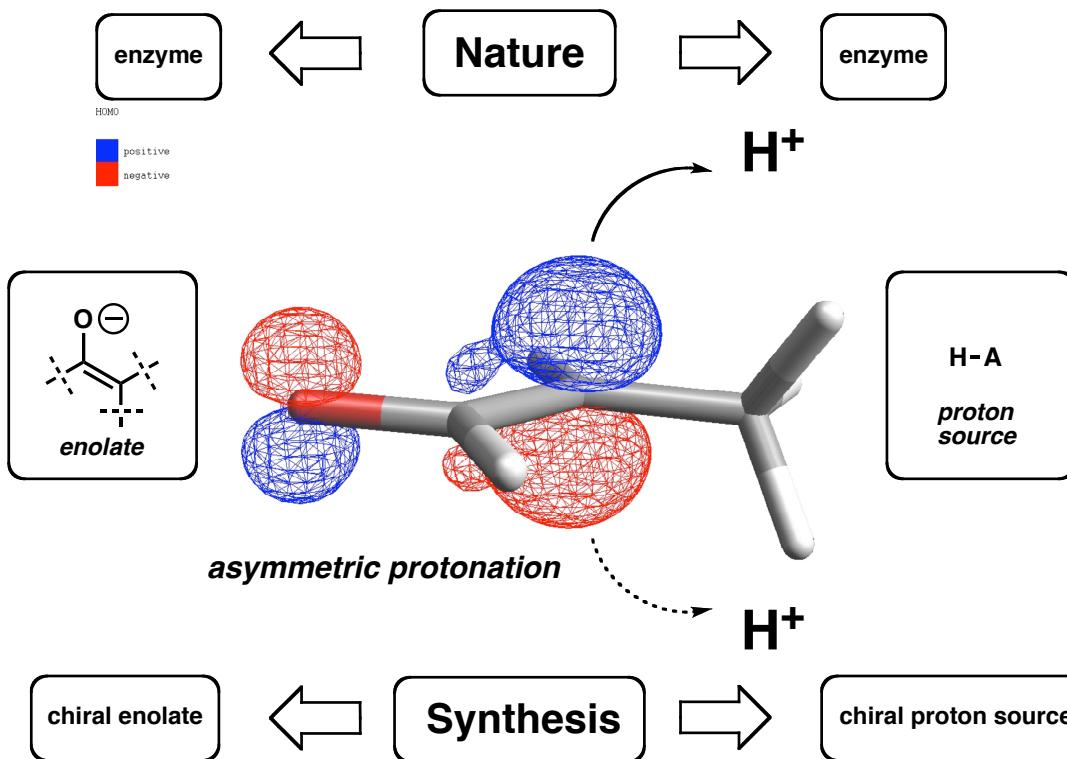
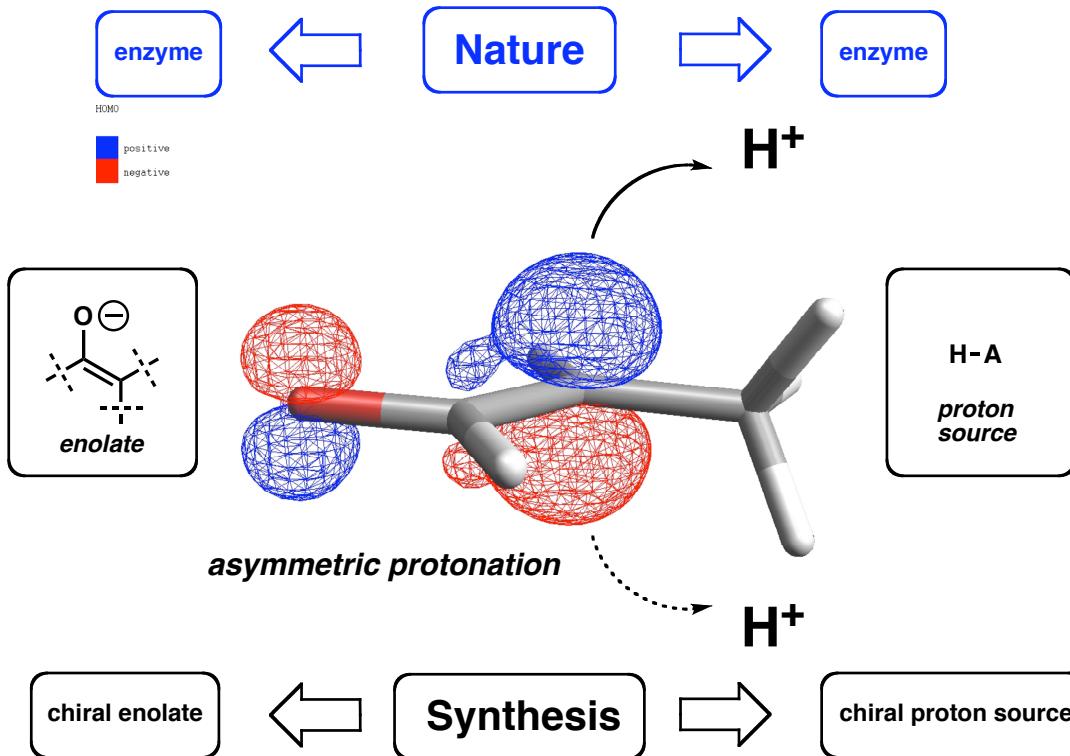


## Approaches to Protonation in Nature and Synthesis

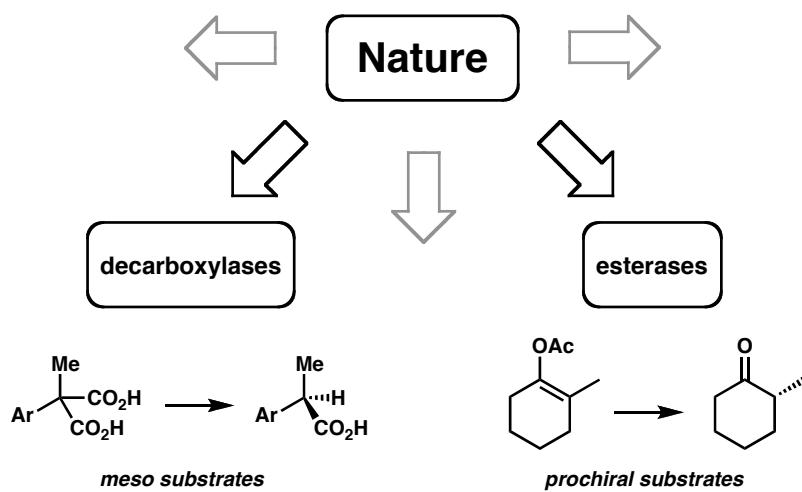


# Approaches to Protonation in Nature and Synthesis



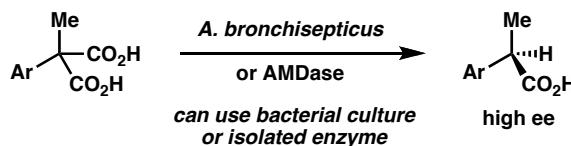
## Bioenzymatic Protonation

Nature has evolved classes of enzymes that can catalyze asymmetric protonation



# Bioenzymatic Protonation by Decarboxylases

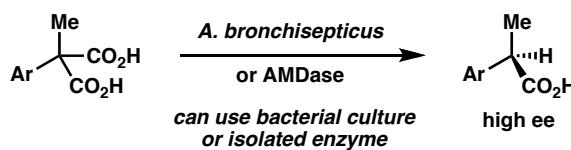
AMDase (arylmalonate decarboxylase) isolated from *Alcaligenes bronchisepticus*



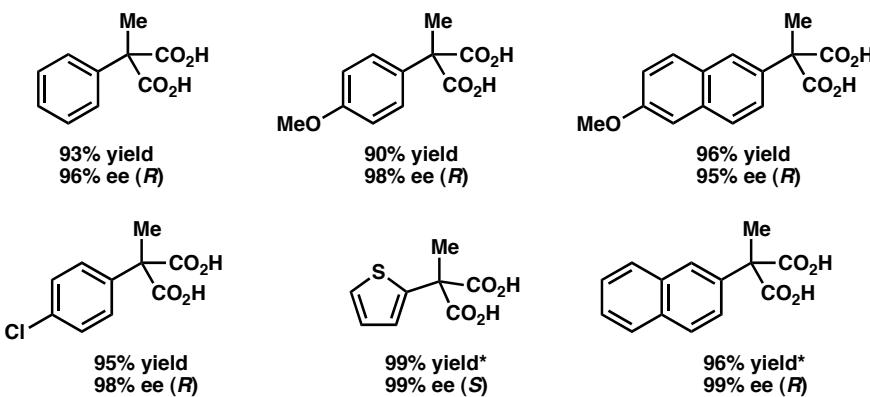
Ohta, J. Am. Chem. Soc. 1990, 112, 4077-4078.  
Ohta, J. Mol. Catal. B: Enzym. 2004, 27, 161-168.

# Bioenzymatic Protonation by Decarboxylases

AMDase (arylmalonate decarboxylase) isolated from *Alcaligenes bronchisepticus*



## Substrates

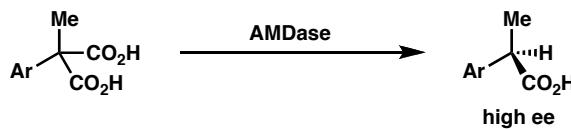


\* performed with isolated enzyme

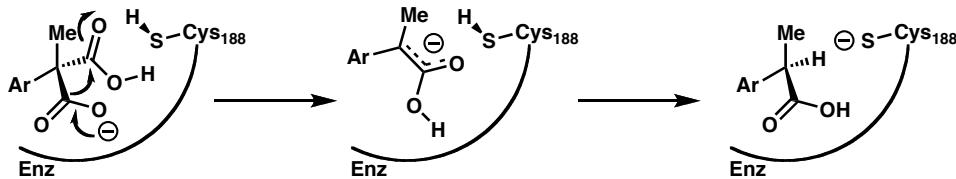
Ohta, J. Am. Chem. Soc. 1990, 112, 4077-4078.  
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# Bioenzymatic Protonation by Decarboxylases

AMDase (arylmalonate decarboxylase)



Proposed Mechanism



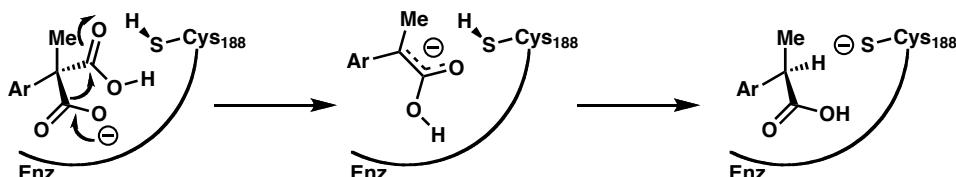
Ohta, J. Mol. Catal. B: Enzym. 2004, 27, 161-168.

# Bioenzymatic Protonation by Decarboxylases

AMDase (arylmalonate decarboxylase)



Proposed Mechanism



Cys188 residue is necessary for activity and serves as a proton donor

Pro-(R) carboxyl group is lost as carbon dioxide and remaining carboxyl group undergoes inversion

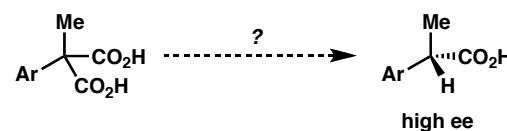
Ohta, J. Mol. Catal. B: Enzym. 2004, 27, 161-168.

# Bioenzymatic Protonation by Decarboxylases

AMDase (arylmalonate decarboxylase)



Opposite enantiomeric series?



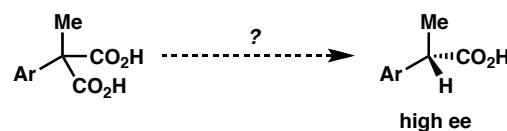
Ohta, *J. Mol. Catal. B: Enzym.* **2007**, 45, 15-20.  
Ohta, *Chem. Commun.* **2005**, 877-879.

# Bioenzymatic Protonation by Decarboxylases

AMDase (arylmalonate decarboxylase)



Opposite enantiomeric series?



AMDase was found to be homologous to well-studied racemases!

Glu racemase	... V V A C N T A ... I M G C T H F ...	Cys188 is essential for AMDase
Asp racemase	... V L T C N T A ... I L G C T E L ...	
Maleate isomerase	... A Y A C L V A ... L S A C V Q M ...	Racemases contain additional Cys74
AMDase	... S L M G T S L ... L L S C G G L ...	

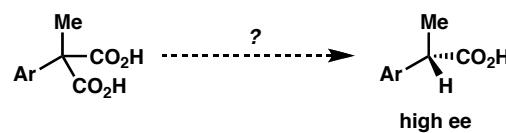
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Maleate isomerase	... A Y A C C L V A ... L S A C V Q M ...
AMDase	... S L M [G] T S L ... L L S C G G L ...

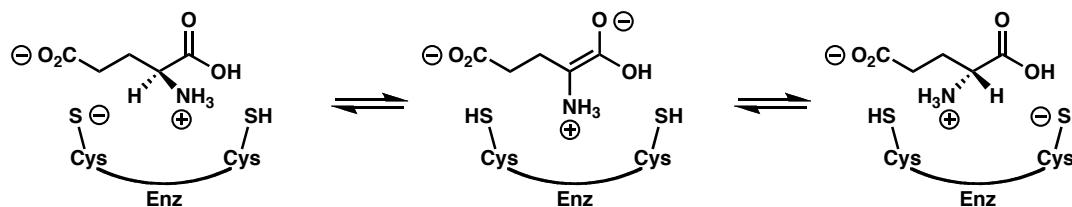
74

188

Cys188 is essential for AMDase

Racemases contain additional Cys74

"Two-base" mechanism of glutamate racemase



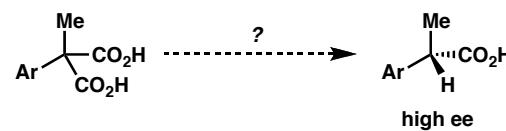
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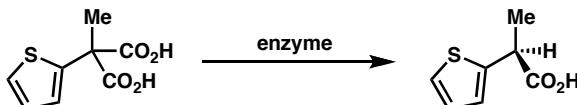
AMDase (arylmalonate decarboxylase)



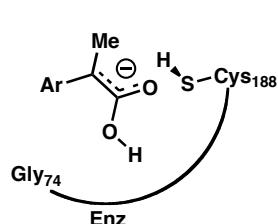
Opposite enantiomeric series?



Site-directed mutagenesis on AMDase and resulting enantioselectivity



enzyme	reaction time (h)	yield (%)	ee (%)
WT	1	99	99, S



enzyme active site

and transition state

normal selectivity

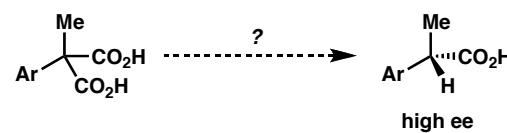
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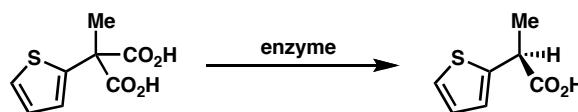
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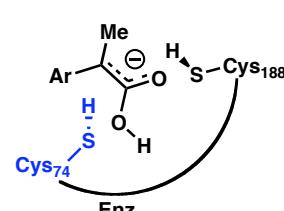
Opposite enantiomeric series?



Site-directed mutagenesis on AMDase and resulting enantioselectivity



enzyme	reaction time (h)	yield (%)	ee (%)
WT	1	99	99, S
G74C	3	37	0



enzyme active site  
and transition state  
  
no selectivity  
racemase mimic

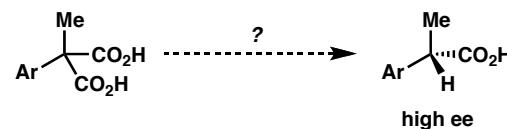
Ohta, *J. Mol. Catal. B: Enzym.* **2007**, 45, 15-20.  
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# Bioenzymatic Protonation by Decarboxylases

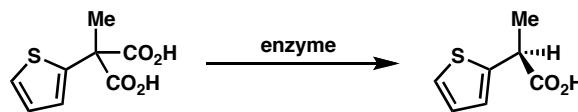
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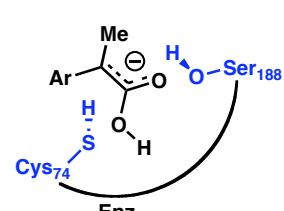
Opposite enantiomeric series?



