

# Asymmetric Deprotonations and Substitutions

Mark Mans

# Outline

## Organolithiums

- Synthesis
- Regioselectivity

## Asymmetric Deprotonations

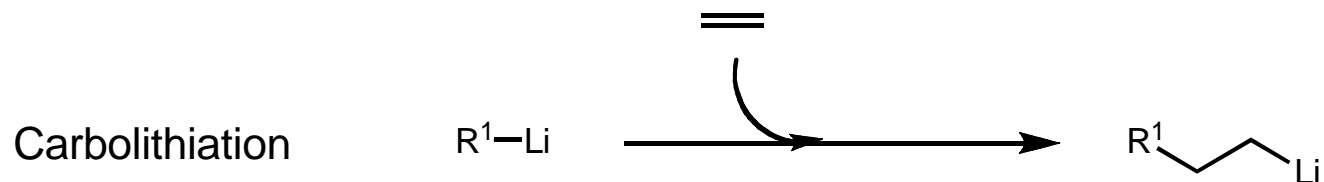
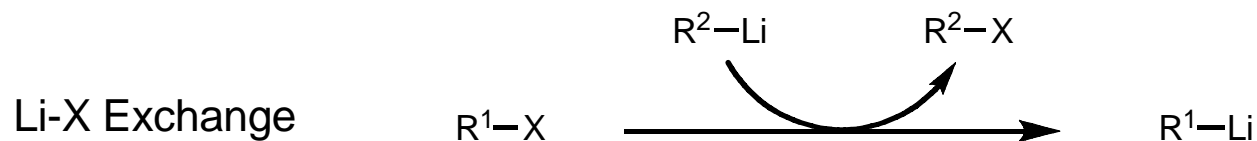
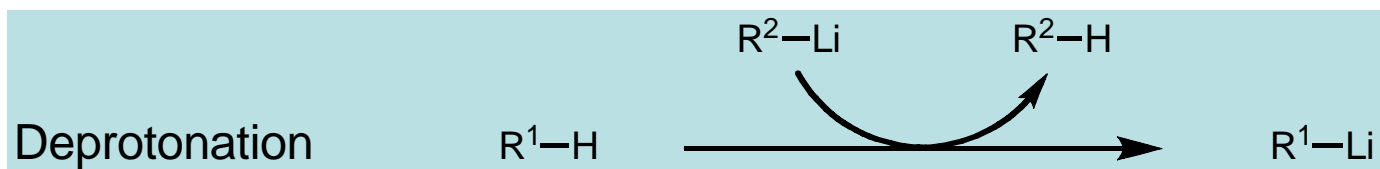
- Configurational Stability
- Transmetallations/Applications
- Catalytic Variants

## Asymmetric Substitutions

- Resolutions
- Dynamic Thermodynamic Resolutions

## Summary

# Synthesis of Organolithiums



# What To Deprotonate

Deprotonation of sp centers works well

Deprotonation adjacent to carbonyl sulfoxide, sulfone, or phosphonate works well

small rings, allylic/benzylic positions work ok

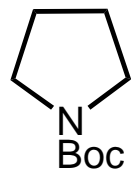
For sp<sup>3</sup> center need:

C-Li adjacent to O or N ( $\alpha$ -lithiation)

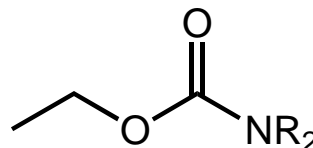
Helpfully positioned heteroatom to stabilise C-Li by coordination

More remote acidifying effect (EWG *ortho* on ring for example)

Today's focus:



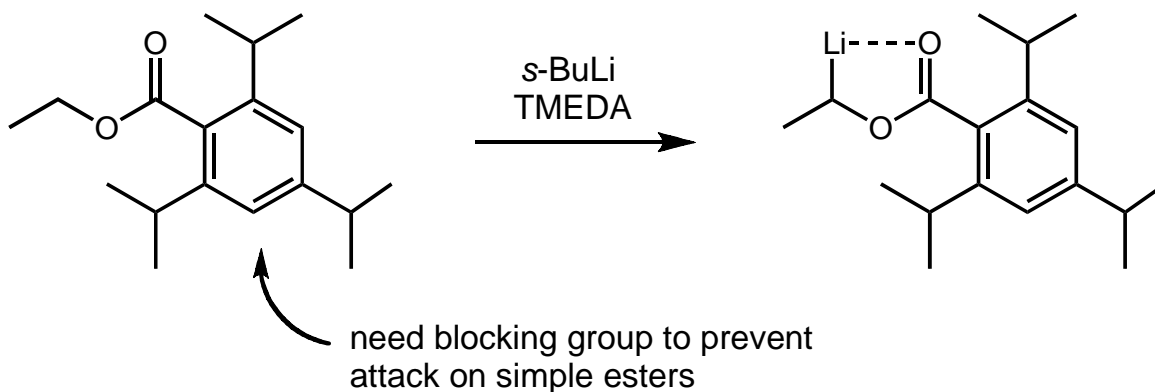
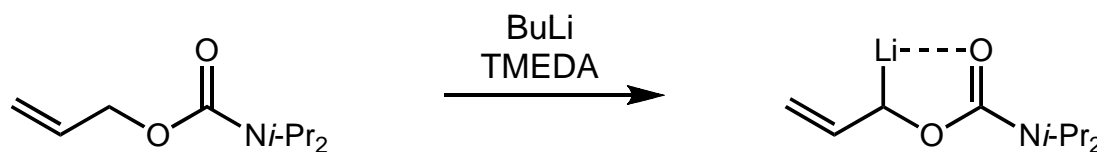
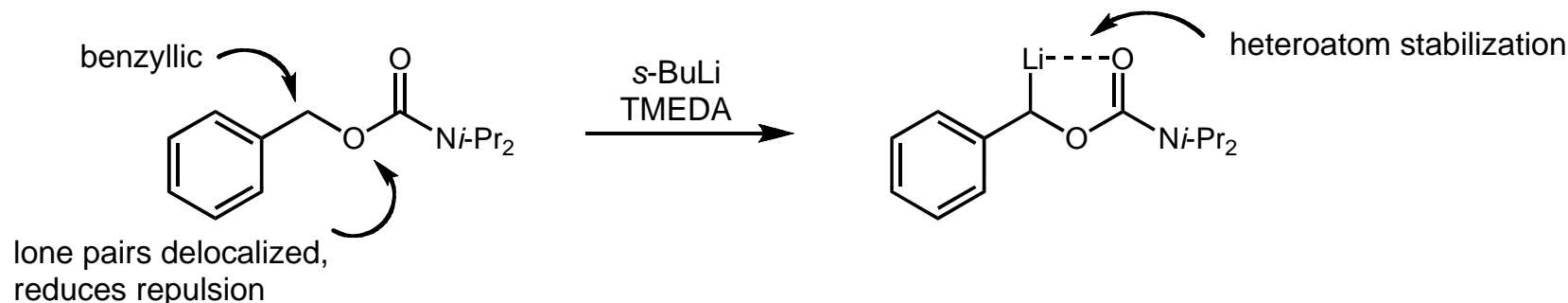
N-Boc pyrolidine  
Beak's Group



O-alkyl carbamates  
Hoppe's Group

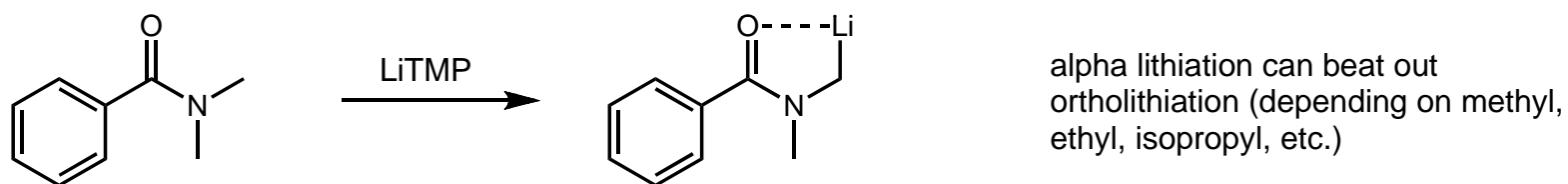
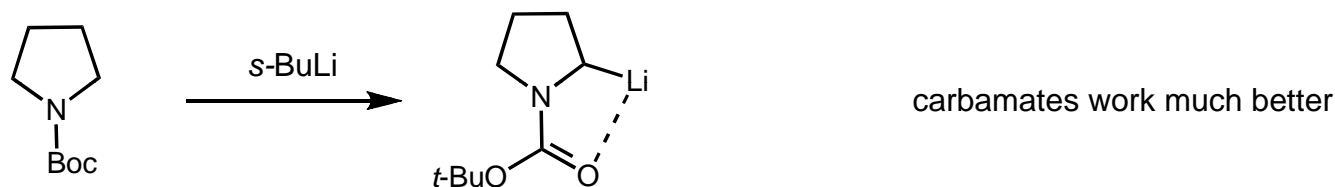
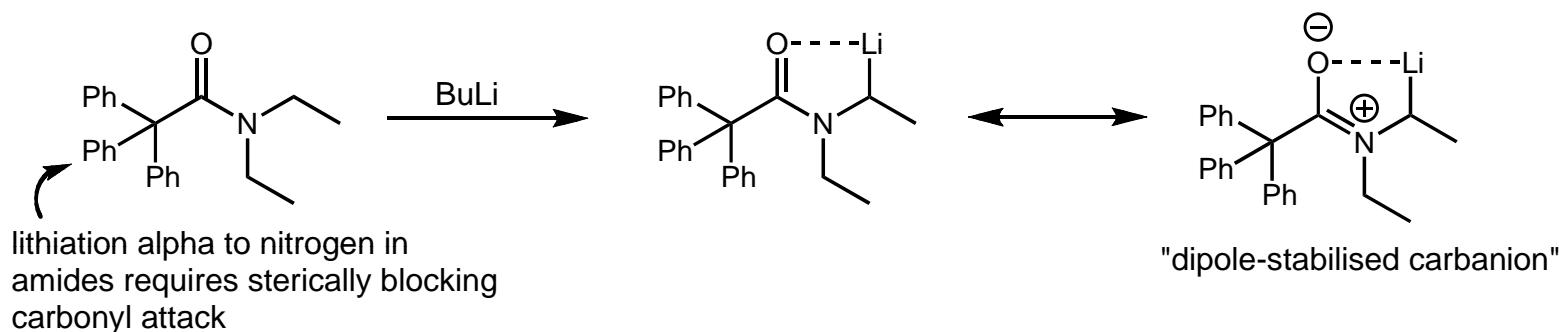
# Lithiation Alpha to Oxygen

In general, deprotonation alpha to oxygen is unfavorable: antibonding interaction of oxygen's lone pairs with C-Li bond overcomes the electron withdrawing effect of oxygen



# Lithiation Alpha to Nitrogen

Antibonding interaction even worse than that of oxygen so direct deprotonation alpha to nitrogen essentially impossible. Must have delocalization.



