Reagent-Controlled Asymmetric Homologation of Boronic Esters by Enantioenriched Main-Group Chiral Carbenoids

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Presented by: John Maciejewski

Presentation Outline

- Introduction
- Recent applications of 1,2-metalate rearrangements
- Key innovations and synthetic utility
- Next directions and future applications

Introduction

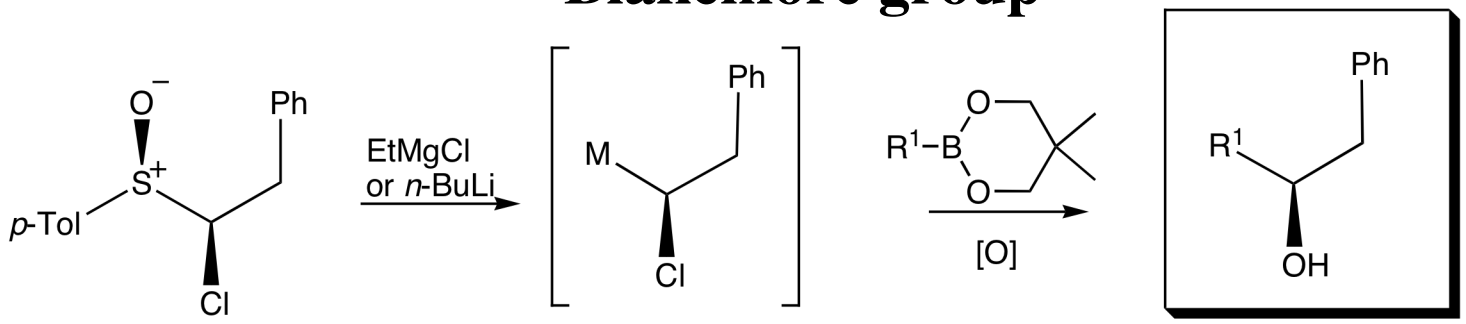
Mattson & Mah

SN_2 displacement of α-haloalkyl boronic esters

Hoffmann group
Chiral carbenoid stability

Satoh group
Metal carbenoid synthesis and stability

Blakemore group



% ee > 98 %

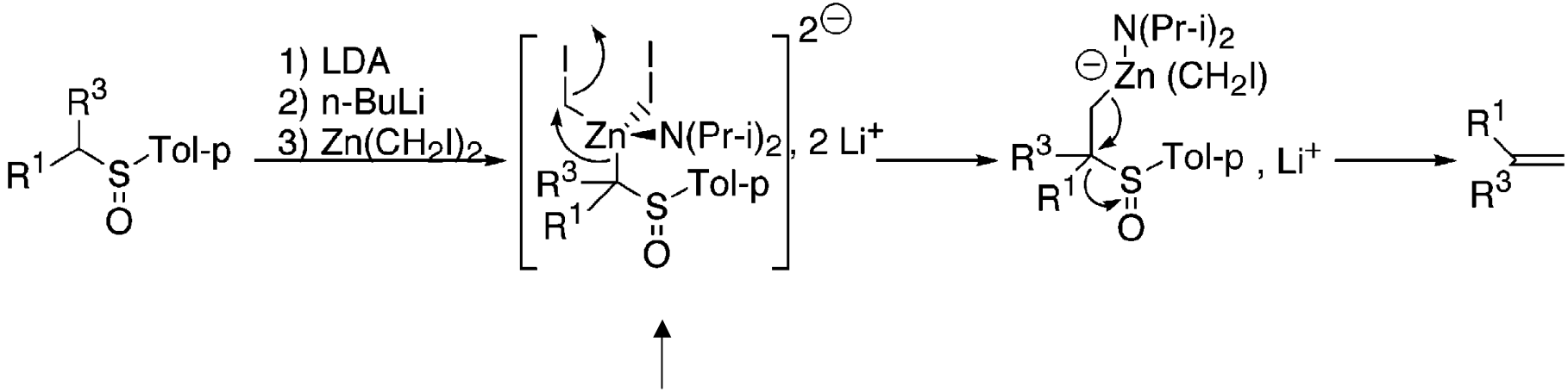
M = MgCl or Li

% ee = 59 - 96 %

High % ee via reagent control through 1,2-metalate rearrangement

Recent Applications of 1,2-Metalate Rearrangements

Substrates act as a new source of olefins

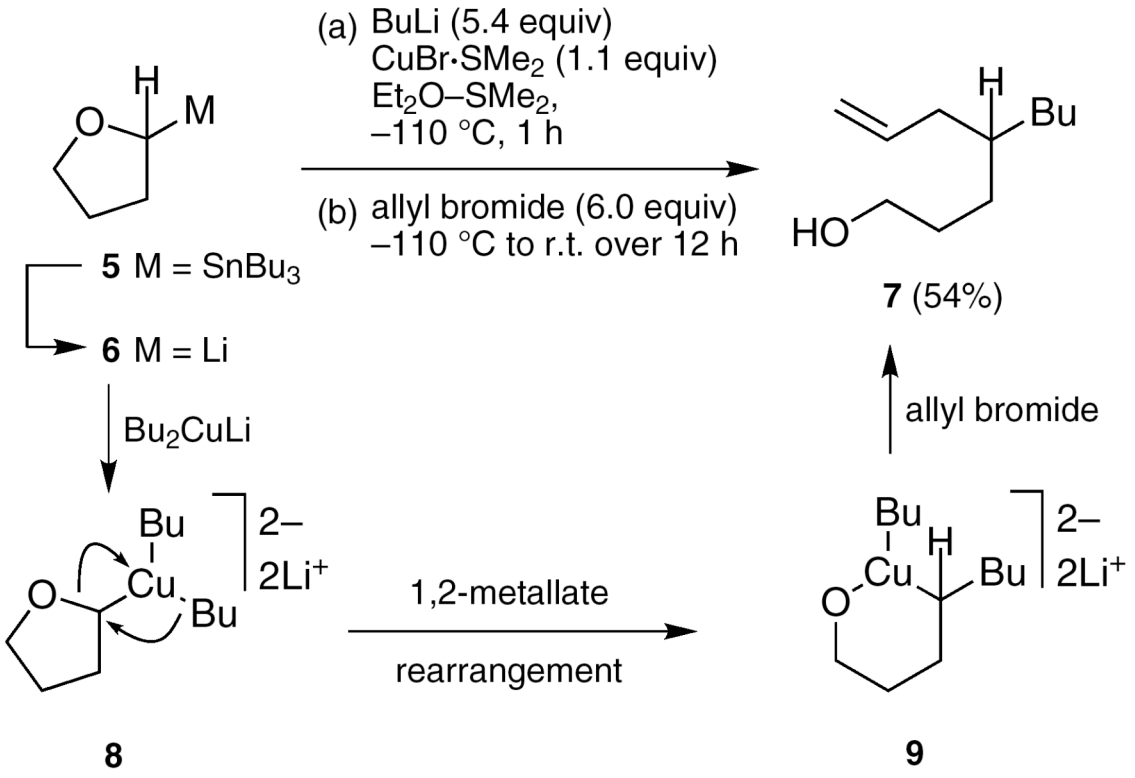


(1,2-rearrangement)

Abramovitch, A.; Varghese, J. P.; Marek, I. *Org. Lett.* **2004,** *6*, 621.

