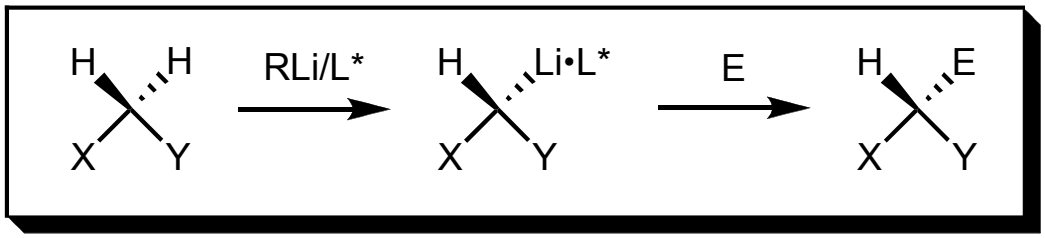
# Enantioselective Lithiation




Spencer Jones
MacMillan Group Meeting
March 19, 2008

## Key Articles:

Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139.

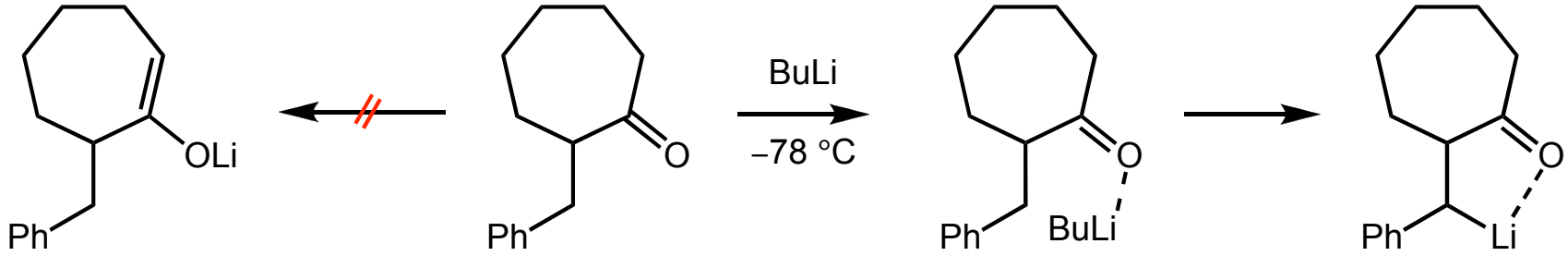
Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282

# Overview

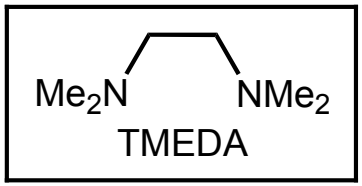
- Introduction to Enantioselective Lithiation
  - Complexation induced proximity effects
  - Use of (–)-sparteine as a ligand for enantioinduction
- Mechanism of Lithiation
  - Kinetics studies
  - Pathways for enantioinduction
  - Substitution phenomena
- Ligands Other Than (–)-Sparteine
  - Initial attempt at finding a sparteine surrogate
  - O'Brien's Ligand
- Catalytic Asymmetric Lithiation
- Synthetically Useful Examples

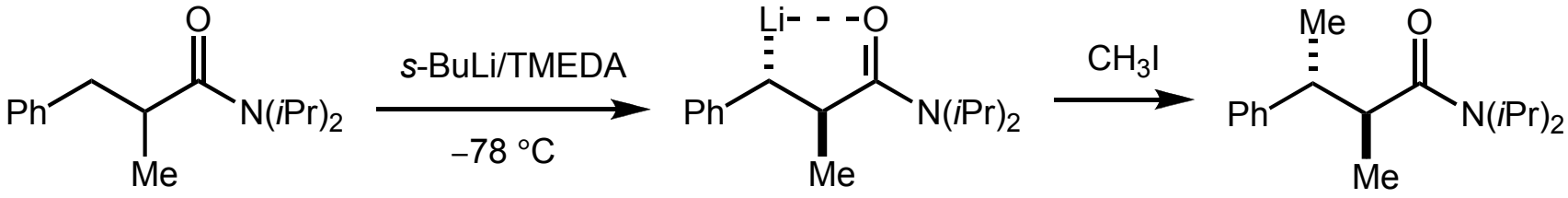
# Complexation Induced Proximity Effects

- Enables Reactivity at sites that are otherwise nonreactive or not thermodynamically favored




Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356

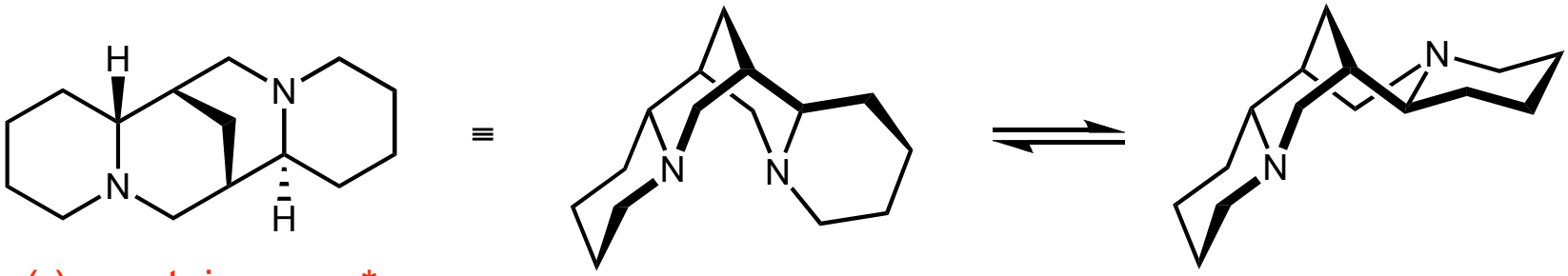



Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938.

# Use of (–)-Sparteine as a Ligand for Enantioinduction

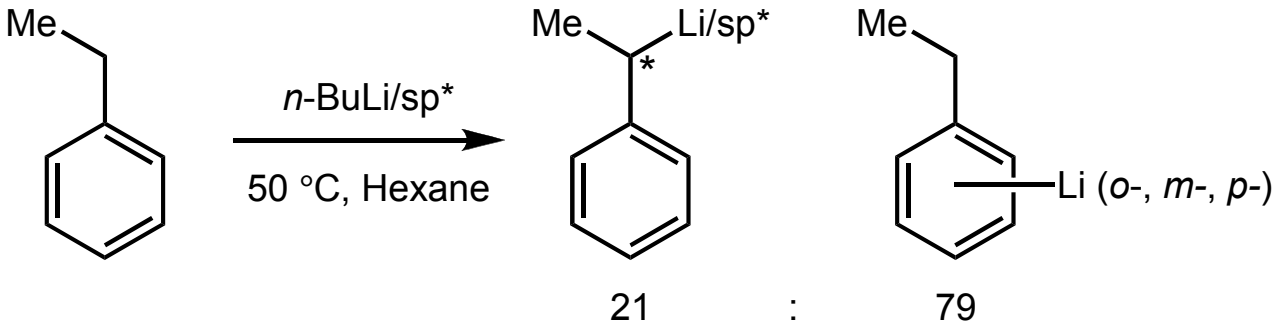
- (–)-Sparteine is a readily available alkaloid that can serve as a ligand for various metals




(-) sparteine = sp*

$116, 100 g

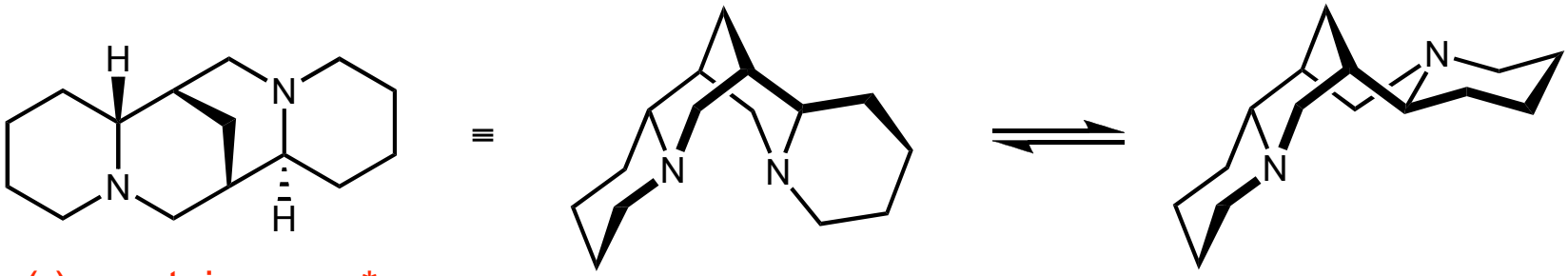
- Metalation in the presence of (–)-sparteine




Nozaki, H.; Toraya, T.; Noyori, R. *Tetrahedron*, **1971**, *27*, 905

# Use of (–)-Sparteine as a Ligand for Enantioinduction

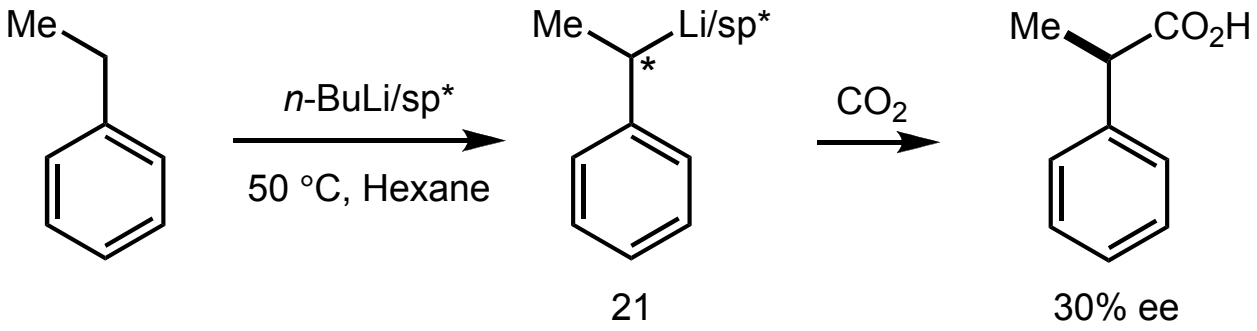
- (–)-Sparteine is a readily available alkaloid that can serve as a ligand for various metals




(-) sparteine = sp*

$116, 100 g

- Metalation in the presence of (–)-sparteine



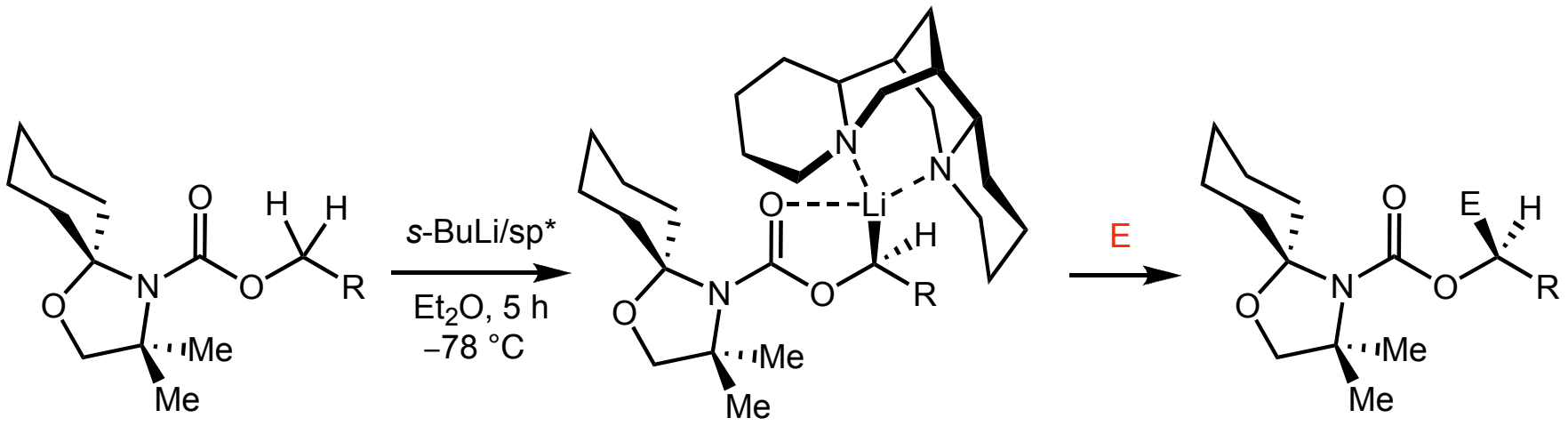

21

30% ee

Nozaki, H.; Toraya, T.; Noyori, R. *Tetrahedron*, **1971**, *27*, 905

# First Highly Enantioselective Lithiation Using Sparteine

- Chelation directed lithiation provides a configurationally stable, dipole stablized carbanion capable of reacting with several electrophiles.
- The bulky carbamate serves to prevent nucleophilic addition into the carbamate




R = $CH_3$, $(CH_2)_5CH_3$, $CH(CH_3)_2$

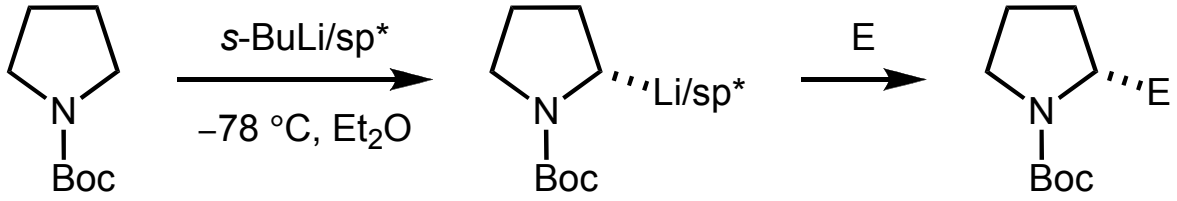
E = $Me_3SnCl$, $CO_2$, $CH_3I$

52 – 81% yields
≥ 95% ee

Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem. Int. Ed. Engl.* **1990**, *12*, 1422.

# Mechanism of Enantioselective Lithiation

- Boc-pyrrolidine is asymmetrically lithiated with *s*-BuLi/sp* and reacts selectively with a variety of electrophiles

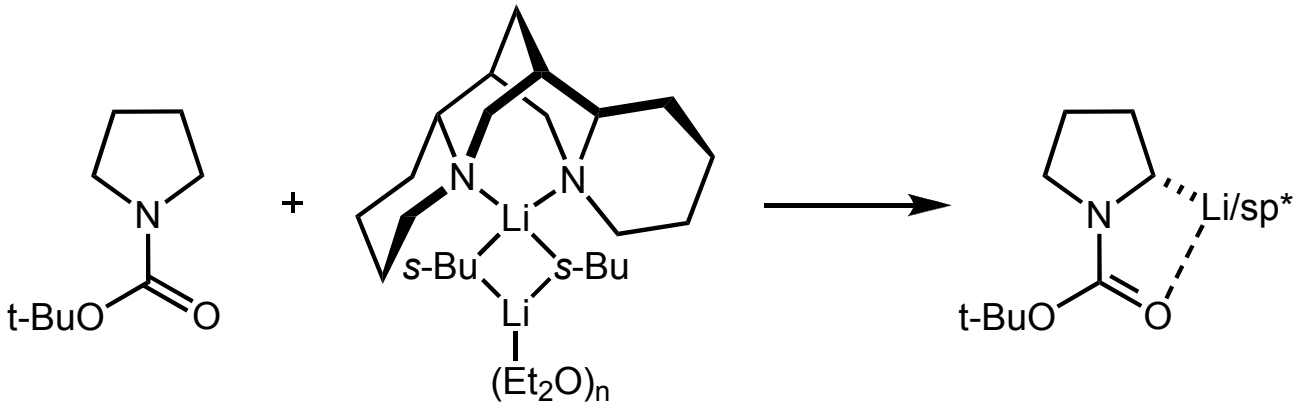



| Electrophile | Yield | ee (%) |
|---|---|---|
| TMS-Cl | 87 | 96 |
| PhCOPh | 75 | 90 |
| $CO_2$ | 55 | 88 |
| $(CH_3)_2SO_4$ | 88 | 94 |
| $Sn(Bu)_3Cl$ | 83 | 96 |

Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231

# Mechanism of Enantioselective Lithiation

- BuLi/sparteine is present in solution as an organolithium dimer
- If the lithiation were to occur in a single step with the dimer, the reaction order in *s*-BuLi should be 1, whereas if the reaction occurs via monomer the order should be 0.5




Reaction Order in Organolithium dimer?

