

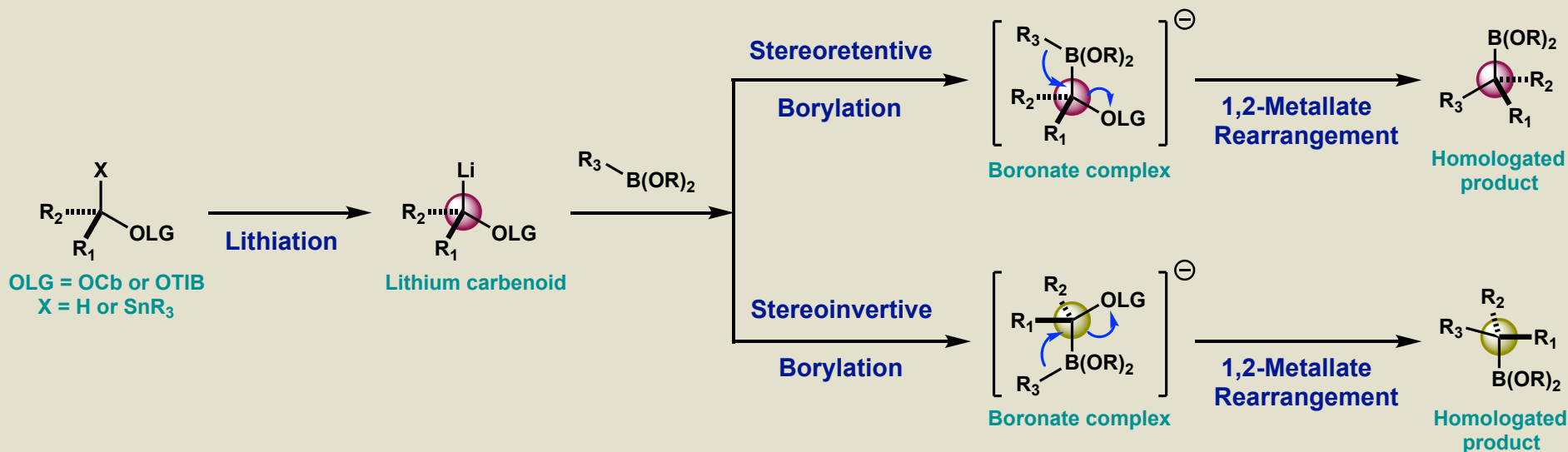
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- Part 1 : Factors responsible for the 1,2-migration
- Part 2 : Factors responsible for stereocontrol
- Part 3 : Application of lithiation-borylation reaction in synthesis
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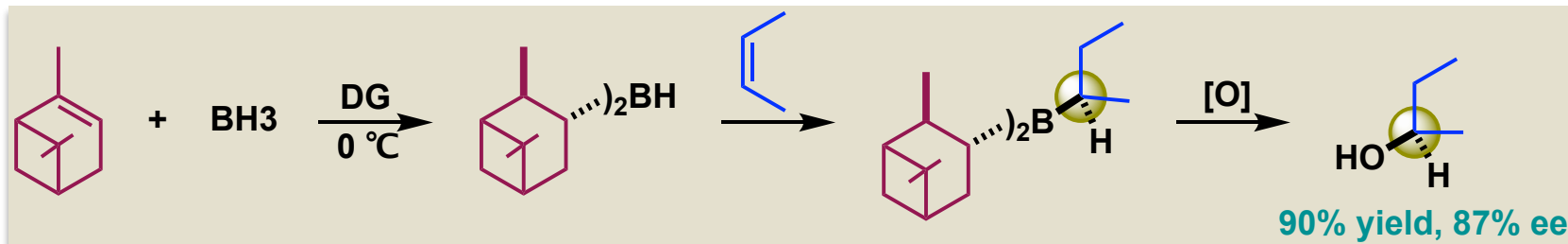
Anatomy of The Lithiation-Borylation Reaction



