

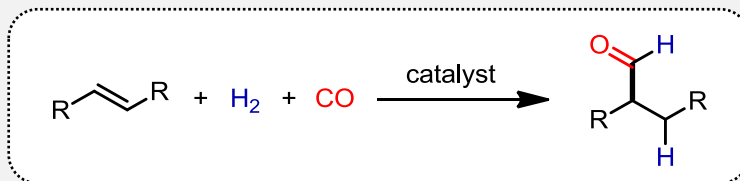


ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

EPFL - ISIC - LSPN

Hydrogen-Mediated C-C Bond Formation

History and selected examples

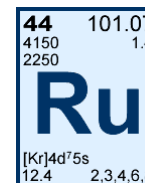
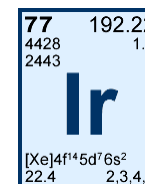
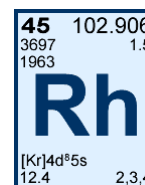
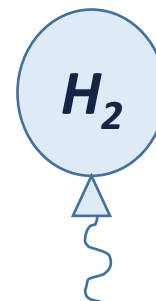


The Research of Prof. Michael Krische
(University of Texas at Austin)

LSPN Group Seminar

Mathias Mamboury
February 18, 2016

- 1) **Introduction**
- 2) **Homogeneous catalytic hydrogenation**
History and hydroformylation
- 3) **Rhodium catalysis**
Aldol couplings
- 4) **Iridium catalysis**
Allylation / crotylation
- 5) **Ruthenium catalysis**
Crotylation & hydroacylation
- 6) **Conclusion**



1) Introduction

2) Homogeneous catalytic hydrogenation

3) Rhodium catalysis

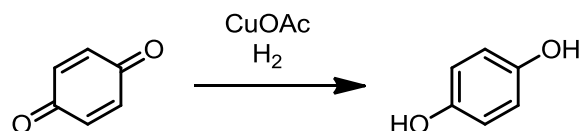
4) Iridium catalysis

5) Ruthenium catalysis

6) Conclusion

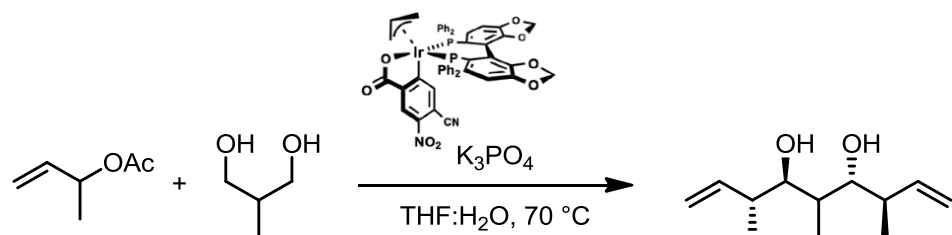
1) Introduction

From the 1st homogeneous catalytic hydrogenation by Calvin in 1938...



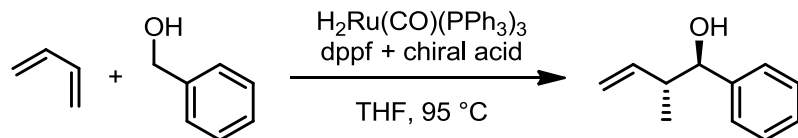
Trans. Faraday Soc. **1938**, 34, 1181-1191

... to highly atom economical transformations of great interest :



J. Am. Chem. Soc. **2011**, 133, 12795-12800

62% yield
6:1 d.r. (1 = all others)
99% e.e.



Without H₂!

Science **2012**, 336, 324-327

5 cts US\$ / mol

86% yield
8:1 dr, 90% e.e.

Worldwide production :
> 10 million tons / year

1) Introduction

Professor Michael J. Krische :



- 1986-1989 : B.S. Chemistry / University of California at Berkeley / Prof. H. Rapoport
- 1990-1996 : Ph.D. Chemistry / Stanford University / Prof. B. M. Trost
- 1997-1999 : NIH Post-Doc. / Université Louis Pasteur / Prof. J.-M. Lehn
- Since 1999 : Professor at the University of Texas at Austin

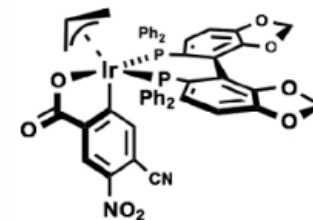
2002

→ 1st H₂-mediated C-C coupling

Early years : Rhodium
Currently : Iridium & Ruthenium

2016

> 90 papers published in this field



Krische Ir-Catalyst

Commercially available:
Aldrich^{CPR} : 92 CHF / 100 mg

1) Introduction

2) Homogeneous catalytic hydrogenation

3) Rhodium catalysis

4) Iridium catalysis

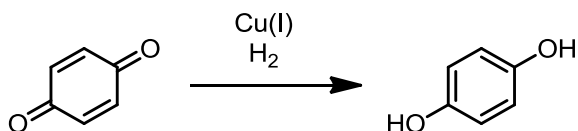
5) Ruthenium catalysis

6) Conclusion

2) Homogeneous catalytic hydrogenation

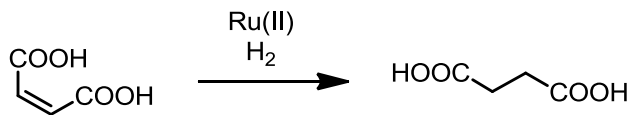
The History of homogeneous catalytic hydrogenation :

- 1938, Calvin : 1st homogeneous catalytic hydrogenation



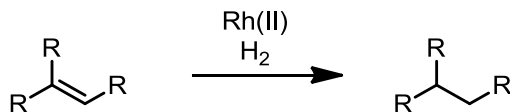
Trans. Faraday Soc. **1938**, 34, 1181-1191

- 1961, Halpern : 1st hydrogenation of activated alkenes



J. Am. Chem. Soc. **1981**, 63, 753-754

- 1966, Wilkinson : 1st hydrogenation of unactivated alkenes and alkynes

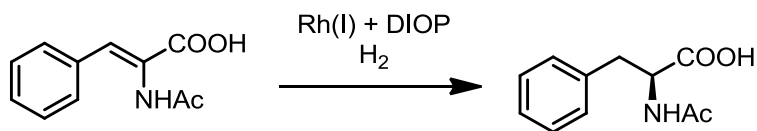


J. Chem. Soc. A **1966**, 1711-1732

2) Homogeneous catalytic hydrogenation

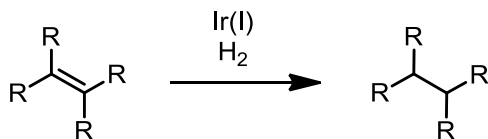
The History of homogeneous catalytic hydrogenation :

- 1971, Kagan : 1st enantioselective hydrogenation of alkenes



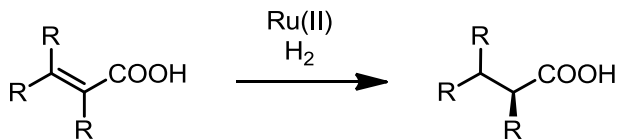
J. Chem. Soc. D **1971**, 481

- 1977, Crabtree : highly efficient Ir-catalyst for the hydrogenation of alkenes



J. Organomet. Chem. **1977**, 135, 395-403

- 1987, Noyori : Ru-catalyst for the hydrogenation of alkenes

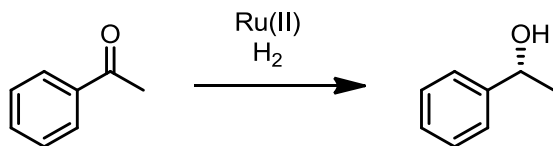


J. Org. Chem. **1987**, 52, 3174-3176

2) Homogeneous catalytic hydrogenation

The History of homogeneous catalytic hydrogenation :

- 1995, Noyori : 1st efficient enantioselective hydrogenation of aromatic ketones



J. Am. Chem. Soc. **1995**, *117*, 2675-2676

- Ater 2000 :

Early transition metals.

