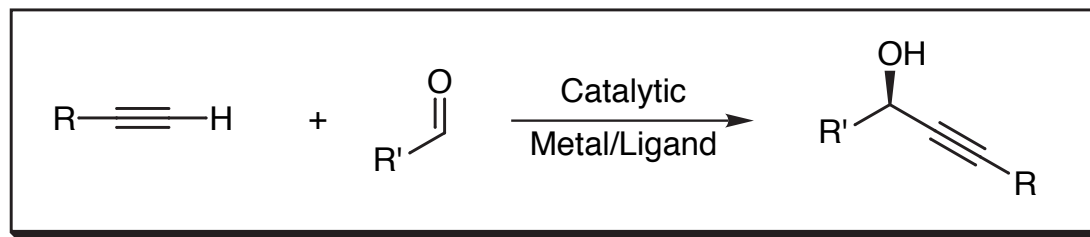


# Catalytic, Enantioselective Carbonyl Addition Reactions of Metal Acetylides

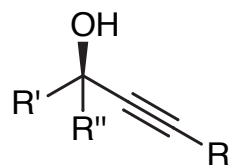
An Evans Group Afternoon Seminar  
Jake Janey  
May 31st, 2002



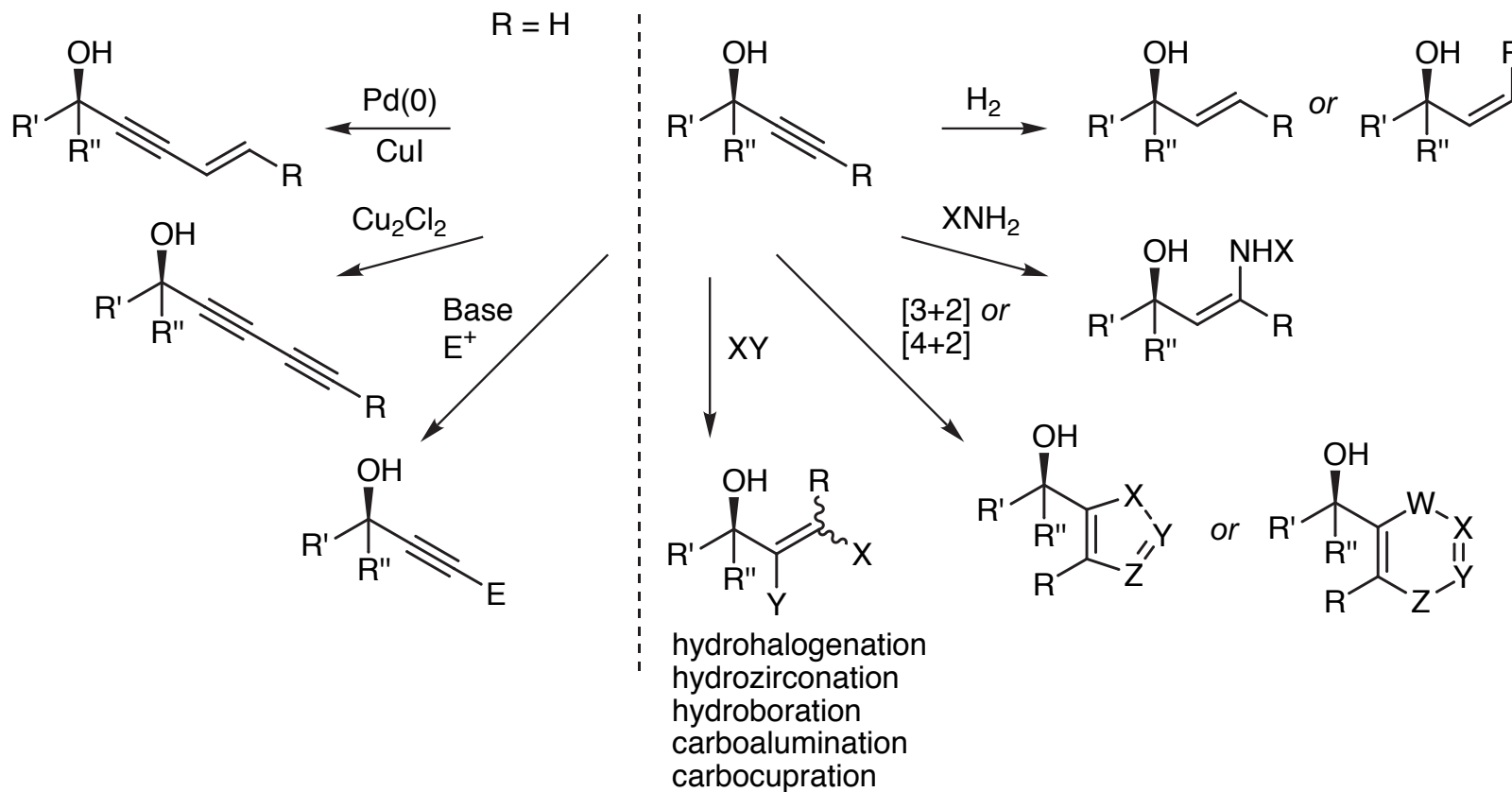
- I. Introduction
- II. Stoichiometric Zn, catalytic ligand
- III. Catalytic Zn and ligand (Carreira)
- IV. Other metal acetylides

Keywords: Acetylene, Metal Acetylide, Enantioselective, Carbonyl, Catalytic, Zinc, Copper, Iridium, Lithium, Ephedrine, Asymmetric, Addition, Imine, Nitron, Aldehyde, Alkyne

## A Versatile Synthetic Intermediate

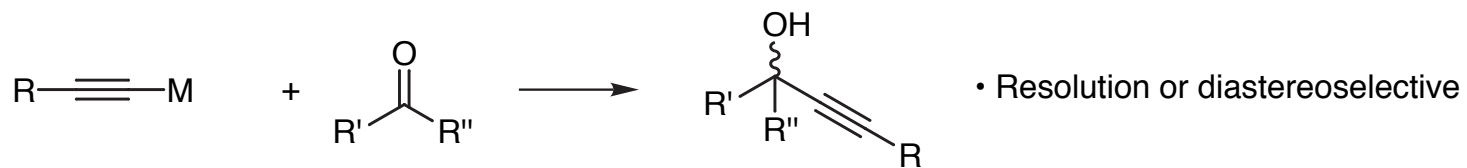


- Propargylic alcohols are an important synthetic building block
- Subunit in Merck's HIV-1 reverse transcriptase inhibitor Efavirenz

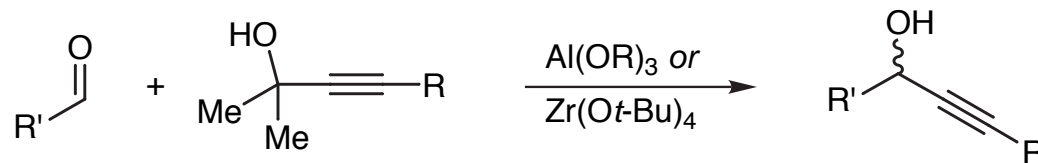
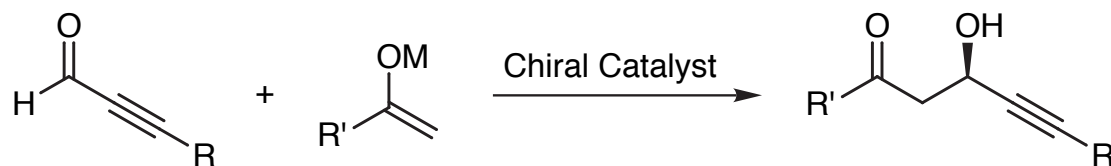
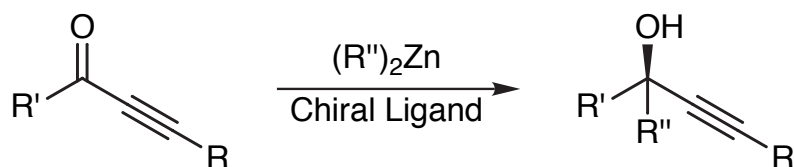
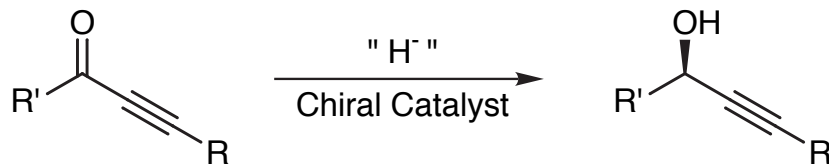


*The Chemistry of Triple Bonded Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983  
*Preparative Acetylene Chemistry*, Brandsma, L., Ed.; 2nd ed.; Elsevier: Amsterdam, 1988  
*Modern Acetylene Chemistry*, Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995

## Common Methodology

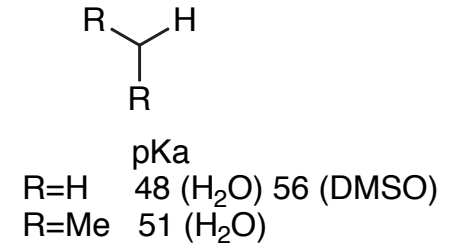
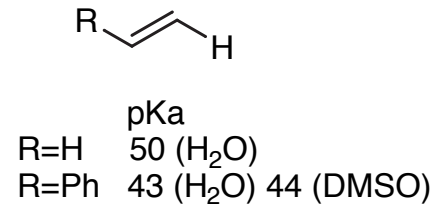
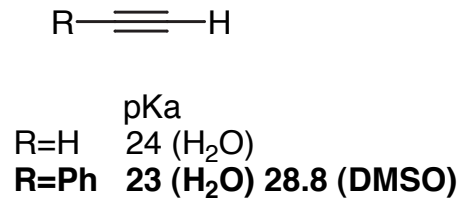
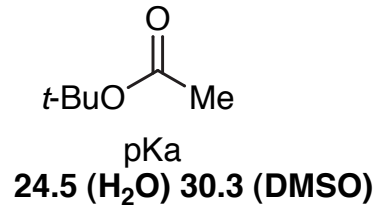


M = Li, MgBr, Cs, K, Na, SnX<sub>3</sub>



Maruoka, K. *et. al. Tetrahedron*, **2001**, 867-873 (and ref. cited therein)

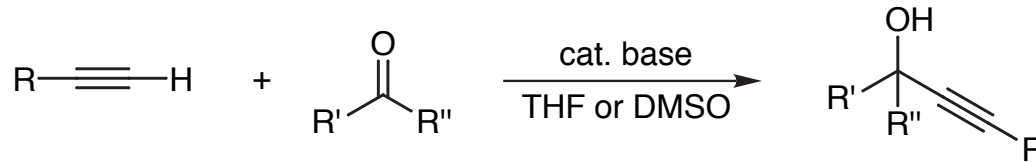
# Alkyne Acidity



High kinetic acidity

Typical Bases: *n*-BuLi or EtMgBr

*A few known examples of catalytic base...*

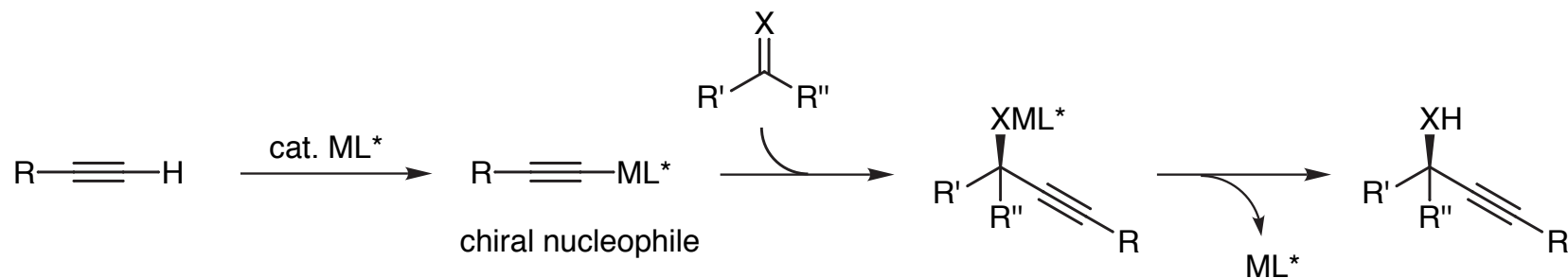


**KOH or NaOH:** Shachat, N.; Bagnell, J. J. *J. Org. Chem.* **1962**, 27, 1498-1504

**KOt-Bu:** Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, 61, 416-417

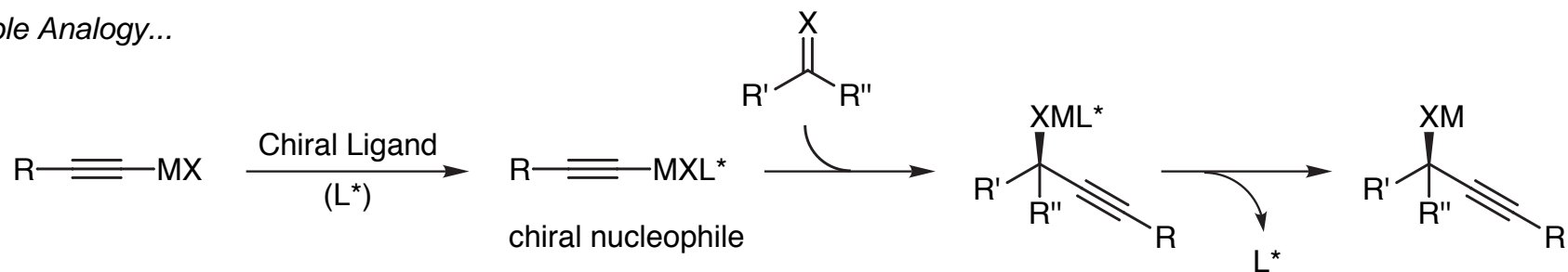
**CsOH:** Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, 38, 1463-1465

## Catalytic, Enantioselective Alkynylation



- Need either catalytic base to transfer proton, or a metal capable of oxidative addition

*A Simple Analogy...*



- Stoichiometric formation of a metal acetylide with a catalytic amount of chiral ligand

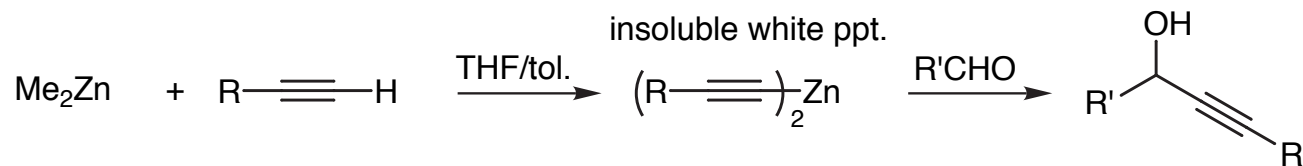
Reviews of organozinc additions:

Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69

Pu, L.; Yu, H. -B. *Chem. Rev.* **2001**, *101*, 757-824

Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856

## Why Zn Acetylides?

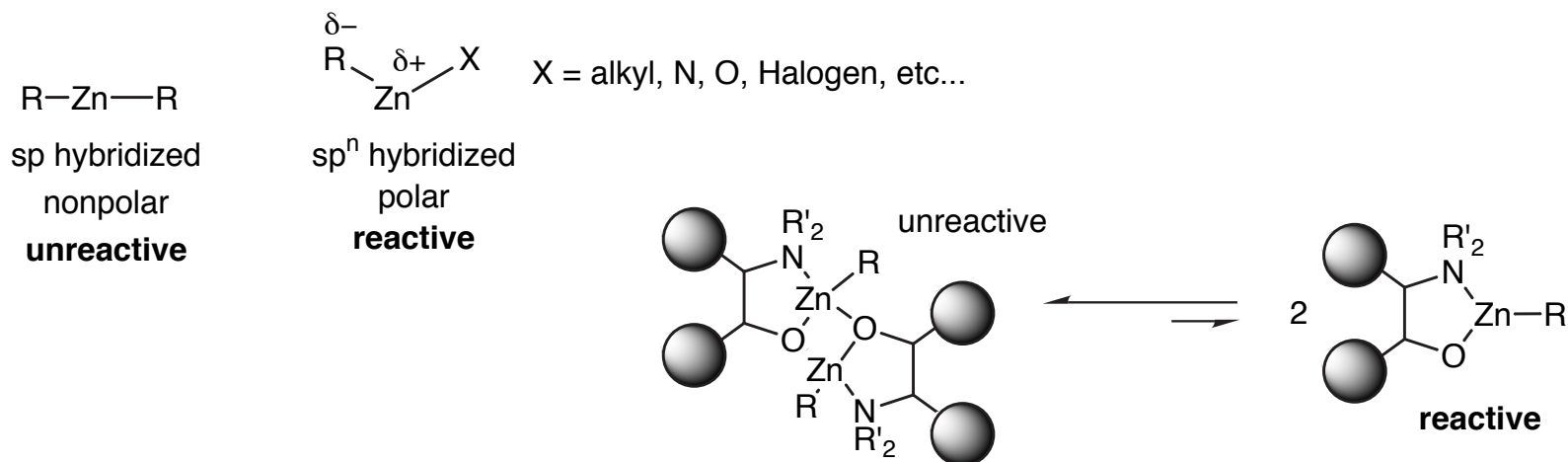


- conditions:
- 30% conversion in 17h at 0 °C without ligand
  - NMR shows no dialkynyl zinc formation when  $\text{Me}_2\text{Zn}$  and alkyne mixed without ligand
  - Addition of chiral ligand gives 100% conversion in 3h at 0 °C

⇒ Ligand Acceleration !

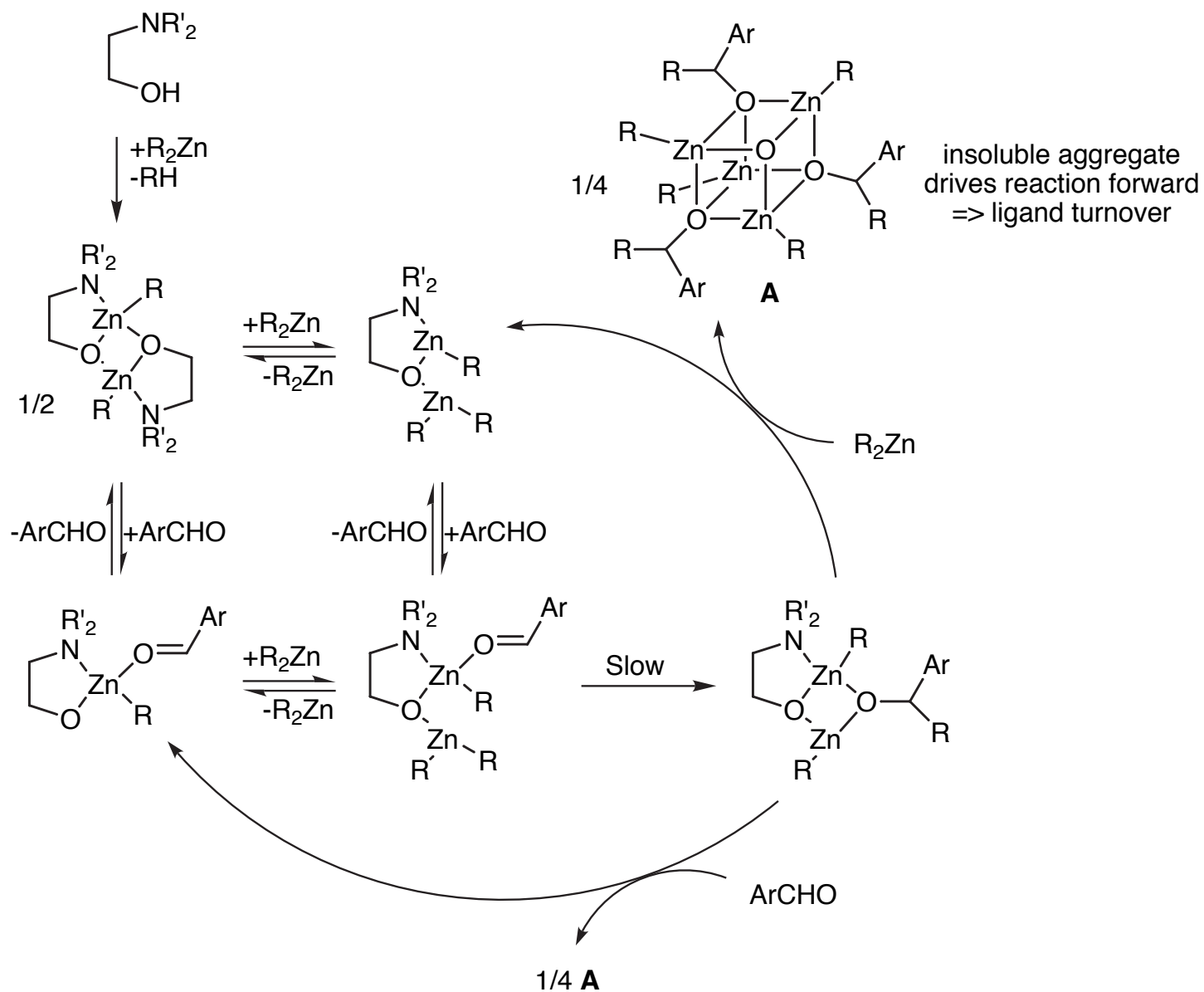
Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453-1458

Why?



Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 49-69

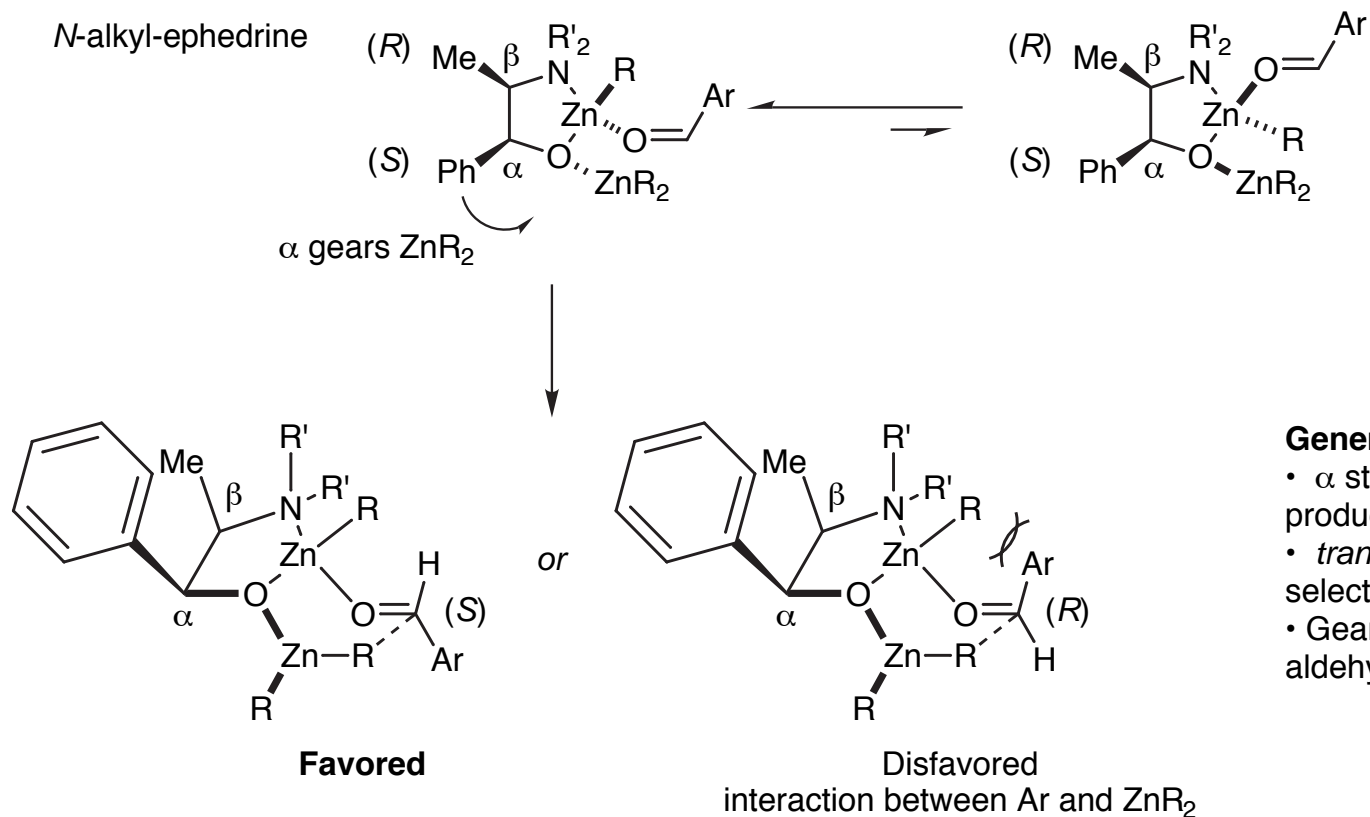
# Organozinc Catalytic Cycle



Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69

# Model for Asymmetric Induction

General for  $\beta$ -Amino Alcohols



## General Features:

- $\alpha$  stereocenter dictates observed product selectivity without exception
- *trans*  $\alpha,\beta$  chelate offset and show lower selectivity,  $\alpha$  still dominates --> *Cis* best
- Gearing effect --> direct sterics between aldehyde and ligand unimportant

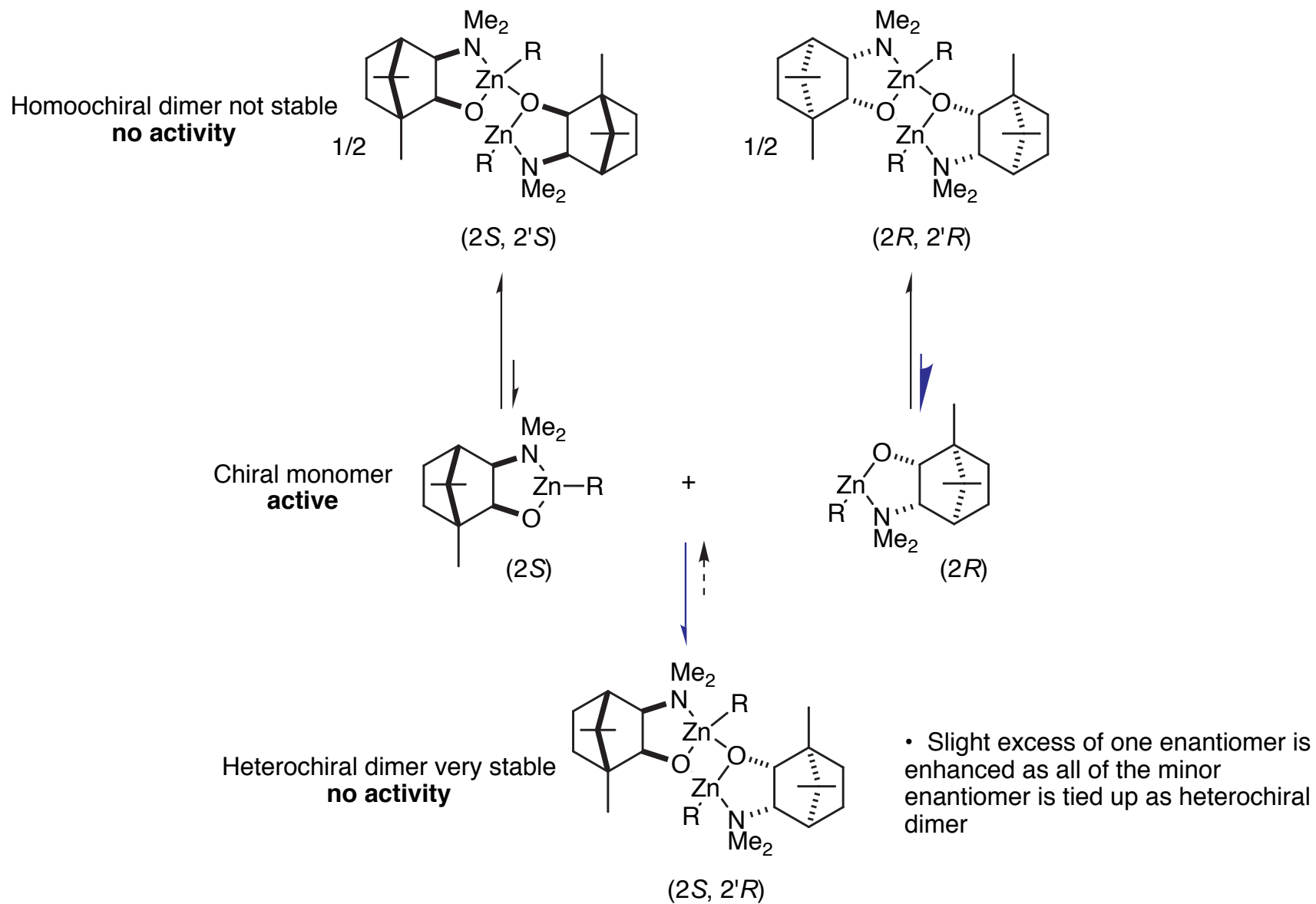
Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69

Evans, D. A. *Science* **1988**, *240*, 420-426.