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## Asymmetric Deprotonations

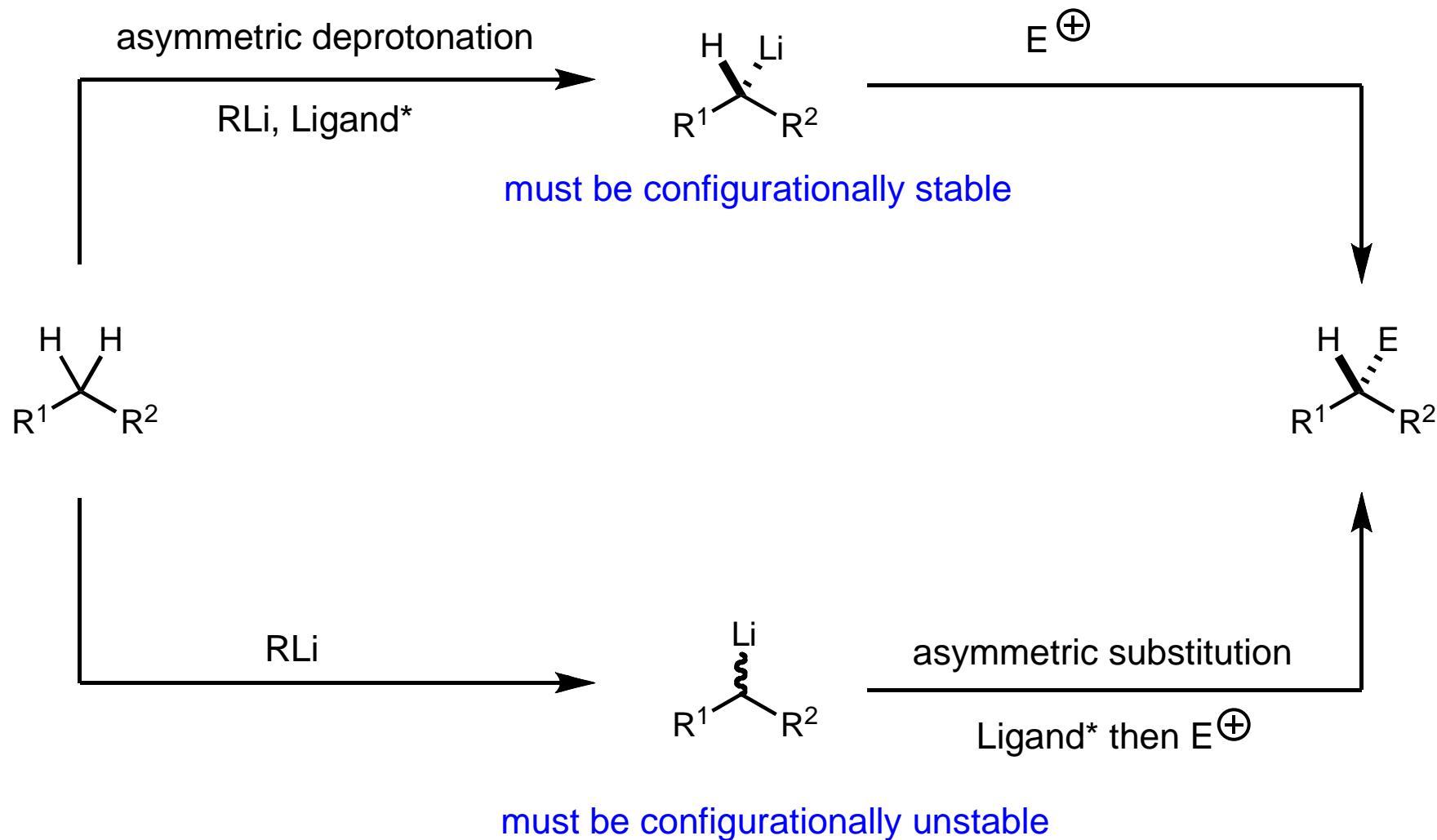
- Configurational Stability
- Transmetallations/Applications
- Catalytic Variants

## Asymmetric Substitutions

- Resolutions
- Dynamic Thermodynamic Resolutions

## Summary

# Asymmetric Deprotonation or Substitution



# Configurational Stability

Need  $sp^3$  hybridized organolithium to be configurationally stable for asymmetric deprotonation.

## ***Hoffmann test for configurational stability:***

### ***Advantages***

Previously had to lithiate enantiomerically enriched or diastereomerically pure compounds (which were often a pain to make).

Hoffman test allows you to use a racemic organolithium generated from prochiral s.m.

### ***The Test***

Rxn 1 - A *racemic* organolithium is reacted with an *enantiomerically enriched* electrophile.

Measure the ratio of  $^{1,3}\text{syn}:^{1,3}\text{anti}$  products.

Rxn 2 - A *racemic* organolithium is reacted with a *racemic chiral* electrophile. Measure the ratio of  $^{1,3}\text{syn}:^{1,3}\text{anti}$  products.

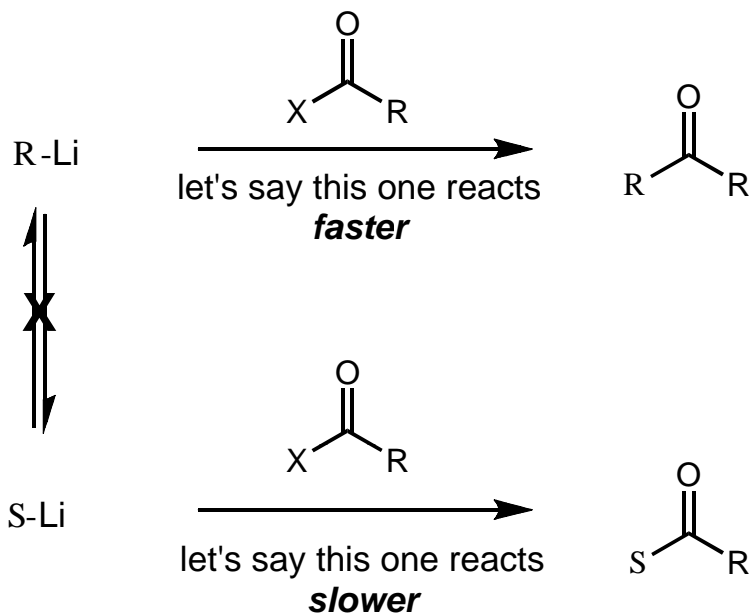
### ***Bottom Line***

A difference in the ratios between the two rxns = configurational stability

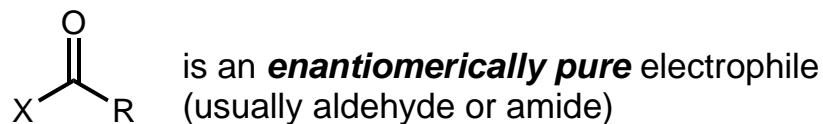
# Configurational Stability

Case 1 - Configurationally stable organolithium with enantiomerically pure electrophile (Rxn 1)

configurationally **stable**  
so no interconversion...  
should have 50:50 mixture  
of each after deprotonation



As long as we run this rxn to completion then we should eventually have the same 50:50 mixture that we started off with. It just takes the slower one a little longer to get there.

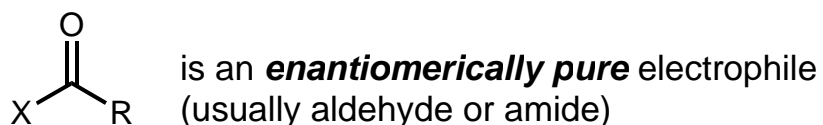
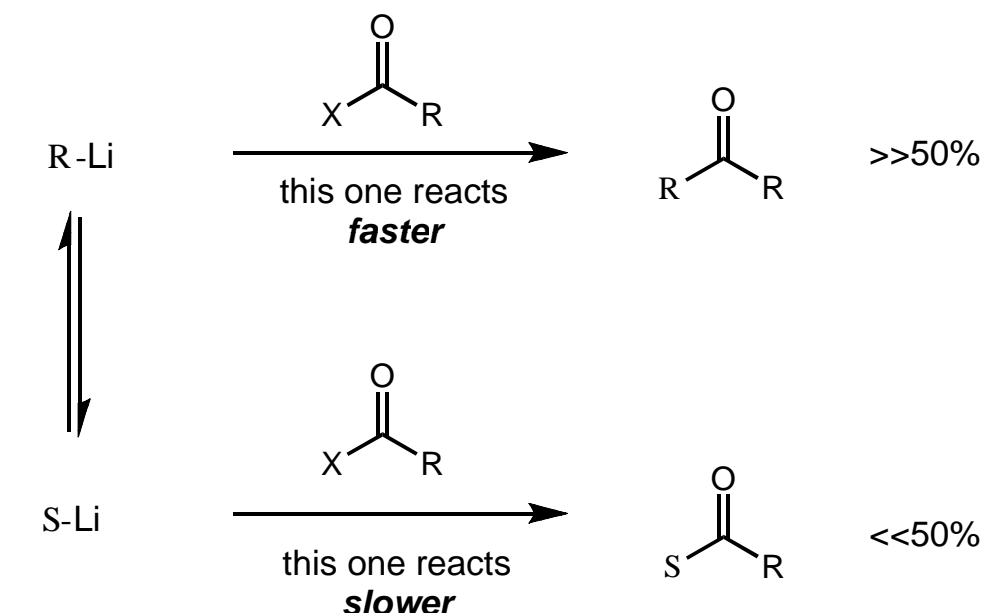


**Potential Problem** - Must run to completion or may get a non-50:50 ratio even though the organolithium is stable

# Configurational Stability

Case 2 - Configurationally unstable organolithium with enantiomerically pure electrophile (Rxn 1)

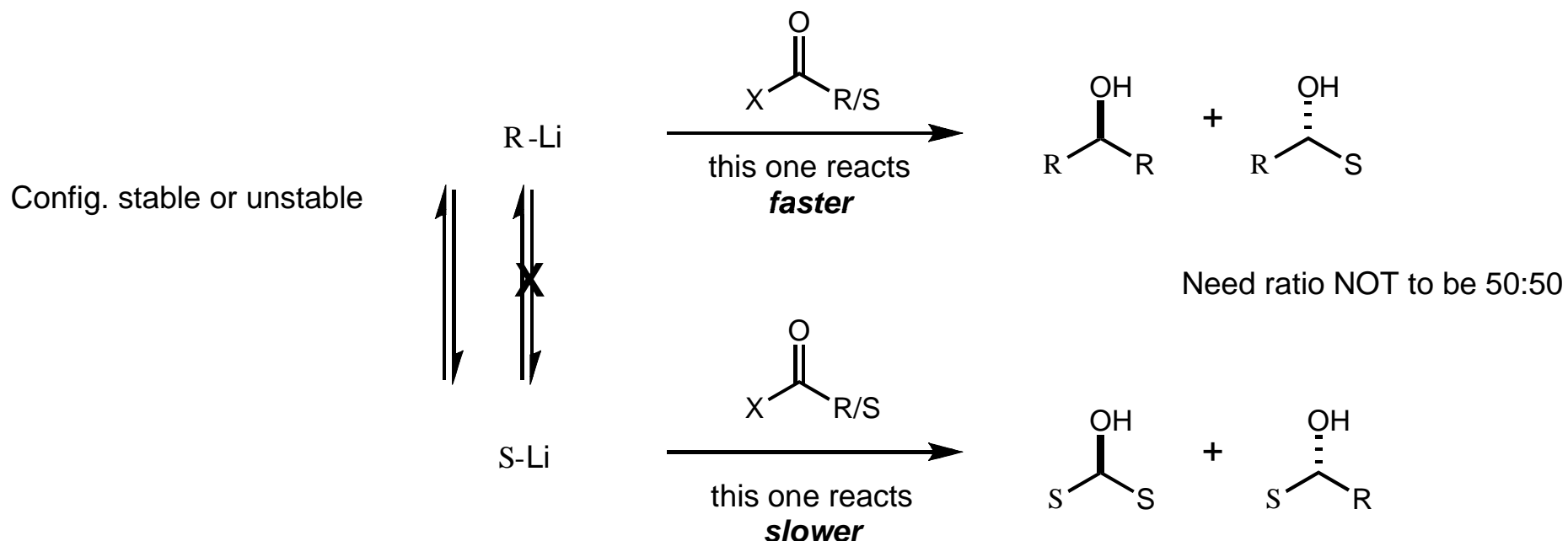
Deprotonate to get 50:50 mixture. But now **can interconvert**. Difference in rates (b/c different TS energies) lead to formation of one product over the other.