Site-directed mutagenesis on AMDase and resulting enantioselectivity



enzyme	reaction time (h)	yield (%)	ee (%)
WT	1	99	99, S
G74C	3	37	0
G74C/C188S	72	60	96, R

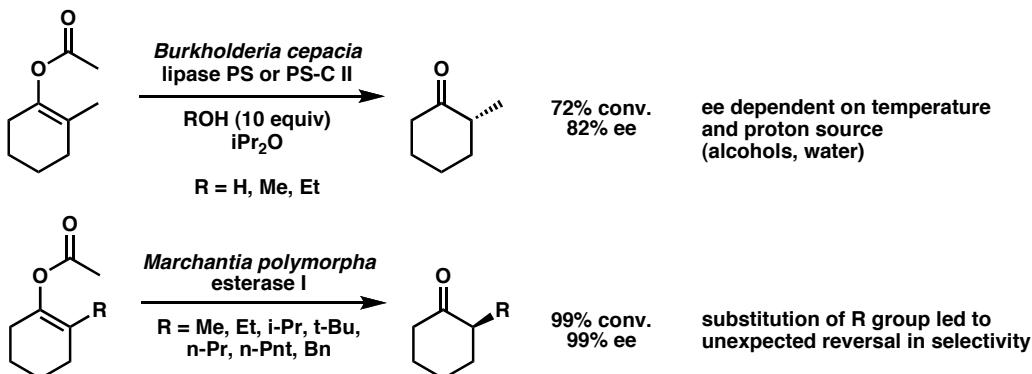


enzyme active site  
and transition state  
  
reversed selectivity

Ohta, *J. Mol. Catal. B: Enzym.* **2007**, 45, 15-20.  
Ohta, *Chem. Commun.* **2005**, 877-879.

# Bioenzymatic Protonation by Esterases

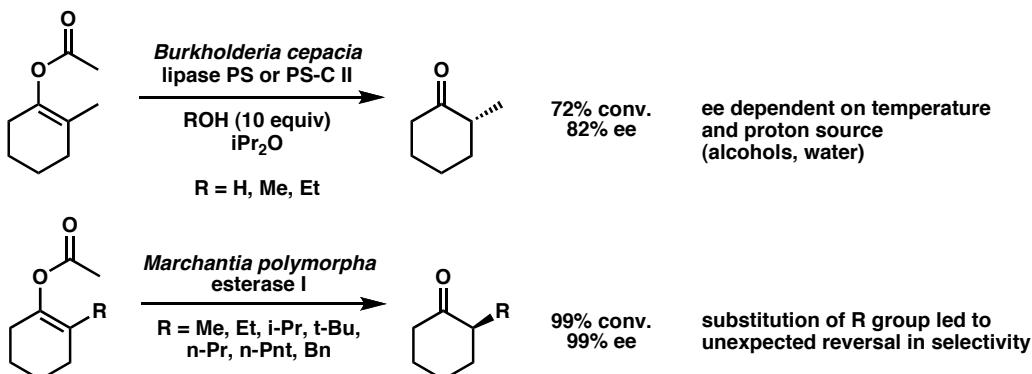
Isolated esterases used for asymmetric protonation



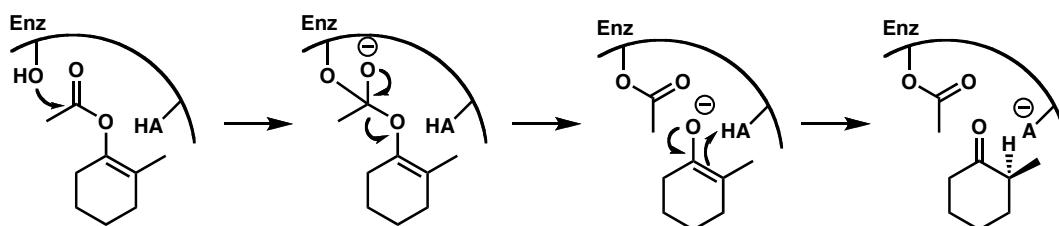
Sakai, *Tetrahedron: Asymmetry* 2004, 15, 11929-1932.  
Hirata, *Tetrahedron: Asymmetry* 2000, 11, 1063-1066.

# Bioenzymatic Protonation by Esterases

Isolated esterases used for asymmetric protonation



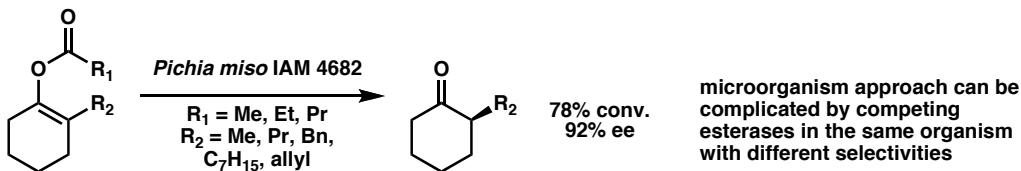
One possible mechanism



Sakai, *Tetrahedron: Asymmetry* 2004, 15, 11929-1932.  
Hirata, *Tetrahedron: Asymmetry* 2000, 11, 1063-1066.

## Bioenzymatic Protonation by Esterases

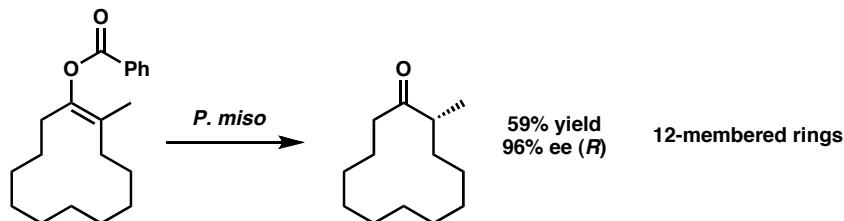
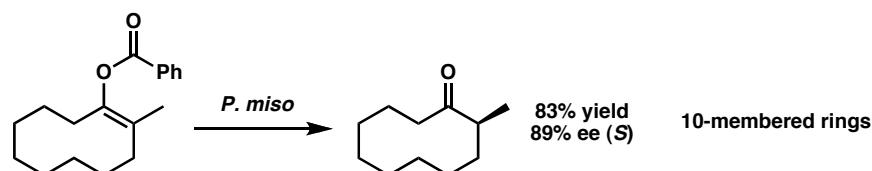
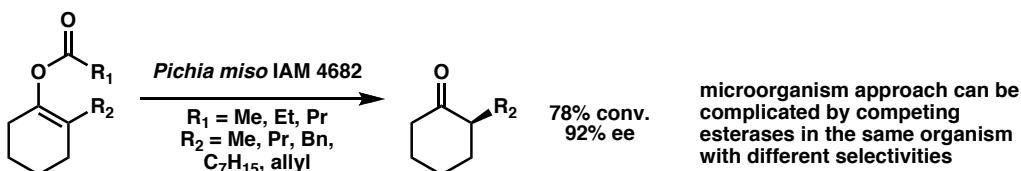
Cell cultures used for asymmetric protonation



Ohta, *J. Am. Chem. Soc.* 1990, 112, 9614-9619.

## Bioenzymatic Protonation by Esterases

Cell cultures used for asymmetric protonation

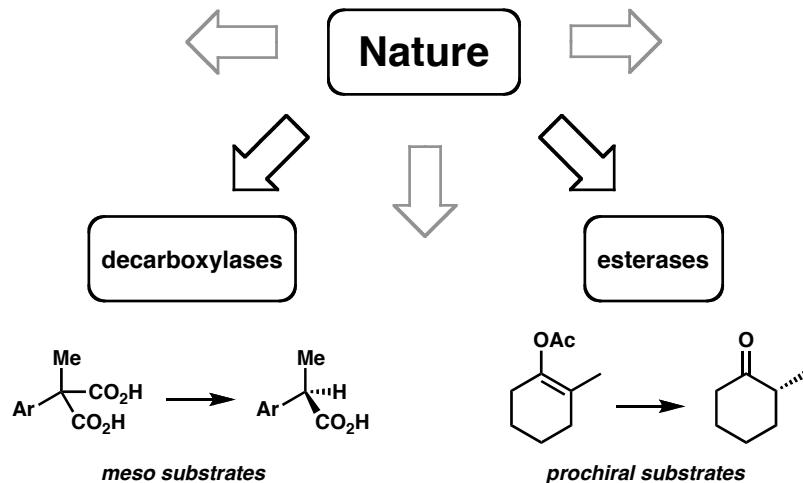


15-membered ring substrates give poor ee's

Ohta, *J. Am. Chem. Soc.* 1990, 112, 9614-9619.

# Bioenzymatic Protonation

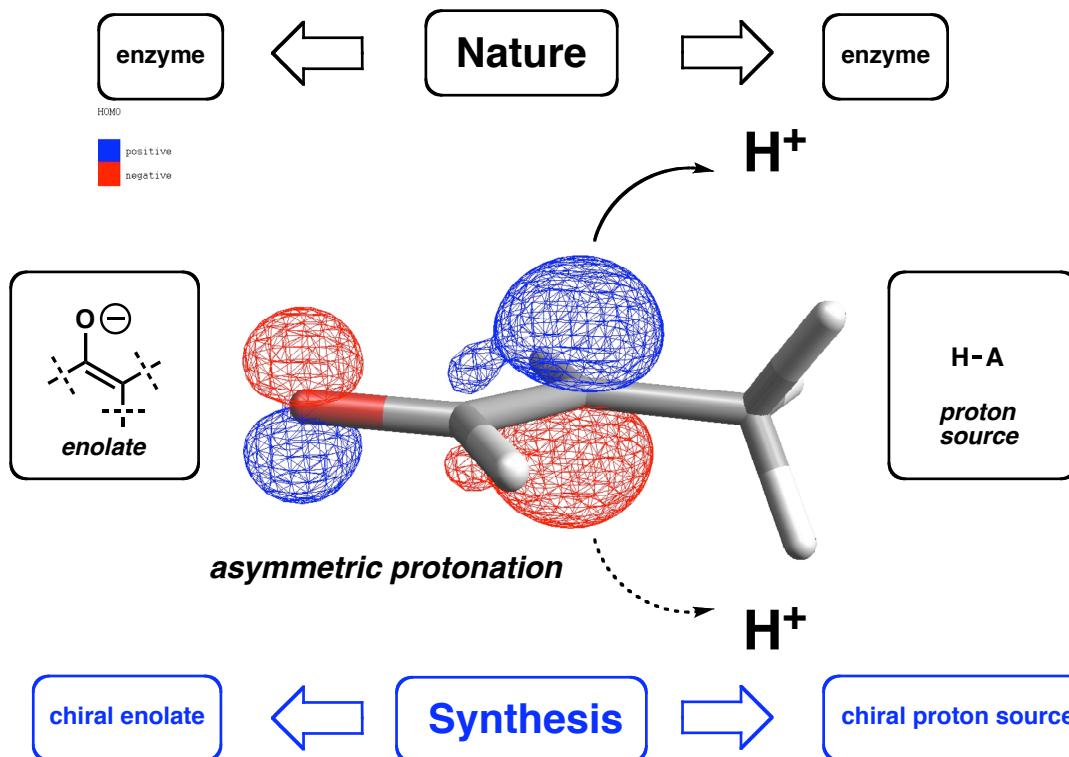
Nature has evolved classes of enzymes that can catalyze asymmetric protonation



enzymes can be efficient and selective, but...

- optimization can be challenging
  - enzymes provide only one enantiomeric series
  - substrate specificity may limit reaction scope
  - reaction medium requirements may require water or buffer solutions
- *how can we create a chiral environment for catalytic asymmetric protonation?*

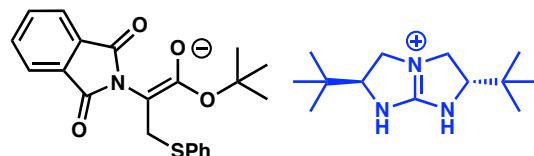
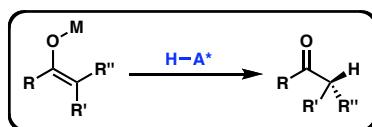
## Approaches to Protonation in Nature and Synthesis



## Asymmetric Protonation Approaches

### Achiral Enolate and Chiral Proton Source

—chiral information resides on proton source  
—enolate has no chiral information

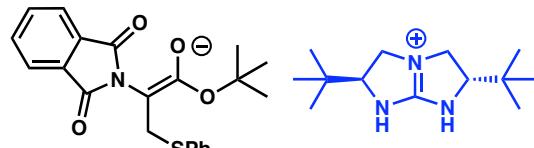
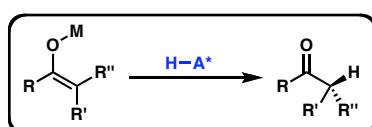


Tan, *Angew. Chem. Int. Ed.* 2008, 47, 5641-5645.

## Asymmetric Protonation Approaches

### Achiral Enolate and Chiral Proton Source

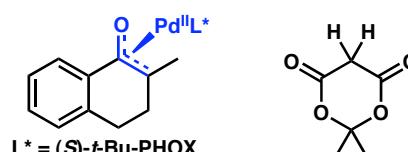
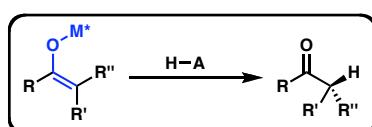
—chiral information resides on proton source  
—enolate has no chiral information



Tan, *Angew. Chem. Int. Ed.* 2008, 47, 5641-5645.

### Chiral Enolate and Achiral Proton Source

—proton source has no chiral information  
—chiral information resides on enolate-bound M\*

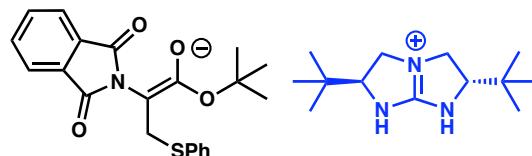
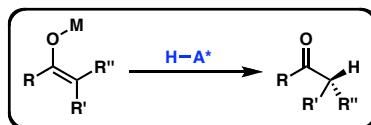


Stoltz, *Org. Lett.* 2008, 10, 1039-1042.

# Asymmetric Protonation Approaches

## Achiral Enolate and Chiral Proton Source

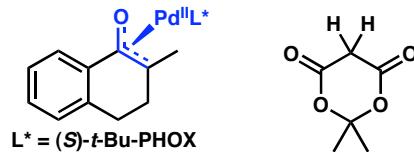
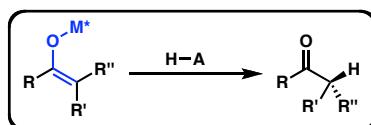
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## Chiral Enolate and Achiral Proton Source

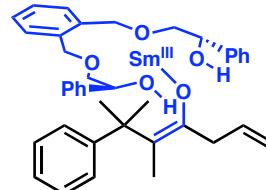
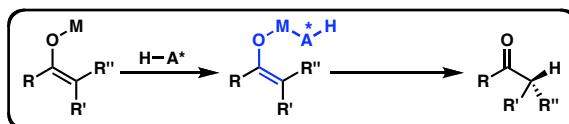
–proton source has no chiral information  
–chiral information resides on enolate-bound M\*



Stoltz, *Org. Lett.* 2008, 10, 1039-1042.

## Chiral Enolate-Proton Source Aggregate

–hybrid case when chiral information resides on proton source, which also serves as a ligand for M

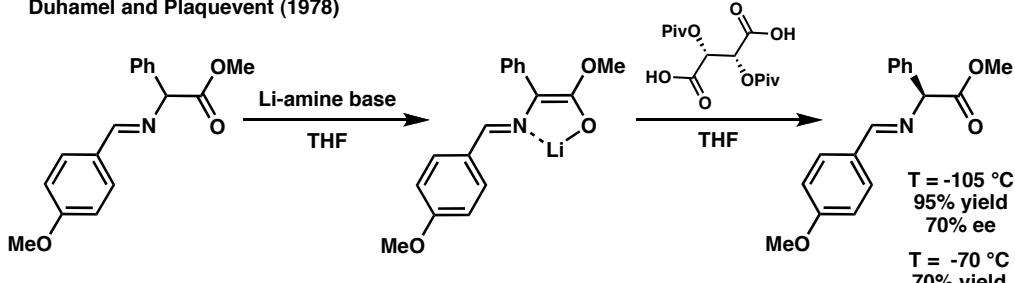


Takeuchi, *Tetrahedron Lett.* 1998, 39, 8691-8694.