# Origins of Non-Linear Effect

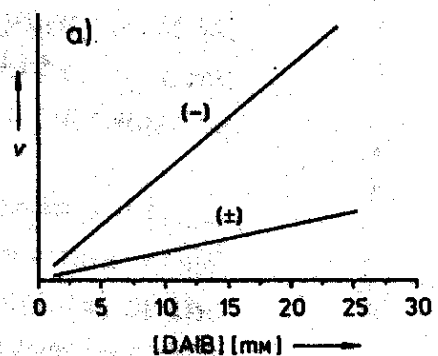
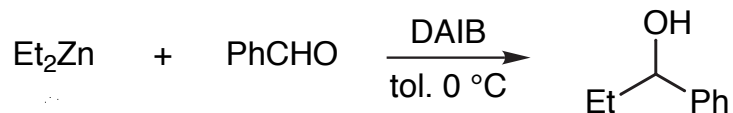
Large positive non-linear effect: **15% ee catalyst** delivers **95% ee product** for diethylzinc addition to benzaldehyde in presence of 3-exo-(dimethylamino)isoborneol [DAIB]



Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69

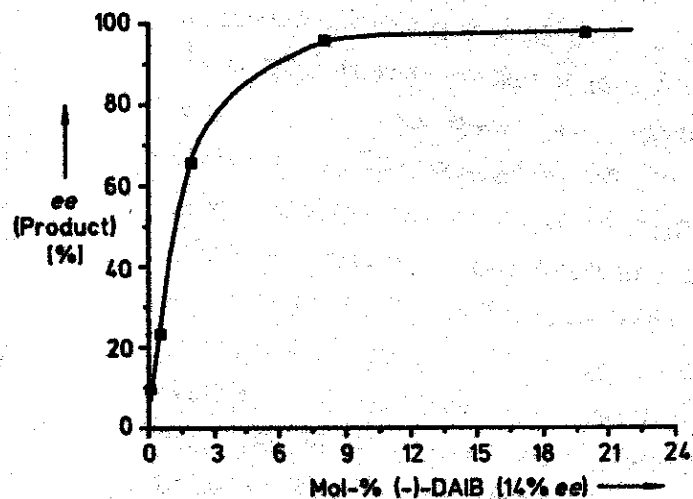
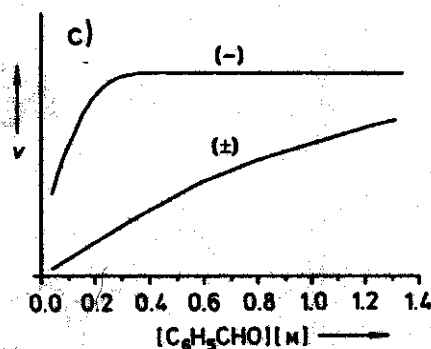
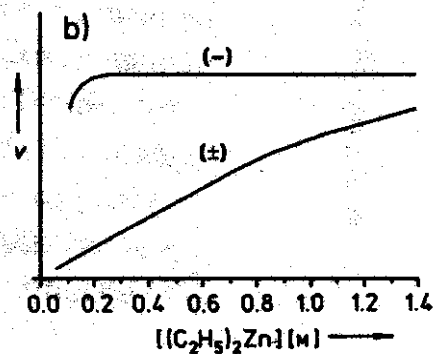
# Kinetic Chicanery...

(Don't be fooled by rates)



- Example: using 34 mM DAIB, 0.42M  $\text{Et}_2\text{Zn}$ , and 0.42M PhCHO indicates that (-)-DAIB is merely **14-times** faster than (±)-DAIB
- 15% ee catalyst gives 95% ee product indicates that chiral is **171-times** faster than racemic

The independent and competitive figures are not the same !

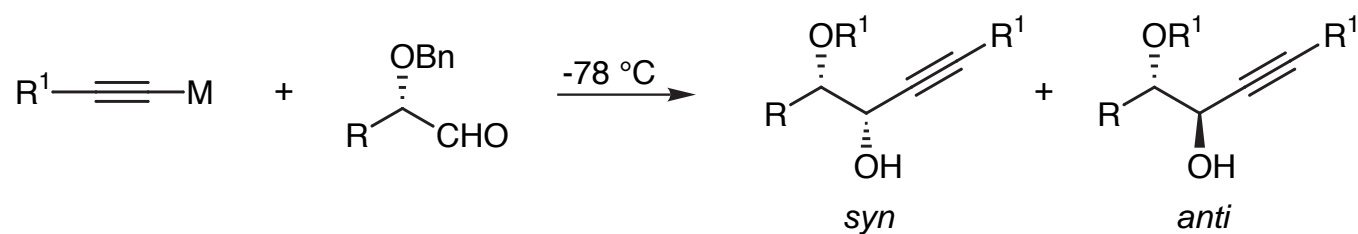


- **Answer:** The rate of (-)-DAIB catalysis is not as affected by  $[\text{Et}_2\text{Zn}]$  or  $[\text{PhCHO}]$ , whereas rate for (±)-DAIB is very dependent upon substrate concentration.

Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69

Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028-4036

## Chelate Controlled Additions



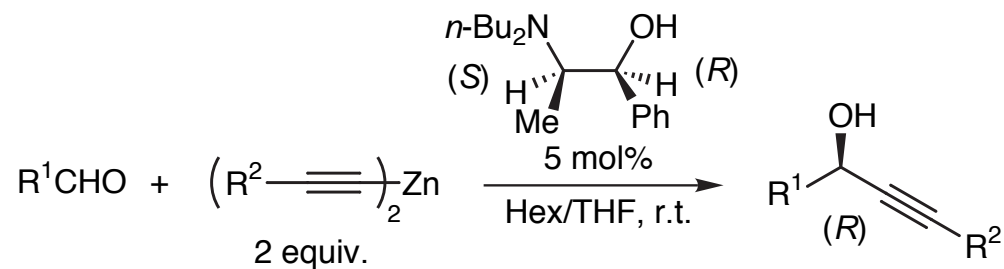
Entry	R'	Aldehyde (R)	M	Solvent	<i>syn</i> : <i>anti</i>	Yield (%)
1	Ph	Me	Li	THF	45:55	-
2	Ph	Me	MgBr	THF	62:38	-
3	Ph	Me	ZnCl	THF	66:34	-
4	Ph	Me	ZnBr	THF	81:19	75
5	Ph	Me	ZnBr	THF, 0 °C	76:24	70
6	Ph	Me	MgBr	Et <sub>2</sub> O	74:26	82
7	Ph	Me	ZnCl	Et <sub>2</sub> O	88:12	65
8	Ph	Me	ZnBr	Et <sub>2</sub> O	95:5	95
9	Ph	<i>i</i> -Pr	ZnBr	Et <sub>2</sub> O	99:1	92
10	Ph	BnOCH <sub>2</sub>	ZnBr	Et <sub>2</sub> O	86:14	76
11	<i>n</i> -Hex	Me	ZnBr	Et <sub>2</sub> O	84:16	79
12	<i>n</i> -Hex	<i>i</i> -Pr	ZnBr	Et <sub>2</sub> O	98:2	78

- Zn acetylide formed by transmetalation of Li acetylide with  $ZnX_2$
- 2 equiv. of Zn acetylide used, as 1 equiv. gave same selectivity, but lower yields.
- Zn chelate is proposed to explain *syn* selection

Mead, K. T. *Tetrahedron Lett.* **1987**, 28, 1019-1022

For chelate controlled Sn-acetylide additions, see: Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, 40, 4461-4462

## Early Example of Zn Acetylide Addition

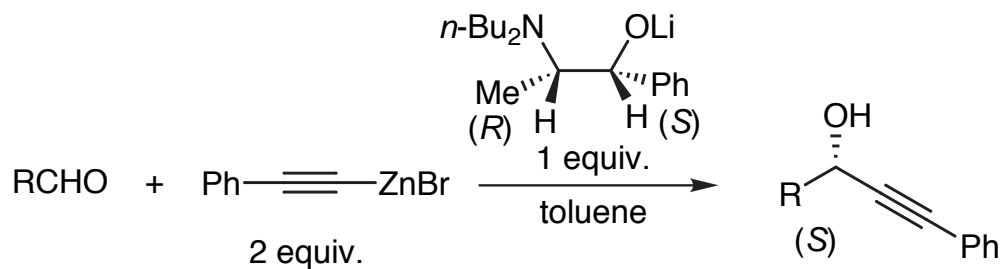


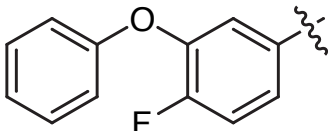
Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%)	ee (%)
1	Ph	Ph	14	99	34
2	<i>n</i> -Octyl	Ph	5	78	9
3	PhCH=CH	Ph	14	97	10
4	Ph	<i>n</i> -Hex	44	81	22
5	Ph	Bu	52	93	20
6	Ph	Me <sub>3</sub> Si	168	36	21
7	<i>n</i> -Octyl	Me <sub>3</sub> Si	48	80	24
8	Ph	<i>c</i> -Hex	48	88	7

- Zn-acetylides formed by heating Et<sub>2</sub>Zn and the acetylene
- Stereochemistry in accord with Noyori's model
- Mixed alkylalkynyl zinc reagents (e.g. MeZn≡C-Ph) gave only alkynylation with 40% ee

Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937-943

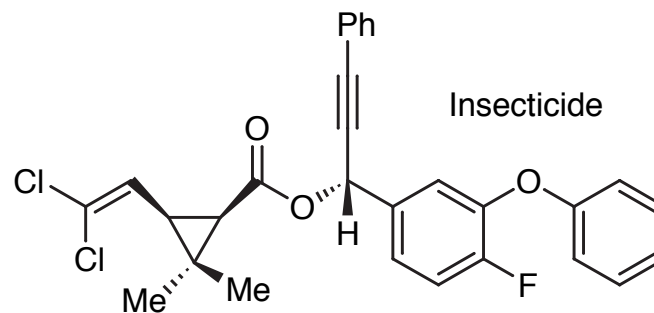
## Improved Zn Acetylide Addition



Entry	R	T (°C)	Time (h)	Yield (%)	ee (%)
1	Ph	-30	19	70	80
2	<i>t</i> -Bu	-30	24	50	67
3	<i>n</i> -Pent	-30	20	90	19
4		0-5	20	80	88

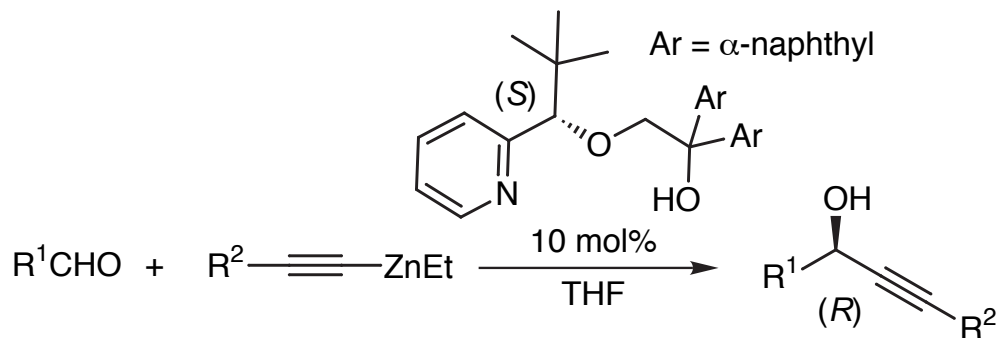
$\text{Ph-C}\equiv\text{C-ZnEt}$   
 delivers product in  
 42% ee

• Catalytic reaction with 10 mol% isolated Zn acetylide amino alcohol complex gives product in only 35% ee



Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett*. **1990**, 547-548

## Tridentate Chiral Ligand



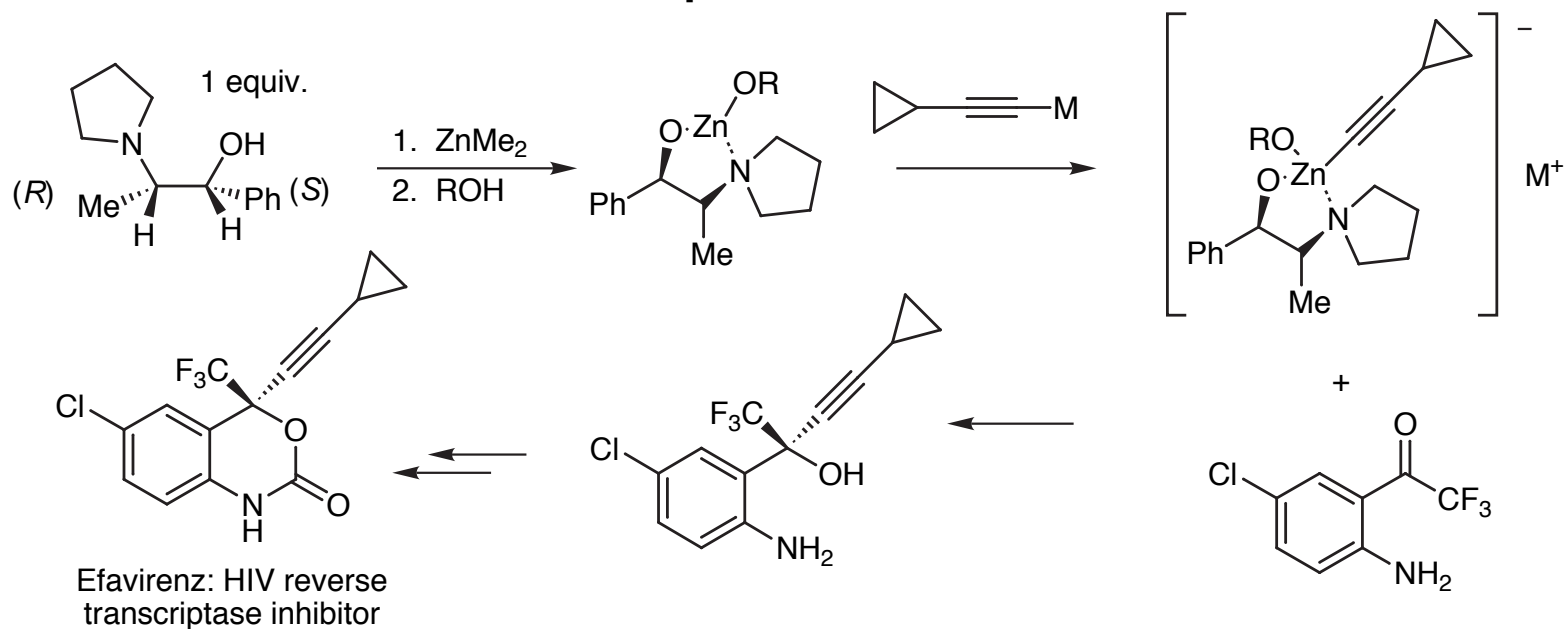
Entry	R <sup>1</sup>	R <sup>2</sup>	Temp. (°C)	Time (h)	Yield (%) <sup>*</sup>	ee (%)
1	Ph	Ph	0	15	64	90
2	<i>n</i> -Octyl	Ph	0	4	65	83
3	<i>c</i> -Hex	Ph	0	10	88	91
4	<i>t</i> -Bu	Ph	0	10	61	95
5	Ph	<i>n</i> -Hex	r.t.	2	41(52)	78
6	<i>n</i> -Octyl	<i>n</i> -Hex	r.t.	1	62(22)	73
7	<i>c</i> -Hex	<i>n</i> -Hex	r.t.	3	79(18)	82
8	<i>t</i> -Bu	<i>n</i> -Hex	r.t.	3	67	87
9	<i>c</i> -Hex	Ph <sub>3</sub> Si	r.t.	5	55	91