**Potential Problem** - If the TS energies aren't very different, may get ~50:50 ratio even though organolithium is unstable (hence the reason for Rxn 2 of Hoffmann test).

# Configurational Stability

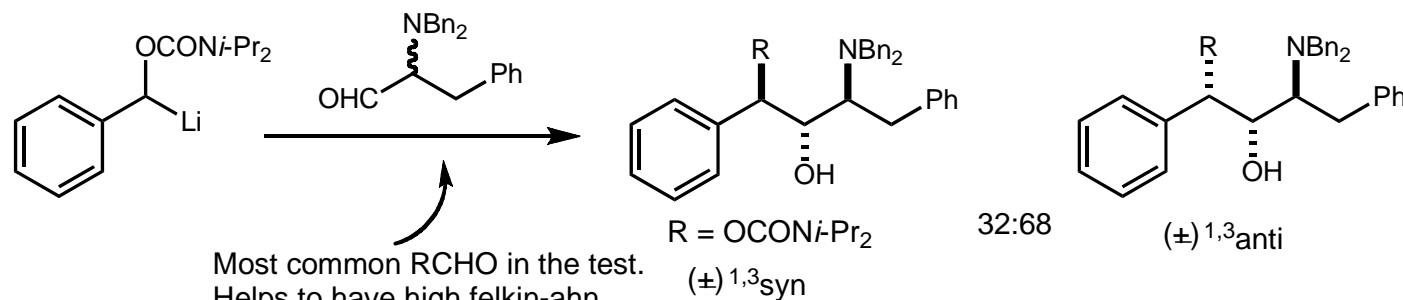
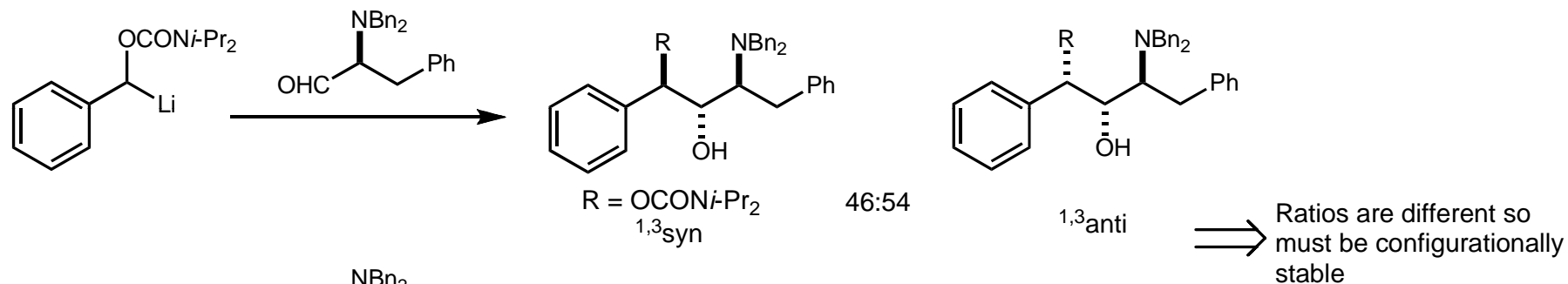
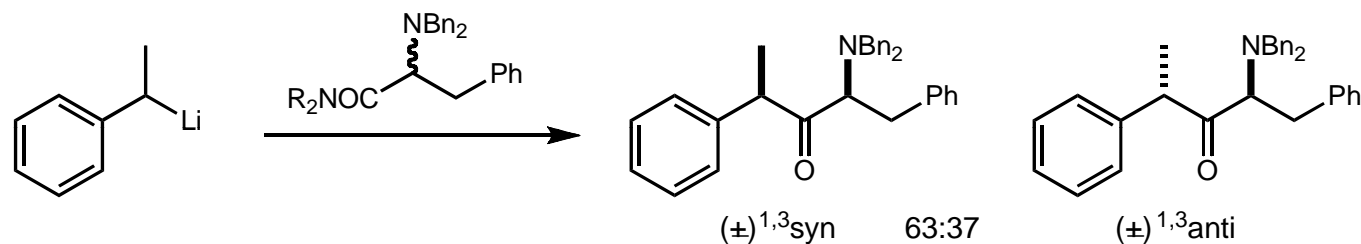
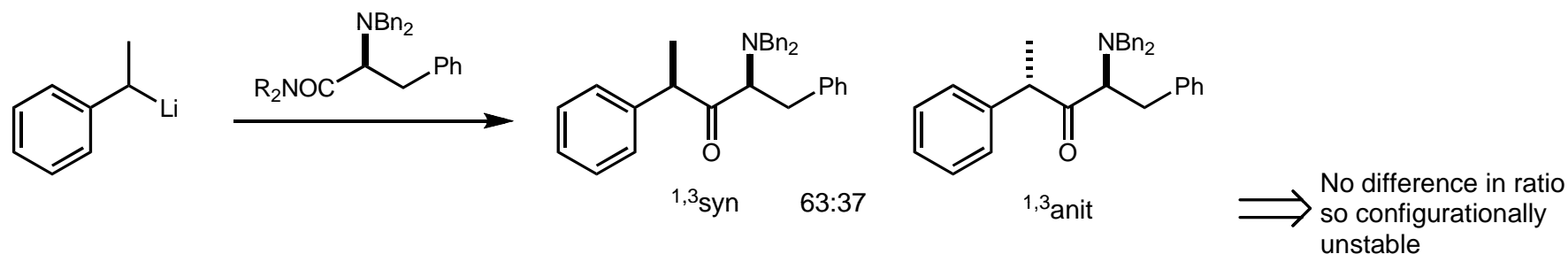
## Case 3 - Racemic organolithium with a racemic electrophile (Rxn 2)



If organolithium is unstable...situation is just like Case 2 and the organolithium can ignore the stereochem of the electrophile... and **the same ratio of diastereomers ensues from the racemic as from the enantiomerically pure electrophile.**

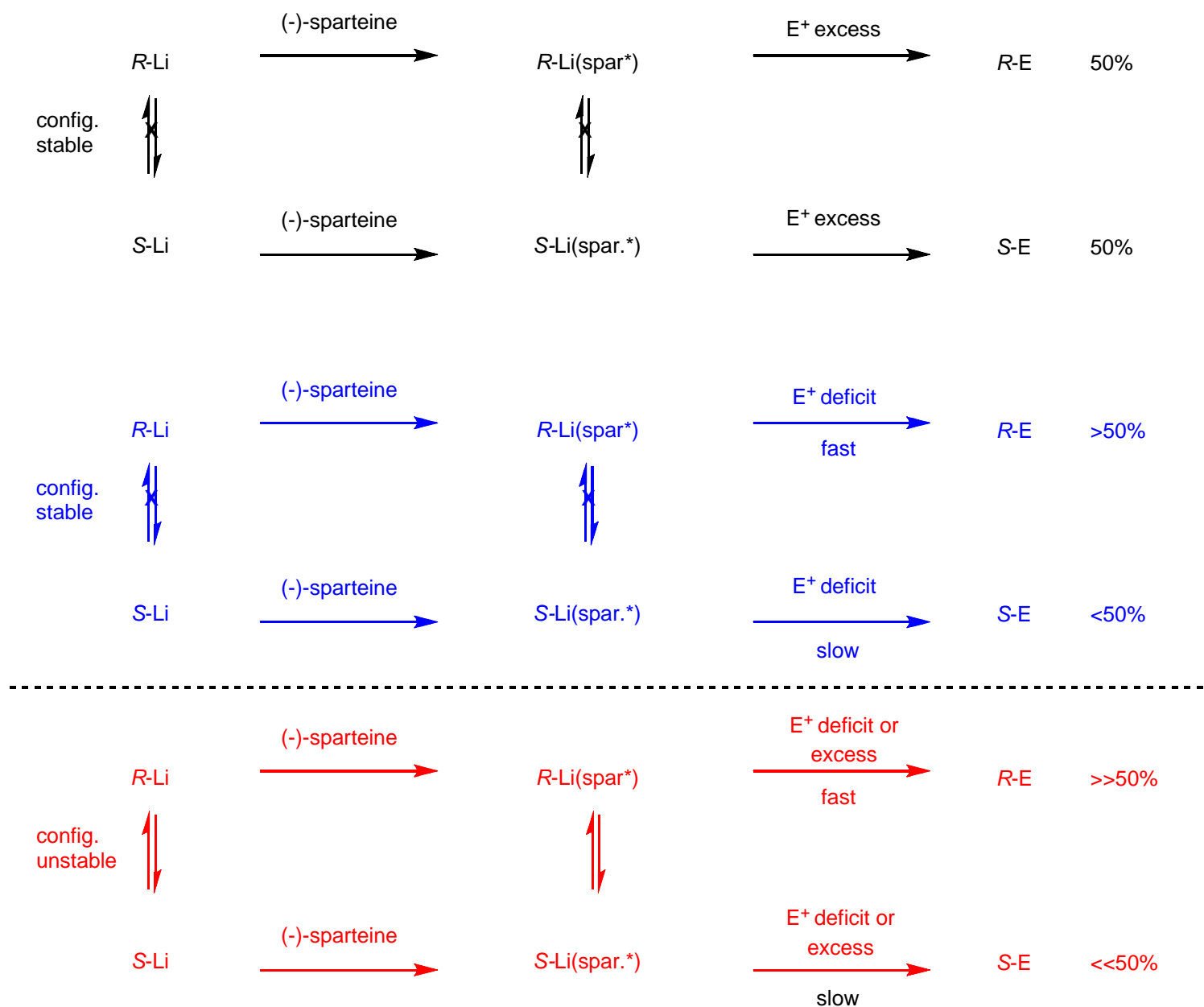
If organolithium is stable...both enantiomers have the opportunity to react at the rate of the faster-reacting enantiomer from before. Thus **the ratio of diastereomers here will differ from the ratio using enantiomerically pure electrophile.**

