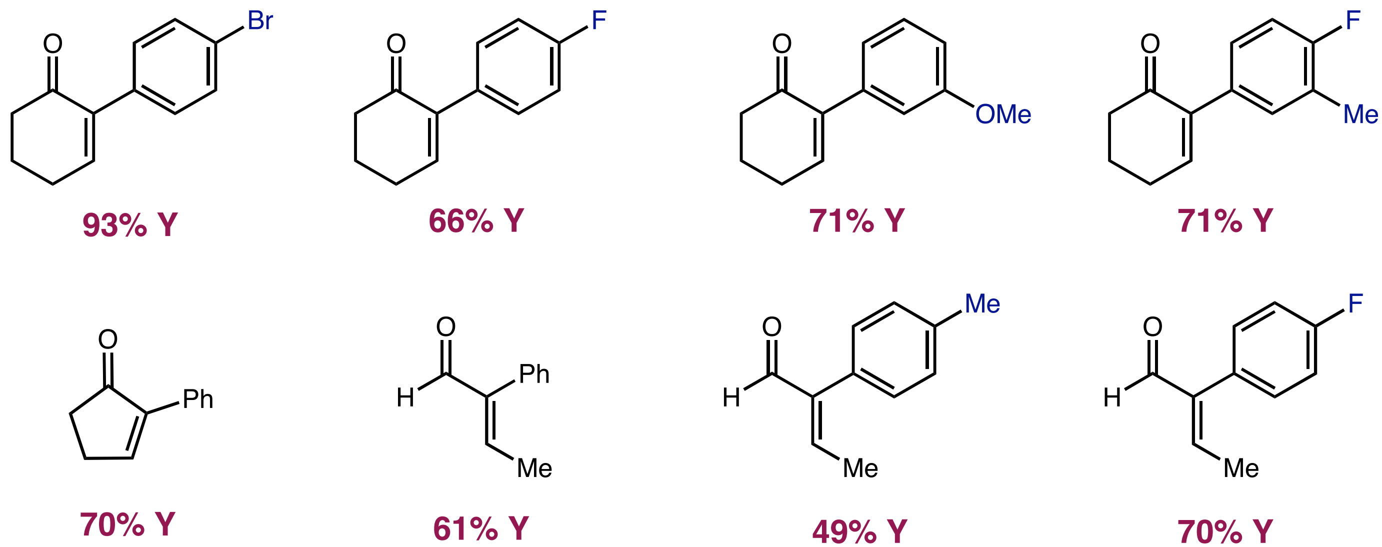
Nucleophilic Catalysis via Phosphine Conjugate Addition

