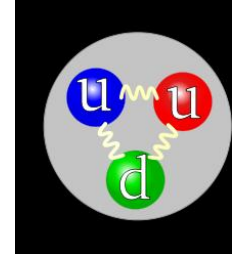


Charge = $1.60217653(14) \times 10^{-19}$ C
Diameter = 1.65×10^{-15} m
Mass = 1.6726×10^{-27} kg or about 1836 times
the mass of an electron



Quark Structure

Enantioselective Protonation

Group Meeting

07-08-2008

Timothy Chang

Outline

Introduction

- Challenges

Stoichiometric Enantioselective Protonation (EP)

- Pioneering Work
- EP involving an enolate (basic/neutral condition)
- EP involving a silyl enol ether (acidic condition)

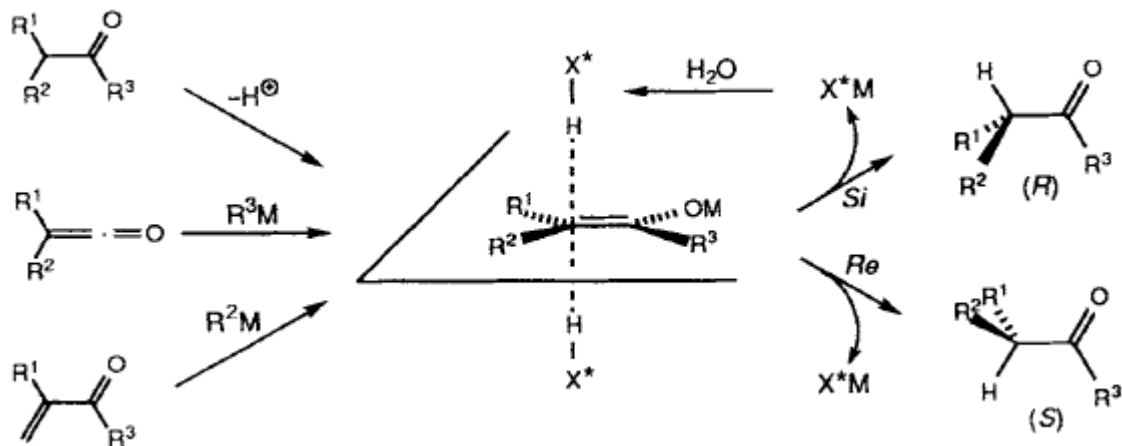
Catalytic Enantioselective Protonation

Recent Examples in Catalytic EP (2004 -)

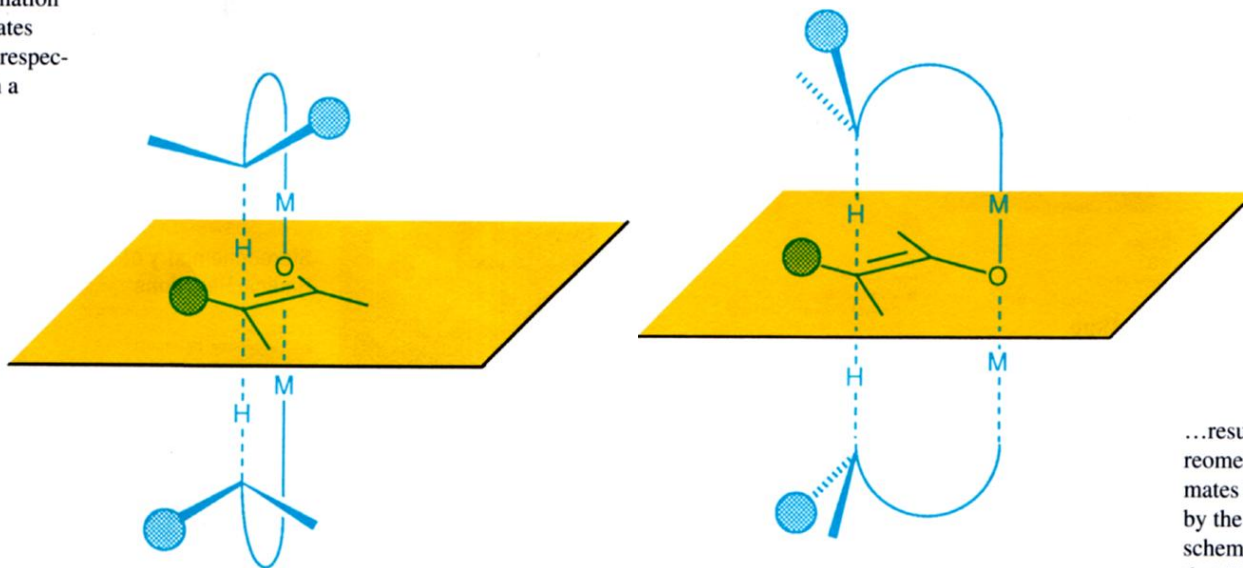
Conclusion

Not covered: enzyme mediated, antibody-catalyzed, polymer-supported EP

Introduction



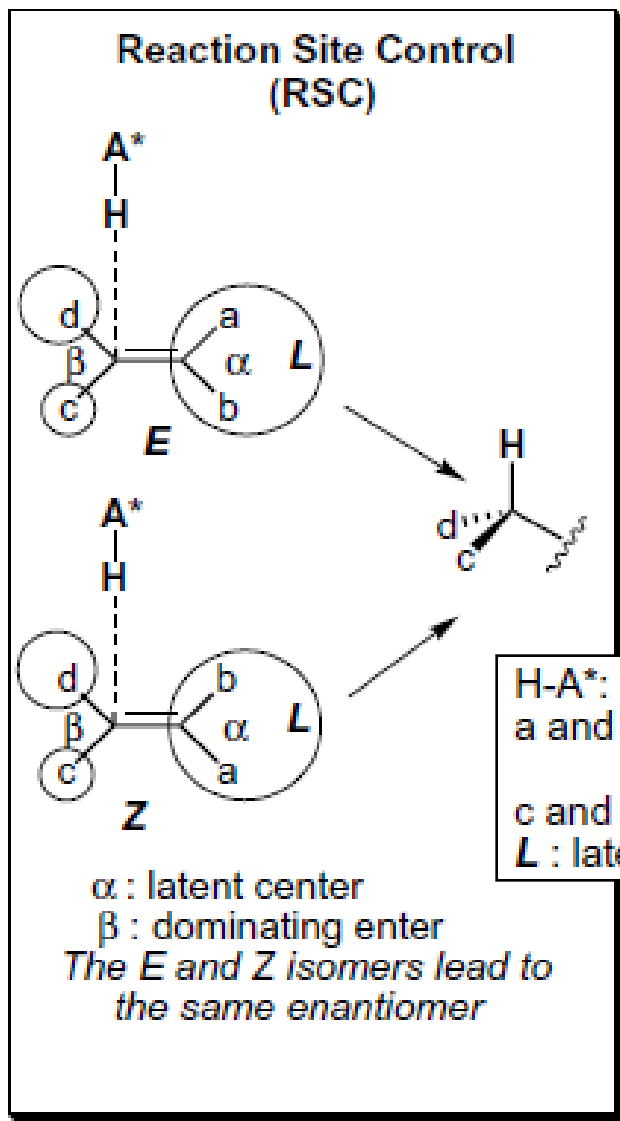
The enantioselective protonation of prochiral *Z*- and *E*-enolates (top right and bottom left, respectively) by protonation with a chiral proton donor...



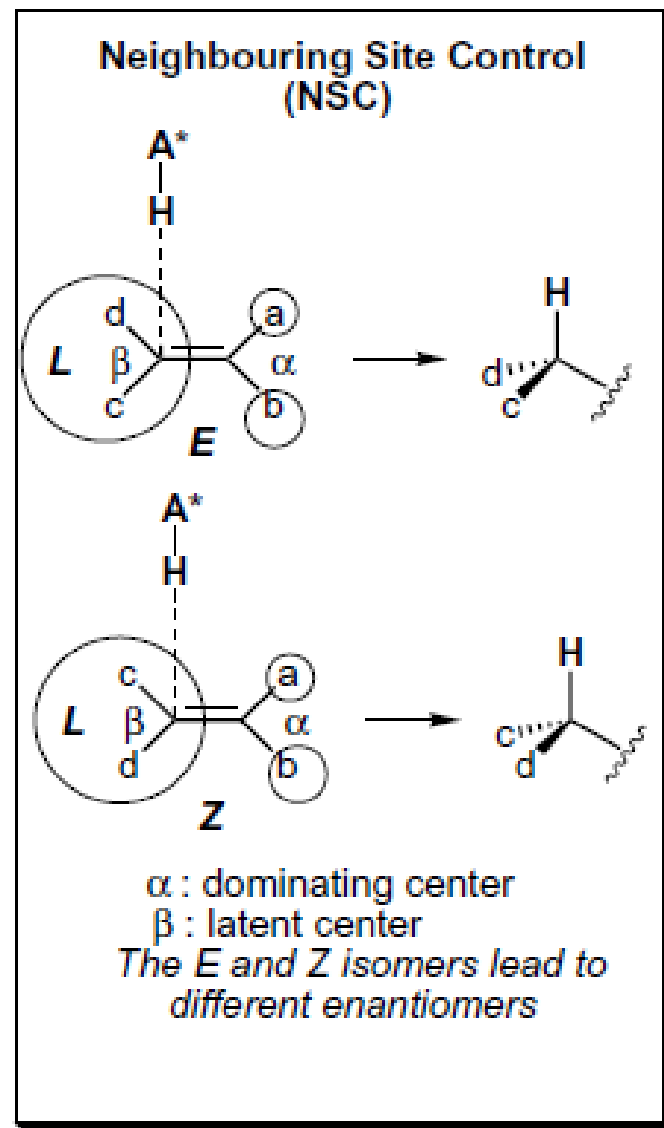
...results in a total of four diastereomeric transition states. Racemates can thus be "deracemized" by the formation of enolates. This schematic representation indicates that *Z*- and *E*-enolates react with different enantiofacial selectivities.