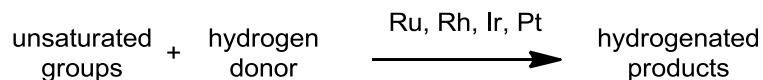
Ability to reduce almost any unsaturated functional group.

etc.

Chemo-, diastereo- and enantioselectivity.

Applications for energy and environment ?

- Late 1960 : homogeneous transfer hydrogenation

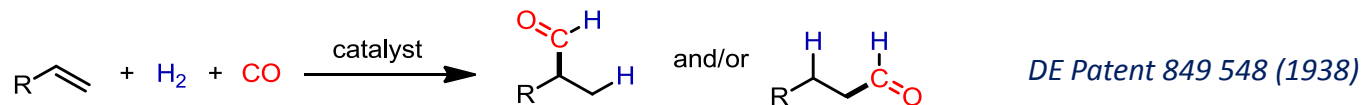


Chem. Rev. **1974**, *74*, 567-580 (refs 9-13)

2) Homogeneous catalytic hydrogenation

An intriguing and inspiring reaction left aside :

- 1938, Roelen: Hydroformylation



« Hydroformylation is one of the most important industrial processes based on homogeneous catalysis ».

Acc. Chem. Res. **2003**, 36, 264–275

Another point of view :

C-C bond formation with H₂ as terminal reductant !

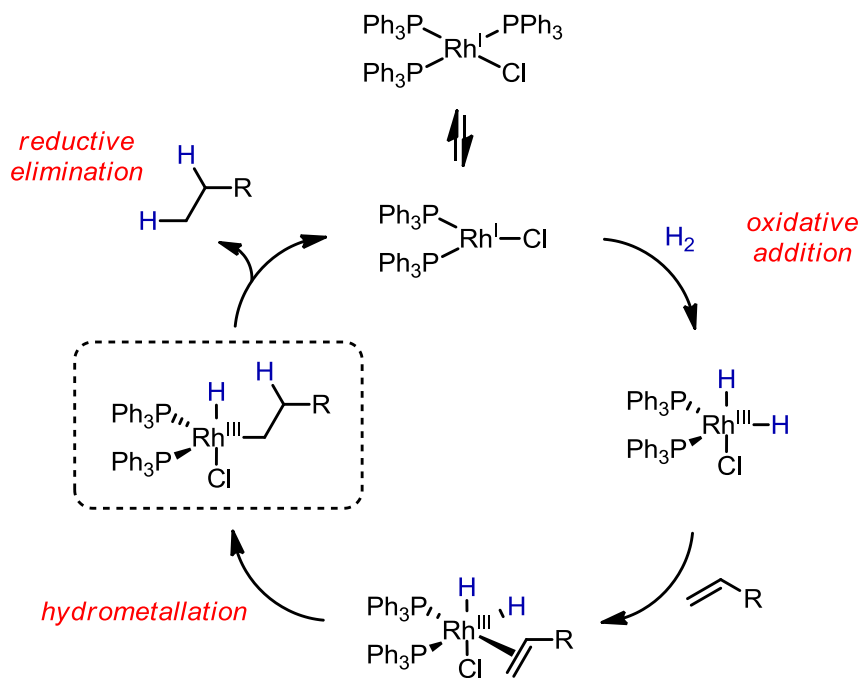
Powerfull concept :

- Atom economic
- Versatile if applicable with...
 - ... any carbonyl group other than CO
 - ... any alkene or alkyne

- 1) Introduction
- 2) Homogeneous catalytic hydrogenation
- 3) Rhodium catalysis
- 4) Iridium catalysis
- 5) Ruthenium catalysis
- 6) Conclusion

3) Rhodium-catalysis

Hydrogenation with the Wilkinson catalyst :



How could we form a C-C bond ?

Strategy :

Trap a carbonyl compound with one of the intermediates (or similar).

Challenge :

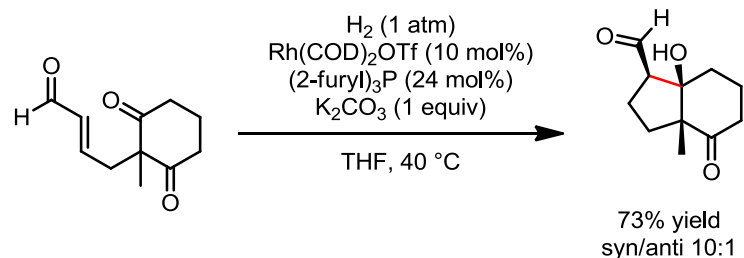
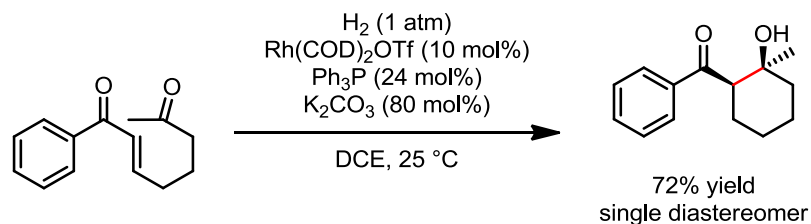
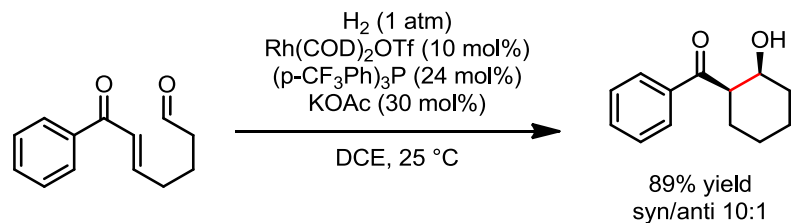
Generate a Rh-intermediate that is nucleophilic enough to attack the carbonyl.

Proposal :

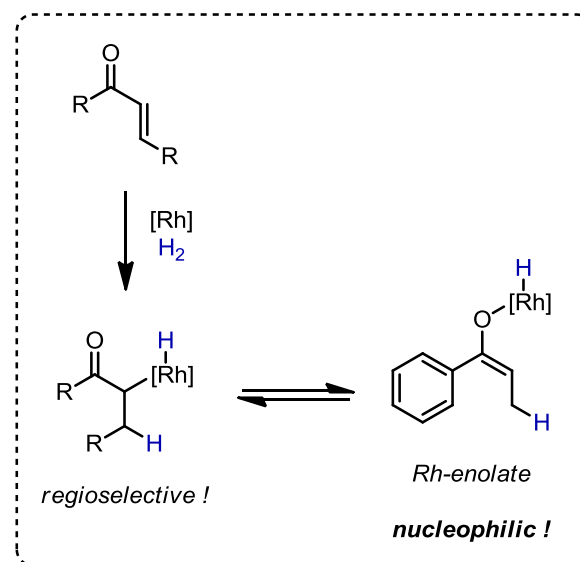
Rh-enolate !

3) Rhodium-catalysis

1st (almost) H₂-mediated C-C coupling beyond hydroformylation : aldol coupling



Postulated intermediate :