Extensions

■ α-Arylation using hypervalent bismuth reagents



■ Enones and Enals

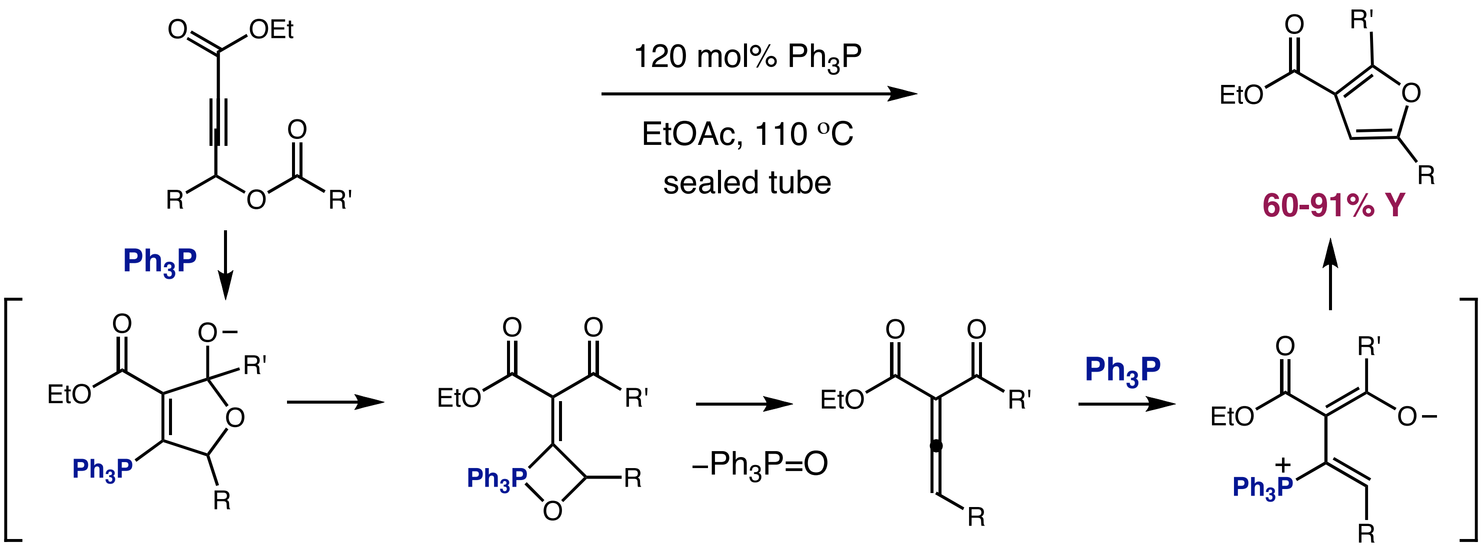


J. Am. Chem. Soc. **2004**, *126*, 5350.

Nucleophilic Catalysis via Phosphine Conjugate Addition

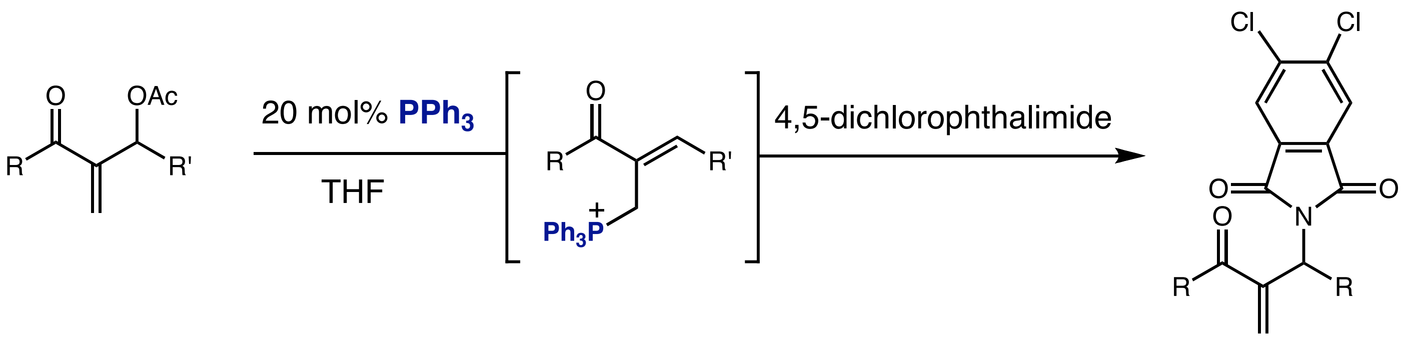
Extensions

■ Reductive condensation of γ-acyloxy butynoates



J. Am. Chem. Soc. **2004**, *126*, 4118.

■ Allylic amination

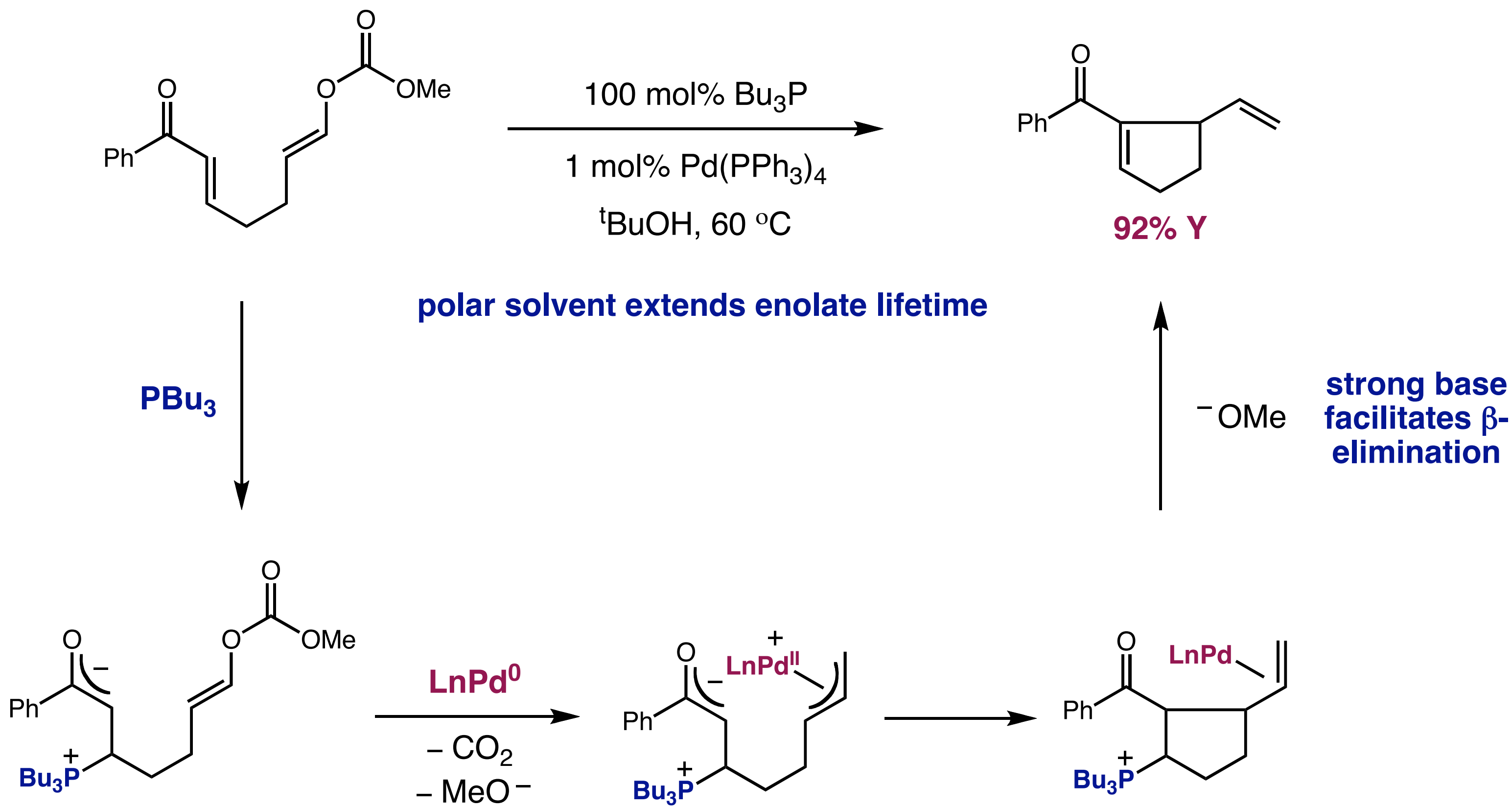


Org. Lett. **2004**, *6*, 1337.

Nucleophilic Catalysis via Phosphine Conjugate Addition

Extensions

- The merger of phosphine and Pd-allyl catalysis

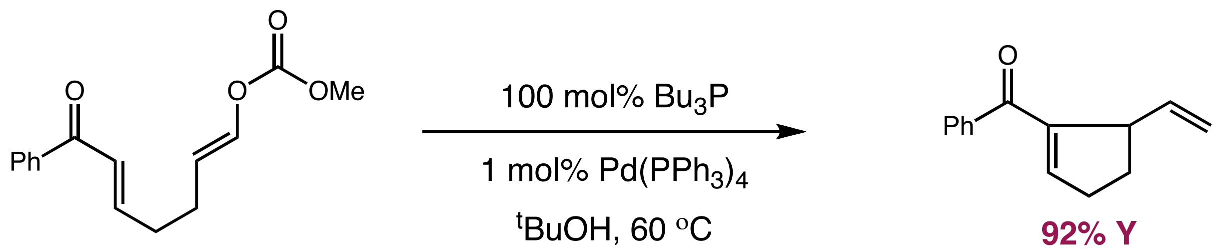


J. Am. Chem. Soc. **2003**, *125*, 7758.

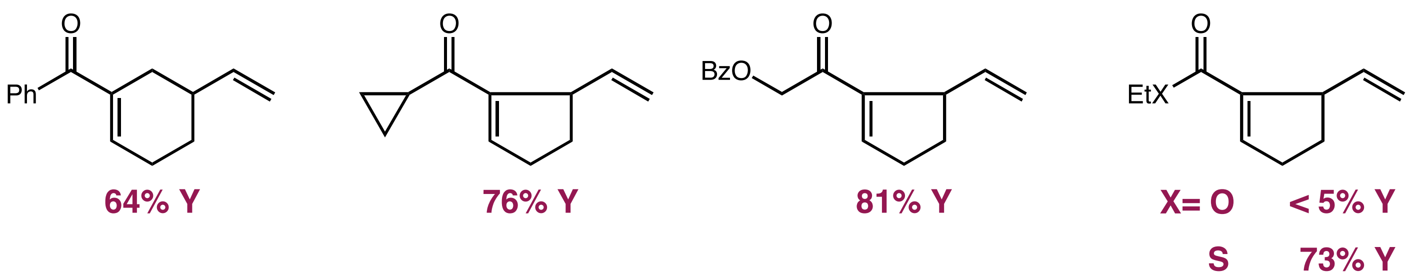
Nucleophilic Catalysis via Phosphine Conjugate Addition

Extensions

- The merger of phosphine and Pd-allyl catalysis



- Scope

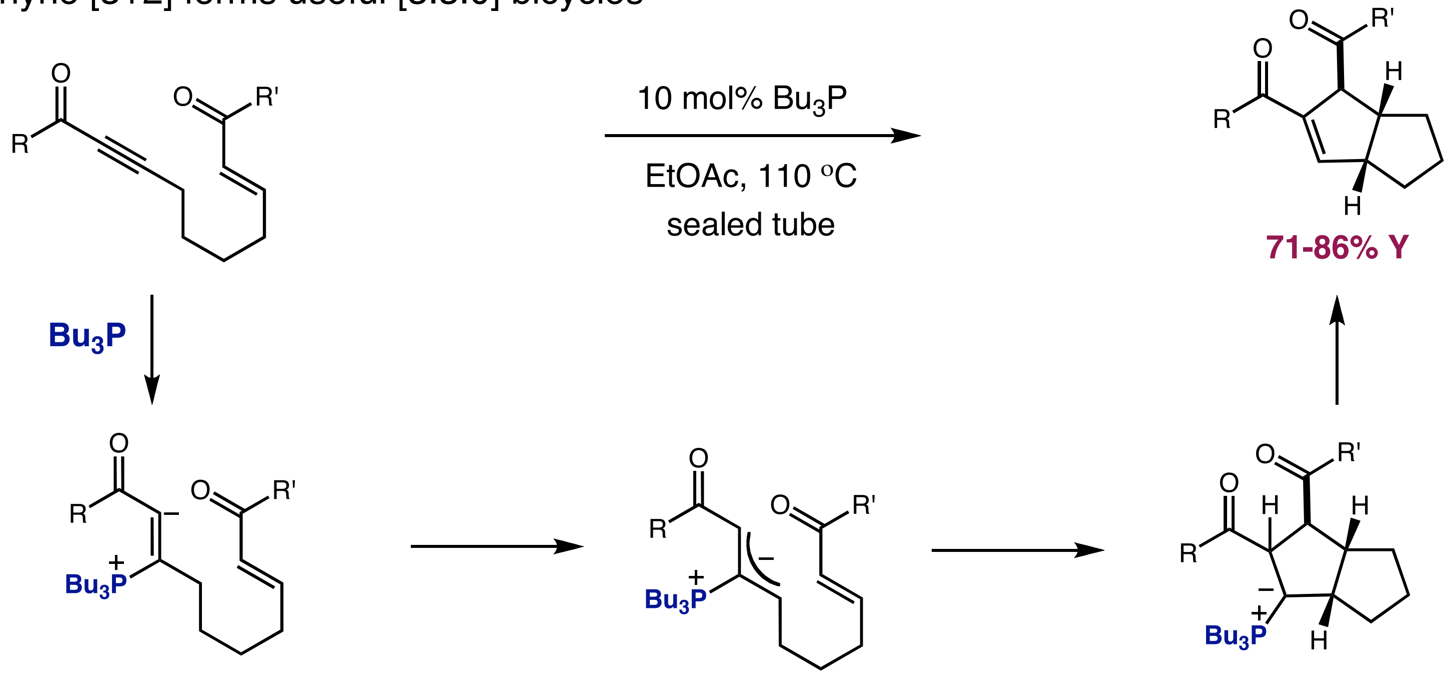


J. Am. Chem. Soc. **2003**, *125*, 7758.

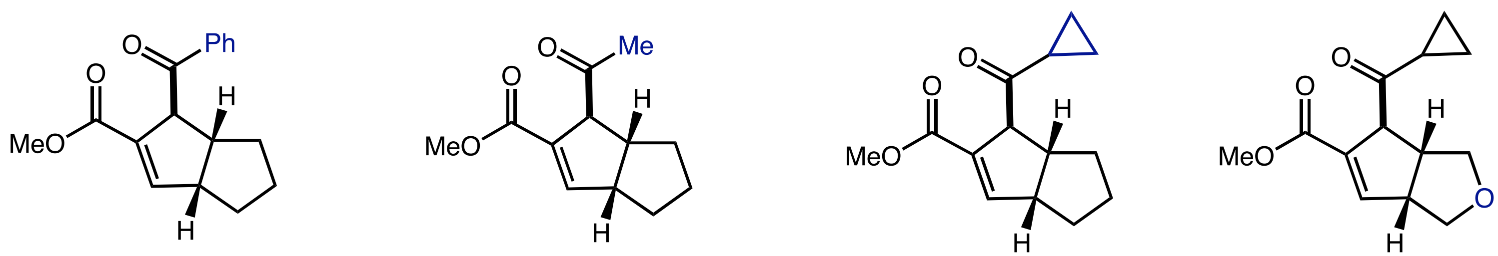
Nucleophilic Catalysis via Phosphine Conjugate Addition