EP is kinetically controlled, racemic products are obtained by thermodynamic control

Influence of the E/Z Configuration



H-A*: Chiral Protonating Agent
a and / or b : electron donating substituents
c and / or d : H or alkyl substituents
L : latent center

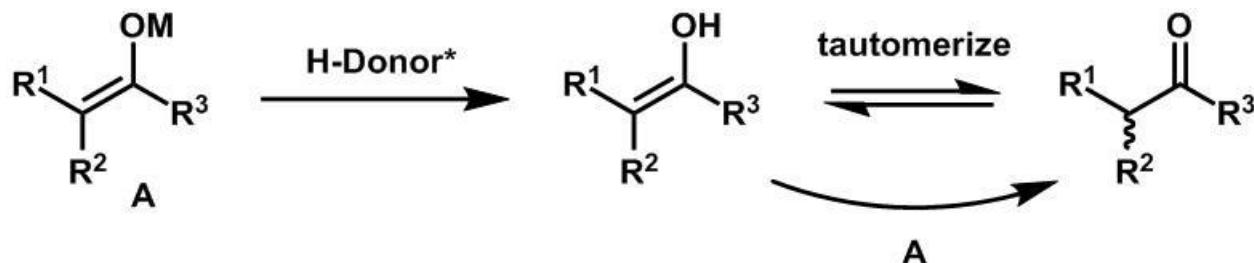


Challenges

Rapid proton exchange (often diffusion controlled)

Chiral reagent should be weakly acidic, lower temperature

Competition with O-protonation



Use excess amount of H-Donor*

Adjust temperature

Racemization of product

Short reaction time

Appropriate acidity of H-Donor and H-Donor*

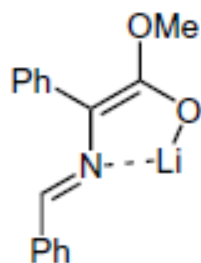
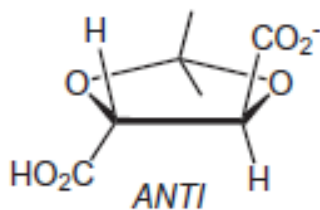
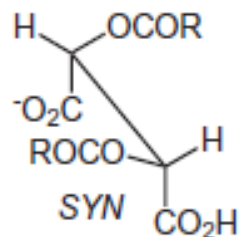
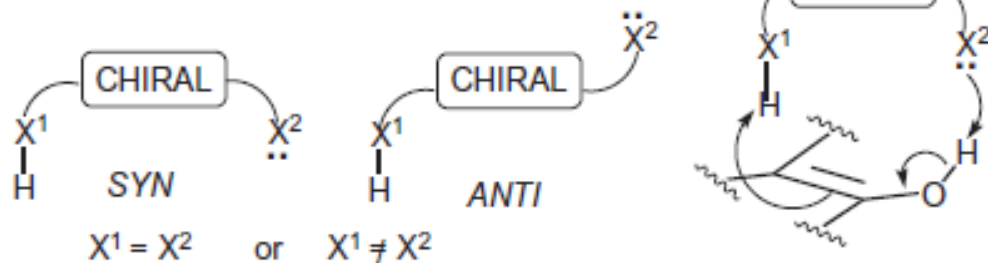
Purity of E/Z isomers

Solvation, Aggregation, Complexation

Trend: efficient chiral proton donors or chiral ligands generally have electron-rich groups capable of chelation.

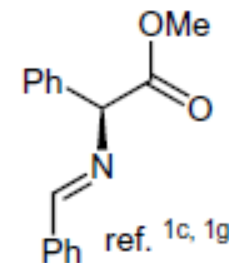
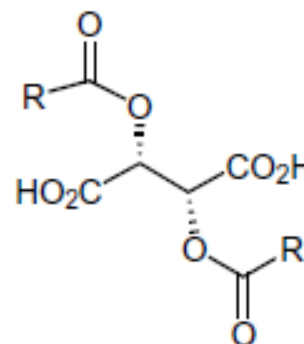
Chiral Protonating Agent (H-Donor*)

Structural Requirements



From racemic amino ester Schiff base and LDA

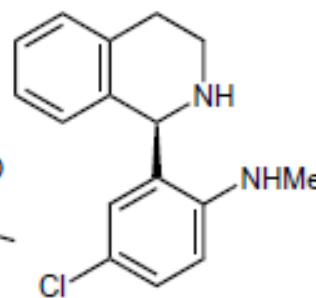
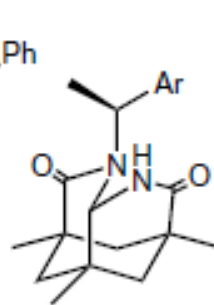
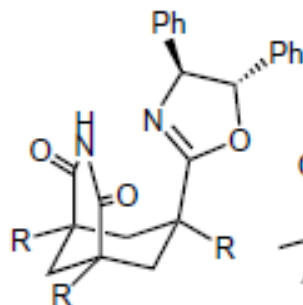
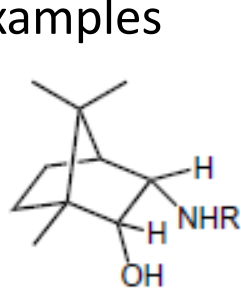
THF, -70°C



R	ee%
Me	3
<i>i</i> -Pr	12
Ph	12
<i>t</i> -Bu	50
adamantyl	53

80 < yd%* < 85

Examples



Rigid backbone

Chiral Protonating Agent (H-Donor*)

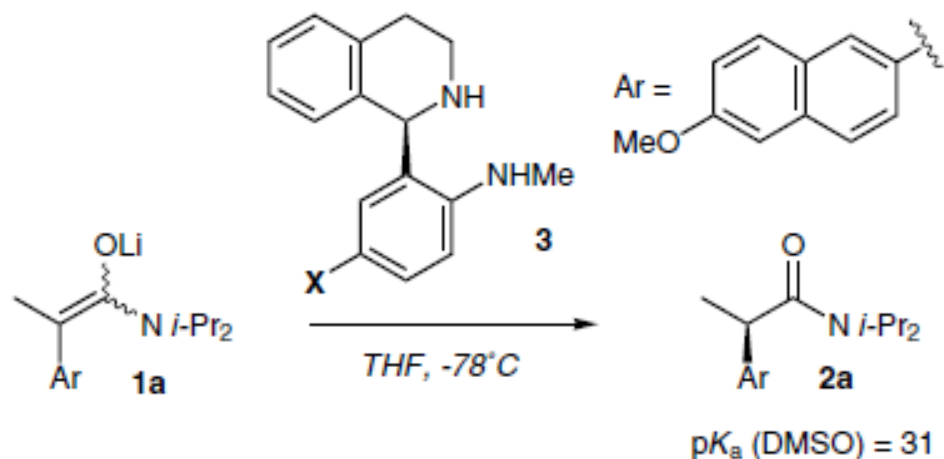
Acidity Requirements

- Protonation by H-Donor* must be as complete as possible
- $\Delta pK_a = 2 \rightarrow 91\%$ protonation
- $\Delta pK_a = 3 \rightarrow 97\%$ protonation
- $\Delta pK_a = 4 \rightarrow 99\%$ protonation
- ($\Delta pK_a = pK_a \text{ substrate} - pK_a \text{ H-Donor}^*$)
- To the first approximation, as the ΔpK_a decreases, the rate of proton transfer is lowered .
- $2 \leq \Delta pK_a \leq 4$ for the optimal enantioselectivity and a complete protonation
- pK_a s of substrates and H-Donor* are rarely established
- pK_a s for the commonly employed H-Donor* ranges from 5 – 25
 - Carboxylic acid ~ 5
 - Phenol ~ 10
 - Imide ~ 11
 - Amide ~ 15
 - Alcohols ~ 17
 - Aromatic amines ~ 25

Aim for $2 \leq \Delta pK_a \leq 4$ between substrate and H-Donor*

Chiral Protonating Agent (H-Donor*)

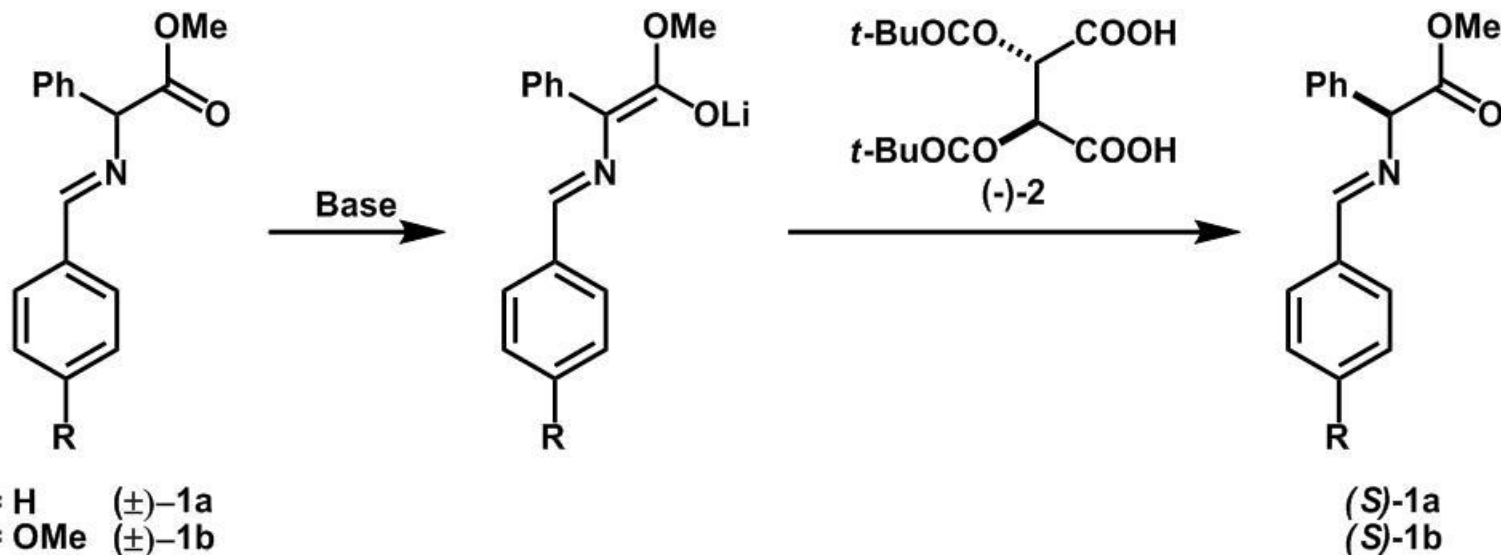
Acidity Requirements: An Example



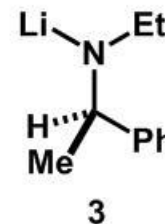
X	H	Cl	CF₃	CO₂Et	Ts	NO₂
3pK_a (DMSO)	29.0	27.7	25.5	24.8	23.3	19.3
2a ee%	90	97	93	40	37	0