# Huh?

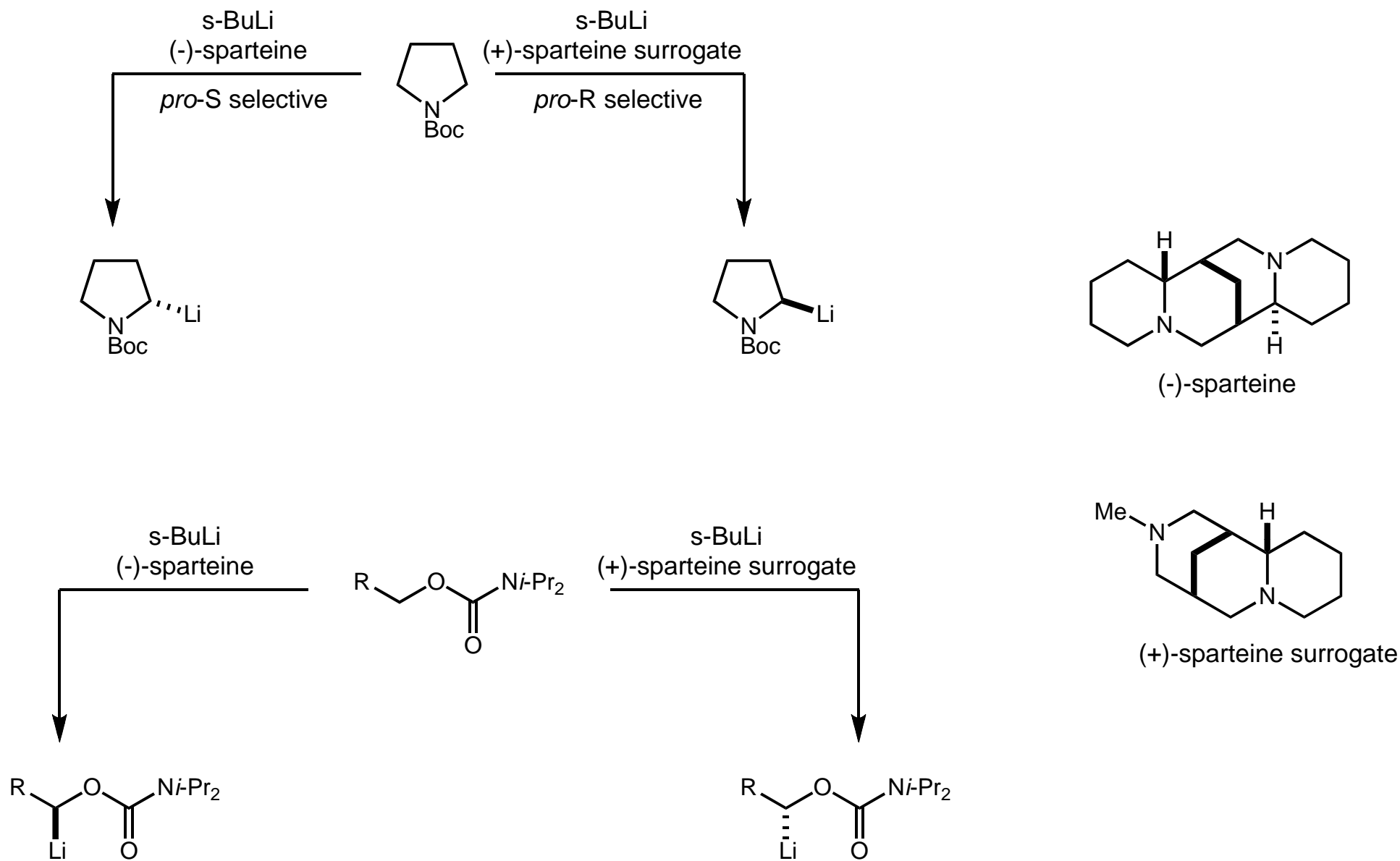


Most common RCHO in the test.  
Helps to have high Felkin-ahn selectivity.

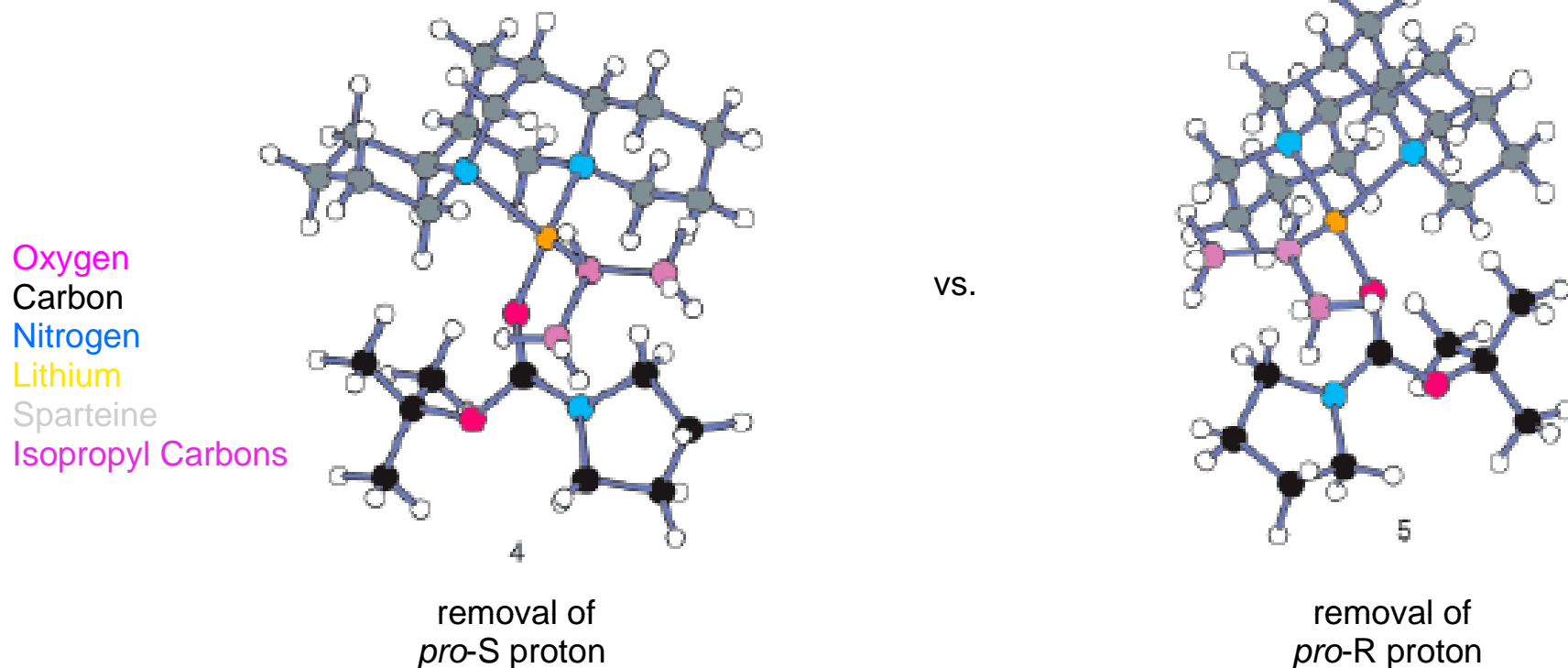
# Poor Man's Hoffmann Test



# Enantioenriched Organolithiums

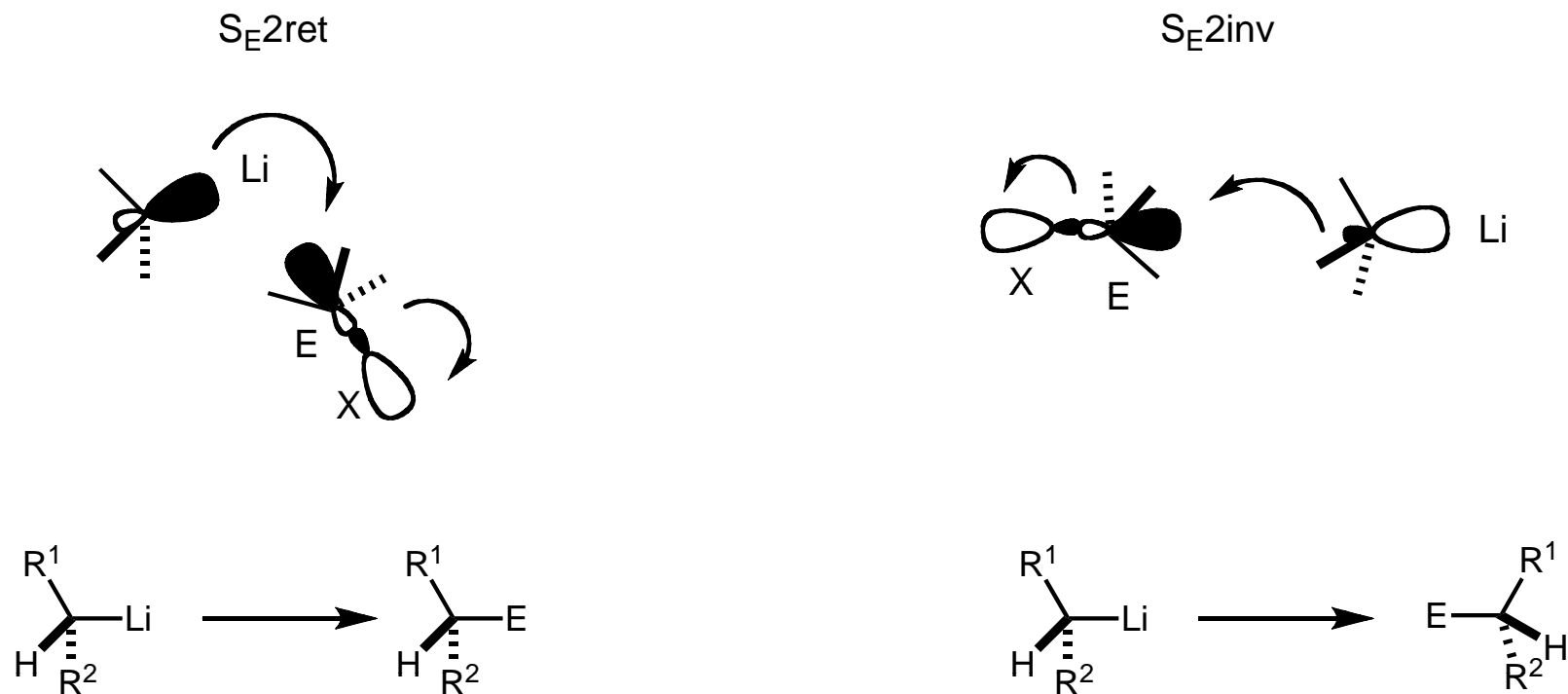


# Model for Enantioselectivity



Enantioselectivity appears to be due mainly to sterics. The major repulsive interactions present in the ground state of the more stable, three-component intermediate complex (**4**), are relieved on going to the TS for transfer of the *pro-S* hydrogen.

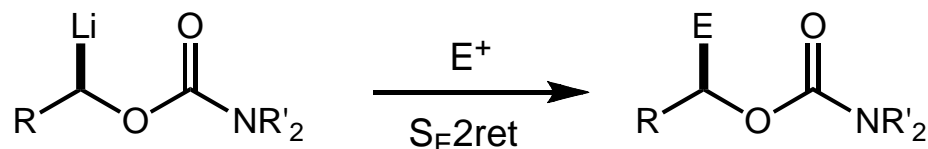
# Reaction with Electrophiles



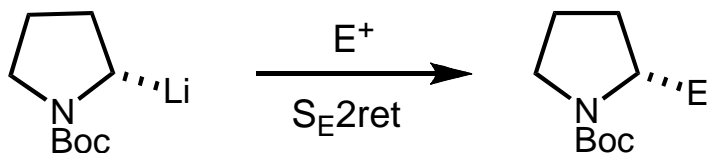
In general these rxns proceed via  $S_{E2ret}$  for non-stabilized (i.e. non-benzylic or allylic) organolithiums.  
When  $S_n$  is electrophile though, see inversion.

Can have inversion or retention with benzylic/allylic organolithiums...tough to tell ahead of time.