Applications to Total Synthesis

■ Enyne [3+2] forms useful [3.3.0] bicycles



■ Scope



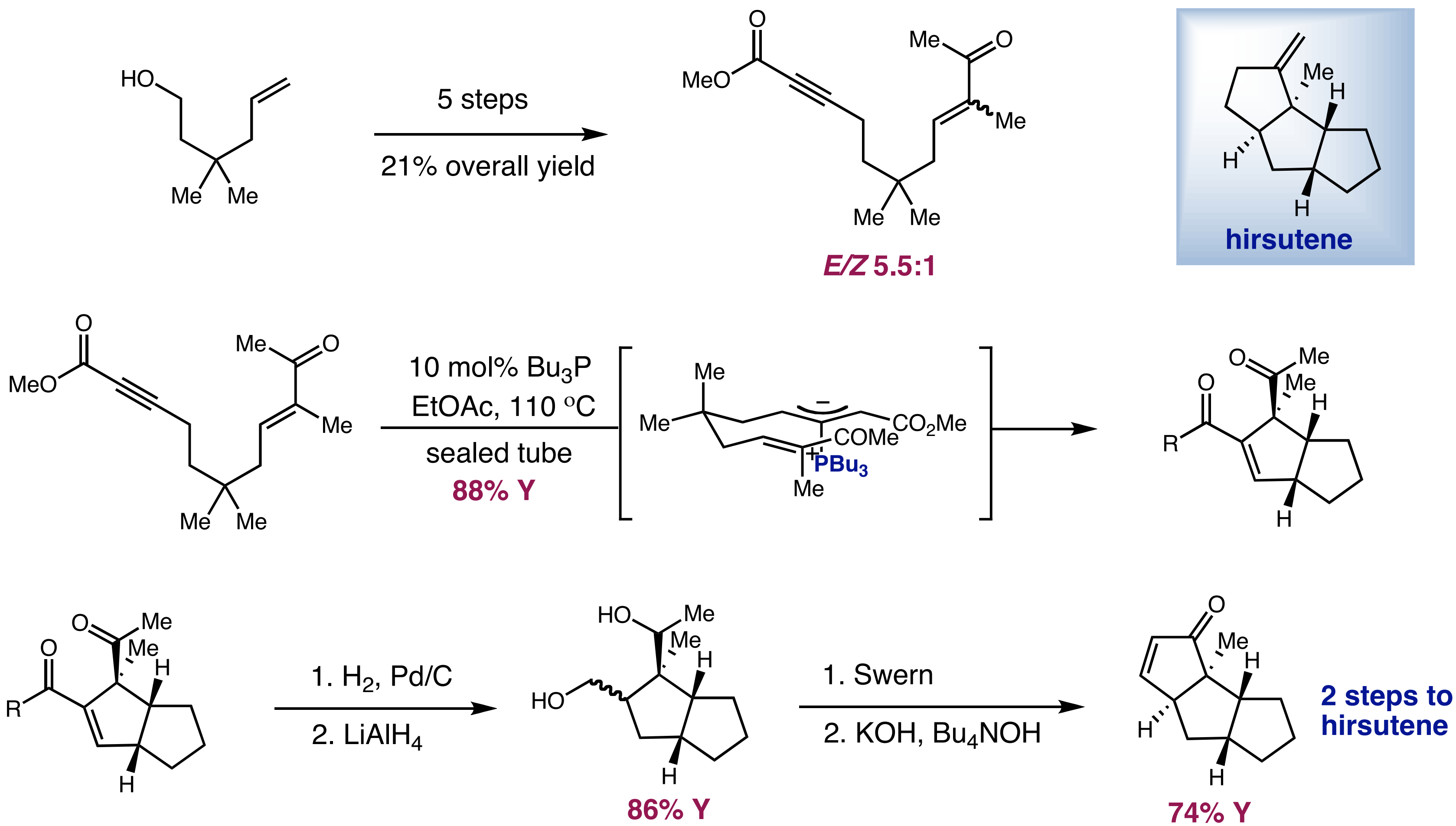
76% Y | 77% Y | 86% Y | 75% Y

J. Am. Chem. Soc. **2003**, *125*, 3683.

Nucleophilic Catalysis via Phosphine Conjugate Addition

Applications to Total Synthesis

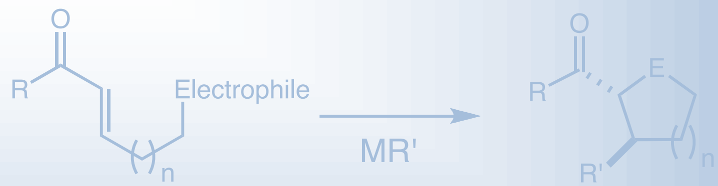
- Formal synthesis of racemic hirsutene



Angew. Chem. Int. Ed. **2003**, *42*, 5855.

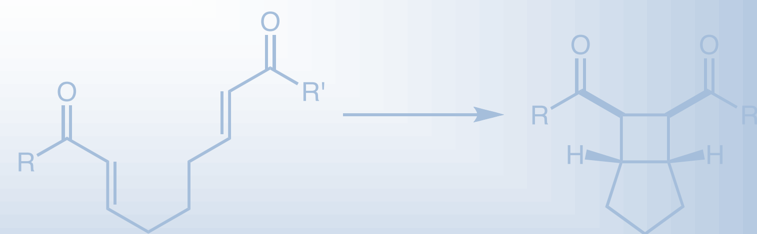
Research Areas

Catalytic Conjugate Addition-Electrophilic Trapping



seminal publication: *JACS* **2003**, *125*, 1110.

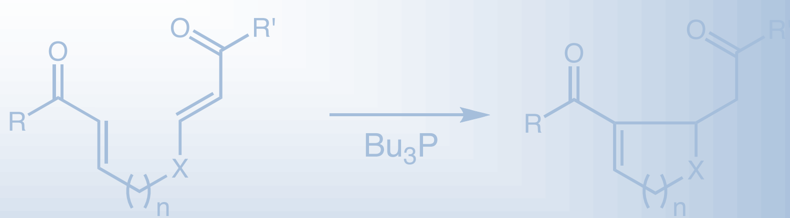
Metal-Catalyzed/Anion Radical [2+2] Cycloaddition



seminal publication: *JACS* **2001**, *123*, 6716.

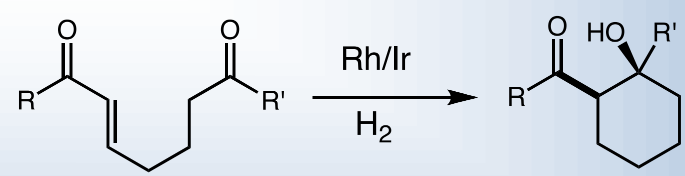
full article: *JACS* **2004**, *126*, 9448.

Nucleophilic Catalysis via Phosphine Conjugate Addn



seminal publication: *JACS* **2002**, *124*, 2402.

Hydrogen Mediated C-C Bond Formation



reviews: *Acc. Chem. Res.* **2004**, *37*, 653.

Acc. Chem. Res. **2007**, *40*, 1394.

Excludes: Supramolecular Chemistry — *JACS* **2000**, *122*, 5006.; *JACS* **2002**, *124*, 5074. (selected publications)

Transfer Hydrogenation — *ACIE* **2009**, *48*, 34. (review)

"...More than half of the chiral compounds produced industrially from

prochiral substrates are made via asymmetric hydrogenation.

This suggests an equally powerful approach to r*eductive C-C bond formation...*

Inspired by this prospect, hydrogen-mediated C-C bond formation has become

the focus of research in our laboratory..."

- *OL* **2006**, *8*, 519

Hydrogenation

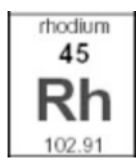
Background

- Motivation

H_2 is completely atom economical

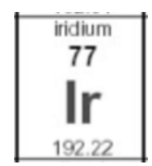
No waste is generated

- On rhodium and iridium



Rhodium(I)

$5s^0 4d^8$



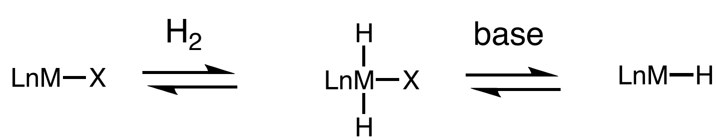
Iridium(I)