$\Delta\text{pK}_a = 3$

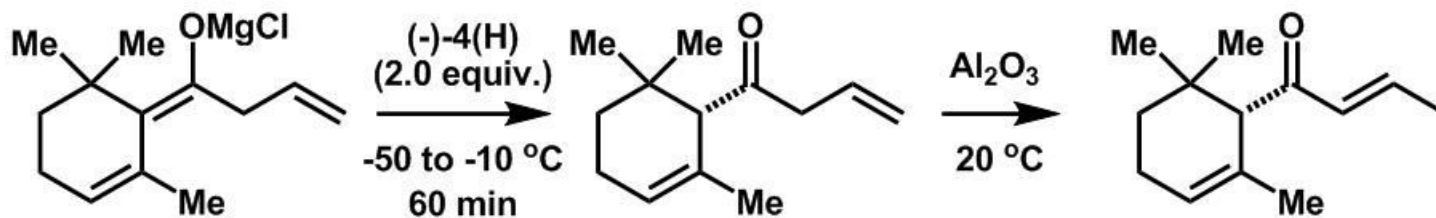
The Pioneering Work



Entry	Substrate	Base	T (°C)	H-Donor	ee (%)	Yield (%)
1	(\pm)-1a	LDA	-70	(-)-2a	50	85
2	(\pm)-1a	LiNEt ₂	-70	(-)-2a	28	
3	(\pm)-1a	LTMP	-70	(-)-2a	22	
4	(\pm)-1a	3	-70	(-)-2a	70	
5	(\pm)-1a	3	-70	(+)-2a	5	
6	(\pm)-1a	3	-70	(\pm)-2a	39	
7	(\pm)-1a	3	-70	meso-2a	24	
9	(\pm)-1b	LDA	-70	(-)-2a	57	70
10	(\pm)-1b	LDA	-105	(-)-2a	70	90

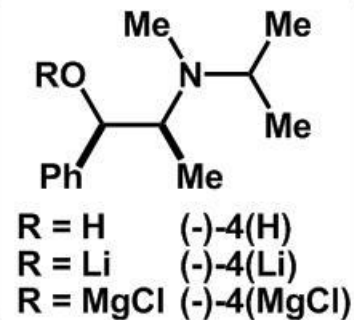


Effect of Counterion (M^+)

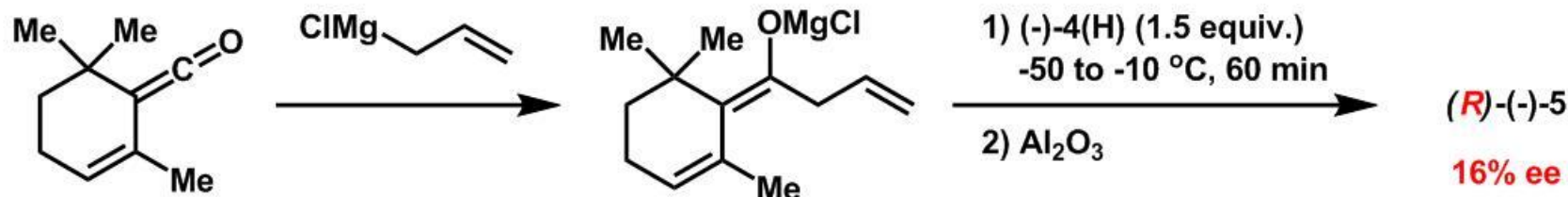


E:Z ~ 9:1
 (from the treatment of the methylester with *n*-BuLi followed by allylMgCl)

(-)- α -damascone
 (S)-(-)-5
 60% yield, 70% ee

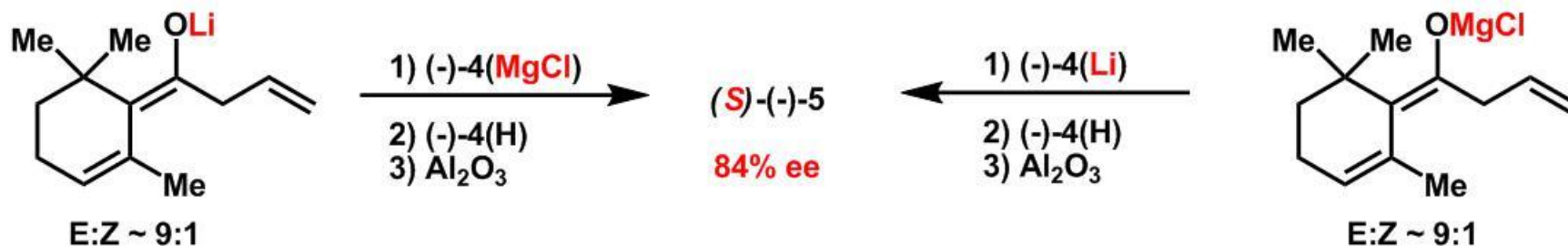


Features of (-)-4(H):
 - weakly acidic
 - chelation capability



16% ee

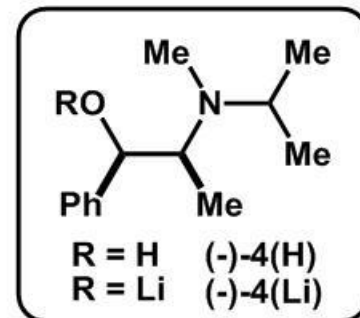
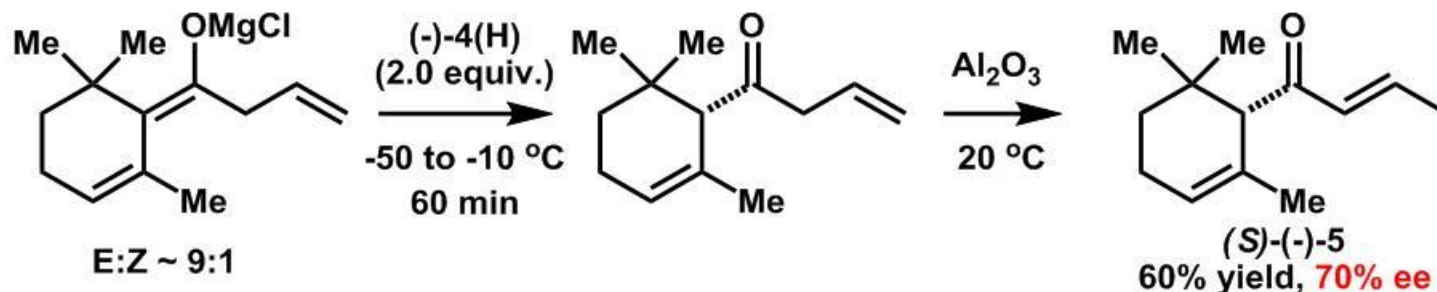
Enantioselectivity depends on the counter ion (M^+)



Exchanges between Li and Mg are rapid

Fehr

Effect of Aggregate



Entry Reaction Condition (equiv.; °C; min) ee (%) Yield (%)

1	1) MeOLi (1.0; 35; 30)		
	2) (-)-4(H) (2.0; -50 → -10; 60)	70 (S)	75
2	1) (-)-4(Li) (1.0; 20; 30)	Potentially a different enolate aggregate from entry 1	
	2) (-)-4(H) (2.0; -50 → -10; 60)	84 (S)	73
3	1) (+)-4(Li) (1.0; 20; 30)		
	2) (+)-4(H) (2.0; -50 → -10; 60)	84 (R)	73
4	1) (-)-4(Li) (1.0; 20; 30)		
	2) (+)-4(H) (2.0; -50 → -10; 60)	63 (R)	Slow proton exchange
5	1) (-)-4(Li) (1.0; 20; 30)		
	2) <i>t</i> -BuOH (2.0; -50 → -10; 60)	62 (S)	70

in-situ generation of chiral enolate-alkoxide complex?

Enantioselectivity depends on the enolate aggregate

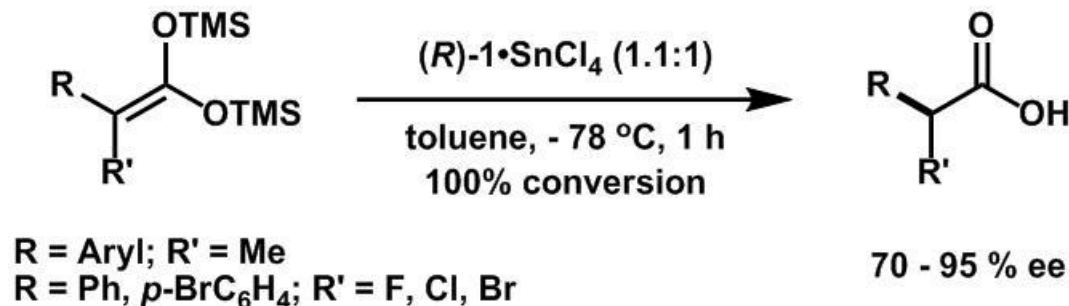
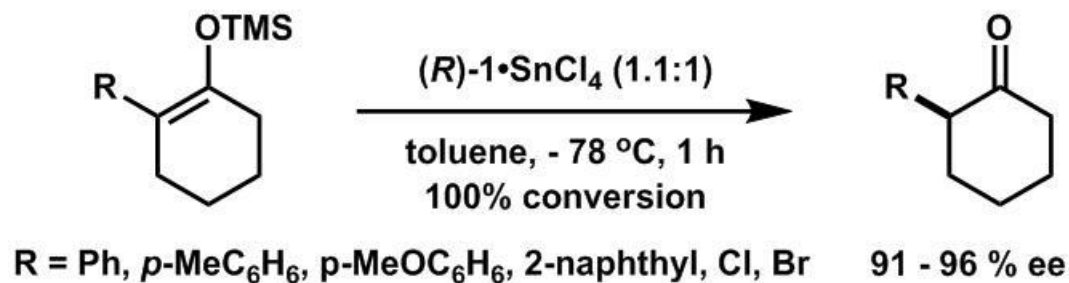
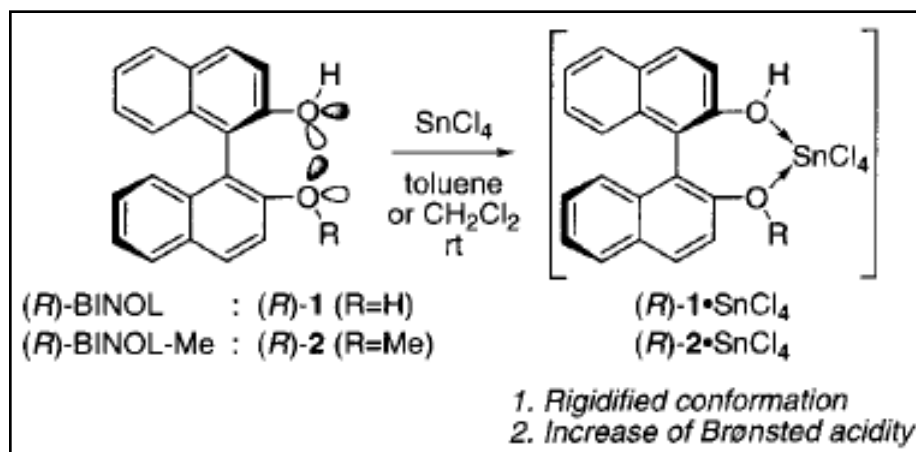
Enantioselectivity is highly dependent on all the chemical species in the solution