J. Am. Chem. Soc. **2002**, *124*, 15156-15157

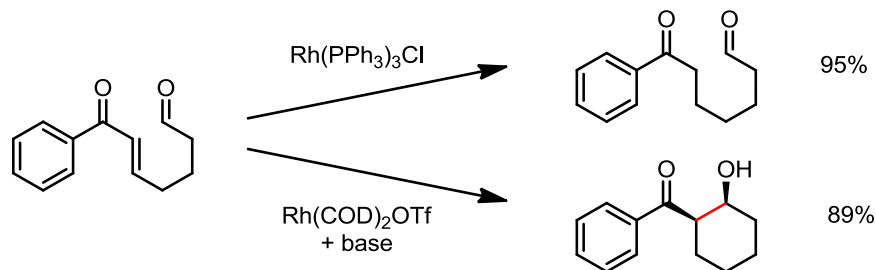
Org. Lett. **2003**, *5*, 1143-1146

Org. Lett. **2004**, *6*, 691-694

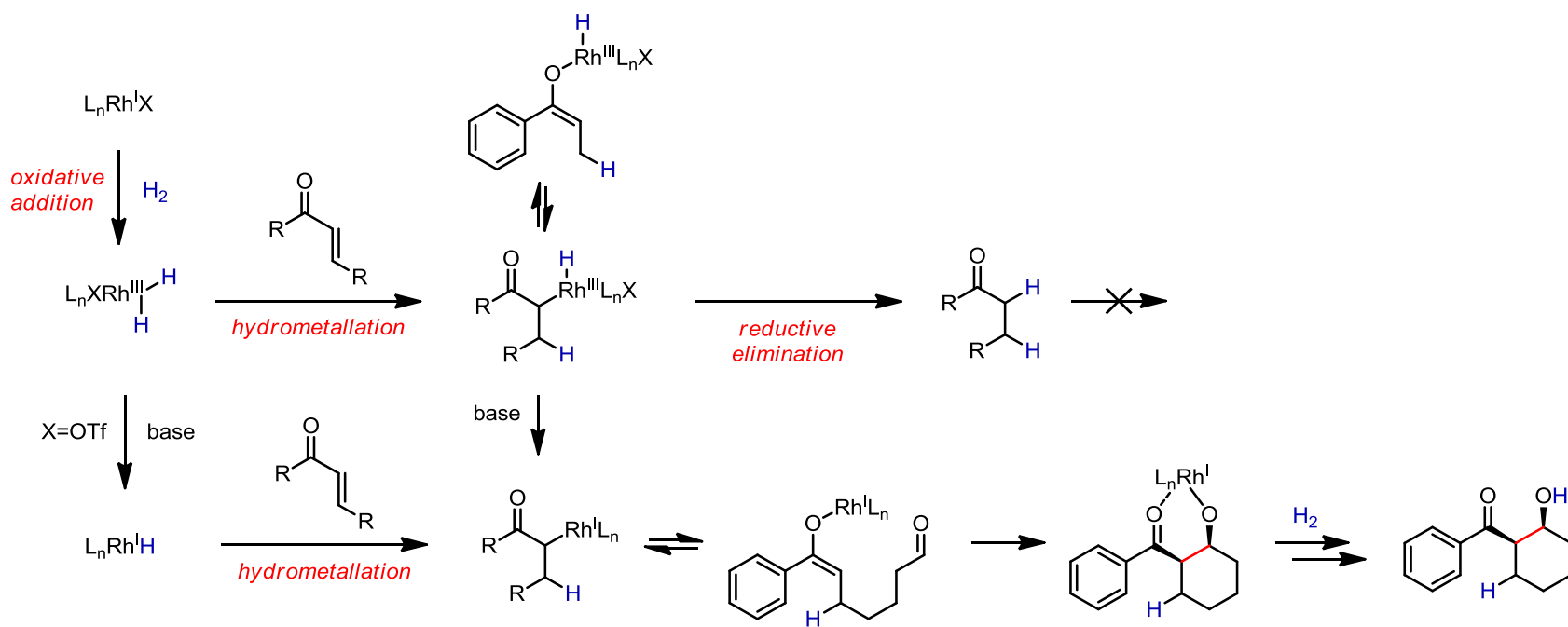
Acc. Chem. Res. **2004**, *37*, 653-661

3) Rhodium-catalysis

Observation during the optimization :



Mechanism :

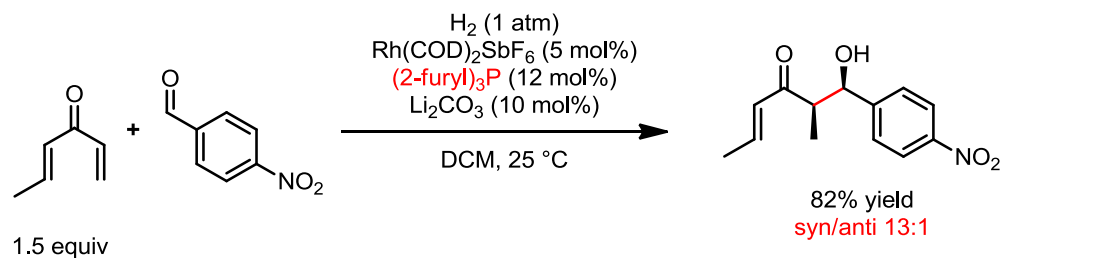
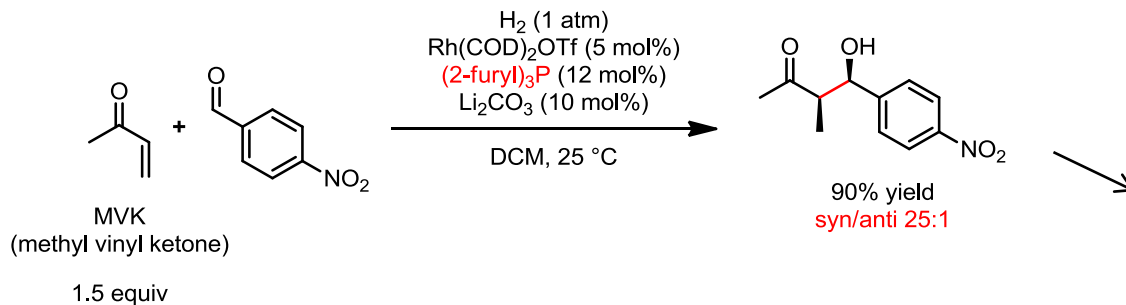


Org. Lett. **2003**, 5, 1143-1146
Acc. Chem. Res. **2004**, 37, 653-661

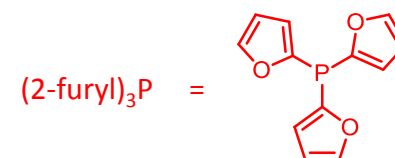
Neutral Rh(I) → homolytic cleavage of H_2 → 1,4-reduction
Cationic Rh(I) + base → heterolytic cleavage of H_2 → trapping

3) Rhodium-catalysis

Intermolecular aldol coupling and diastereoselectivity :

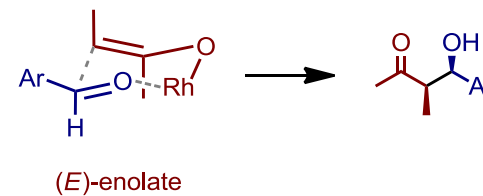


Ligand	Yield	d.r.
PPh ₃	31%	3:1
(2-furyl)Ph ₂ P	24%	6:1
(2-furyl) ₂ PhP	52%	15:1
(2-furyl) ₃ P	74%	19:1



Simplest explanation, among others :

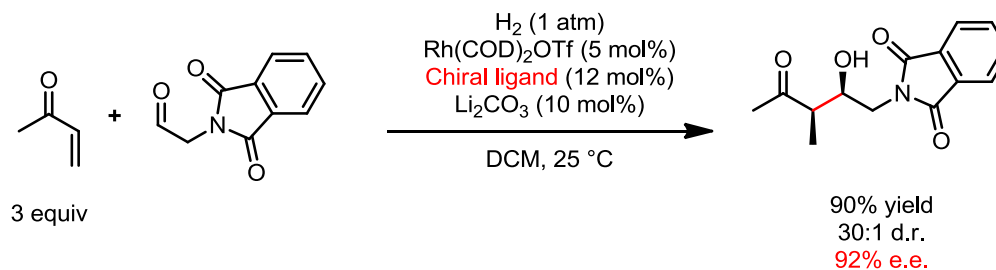
The rhodium center is more Lewis acidic, rendering the Zimmerman-Traxler transition state more «tight» :



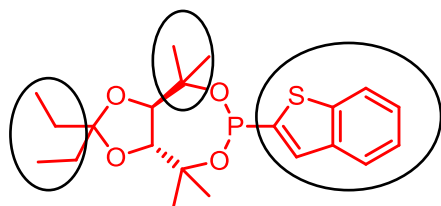
Org. Lett. 2006, 8, 519-522
Org. Lett. 2006, 8, 5657-5660

3) Rhodium-catalysis

Enantioselective aldol coupling (2008) :

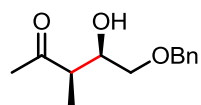


Design of the ligand :

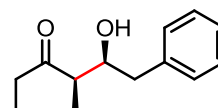


AbbasPhos-I

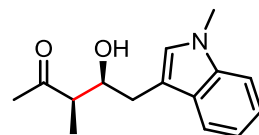
Scope :



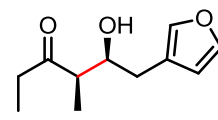
96% yield
21:1 d.r.
88% e.e.