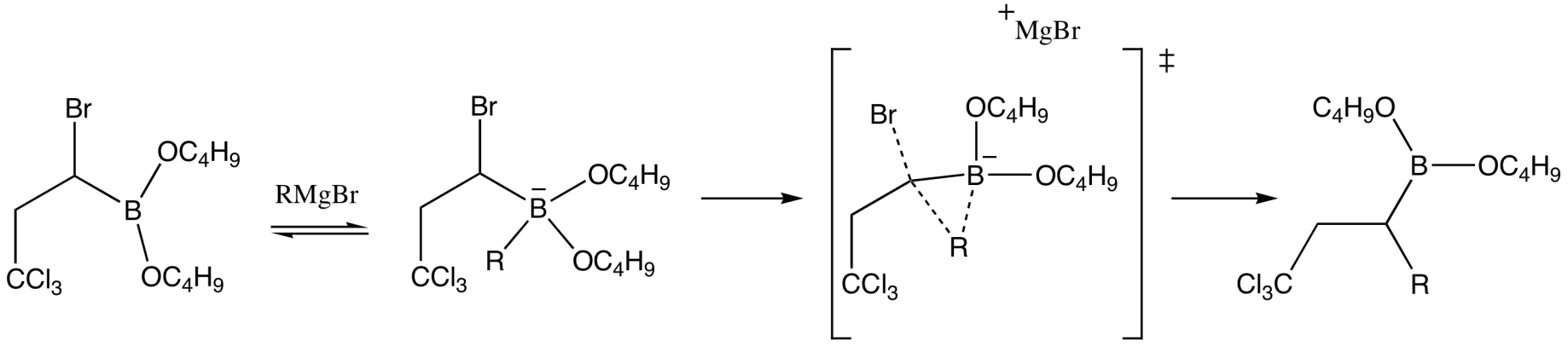
Recent Applications of 1,2-Metalate Rearrangements

1,2-Metalate rearrangements of α-alkoxyalkyl cuprates



Jarowicki, K.; Kocienski, P. J. *Synlett* **2005**, 167.

Nucleophilic Displacement of α-Bromoalkyl Boron Compounds

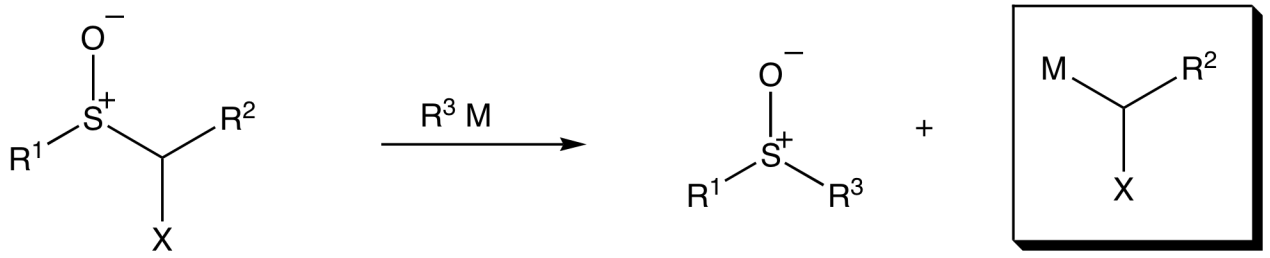


1 1' 2 3

SN_2 displacement of neighboring halogen
Alkyl migration favored over alkoxide due to stronger B-O bond

Matteson, D.S; Mah, R. W. H. *J. Am. Chem. Soc*. **1963,** *85*, 2599.

Preparation of Functionalized Carbenoid Reagents



4 5 6

R^1 = tolyl
X, R^2 = aziridine
R^3 = Ethyl
M = MgBr

Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989,** *54*, 3973-3978

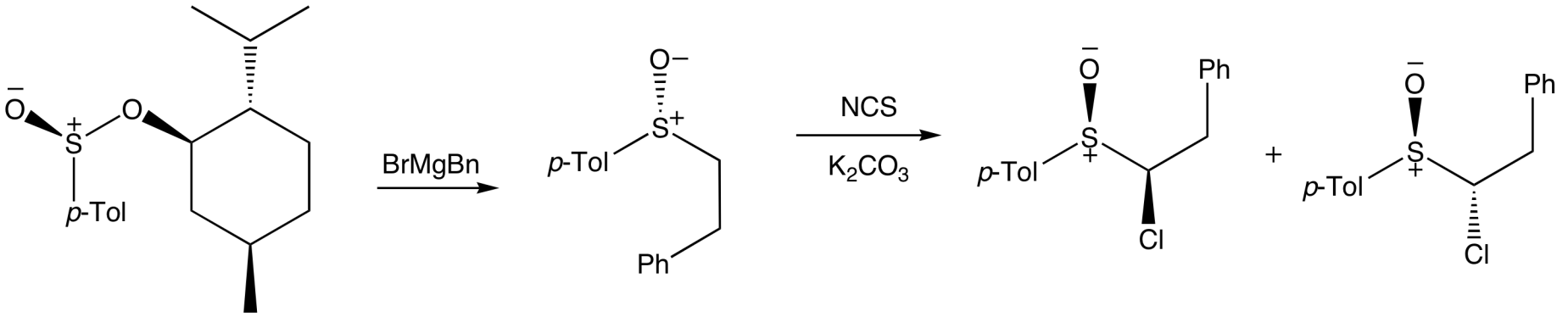
R^1 = Phenyl, tolyl
X = F, Cl, Br
R^2, R^3 = alkyl
M = Li

Satoh, T.; Takano, K. *Tetrahedron* **1996,** *52*, 2349.