\* Values in parenthesis are yields of ethylated product

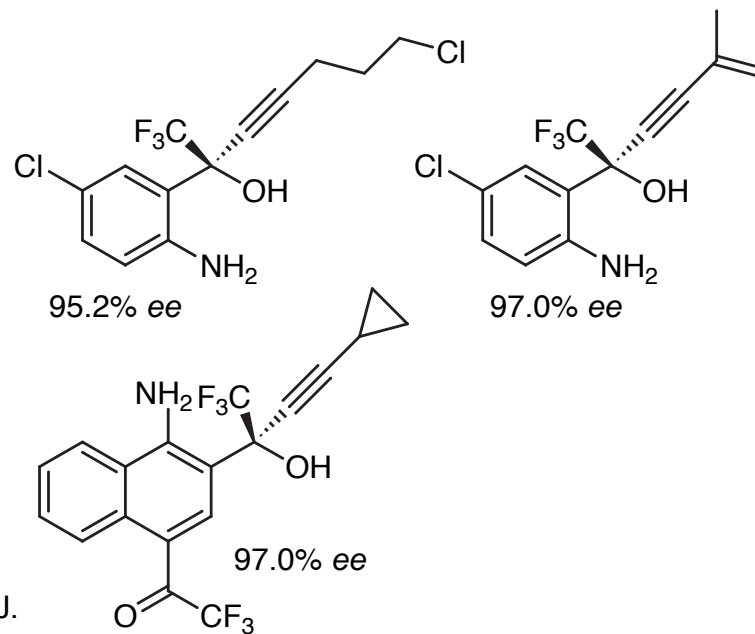
- Opposite facial selectivity as Noyori's bidentate ligand model
- Zn acetylide formed by diethylzinc and acetylene heated at reflux

Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymm.* **1994**, 5, 1901-1904

## Merck's Ephedrine Derivative

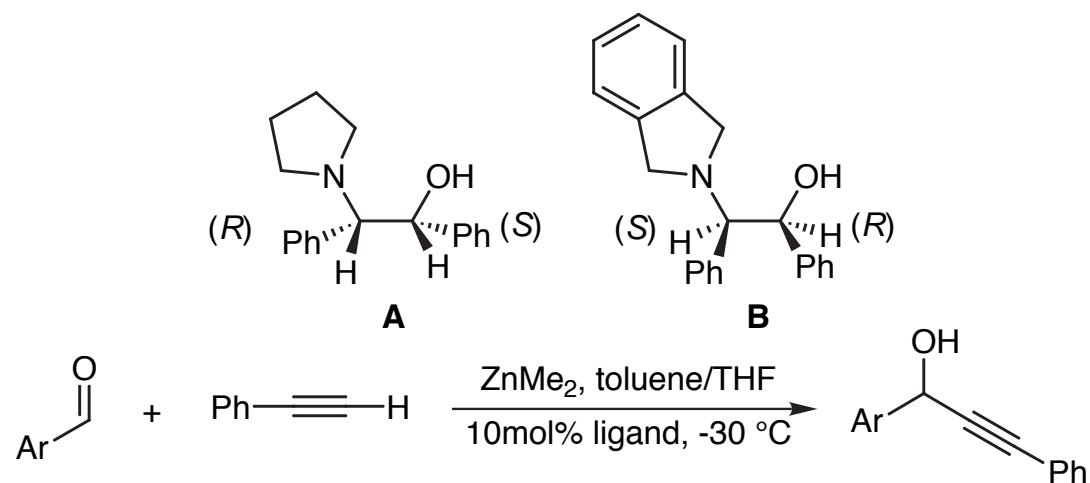


		M = MgCl	
M	ee (%)	ROH	ee (%)
Li	83.0	MeOH	87.0
MgCl	87.0	EtOH	55.0
MgBr	53.6	$(\text{CH}_3)_3\text{CCH}_2\text{OH}$	95.6
MgI	50.6	$\text{CH}_2=\text{CHCH}_2\text{OH}$	90.0
		BnOH	89.0
		$\text{CF}_3\text{CH}_2\text{OH}$	95.7
		$\text{CF}_3\text{CO}_2\text{H}$	89.4
		$(\text{CH}_3)_3\text{CCO}_2\text{H}$	71.6
		<i>p</i> -NO <sub>2</sub> PhOH	89.0



Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711-713

## Merck's Catalytic Process



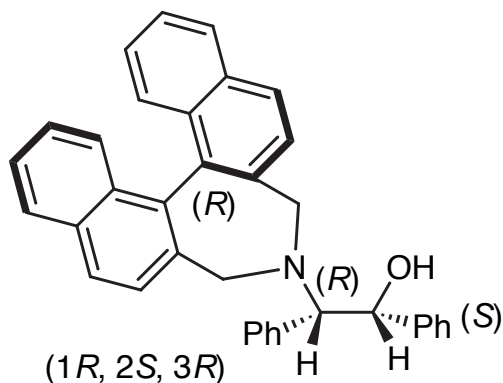
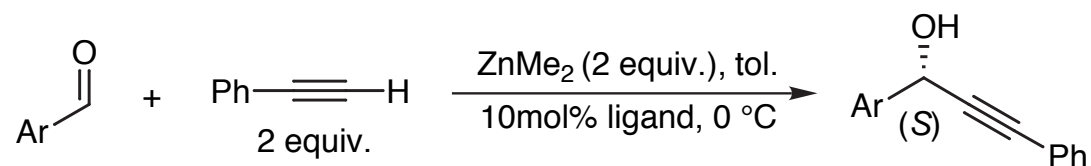
Entry	Ar	Ligand	Yield (%)	ee (%)
1	Ph	<b>A</b>	70	68(-)(S)
2	<i>o</i> -F-Ph	<b>B</b>	90	82(-)
3	<i>m,o</i> -di-F-Ph	<b>B</b>	94	81(+)
4	<i>o</i> -Cl-Ph	<b>A</b>	77	80(+)
5	<i>o</i> -Br-Ph	<b>A</b>	77	80(+)
6	<i>o</i> -NO <sub>2</sub> -Ph	<b>A</b>	81	76(+)
7	<i>o</i> -MeO-Ph	<b>A</b>	74	82(+)
8	<i>o</i> -Me-Ph	<b>A</b>	65	62(+)
9	2-naphthyl	<b>B</b>	87	75(-)

- Use of toluene/THF eliminate methyl addition
- Small non-linear effect observed
- Stereochemistry in accord with Noyori's model
- Zn-acetylide only forms upon addition of ligand (by NMR)

Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453-1458



## BINAP Derived Amino Alcohol

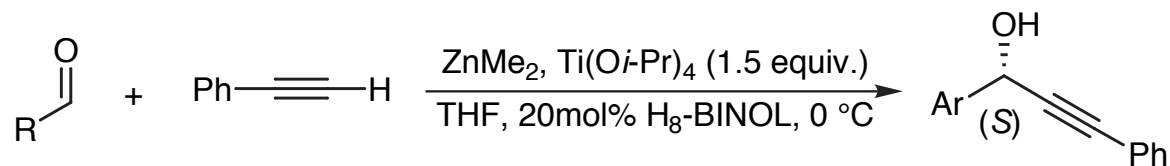
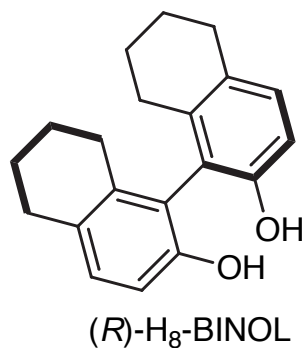


Entry	Ar	Time (h)	Conv. (%)	ee (%)
1	<i>o</i> -F-Ph	12	>95	87(+)
2	<i>o</i> -Br-Ph	12	>95	90(+)
3	<i>o</i> -NO <sub>2</sub> -Ph	24	>95	87(+)
4	<i>o</i> -MeO-Ph	6	>95	71(+)
5	<i>o</i> -Me-Ph	24	>95	71(+)
6	2-naphthyl	24	>95	61(+)
7	Ph	24	>95	70(-)(S)

- Other diastereomers of ligand give low ee
- Stereochemistry in accord with Noyori model
- OH bearing stereocenter on ligand determines facial selectivity

Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymm.* **2001**, 12, 2147-2152

## Titanium H<sub>8</sub>-BINOL Catalyzed

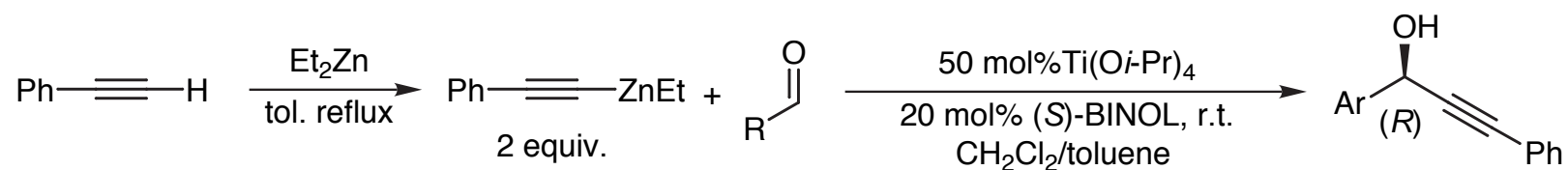


Entry	R	Yield (%)	ee (%)
1	Ph	85	92 (S)
2	<i>o</i> -Cl-Ph	90	76
3	<i>m</i> -Cl-Ph	87	95
4	<i>p</i> -Cl-Ph	91	94
5	<i>p</i> -Me-Ph	84	86
6	<i>p</i> -F-Ph	82	87
7	<i>p</i> -Br-Ph	89	94
8	<i>p</i> -NO <sub>2</sub> -Ph	89	95
9	<i>m</i> -NO <sub>2</sub> -Ph	88	96
10	2-naphthyl	75	80
11	<i>p</i> -CF <sub>3</sub> -Ph	89	93
12	<i>i</i> -Pr	84	82
13	<i>c</i> -Hex	86	74
14	<i>n</i> -Pr	87	77

• BINOL gave slightly reduced yields and selectivity

Lu, G.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172-173

## Titanium BINOL Catalyzed

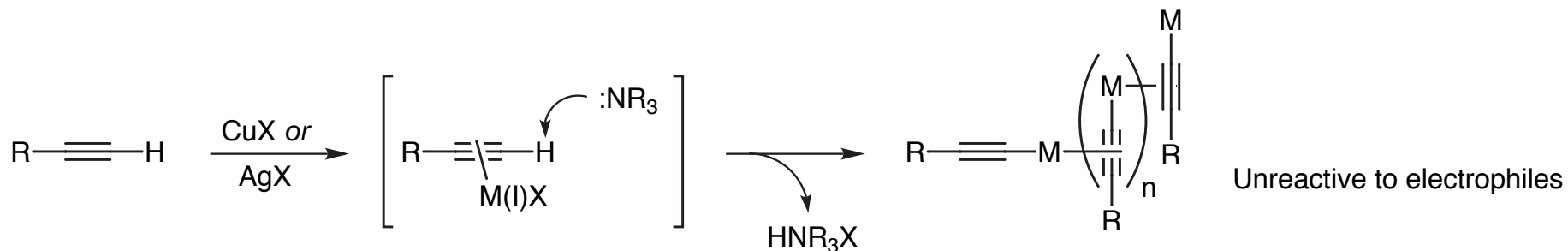


Entry	R	Yield (%)	ee (%)
1	Ph	77	96
2	<i>m</i> -Cl-Ph	79	92
3	<i>p</i> -Cl-Ph	81	92
4	<i>o</i> -Me-Ph	81	96
5	<i>m</i> -Me-Ph	77	94
6	<i>o</i> -MeO-Ph	73	93
7	<i>m</i> -MeO-Ph	78	93
8	<i>p</i> -F-Ph	74	96
9	<i>p</i> -NO <sub>2</sub> -Ph	79	97
10	2-naphthyl	77	98
11	1-naphthyl	71	92

$i\text{-Pr}_3\text{Si}-\text{C}\equiv\text{C}-\text{H} + \text{PhCHO}$   
 gives 75% yield and 92% ee

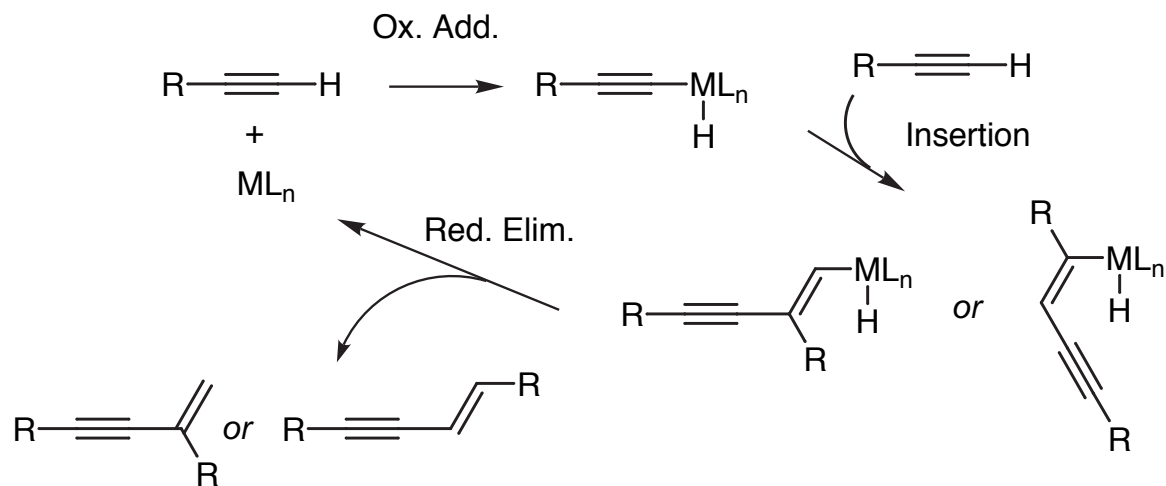
Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855-1857

## "Soft" Metal Acetylide Formation



*Advanced Inorganic Chemistry*, Cotton, F. A., Wilkinson, G.; 5th ed.; Wiley: New York, 1988, p.765, 945

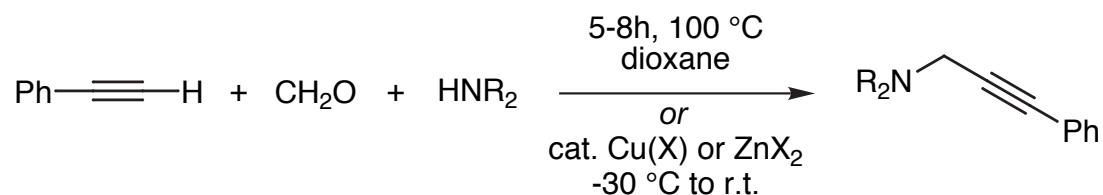
*sp-C-H activation:*



Metals: Ru(II), Ir(I), Ti(IV), Pd(0), Rh(I), others?