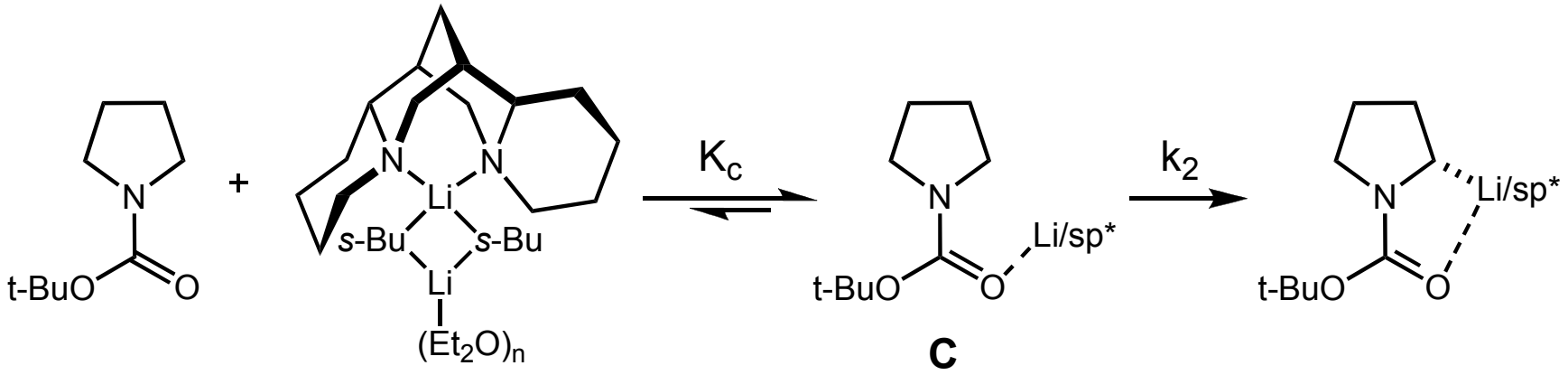
- Kinetics experiments revealed the lithiation is zeroth order in organolithium dimer


Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872

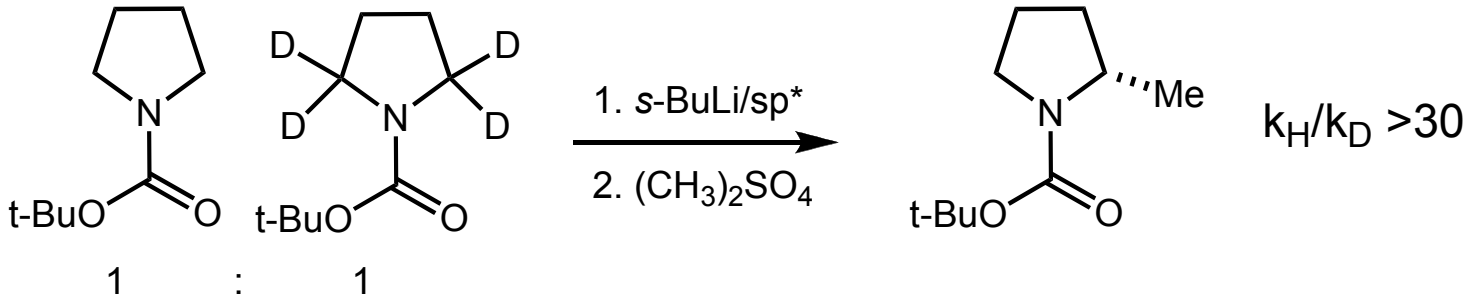
Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092

# Mechanism of Enantioselective Lithiation

- The fact that the lithiation is zeroth order in organolithium dimer under pseudo first order conditions suggests the presence of a prelithiation complex, C, with a large equilibrium constant, $K_c$



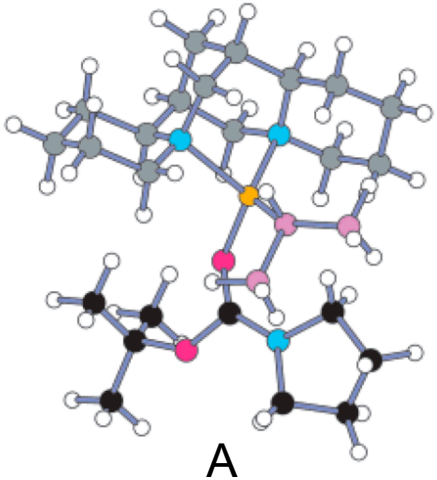

- The RDS was determined to be the deprotonation step due to the high kinetic isotope effect ($k_H/k_D$)



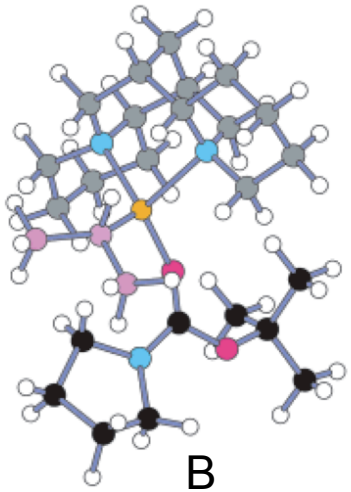

Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092

# Origin of Stereoselectivity in Lithiation

- Calculations of the four possible low energy conformers leads to two prelithiation complexes leading to abstraction of *pro*-S and *pro*-R hydrogens



A
*pro*-S
main pathway

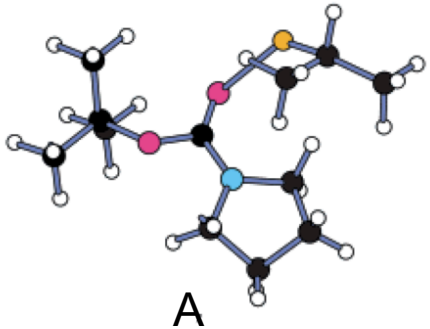


B
*pro*-R
minor pathway

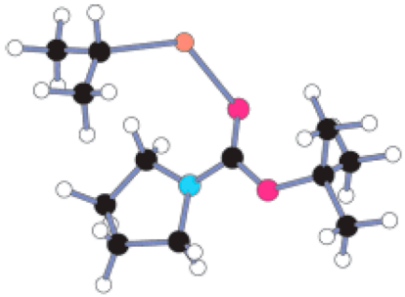
Wilberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231

# Origin of Stereoselectivity in Lithiation

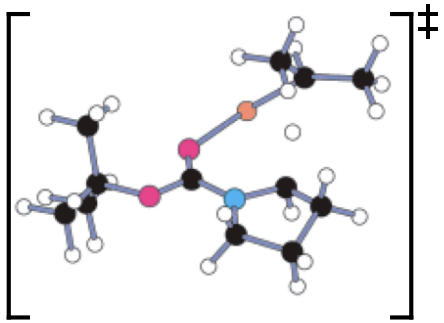
- Calculations reveal that abstraction of the *pro*-S hydrogen is favored due to greater nonbonded interactions in transition state leading to abstraction of the *pro*-R hydrogen.

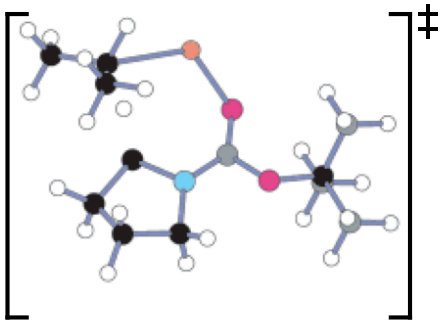


A
*pro*-S
main pathway



B
*pro*-R
minor pathway



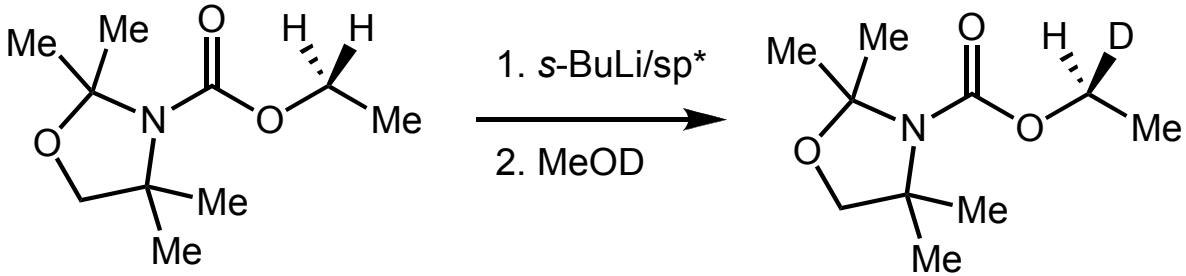


$\Delta\Delta G^{\ddagger}$ (B3P86/6-31G*) 0.0 kcal/mol 3.2 kcal/mol

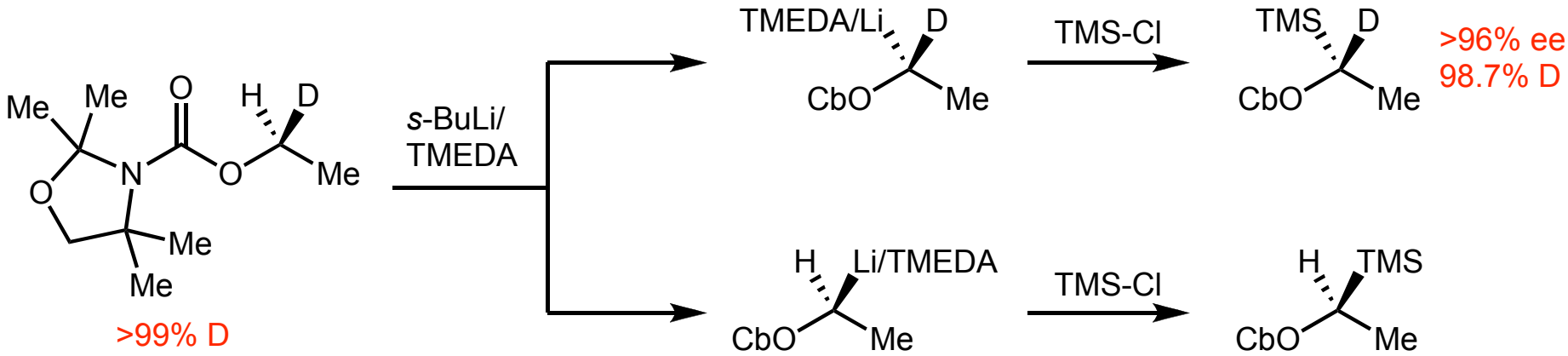
Wilberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231

# Mechanism of Proton Transfer

- Tunneling may be operative for deprotonations




>99% D




>99% D

>96% ee
98.7% D

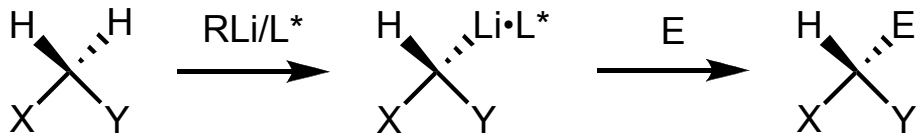
$$k_H/k_D = \frac{98.7\ H}{1.3\ D} = 76$$

Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 394

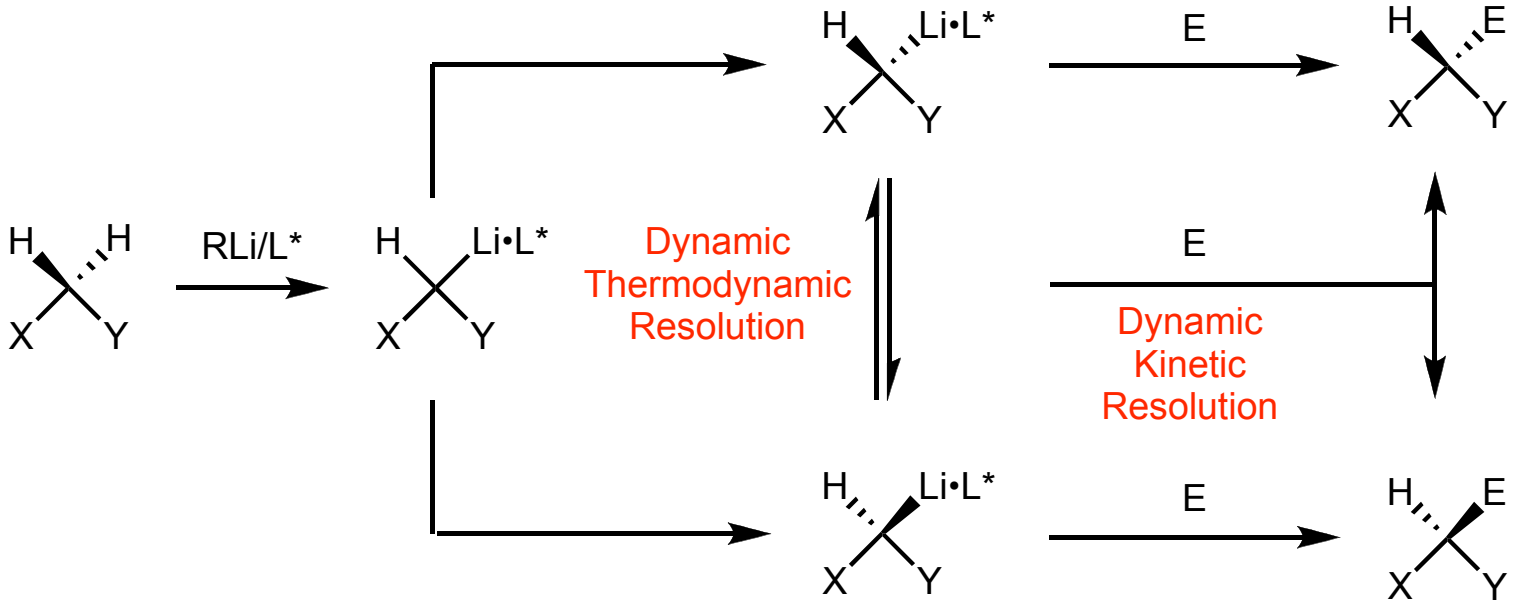
# Pathways for Enantioinduction

- Configurational stability of lithiated intermediate cannot be assumed.
- The two limiting pathways for enantioinduction are asymmetric deprotonation, and asymmetric substitution

Asymmetric Deprotonation

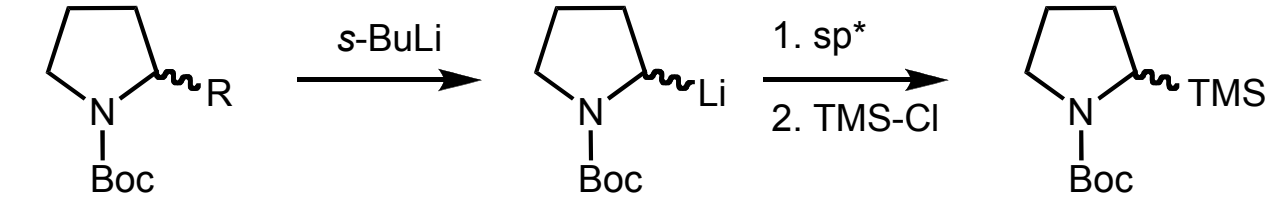



Asymmetric Substitution

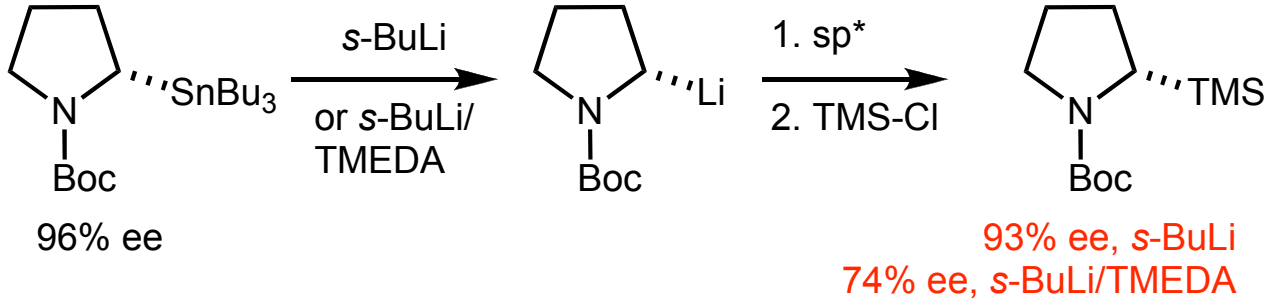


# Establishing the Asymmetric Deprotonation Pathway

- If the enantiodetermining step is postdeprotonative, the ligand should resolve the diastereomeric complexes



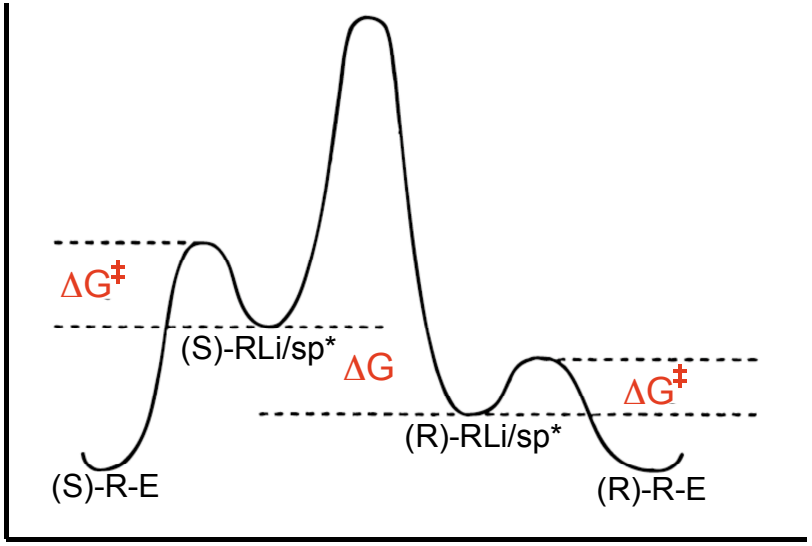

- In addition, the enantioenriched lithiated species should remain enantioenriched in the absence of a chiral ligand



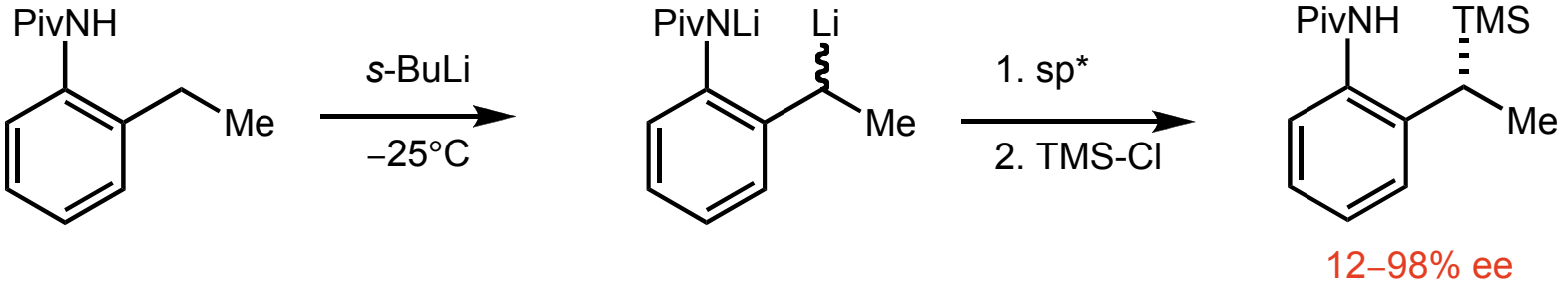

Kerrick, S. T.; Beak, P *J. Am. Chem. Soc.* **1991**, *113*, 9708

# Dynamic Thermodynamic Resolution Asymmetric Substitution

- In a dynamic thermodynamic resolution, the enantioselectivity is controlled by ΔG