76% yield
25:1 d.r.
90% e.e.



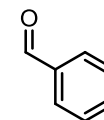
97% yield
25:1 d.r.
90% e.e.



83% yield
25:1 d.r.
88% e.e.

Etc.

Limitations :



good reactivities and
diastereoselectivities
but poor enantioselectivities



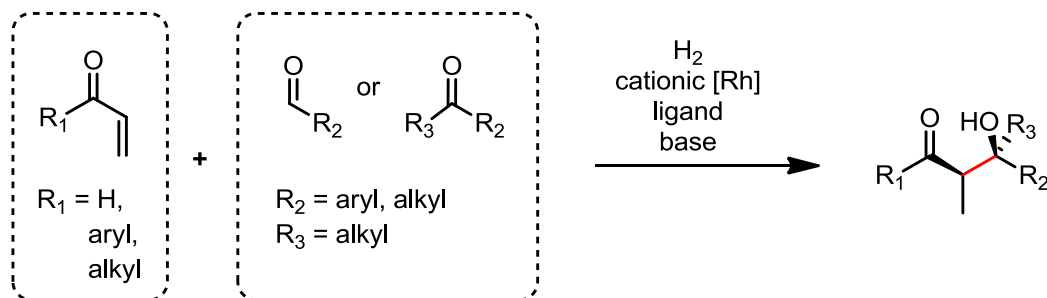
poor reactivities

J. Am. Chem. Soc. **2008**, *130*, 2746-2747

3) Rhodium-catalysis

Summary :

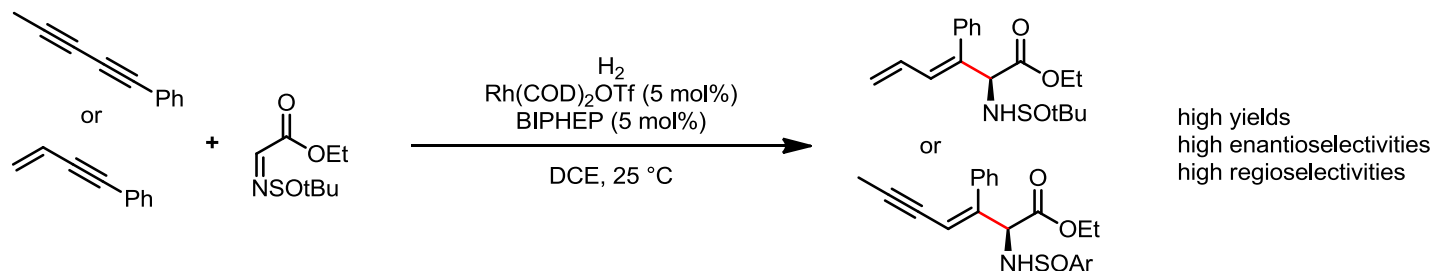
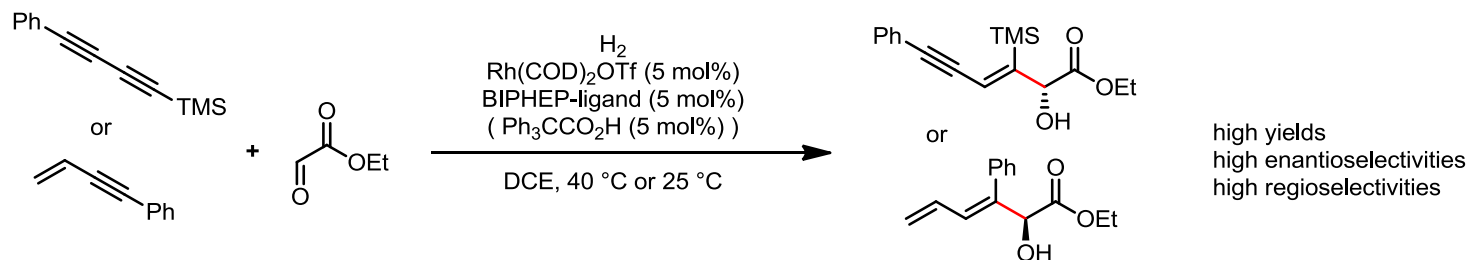
Rh-catalyzed aldol couplings are the first H₂-mediated C-C couplings beyond hydroformylation :



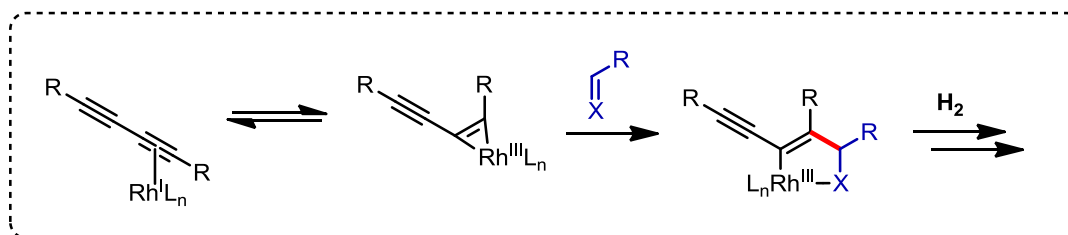
- **Atom economic**
- Mild conditions
- Intra- and intermolecular
- High diastereoselectivities
- Enantioselective for MVK

3) Rhodium-catalysis

Other transformations with rhodium :



Postulated intermediates :



J. Am. Chem. Soc. **2005**, 127, 11269-11276

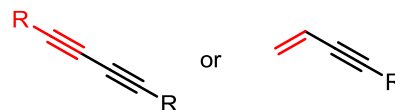
Org. Lett. **2006**, 8, 3873-3876

Org. Lett. **2007**, 89, 3745-3748

3) Rhodium-catalysis

From rhodium to iridium :

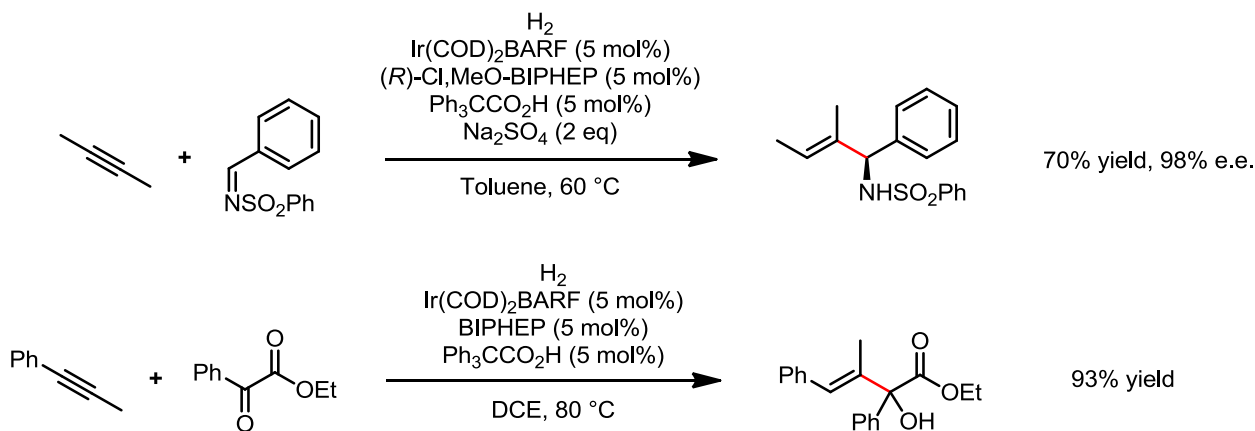
Major limitation : only works with conjugated alkynes