Potential for catalytic reaction using stoichiometric amount of achiral proton source to regenerate chiral proton (entry 5)

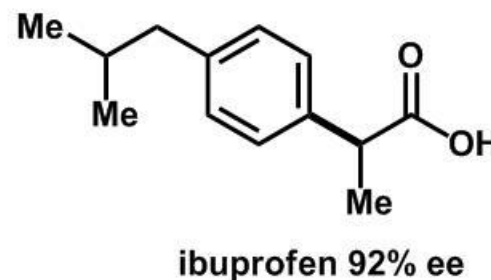
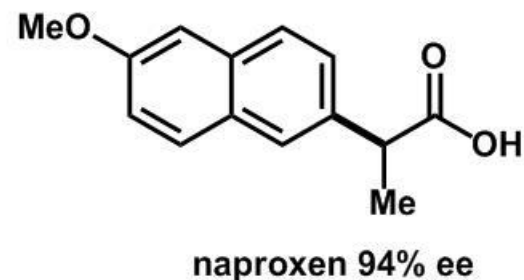
Fehr

J. Am. Chem. Soc. 1988, 110, 6909

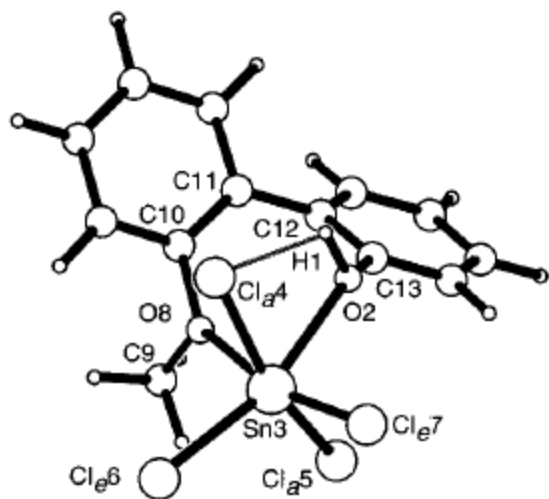
EP with a Lewis Acid-Assisted Chiral Brønsted Acid (LBA)



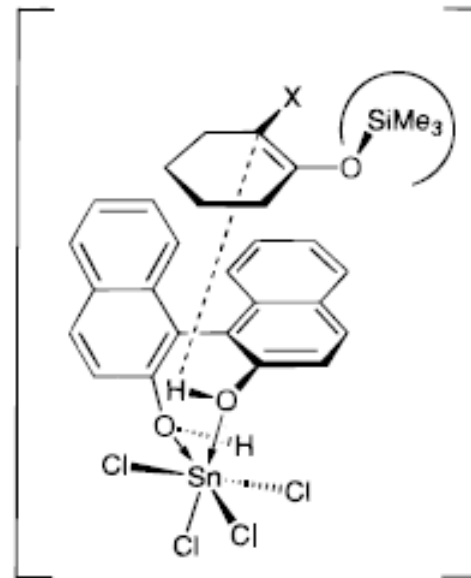
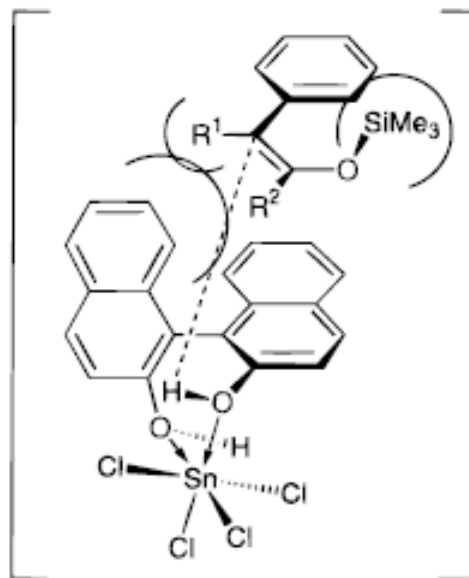
Low ee values were observed for bulkier R'
Enantioselectivity is dependent on ring size



A Model for EP with LBA



B3LYP/LANL2DZ level

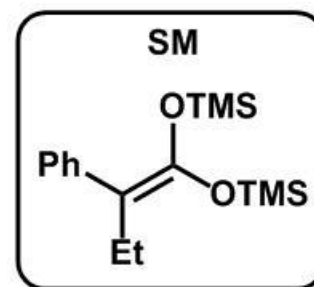


Potential electrostatic interaction between the acidic proton and Cl_{a4} (2.462 Å)

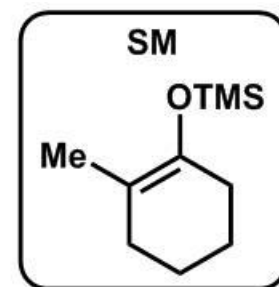
Charge on the proton: biphenol 0.489, biphenol- SnCl_4 0.546

- Model
- 1) TMSO points away from binaphthyl
 - 2) π stacking between the aryl rings
 - 3) bulky R^1 leads to low ee (as shown by experiment)

How to explain?