# Early Examples of Asymmetric Protonation

## Enantioenrichment of $\alpha$ -amino acids by stoichiometric asymmetric protonation

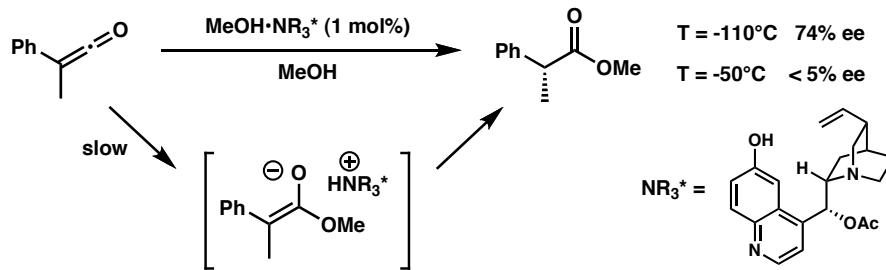
Duhamel and Plaquevent (1978)



Duhamel, Plaquevent, *J. Am. Chem. Soc.* 1978, 100, 7415-7416.

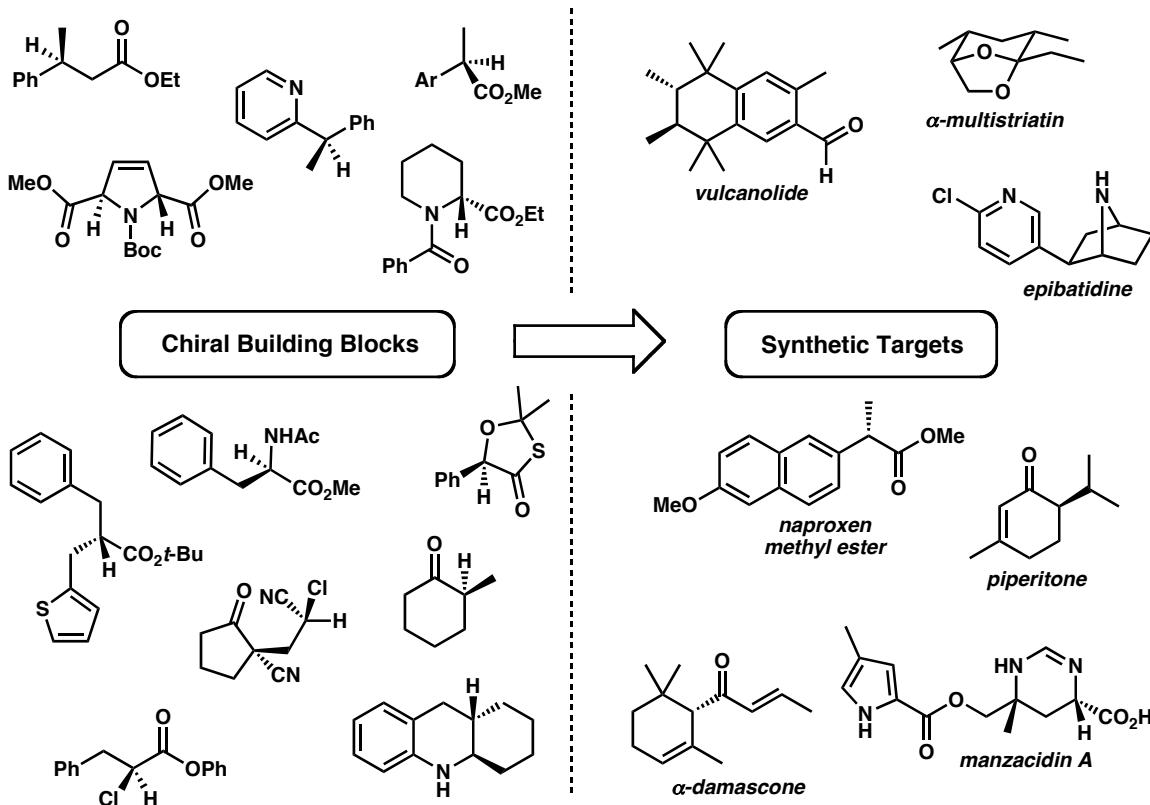
## Ketene addition with catalytic asymmetric protonation

Pracejus (1960)

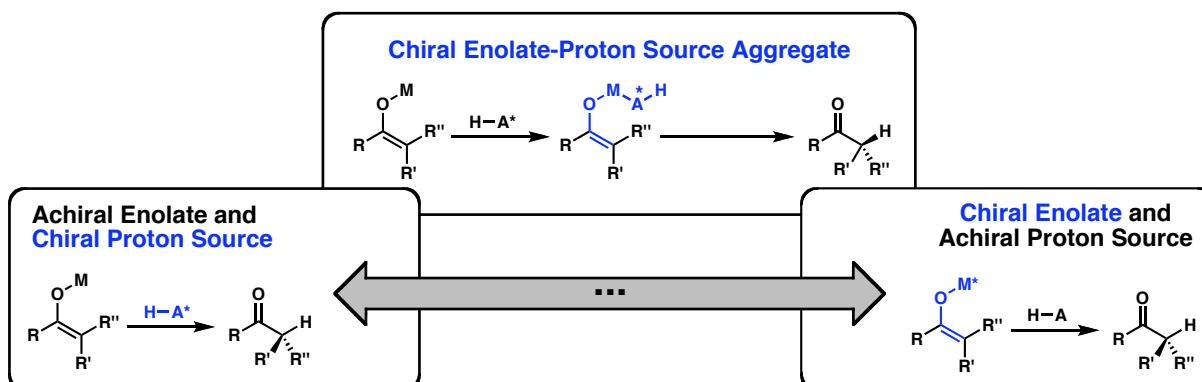


Pracejus, *Liebigs Ann. Chem.* 1960, 634, 9-22.

## Applications of Asymmetric Protonation Chemistry

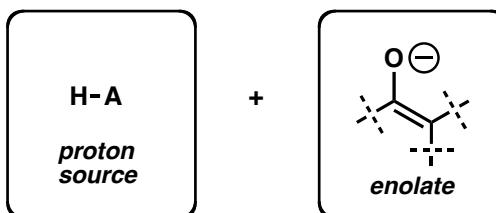


## Approaches to Enantioselective Protonation

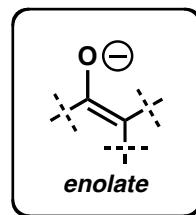


Two theoretical cases are represented by having chirality on either the enolate *or* the proton source

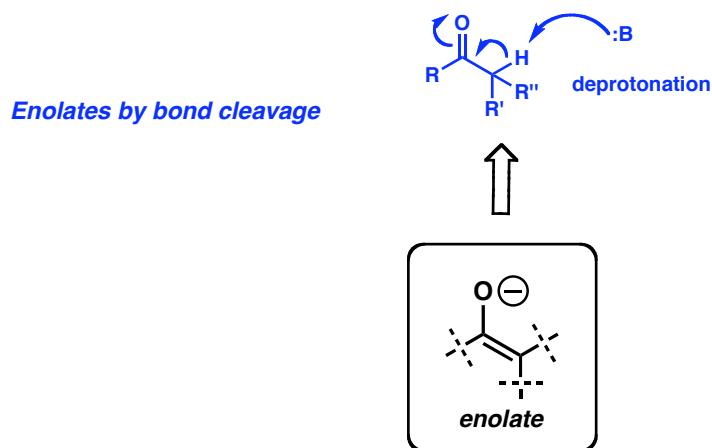
Case of chiral aggregate can be viewed as an intermediate case with qualities of both extremes



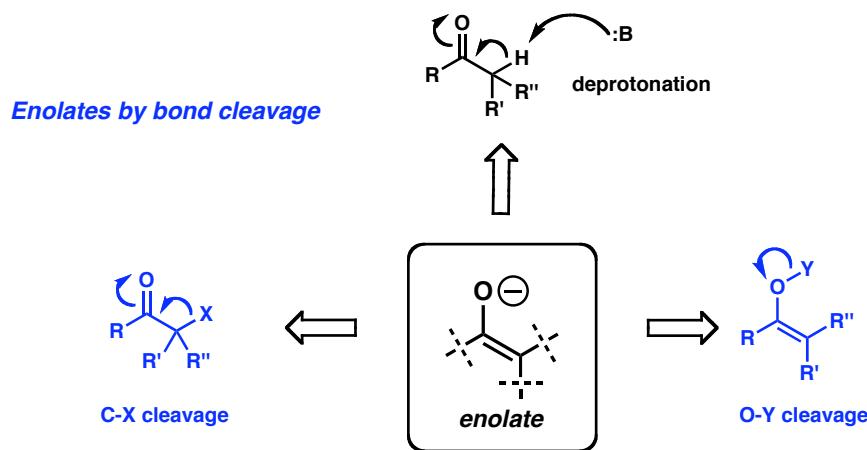
## *Several Methods for Generating Enolates*



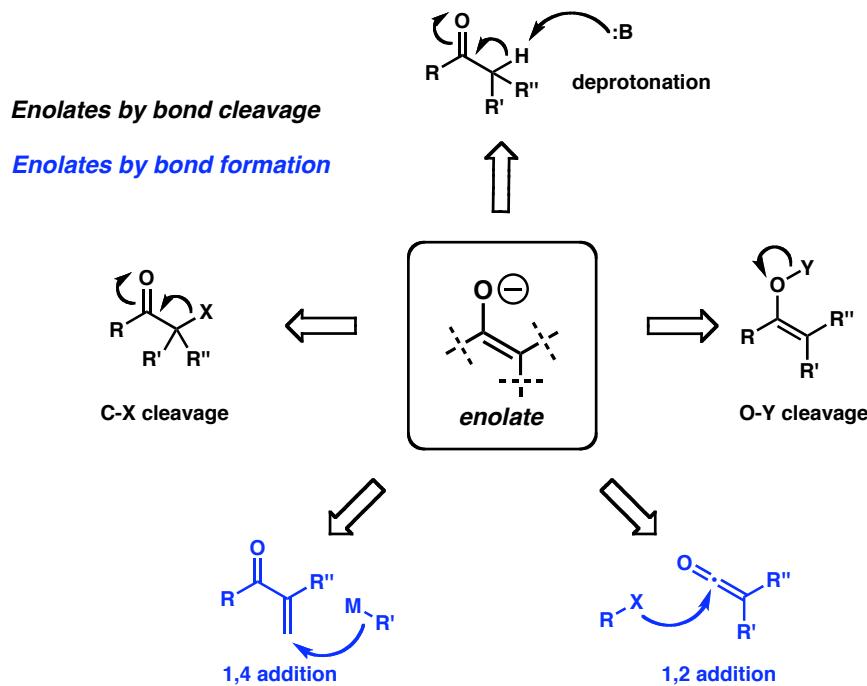
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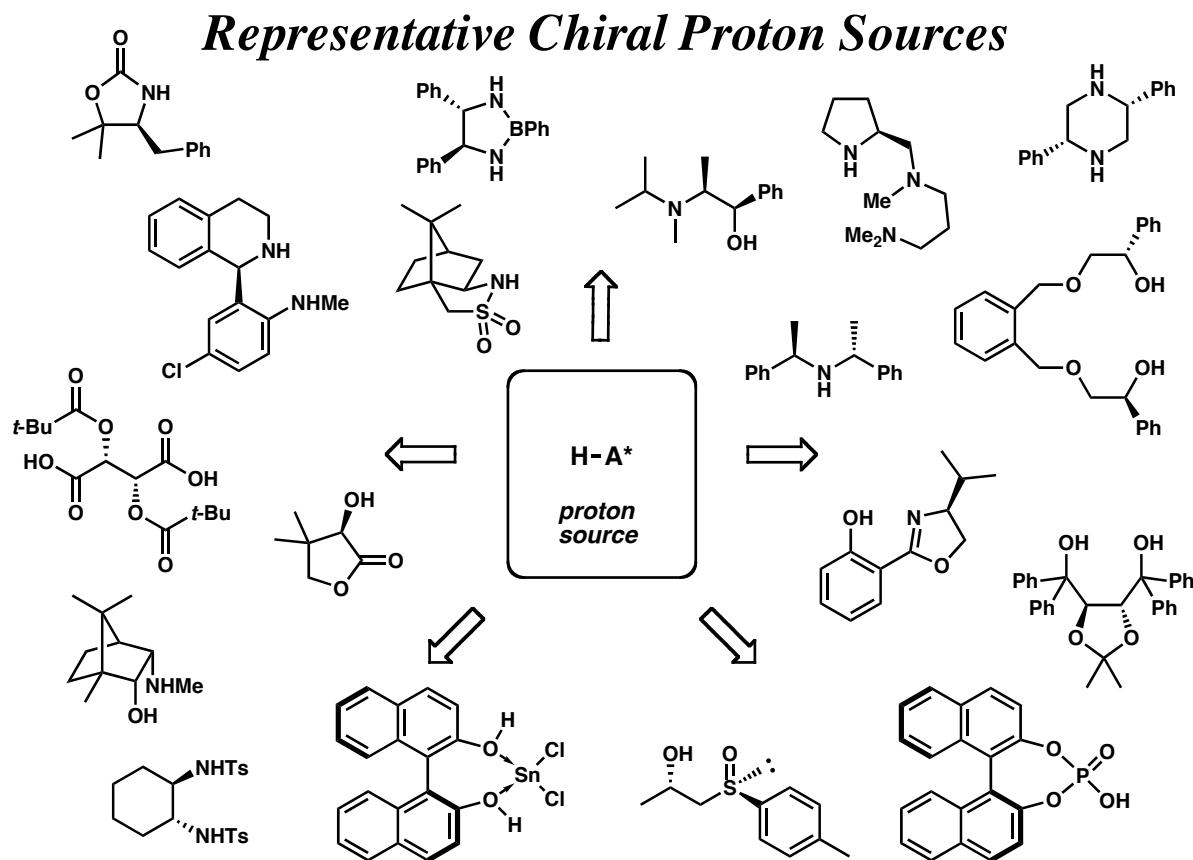
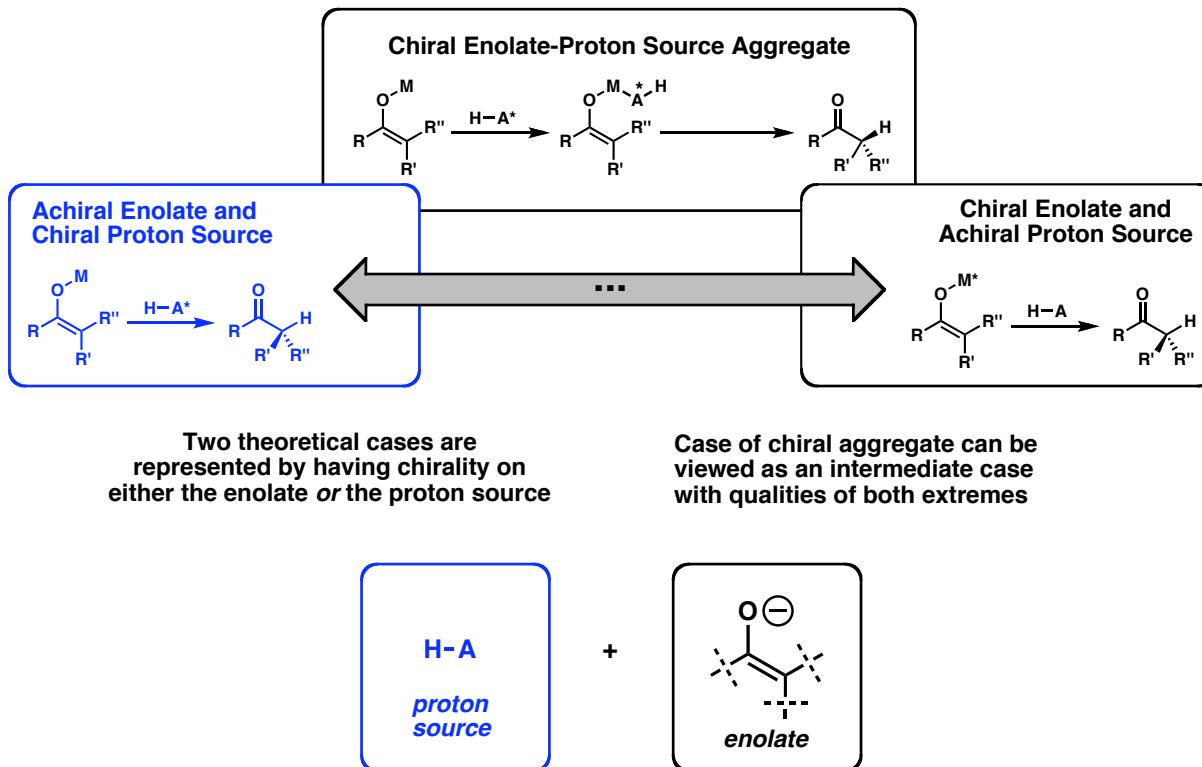
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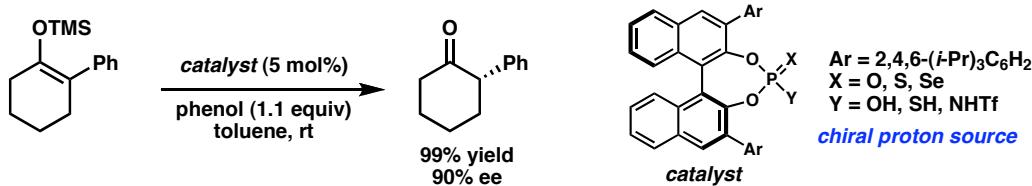


# Approaches to Enantioselective Protonation



## Protonation with Chiral Phosphoric Acid Derivatives

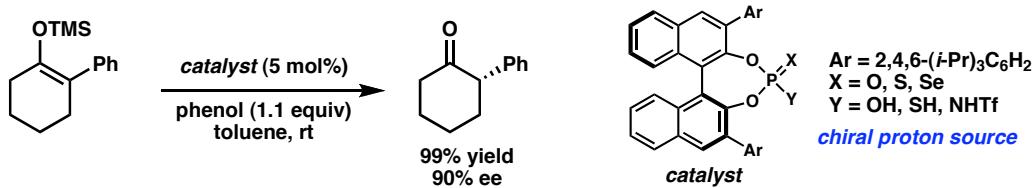
Asymmetric protonation of silyl enol ethers with BINOL derivatives  
(achiral enolate and chiral proton source)



Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246-9247.