Alternative :

77	192.22
4428	1.6
2443	
Ir	
[Xe]4f ¹⁴ 5d ⁷ 6s ²	
22.4	2,3,4,6

- Stronger π -donor than Rh (relativistic effects)
- May react with higher lying non-conjugated LUMOs
- π -backbonding to alkyne may render the Ir-alkyne intermediate more nucleophilic*



J. Am. Chem. Soc.* **2007, 129, 8432-8433 (note 9)

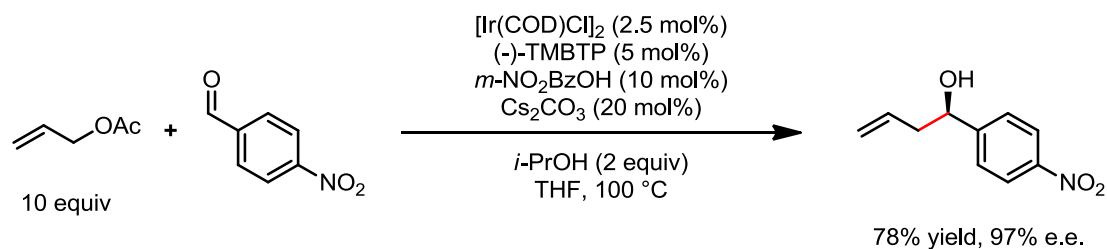
J. Am. Chem. Soc. **2007**, 129, 12644-12645

J. Am. Chem. Soc. **2007**, 129, 280-281

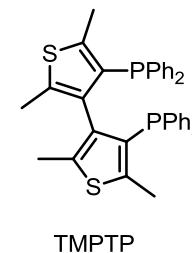
- 1) Introduction
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- 5) Ruthenium catalysis
- 6) Conclusion

4) Iridium-catalysis

Enantioselective carbonyl allylation :



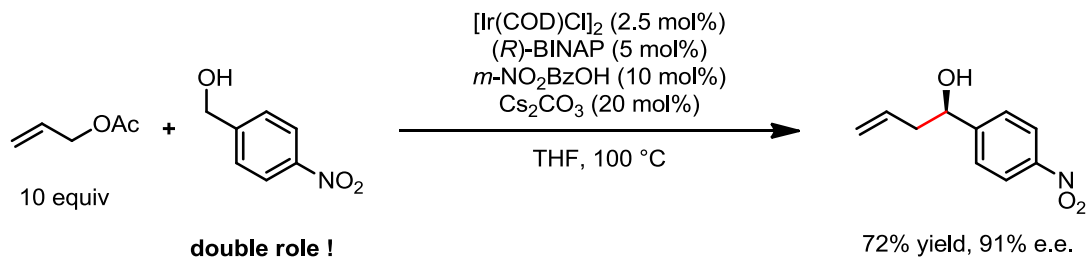
→ **Transfer hydrogenation (= TH)**
with *i*-PrOH as hydrogen donor !



Only byproducts:

- Acetone
- Acetic acid

One step further :



→ **Hydrogen auto-transfer !**

Only byproduct:

- Acetic acid

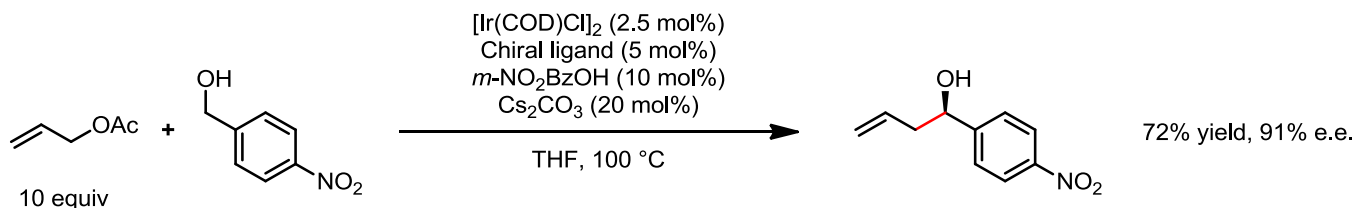
Highly atom economic !

J. Am. Chem. Soc. **2008**, *130*, 6340-6341

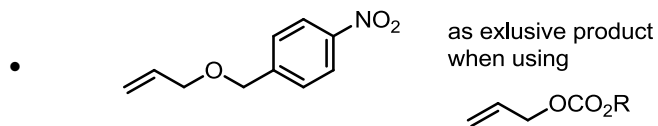
J. Am. Chem. Soc. **2008**, *130*, 14891-14899

4) Iridium-catalysis

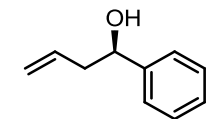
Enantioselective carbonyl allylation :



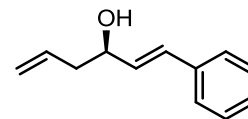
Optimization :



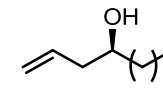
Scope :



62% yield, 93% e.e.

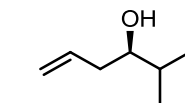


72% yield, 91% e.e.

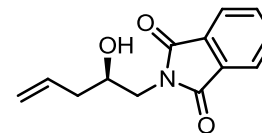


78% yield, 95% e.e.

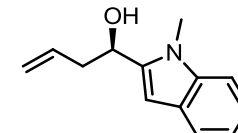
Benzoic acid	Yield
<i>o</i> -NO ₂ BzOH	39%
<i>m</i> -NO ₂ BzOH	81%
<i>p</i> -NO ₂ BzOH	49



83% yield, 94% e.e.



51% yield, 88% e.e.



83% yield, 94% e.e.

Etc.

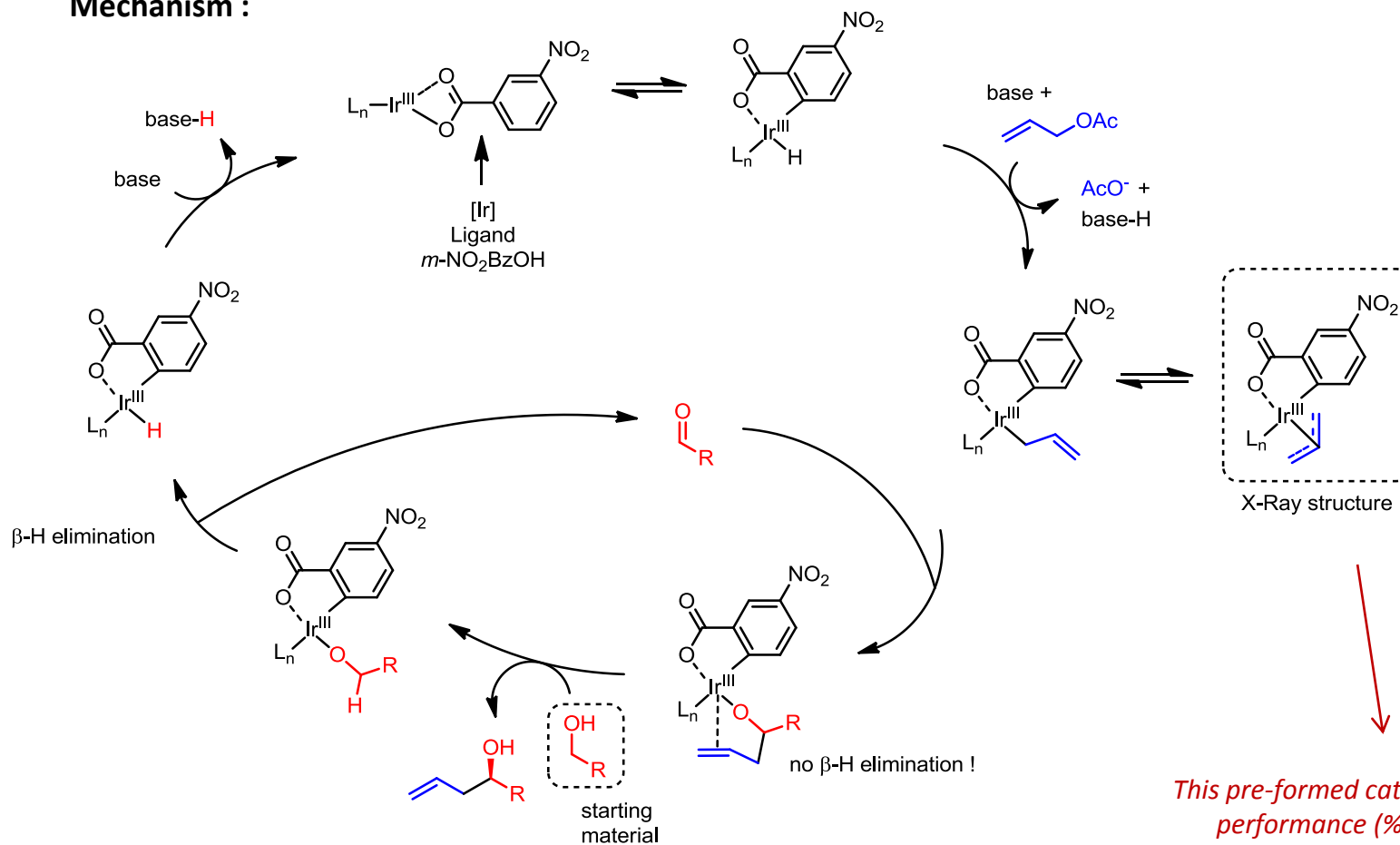
J. Am. Chem. Soc. **2008**, *130*, 6340-6341