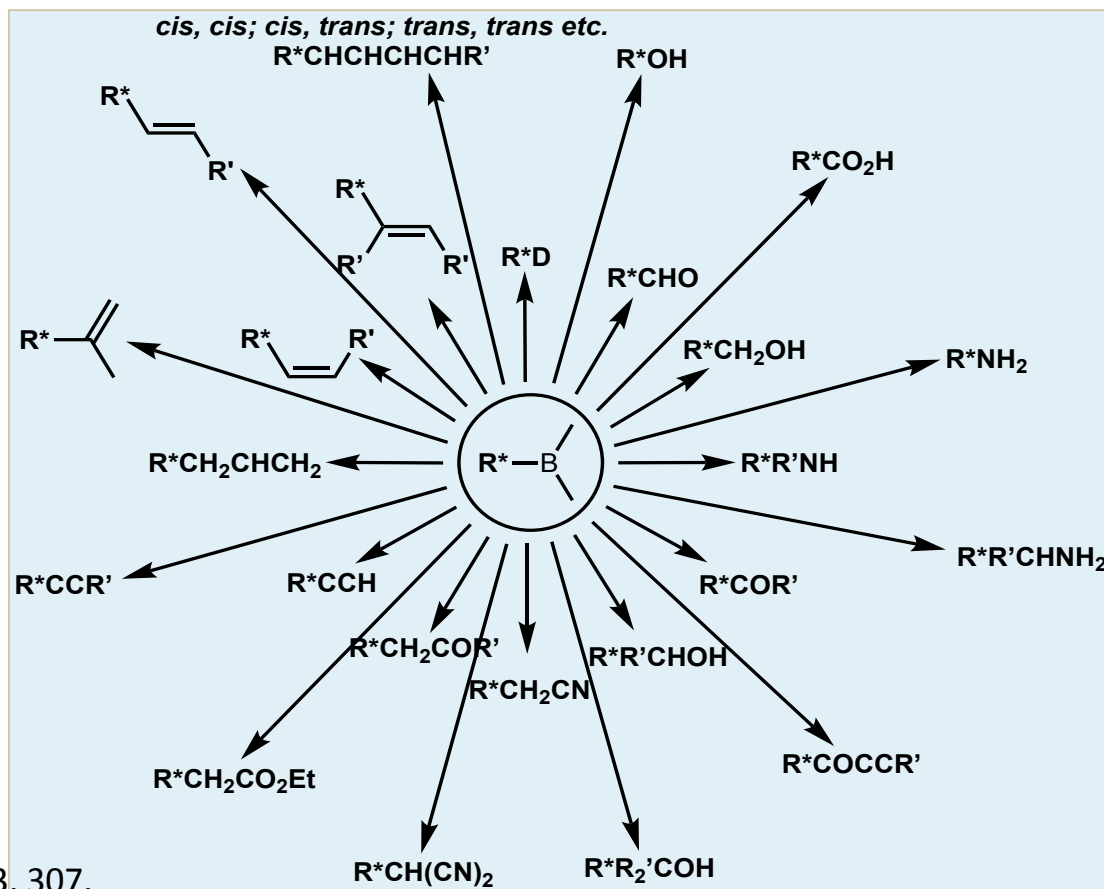
- R_1 , R_2 and R_3 = Alkyl, Alkenyl or Aryl
- Reagent Control
- Complete Stereospecificity
- Contiguous Stereocenters
- Quaternary Stereocenters
- Natural Product Synthesis
- Assembly-Line Synthesis

Arylation
 Alkynylation
 Oxidation
 Fluorination
Assembly-Line Synthesis

The First Nonenzymatic Asymmetric Synthesis (H. C. Brown, 1961)