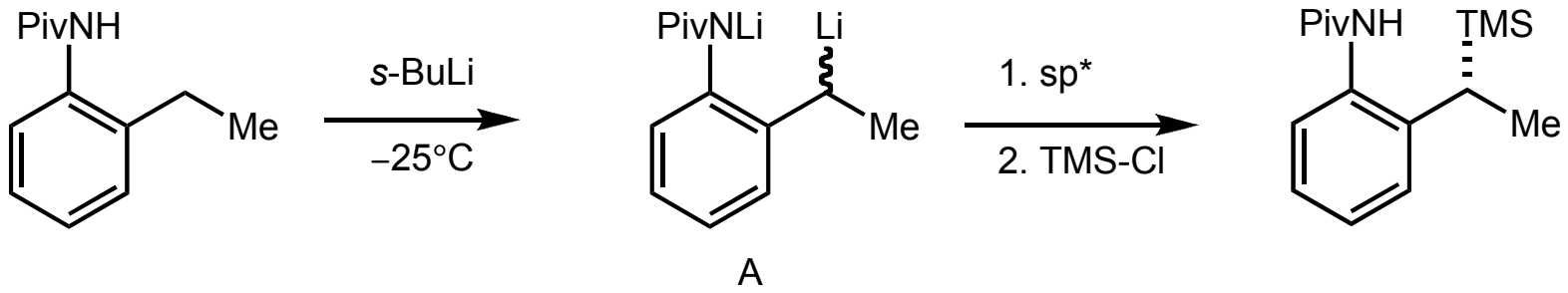

- Lithiation of *o*-ethylaniline gives a slowly equilibrating benzyl lithium. The asymmetric deprotonation pathway is immediately ruled out

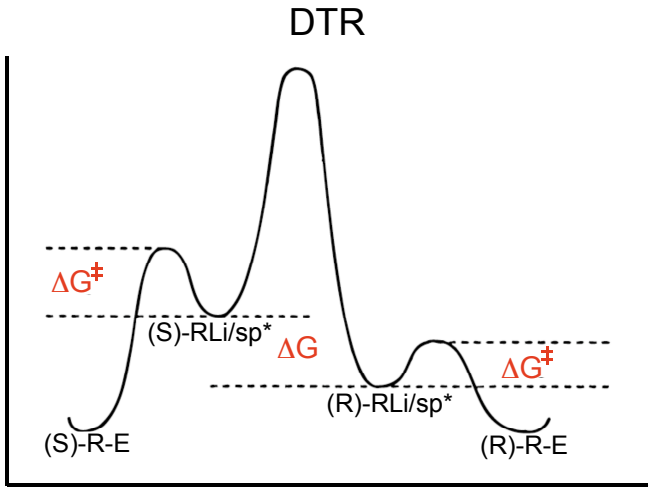



Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

# Dynamic Thermodynamic Resolution Asymmetric Substitution

## Proving a dynamic thermodynamic resolution



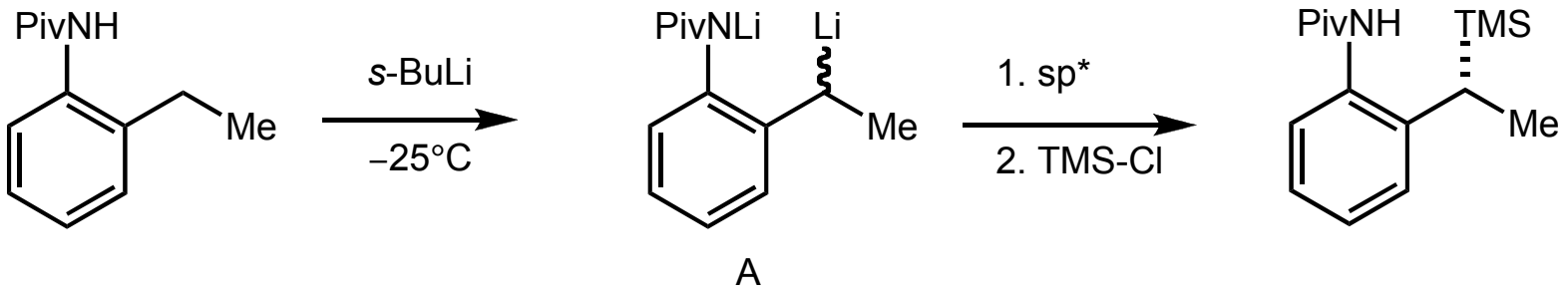



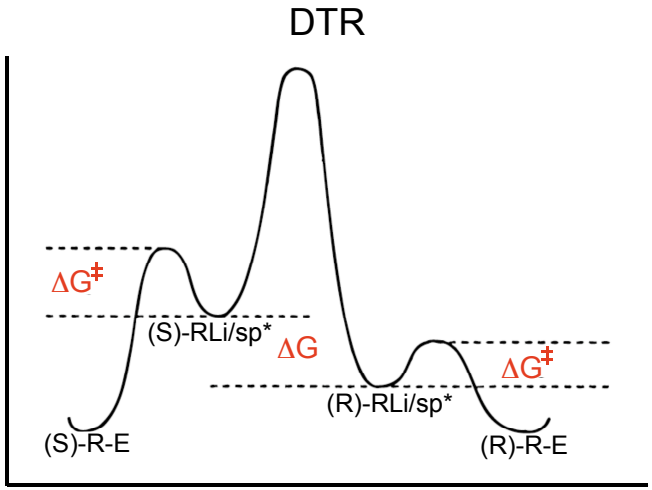

| entry | exposure of A to sp* prior to addition of TMS-Cl | TMS-Cl (equiv.) | %ee |
|---|---|---|---|
| 1 | –78°C, 15 min | 2.3 | 12 |
| 2 | –78°C, 15 min | 0.10 | 82 |
| 3 | –25°C, 45 min then –78°C, 30 min | 2.1 | 84 |
| 4 | –25°C, 45 min then –78°C, 30 min | 0.1 | 98 |
| 5 | –25°C, 45 min then –78°C, 30 min | 0.50 | 96 |
| 6 | –25°C, 45 min then –78°C, 30 min | 0.45 | |
| | –25°C, 45 min then –78°C, 30 min | 0.45 | 94 |

Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

# Dynamic Thermodynamic Resolution Asymmetric Substitution

## Proving a dynamic thermodynamic resolution



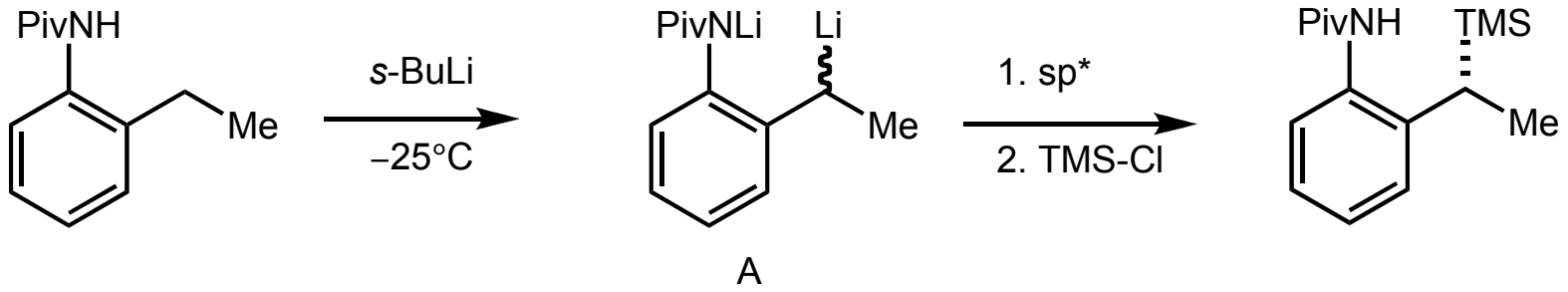



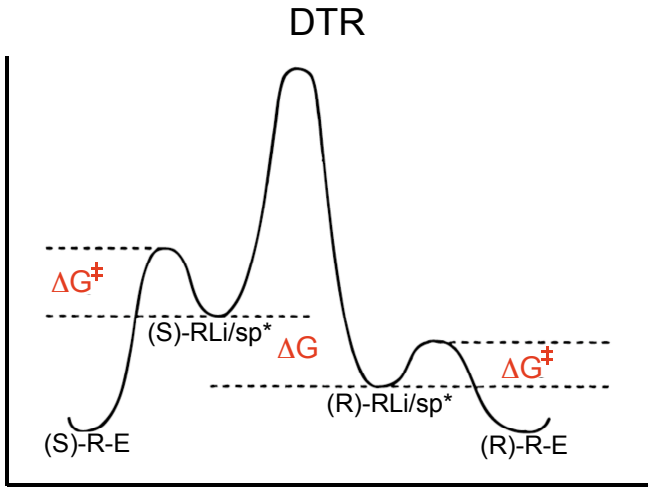

| entry | exposure of A to sp* prior to addition of TMS-Cl | TMS-Cl (equiv.) | %ee |
|---|---|---|---|
| 1 | –78°C, 15 min | 2.3 | 12 |
| 2 | –78°C, 15 min | 0.10 | 82 |
| 3 | –25°C, 45 min then –78°C, 30 min | 2.1 | 84 |
| 4 | –25°C, 45 min then –78°C, 30 min | 0.1 | 98 |
| 5 | –25°C, 45 min then –78°C, 30 min | 0.50 | 96 |
| 6 | –25°C, 45 min then –78°C, 30 min | 0.45 | |
| | –25°C, 45 min then –78°C, 30 min | 0.45 | 94 |

Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

# Dynamic Thermodynamic Resolution Asymmetric Substitution

## Proving a dynamic thermodynamic resolution



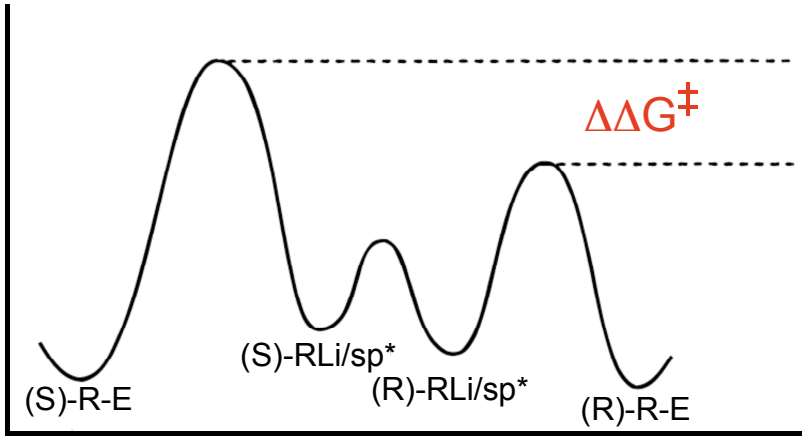




| entry | exposure of A to sp* prior to addition of TMS-Cl | TMS-Cl (equiv.) | %ee |
|---|---|---|---|
| 1 | –78°C, 15 min | 2.3 | 12 |
| 2 | –78°C, 15 min | 0.10 | 82 |
| 3 | –25°C, 45 min then –78°C, 30 min | 2.1 | 84 |
| 4 | –25°C, 45 min then –78°C, 30 min | 0.1 | 98 |
| 5 | –25°C, 45 min then –78°C, 30 min | 0.50 | 96 |
| 6 | –25°C, 45 min then –78°C, 30 min | 0.45 | |
| | –25°C, 45 min then –78°C, 30 min | 0.45 | 94 |

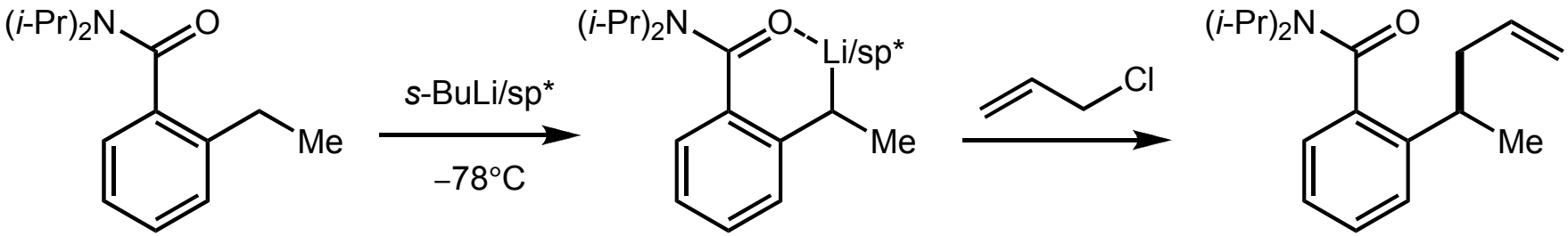
Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718.

# Dynamic Kinetic Resolution Asymmetric Substitution

- In a dynamic kinetic resolution, the enantioselectivity is controlled by $\Delta\Delta G^{\ddagger}$




- Lithiation of *o*-ethylbenzamide gives rapidly equilibrating benzyl lithium

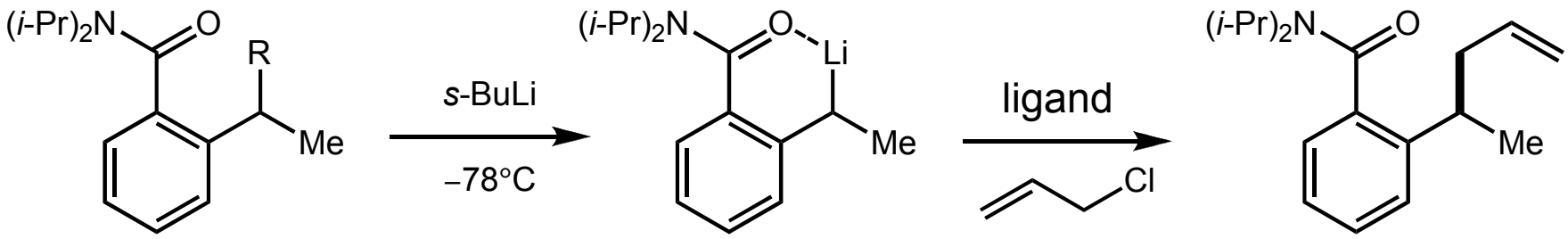



89%, 92% ee

Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755

# Dynamic Kinetic Resolution Asymmetric Substitution

■ Proving that the reaction proceeds under asymmetric substitution




A, R = H
B, R = $SnBu_3$

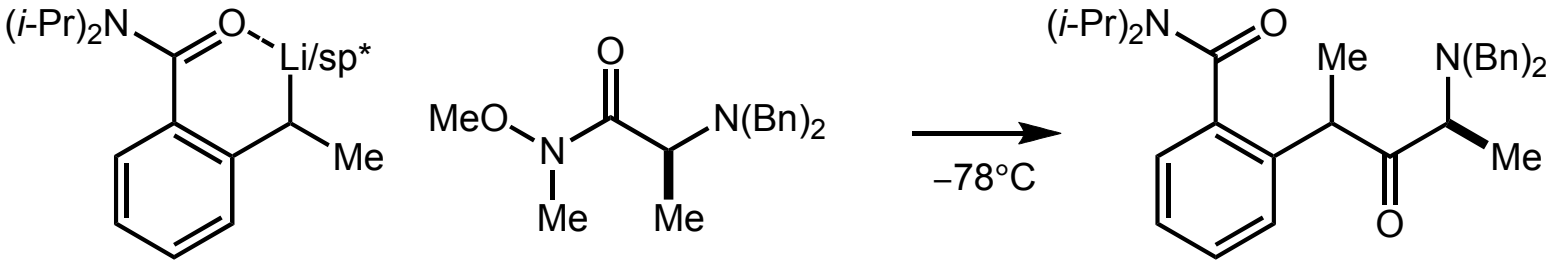
C

| reactant (ee) | Ligand | %ee of C |
|---|---|---|
| A or B (0%) | sp* | 87 |
| B (87%) | none | 5 |
| B (87%) | TMEDA | 1 |

Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755

# Dynamic Kinetic Resolution Asymmetric Substitution

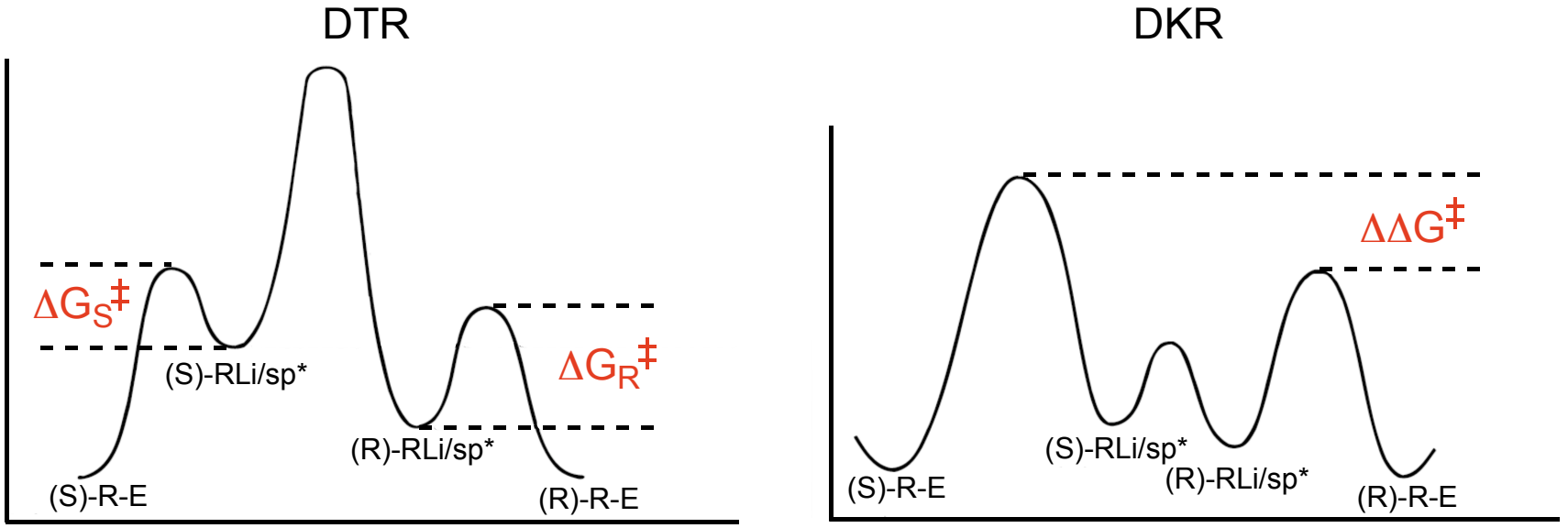
- Proving dynamic kinetic resolution over dynamic thermodynamic resolution




1.0 equiv. or
0.1 equiv.

dr 1:1.6
1:1.6

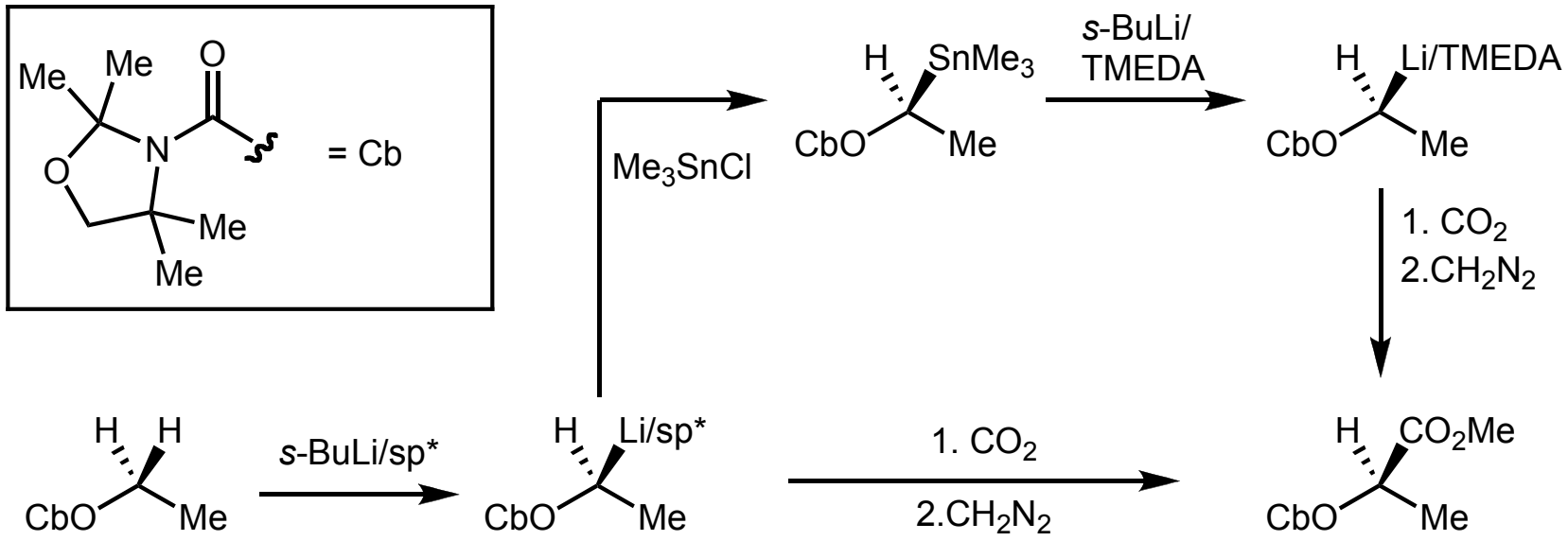
- The results suggest a dynamic kinetic resolution, but do not explicitly rule out a dynamic thermodynamic resolution where $\Delta G^{\ddagger}$ are the same.




Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755

# Invertive or Retentive $S_E2$

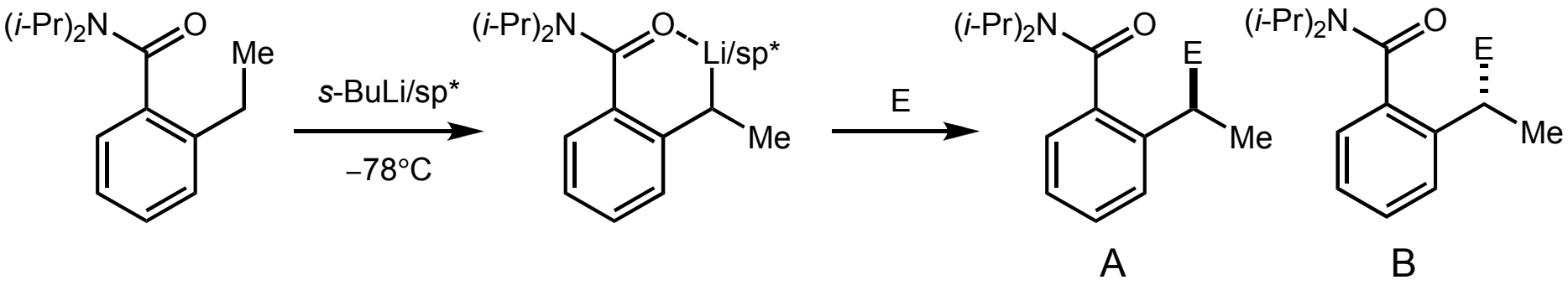
- The stereochemistry in the substituted product may or may not correspond to the stereochemistry of the lithium complex.
- For most non-resonance stabilized carbanions, retentive substitution is usually the observed $S_E2$ pathway




Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem.* Int. Ed. Engl. **1990**, *29*, 1422

# Invertive or Retentive $S_E2$

- Resonance stabilized carbanions may undergo invertive or retentive substitution depending on the electrophile

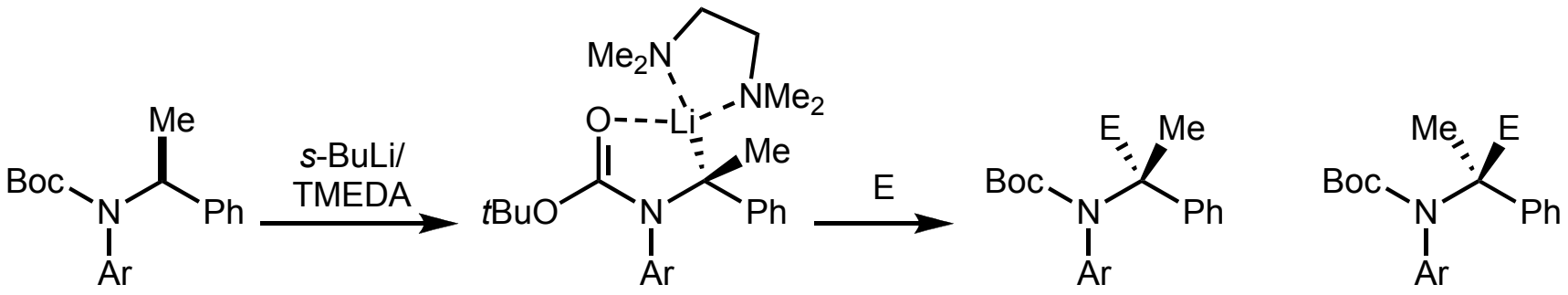



| Electrophile | enantiomeric ratio A | | B |
|---|---|---|---|
| $H_2C{=}CHCH_2OTs$ | 6 | : | 94 |
| $H_2C{=}CHCH_2Cl$ | 96 | : | 4 |
| *n*-BuOTs | 2 | : | 98 |
| *n*-BuCl | 90 | : | 10 |
| *n*-BuBr | 87 | : | 13 |
| *n*-BuI | 64 | : | 36 |

Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755

# Invertive or Retentive $S_E2$

- Retention or inversion can be a function of the reactivity of the electrophile




Ar = *p*-$MeOC_6H_4$

Retention

Inversion

| Inverting Electrophiles | |
|---|---|
| $CO_2$ | 98% ee |
| allyl triflate | 96% ee |

| Retaining Electrophiles | |
|---|---|
| MeOD | 94% ee |
| $ClCO_2Me$ | 90% ee |

| Non Selective Electrophiles | |
|---|---|
| allyl bromide | 33% ee[a] |
| allyl iodide | 6% ee[a] |

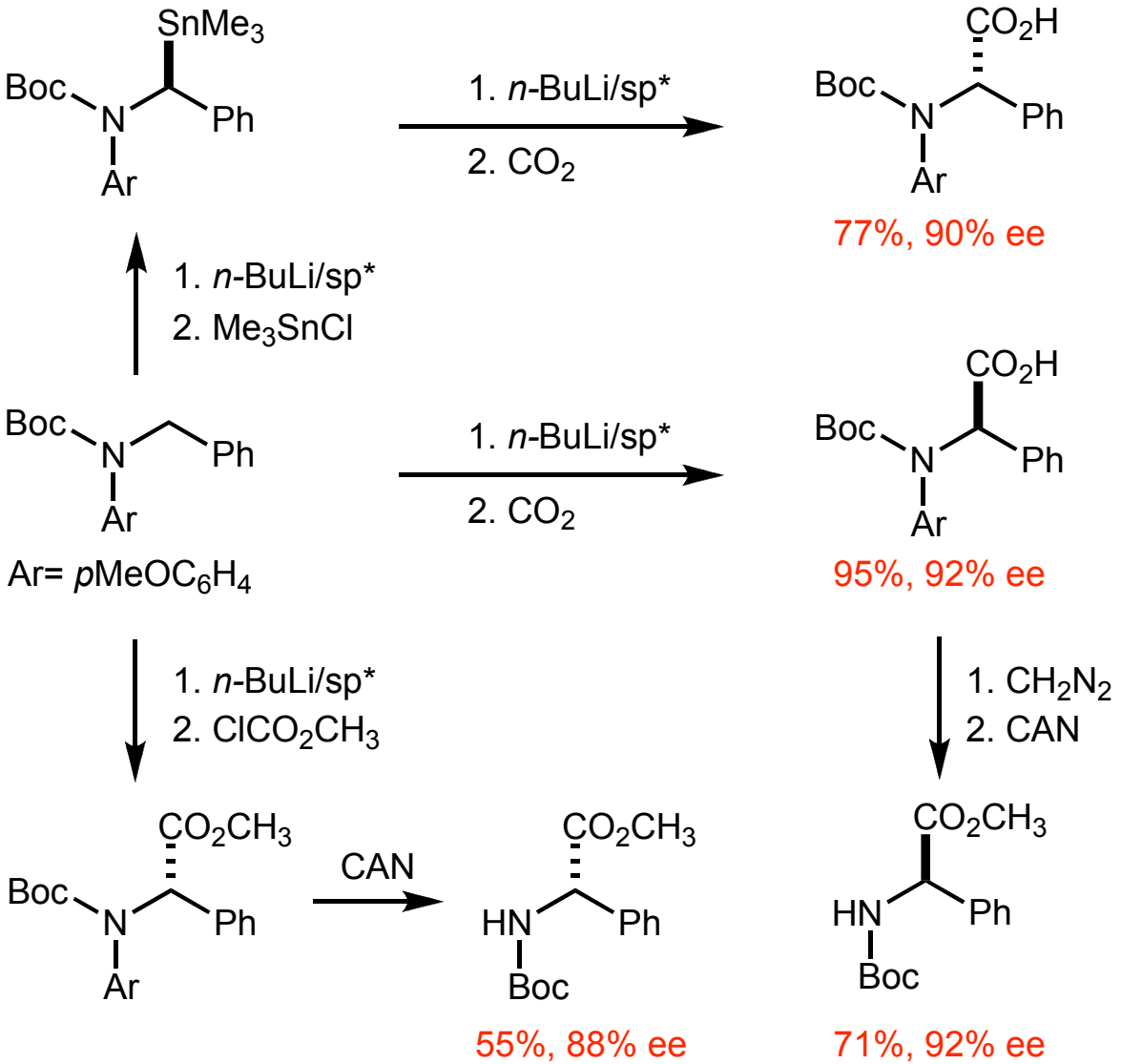
[a] favoring inversion

- Beak et al. suggest that for resonance stabilized carbanions, highly reactive and/or non-lithium coordinating electrophiles proceed with inversion, while less reactive and/or lithium coordinating electrophiles proceed with retention

Fabish, N. C.; Park, Y. S.; Lee. S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561

# Using Invertive or Retentive $S_E2$ to Access Either Enantiomer

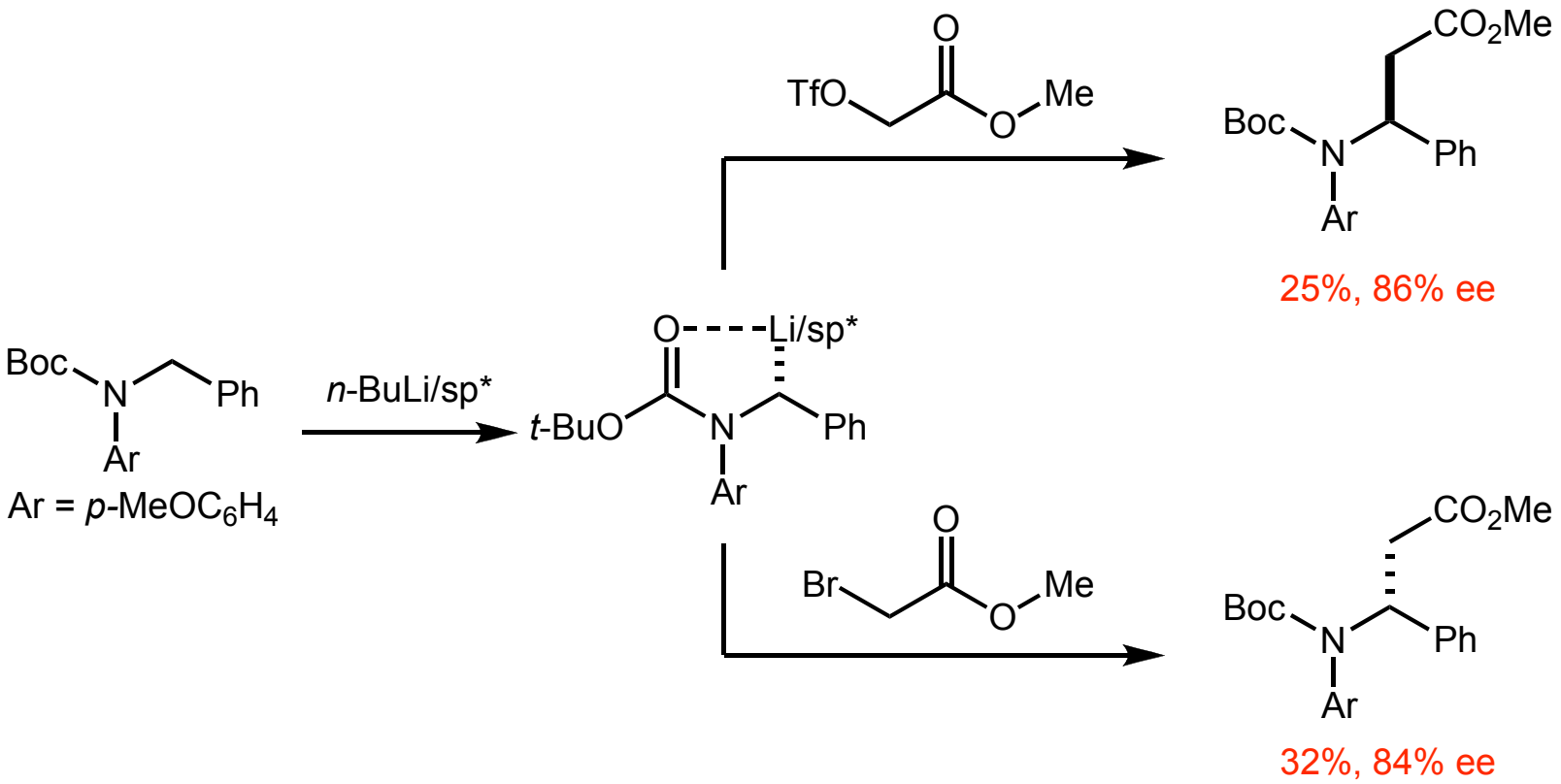
- Because (–)-sparteine is only readily available as one enantiomer the preference for inversion or retention can allow access to either enantiomer




Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574

# Using Invertive or Retentive $S_E2$ to Access Either Enantiomer

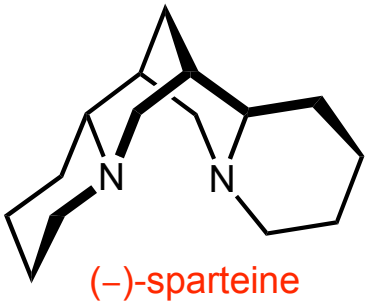
- Because (–)-sparteine is only readily available as one enantiomer the preference for inversion or retention can allow access to either enantiomer