# Electrophiles



$E^+$	E	ee
$CO_2$	$CO_2H$	>95
MeI	Me	>95
$Me_3SiCl$	$Me_3Si$	>95
allyl bromide	allyl	42
$Me_3SnCl$	$Me_3Sn$	>95, inverted

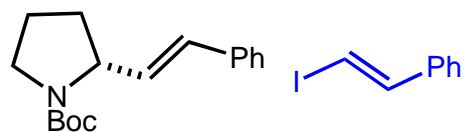
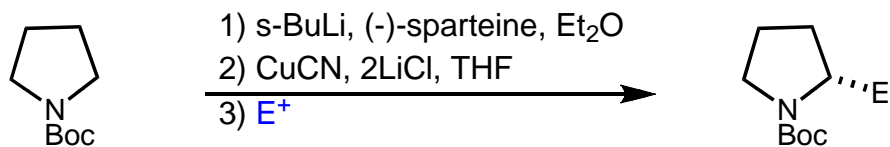


$E^+$	E	ee
$Ph_2CO$	$C(OH)Ph_2$	90
$CO_2$	$CO_2H$	88
$Me_3SiCl$	$Me_3Si$	96
$Me_2SO_4$	Me	94
$Bu_3SnCl$	$Bu_3Sn$	94, inverted

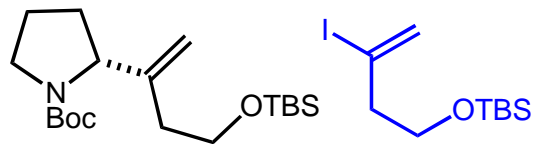
In general the range of electrophiles is somewhat limited

# Increased Substrate Scope

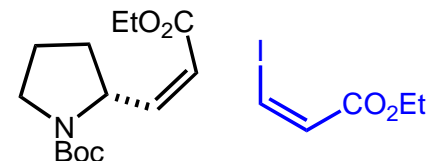
Transmetalation from lithium to copper greatly increases range of electrophiles



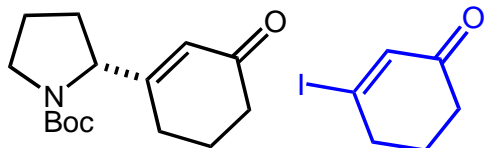
70%  
89:11 er



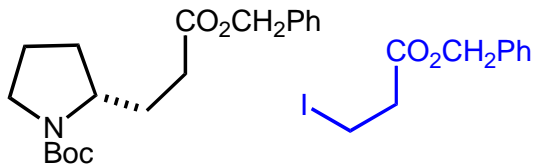
84%  
94:6 er



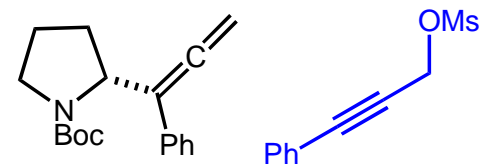
89%  
95:5 er



79%  
80:20 er



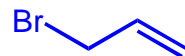
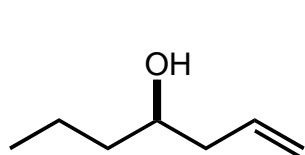
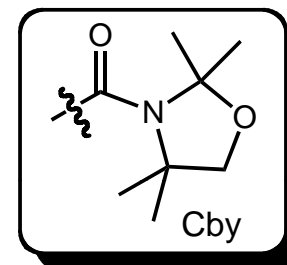
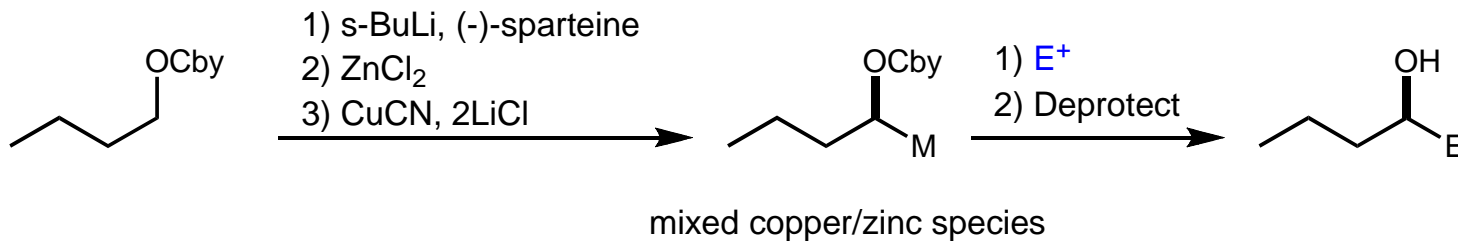
95%  
racemic



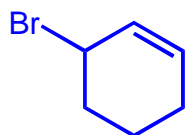
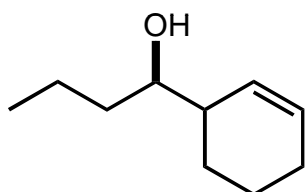
57%  
65:35 er

For the most part, the transmetalation proceeds with retention of configuration.  
However there can be a loss in the enantioselectivity during the transmetalation.

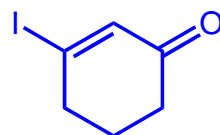
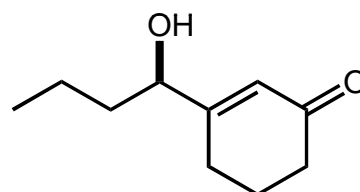
# Increased Substrate Scope



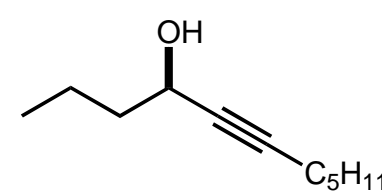
90%  
99% ee



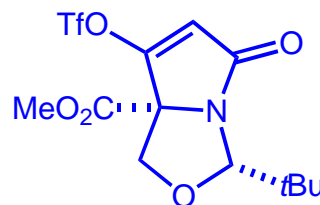
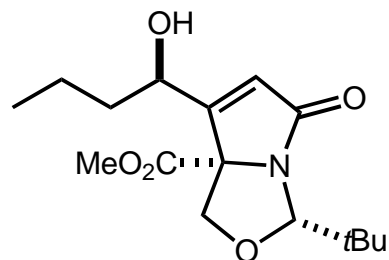
83%  
n.a.



61%  
97% ee



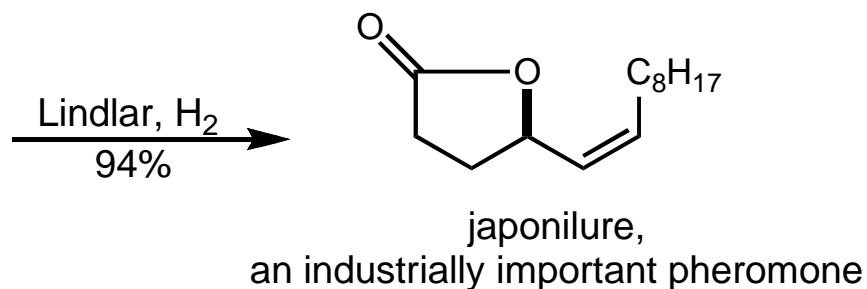
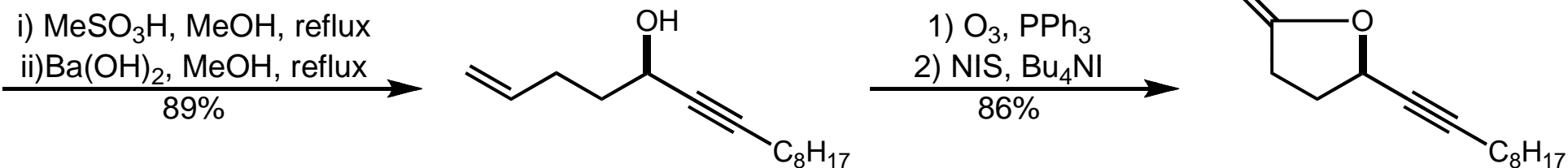
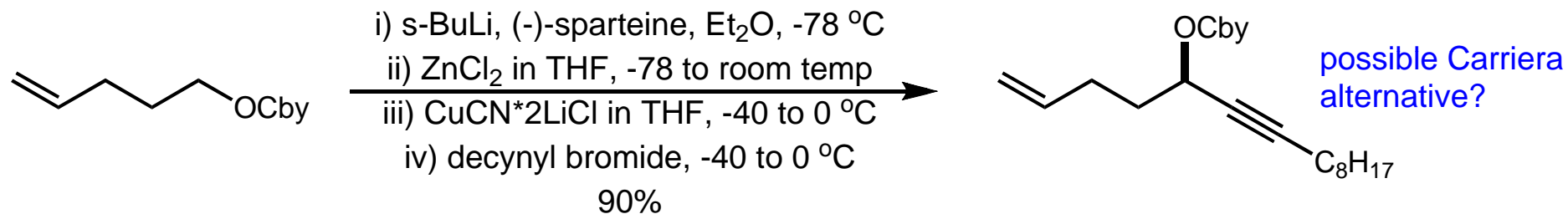
98%  
>99% ee



69%  
one diastereomer by NMR

Unlike the *N*-Boc-pyrrolidines,  
could not transmetallate directly to  
copper

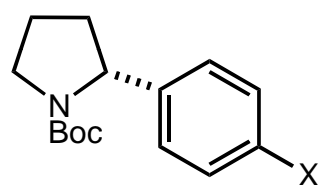
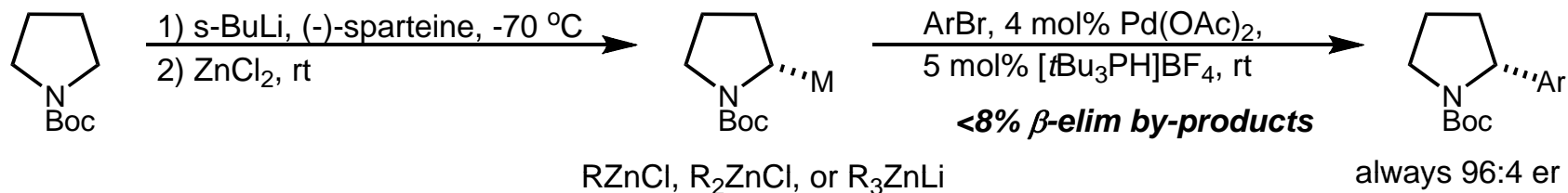
# Application in Synthesis



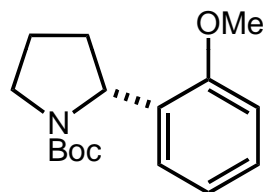
The Cu approach doesn't work well for arylation though

# Transmetalation/Cross Coupling for Arylation

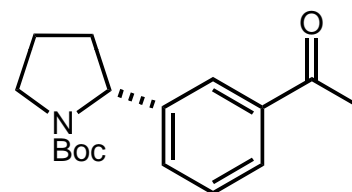
*First direct asymmetric arylation of an enantioenriched carbanion*