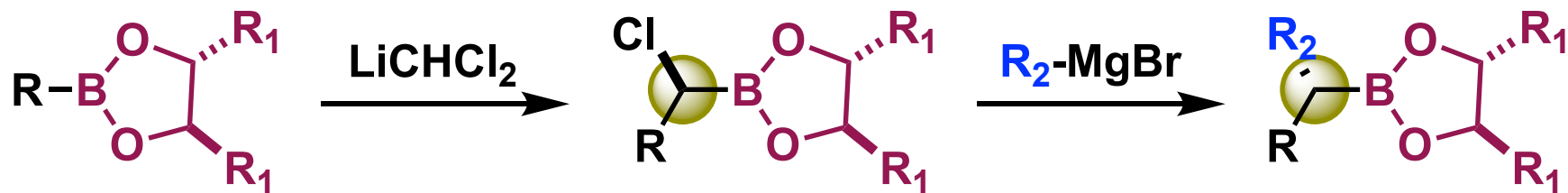


General Asymmetric Synthesis
via Chiral Organoboranes

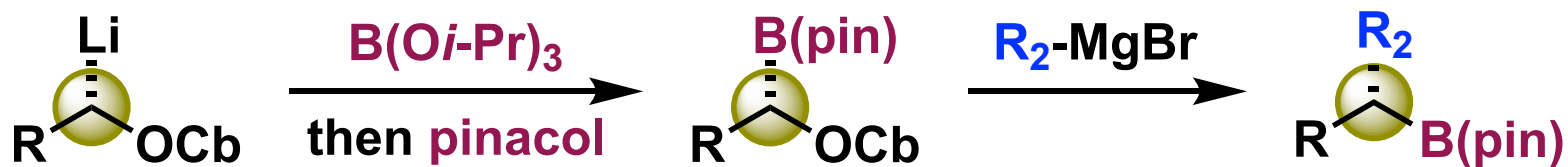


Complementary Routes to Chiral Boronic Esters

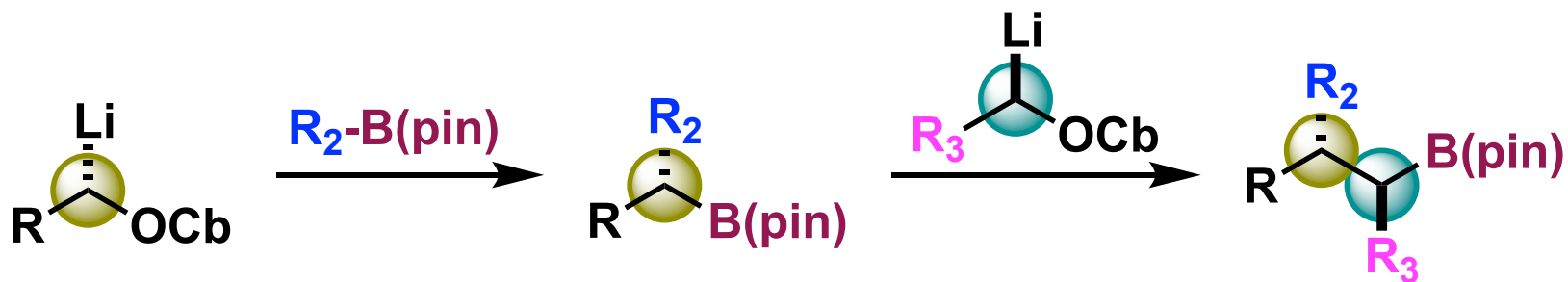
A) **Matteson**: Stepwise substrate-controlled approach



B) **Hoppe**: Stepwise reagent-controlled approach



C) **Lithiation-Borylation**: Iterative reagent-controlled approach



Prof. Varinder Kumar Aggarwal



1980-1983 BA, University of Cambridge

1983-1986 PhD, University of Cambridge
(Prof. Stuart Warren)

1986-1988 Postdoctoral Position, Columbia University
(Prof. Gilbert Stork)

1988-1991 Lecturer in Chemistry, University of Bath

1991-1995 Lecturer in Chemistry, University of Sheffield

1995-1997 Reader in Chemistry, University of Sheffield

1997-2000 Professor in Chemistry, University of Sheffield

2000-present Professor in Synthetic Chemistry, University of
Bristol

Current Research Interests: Stereoselective synthesis / Mechanistic studies / Total synthesis of natural and non-natural products

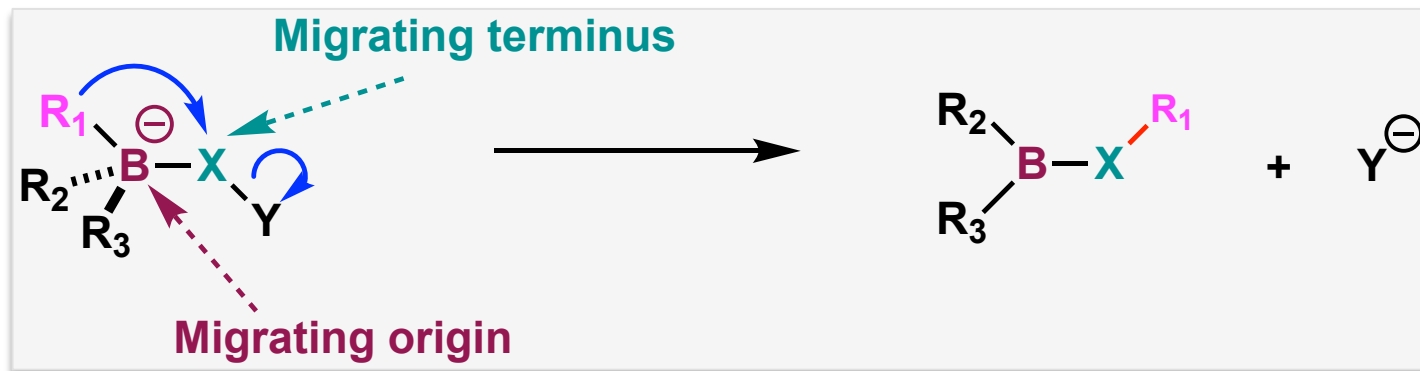
“Our current focus is in the field of organoboron chemistry, since boron seems to possess a unique ability to orchestrate many processes cleanly and with high stereochemical fidelity.”

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What Affects the Migratory Aptitude of Alkyl Groups ? (Steric & Electronic Factors)

1,2-Rearrangement of borate complexes



1. Steric hindrance around boron.
2. Steric hindrance around the migrating terminus.
3. Compression of the bond angles in the migrating group at the transition state for migration.
4. Nonbonded interactions of the substituents at the migrating terminus with the substituents attached to boron.
5. The stability of the migrating group which carries partial negative charge.