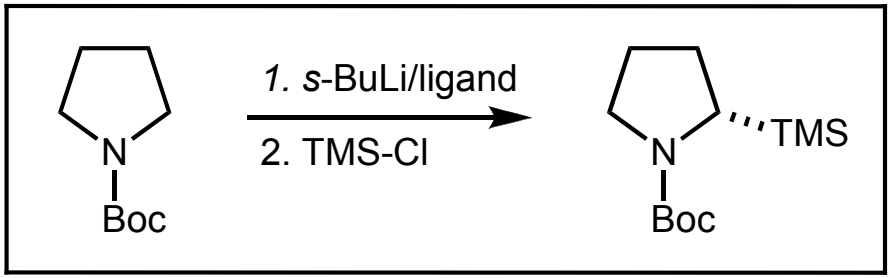

Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574

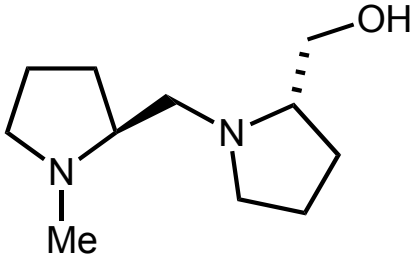
# Ligands Other Than (–)-Sparteine

- For carbanions that only undergo retentive substitution, a (+)-sparteine surrogate is required to enter the opposite enantiomeric series
- Deprotonation/trimethylsilylation of Boc-pyrrolidine used as a benchmark

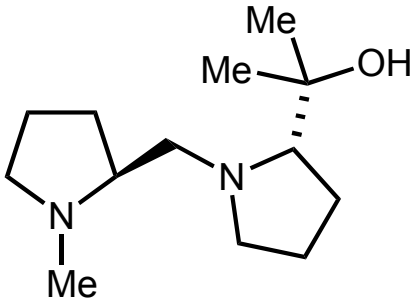



(–)-sparteine
87%, 96% ee

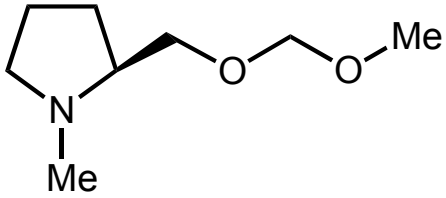


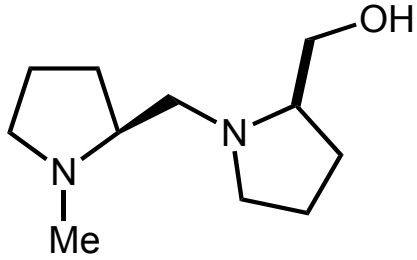

51%, 84% ee




18%, –41% ee




89%, –30% ee



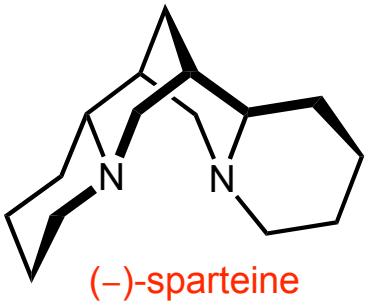

–64% ee


Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.*, **1994**, *116*, 3231

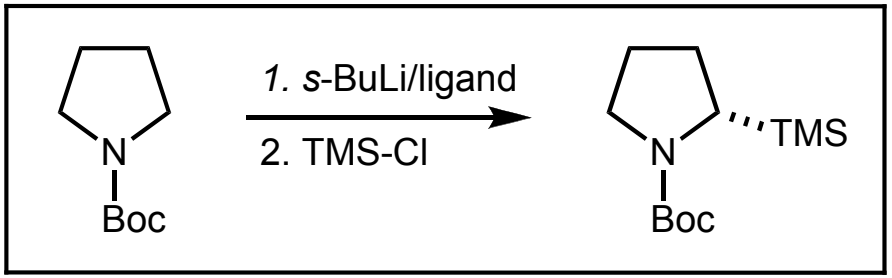
Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148

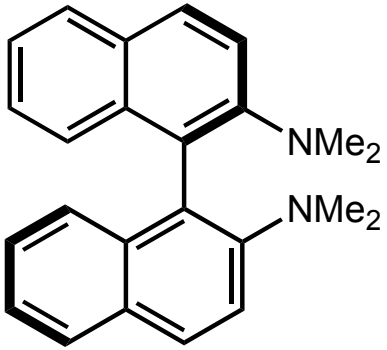
# Ligands Other Than (–)-Sparteine

- For carbanions that only undergo retentive substitution, a (+)-sparteine surrogate is required to enter the opposite enantiomeric series
- Deprotonation/trimethylsilylation of Boc-pyrrolidine used as a benchmark

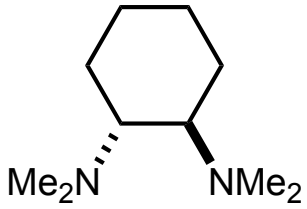



(–)-sparteine
87%, 96% ee

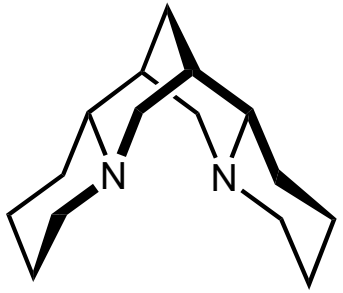



<10%, 0% ee




90%, 0% ee



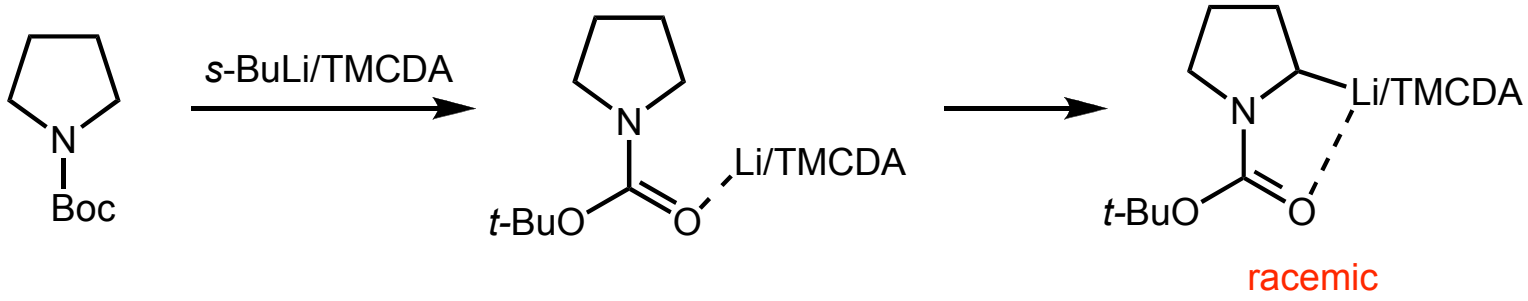

(–)-isosparteine
<10%, 60% ee


Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.*, **1994**, *116*, 3231

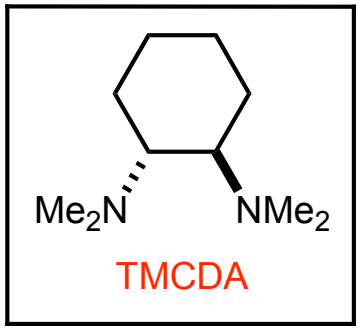
Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148

# Reason Why Cyclohexanediamine is a Poor Ligand

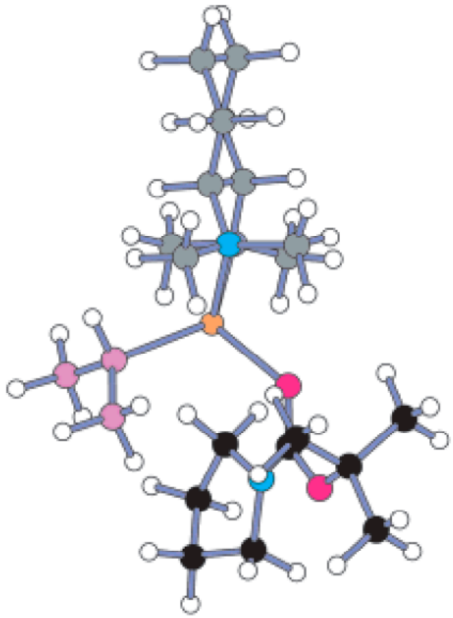
- Transition state models for removal of the *pro*-R and *pro*-S hydrogens are approximately isosteric



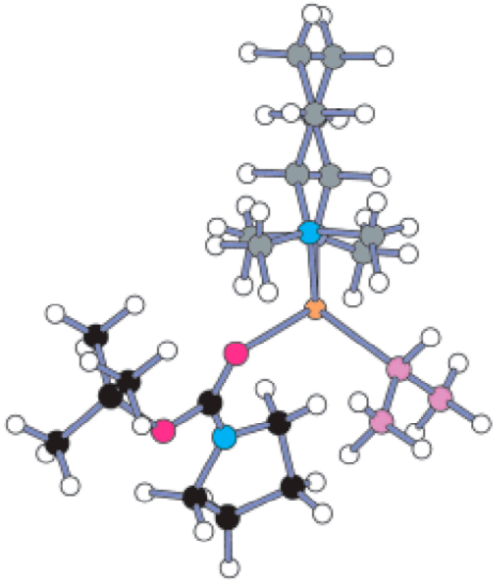

racemic




TMCDA



*pro*-R hydrogen

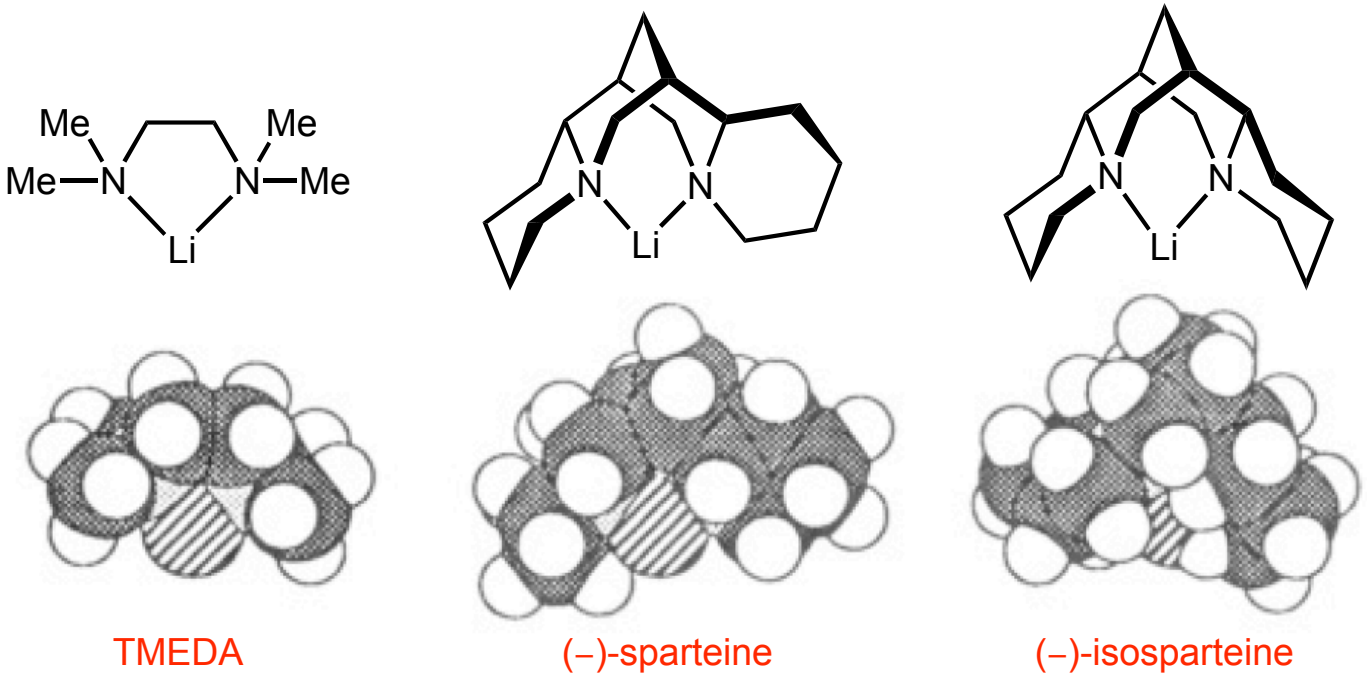


*pro*-S hydrogen

Wilberg, K. B.; Bailey, W. F.; *J. Am. Chem. Soc.* **2001**, *123*, 8231

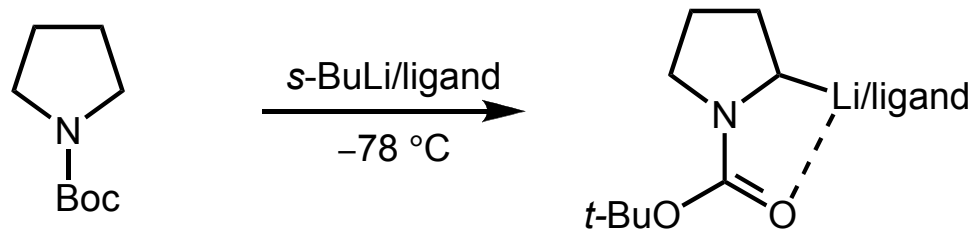
# Reason Why (-) Isosparteine is a Poor Ligand

- Space filling models for complexes of TMEDA, (–)-sparteine and (–)-isosparteine with lithium show that (–)-isosparteine significantly encapsulates lithium




TMEDA (–)-sparteine (–)-isosparteine

- The rate of lithiation follows the degree of encapsulation.

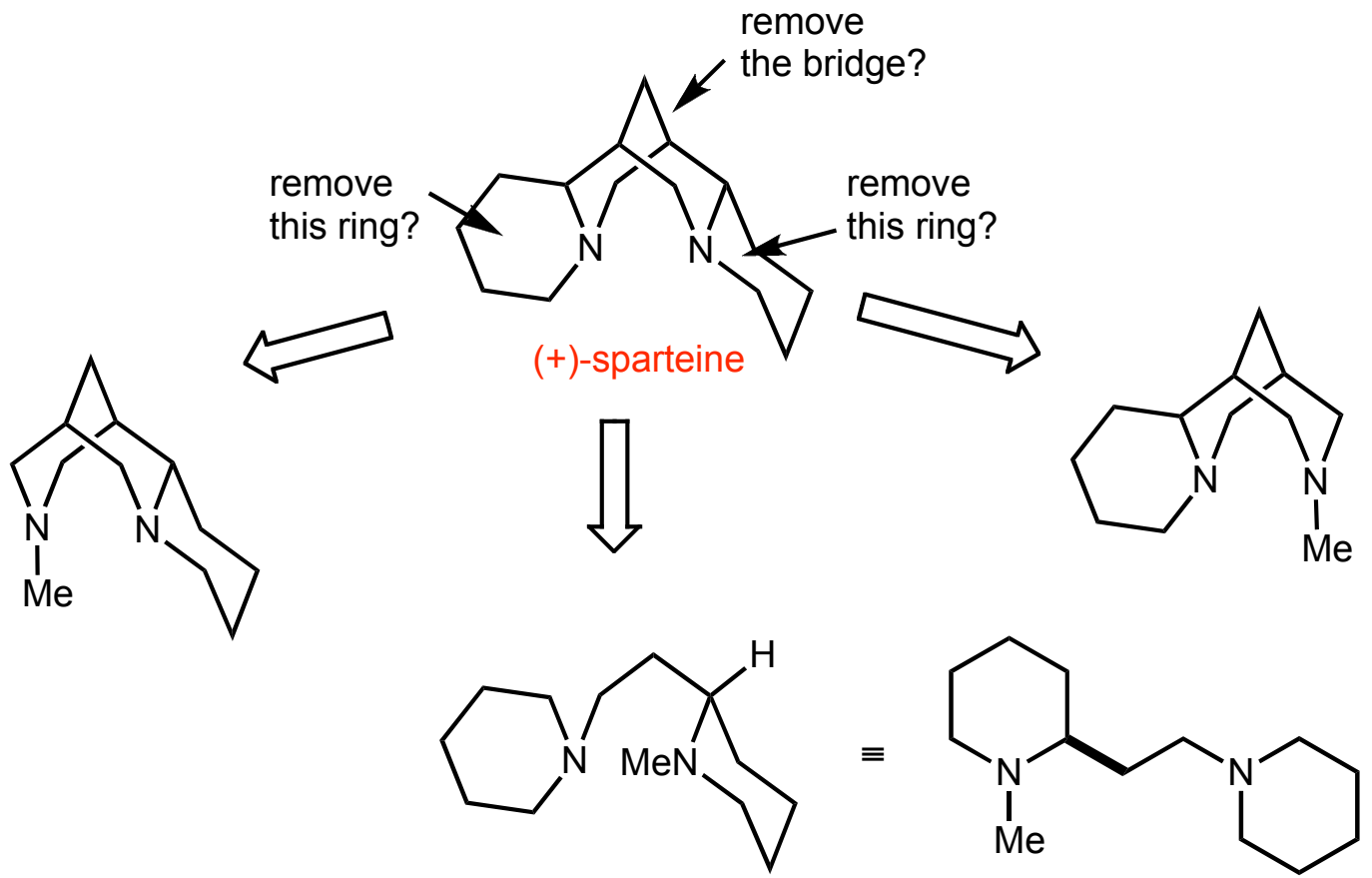



| ligand | lithiation time |
|---|---|
| TMEDA | 30 min |
| sparteine | 4 h |
| isosparteine | <10%, 4 h |

Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148

# Finding a (+)-Sparteine Surrogate

- O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction



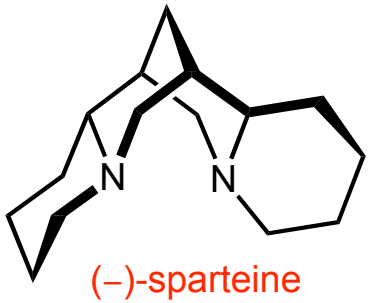


Dearden, M. J.; Firkin, C. R.; Hermet, J. R.; O'Brien, P.; *J. Am. Chem. Soc.* **2002**, *124*, 11870