## Protonation with Chiral Phosphoric Acid Derivatives

Asymmetric protonation of silyl enol ethers with BINOL derivatives  
(achiral enolate and chiral proton source)



### Experimental observations

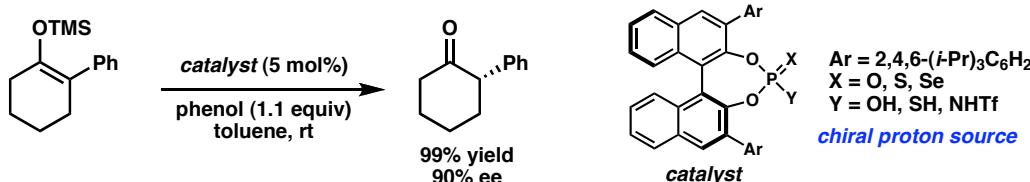
- only strongly acidic *catalysts* showed appreciable conversion
- selectivity sensitive to  $\alpha$ -group and ring size

- even with 1 equiv optimized *catalyst*, absence of achiral proton source led to no reaction, even after 2 d

Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246-9247.

# Protonation with Chiral Phosphoric Acid Derivatives

Asymmetric protonation of silyl enol ethers with BINOL derivatives  
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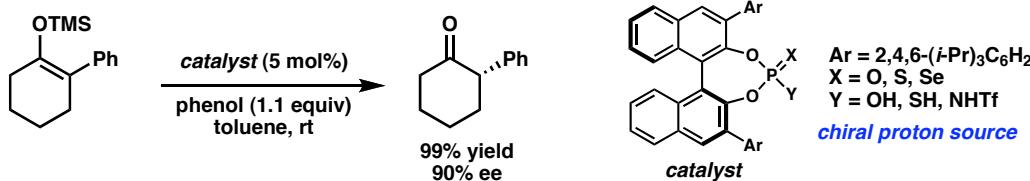
## Proposed Mechanism



Yamamoto, *J. Am. Chem. Soc.* 2008, 130, 9246-9247.

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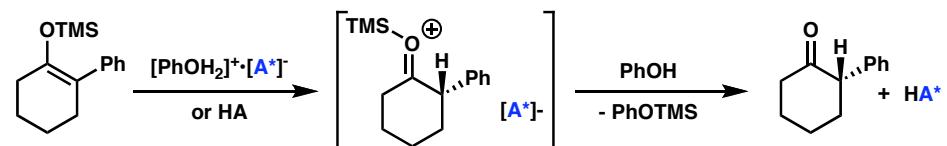
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- only strongly acidic *catalysts* showed appreciable conversion
- even with 1 equiv optimized *catalyst*, absence of achiral proton source led to no reaction, even after 2 d
- selectivity sensitive to  $\alpha$ -group and ring size

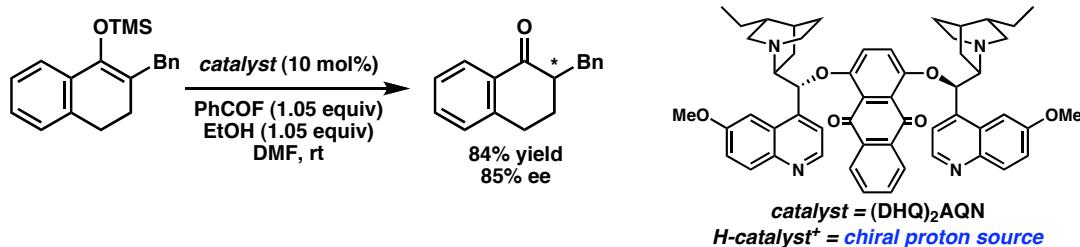
## Proposed Mechanism



Yamamoto, *J. Am. Chem. Soc.* 2008, 130, 9246-9247.

## Protonation with Cinchona Alkaloid Salts

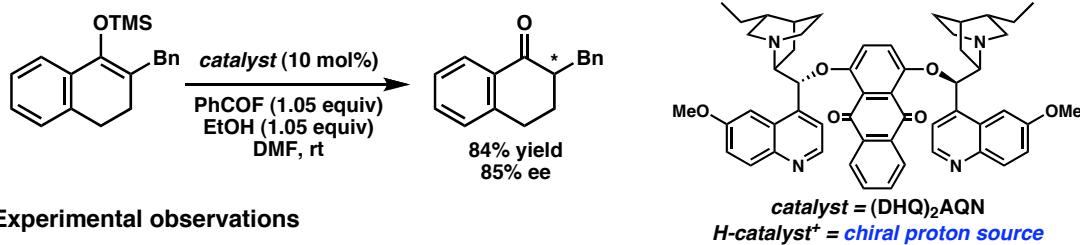
Asymmetric protonation of silyl enol ethers with cinchoninium fluoride  
(achiral enolate and chiral proton source)



Levacher, *Angew. Chem. Int. Ed.* **2007**, 146, 7090-7093.

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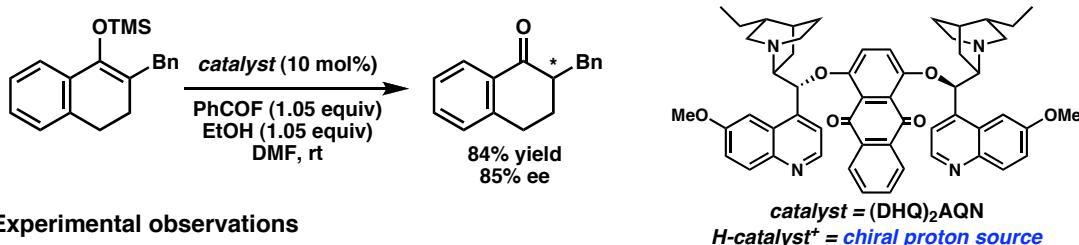
### Experimental observations

- no reaction when cinchona catalyst was absent (no HF formed)
- D labeling shows 95% D incorporation from EtOD
- better selectivities in polar solvents
- using benzoic anhydride instead of benzoyl fluoride lowered ee

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# Protonation with Cinchona Alkaloid Salts

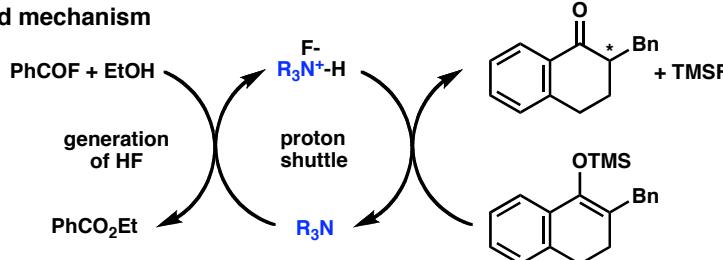
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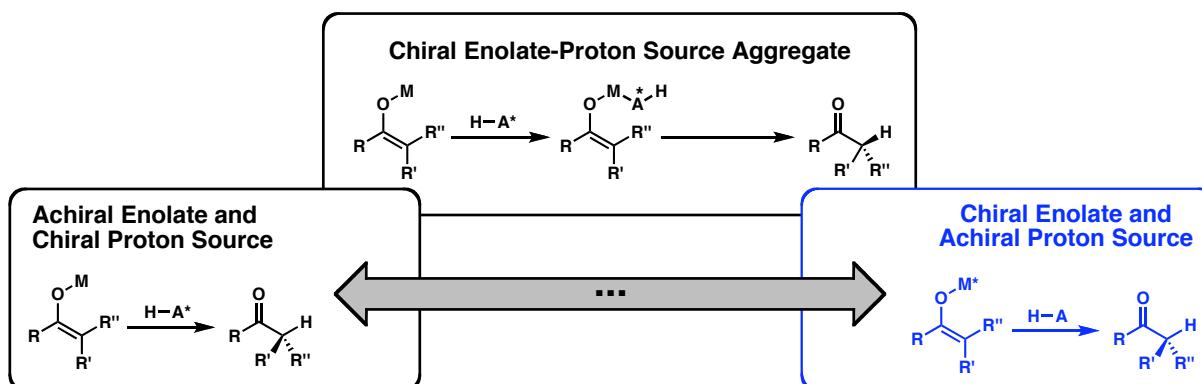
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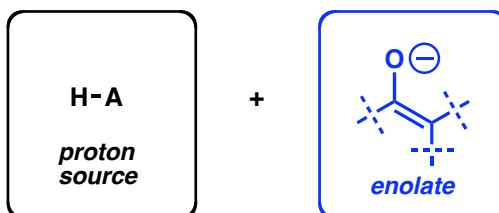
Levacher, *Angew. Chem. Int. Ed.* 2007, 146, 7090-7093.

# Approaches to Enantioselective Protonation



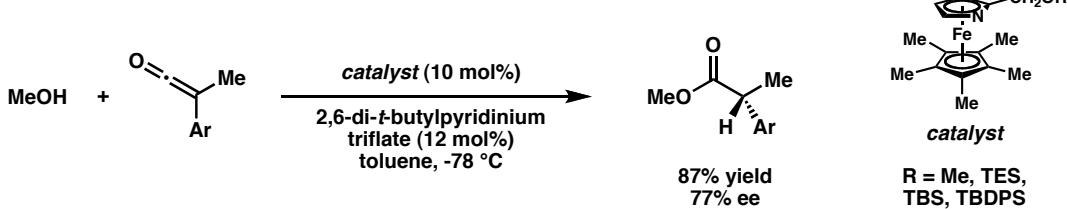
Two theoretical cases are represented by having chirality on either the enolate or the proton source

Case of chiral aggregate can be viewed as an intermediate case with qualities of both extremes



# Azaferrocene-Catalyzed Ketene Additions

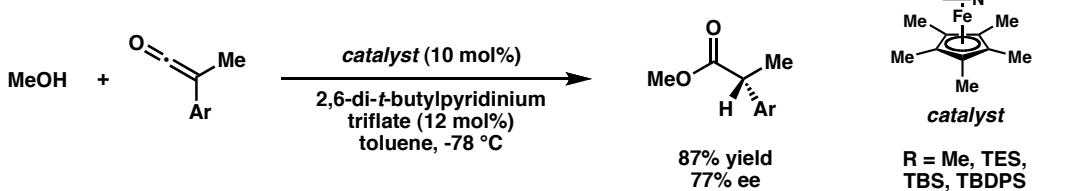
Addition of Alcohols to Ketenes  
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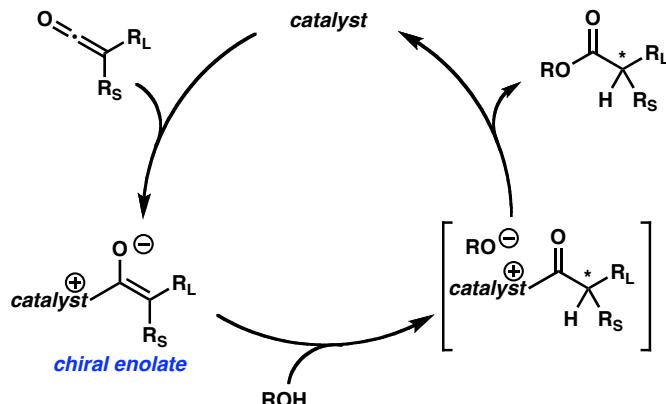
Fu, J. Am. Chem. Soc. 1999, 121, 2637-2638.

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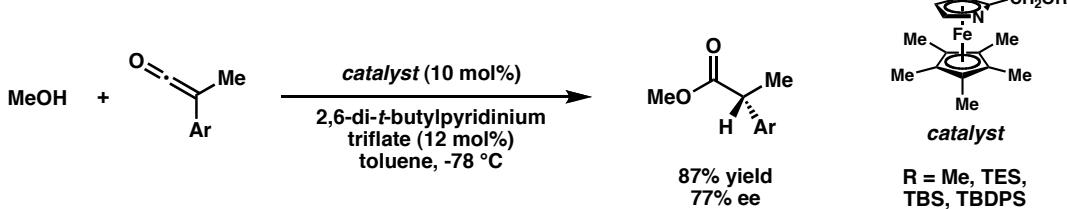
Proposed mechanism



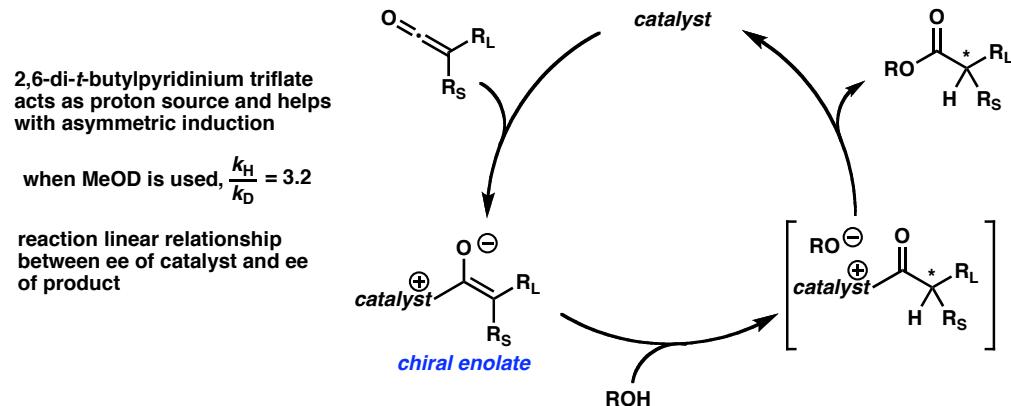
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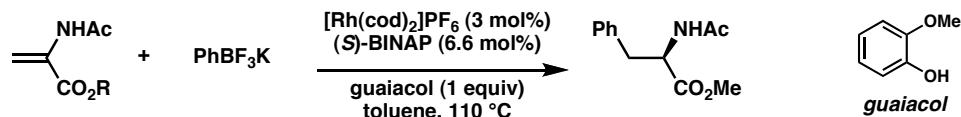
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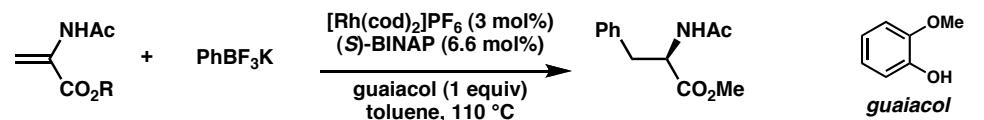
# Rh-Catalyzed Conjugate Addition-Protonation

Coupling of dehydroalanines and potassium (trifluoro)organoborates  
(achiral proton source and chiral enolate)