Sulfoxide/metal exchange occurs
α-alkylhalo magnesium species more stable
α-alkylhalo lithium species more reactive

7

Synthesis of α-Chiral Sulfoxides

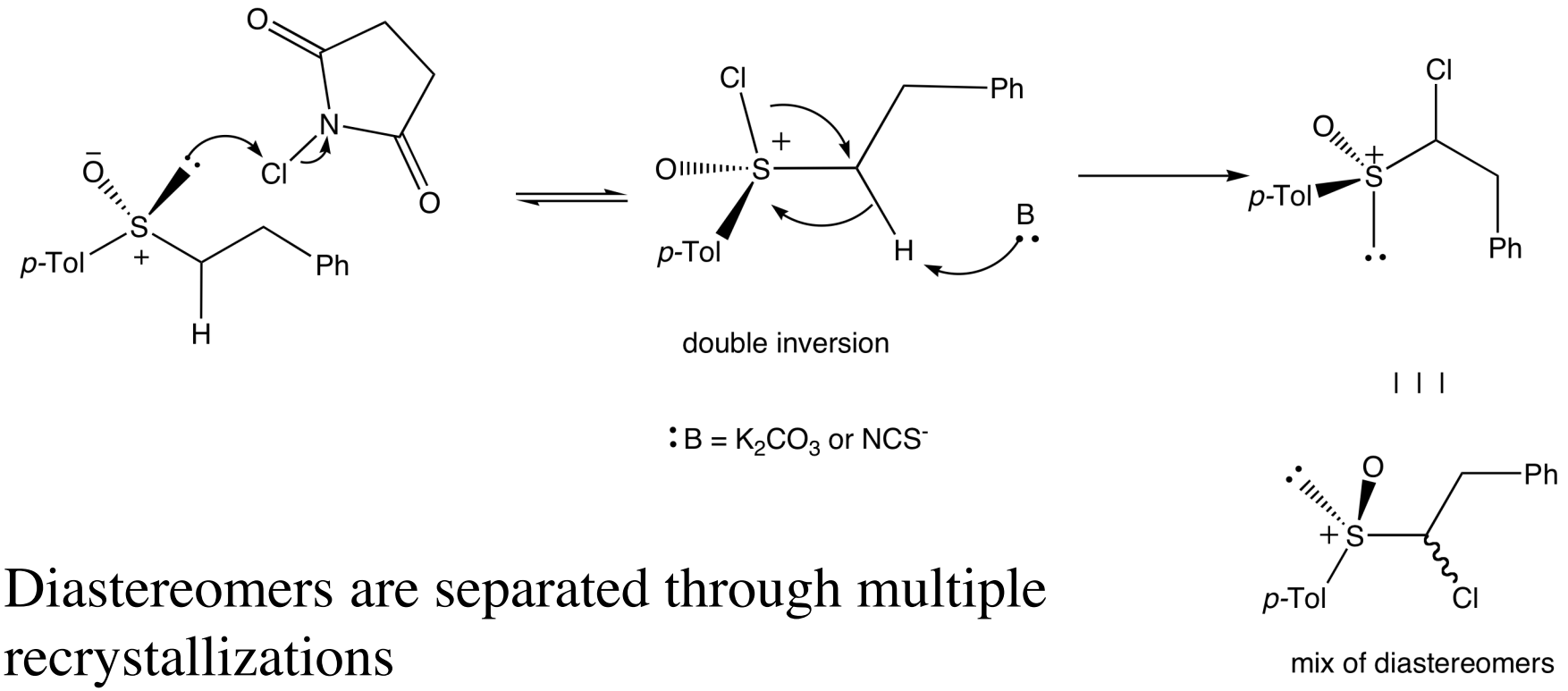


7 8 9 10

α-Halogenation occurs with inversion at sulfur center
Diastereomers (**9** & **10**) isolated via multiple recrystallization in acetone
Isolate enantiomer **9** in >97 % ee (HPLC)

Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000,** *6,* 3359.

Mechanism of α-Halogenation

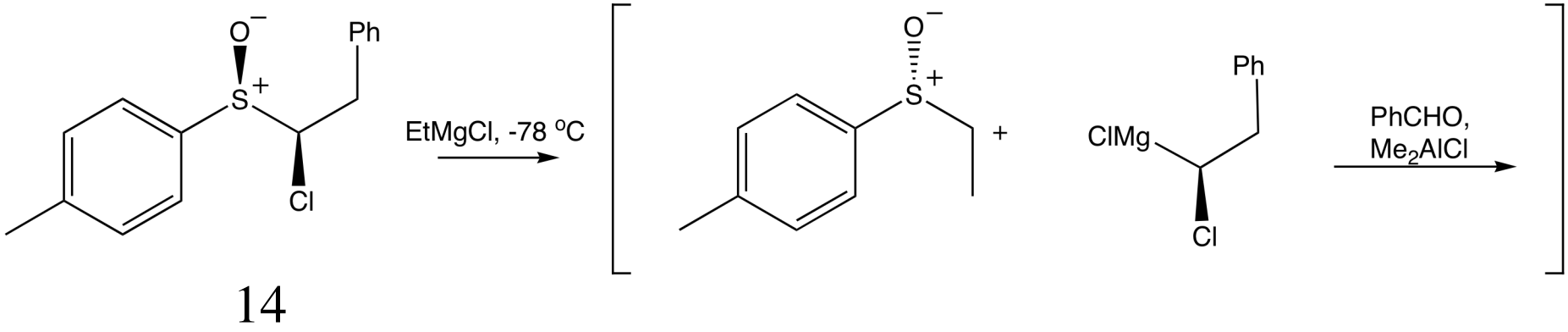


mix of diastereomers

Diastereomers are separated through multiple recrystallizations

International Conference on Organic Sulphur Chemistry. *Organic Sulphur Chemistry: Structure, Mechanism, and Synthesis*. Stirling, C. J. M., Ed.; Sulphur Institute: London, 1975; pp 196 - 198.