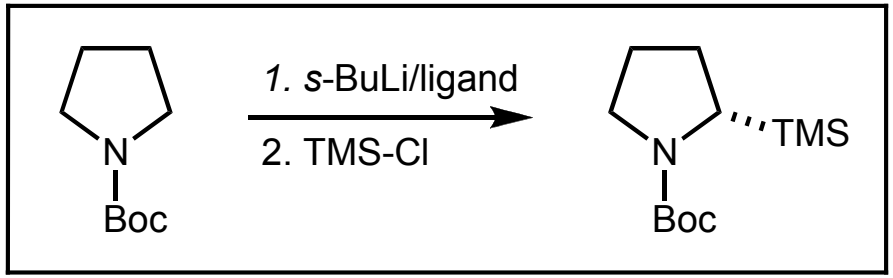
Hermet, J. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977

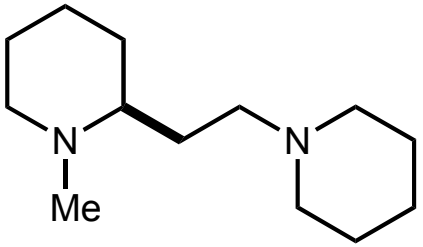
# Finding a (+)-Sparteine Surrogate

- O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction

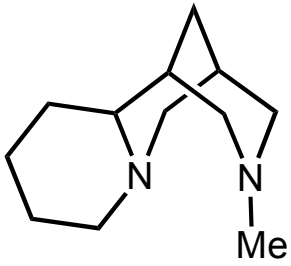



(–)-sparteine
87%, 90% ee




A (90% ee)
37%, racemic



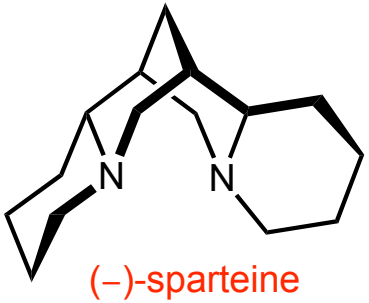

B (98% ee)
31%, 21% ee


Dearden, M. J.; Firkin, C. R.; Hermet, J. R.; O'Brien, P.; *J. Am. Chem. Soc.* **2002**, *124*, 11870

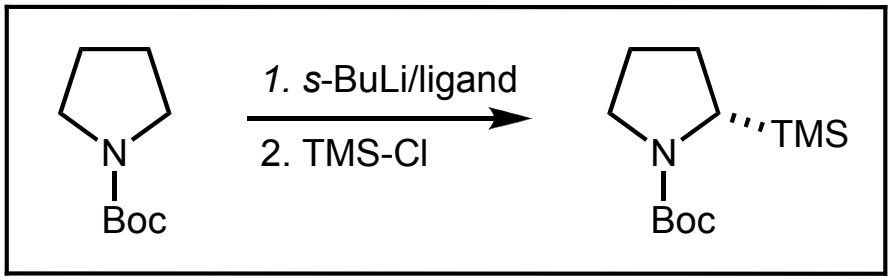
Hermet, J. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977

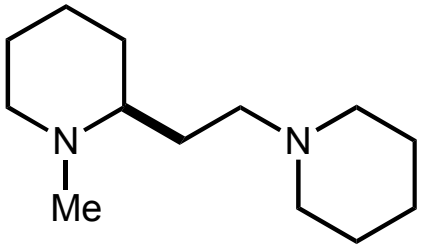
# Finding a (+)-Sparteine Surrogate

- O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction

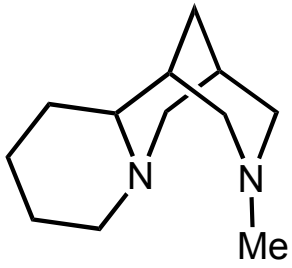



(–)-sparteine
87%, 90% ee

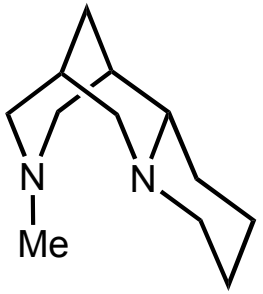



A (90% ee)
37%, racemic




B (98% ee)
31%, 21% ee



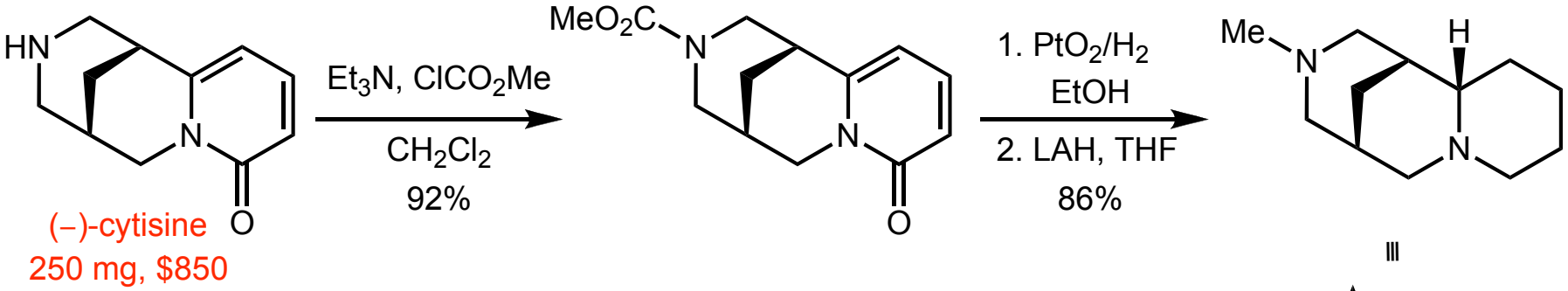

C (>90% ee)
84%, 90% ee

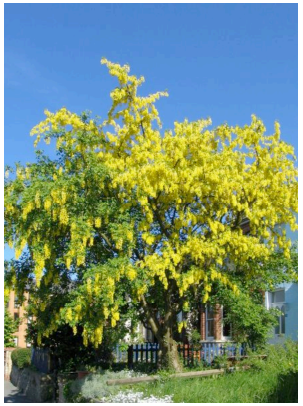

Dearden, M. J.; Firkin, C. R.; Hermet, J. R.; O'Brien, P.; *J. Am. Chem. Soc.* **2002**, *124*, 11870

Hermet, J. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977

# Synthesis of O'Brien's (+)-Sparteine Surrogate

■ (–)-Cytisine has a structure closely related to O'Brien's (+)-sparteine surrogate



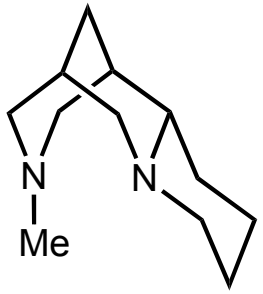
*Laburnum anagyroides*

seeds $70/Kg

from Vilmorin, France

(–)-cytisine

18 g/Kg seeds



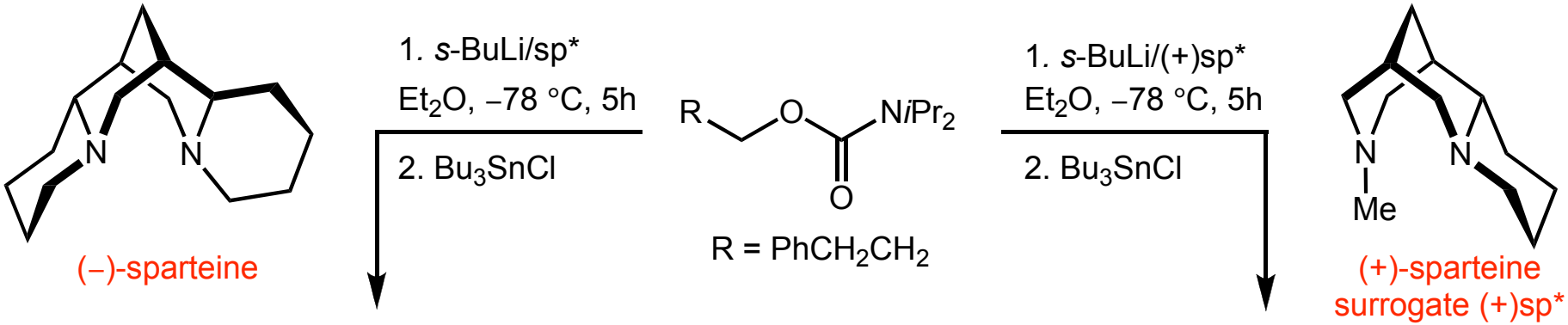

(+)-sparteine surrogate

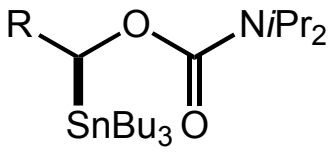

Dearden, M. J.; Firkin, C. R.; Hermet, J. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870

Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Syn.* **2005**, *83*, 141

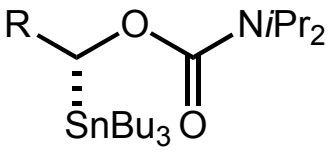
# Comparison of (–)-Sparteine to O'Brien's Ligand

- O'Brien's (+)-sparteine surrogate demonstrates approximately equal levels of enantioinduction as that achieved with (–)-sparteine




68%, 98% ee

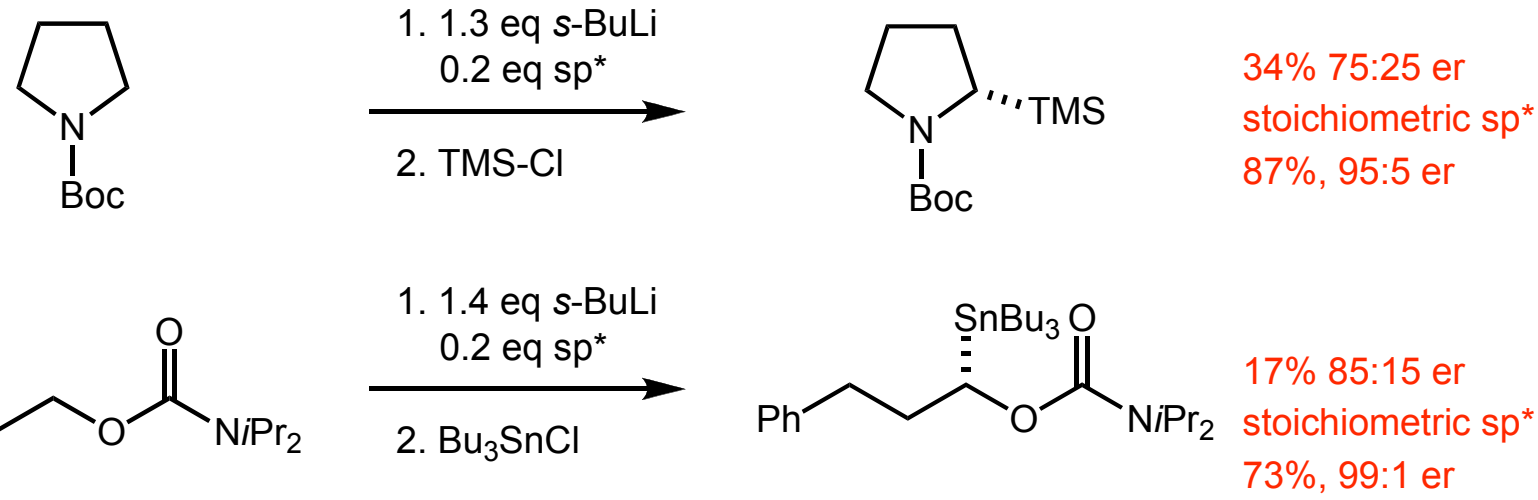



84%, 92% ee

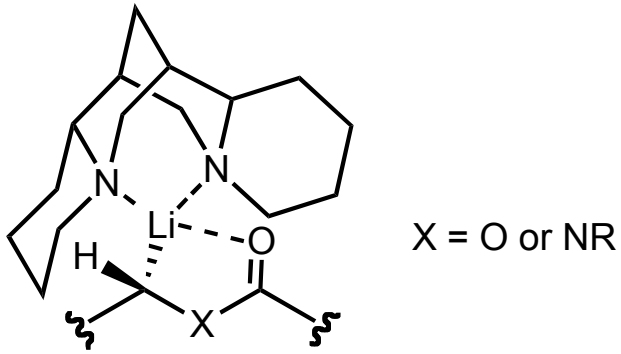
Dearden, M. J.; Firkin, C. R.; Hermet, J. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870

# Catalytic Asymmetric Lithiation

- Using a substoichiometric amount of (–)-sparteine affords low yields and selectivities in the deprotonation/substitution sequence



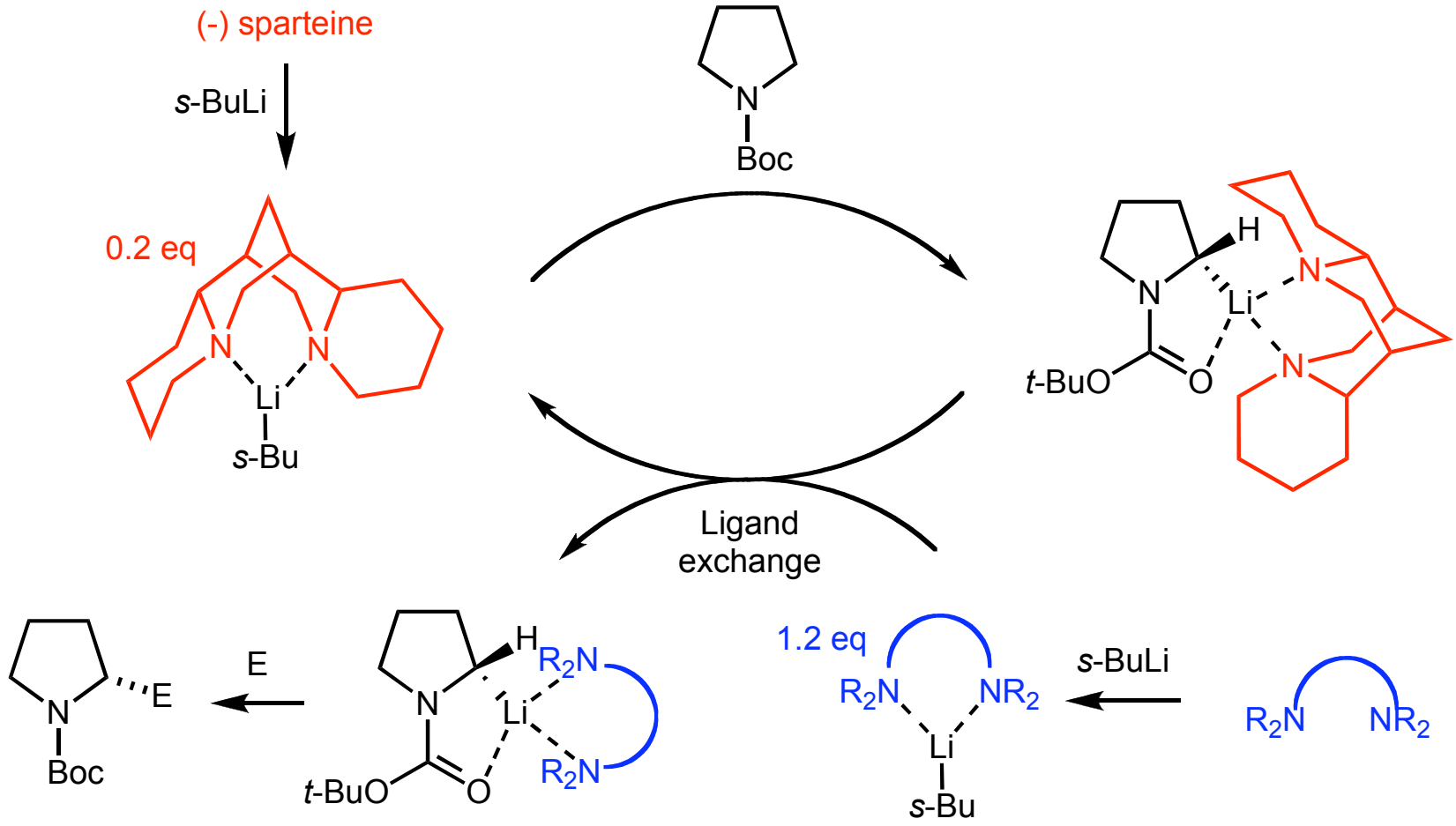

- The diamine does not dissociate from the lithiated complex




McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

# Catalytic Asymmetric Lithiation

- In order to achieve ligand turnover, O'Brien et al proposed the use of an achiral stoichiometric diamine to displace the chiral diamine



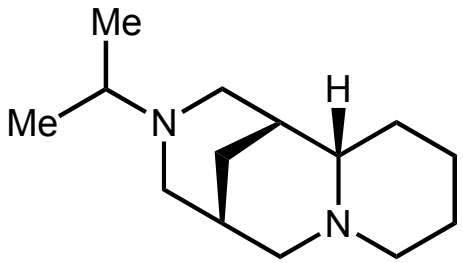

McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

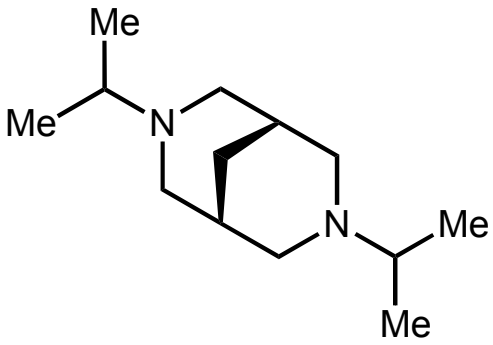
# Catalytic Asymmetric Lithiation

- Several criteria must be met in order to achieve enantioselective lithiation/ subsitution

    1. Ligand exchange must occur
    2. Organolithium must be configurationally stable during and after ligand exchange
    3. Deprotonation with *s*-BuLi/sp* must be faster than with the achiral complex