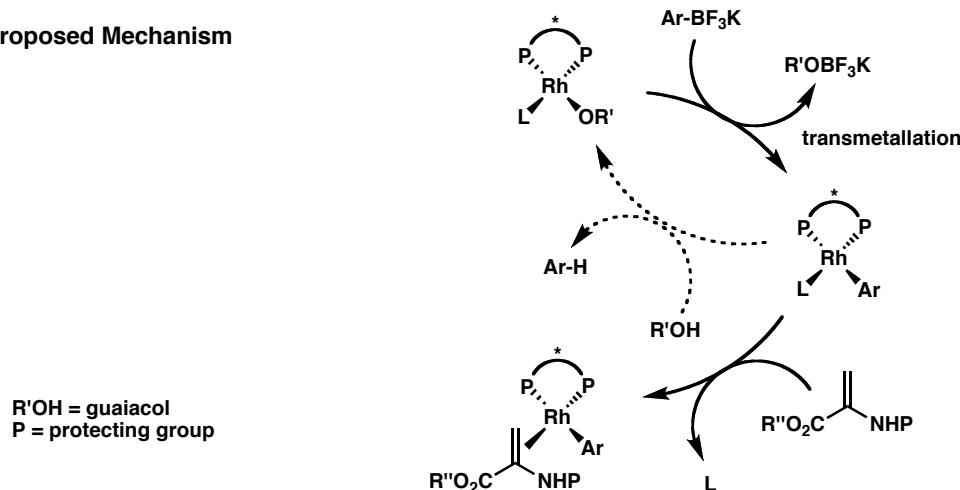


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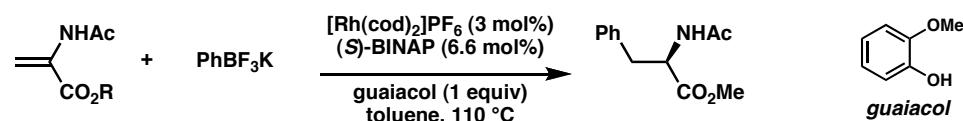
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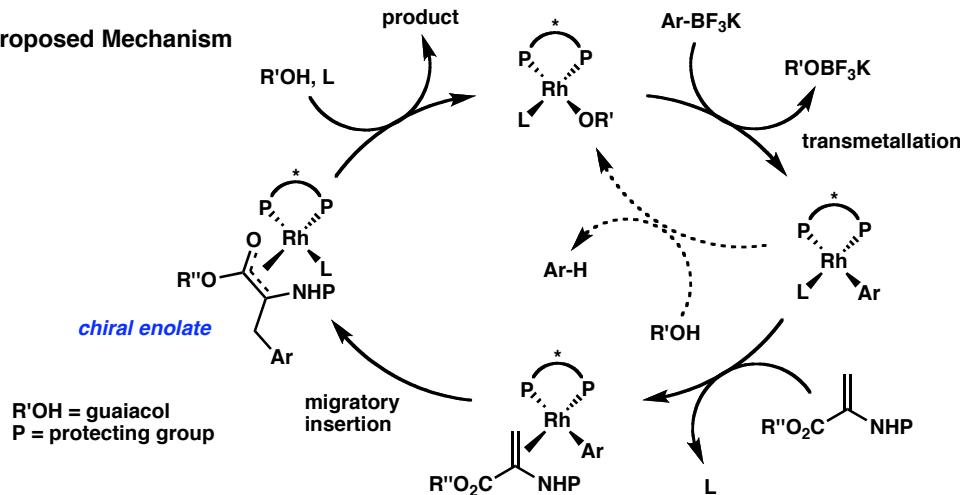
Genet, Darses, *Angew. Chem. Int. Ed.* **2004**, *43*, 719-723.  
Genet, Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159-6159.

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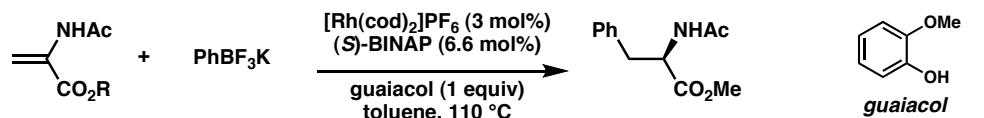
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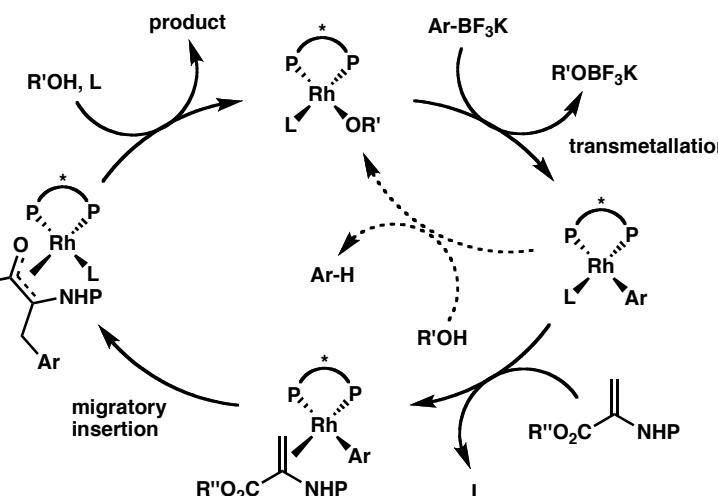


## Proposed Mechanism

catalyst has complete control over product stereochemistry

when (*S*)-BINOL, (*R*)-BINOL, or *rac*-BINOL is used as proton source, same ee is observed

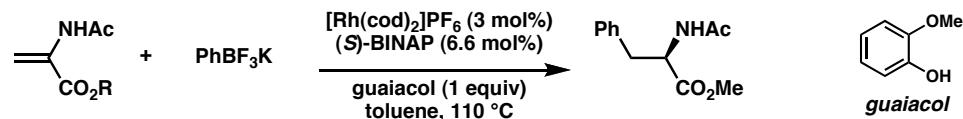
*chiral enolate*  
 $\text{R}'\text{OH}, \text{L}$



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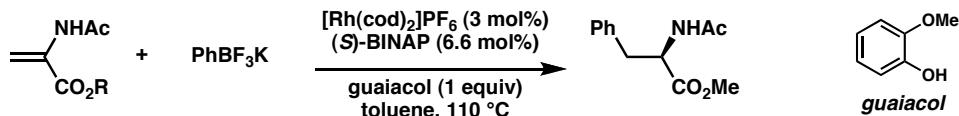


organosilanes or other organoborane derivatives give low conversion or ee  
organostannanes can be used with this method

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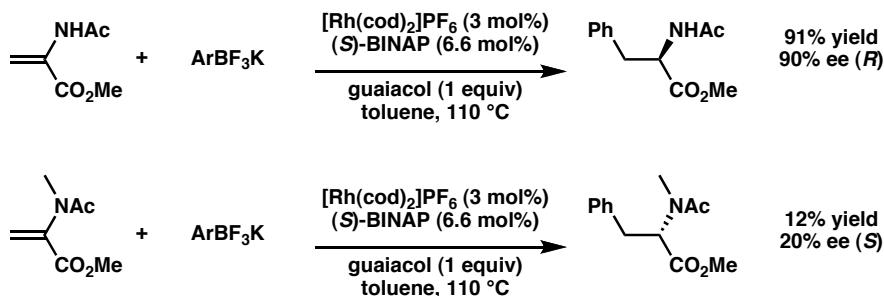
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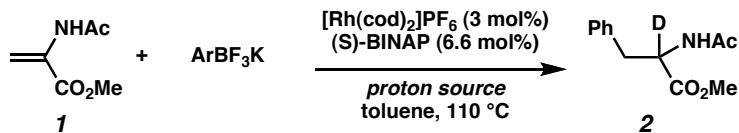
**Surprising Result... Is N-H is important for reactivity and selectivity?**



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Genet, Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159-6159.

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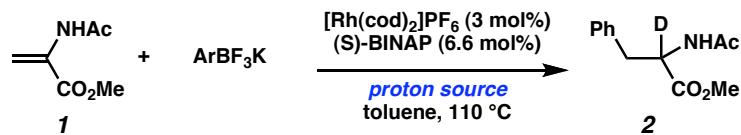
Deuterium labeling experiments



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# Rh-Catalyzed Conjugate Addition-Protonation

## Deuterium labeling experiments



substrate	proton source	overall yield (%)	D incorporation (%)	ee (%)
1	D <sub>2</sub> O	96	100	10
1	guaiacol-d <sub>1</sub>	86	28	90
1-d <sub>1</sub>	guaiacol	93	41	90

D<sub>2</sub>O gives rapid and quantitative protonation

D incorporation with deuterated proton source is low

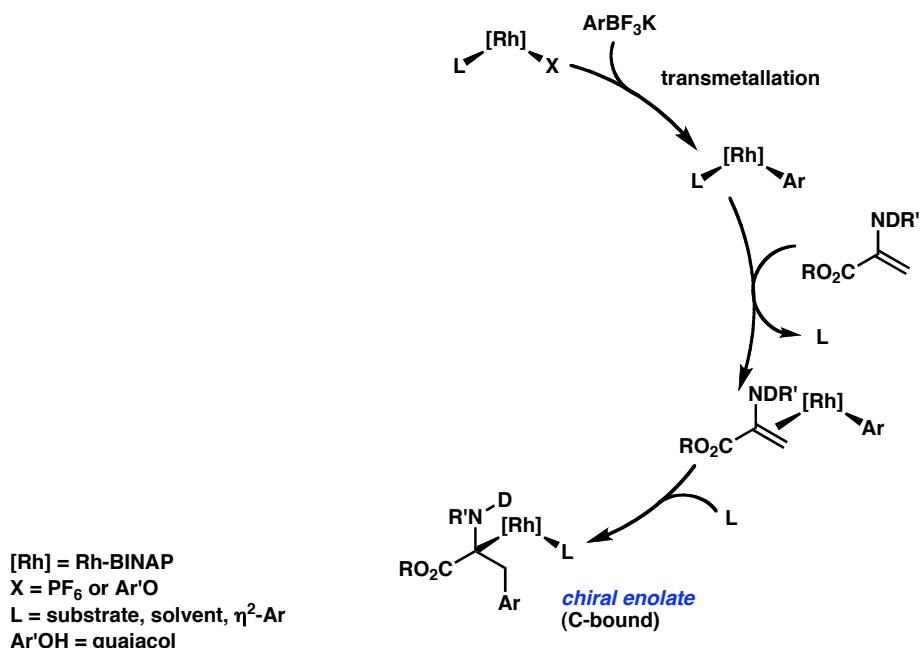
D incorporation with deuterated substrate suggests that amide proton is involved in mechanism

→ Perhaps Rh-catalyzed isomerization can explain these results and poor reaction with N-H to N-Me substitution

Genet, Darses, *Angew. Chem. Int. Ed.* **2004**, *43*, 719-723.  
Genet, Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159-6159.

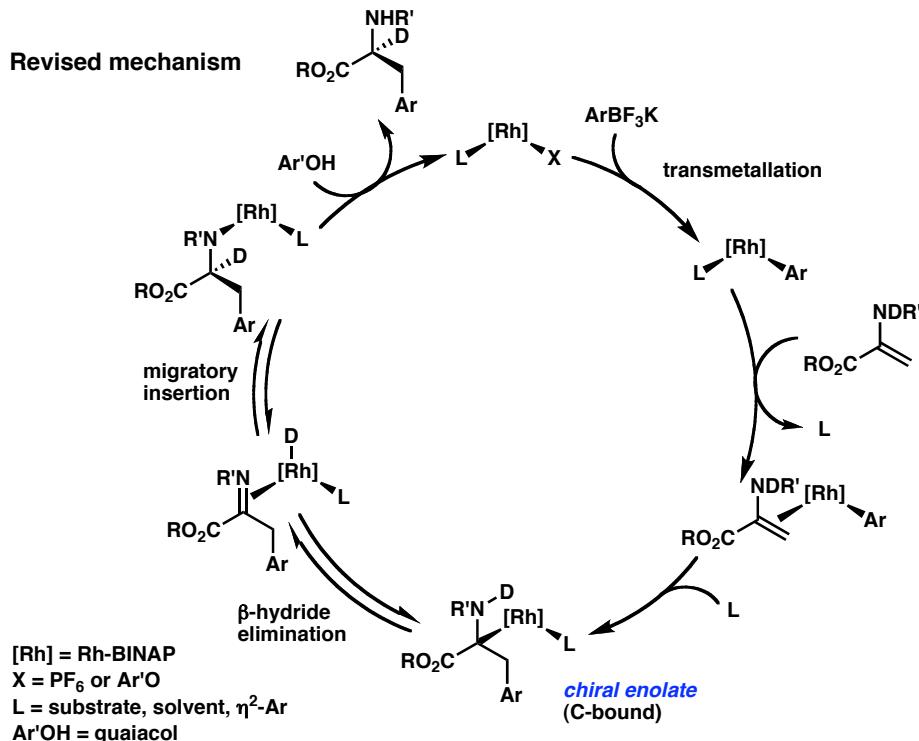
# Rh-Catalyzed Conjugate Addition-Protonation

## Revised mechanism



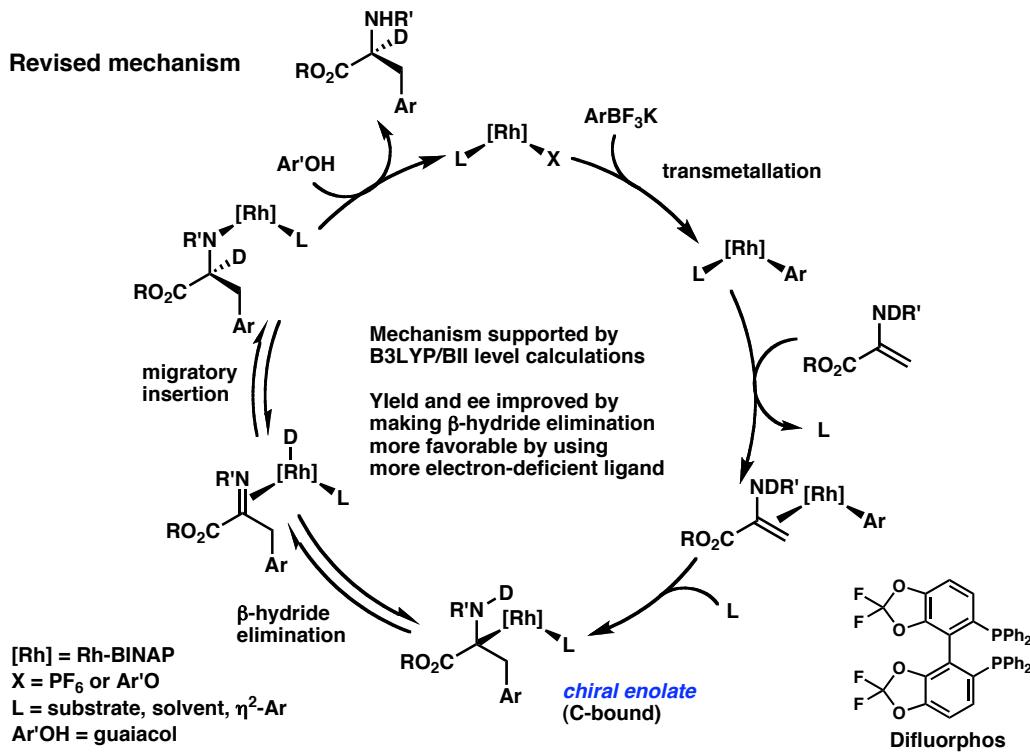
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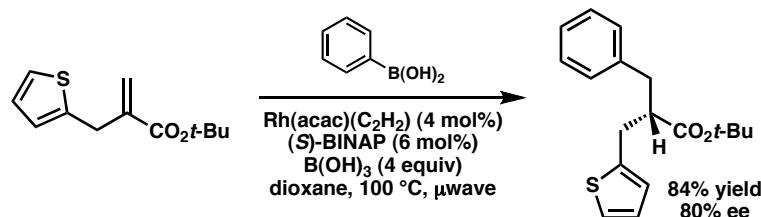
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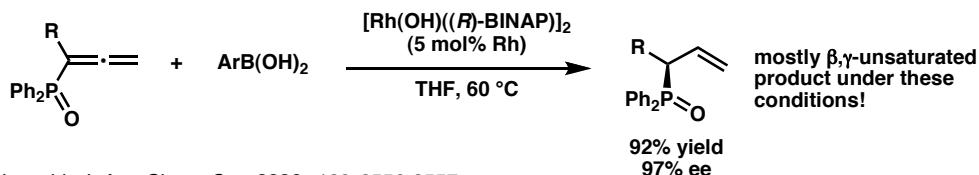
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## Rh-Catalyzed Conjugate Addition-Protonation

### Related Rh conjugate addition-protonations



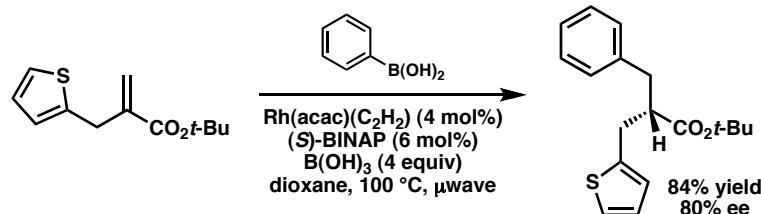
Frost, *Org. Lett.* 2007, 9, 2119–2122.