$6s^0 4f^{14} 5d^8$

weak π-donor

stronger π-donor due to relativisitic effects

heterolytic hydrogen activation

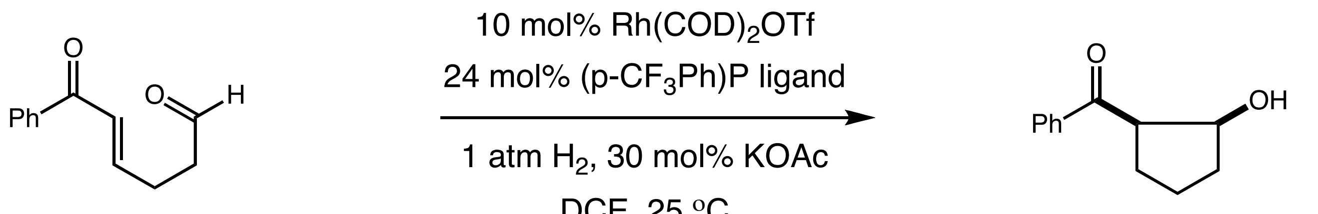


J. Am. Chem. Soc. **2002**, *124*, 15156.

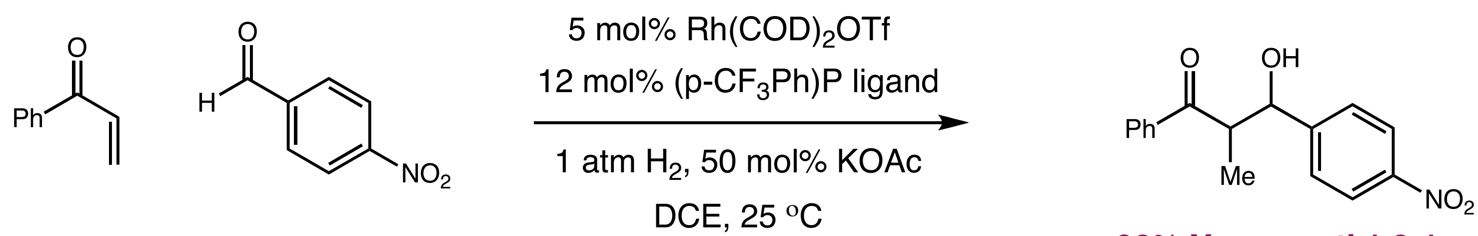
Hydrogenation

Seminal Publication

- Reductive aldol

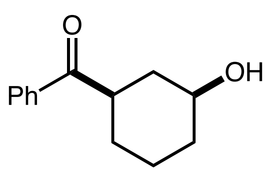


71% Y, syn:anti 24:1

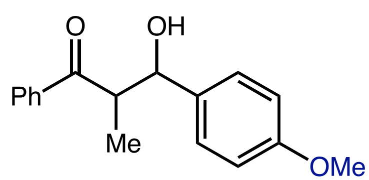


92% Y, syn:anti 1.8:1

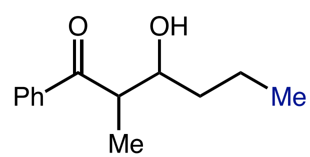
- Scope



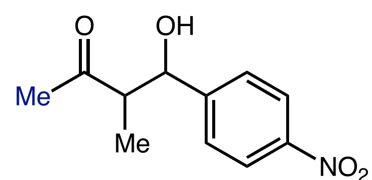
89% Y, syn:anti 10:1



75% Y, syn:anti 1.7:1



44% Y, syn:anti 2:1



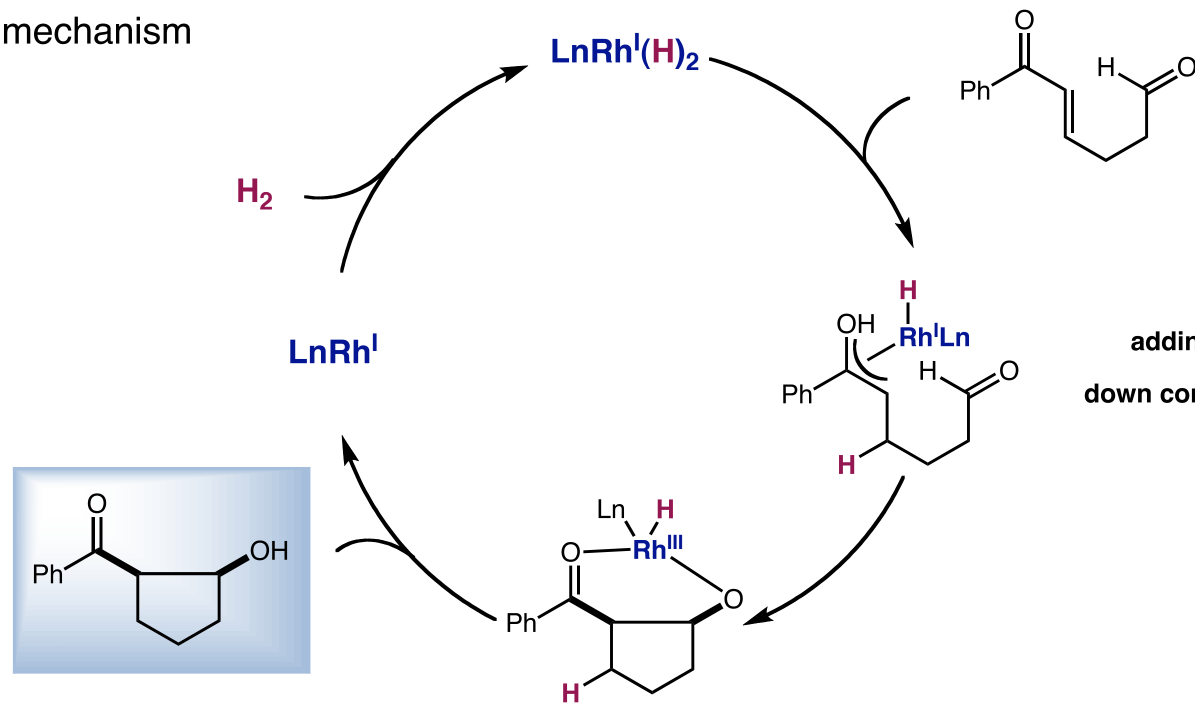
70% Y, syn:anti 2:1

J. Am. Chem. Soc. **2002**, *124*, 15156.

Hydrogenation

Mechanism

- Proposed mechanism



adding base slows

down conjugate reduction

- Triaryl phosphines do not add to substrate

Baylis-Hillman cyclization-conjugate reduction is not observed

- Phosphine ligand affects reactivity

Ln	yield
PPh_3	59%
$P(p\text{-}CF_3Ph)_3$	89%

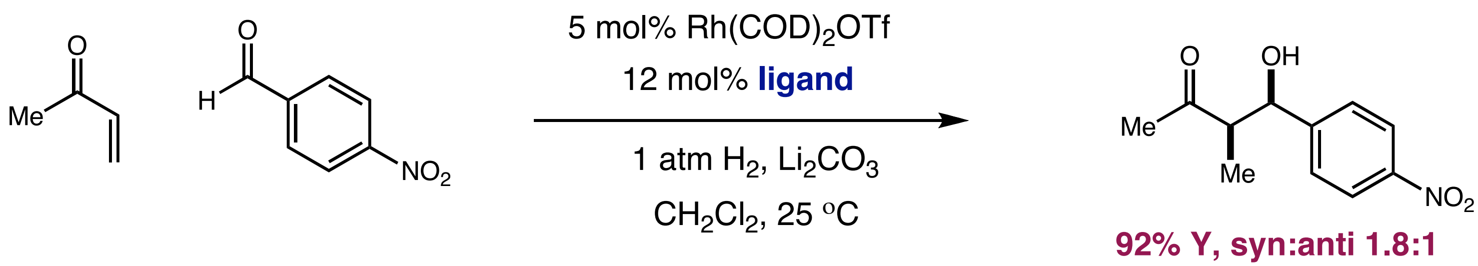
Increasing Lewis acidity of Rh improves aldehyde coordination

J. Am. Chem. Soc. **2002**, *124*, 15156.

Hydrogenation

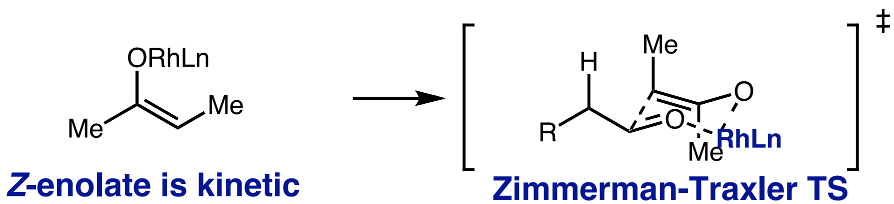
Improvements

■ *syn*-Selectivity improved for intermolecular reaction



ligand	yield	dr	
(p-$CF_3Ph)_3P$	**70**	**2:1**	*from prev work
Ph_3P	**31**	**3:1**	
(2-Fur)Ph_2P	**24**	**6:1**	increasing
$(2\text{-Fur})_2PhP$	**52**	**15:1**	π-acidity
$(2\text{-Fur})_3P$	**74**	**19:1**	