- Using information gained from their studies into designing a (+)-sparteine surrogate, the designed a ligand that should not facilitate deprotonation



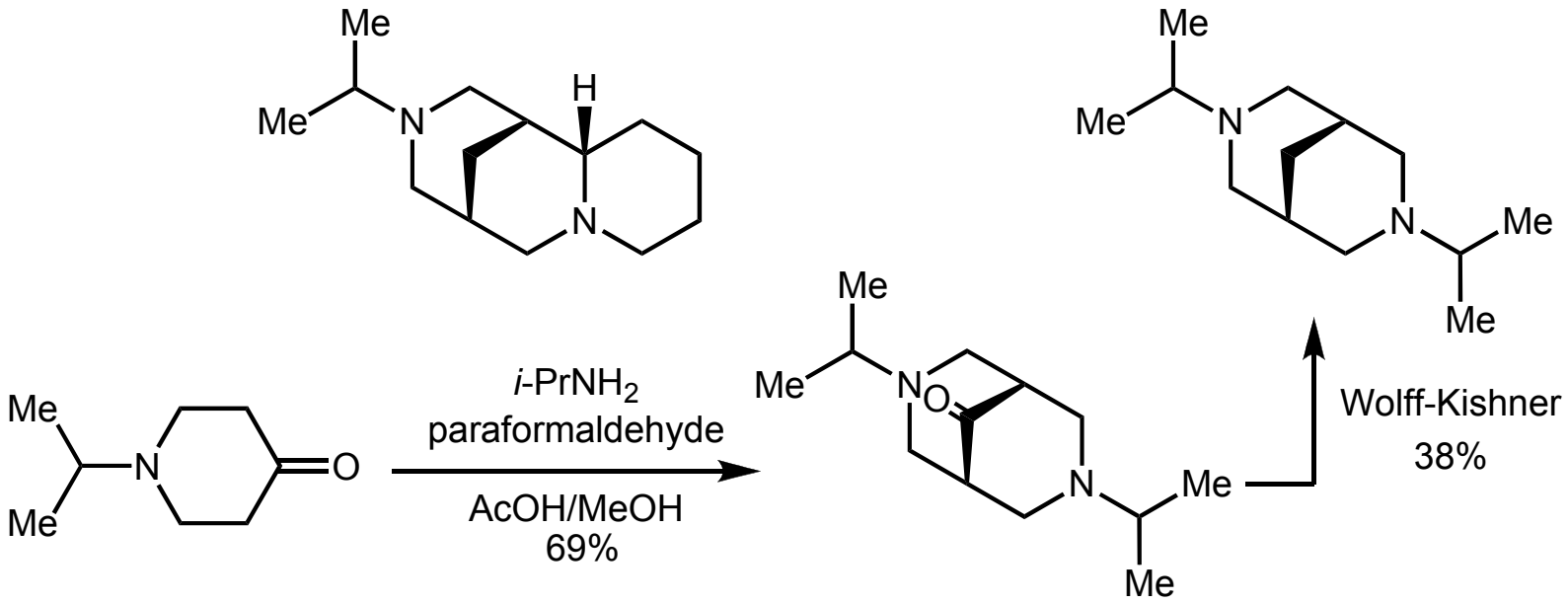

McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

# Catalytic Asymmetric Lithiation

- Several criteria must be met in order to achieve enantioselective lithiation/ subsitution

  1. Ligand exchange must occur
  2. Organolithium must be configurationally stable during and after ligand exchange
  3. Deprotonation with *s*-BuLi/sp* must be faster than with the achiral complex

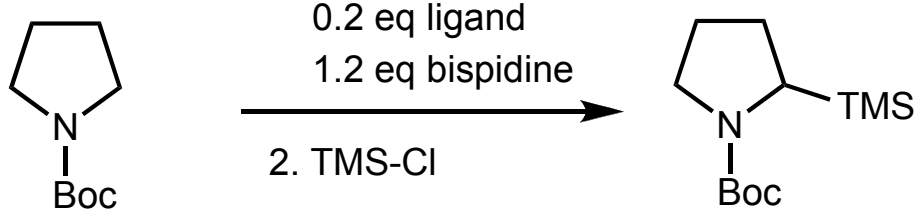
- Using information gained from their studies into designing a (+)-sparteine surrogate, the designed a ligand that should not facilitate deprotonation

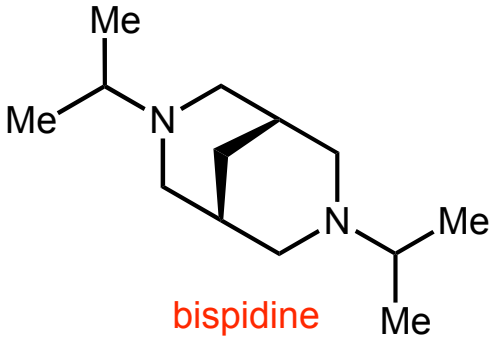



McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

# Catalytic Asymmetric Lithiation

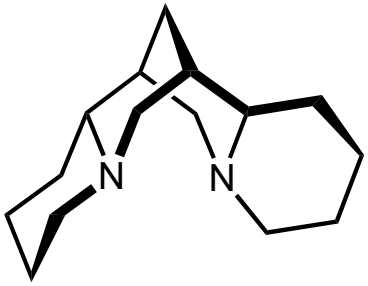
- Catalytic enantioselective lithiation/substitution works efficiently using the achiral bispidine ligand



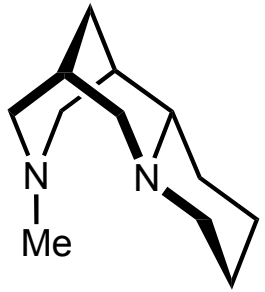




bispidine

| ligand | product | yield | er |
|---|---|---|---|
| sp* | S-TMS | 76 | 90:10 |
| (+)-sp* | R-TMS | 66 | 6:94 |




(–)-sparteine, sp*

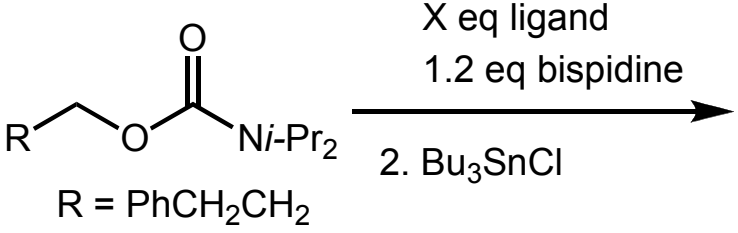


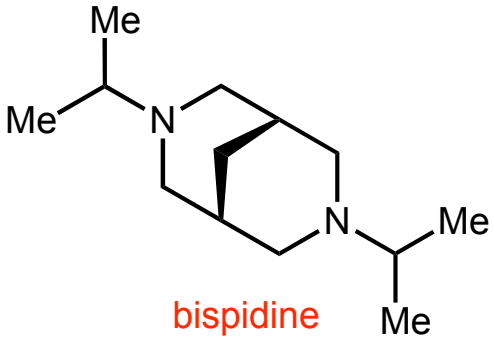

(+)-sparteine surrogate (+)-sp*

McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

# Catalytic Asymmetric Lithiation

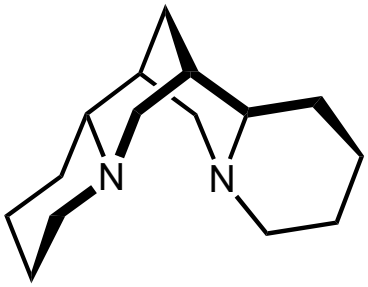
- Catalytic enantioselective lithiation/substitution works efficiently using the achiral bispidine ligand



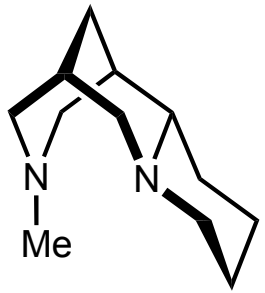




bispidine

| ligand | eq | product | yield | er |
|---|---|---|---|---|
| sp* | 0.2 | S-$SnR_3$ | 77 | 92:8 |
| (+)-sp* | 0.2 | R-$SnR_3$ | 72 | 6:94 |
| sp* | 0.1 | S-$SnR_3$ | 54 | 81:19 |
| (+)-sp* | 0.06 | R-$SnR_3$ | 63 | 15:85 |




(–)-sparteine, sp*

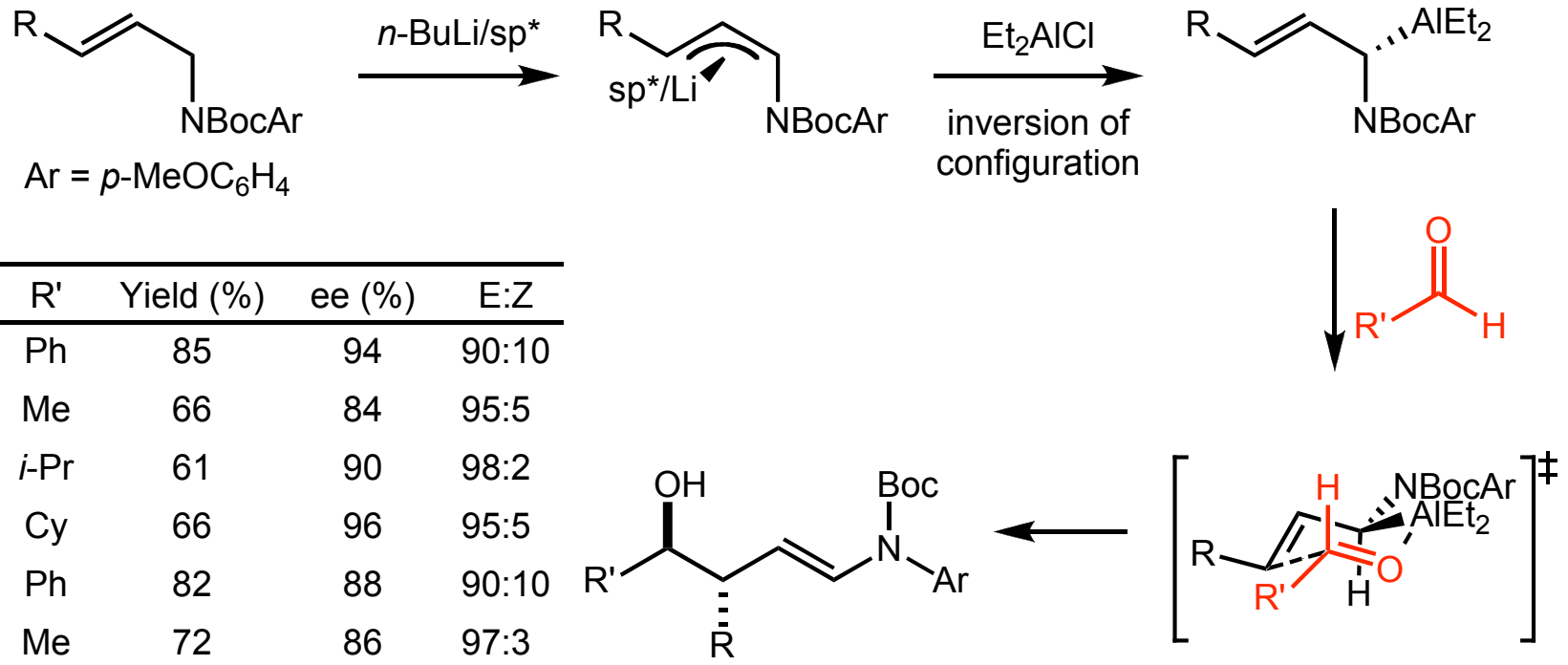



(+)-sparteine surrogate (+)-sp*

McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378

# Synthetic Utility of Asymmetric Lithiation

- Anti-homoaldol reaction of allylic N-Boc amines proceeds with high levels of selectivity

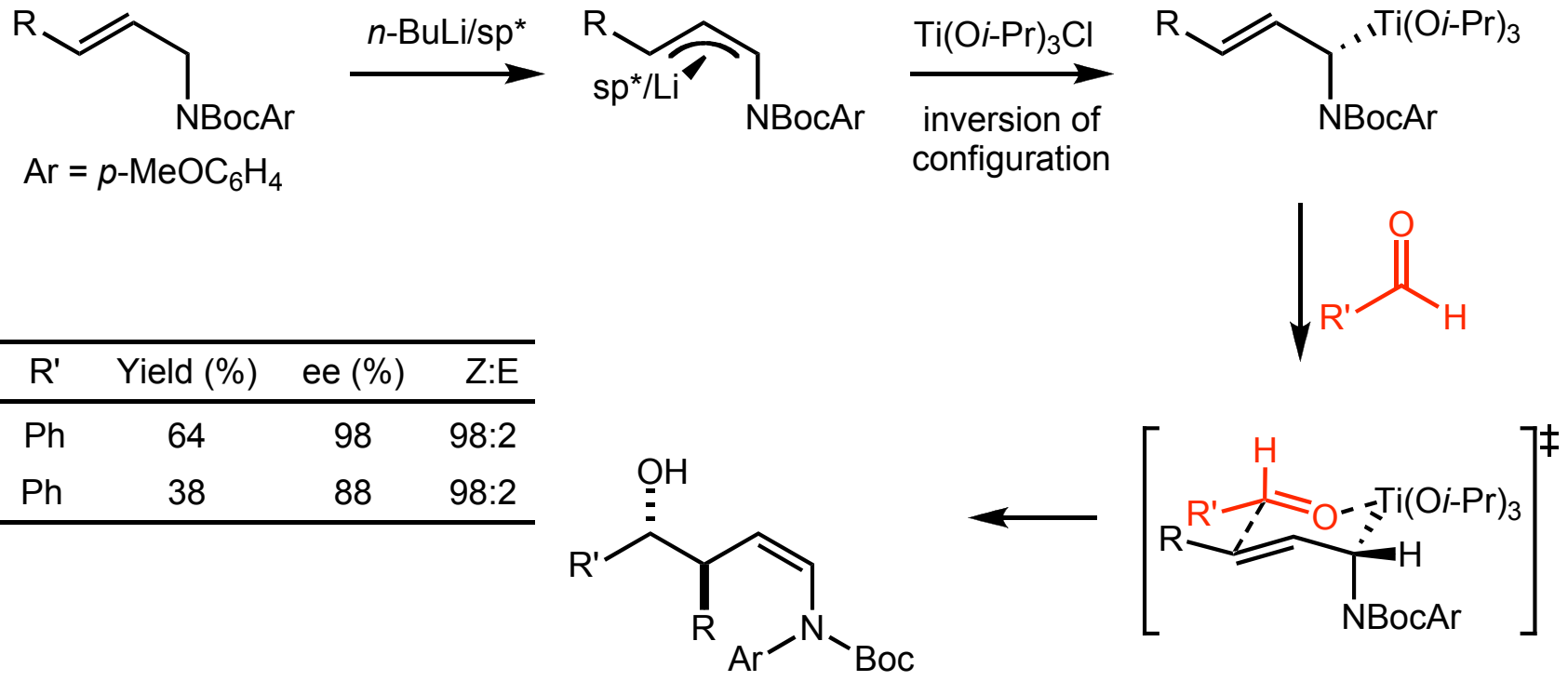



| R | R' | Yield (%) | ee (%) | E:Z |
|---|---|---|---|---|
| Ph | Ph | 85 | 94 | 90:10 |
| Ph | Me | 66 | 84 | 95:5 |
| Ph | *i*-Pr | 61 | 90 | 98:2 |
| Ph | Cy | 66 | 96 | 95:5 |
| Cy | Ph | 82 | 88 | 90:10 |
| Cy | Me | 72 | 86 | 97:3 |
| Cy | *i*-Pr | 81 | 88 | 98:2 |
| Cy | *Cy* | 84 | 90 | 98:2 |

Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655

# Synthetic Utility of Asymmetric Lithiation

- Changing the lewis acid from $Et_2AlCl$ to $Ti(O\textit{i}\text{-}Pr)_3Cl$ results in an inversion in the enantiomeric series of the product due to a differing transition state

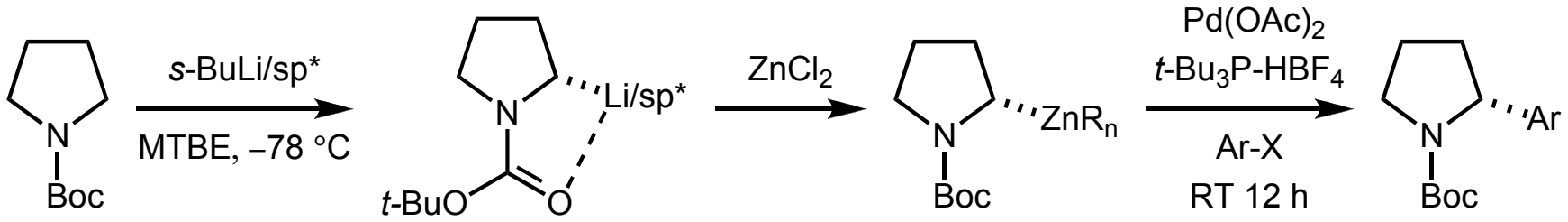



| R | R' | Yield (%) | ee (%) | Z:E |
|---|---|---|---|---|
| Ph | Ph | 64 | 98 | 98:2 |
| Cy | Ph | 38 | 88 | 98:2 |

Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655

# Synthetic Utility of Asymmetric Lithiation

- Transmetalation of lithiated Boc-pyrrolidine to zinc enables Negishi coupling with a range of aryl halides



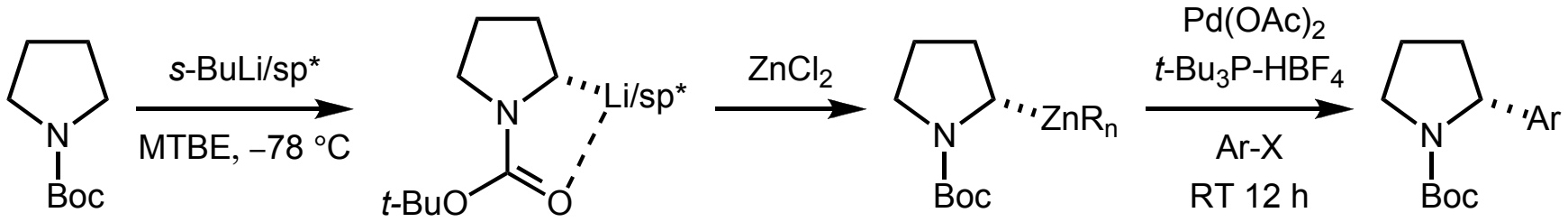

| entry | Ar-X | eq $ZnCl_2$ | % yield | er |
|---|---|---|---|---|
| 1 | Ph-Br | 1.0 | 82 | 96:4 |
| 2 | Ph-Br | 0.6 | 80 | 96:4 |
| 3 | Ph-Br | 0.3 | 79 | 96:4 |
| 4 | Ph-Cl | 1.0 | 48 | 96:4 |
| 5 | Ph-OTf | 1.0 | <5 | 96:4 |
| 6 | *p*-F-PhBr | 1.0 | 75 | 96:4 |
| 7 | *p*-$NH_2$-PhBr | 1.0 | 70 | 96:4 |
| 8 | *o*-MeO-PhBr | 1.0 | 72 | 96:4 |
| 9 | 5-Br-NBoc-indole | 1.0 | 81 | 96:4 |
| 10 | 4-Br-indole | 1.0 | 77 | 96:4 |
| 11 | 3-Br-pyridine | 1.0 | 60 | 96:4[a] |

4 mol% $Pd(OAc)_2$, 5 mol% *t*-$Bu_3P$-$HBF_4$.[a]coupling performed at 60 °C.