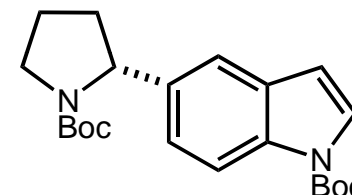
75-81%



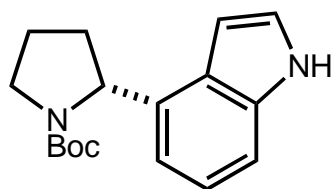
71%



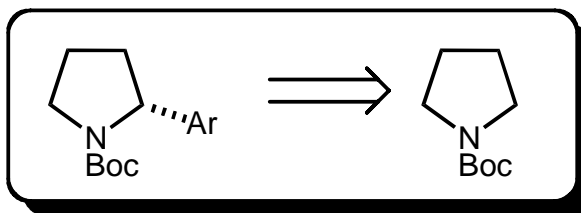
78%



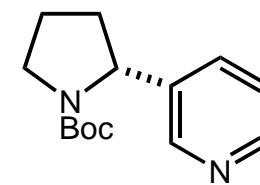
81%



77%

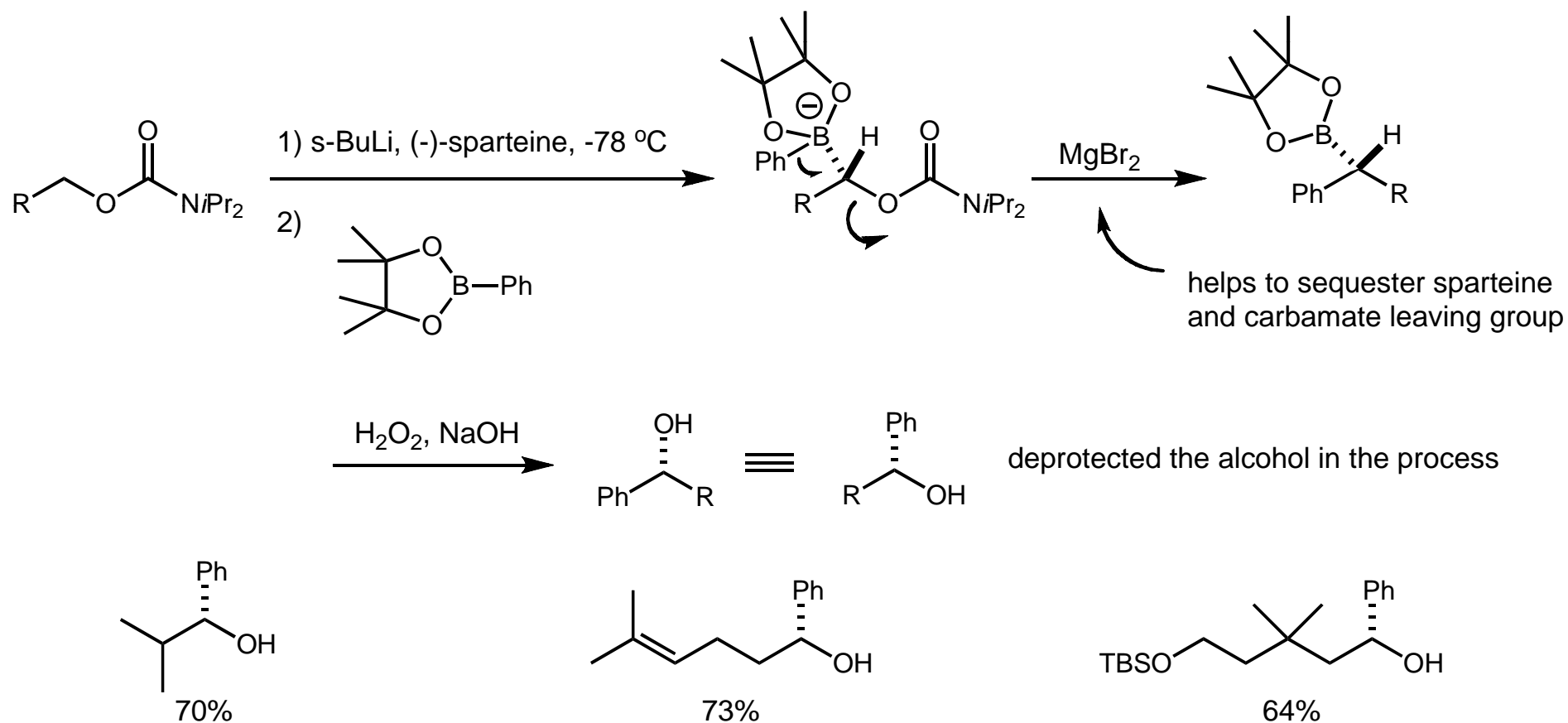


Could use 1, 0.6, or 0.35 eq of ZnCl<sub>2</sub> suggesting that all types of organozincs can be involved.