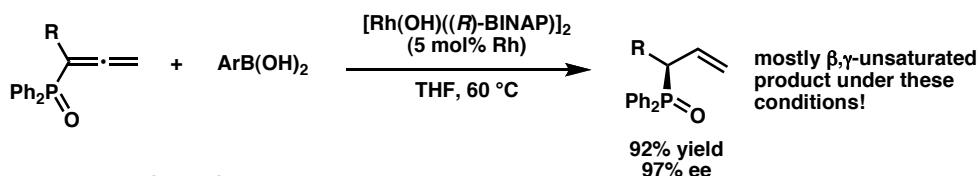
Hayashi, *J. Am. Chem. Soc.* 2006, 128, 2556–2557.

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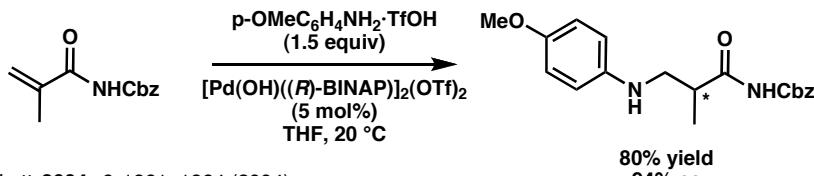


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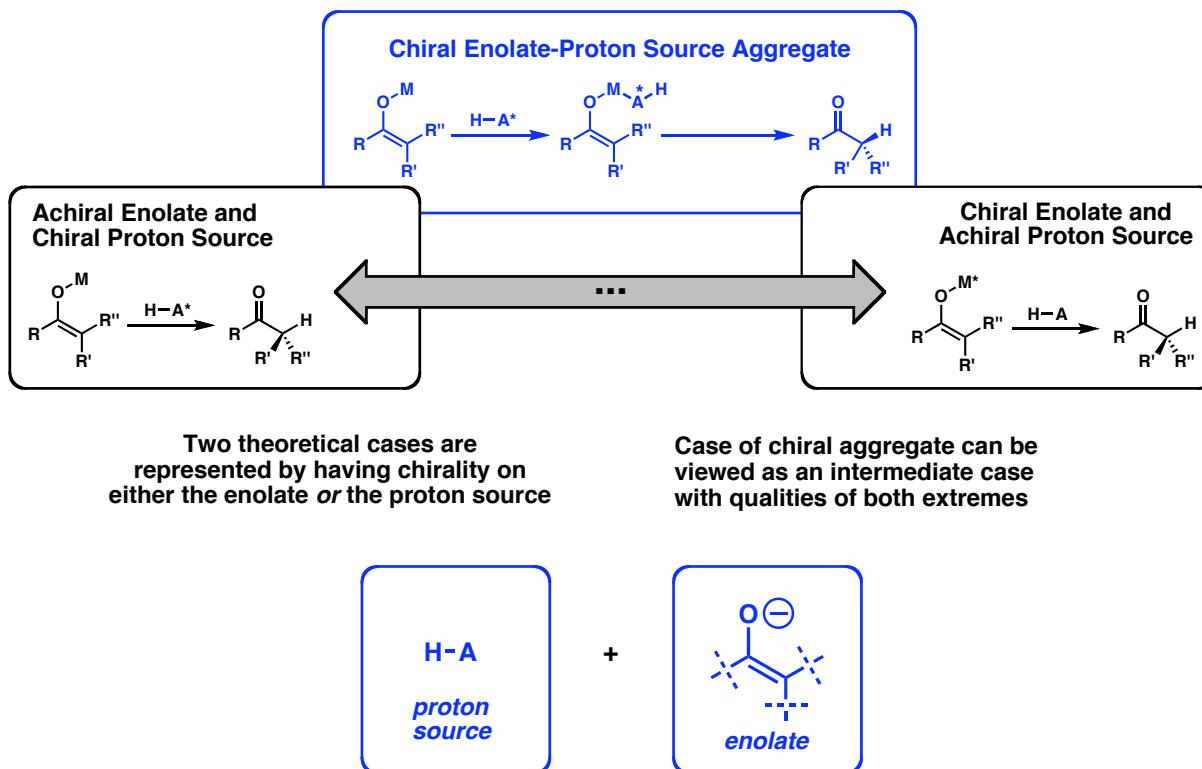
Hayashi, *J. Am. Chem. Soc.* 2006, 128, 2556–2557.

### Conjugate addition-protonation with Pd



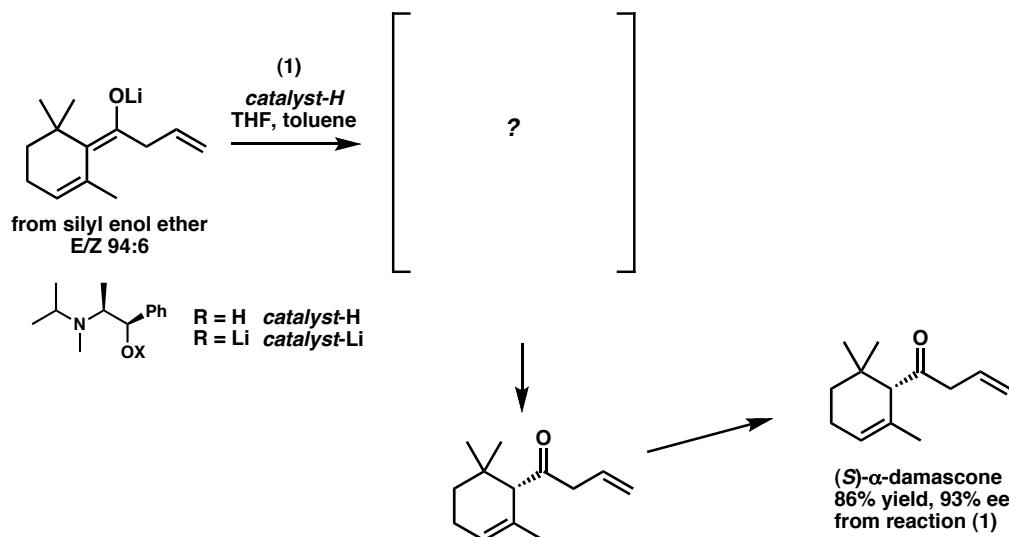
Sodeoka, *Org. Lett.* 2004, 6, 1861–1864 (2004).

## Approaches to Enantioselective Protonation



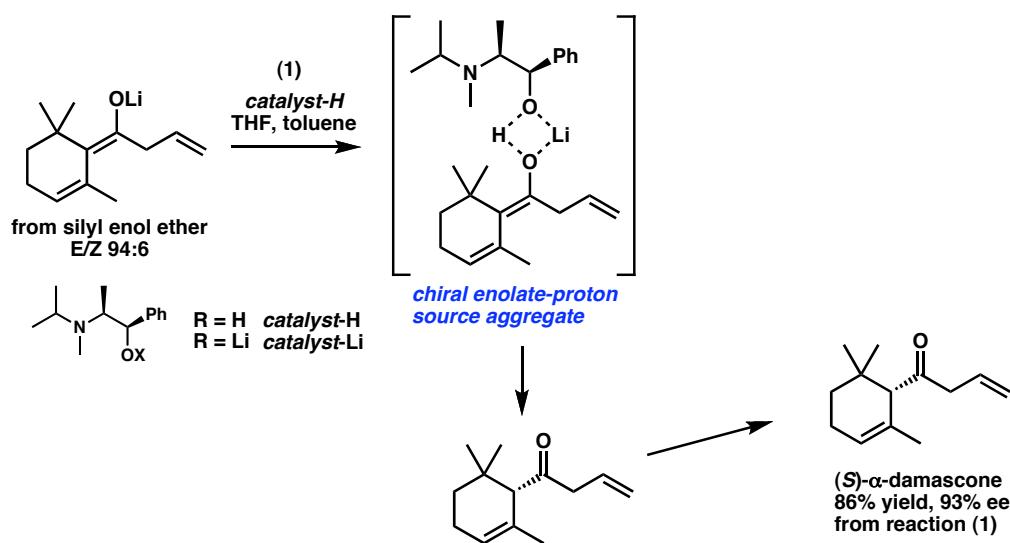
## Catalytic Enantioselective Tautomerization

Li-alkoxide catalyzed enantioselective protonation  
(chiral enolate-proton source aggregate)



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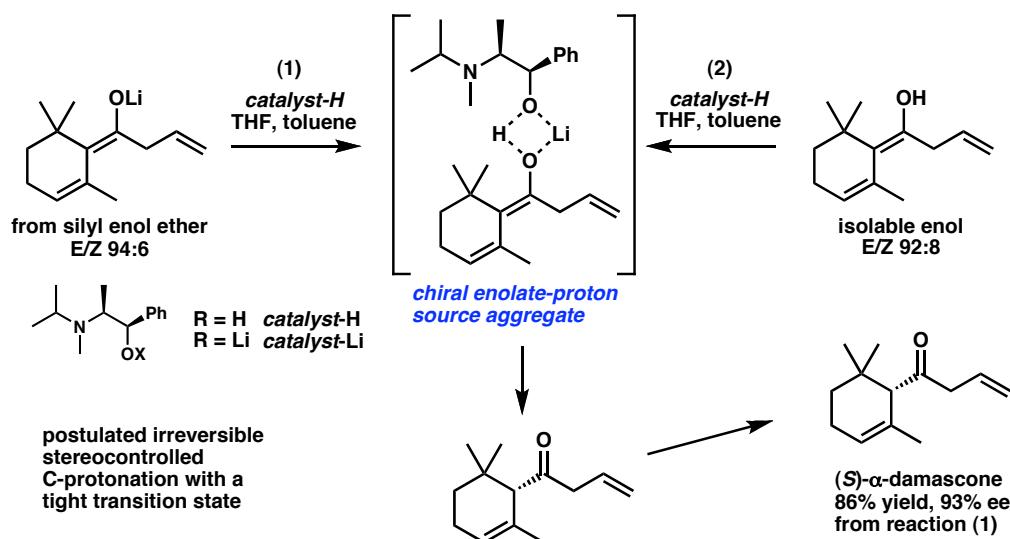
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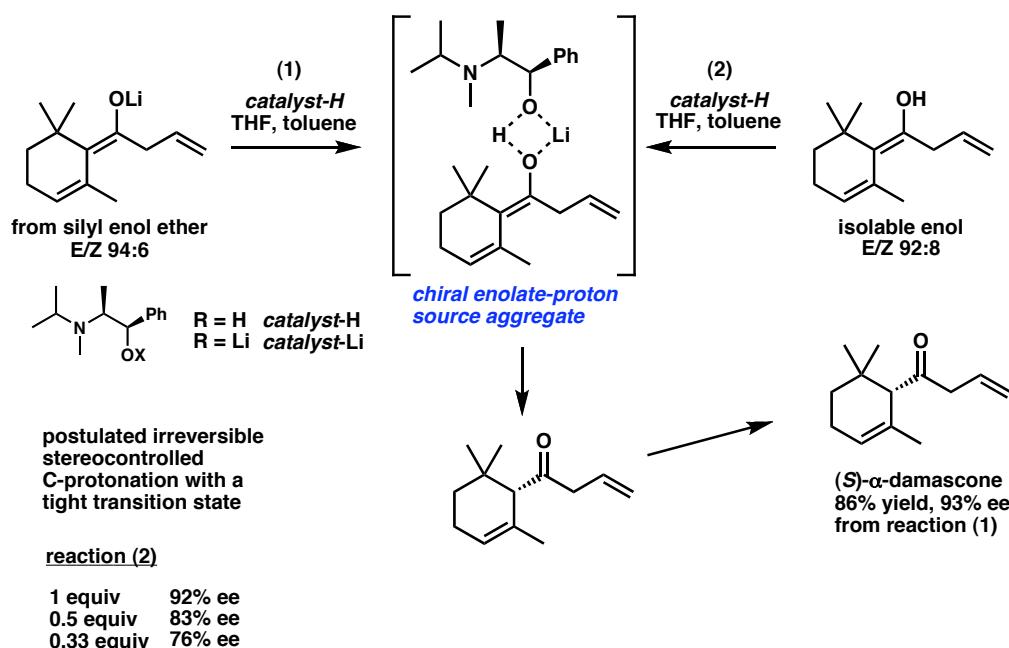
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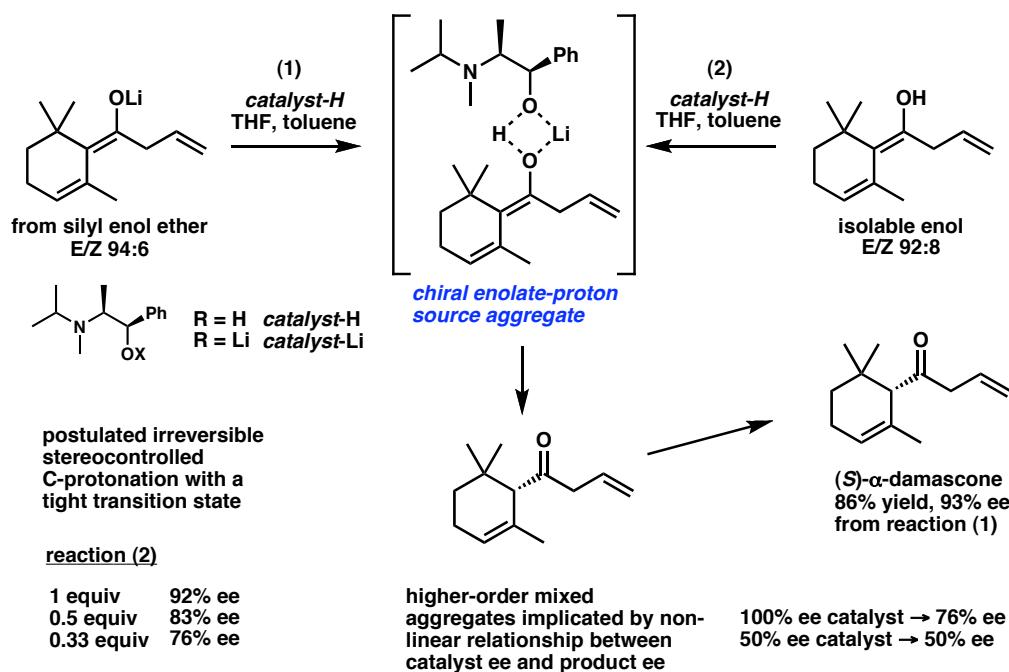
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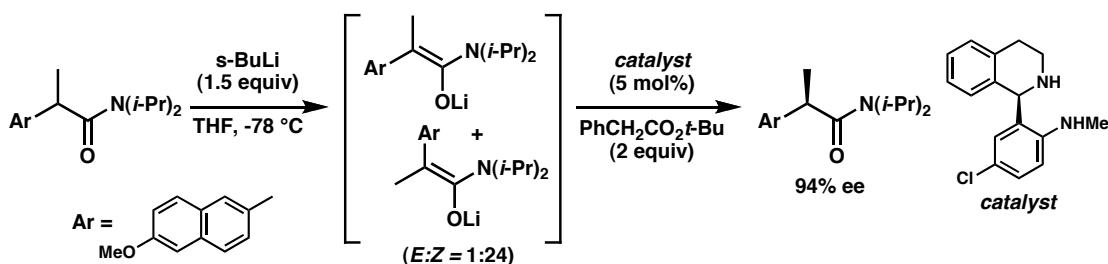
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# Chiral Aniline-Catalyzed Protonation