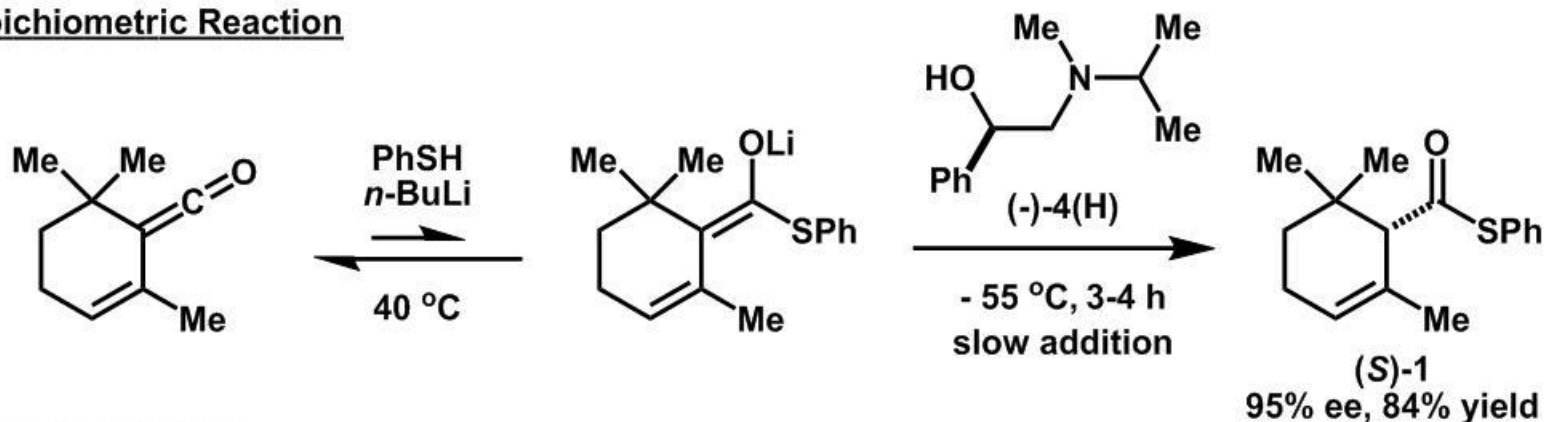
Product 60% ee



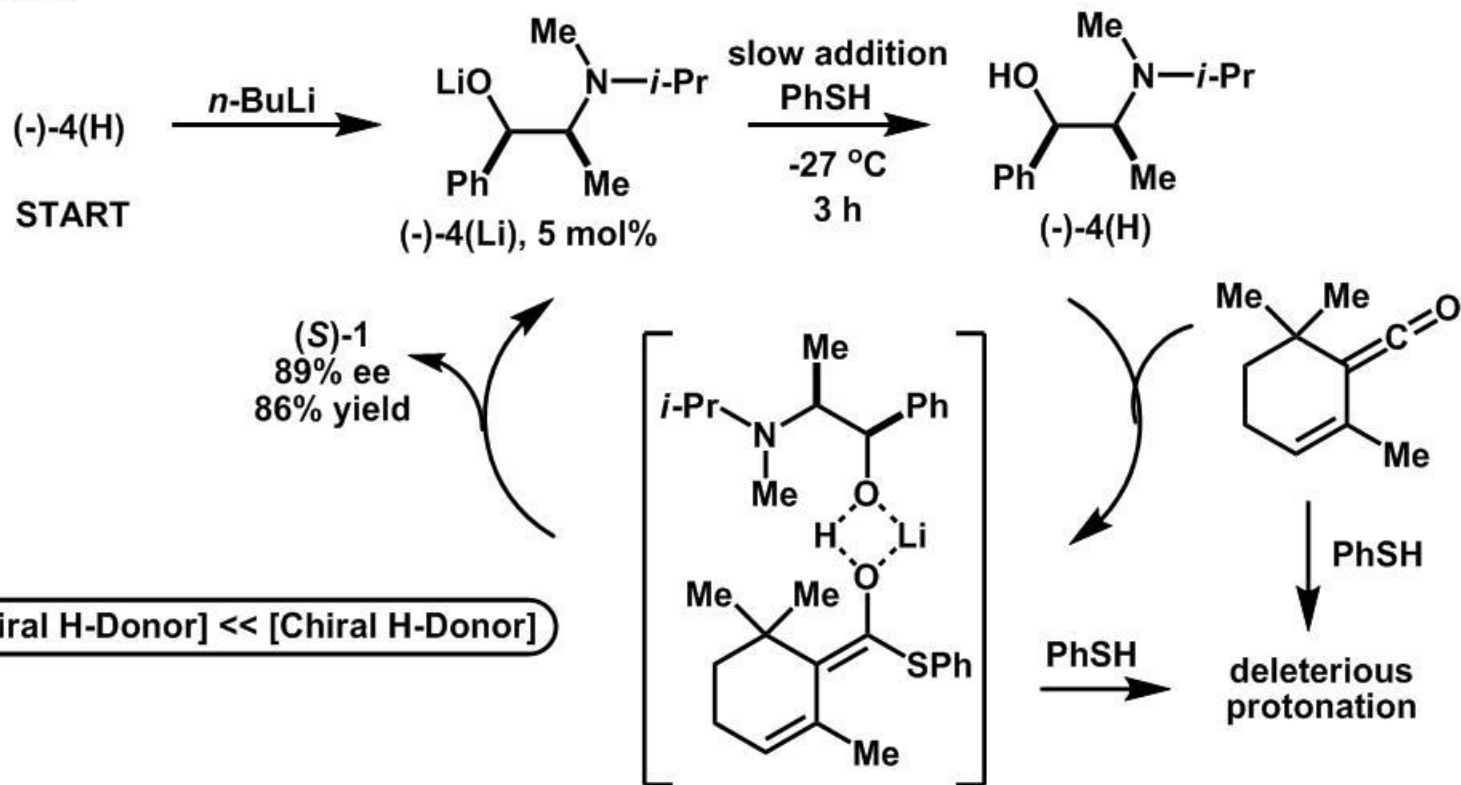
Product 51% ee

Catalytic Reaction – Slow Addition of an Achiral H-Donor

Stoichiometric Reaction

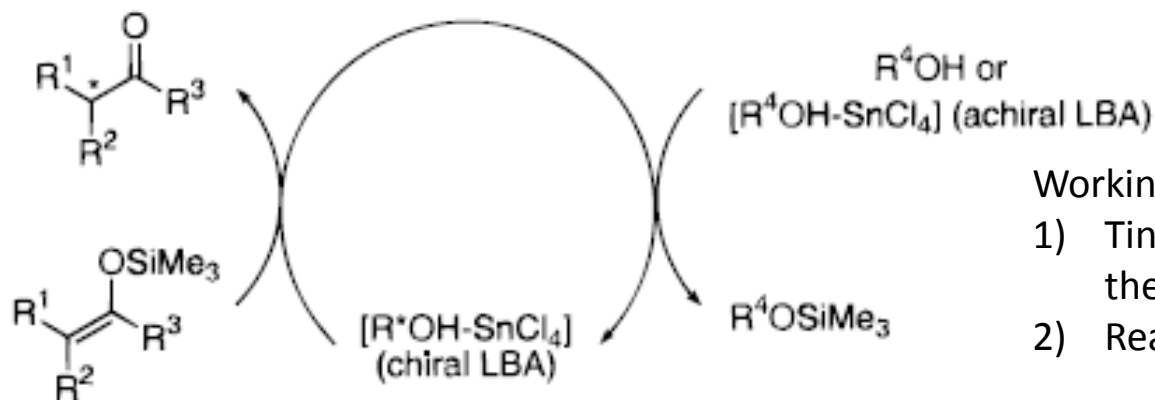


Catalytic Reaction



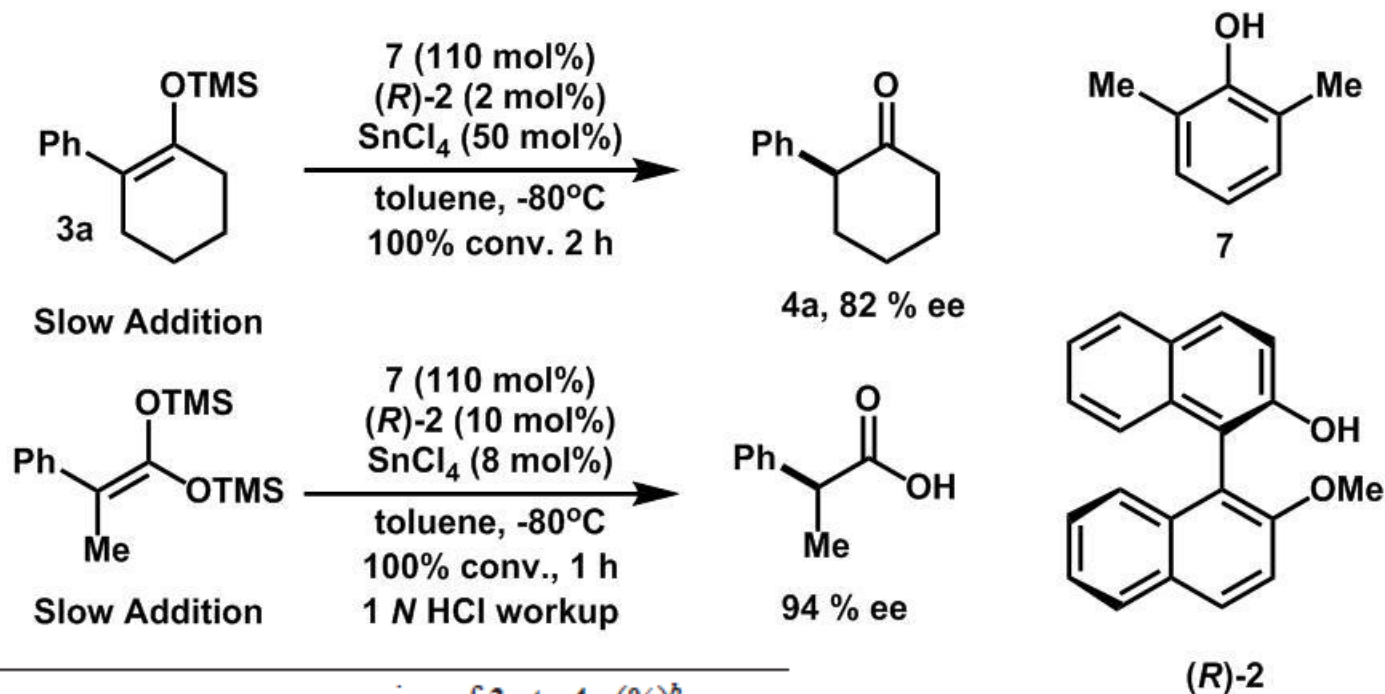
Fehr

Catalytic Reaction – EP with LBA



Working hypothesis:

- 1) Tin tetrachloride must coordinate to the chiral H-Donor (chiral LBA)
- 2) Reactivity of chiral LBA \gg achiral LBA

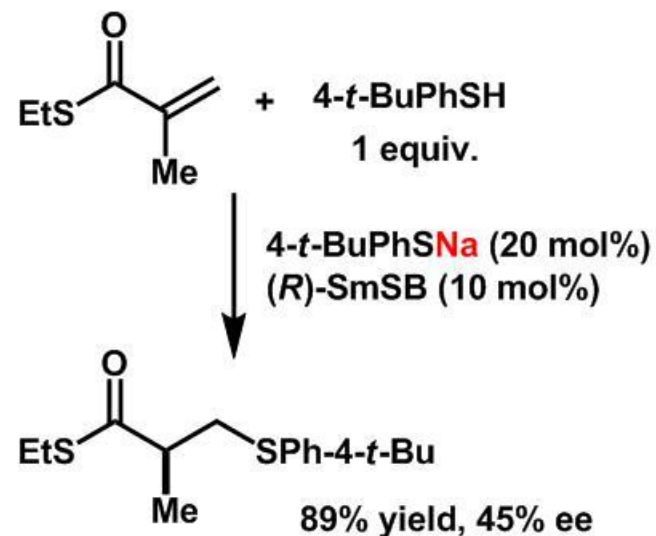
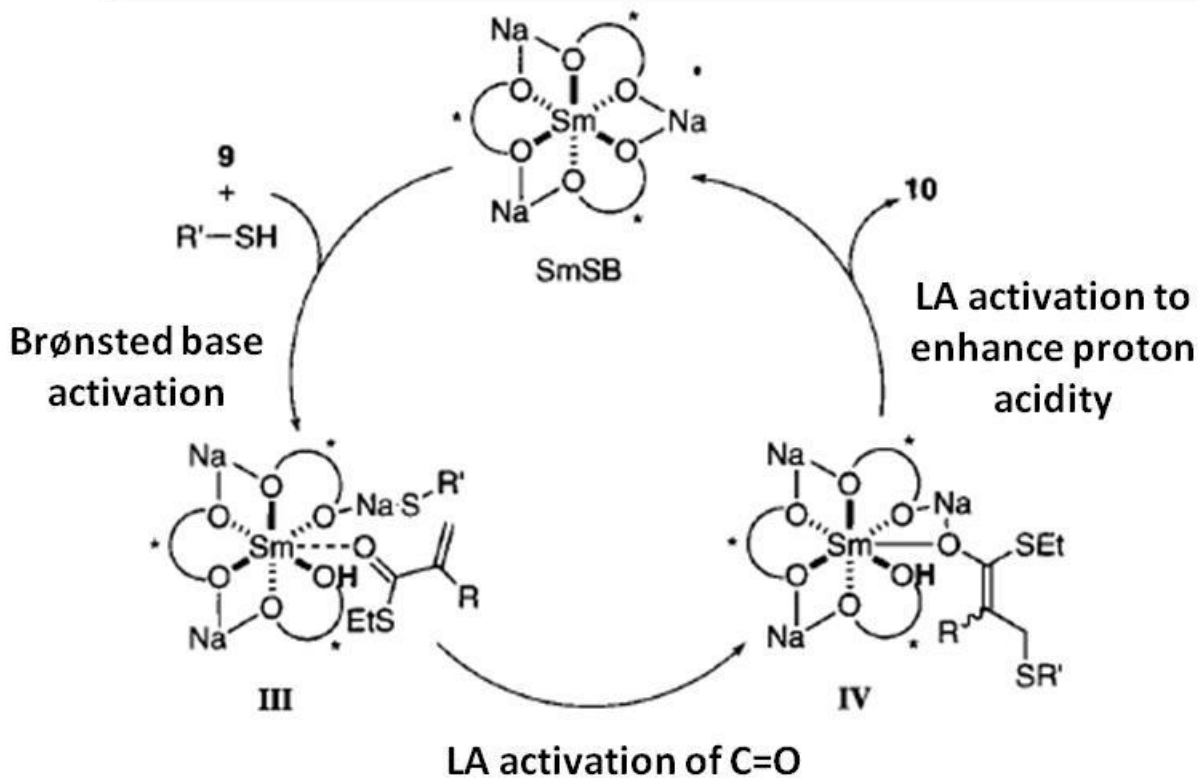
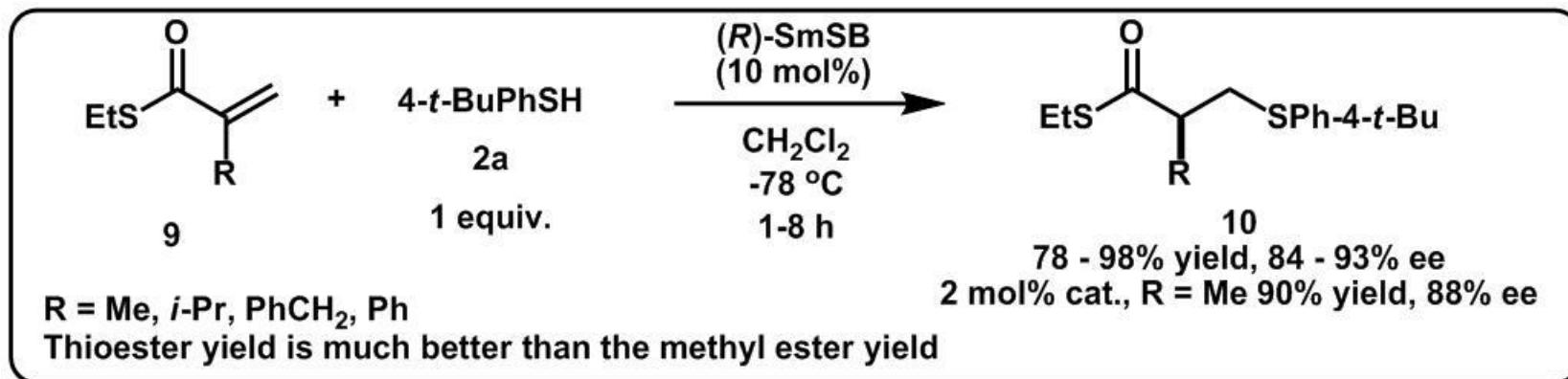