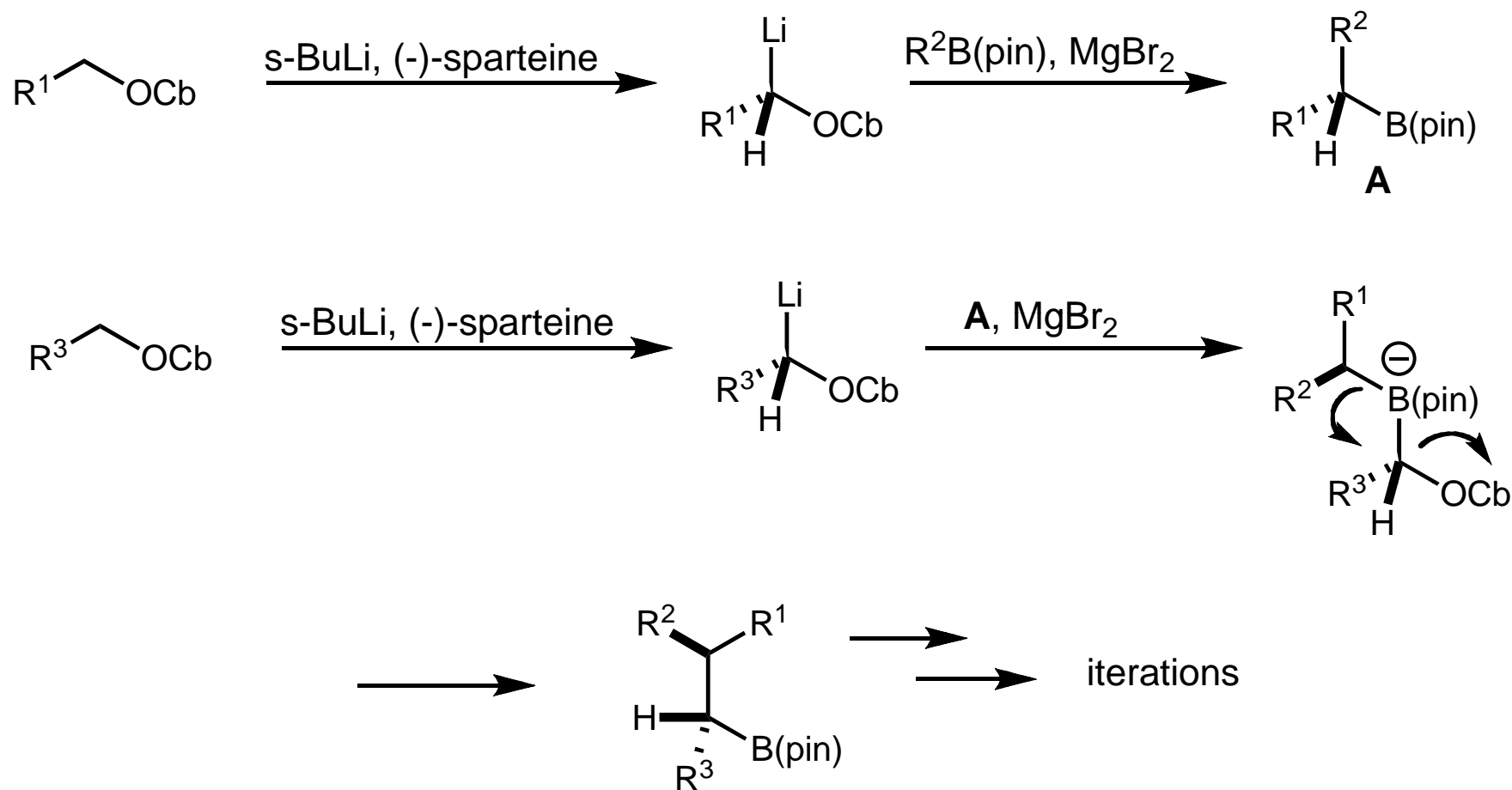
60%  
precursor to (*R*)-nicotine

# Transmetalation/1,2-Metalate Rearrangement

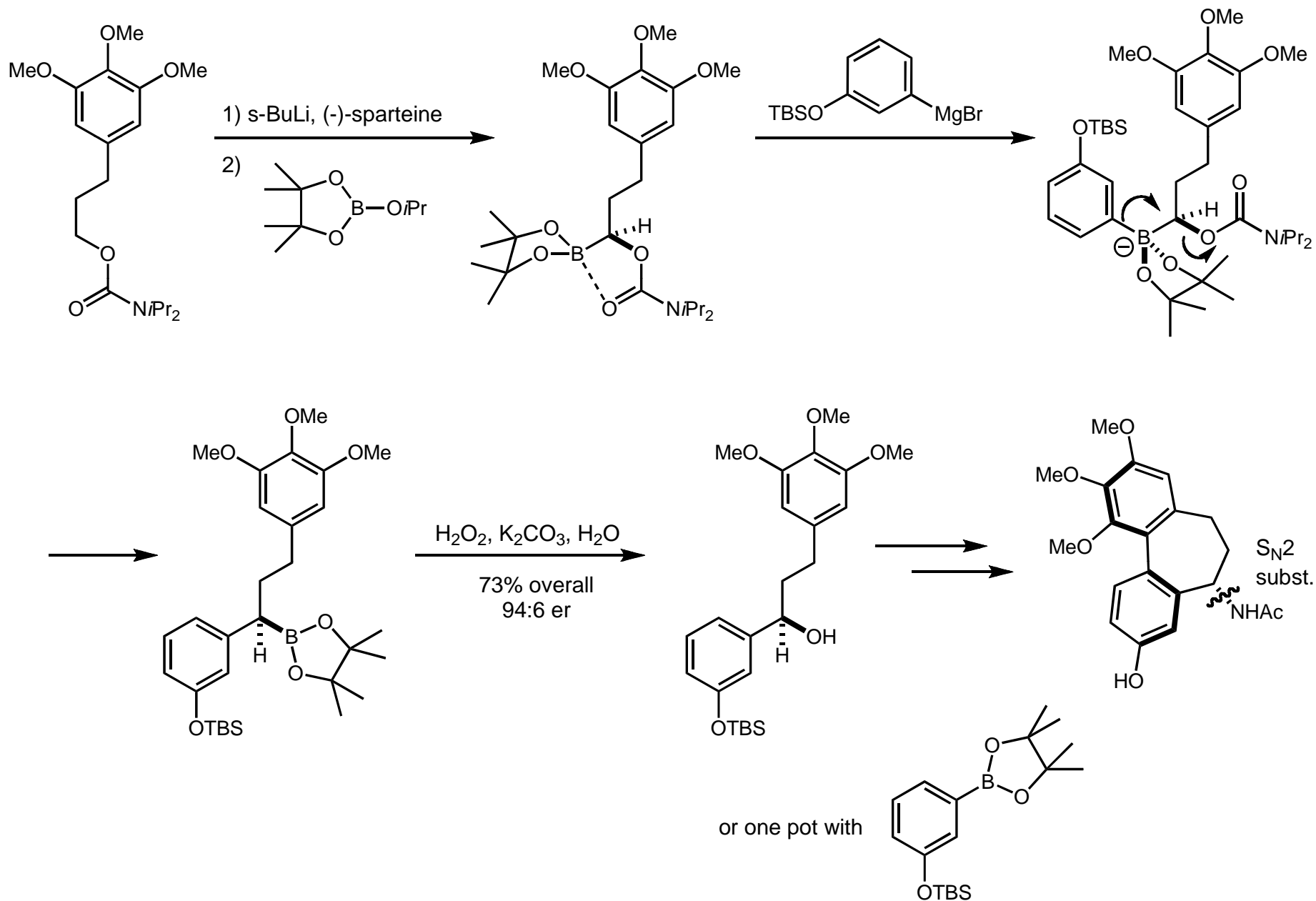


# Transmetalation/1,2-Metalate Rearrangement

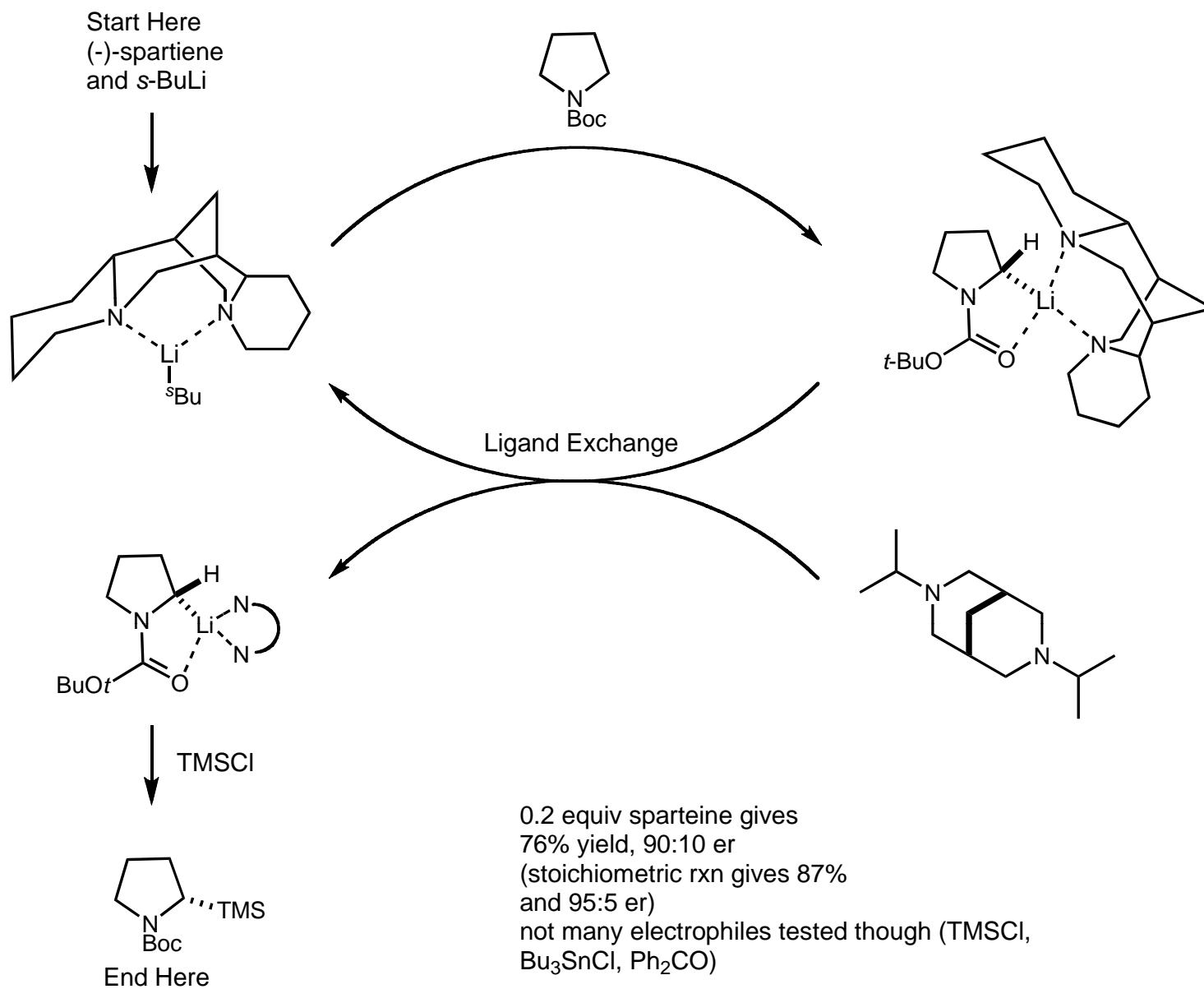
*Iterative homologation possible*



# Application in Synthesis



# Catalytic Asymmetric Deprotonation



# Outline

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- Synthesis
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## Asymmetric Deprotonations

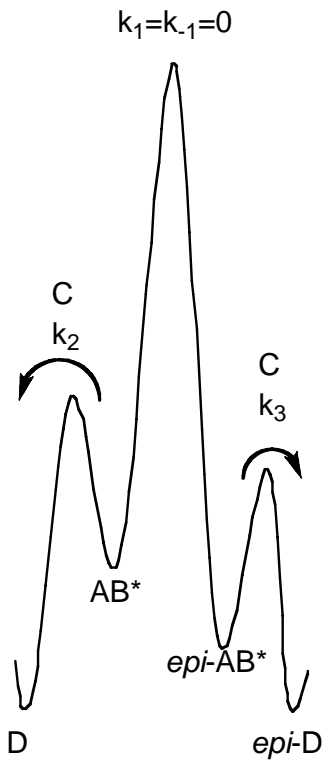
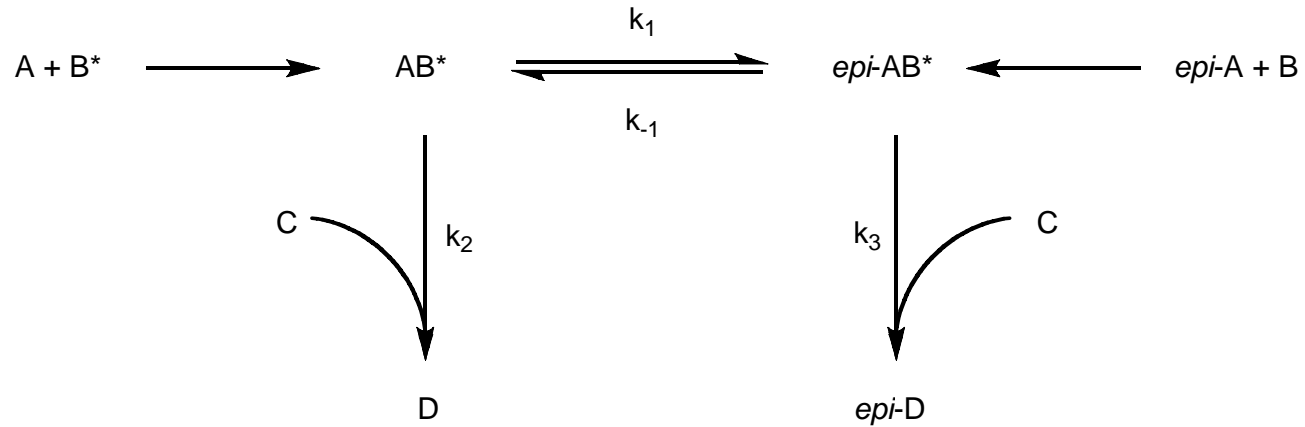
- Configurational Stability
- Transmetallations/Applications
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## Asymmetric Substitutions

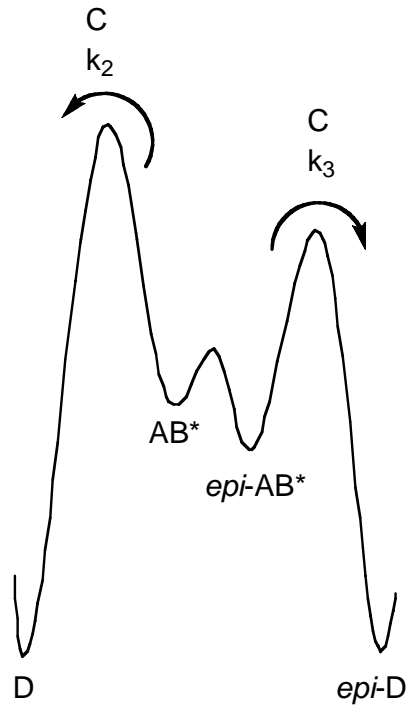
- Resolutions
- Dynamic Thermodynamic Resolutions