■ Stereochemical rational for *anti*-Felkin model



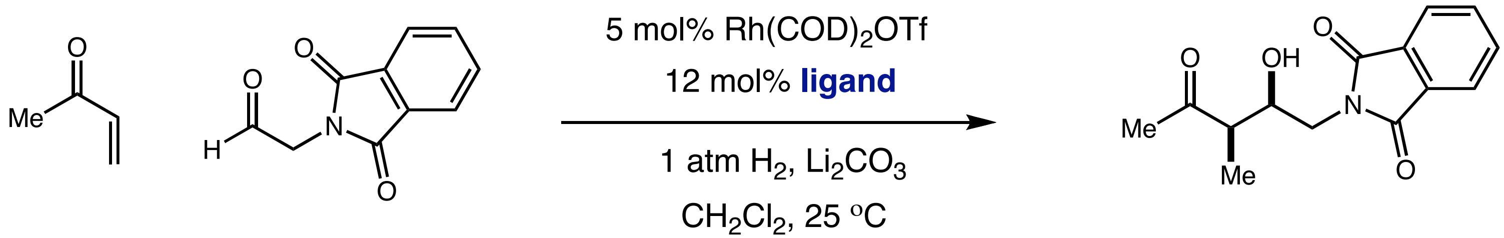
enolization and aldolization are irreversible

J. Am. Chem. Soc. **2002**, *124*, 15156.
Org. Lett., **2006**, *8*, 519.

Hydrogenation

Enantioselective Reductive Aldol

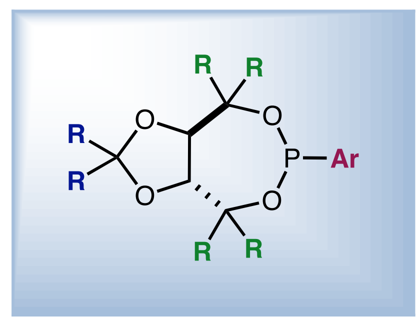
- Development of a chiral ligand



- Commercially available chiral ligands are too π-acidic: only trace amount of product observed
- Catalyst development based on TADDOL scaffold

monodentate ligand

independent modification sites



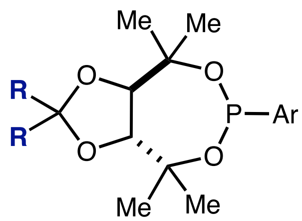
J. Am. Chem. Soc. **2008**, *130*, 2746.

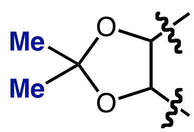
Hydrogenation

Enantioselective Reductive Aldol

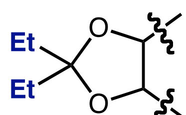
- TADDOL-like phosphonite ligand evolution

ketal

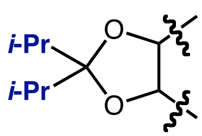




64% Y, 66% ee

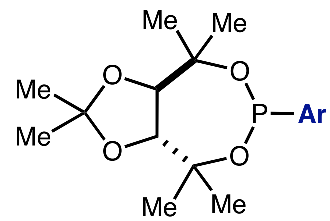


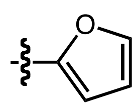
75% Y, 75% ee



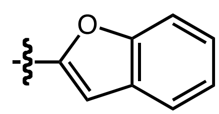
76% Y, 69% ee

aryl

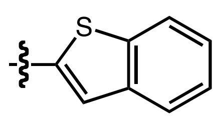




90% Y, 59% ee

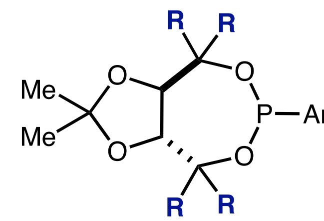


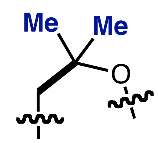
64% Y, 66% ee



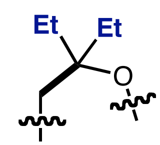
65% Y, 86% ee

carbinol

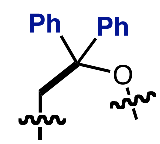




64% Y, 66% ee



32% Y, 66% ee



15% Y, 30% ee

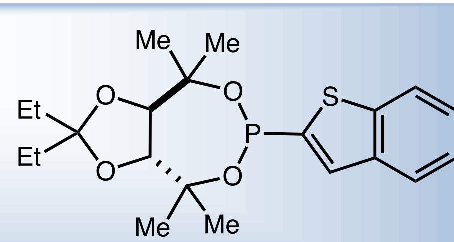
J. Am. Chem. Soc. **2008**, *130*, 2746.

Hydrogenation

Enantioselective Reductive Aldol

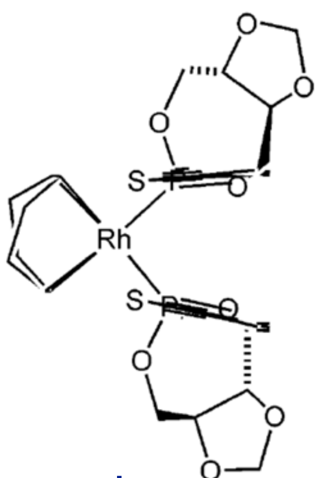
- TADDOL-like phosphonite ligand: optimized structure

optimized ligand

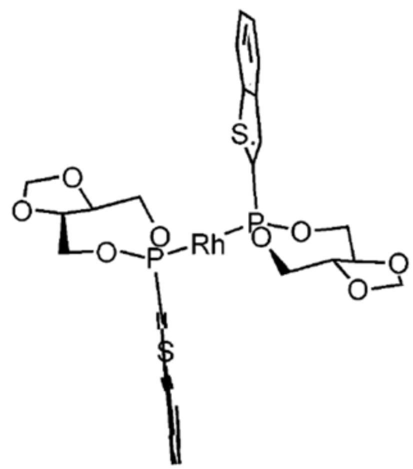


90% Y, 92% ee

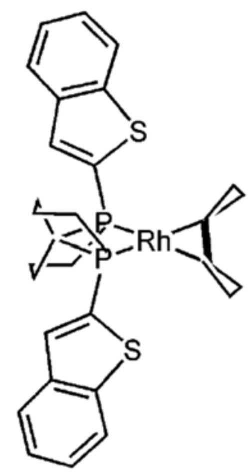
- Enantioinduction results from C_2-symmetric catalyst: $Rh(COD)Ln_2OTf$: crystal structure