LBA	conversion of 3a to 4a (%) ^b
(R)-2·SnCl ₄	100
7·SnCl ₄	17
SnCl ₄ ^c	0

Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 8120

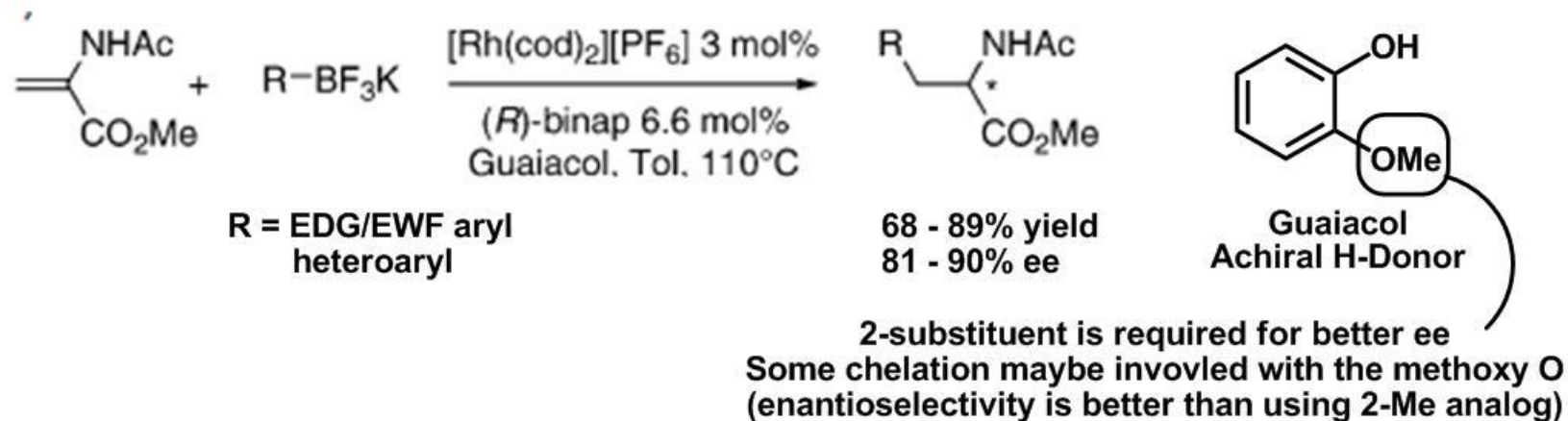
Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854

Catalytic EP in Michael Addition Reaction

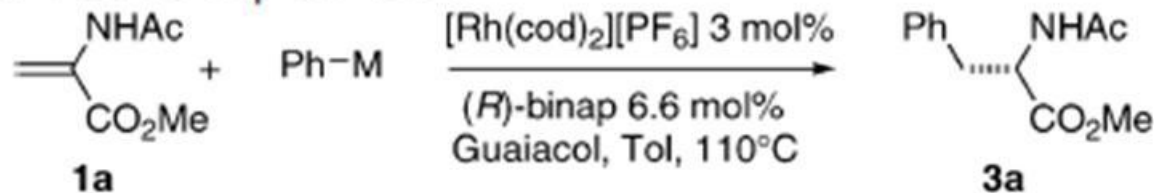


SmSB = SmNa₃tris(binaphthoxide) complex

Tandem 1,4-Addition/Enantioselective Protonation



Other Ph-M Donors:

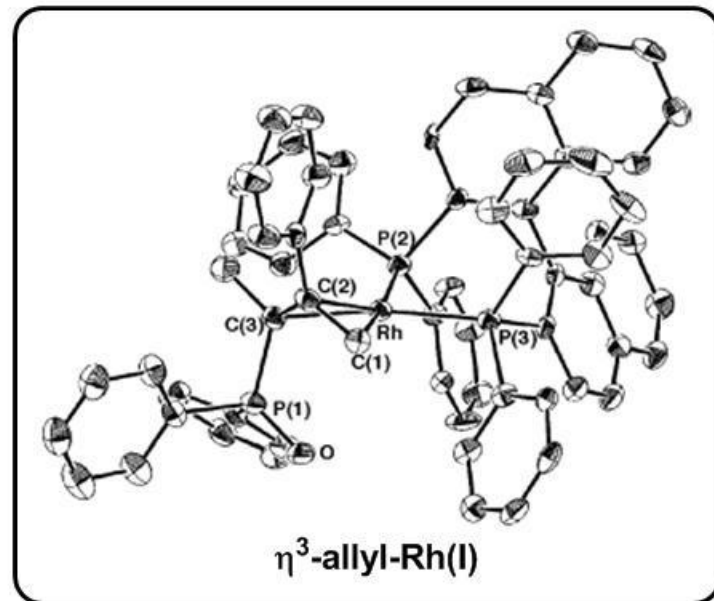
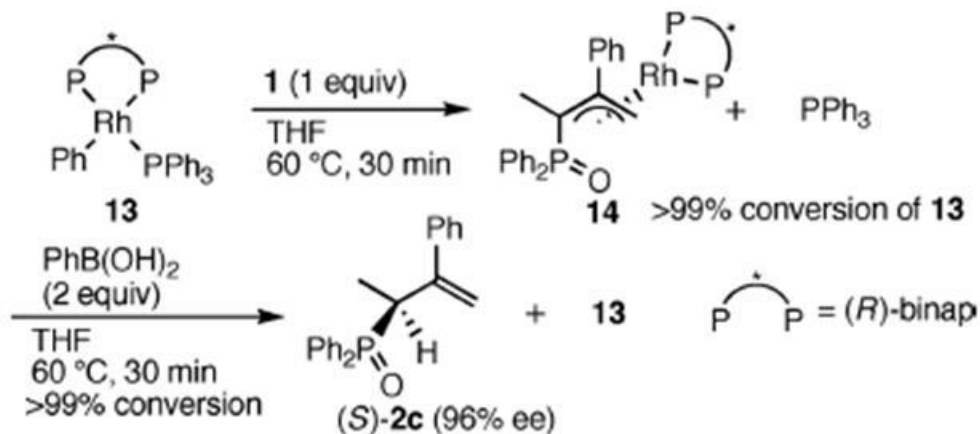
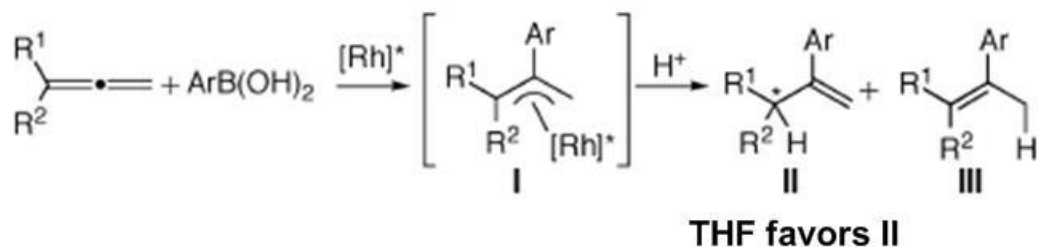
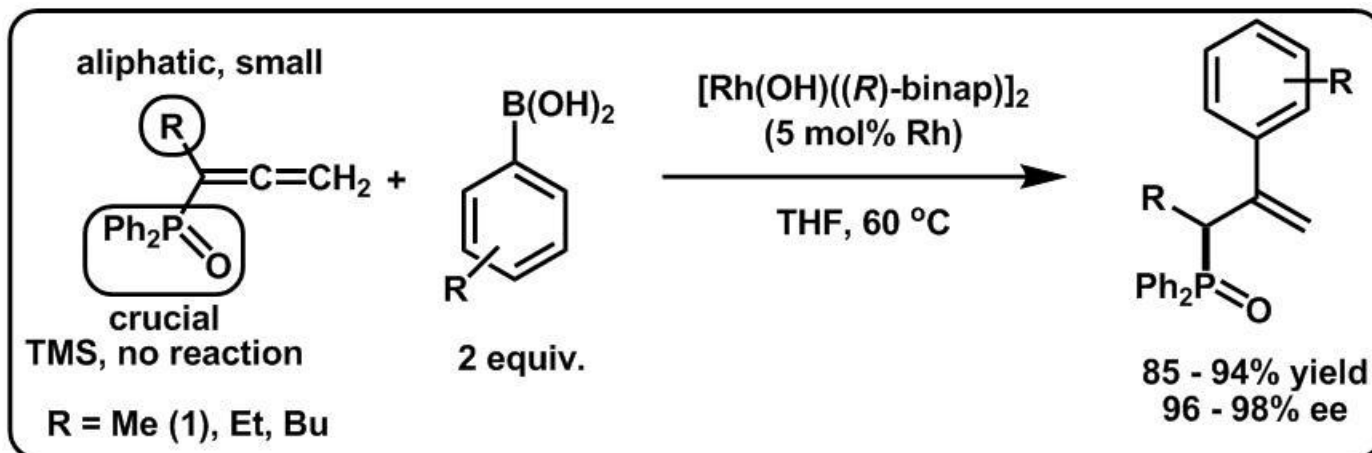