Stability of α-Chiral Magnesium Carbenoids *



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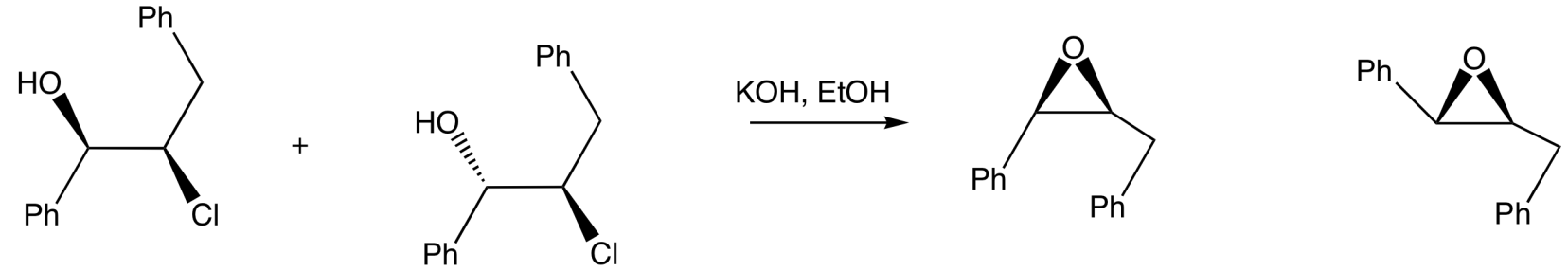


dr 93 : 7

(***R, R***) (***S, R***)

15 16

dr 94 : 6

cis *trans*

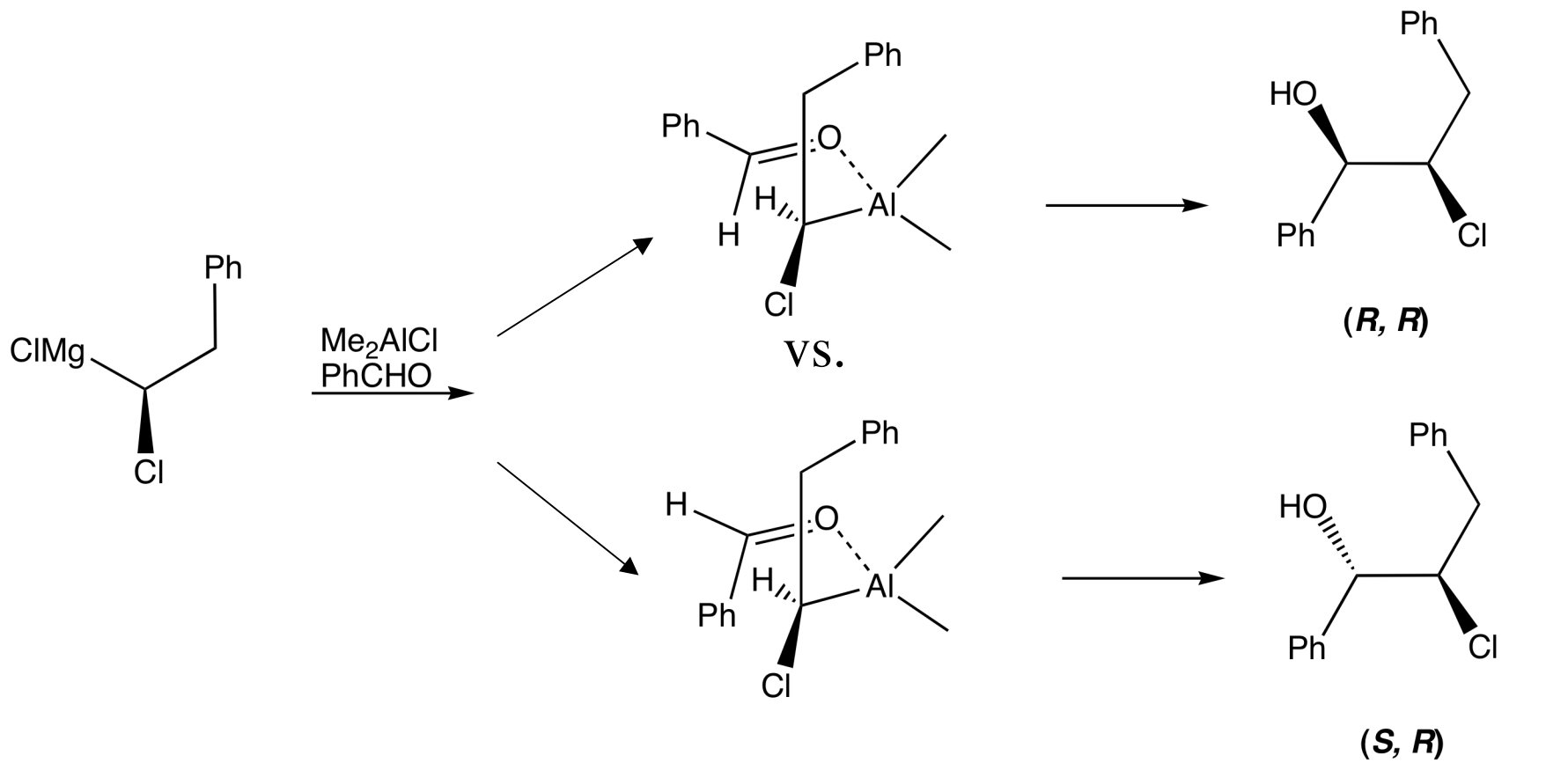
98.4% ee > 98% ee

17 18

* Results reproduced by Blakemore

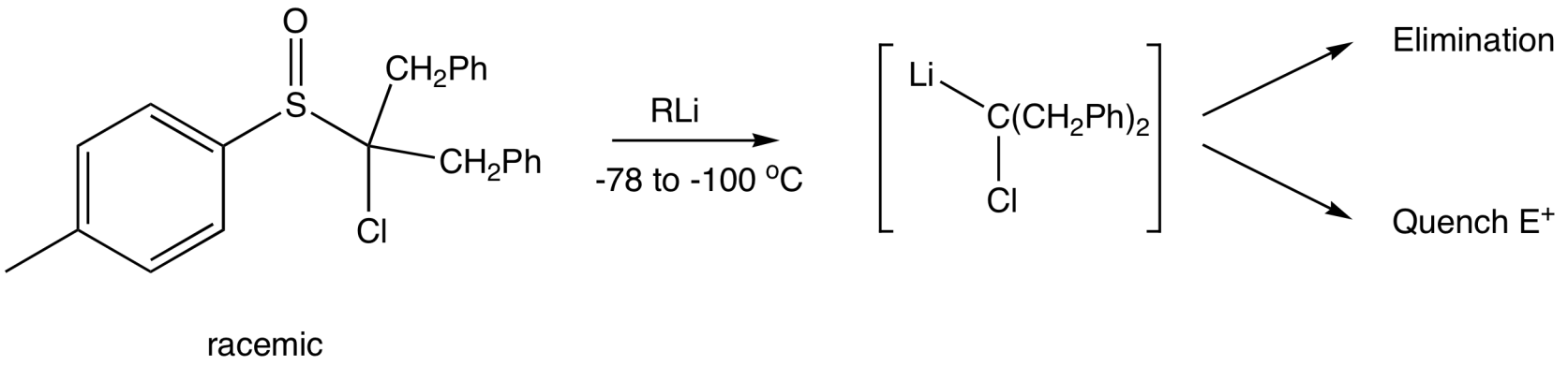
Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000,** *6,* 3359.