top



front



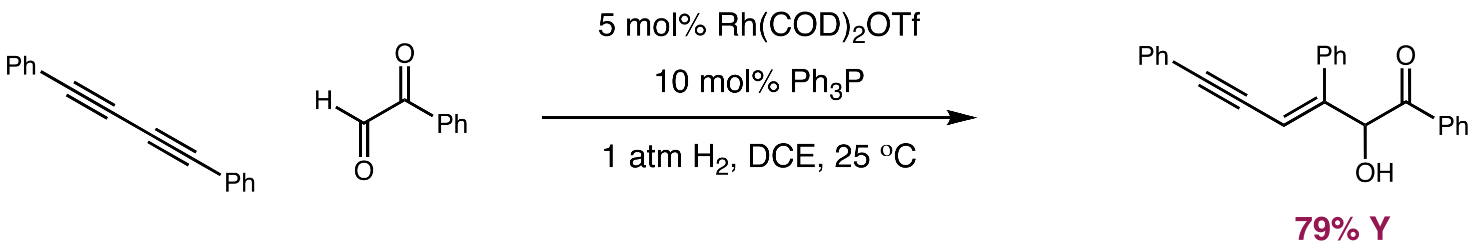
side

J. Am. Chem. Soc. **2008**, *130*, 2746.

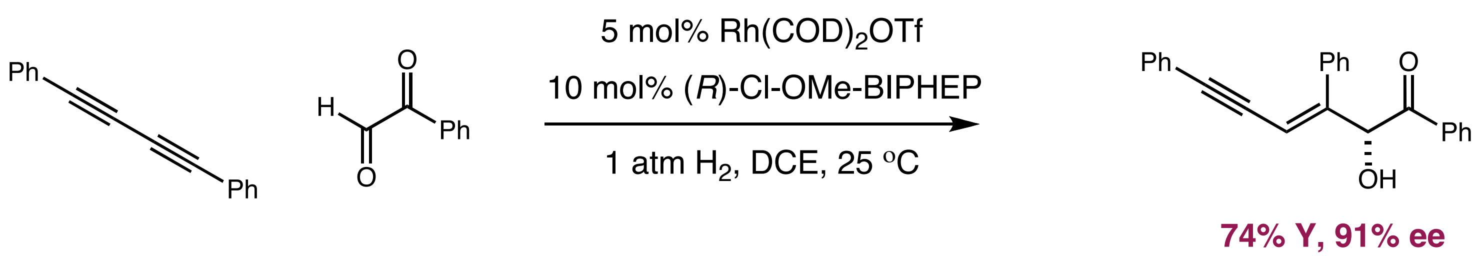
Hydrogenation

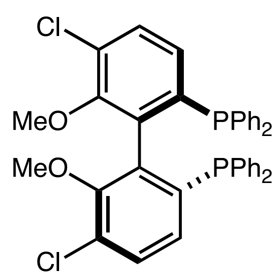
Reductive Rh-Alkyne Coupling

- Reductive 1,3-diyne coupling to carbonyls



- Enantioselective with chiral ligand





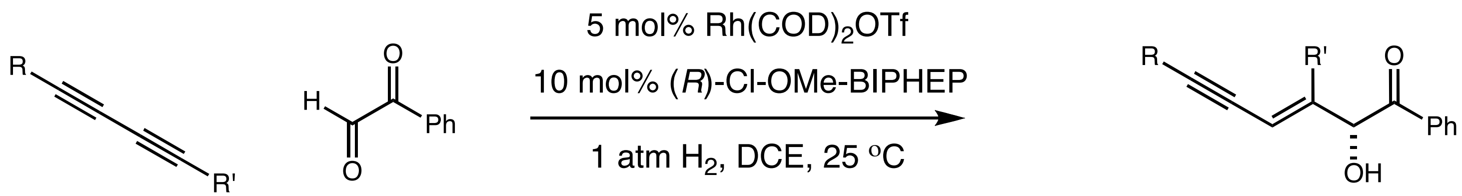
(*R*)-Cl-OMe-BIPHEP

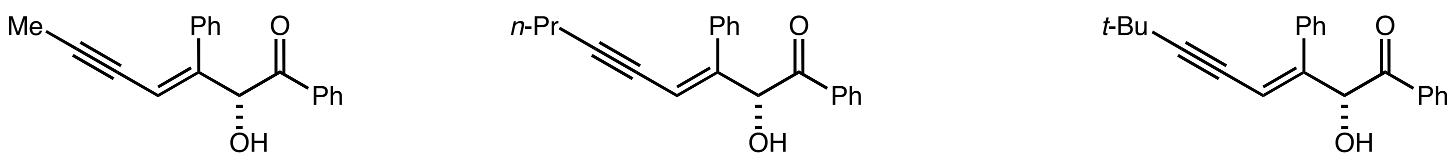
J. Am. Chem. Soc. **2003**, *125*, 11488.

Hydrogenation

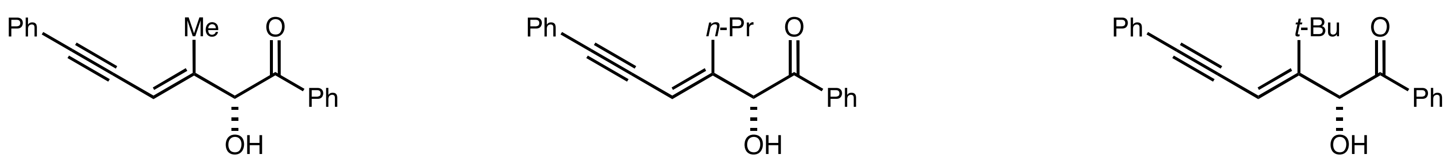
Reductive Rh-Alkyne Coupling

■ Selectivity





80% Y, 5.2:1 | **64% Y, 4:1** | **57% Y, >99:1**



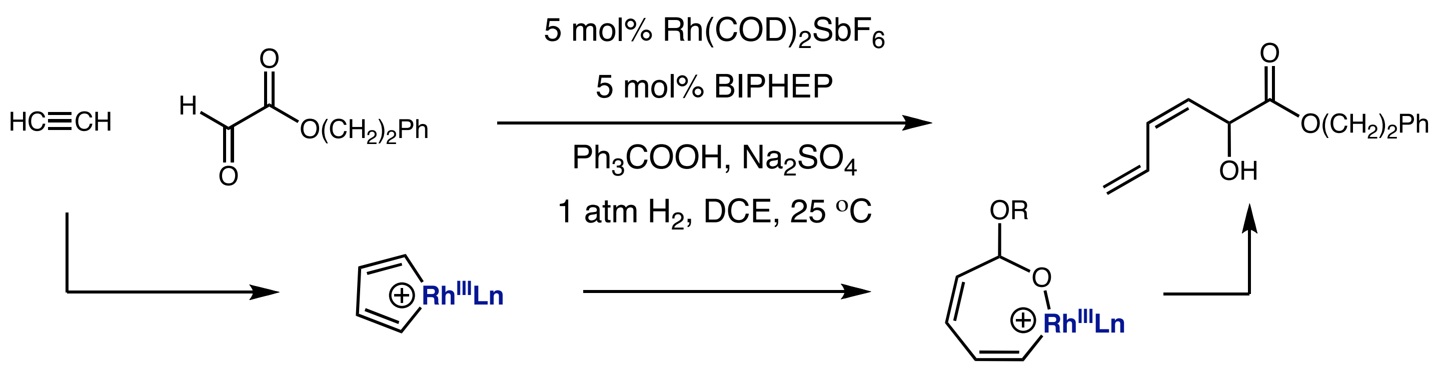
J. Am. Chem. Soc. **2003**, *125*, 11488.

Org. Lett. **2006**, *8*, 3873.

Hydrogenation

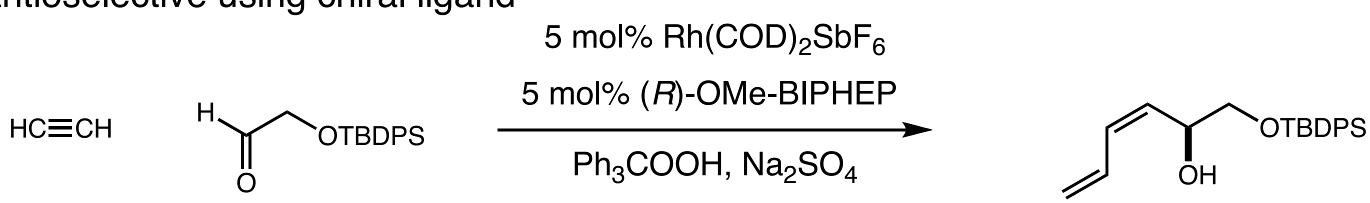
Reductive Rh-Alkyne Coupling

- Reductive acetylene coupling: the effect of counterions



counterion	yield	
Cl	**0**	
OTf	**32**	noncoordinating ligands
BF_4	**41**	
SbF_6	**51**	