J. Am. Chem. Soc. **2008**, *130*, 14891-14899

4) Iridium-catalysis

Enantioselective carbonyl allylation :

Mechanism :



This pre-formed catalyst shows higher performance (% and e.e.) than the in-situ prepared catalyst !

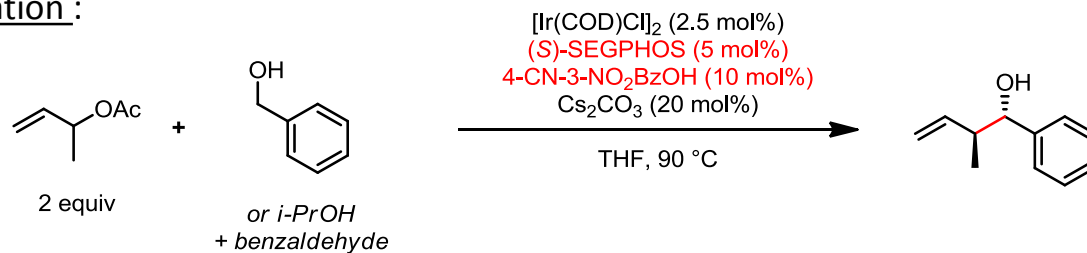
J. Am. Chem. Soc. **2008**, *130*, 14891-14899

J. Am. Chem. Soc. **2009**, *131*, 2514-2520

4) Iridium-catalysis

Related reactions : crotylation & alkoxyallylation

Crotylation :



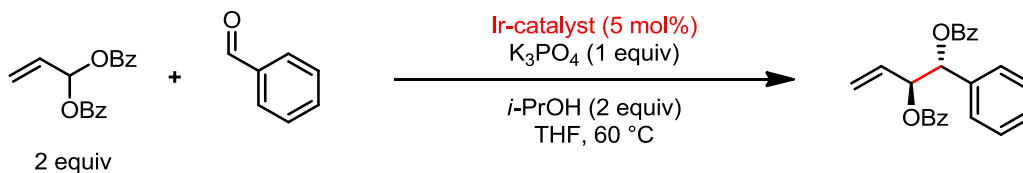
From benzylic alcohol:
65% yield, 95% e.e., 6:1 *anti:syn*

From benzaldehyde:
77% yield, 98% e.e., 9:1 *anti:syn*



Chem. Commun. **2011**, 47, 10028-10030

Alkoxyallylation :



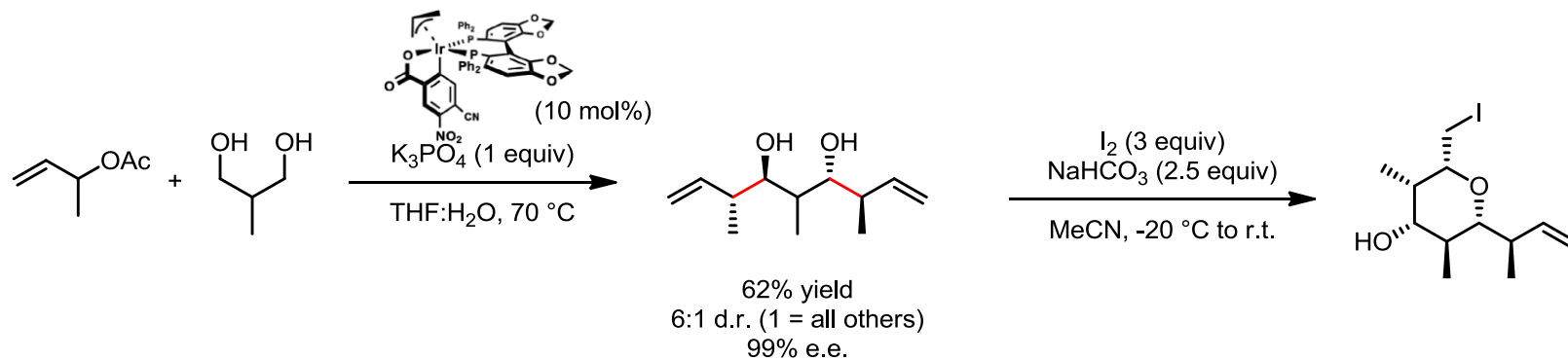
63% yield, 99% e.e., 18:1 *anti:syn*

J. Am. Chem. Soc. **2009**, 131, 2514-2520

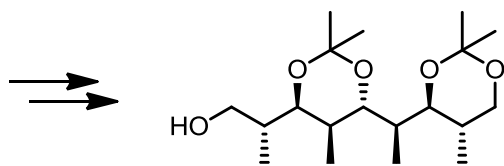
J. Am. Chem. Soc. **2010**, 132, 1760-1761

4) Iridium-catalysis

Addition to diols :

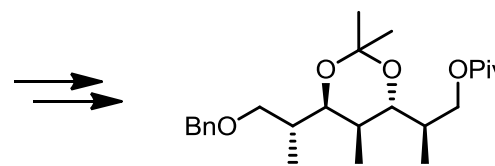


16 possible stereoisomers !



8 steps from the diol

Originally made in 26 steps :
see *Tetrahedron* **2010**, 66, 9738



8 steps from the diol

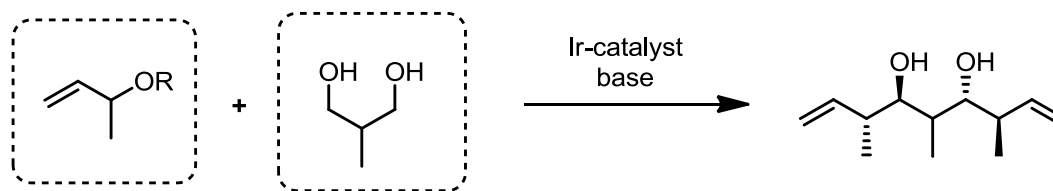
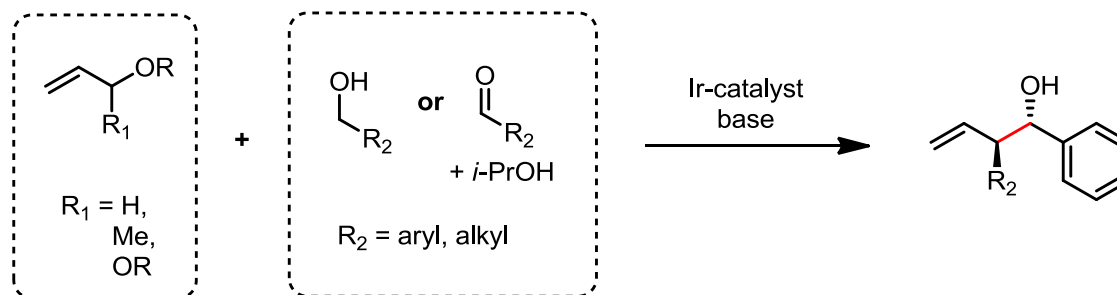
Originally made in 15 steps :
see *J. Am. Chem. Soc.* **1996**, 118, 3059