Transition State of Carbenoid Addition



dr = 93 (*R, R*): 7 (*S, R*)

Sulfoxide/Lithium Exchange



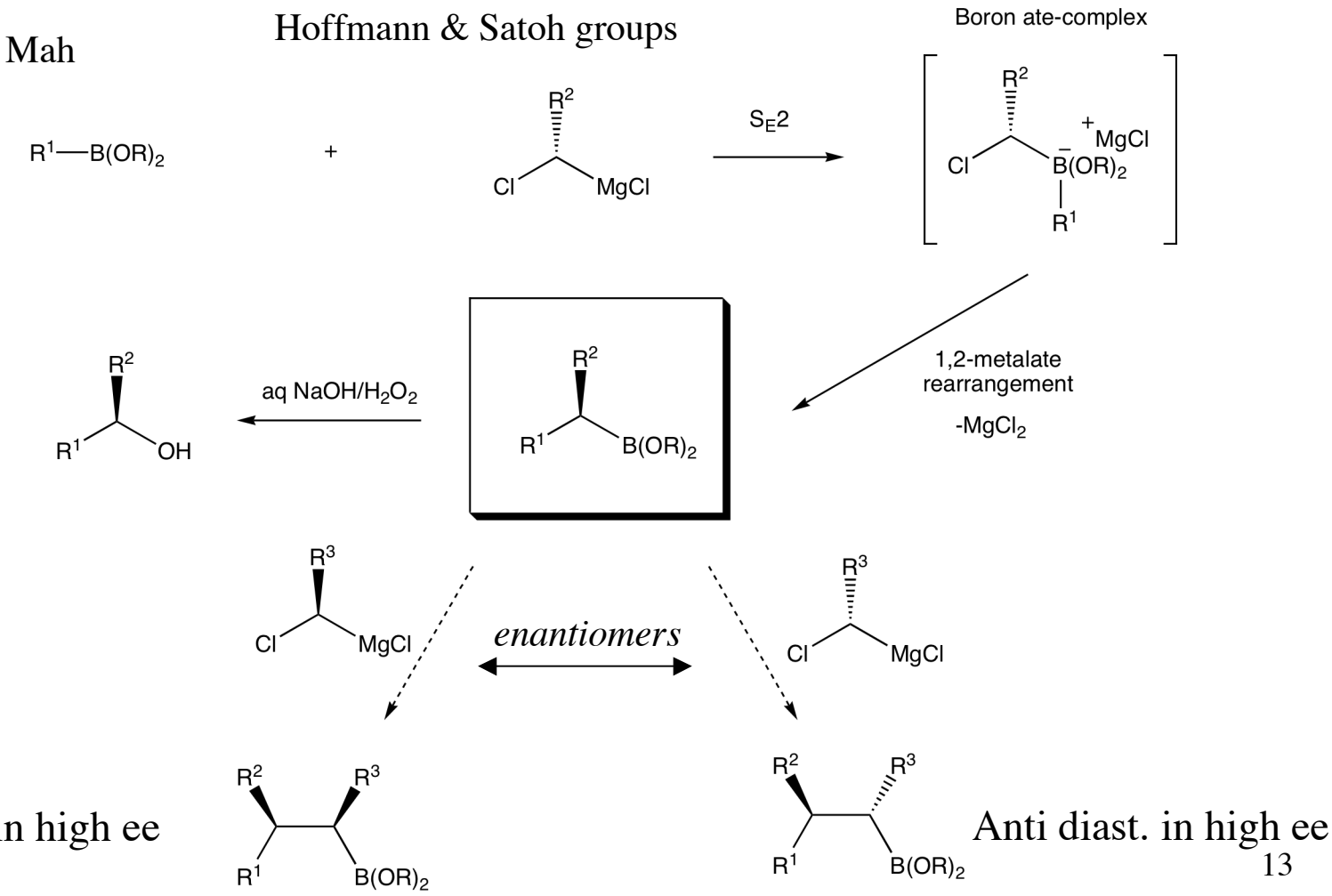
Evidence of lithium carbenoid generation from α-halosulfoxides

Satoh, T.; Takano, K. *Tetrahedron* **1996,** *52*, 2349.

Stereospecific Reagent Controlled Homologation (SRHC)