- Enantioselective using chiral ligand



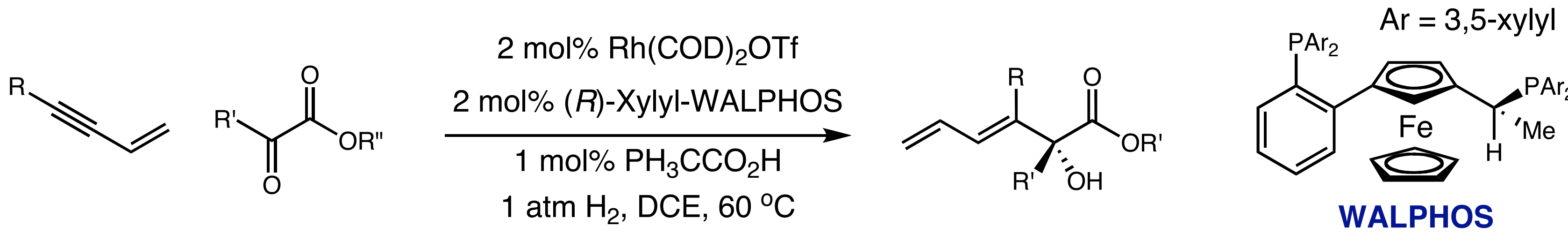
77% Y, 89% ee

J. Am. Chem. Soc. **2006**, *128*, 16041.

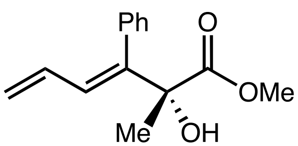
Hydrogenation

Reductive Rh-Alkyne Coupling

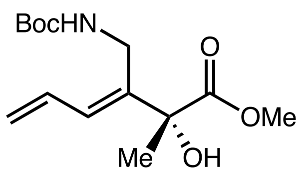
■ Enyne coupling



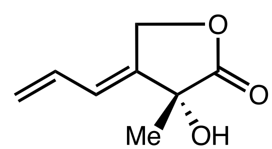
■ Scope



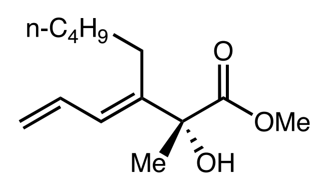
92% Y, 92% ee



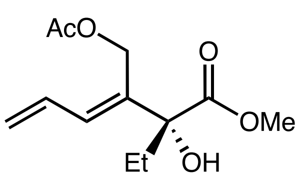
88% Y, 90% ee



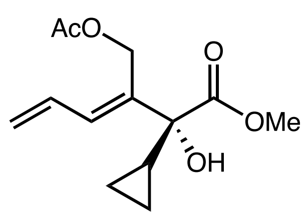
80% Y, 91% ee



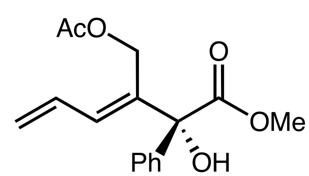
96% Y, 91% ee



97% Y, 86% ee



85% Y, 88% ee



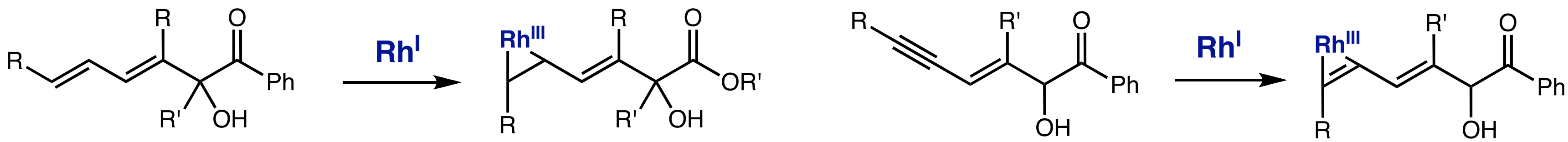
73% Y, 91% ee

J. Am. Chem. Soc. **2003**, *125*, 11488.
Org. Lett. **2006**, *8*, 3873.

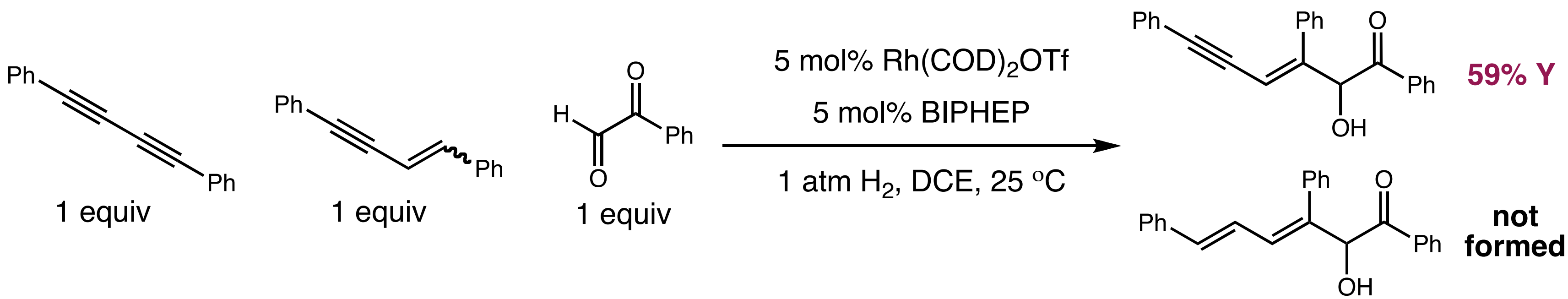
Hydrogenation

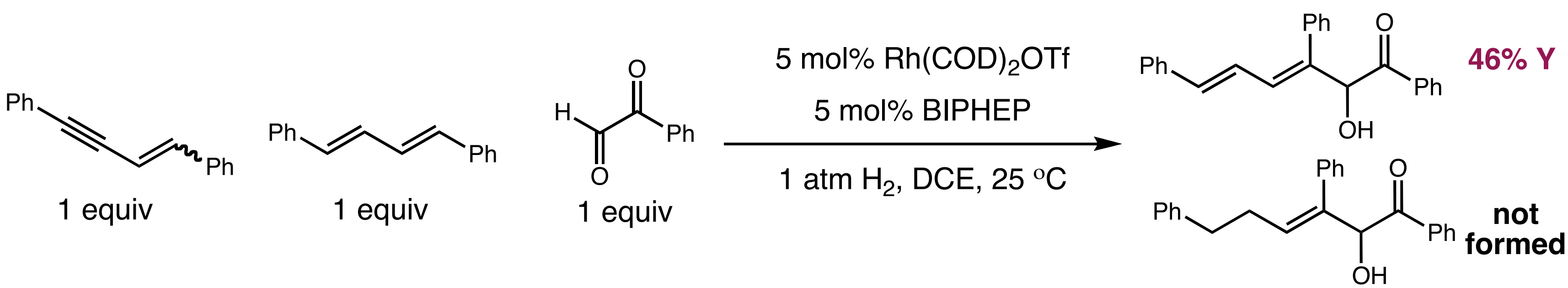
Reductive Rh-Alkyne Coupling

■ How are over-addition and over-reduction avoided?