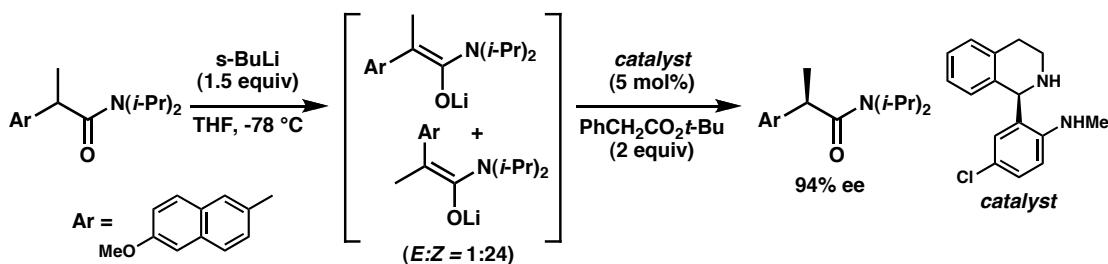
Li-amide catalyzed deracemization of bulky amide enolates  
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Vedejs, *J. Org. Chem.* **1998**, *63*, 2792-2793.  
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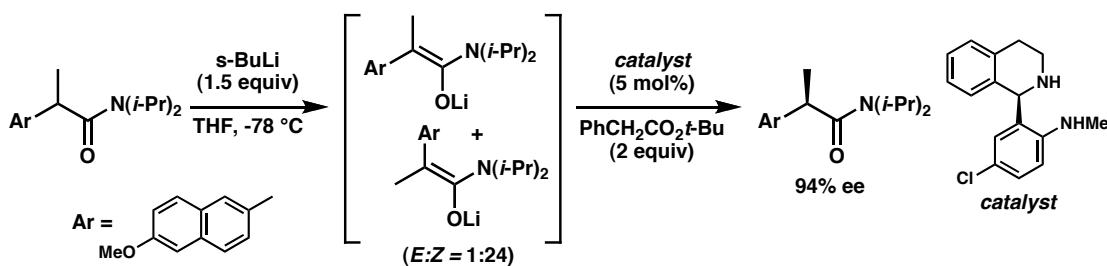


With stoichiometric diamine as proton source:  
changing catalyst aniline NHMe → NMe<sub>2</sub>, 4% ee  
changing catalyst piperidine NH → NMe, <5% ee

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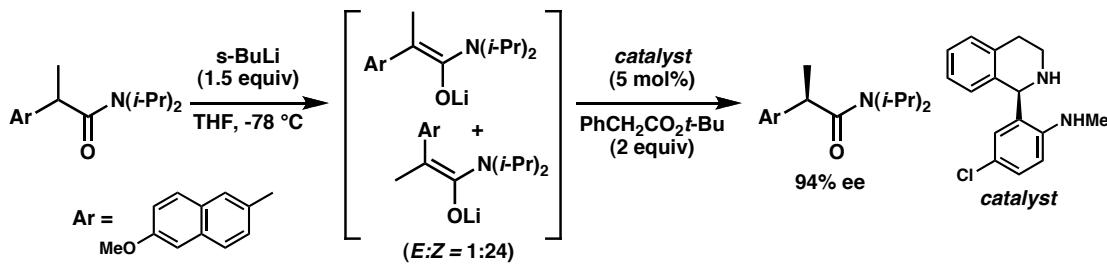
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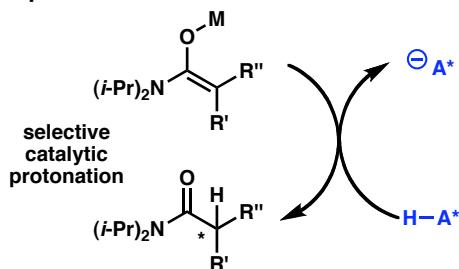
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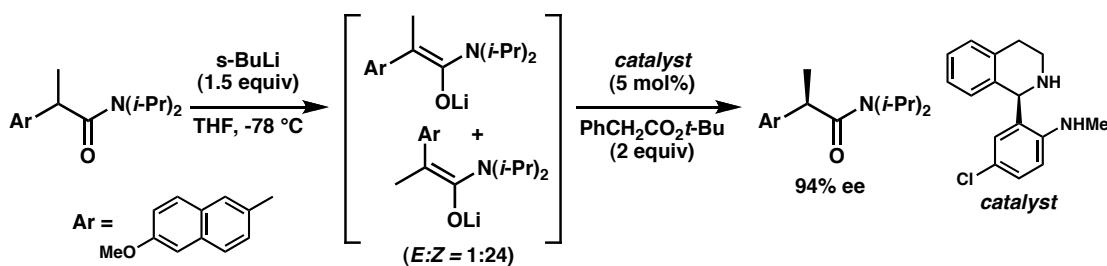
## Proposed mechanism



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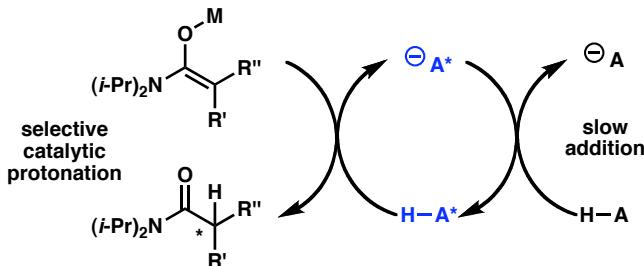
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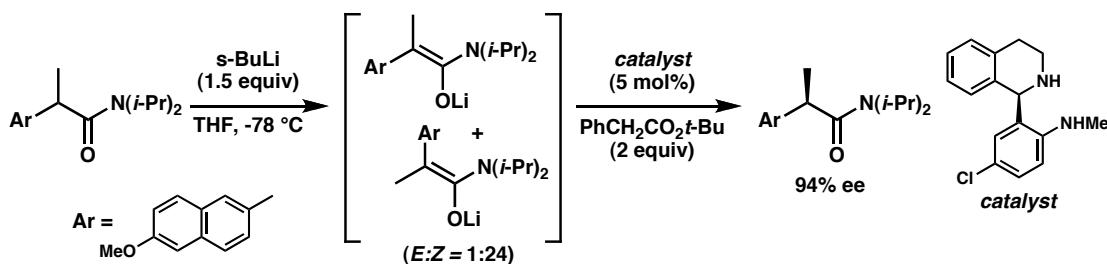
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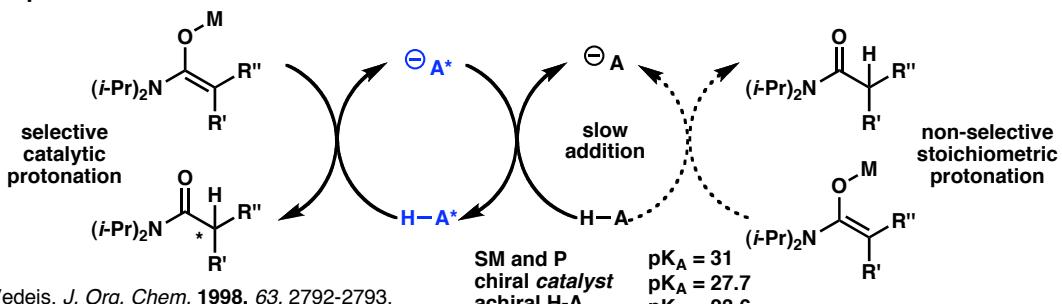
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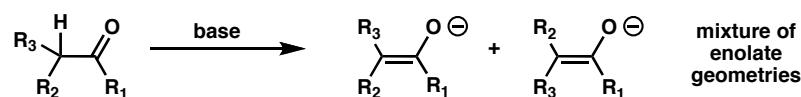
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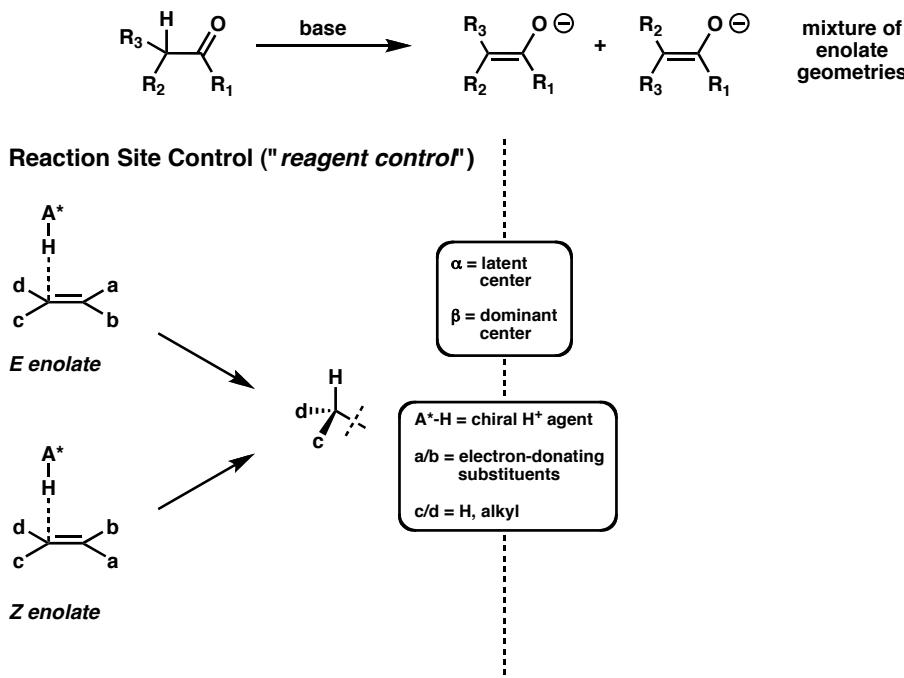
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Deprotonation of ketones can give a mixture of E and Z isomers... *but does it matter?*



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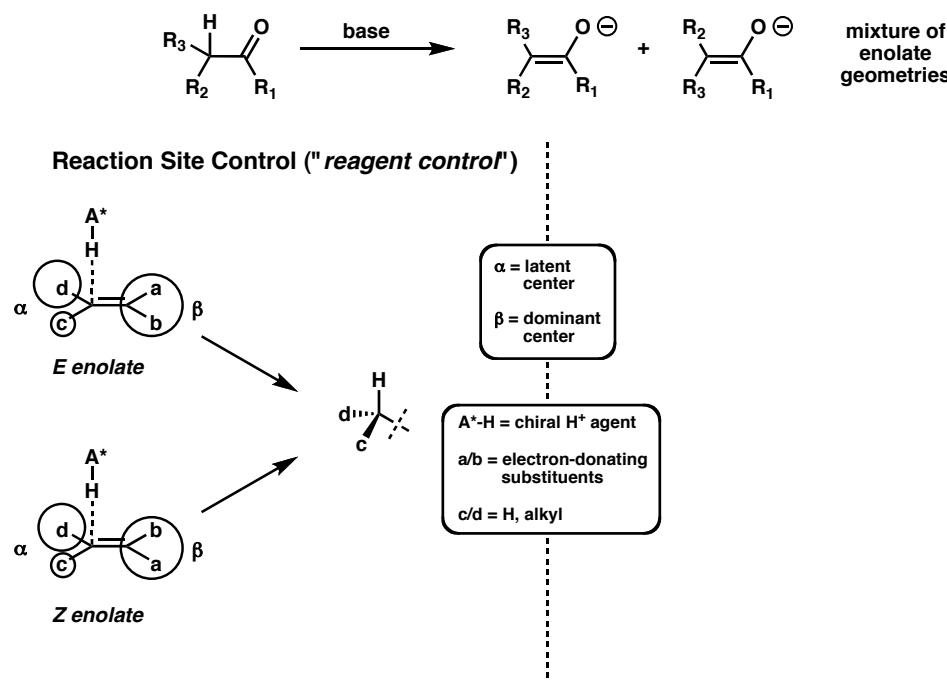
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Duhamel, *Tetrahedron: Asymmetry* 2004, 15, 3253-3691.

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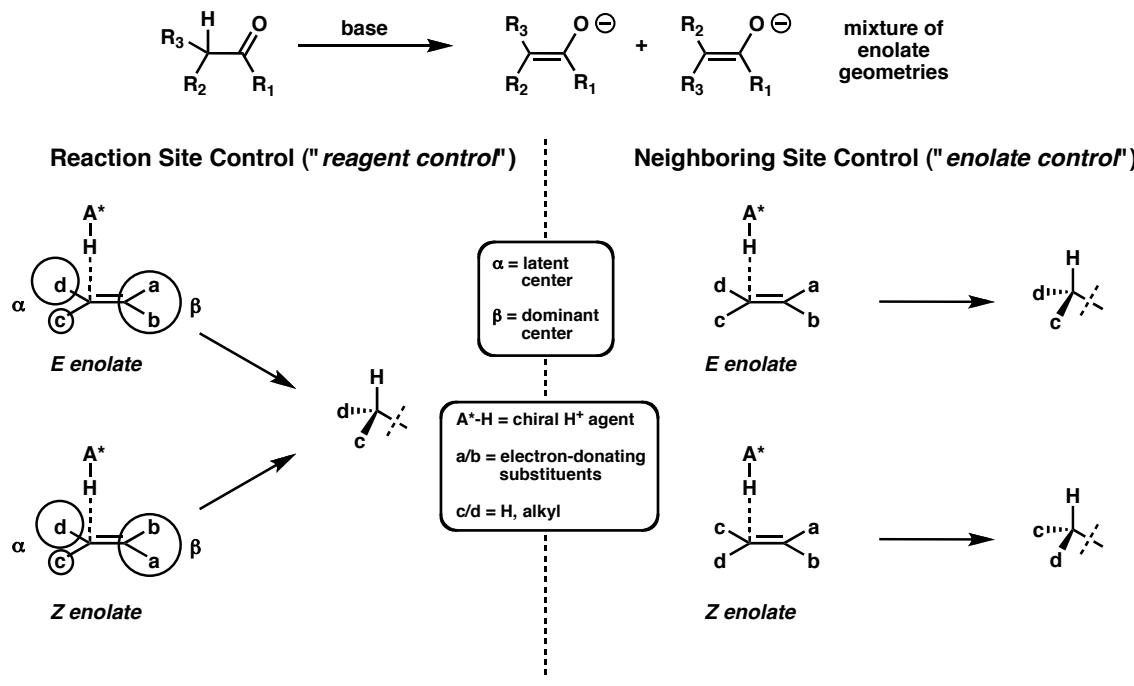
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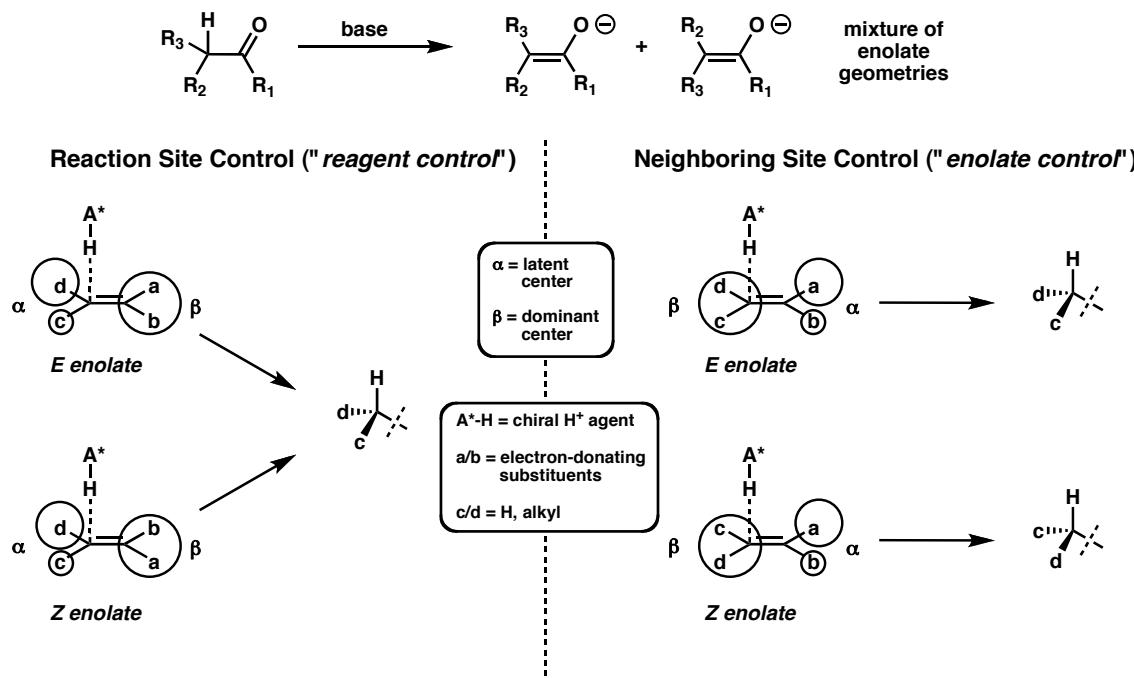
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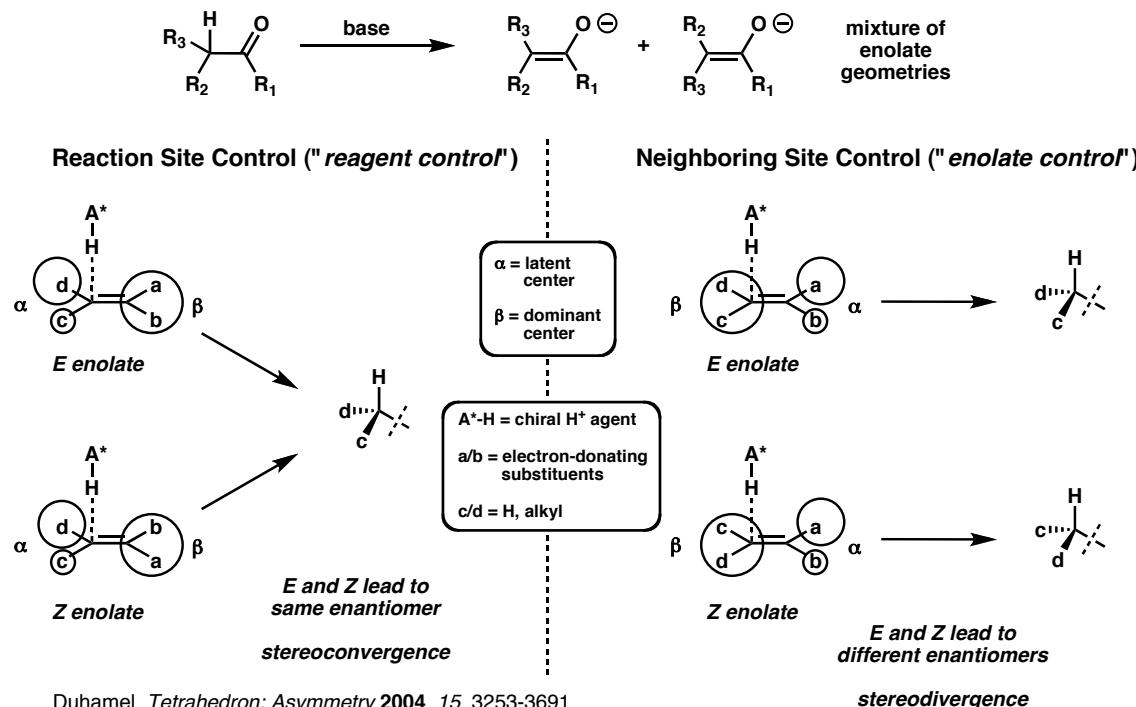
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## Examples of RSC and NSC in Protonation