Matteson and Mah

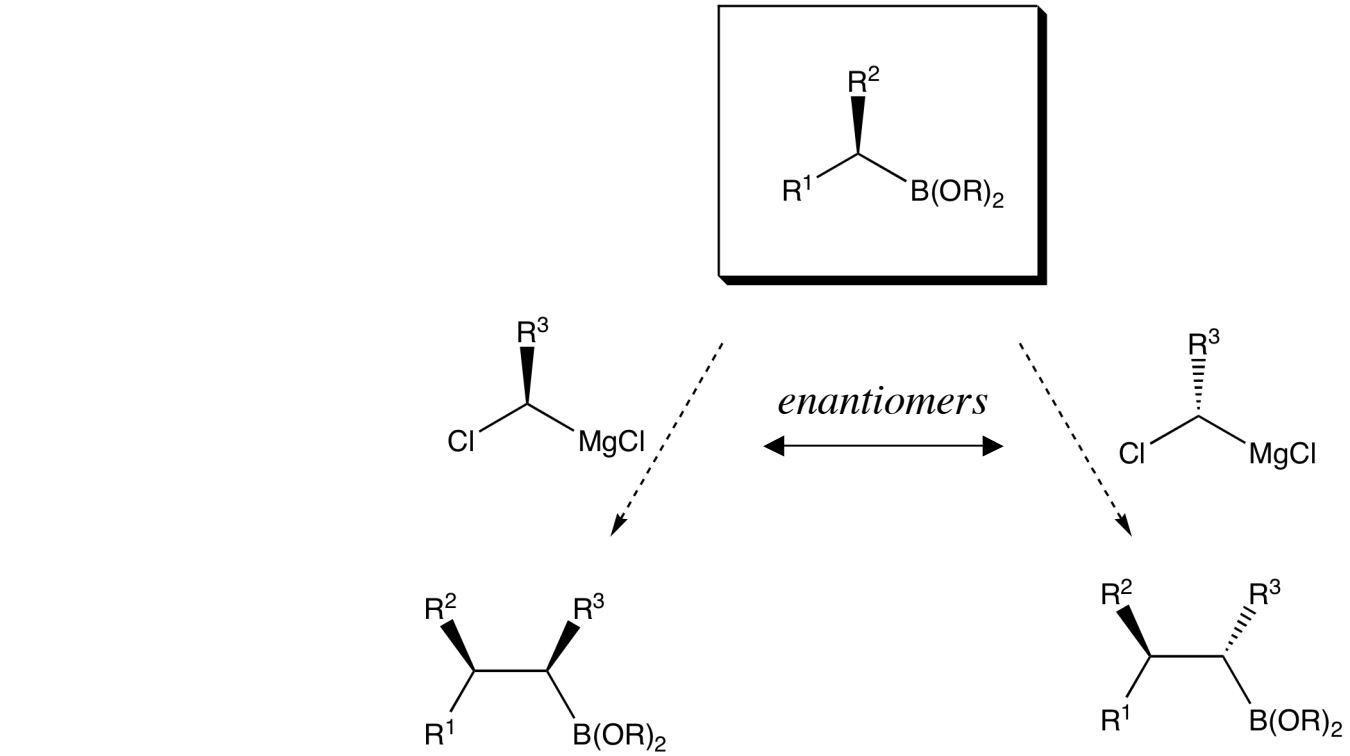
Hoffmann & Satoh groups



Syn diast. in high ee

Anti diast. in high ee

Powerful Synthetic Applications



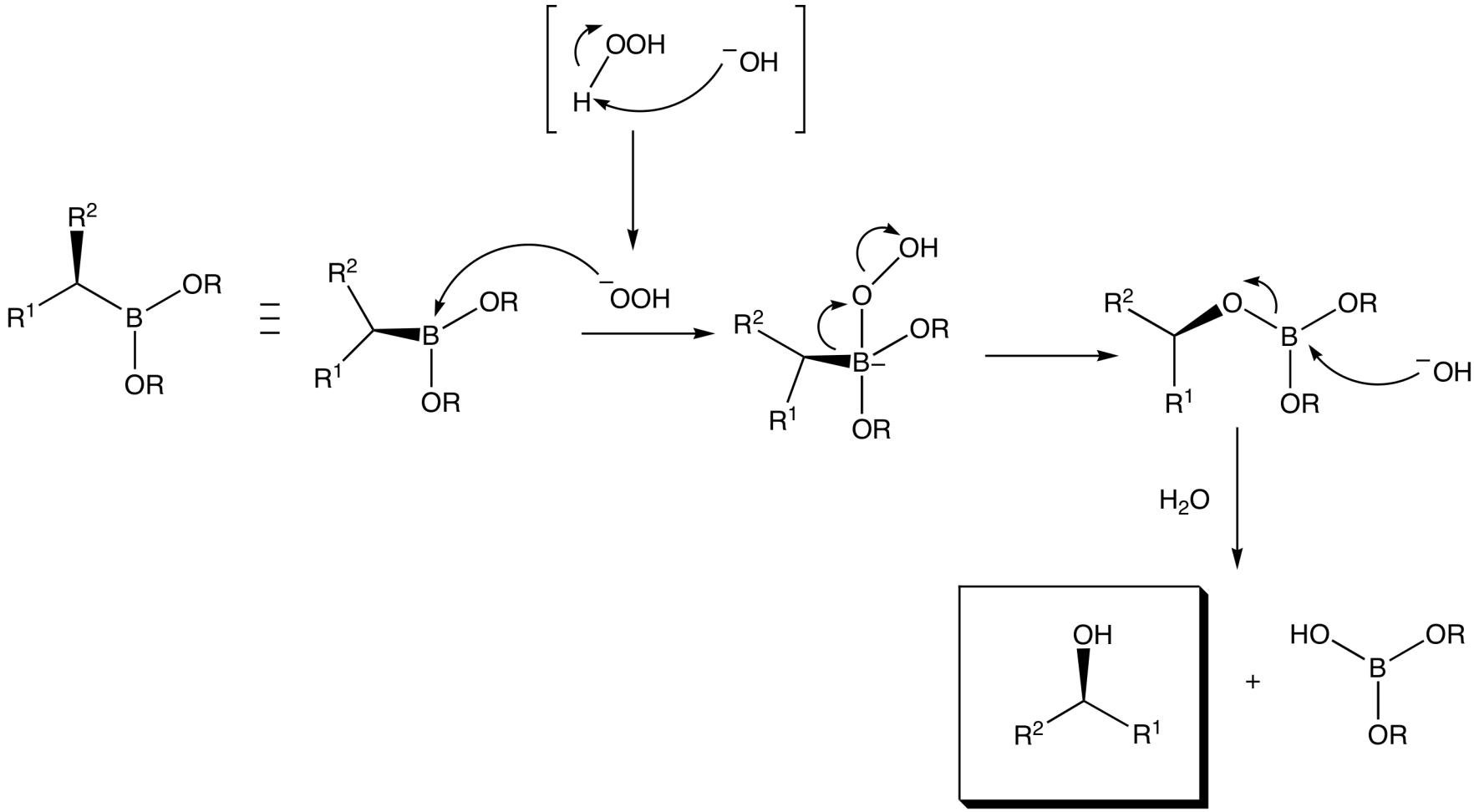
Syn diast. in high ee

Anti diast. in high ee

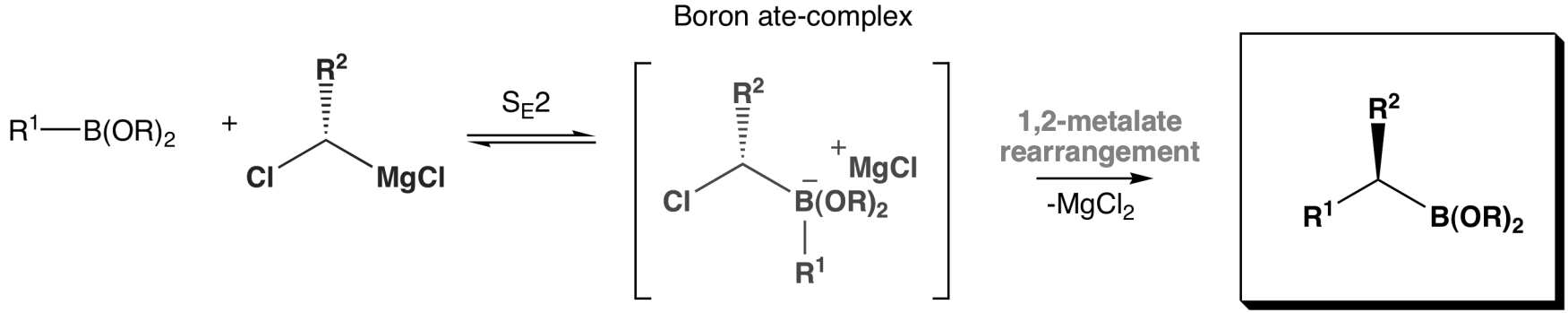
Methodology allows (via reagent control):