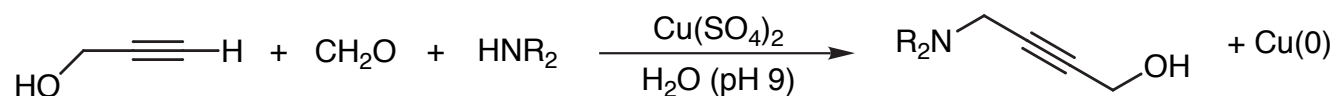
Ru(II): Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem Rev.* **1998**, 98, 2599-2660

## Early Examples of Catalytic Metal



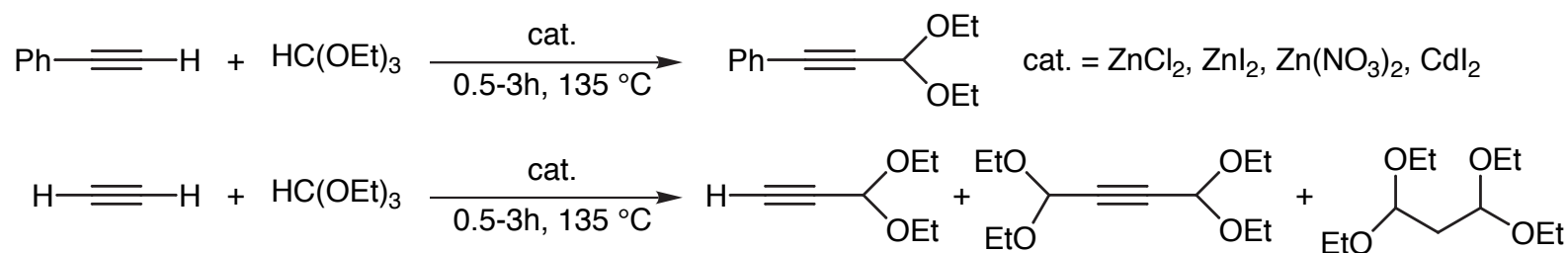
Thermal: Mannich, C.; Chang, F. T. *Ber.* 1933, 418-420

Catalytic  $\text{ZnX}_2$  or  $\text{CuX}$ : for an example, see: Stutz, A.; Granitzer, W.; Roth, S. *Tetrahedron* **1985**, 41, 5685-5696.



- A copper acetylide is proposed
- Extensive screening found basic medium is best, as acidic conditions cannot form Cu-acetylide

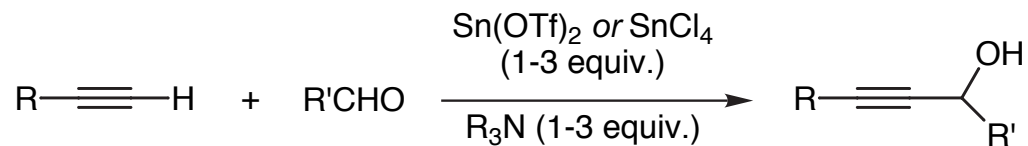
Salvador, R. L.; Simon, D. *Can. J. Chem.* **1966**, 44, 2570-2575



Howk, B. W.; Sauer, J. C. *J. Am. Chem. Soc.* **1958**, 80, 4607-4609

indicates ionic mechanism

## Sn Acetylide Formation

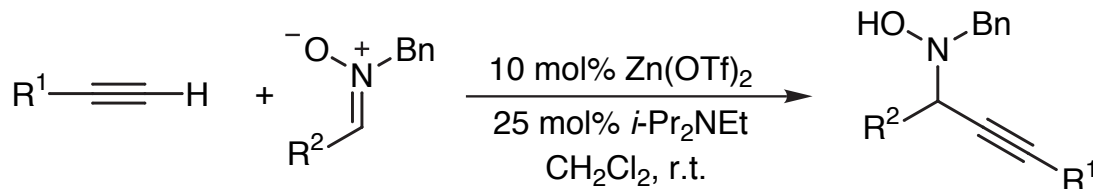


- Propose formation of Sn-acetylide
- Also reacts with acetals and adds 1,4 to enones


*"...copper or palladium acetylides have been generated with amine bases, although these species are not reactive enough to add to aldehydes. It seemed to us that the proper selection of a metal salt in combination with an amine base might allow generation of metal acetylides that are reactive enough to add to C=O bonds."*

Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem.* **1991**, *56*, 4091-4092  
Yamaguchi, M.; Hayashi, A.; Hiramata, M. *Chem. Lett.* **1992**, 2479-2482

## Zn(OTf)<sub>2</sub> Catalyzed Additions to Nitrones



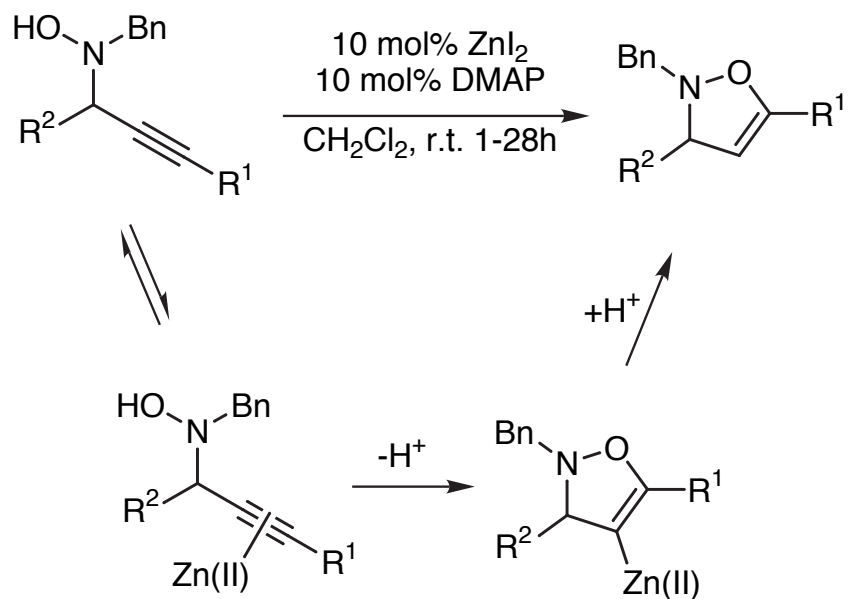
"In this context, we have been interested in developing methods that lead to the generation of metal alkynilides directly from terminal acetylenes under conditions that parallel those involving Ag(I) or Cu(I) in simplicity and mildness but that can be utilized in catalytic nucleophilic C=O and C=N addition reactions."

Entry	R <sup>1</sup>	R <sup>2</sup>	Time (h)	Yield (%)
1	TMS	<i>c</i> -Hex	12	95
2	TMS	Ph	24	43
3	TMS	<i>n</i> -Pent	12	62
4	TMSCH <sub>2</sub>	<i>n</i> -Pent	12	90
5	TMSCH <sub>2</sub>	<i>t</i> -Bu	12	67
6	TMS	<i>i</i> -Pr	12	99
7	<i>n</i> -Bu	<i>i</i> -Pr	3	95
8	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>i</i> -Pr	3	96
9	TBSOCH <sub>2</sub>	<i>i</i> -Pr	6	85
10	Ph	<i>i</i> -Pr	1	94
11	<i>t</i> -Bu	<i>i</i> -Pr	1	93
12	BrCH <sub>2</sub>	<i>i</i> -Pr	3	68
13		<i>i</i> -Pr	3	85

- Zn-acetylides detected by <sup>13</sup>C NMR
- Also adds to ketones, aldehydes, *N*-Ts imines
- ZnCl<sub>2</sub> and ZnO also catalyze reaction (unpub.)

Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245-11246

## ZnI<sub>2</sub> Catalyzed 5-endo Dig Cyclization

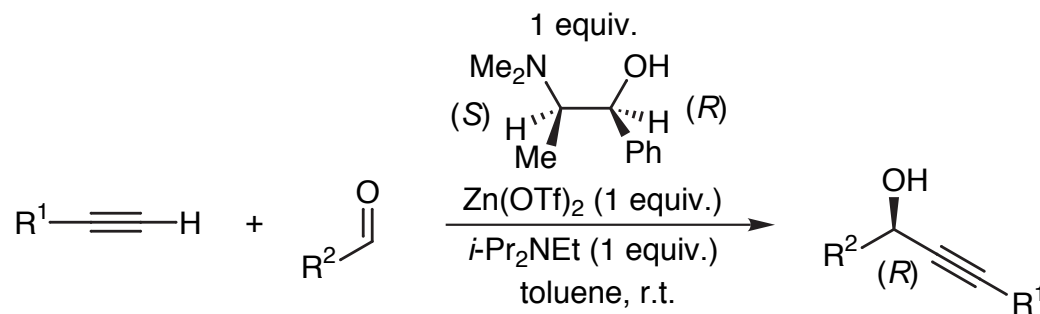


- DMAP is vital, as Et<sub>3</sub>N gives no product
- Other Zn(II) salts work, but ZnI<sub>2</sub> is fastest
- Other Lewis acids and protic acids gave no product
- Crossover experiments preclude retro-addition followed by [3+2]


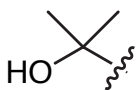
Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, 2, 2331-2333



## Enantioselective Addition (Stoichiometric)



Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
1	Ph	<i>c</i> -Hex	99	96
2	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>c</i> -Hex	98	99
3	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>i</i> -Pr	90	99
4	Ph	<i>i</i> -Pr	95	90
5	Ph(CH <sub>2</sub> ) <sub>2</sub>	PhCH=CH	39	80
6	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>t</i> -Bu	84	99
7	Ph	<i>t</i> -Bu	99	95
8	Ph(CH <sub>2</sub> ) <sub>2</sub>	Ph	52	96
9	Ph	Ph	53	94

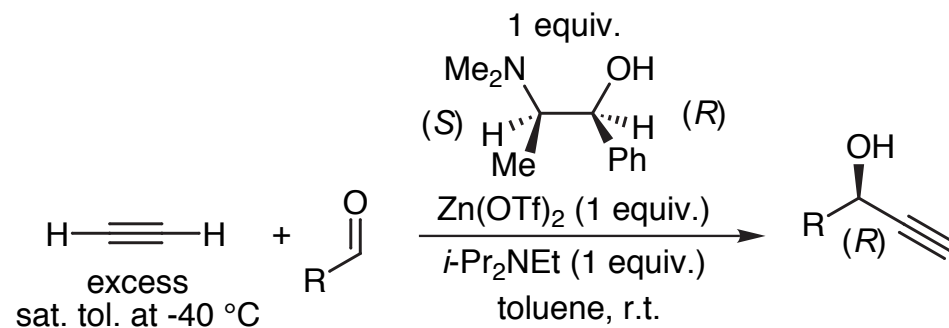
Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
10	TMS	<i>c</i> -Hex	93	98
11	Ph(CH <sub>2</sub> ) <sub>2</sub>	Me <sub>3</sub> CCH <sub>2</sub>	72	99
12	Ph	Me <sub>3</sub> CCH <sub>2</sub>	90	97
13	TMSCH <sub>2</sub>	<i>c</i> -Hex	84	98
14	TBDMSOCH <sub>2</sub>	<i>c</i> -Hex	83	98
15	(EtO) <sub>2</sub> CH	<i>c</i> -Hex	90	98
16		<i>c</i> -Hex	94	98
17		<i>i</i> -Pr	97	98

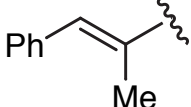
- Aliphatic aldehydes more reactive than aromatic
- Unbranched aliphatic aldehydes give good ee, but poor yield from self-aldol condensation
- Facial selectivity of (2*R*) ephedrine in accord with Noyori model
- Slight non-linear (20% ee ephedrine gives 39% ee product)
- Insensitive to moisture and oxygen

Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807

Epothilone Synthesis: Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611-3612

## Acetylene as a Nucleophile

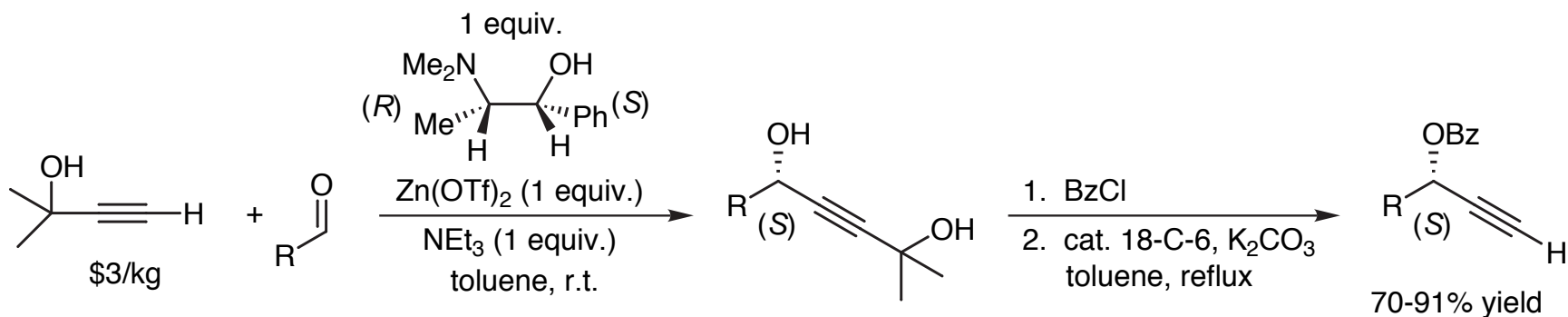


Entry	R	Yield (%)	ee (%)
1	<i>n</i> -Pent	30	97
2	<i>i</i> -Pr	76	98
3	<i>c</i> -Hex	70	98
4	<i>t</i> -Bu	92	98
5	Ph	35	97
6	PhCH=CH	34	92
7		28	91

- Reactions were sluggish, 7-14 days
- Mass balance was recovered s.m.

Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964-971

## An Acetylene Equivalent

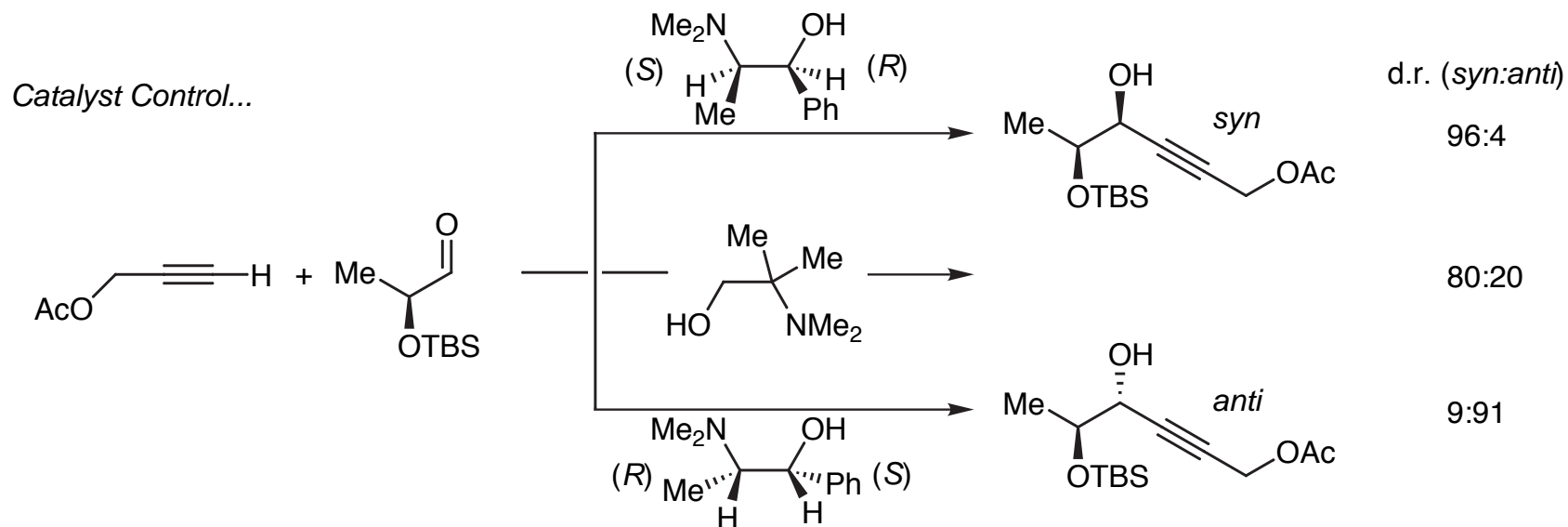
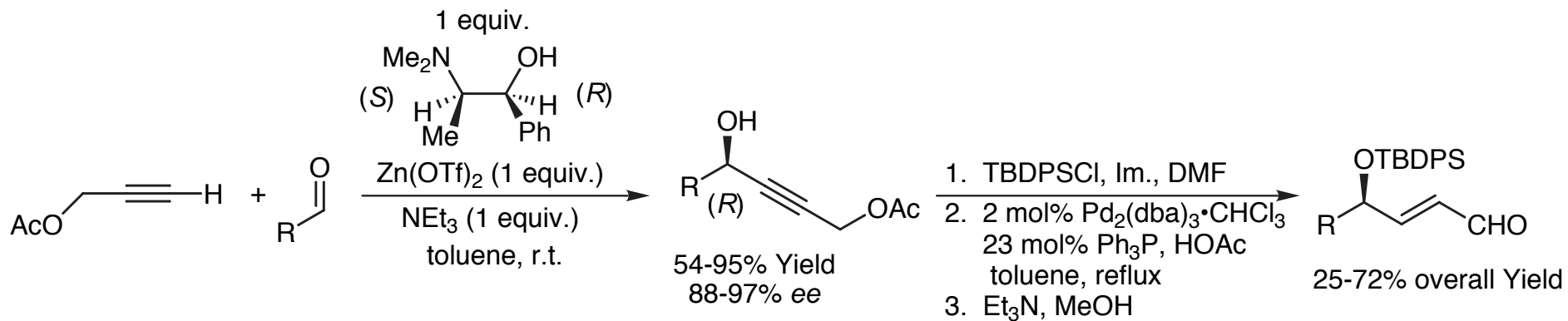


Entry	R	Yield (%)	ee (%)
1	<i>i</i> -Pr	97	98
2	<i>c</i> -Hexyl	89	99
3	<i>t</i> -Bu	82	98
4	<i>n</i> -Pentyl	81	98
5	<i>n</i> -Propyl	77	99
6	Ph	96	98
7	PhCH=CH	99	88
8	TIPSO(CH <sub>2</sub> ) <sub>2</sub>	82	97

- Protection of alcohol needed for good yields in fragmentation reaction
- Protection performed in same pot as Zn reaction
- Many aldehydes required 2-3 equivalents of Zn(OTf)<sub>2</sub> and ephedrine

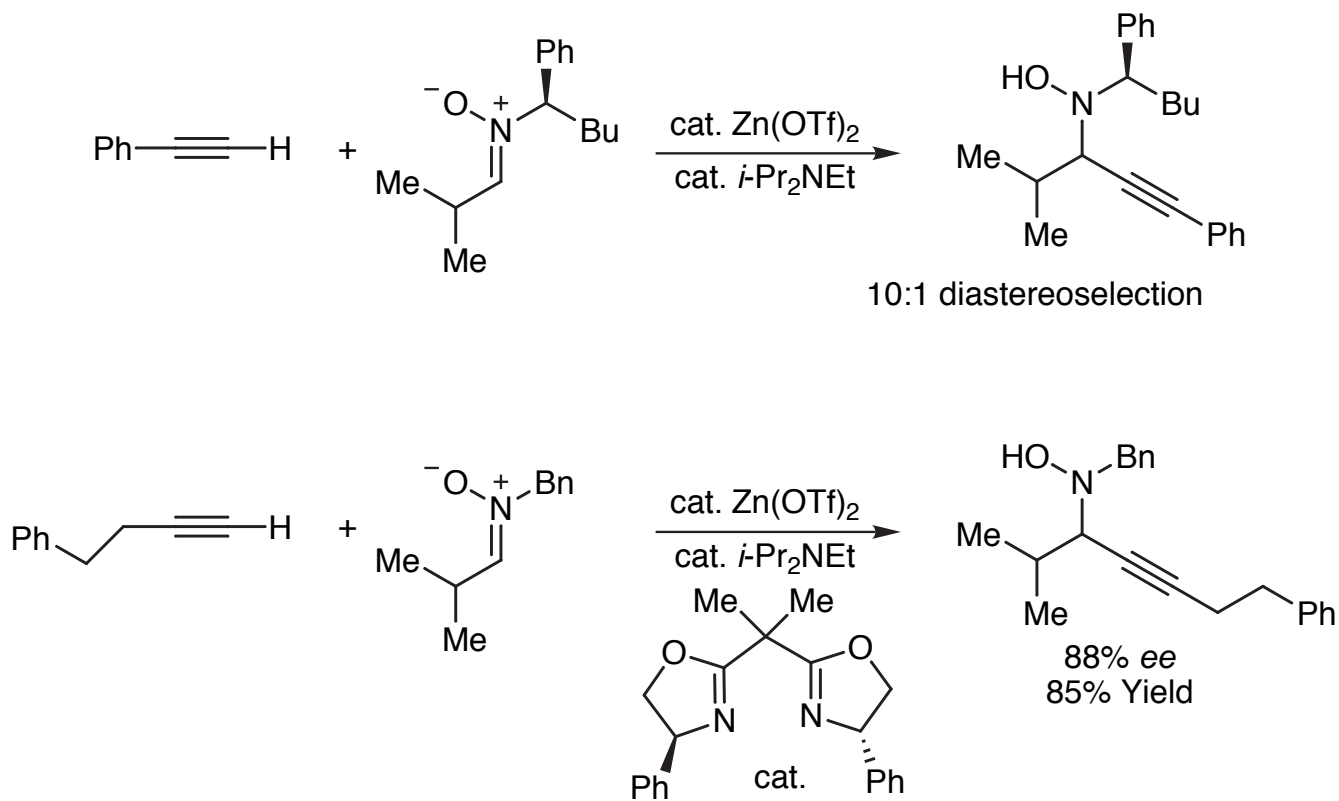
Boyll, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, 2, 4233-4236

## Propargyl Alcohol Functionalization



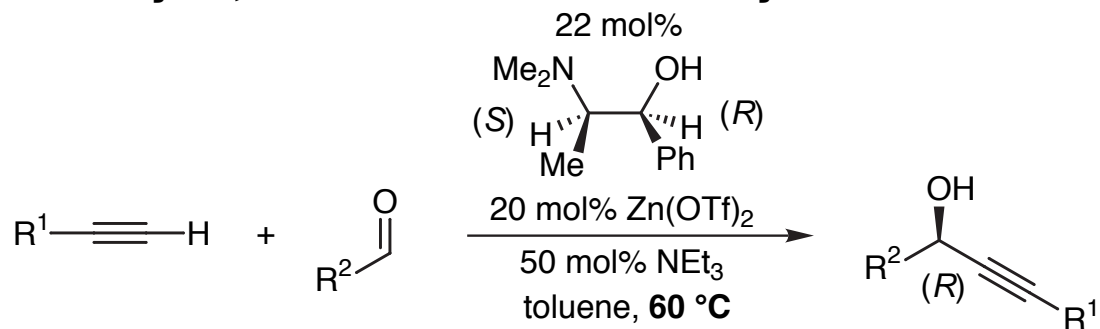
El-Sayed, E.; Anand, N. K.; Carreira, E.M. *Org. Lett.* **2001**, *3*, 3017-3020

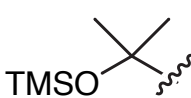
## Enantioselective Nitron Addition

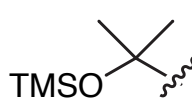
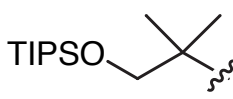
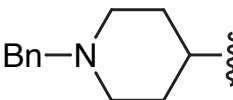



Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Rec.* **2000**, 33, 373-381

# Catalytic, Enantioselective Acetylene Addition

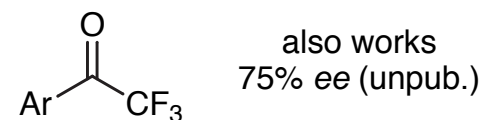


Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
1	Bn <sub>2</sub> NCH <sub>2</sub>	c-Hex	91	97
2	Ph(CH <sub>2</sub> ) <sub>2</sub>	c-Hex	89	94
3	Ph	c-Hex	94	86
4		<i>i</i> -Pr	77	98
5	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>n</i> -Heptyl	45	92
6	Ph(CH <sub>2</sub> ) <sub>2</sub>	<i>t</i> -Bu	77	93
7	TBSOCH <sub>2</sub>	<i>t</i> -Bu	81	93
8	(EtO) <sub>2</sub> CH	c-Hex	88	94

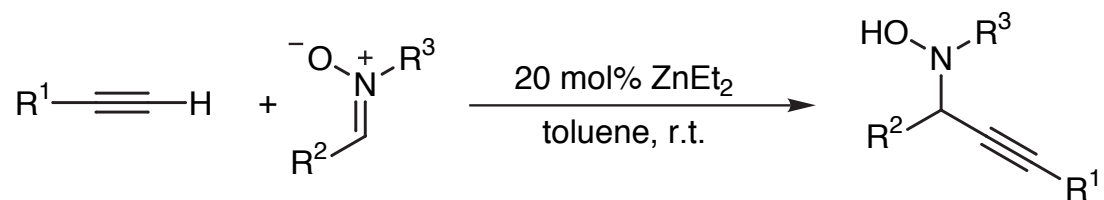
Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
9	<i>n</i> -Bu	c-Hex	81	93
10		c-Hex	80	99
11	TES	c-Hex	85	96
12	Bn <sub>2</sub> NCH <sub>2</sub>		80	95
13	TBSOCH <sub>2</sub>	c-Hex	88	90
14	Bn <sub>2</sub> NCH <sub>2</sub>		81	94
15	Ph(CH <sub>2</sub> ) <sub>2</sub>		80	93
16	Bn <sub>2</sub> NCH <sub>2</sub>	<i>n</i> -Heptyl	55	91

- Racemic reaction proceeds in CH<sub>3</sub>CN w/o ephedrine
- ArCHO yields are low due to Cannizzaro reaction
- Reactions proceed neat
- Some self-aldol condensation observed

Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688

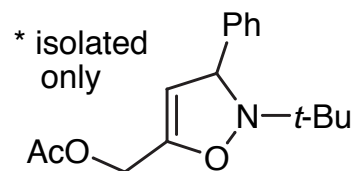


## Catalytic Nitron Addition



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)
1	<i>n</i> -Bu	Ph	Bn	92
2	<i>n</i> -Decyl	Ph	Bn	82
3		Ph	Bn	88
4	<i>p</i> -Pent-Ph	Ph	Bn	92
5	Cl(CH <sub>2</sub> ) <sub>3</sub>	Ph	Bn	96
6	TMS	Ph	Bn	90
7	NC(CH <sub>2</sub> ) <sub>3</sub>	Ph	Bn	78
8	MeCO <sub>2</sub> CH <sub>2</sub>	Ph	Bn	62
9	(EtO) <sub>2</sub> CH	Ph	Bn	90
10	<i>t</i> -BuOCH <sub>2</sub>	Ph	Bn	82

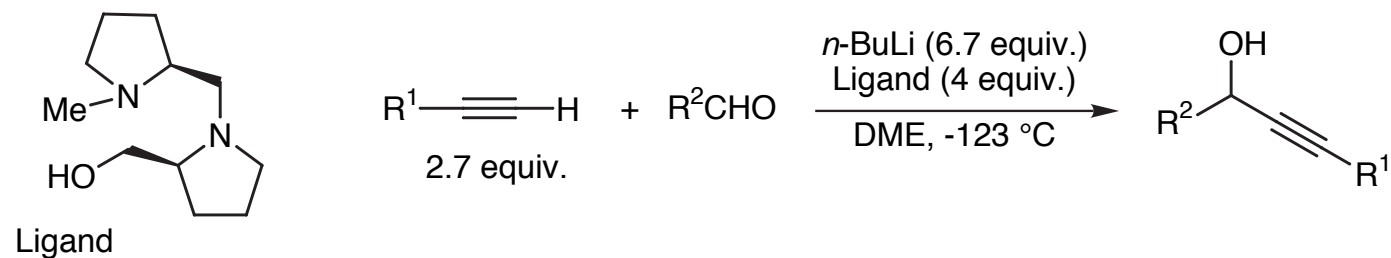
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)	d.r.
11	<i>t</i> -BuO <sub>2</sub> C	Ph	Bn	<42	-
12	<i>n</i> -Bu	<i>p</i> -MeO-Ph	Ph	72	-
13	<i>p</i> -Pent-Ph	<i>p</i> -MeO-Ph	Ph	56	-
14	Cl(CH <sub>2</sub> ) <sub>3</sub>	<i>p</i> -MeO-Ph	Ph	61	-
15	MeCO <sub>2</sub> CH <sub>2</sub>	Ph	<i>t</i> -Bu	>99*	-
16	<i>n</i> -Bu	Ph(Me)CH	Me	94	78:22
17		Ph(Me)CH	Me	97	74:26
18	TMS	Ph(Me)CH	Me	87	76:24
19	MeCO <sub>2</sub> CH <sub>2</sub>	Ph(Me)CH	Me	91	77:23



Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, *4*, 1463-1466

# Enantioselective Li-Acetylide Additions

## Early Examples



Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)	Entry	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	ee (%)
1	H	Ph	76	54	7	TMS	Et	77	68
2	TMS	Ph	87	92	8	TMS	<i>n</i> -Pent	87	76
3	TES	Ph	93	80	9	TMS	<i>n</i> -Octyl	83	80
4	TBS	Ph	67	72	10	TMS	<i>n</i> -C <sub>11</sub> H <sub>23</sub>	82	70
5	Ph <sub>2</sub> MeSi	Ph	88	80	11	TMS	<i>n</i> -C <sub>13</sub> H <sub>27</sub>	76	73
6	TPS	Ph	83	76	12	TMS	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	54	65
					13	TMS	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH=CH	74	40