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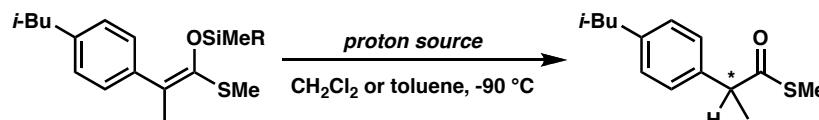
**Reaction Site Control ("reagent control")**

*E and Z lead to same enantiomer*  $\longrightarrow$  *stereoconvergence*

**Neighboring Site Control ("enolate control")**

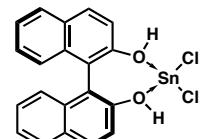
*E and Z lead to different enantiomers*  $\longrightarrow$  *stereodivergence*

Pure RSC case: protonation of silyl enol ether



R	E/Z	R/S
Me	15 / 85	64%
Me	32 / 68	66%
Me	92 / 8	68%
t-Bu	15 / 85	76%
t-Bu	48 / 52	80%

ratio of enantiomers is independent of ratio of E and Z isomers



assuming 100 : 0 enantioface selectivity

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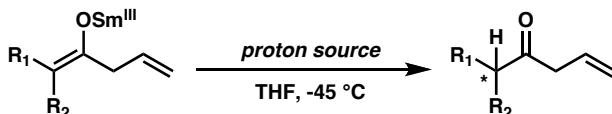
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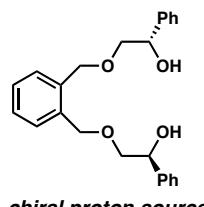
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Pure NSC case: protonation of a samarium enolate



R <sub>1</sub>	R <sub>2</sub>	Z/E	R/S
Bn	i-Pr	14 / 86	8 / 92
Et	Bn	35 / 65	35 / 65
Ph	Me	96 / 4	96 / 4
Ph	Et	93 / 7	92 / 8



mixtures of E and Z isomers give rise to mixture of enantiomers with roughly the same ratio

assuming 100 : 0  
enantioface selectivity

Takeuchi, *Tetrahedron: Asymmetry* 1994, 5, 1763-1780.

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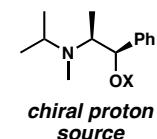
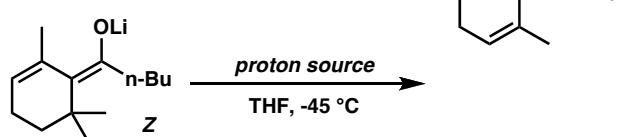
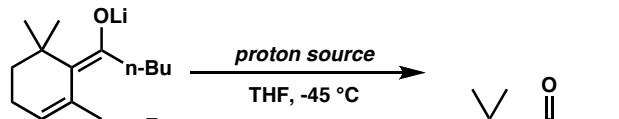
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Mixed RSC/NSC case: protonation of lithium enolate



pure E isomer  $\rightarrow$  99 : 1 (S : R)

pure Z isomer  $\rightarrow$  70 : 30 (S : R)

Fehr, *Angew. Chem. Int. Ed.* 1996, 35, 2566-2587.

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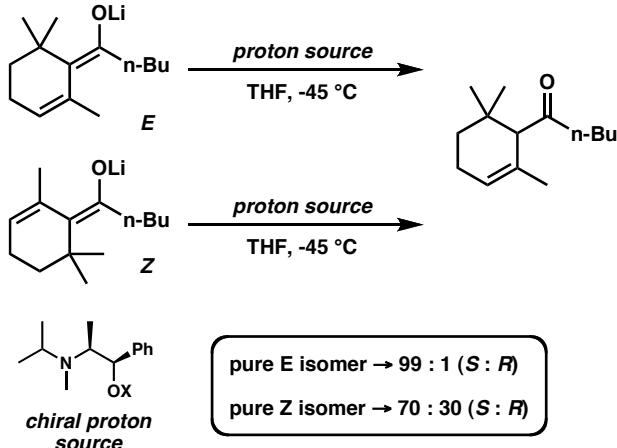
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RSC contribution      NSC contribution

$E \rightarrow S$        $E \rightarrow S$   
 $Z \rightarrow S$        $Z \rightarrow R$

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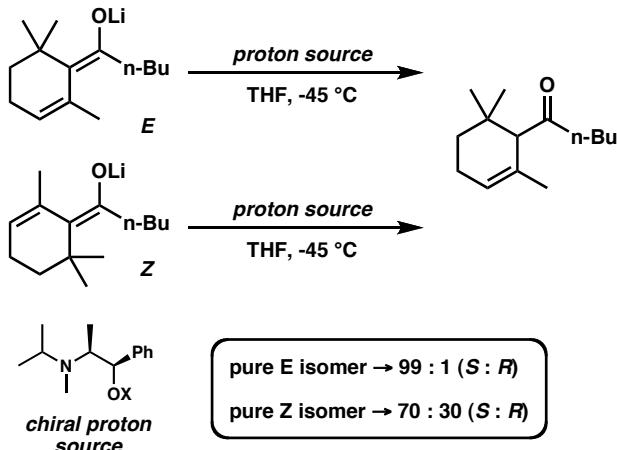
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Combined results for each isomer from two pathways

E isomer: S + S = 99 : 1

Z isomer: S + R = 70 : 30

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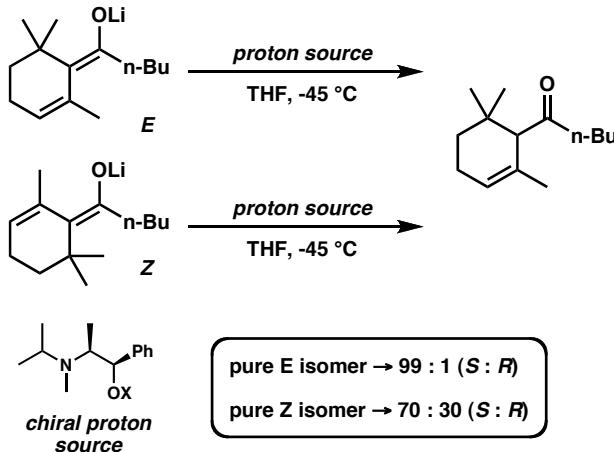
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RSC contribution      NSC contribution

E  $\rightarrow$  S      E  $\rightarrow$  S  
Z  $\rightarrow$  S      Z  $\rightarrow$  R

Combined results for each isomer from two pathways

E isomer: S + S = 99 : 1

Z isomer: S + R = 70 : 30

suggests 70% RSC and 30% NSC

assuming 100 : 0 enantioface selectivity

Fehr, *Angew. Chem. Int. Ed.* **1996**, 35, 2566-2587.

## Challenges in Enantioselective Protonation

Protonation is a conceptually simple reaction, but catalytic enantioselective methods are challenging for many reasons:

Broad substrate scope and general methods can be elusive

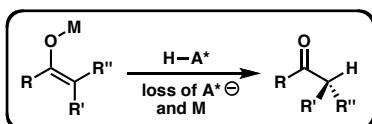
- newly-generated chirality can be sensitive to reaction conditions
- moving beyond cyclic substrates and controlling enolate geometry in acyclic cases
- complex aggregate interactions difficult to predict
- relative reaction rates between multiple catalytic cycles
- difficult to verify the presence of reactive intermediates

Extensive screening is often needed to find the right conditions

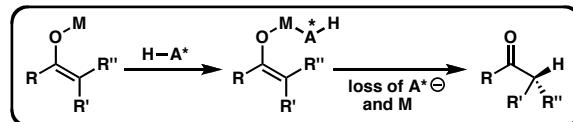
- matching of chiral and achiral proton donors for effective coupling needs to consider pK<sub>A</sub> and sterics
- finding suitable ligand sterics and electronics to provide optimal chiral environment
- temperature can be a very important parameter
- solvent effects can affect protonation

## Extending Protonation Chemistry?

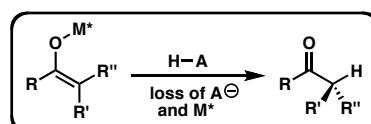
### Achiral Enolate and Chiral Proton Source



### Chiral Enolate-Proton Source Aggregate

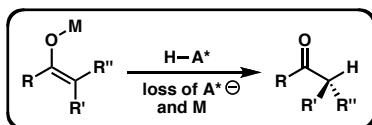


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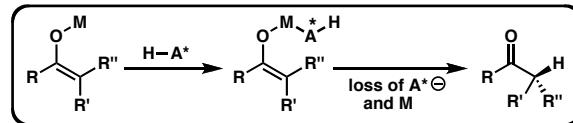
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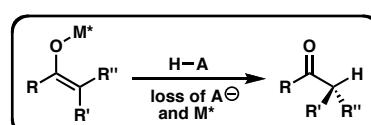
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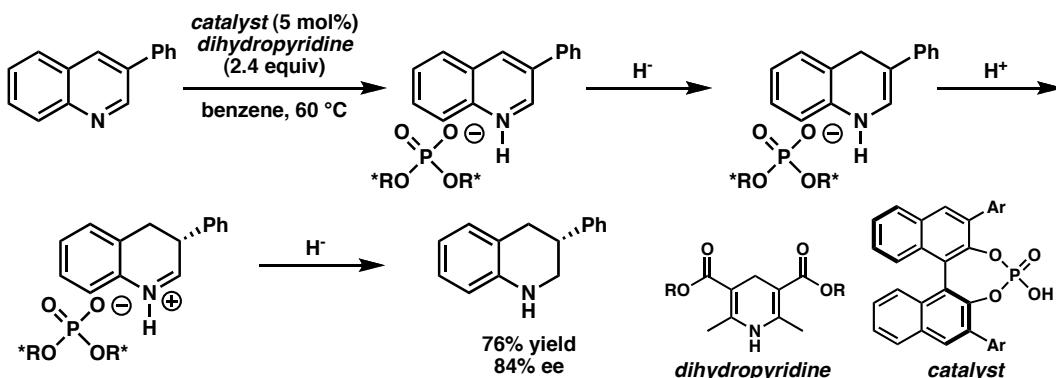
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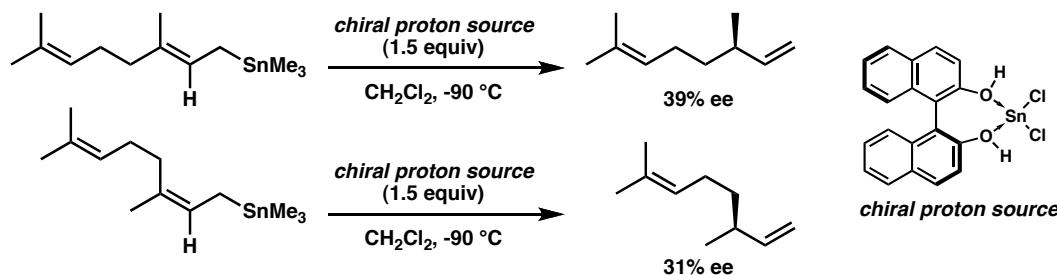
?

# Extending Asymmetric Protonation Chemistry

## Protonation of non-enolate systems



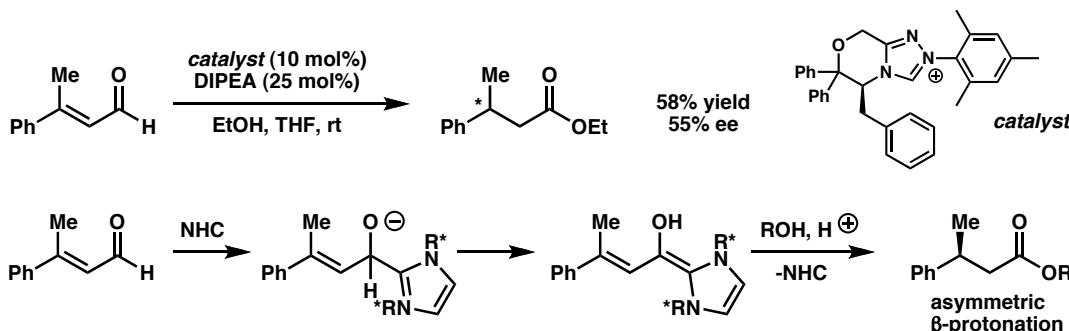
Rueping, *Adv. Synth. Catal.* 2008, 350, 1001-1006.



Yamamoto, *Synlett* 1998, 758-760.

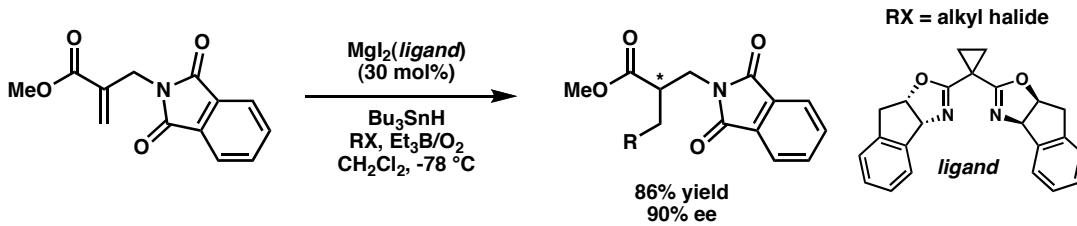
# Extending Asymmetric Protonation Chemistry

## $\beta$ -protonation of carbonyls



Scheidt, *Synthesis*. 2008, 8, 1306-1315.

## Asymmetric addition of $\text{H}\cdot$ radical



Sibi, *Angew. Chem. Int. Ed.* 2004, 43, 1235-1238.

## *Acknowledgments*