Entry	Ph-M	Yield [%]	$ee^{[b]}$ [%]
1	PhBF_3K 2a	89	89.5
2	$\text{PhB}(\text{OH})_2$ 2b	42 (due to reduction)	42
3	$\text{PhBpin}^{[c]}$ 2c	0	
4	Ph_2SiCl_2 2d	0	
5	2d / $\text{NaF}^{[d]}$	0	
6	PhSnBu_3 2e	52	88
7	PhSnMe_3 2f	89	71

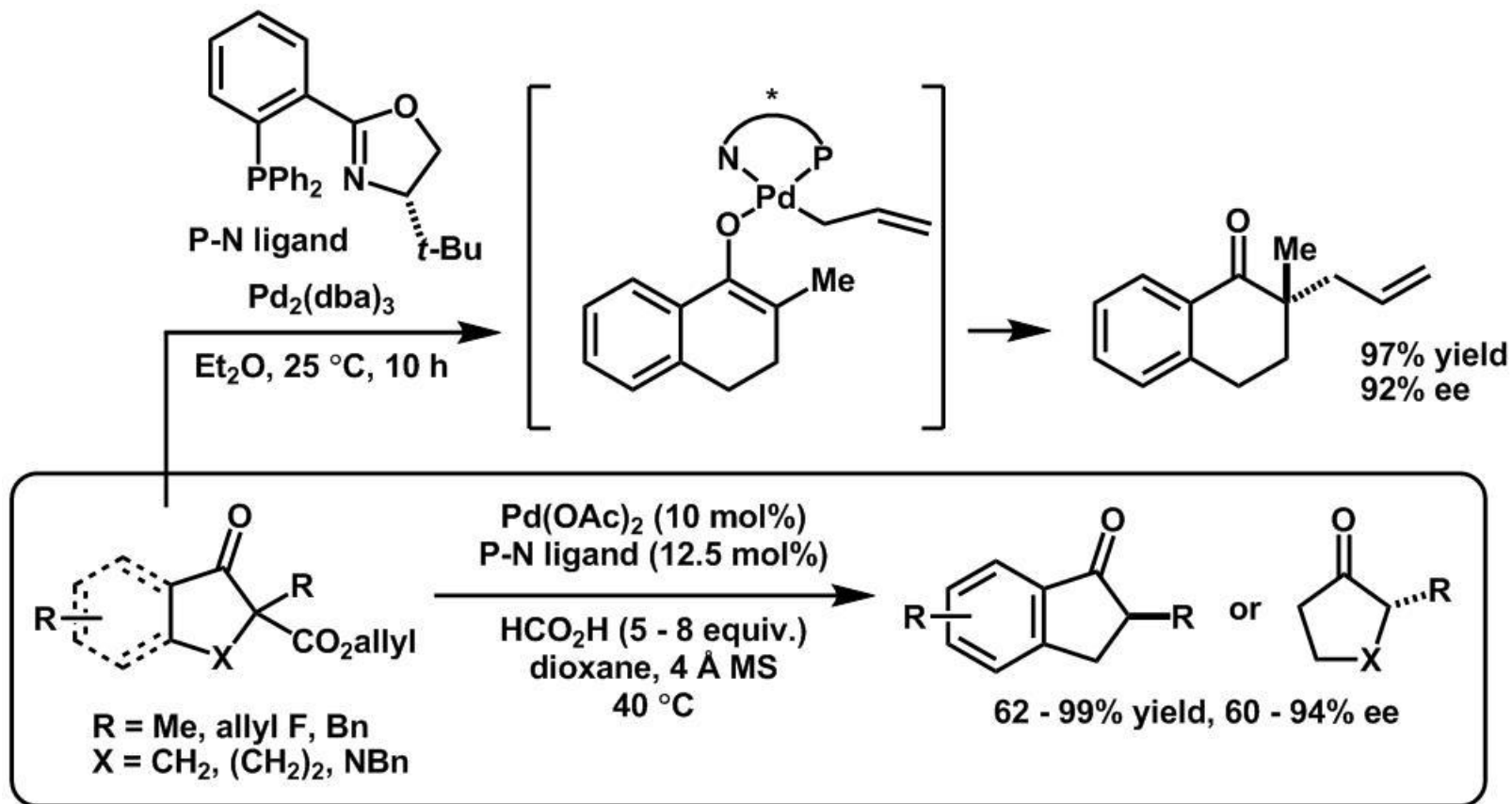
Hayashi was able to use boronic acid (see next slide)

Opportunity for SILANOL?

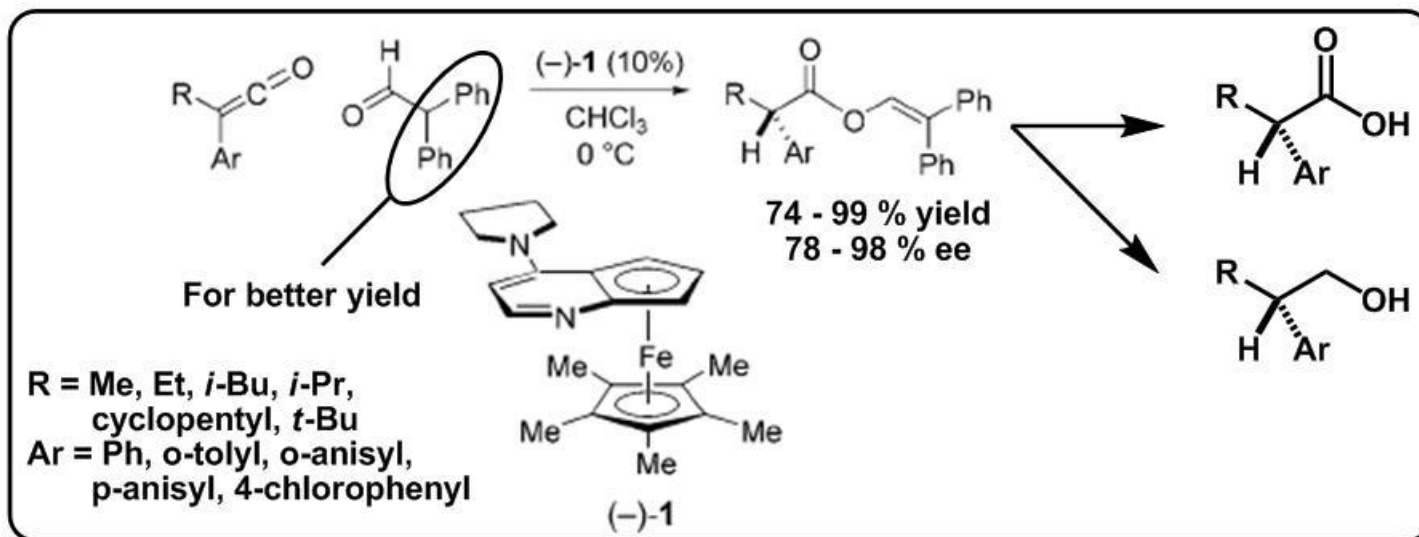
Rh-Catalyzed Asymmetric Hydroarylation



Catalytic Enantioselective Decarboxylative Protonation



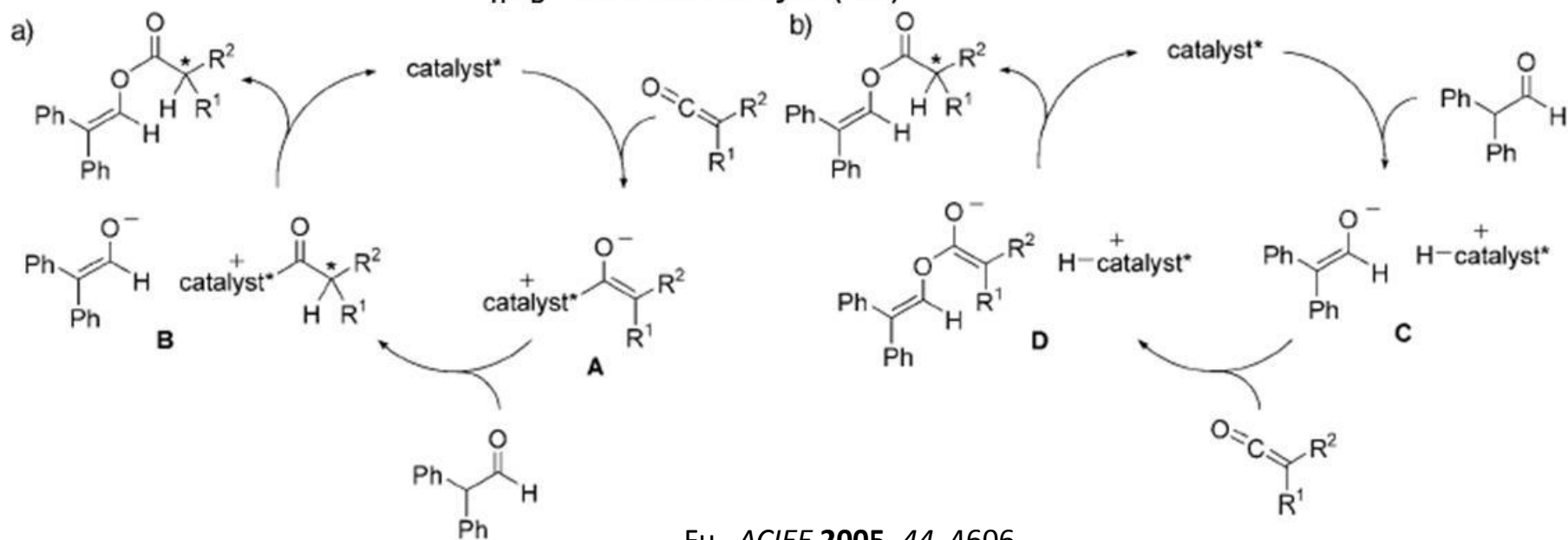
Catalytic Asymmetric Couplings of Ketenes with Aldehydes