Campos, K. R.: Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538

# Synthetic Utility of Asymmetric Lithiation

- Transmetalation of lithiated Boc-pyrrolidine to zinc enables Negishi coupling with a range of aryl halides



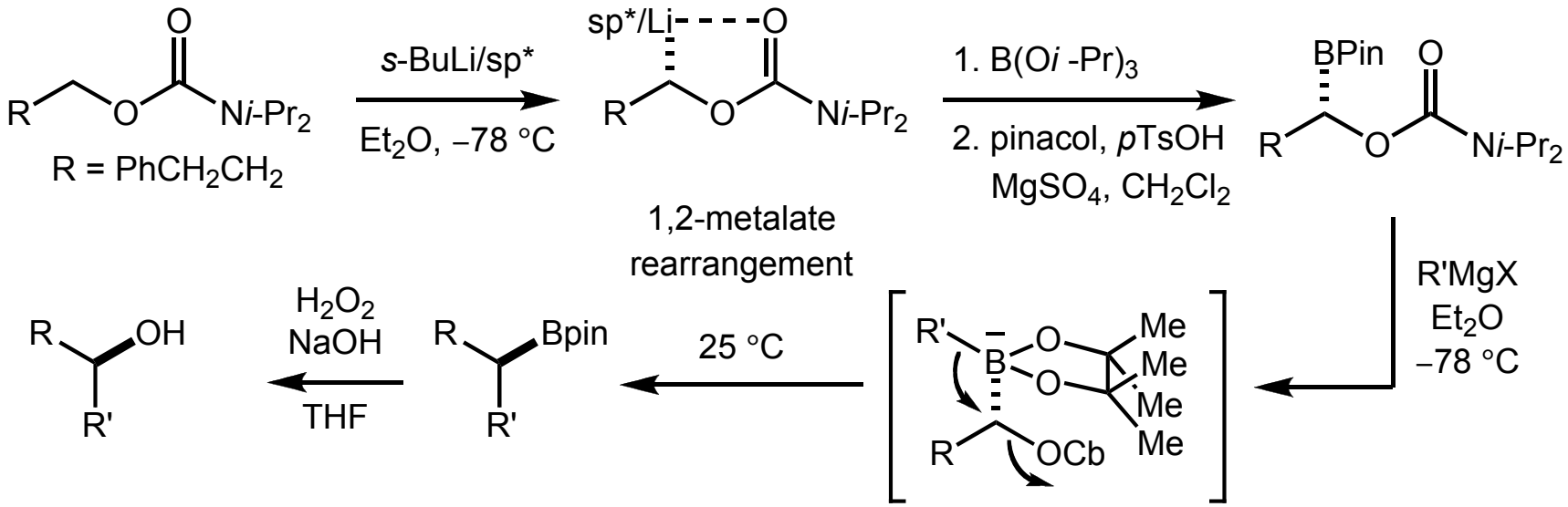

| entry | Ar-X | eq $ZnCl_2$ | % yield | er |
|---|---|---|---|---|
| 1 | Ph-Br | 1.0 | 82 | 96:4 |
| 2 | Ph-Br | 0.6 | 80 | 96:4 |
| 3 | Ph-Br | 0.3 | 79 | 96:4 |
| 4 | Ph-Cl | 1.0 | 48 | 96:4 |
| 5 | Ph-OTf | 1.0 | <5 | 96:4 |
| 6 | *p*-F-PhBr | 1.0 | 75 | 96:4 |
| 7 | *p*-$NH_2$-PhBr | 1.0 | 70 | 96:4 |
| 8 | *o*-MeO-PhBr | 1.0 | 72 | 96:4 |
| 9 | 5-Br-NBoc-indole | 1.0 | 81 | 96:4 |
| 10 | 4-Br-indole | 1.0 | 77 | 96:4 |
| 11 | 3-Br-pyridine | 1.0 | 60 | 96:4[a] |

4 mol% $Pd(OAc)_2$, 5 mol% *t*-$Bu_3P$-$HBF_4$.[a]coupling performed at 60 °C.

Campos, K. R.: Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538

# Synthetic Utility of Asymmetric Lithiation

- Hoppe demonstrated that O-alkylcarbamates can be deprotonated and trapped with boronic esters to yield precursors to 1,2 metalate rearrangement products

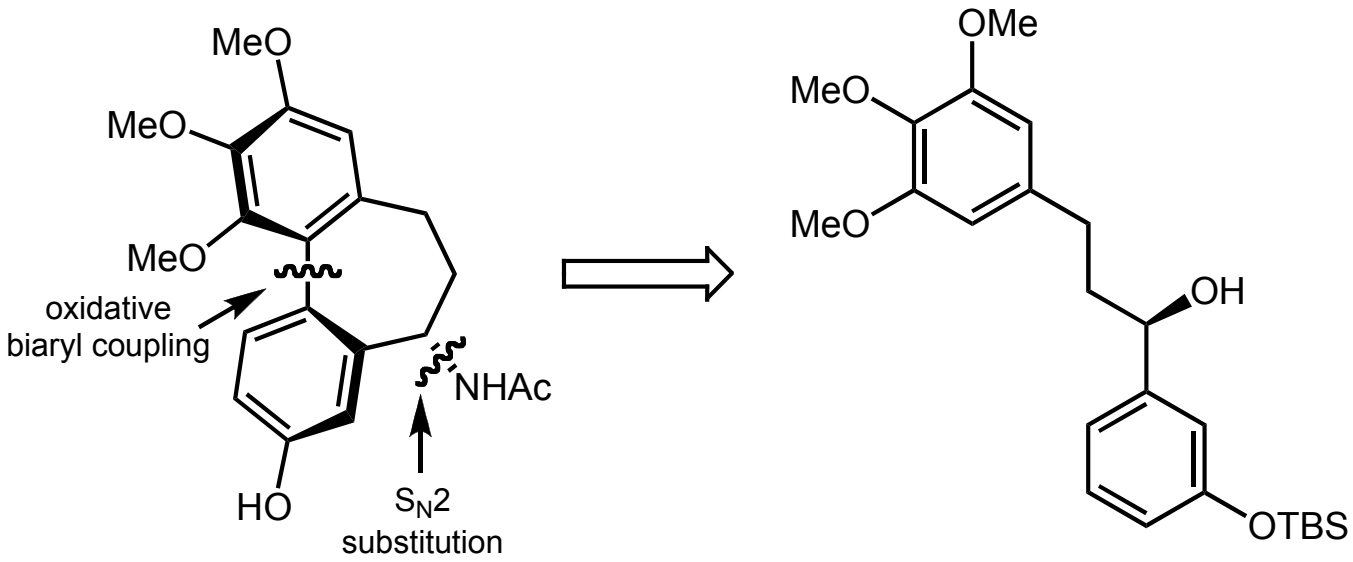



| Grignard reagent, R' | % yield | ee (%) |
|---|---|---|
| PrMgCl | 50 | >95 |
| CyMgBr | 70 | >95 |
| *i*-PrMgCl | 56 | >95 |
| *t*-BuMgCl | 64 | >95 |

Beckmann, E.; Desai, V.; Hoppe, D. *Synlett*, **2004**, *13*, 2275

# Synthetic Utility of Asymmetric Lithiation

- Kocienski et al. recently applied this methodology toward the synthesis of (S)-(–)-N-Acetylcolchinol

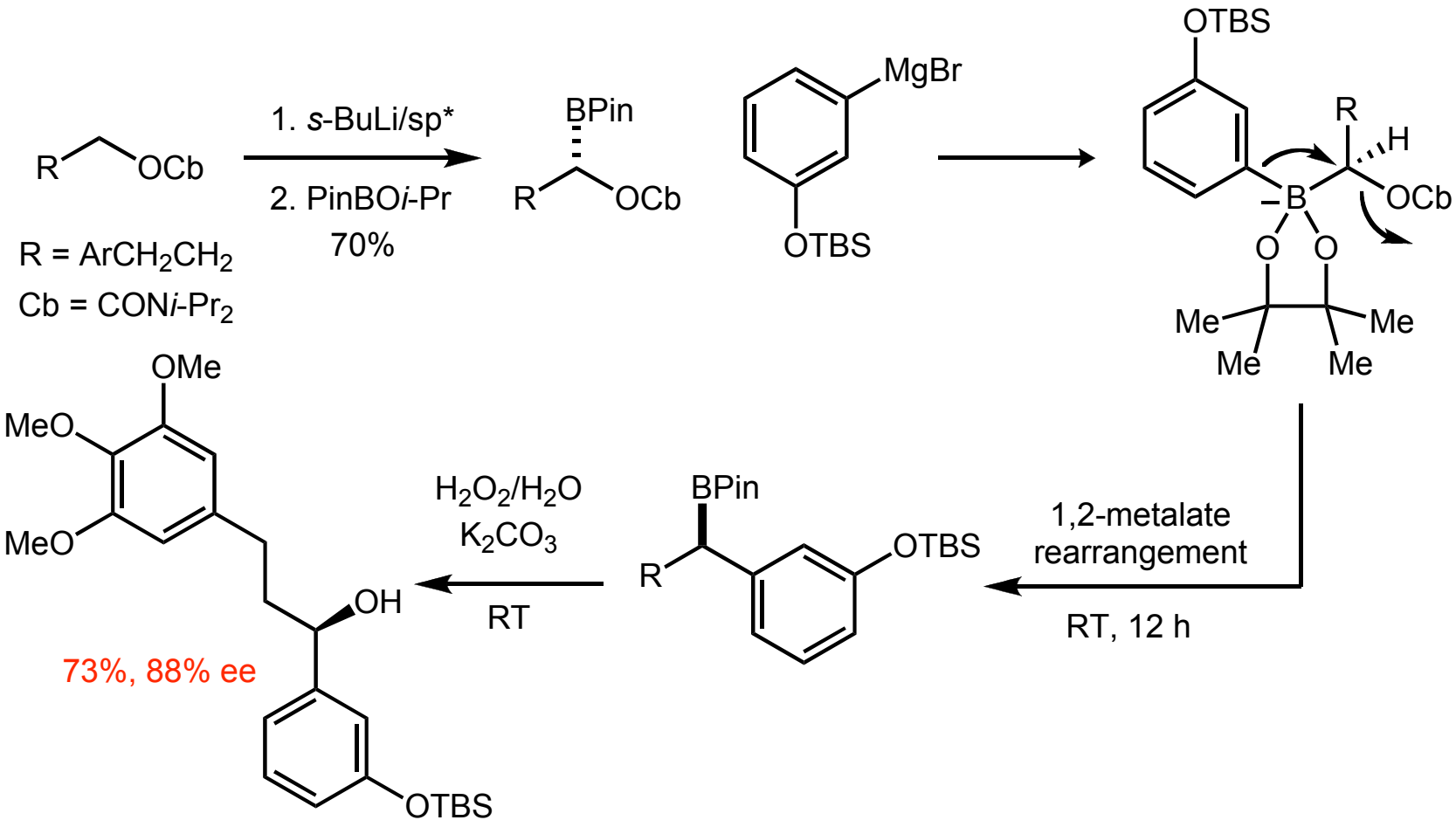



(S)-(–)-N-Acetylcolchinol

Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyl, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193

# Synthetic Utility of Asymmetric Lithiation

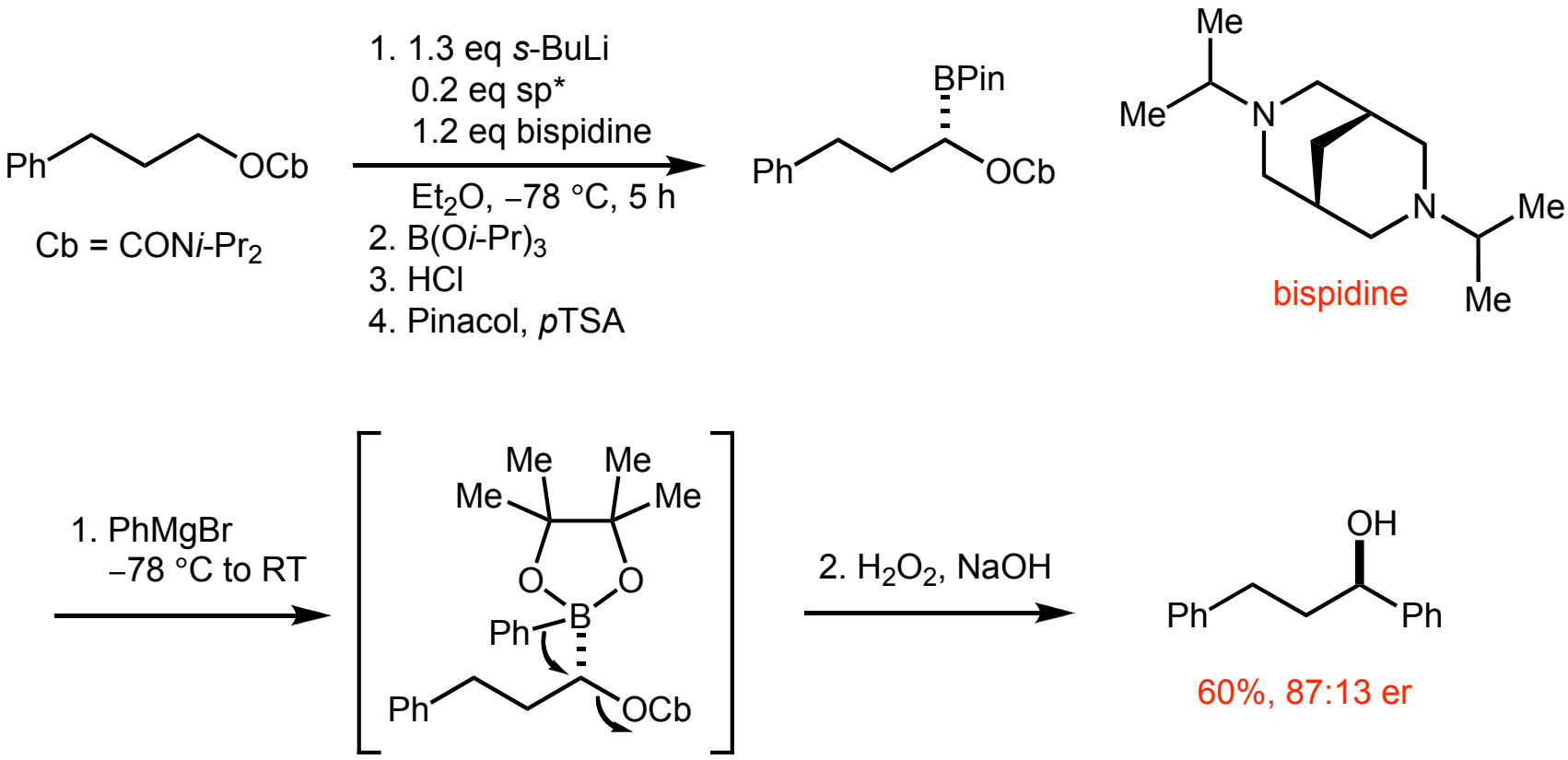
- Kocienski et al. recently applied this methodology toward the synthesis of (S)-(–)-N-Acetylcolchinol




Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyl, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193

# Catalytic Asymmetric Variant of Hoppe's Methodology

- Using his bispidine exchange ligand, O'Brien was able to a achieve a metalation, electrophile trapping, 1,2-metalate rearrangement under catalytic conditions




McGrath, M. J.; O'Brien, P. *Synthesis*, **2006**, *13*, 2233

# Conclusions

- Enantioselective Lithiation/Substitution Generally Proceeds Through Two Limiting Pathways:

  - Asymmetric deprotonation

  - Asymmetric substitution

    Dynamic thermodynamic resolution

    Dynamic kinetic resolution

- Work By O'Brien has Produced a (+)-Sparteine Surrogate as Well as the First Catalytic Asymmetric Lithiation/Substitution Reaction

- Lithiated Intermediates Can Be Precursors to Various Transmetallative Processes Such as Homo-Aldol Reactions, Negishi Couplings and 1,2-Metallate Rearrangements