J. Am. Chem. Soc. **2010**, 132, 1760-1761

4) Iridium-catalysis

Summary :

Ir-catalyzed allylations (and similar transformations) are among the first TH-mediated C-C couplings :

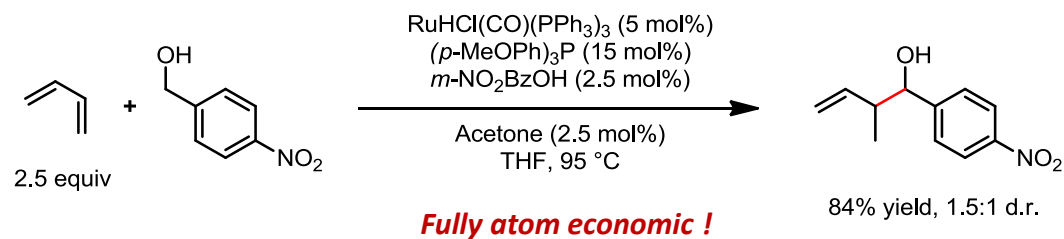


- Atom economic
- No H₂ gas
- Simple conditions
- Diastereo- and enantioselectivity
- Bypasses redox manipulations

- 1) Introduction**
- 2) Homogeneous catalytic hydrogenation**
- 3) Rhodium catalysis**
- 4) Iridium catalysis**
- 5) Ruthenium catalysis**
- 6) Conclusion**

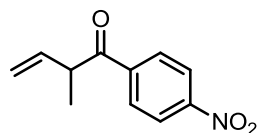
5) Ruthenium-catalysis

Crotylation : 1st C-C bond formation with ruthenium under TH



→ All attempts using iridium failed for non-cyclic dienes !

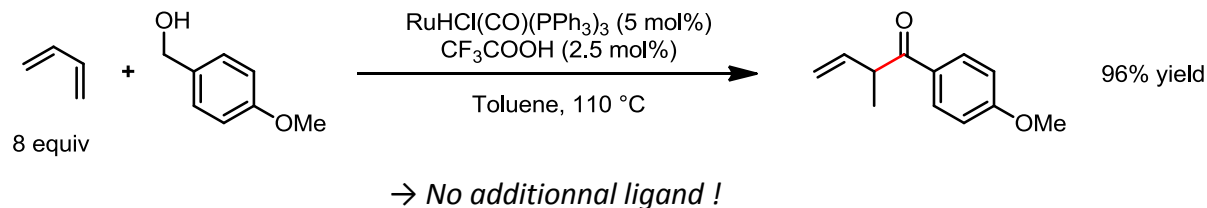
Observation:



as major side-product

→ Suppressed by addition of a ligand to block the coordination sites required for β -hydride elimination.

Hydroacylation :



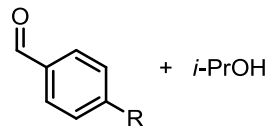
J. Am. Chem. Soc. **2008**, *130*, 6338-6339

J. Am. Chem. Soc. **2008**, *130*, 14120-14122

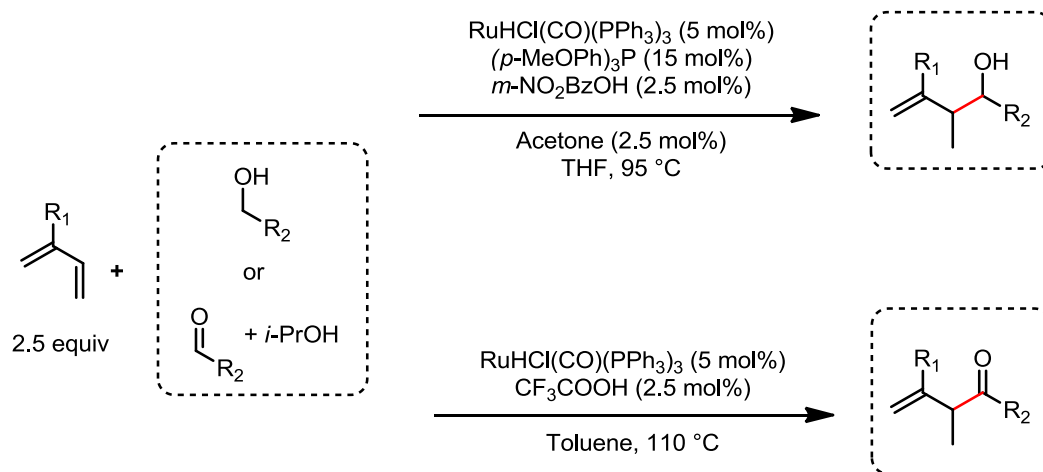
5) Ruthenium-catalysis

Crotylation and hydroacylation :

These 2 reactions also work with



→ All oxidation levels of substrate and product are accessible !



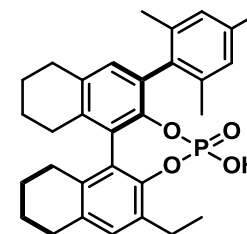
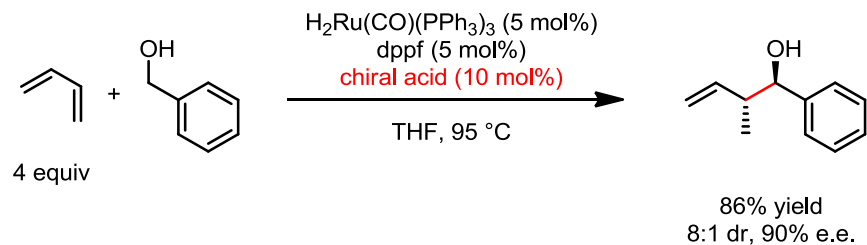
→ No redox manipulations of starting materials et products required !

J. Am. Chem. Soc. **2008**, *130*, 6338-6339

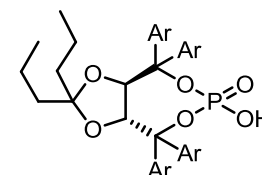
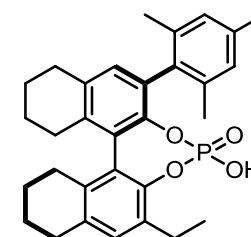
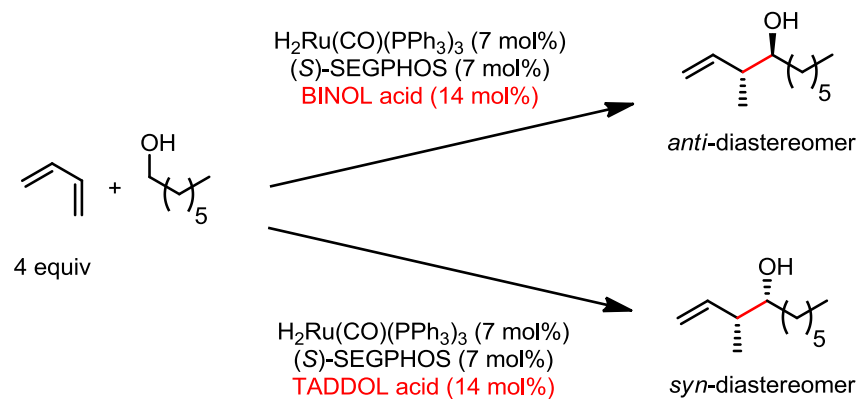
J. Am. Chem. Soc. **2008**, *130*, 14120-14122

5) Ruthenium-catalysis

Enantioselective crotylation :



Inversion of diastereoselectivity :