■ Competition experiments



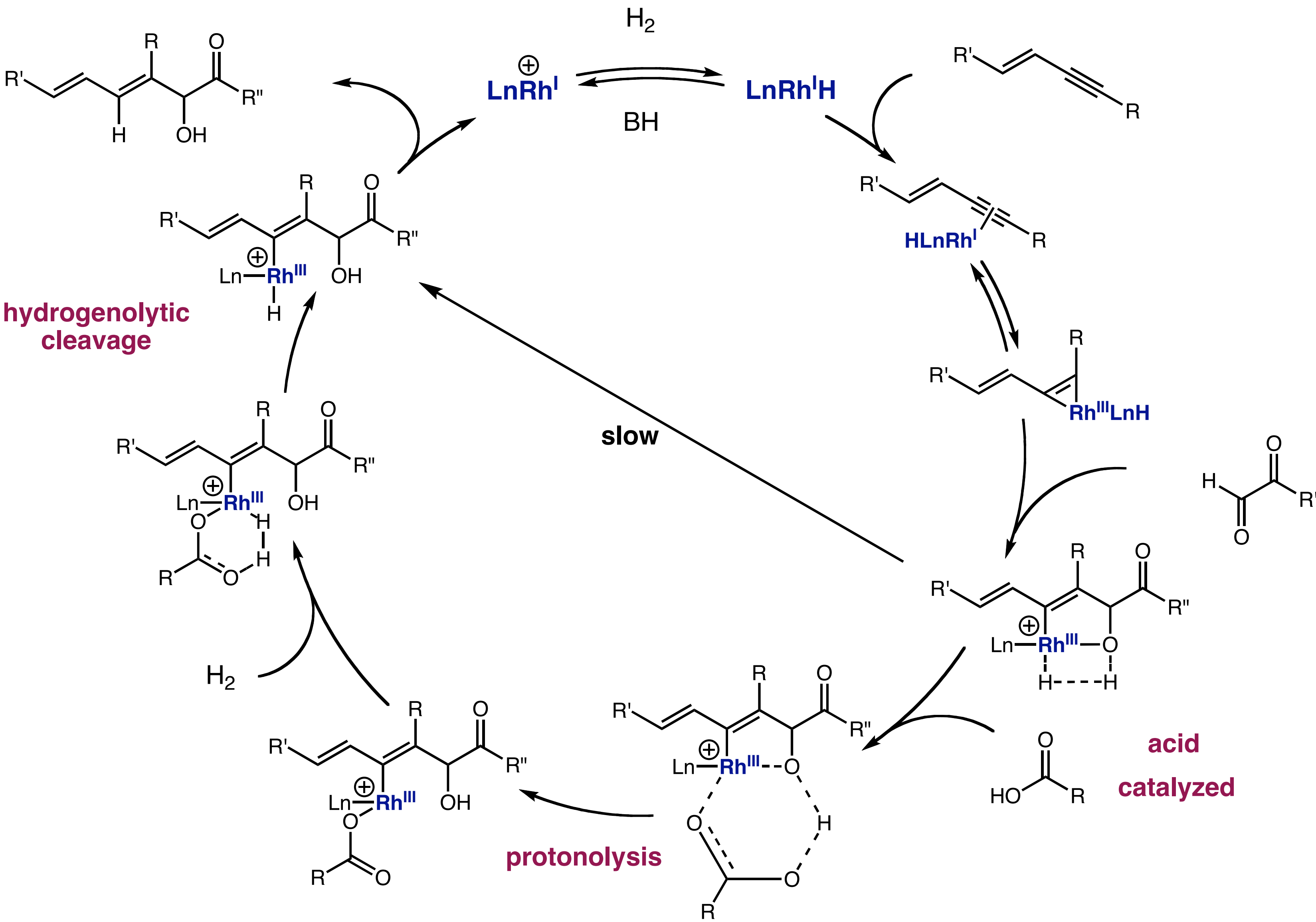


pre-equilibrium/exchange of π-unsaturated substrates prior to C-C bond formation

J. Am. Chem. Soc. **2004**, *126*, 4664.

Hydrogenation

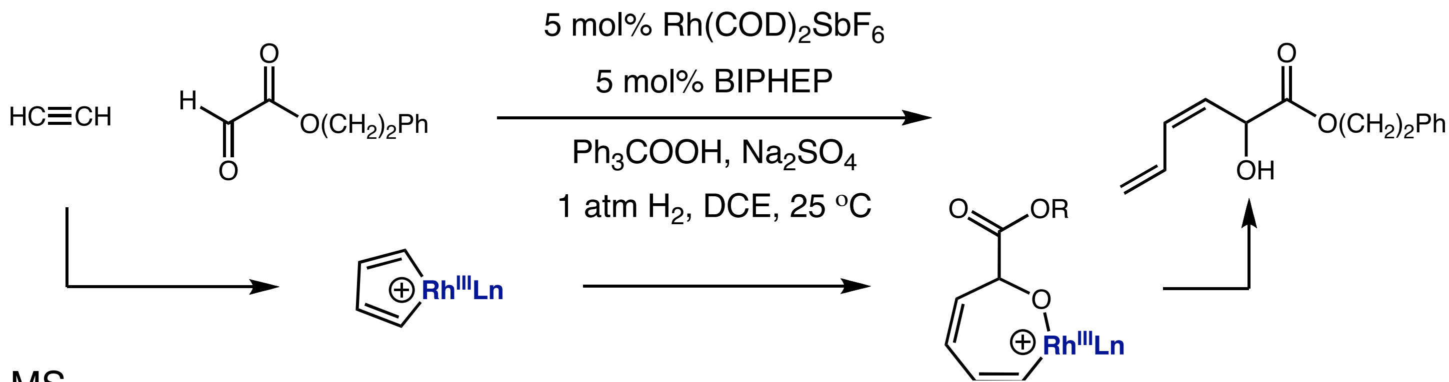
Reductive Rh-Alkyne Coupling Mechanism



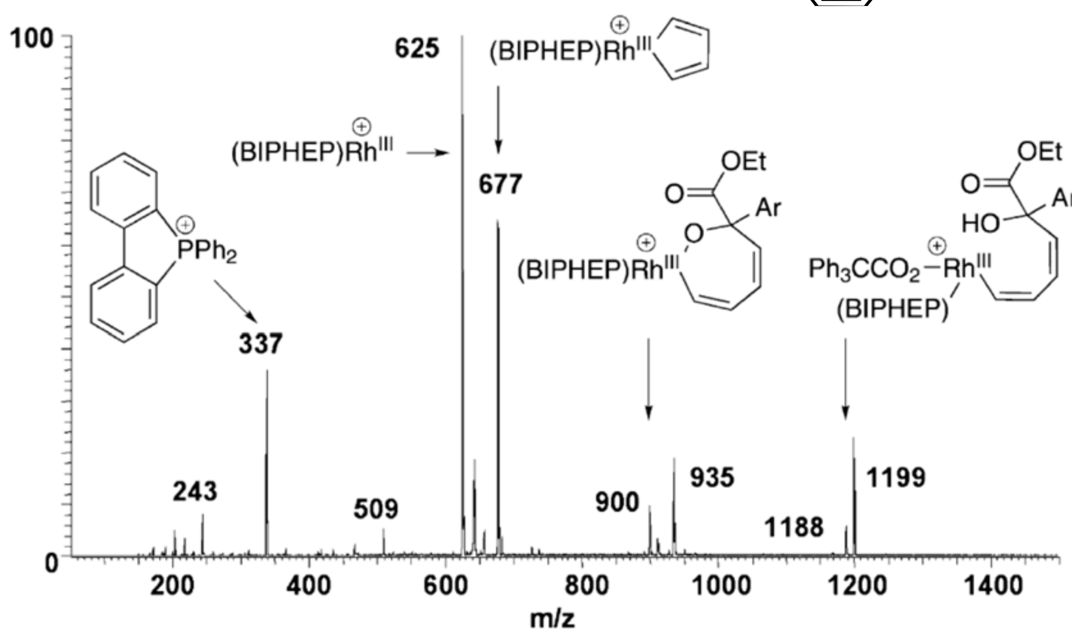
Hydrogenation

Reductive Rh-Alkyne Coupling

■ Reductive acetylene coupling



■ ESI-MS

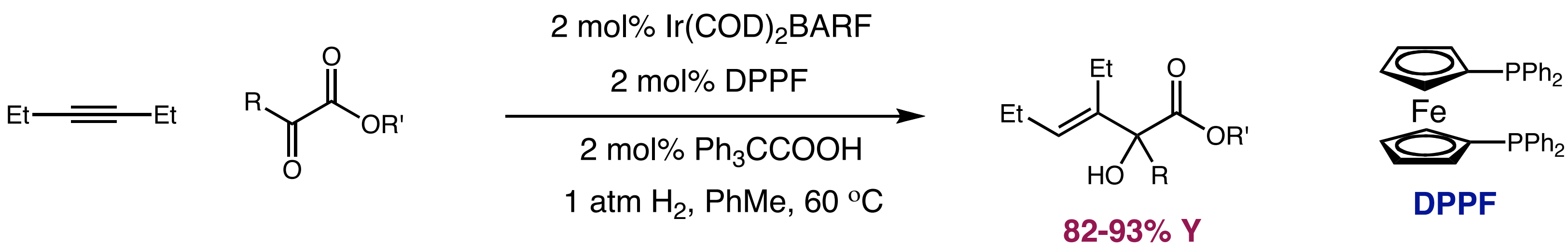


J. Am. Chem. Soc. **2006**, *128*, 16041.

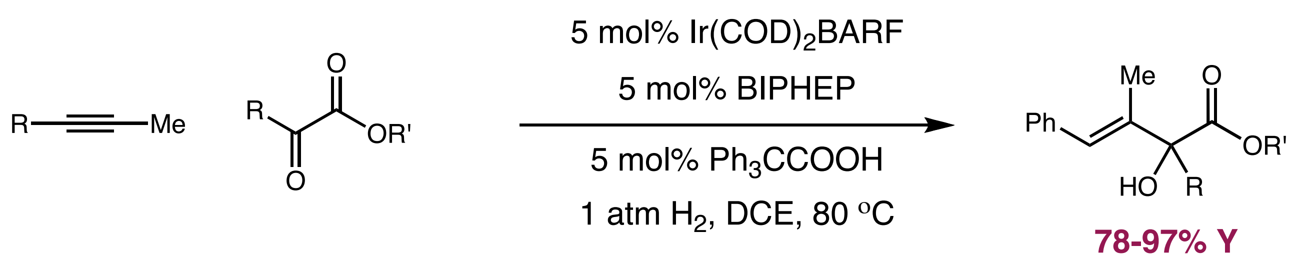
Hydrogenation

Reductive Ir-Alkyne Coupling

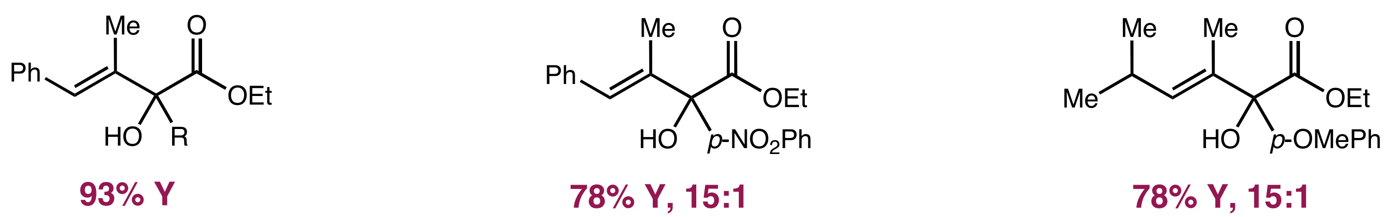
- Iridium catalyzed reductive coupling of alkyl-substituted alkynes



- Stronger backbonding due to relativistic effects allows Ir to coordinate to less reactive substrates
- Reaction is regioselective



- Scope

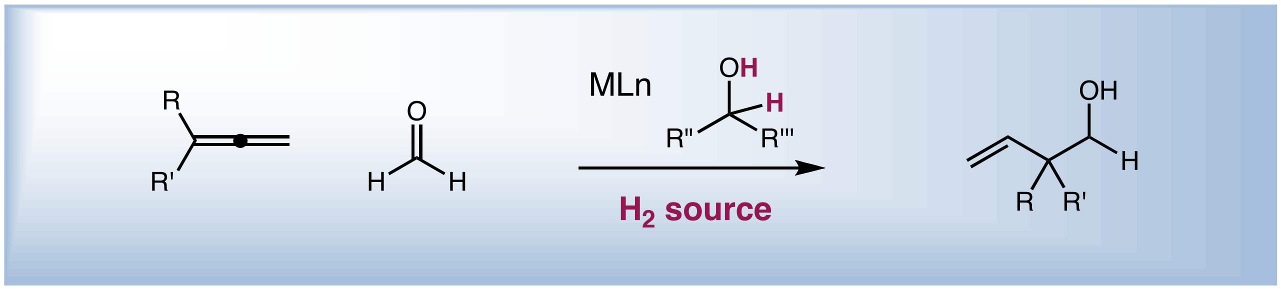


J. Am. Chem. Soc. **2007**, *129*, 280.

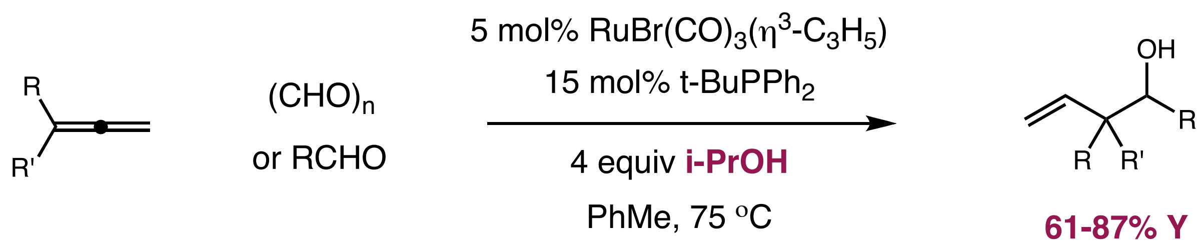
A Sneak Peek at Transfer Hydrogenation

Seminal Publication

- Strategy



- The formation of homoallylic alcohols



Org. Lett, **2008**, *10*, 2705.

- For more, read on...

Review article: "Catalytic Carbonyl Addition through Transfer Hydrogenation" *ACIE* **2009**, *48*, 34.