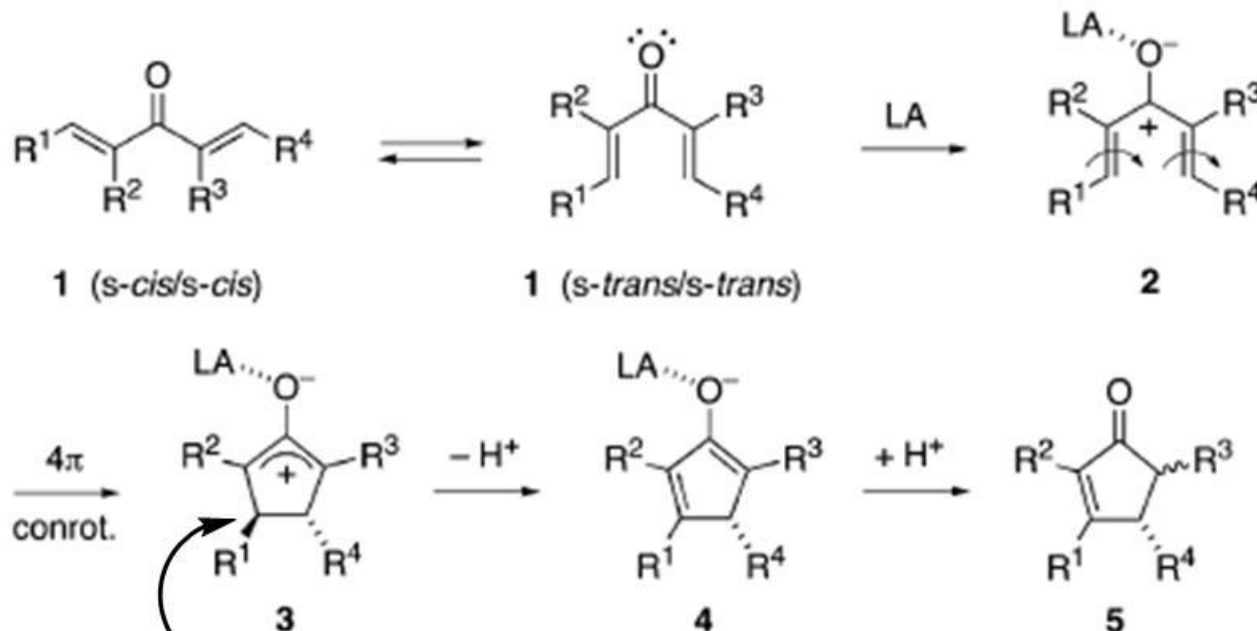
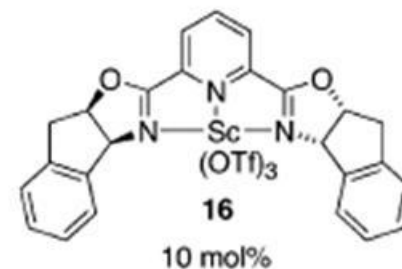
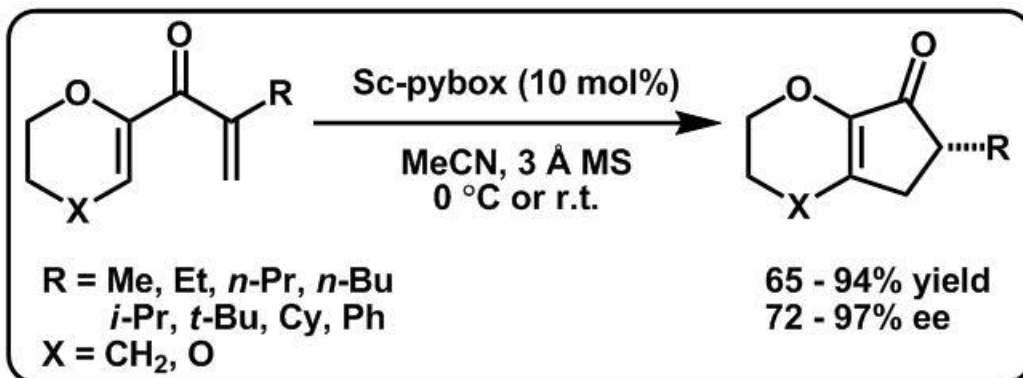
Proposed Mechanisms:

no non-linear effect

rapid H/D exchange between the aldehyde (α -H) and D₂O in the presence of 1
 $k_H/k_D \sim 2$ for the aldehyde (α -H)



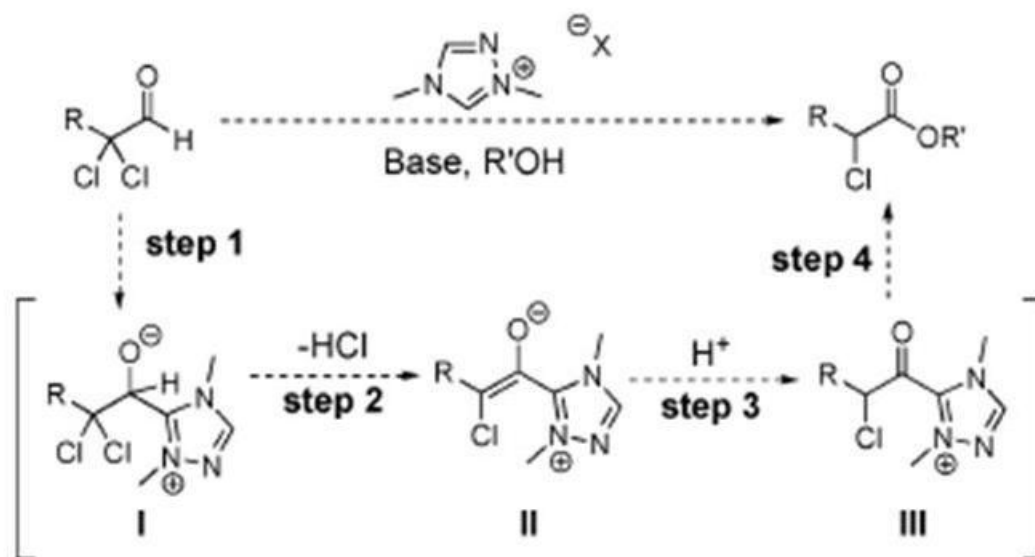
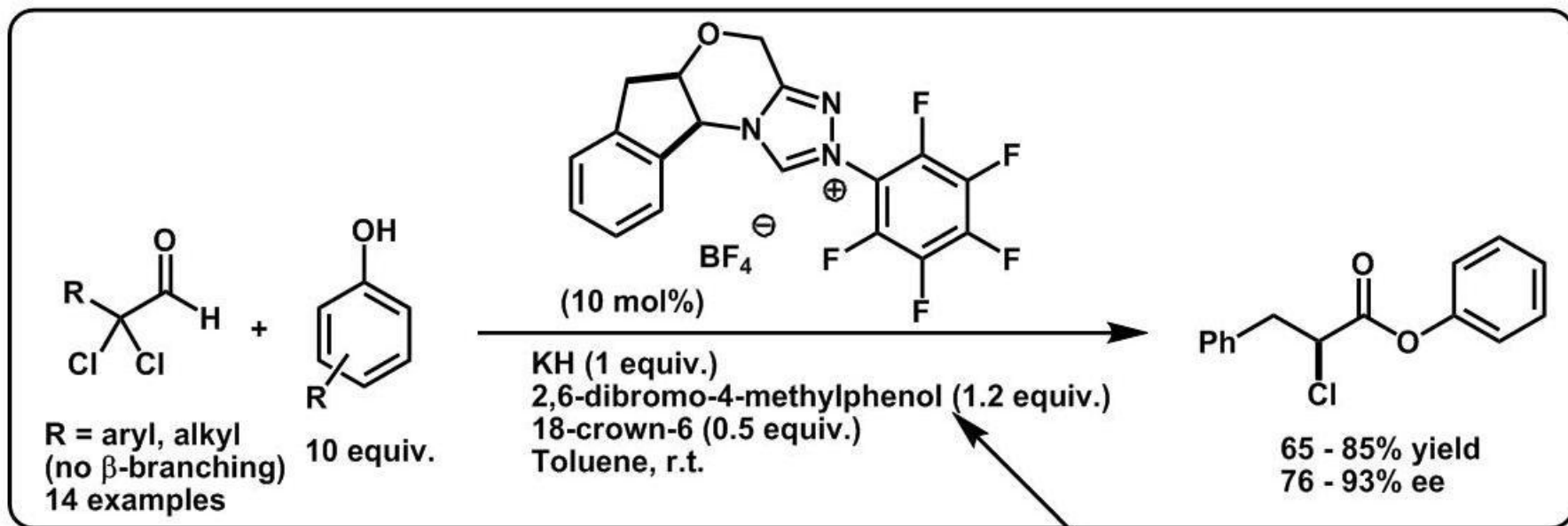
Catalytic EP in Nazarov Reaction



* destroyed
EP is controlled by pybox ligand

No external proton source required!

Catalytic EP in Umpolung



Bulky phenol for better enantioselectivity

Presumably acting as a buffer to minimize background epimerization of the product

Conclusion

Enantioselective protonation, an easy and practical way to generate a new stereogenic center – Not So Simple!

- Reaction optimization is required for different classes of substrate
- Enantioselectivity can be highly dependent on substituent pattern
- Ligand screening is still the best approach
- **Catalyst can be recycled easily**
- Attractive for large scale production once condition is found

To further advance in this area, thorough understanding of the aggregate and the effect of additives are required experimentally and computationally in order to understand the mechanism and to rationally design a catalyst for enantioselective protonation.

Reviews:

Fehr *ACIEE* **1996**, 35, 2566

Plaquet *Tetrahedron: Asymmetry* **2004**, 15, 3653

Eames *Tetrahedron: Asymmetry* **2001**, 12, 1

Yamamoto *Synlett* **1997**, 411