1) Choice of desired diastereomer product
2) Formation of desired diastereomer in high ee

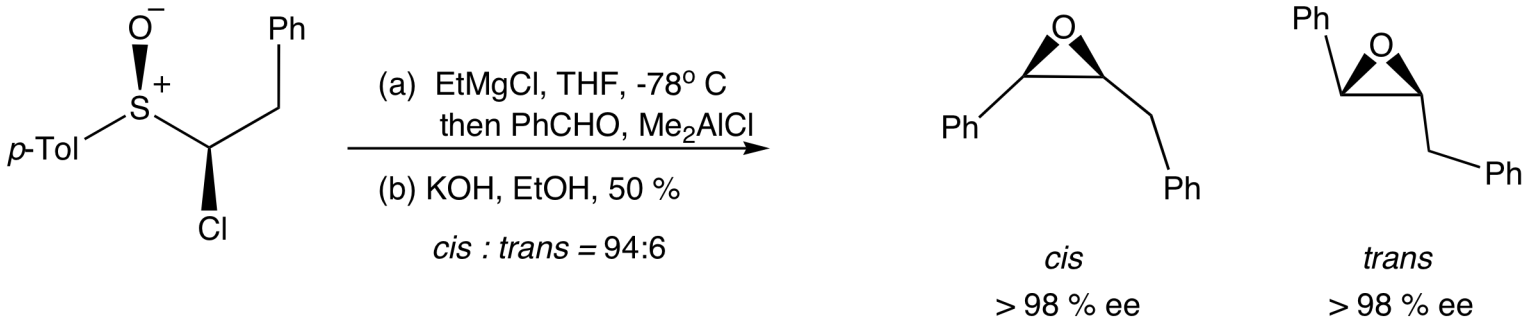
Oxidative Workup



Stereospecific Reagent Controlled Homologation (SRCH)

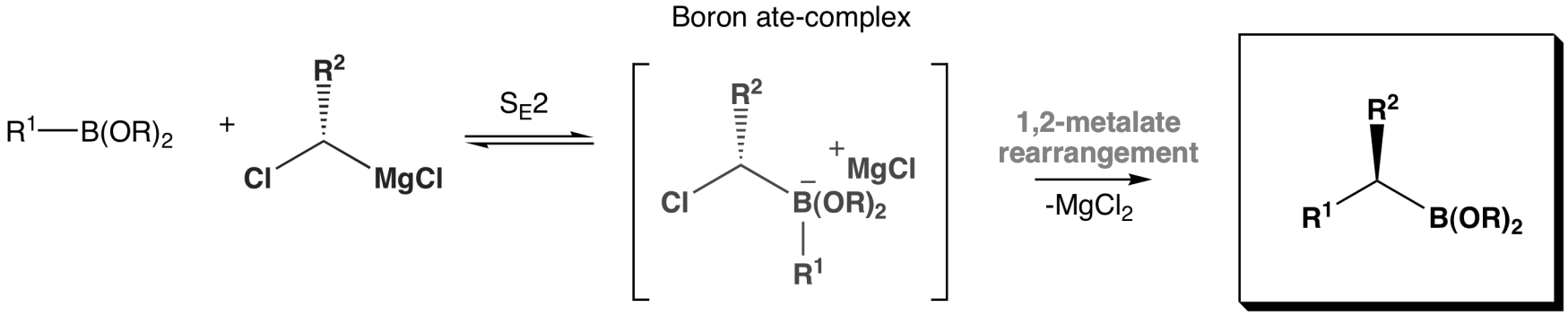


1) Carbenoid reagents must be configurational and chemically stable



Results from Blakemore

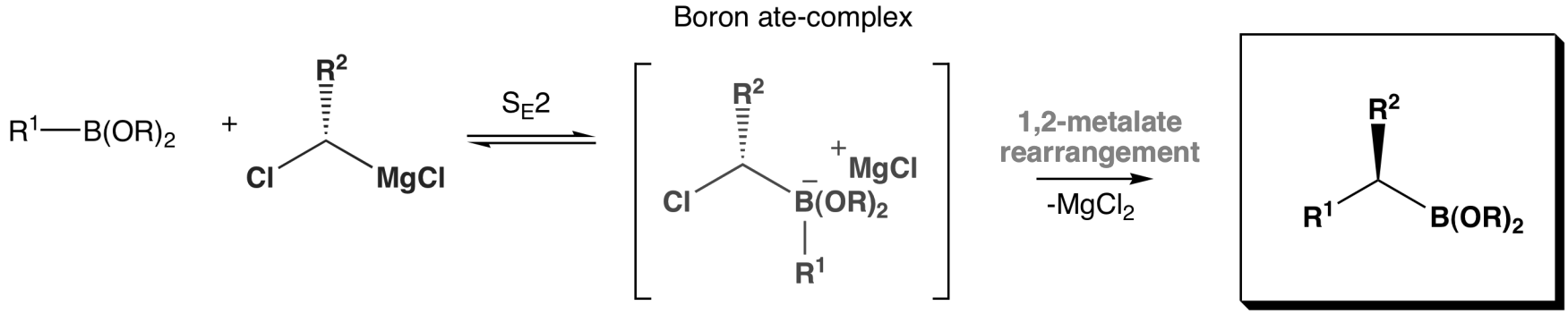
Stereospecific Reagent Controlled Homologation (SRCH)



2) Ate-complex formation and breakdown must occur stereospecifically

Indirect SN_2 displacement of chlorine (1,2-rearrangement)
Inversion of stereochemistry at chiral center

Stereospecific Reagent Controlled Homologation (SRCH)



3) Metalate rearrangement must occur after ate-complex formation

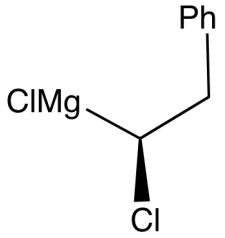
Product not allowed to reenter the coupling reaction cycle