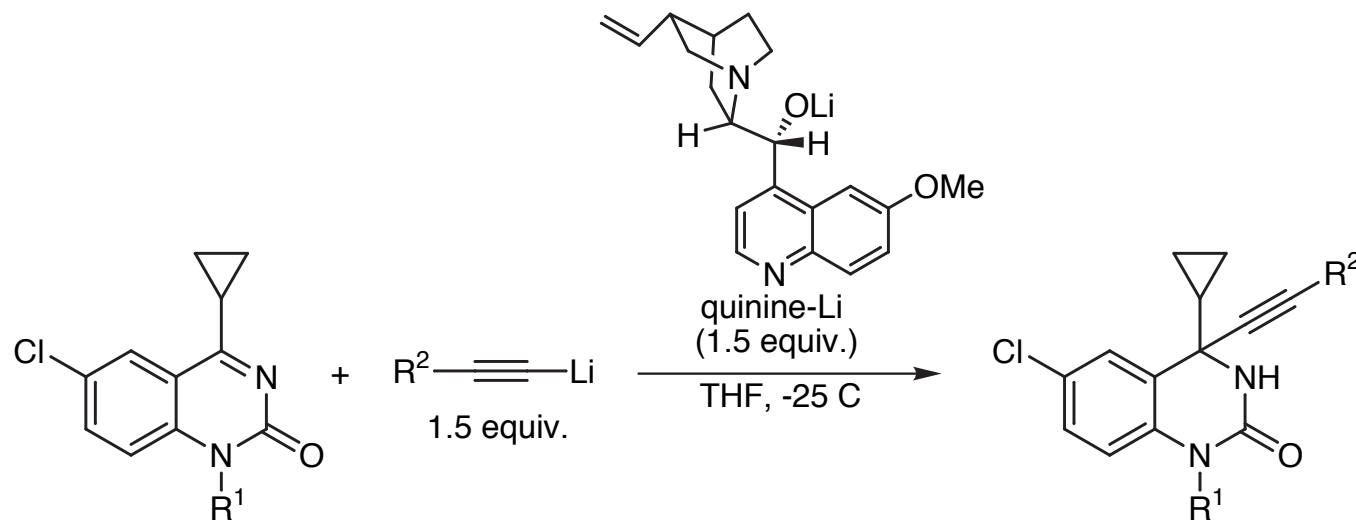
- Aromatic aldehydes gave (*S*) alcohol, whereas aliphatic gave (*R*)

Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447-448  
 Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255-256

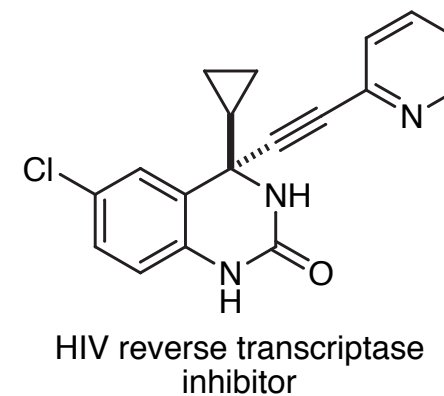


## Enantioselective Li-Acetylide Additions

### Early Merck Examples

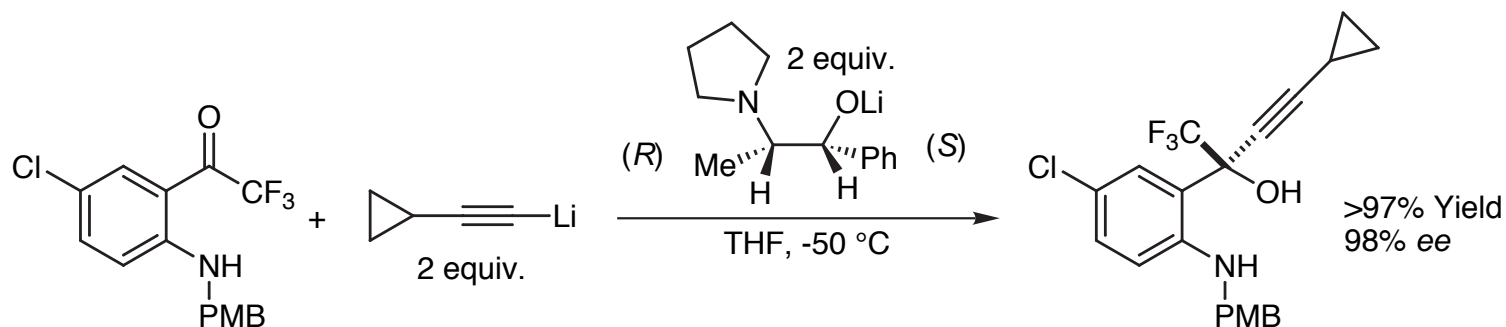


Entry	R <sup>1</sup>	R <sup>2</sup>	best ee (%)	Entry	R <sup>1</sup>	R <sup>2</sup>	ee (%)
1	PMB	2-pyridyl	64	8	9-anthrylmethyl	2-pyridyl	94
2	Bn	2-pyridyl	56	9	9-anthrylmethyl	3-pyridyl	22
3	<i>p</i> -Cl-Bn	2-pyridyl	37	10	9-anthrylmethyl	4-pyridyl	6
4	Me	2-pyridyl	70	11	9-anthrylmethyl	<i>p</i> -MeOPh	86
5	2,4,6-Me <sub>3</sub> Bn	2-pyridyl	74	12	9-anthrylmethyl	Ph	65
6	2,6-Cl <sub>2</sub> Bn	2-pyridyl	80	13	9-anthrylmethyl	<i>p</i> -Cl-Ph	58
7	9-anthrylmethyl	2-pyridyl	97	14	9-anthrylmethyl	Bu	77
				15	9-anthrylmethyl	TMS	82

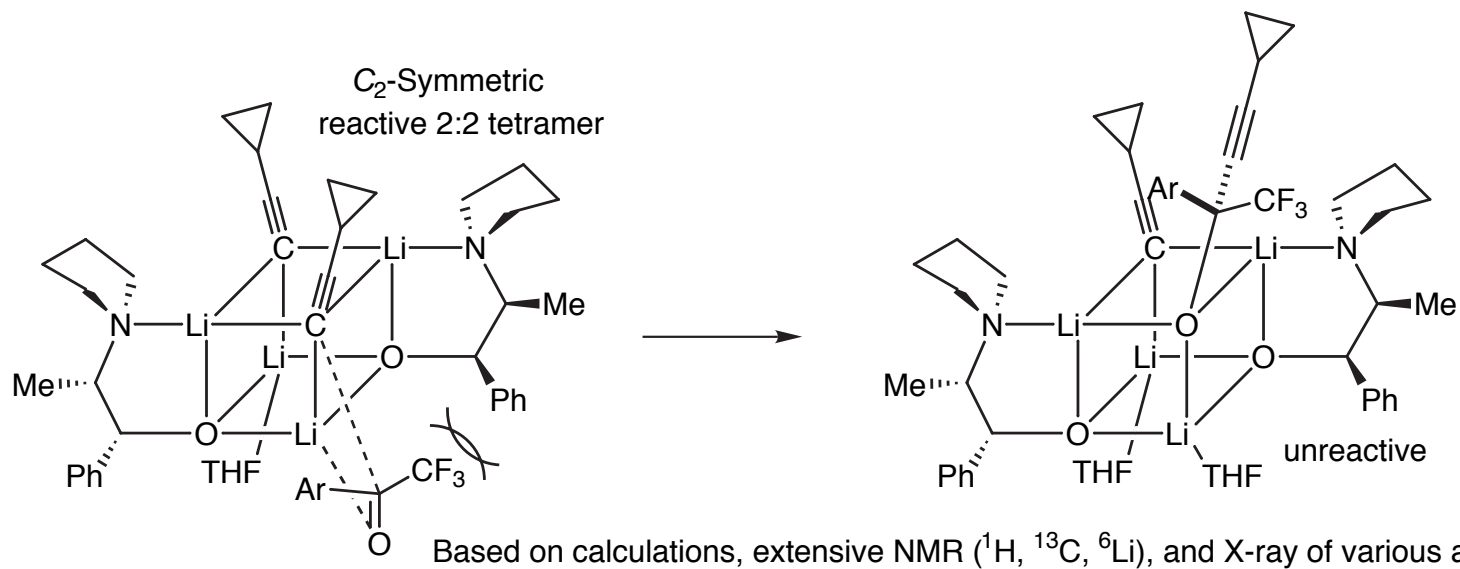


Huffman, M. A.; Yasuda, N.; DeCamp, A.E.; Grabowski, E. J. *J. Org. Chem.* **1995**, *60*, 1590-1594

## Enantioselective Li-Acetylide Additions Ephedrine Mediated



- 2 equiv. of ligand and acetylide required for complete conversion
- Low ee if ephedrine and Li-acetylide not warmed above -40 °C prior to addition at -50 °C



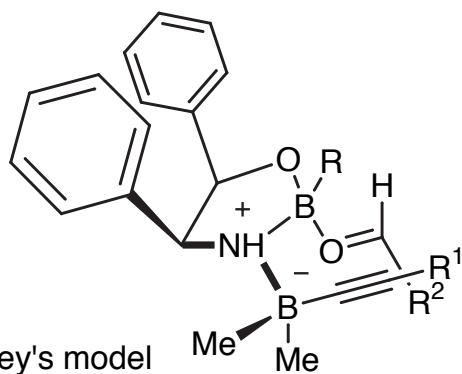
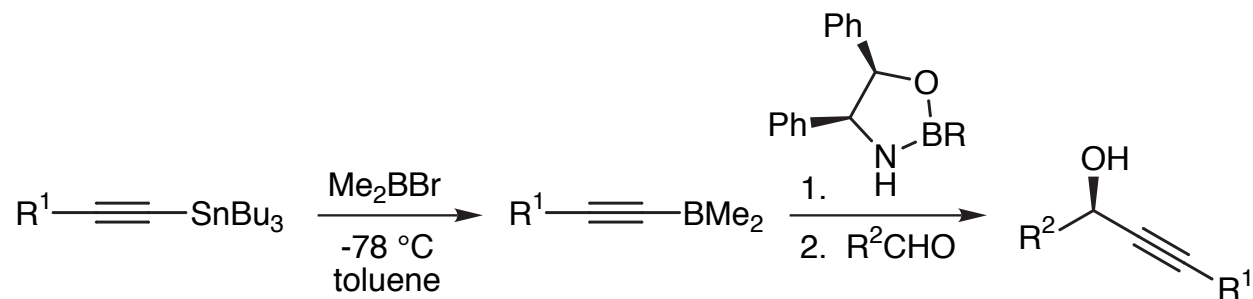
Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, 36, 8937-8940

Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, 120, 2028-2038

Pierce, M. E.; Chen, C.; Tillyer, R. D. et. al. *J. Org.Chem.* **1998**, 63, 8536-8543 (Efavirenz Synthesis)

Xu, F.; Reamer, R. A.; Collum, D. B.; Huffman, J. C.; et. al. *J. Am. Chem. Soc.* **2000**, 122, 11212-11218 (X-Ray)

## Enantioselective B-Acetylide Additions



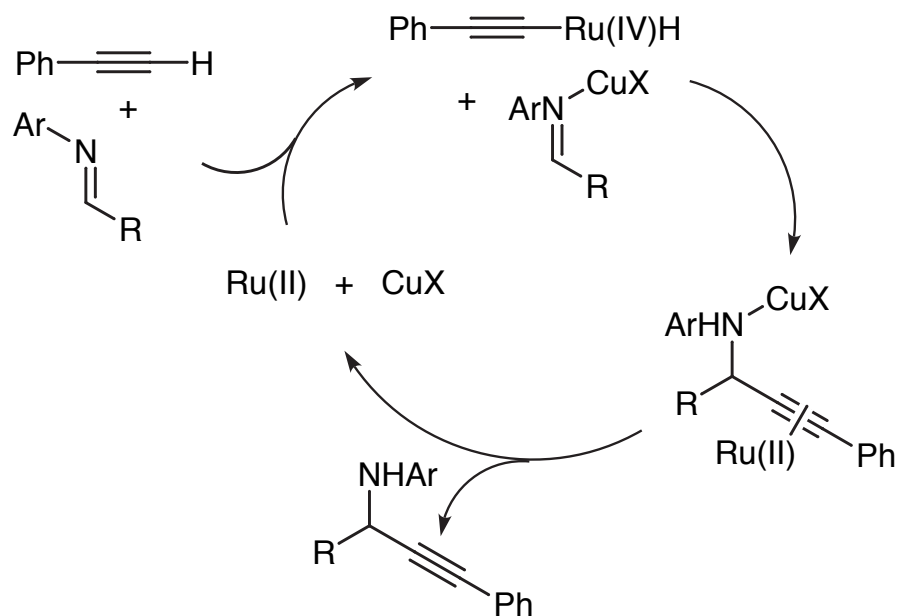
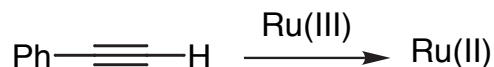
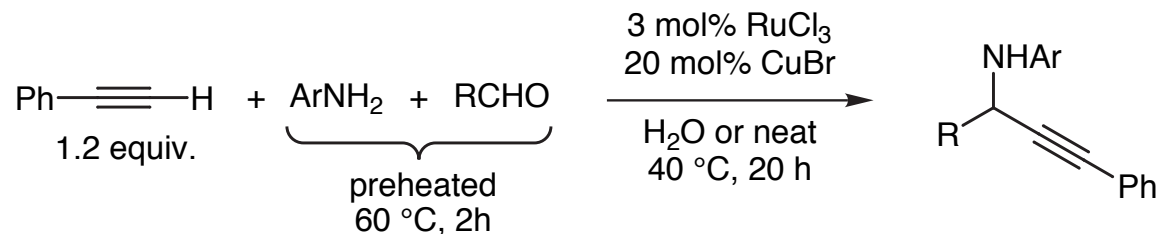
Corey's model  
(also similar to his model  
for  $R_2Zn$  additions with  
amino alcohols)

• Comments that R = Ph on B is catalytic  
because bulk of Ph promotes dissociation  
from the formed alkoxide

Entry	R <sup>1</sup>	R <sup>2</sup>	R (equiv.)	Yield (%)	ee (%)
1	Ph	<i>c</i> -Hex	Bu (1)	96	90
2	<i>n</i> -Pent	<i>c</i> -Hex	Bu (1)	82	95
3	Ph	Ph	Bu (1)	78	96
4	<i>n</i> -Pent	Ph	Bu (1)	28	94
5	Ph	<i>n</i> -Pent	Bu (1)	90	96
6	<i>n</i> -Pent	<i>n</i> -Pent	Bu (1)	80	96
7	Ph	<i>c</i> -Hex	Me (1)	95	90
8	Ph	<i>t</i> -Bu	Bu (1)	71	97
9	Ph	<i>n</i> -Pent	Ph (0.25)	77	93
10	Ph	Ph	Ph (0.25)	72	97
11	Ph	<i>c</i> -Hex	Ph (0.25)	80	85
12	Ph	<i>p</i> -MeO <sub>2</sub> C-Ph	Me (1)	80	96
13	Ph	<i>p</i> -NO <sub>2</sub> -Ph	Ph (1)	86	96

Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151-3152

## Cu/Ru Catalyzed Addition to Imines

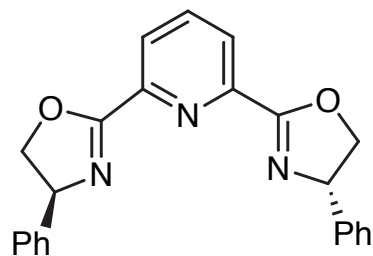


- CuX salts mediate reaction alone (30% yield with CuBr)
- RuCl<sub>3</sub> allowed for complete conversion
- RuCl<sub>3</sub> alone gives no product
- Enolizable aldehydes give self-aldol

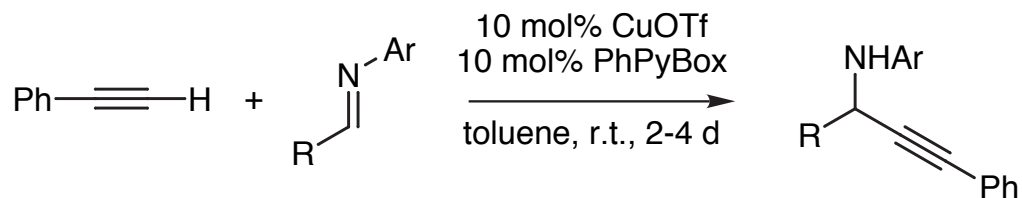
Entry	R	Ar	Yield (%)
1	Ph	Ph	91
2	<i>p</i> -Cl-Ph	Ph	90
3	<i>m</i> -Cl-Ph	Ph	89
4	<i>p</i> -Br-Ph	Ph	95
5	<i>m</i> -Br-Ph	Ph	93
6	<i>p</i> -Me-Ph	Ph	87
7	<i>p</i> -tBu-Ph	Ph	86
8	<i>p</i> -CF <sub>3</sub> -Ph	Ph	87
9	<i>t</i> -Bu	Ph	64
10	<i>p</i> -Ph-Ph	Ph	85*
11	1-naphthyl	Ph	96*
12	Ph	<i>p</i> -Cl-Ph	82*
13	Ph	<i>p</i> -Br-Ph	88*
14	Ph	<i>p</i> -Me-Ph	77*

\* Conducted neat

Li, C. -J.; Wei, C. *Chem. Commun.* **2002**, 268-269



## Cu Catalyzed Asymmetric Addition to Imines

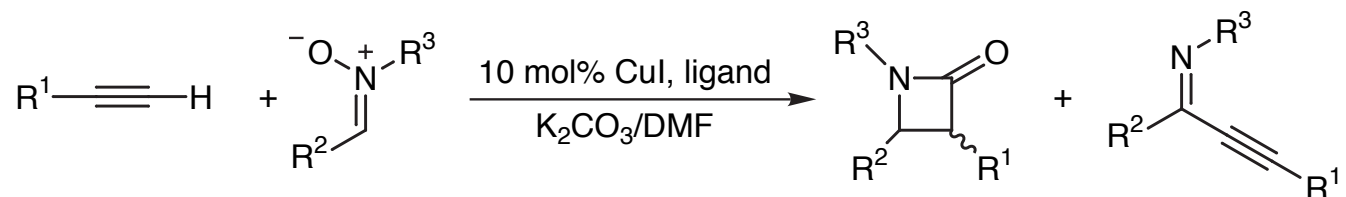


Entry	R	Ar	Yield (%)	ee (%)
1	Ph	Ph	78	96
2	<i>p</i> -Me-Ph	Ph	85	92
3	<i>p</i> -Et-Ph	Ph	70	96
4	<i>p</i> -Cl-Ph	Ph	85	94
5	<i>p</i> -Br-Ph	Ph	87	94
6	<i>p</i> -Ph-Ph	Ph	81	94
7	2-naphthyl	Ph	63	88
8	<i>p</i> -CF <sub>3</sub> -Ph	Ph	71	93
9	Ph	<i>p</i> -Br-Ph	93	91
10	Ph	<i>p</i> -Cl-Ph	92	91
11	Ph	<i>p</i> -Me-Ph	93	94

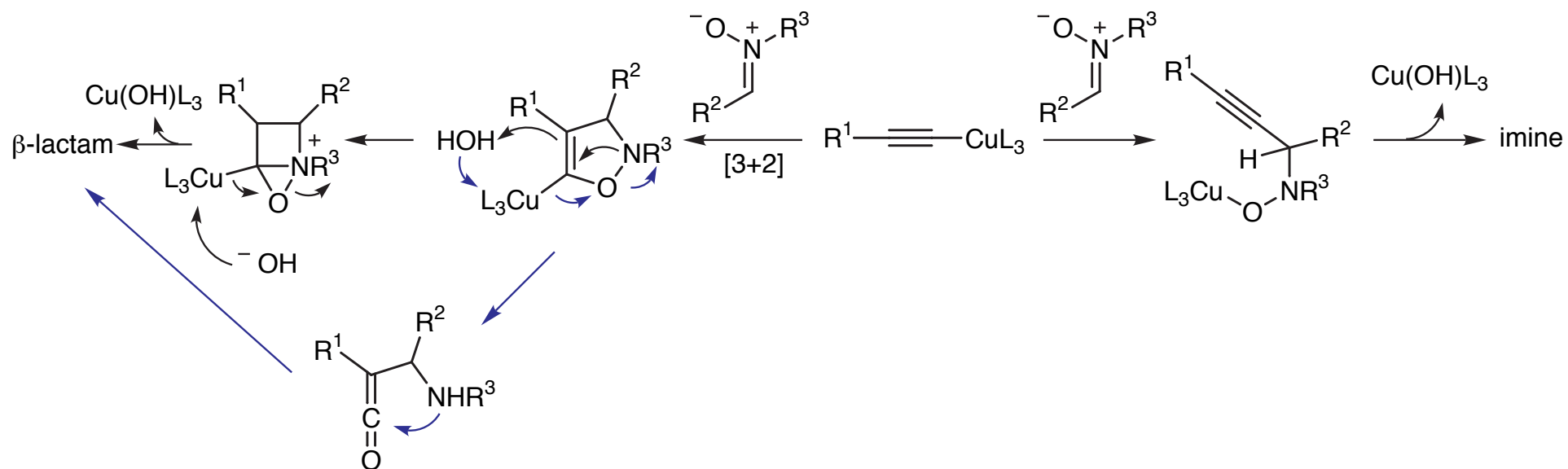
- CuBr gave low ee and CuSbF<sub>6</sub> (in H<sub>2</sub>O) gave good ee, but low yield
- Other Box and PyBox gave low ee
- All reactions conducted in H<sub>2</sub>O gave slightly lower ee and yield

Wei, C.; Li, A. -J. *J. Am. Chem. Soc.* **2002**, *124*, 5638-5639

## Catalytic Cu Acetylide Additions to Nitrones



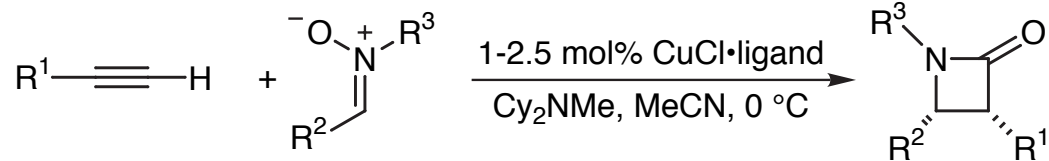
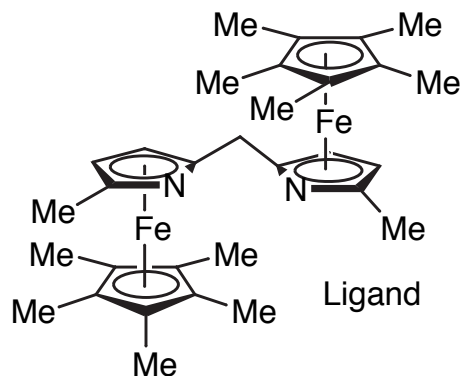
- most ligands (PPh<sub>3</sub>, dppe, dppp, dppb, bpy, phen, pyr, etc...) give a mixture of products
- Box ligands give β-lactam with low d.r. and 40% ee



Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999-5004

Original Reaction: Kinugasa, M.; Hashimoto, S. *J. Chem Commun.* **1972**, 466-467

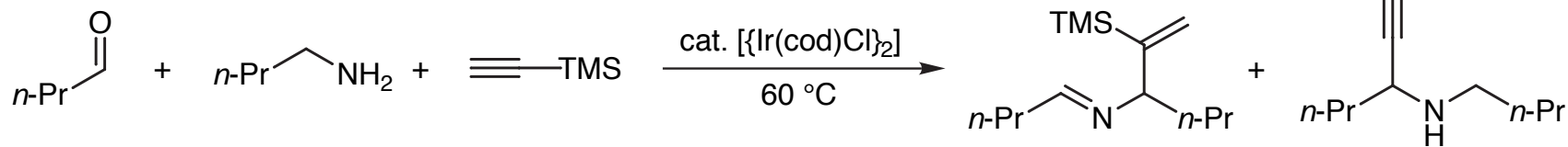
## Catalytic, Asymmetric Cu Acetylide Additions to Nitrones



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	cis:trans	ee (%)	Yield (%)
1	Ph	<i>c</i> -Hex	PMP	>95:5	92	65
2	<i>p</i> -CF <sub>3</sub> -Ph	<i>c</i> -Hex	PMP	>95:5	93	57
3	<i>p</i> -MeO-Ph	<i>c</i> -Hex	PMP	92:8	91	60
4	Bn	<i>c</i> -Hex	PMP	71:29	73	43
5	Ph	PhCO	Ph	90:10	90	56
6	1-cyclohexenyl	PhCO	Ph	90:10	91	45
7	Ph	Ph	PMP	95:5	85	53
8	Ph	<i>p</i> -CF <sub>3</sub> -Ph	PMP	93:7	90	50
9	Ph	<i>p</i> -MeO-Ph	PMP	93:7	83	46
10	Ph	<i>c</i> -Hex	PMP	93:7	89	57
11	Ph	PhCO	PMP	91:9	72	42
12	Ph	Ph	Ph	95:5	77	69
13	Ph	Ph	PMP	95:5	85	53
14	Ph	Ph	<i>p</i> -Br-Ph	94:6	72	74
15	Ph	Ph	<i>p</i> -EtO <sub>2</sub> C-Ph	94:6	67	79

Lo, M. M. -C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572-4573

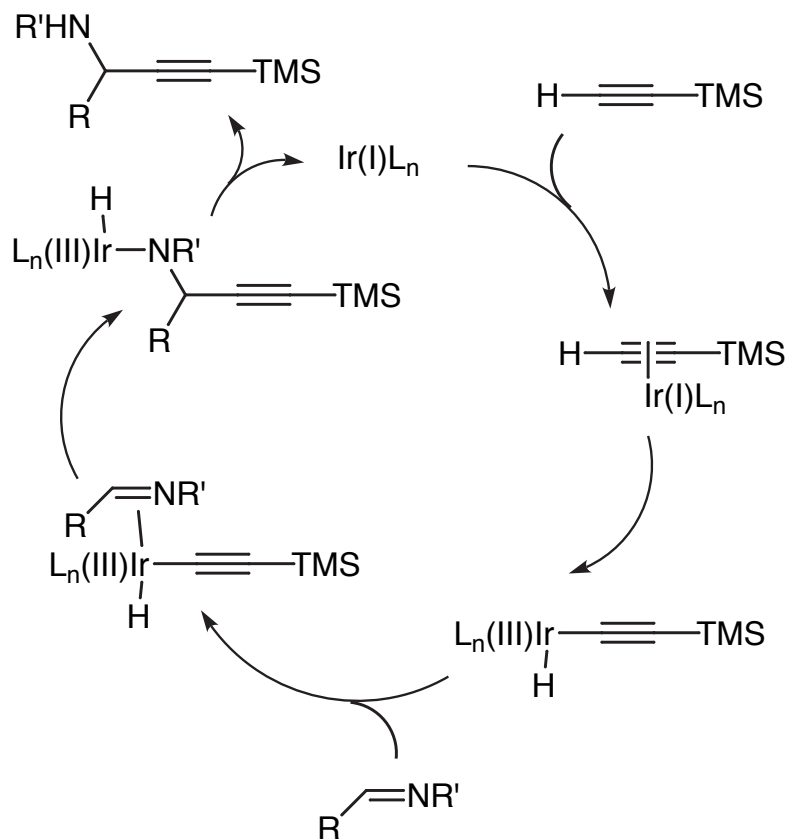
## Ir(I) Catalyzed Acetylene Addition



- All other acetylenes give desired product

Desired  
(C-H activation  
next to N)

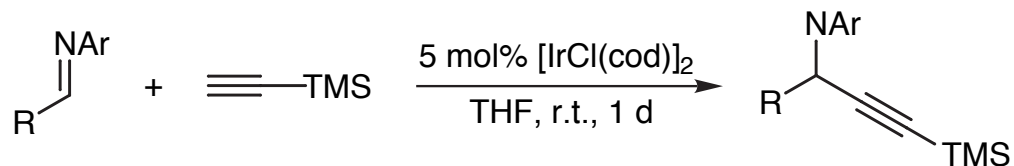
Observed  
(spC-H activation)



Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 2534-2536



## Ir(I) Catalyzed Acetylene Addition



Entry	R	Ar	Yield (%)
1	Ph	Bn	76
2	<i>t</i> -Bu	Bn	84
3	<i>n</i> -Pr	Bn	69
4	<i>i</i> -Pr	Bn	65
5	<i>p</i> -Br-Ph	Bn	54
6	Ph	<i>p</i> -MeO-Ph	85

- Reactions conducted neat gave better yields
- Only effective for silyl acetylenes
- Only (*t*-Bu)<sub>3</sub>P leads to rate acceleration
- Employing 2 mol% MgI<sub>2</sub> allows Ir(I) loading to drop to 0.5 mol% (unpub.)

Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319-4321

## Conclusions

- Metal acetylide additions to carbonyls give versatile and useful synthetic building blocks.
- There are a few examples of stoichiometric, enantioselective additions, the most useful being Zn acetylide additions with a chiral amino alcohol catalyst.
- Carreira's system is catalytic in both metal and chiral ligand and works well for aliphatic aldehydes.
- Cu(I) and Ir(I) offer a more efficient means (C-H activation) of generating transient metal acetylides and show some promising results.