## Summary

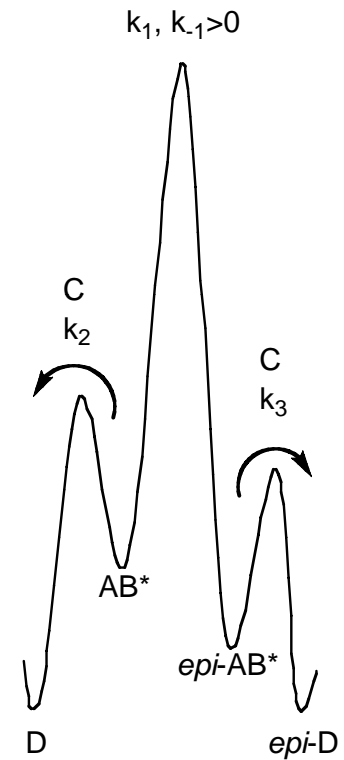
# Resolutions



Kinetic Resolution

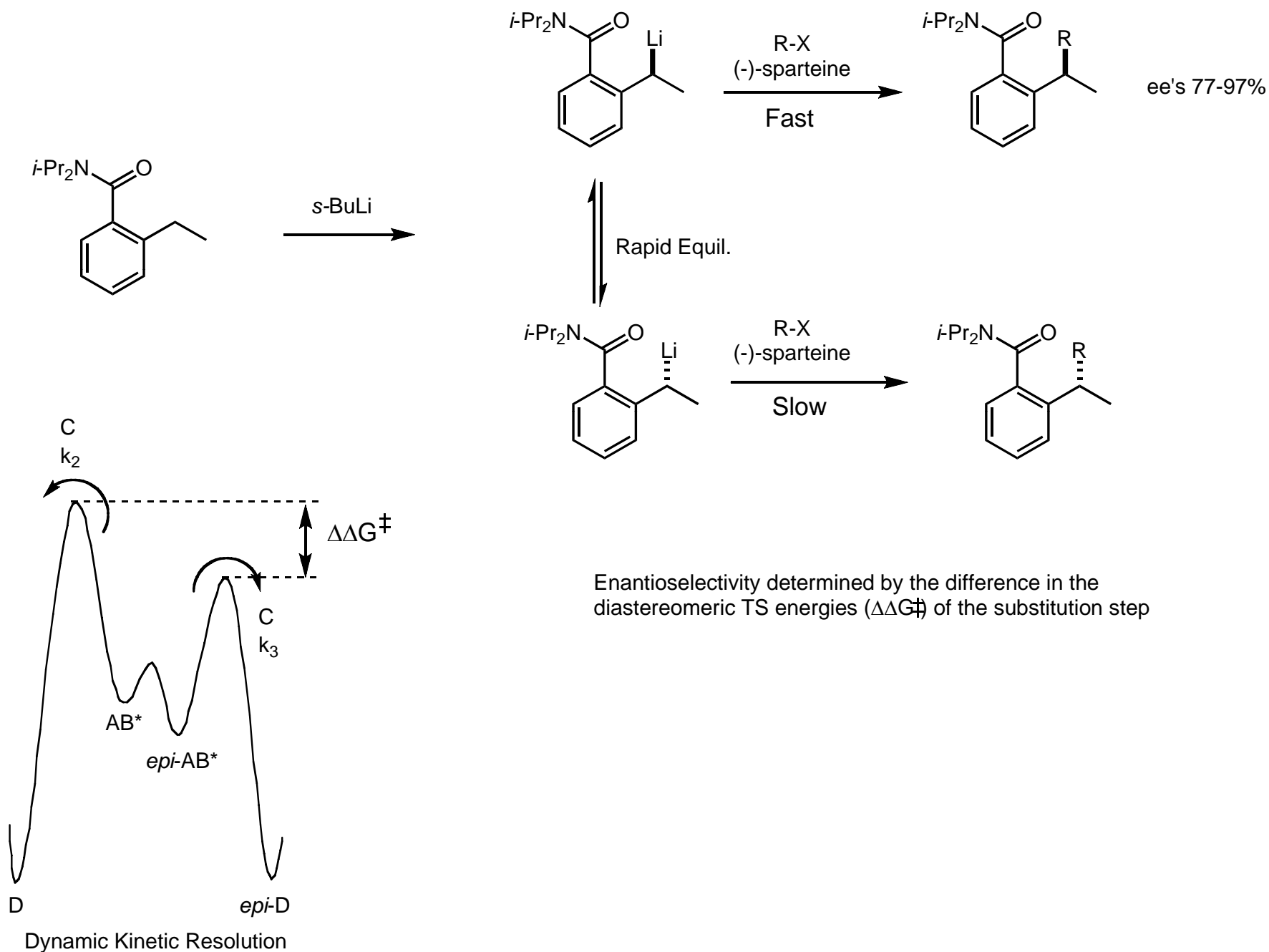


Dynamic Kinetic Resolution

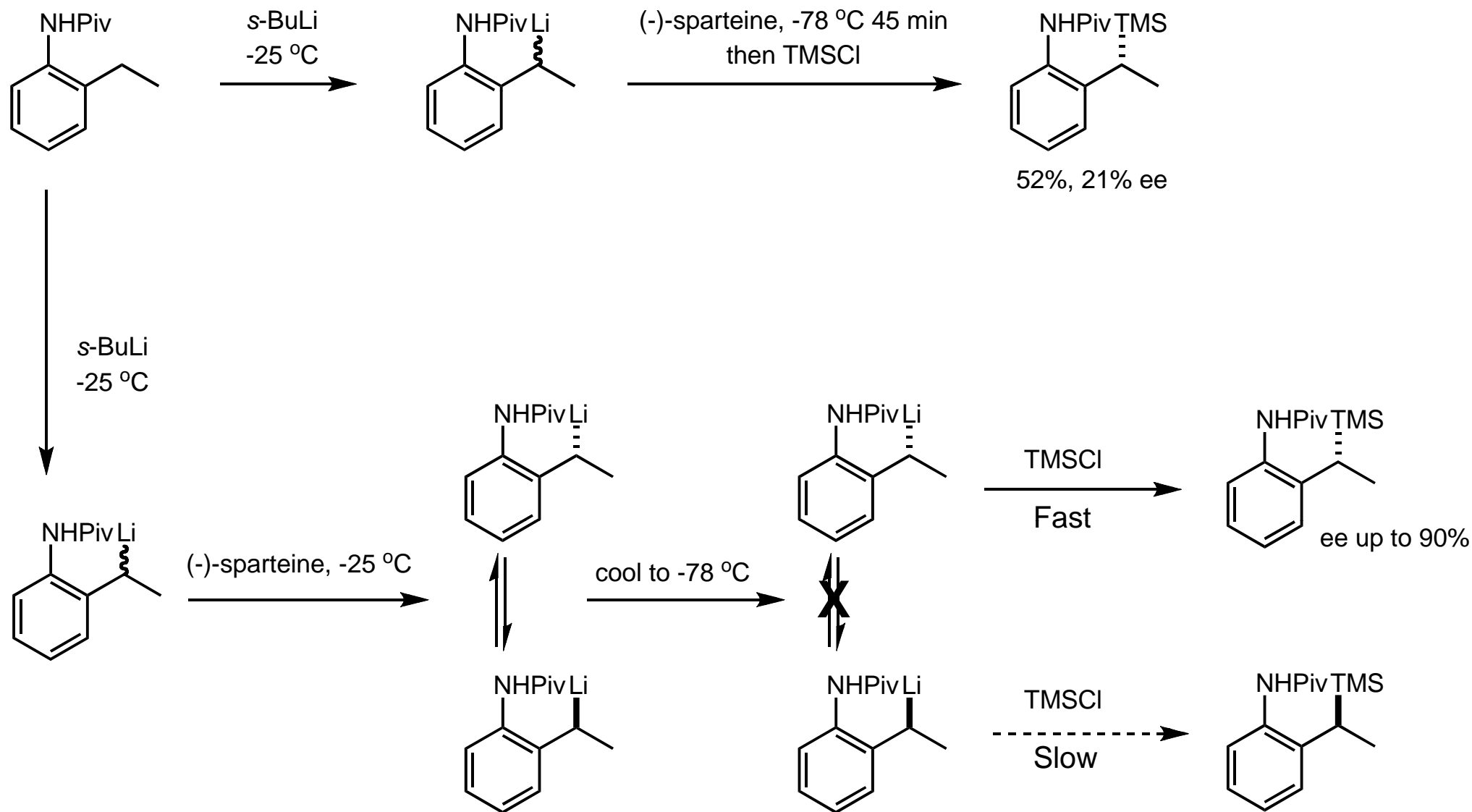


Dynamic Thermodynamic Resolution

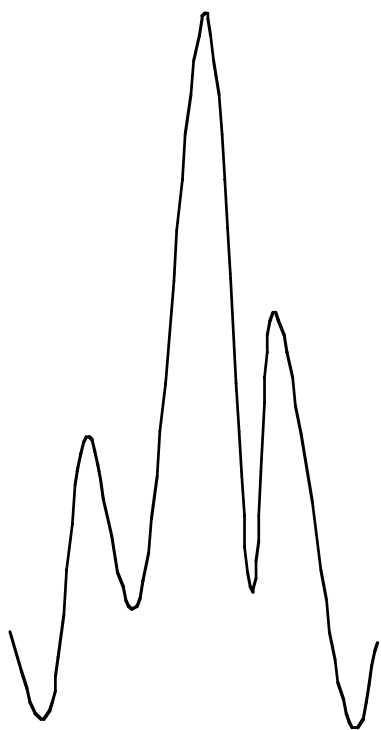
# Kinetic Resolutions



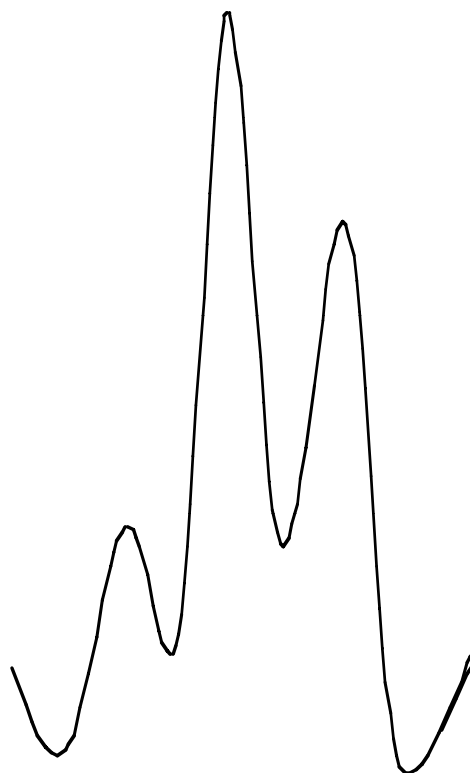
# An Interesting Result



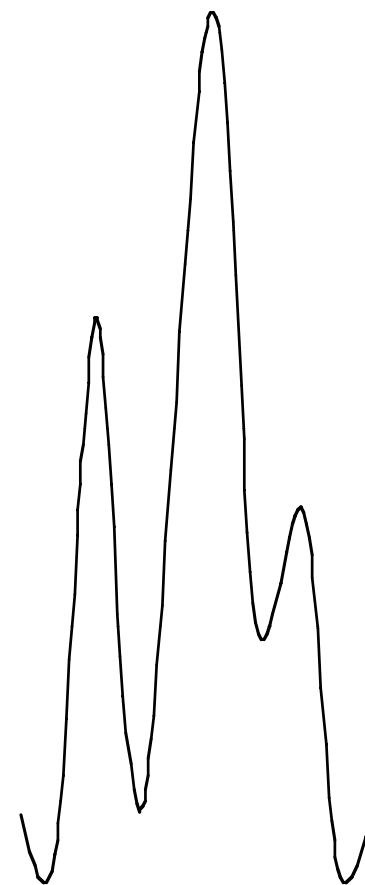
# Scenarios for a Dynamic Thermodynamic Resolution



1:1 population of diastereomers,  
intermediates of equal energy,  
product ratio at complete conversion is  
1:1



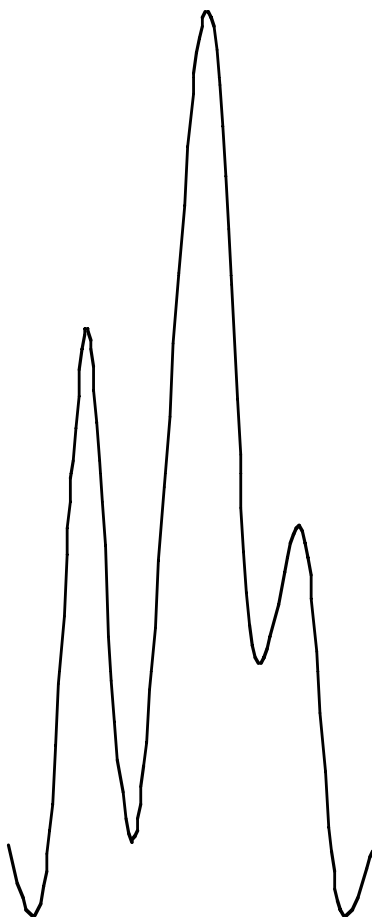
>1:1, the more populated  
stable state reacts more rapidly,  
happy times



>1:1, the more populated  
stable state reacts slowly  
not great times

Beak, P.; Anderson, D.R.; Curtis, M.D.; Laumer, J.M.; Pippel, D.J.; Weisenburger, G.A.  
*Acc. Chem. Rev.* **2000**, *33*, 715-727.

# How to Manipulate the Situation



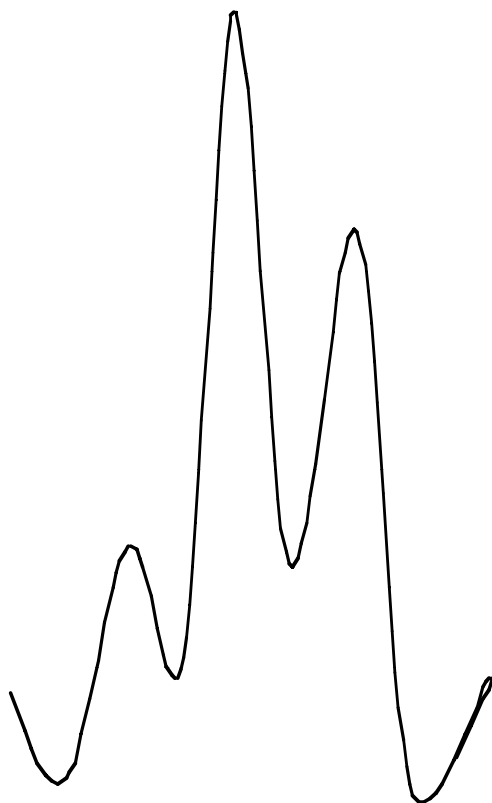
>1:1, the more populated  
stable state reacts slowly  
not great times

If the thermodynamically less favored diastereomer reacts more rapidly, could add two electrophiles.

First  $E^+$  would be a sacrificial electrophile and second would be the desired.

Not great but perhaps better than nothing.

# How to Manipulate the Situation



>1:1, the more populated  
stable state reacts more rapidly,  
happy times

Use warm-cool cycle to product enriched product.  
Allow equilibrium to be reached at high temp.  
Cool down followed by addition of deficient electrophile.  
Repeat

# Summary