Prevents unwanted oligomerization

Observations With Magnesium Carbenoids

Low to modest yields with range of % ee
Reaction performs best using preformed conditions
Non-polar solvent increased % yield and % ee

Mg carbenoid	Boronic ester	% Yield range	% ee range
19	Catechol (20)	11 - 44	36 - 76
19	Neopentyl glycol (21)	0 - 56	n/a - 82



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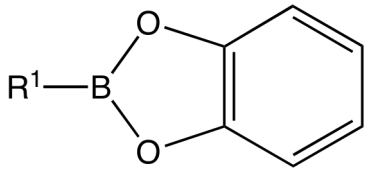

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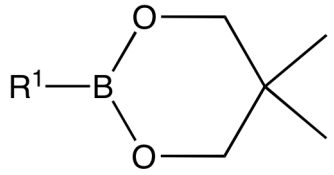

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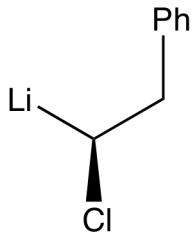
Promising Results With Lithium Carbenoids

Good yields with high % ee
Lithium best if Barbier-type conditions used

Li carbenoid	Boronic ester	% Yield	% ee
22	Neopentyl glycol (21)	0 - 86	n/a - 96



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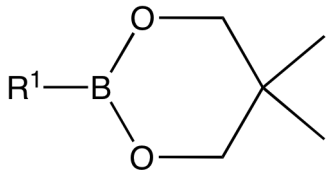

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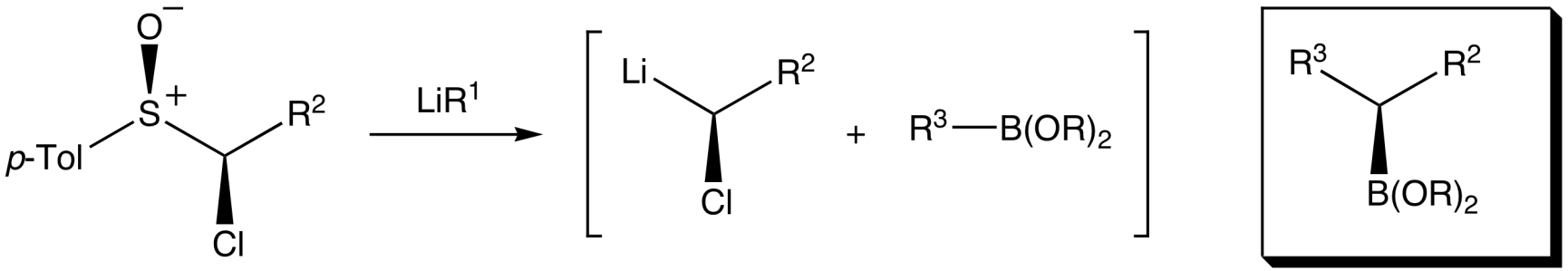
Summary

- New type of C-C bond formation demonstrated
- Methodology allows for stereochemical control of products
- Homologated products obtained in range of % yield and % ee
- Promising results from lithium carbenoids

Next Directions/Future Applications

Continue to expand on unexpected Li carbenoid results



Test methodology using more complex R^2 and R^3 groups
Continue to work to optimize reaction conditions

Thank you

Acknowledgements:

Professor Wipf

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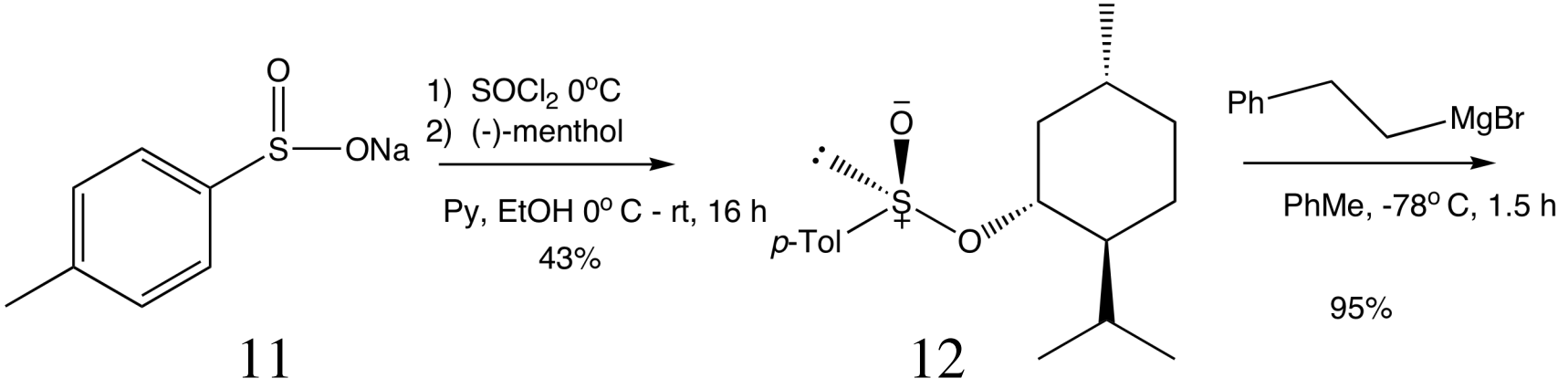
Synthesis of α-Chiral Sulfoxides



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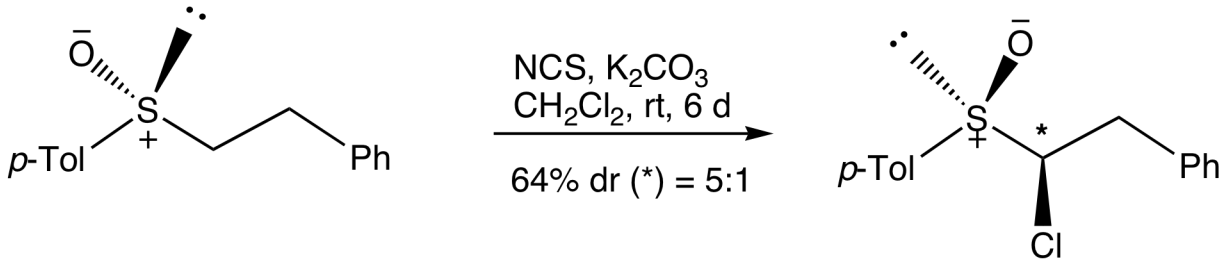

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Carried out by Blakemore and co-workers