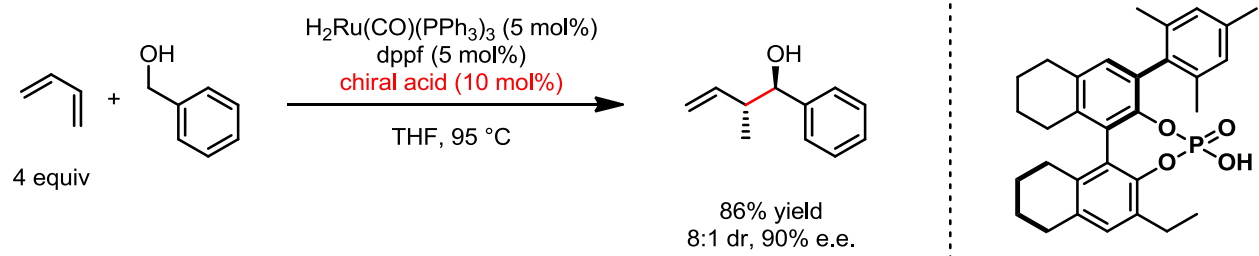


Ar = *m*-xylyl

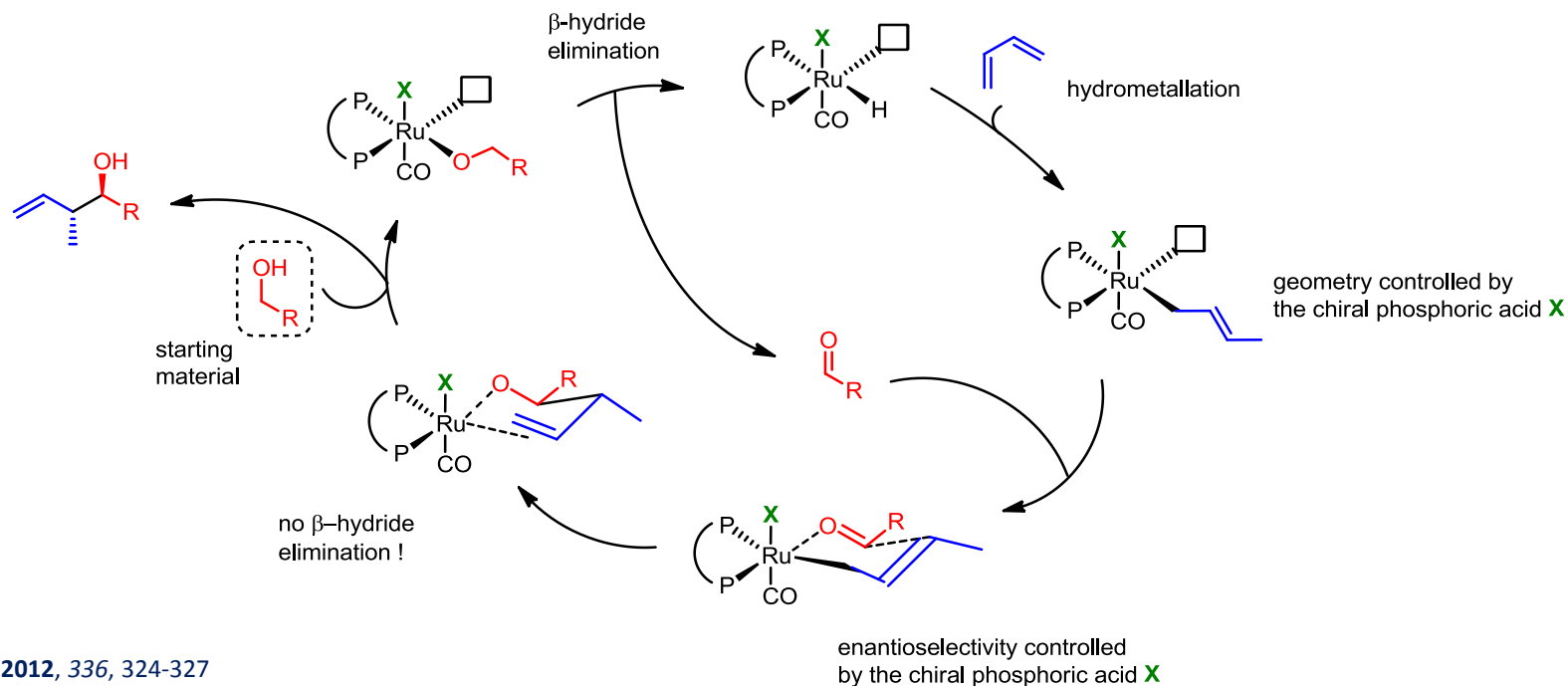
Science **2012**, 336, 324-327
J. Am. Chem. Soc. **2012**, 134, 20628-20631

5) Ruthenium-catalysis

Enantioselective crotylation :



Mechanism :

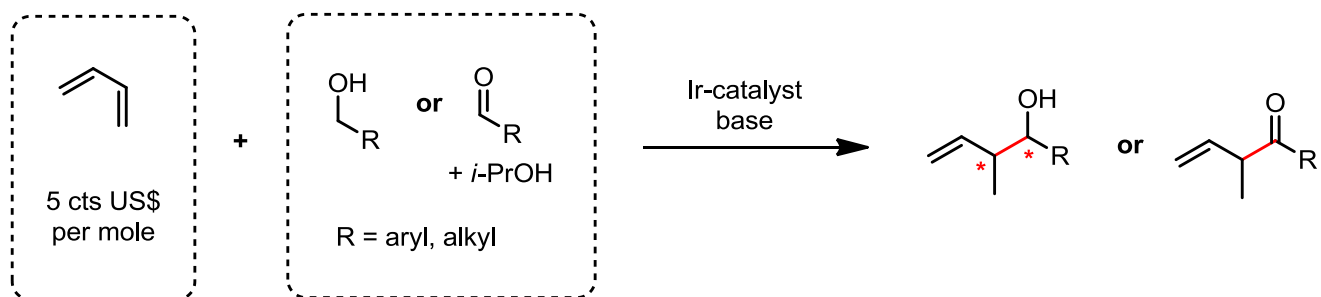


Science 2012, 336, 324-327

5) Ruthenium-catalysis

Summary :

Ru-catalyzed crotylations are among the first TH-mediated C-C couplings :

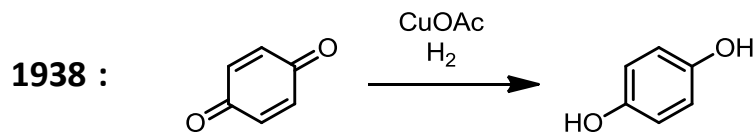


- **Fully atom economic**
- **Bypasses redox manipulations**
- No H₂ gas
- Simple conditions
- Diastereo- and enantioselectivity

- 1) Introduction**
- 2) Homogeneous catalytic hydrogenation**
- 3) Rhodium catalysis**
- 4) Iridium catalysis**
- 5) Ruthenium catalysis**
- 6) Conclusion**

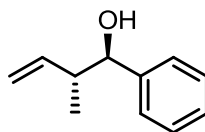
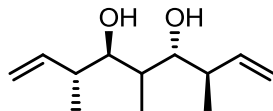
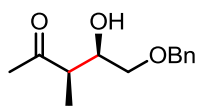
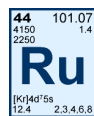
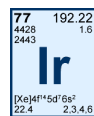
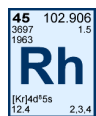
6) Conclusion

A long way :



Trans. Faraday Soc. **1938**, 34, 1181-1191

Years 2000 :



- Beautiful concepts
- Complementary metals
- Modern chemistry :
 - Simple and cheap starting materials
 - Valuable products
 - Diastereo- and enantioselectivity
 - Atom economic / green

« Because organic molecules are compounds composed of C and H, the formation of C-C bonds under (transfer) hydrogenation conditions is a natural end point in the evolution of strategies for organic synthesis ».

Science **2012**, 336, 324-327

Thank you for your attention !

Questions / discussions ?

*This presentation is not a complete review
on H₂-mediated C-C bond formation !*

*See research.cm.utexas.edu/mkrische
for the full list of publications !*