Example 1. Iodine-Induced Rearrangement of Ethynyltrialkylborates (1)

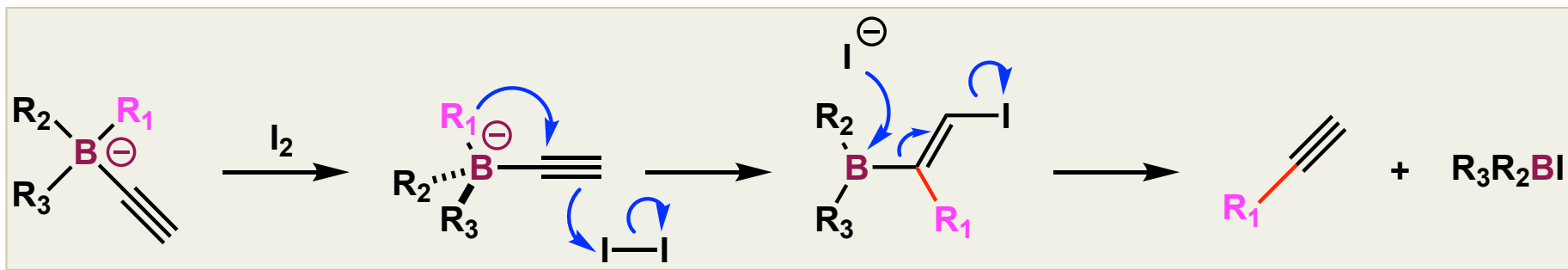


Table I. Percent Alkyl Group Migration in the Iodination of Lithium Ethynyltrialkylborates

compd	trialkylborane ^a		% of alkyne products ^b		% migration ^c
	R	R'	RC≡ CH	R'C≡ CH	
7	cyclohexyl	<i>n</i> -butyl	15	85	59
8	cyclohexyl	<i>sec</i> -butyl	41	59	55
9	cyclohexyl	isobutyl	32	68	64
10	<i>n</i> -butyl	9-BBN	0	(100) ^d	
11	<i>sec</i> -butyl	9-BBN	0	(100) ^d	
12	isobutyl	9-BBN	0	(100) ^d	
13	cyclohexyl	9-BBN	6 ^e	(94) ^d	
For RR ₂ 'B					
1	thexyl	<i>n</i> -butyl	0	100	95
2	thexyl	<i>sec</i> -butyl	0	100	76
3	thexyl	isobutyl	0	100	83
4	<i>n</i> -butyl	cyclohexyl	37	63	75
5	<i>sec</i> -butyl	cyclohexyl	25	75	72
6	isobutyl	cyclohexyl	14	86	68
For CH(CH ₃) ₂ C(CH ₃) ₂ BRR'					
14	cyclohexyl	<i>n</i> -butyl	27	73	76
15	cyclohexyl	<i>sec</i> -butyl	58	42	52
16	cyclohexyl	isobutyl	48	52	69
17	isobutyl	<i>n</i> -butyl	23	77	66
18	<i>sec</i> -butyl	<i>n</i> -butyl	25	75	82

Example 1. Iodine-Induced Rearrangement of Ethynyltrialkylborates (2)

Table I. Percent Alkyl Group Migration in the Iodination of Lithium Ethynyltrialkylborates

compd	trialkylborane ^a		% of alkyne products ^b		% migration ^c
	R	R'	RC≡ CH	R'C≡ CH	
For RR ₂ 'B					
1	thexyl	<i>n</i> -butyl	0	100	95
2	thexyl	<i>sec</i> -butyl	0	100	76
3	thexyl	isobutyl	0	100	83
4	<i>n</i> -butyl	cyclohexyl	37	63	75
5	<i>sec</i> -butyl	cyclohexyl	25	75	72
6	isobutyl	cyclohexyl	14	86	68
7	cyclohexyl	<i>n</i> -butyl	15	85	59
8	cyclohexyl	<i>sec</i> -butyl	41	59	55
9	cyclohexyl	isobutyl	32	68	64
10	<i>n</i> -butyl	9-BBN	0	(100) ^d	
11	<i>sec</i> -butyl	9-BBN	0	(100) ^d	
12	isobutyl	9-BBN	0	(100) ^d	
13	cyclohexyl	9-BBN	6 ^e	(94) ^d	
For CH(CH ₃) ₂ C(CH ₃) ₂ BRR'					
14	cyclohexyl	<i>n</i> -butyl	27	73	76
15	cyclohexyl	<i>sec</i> -butyl	58	42	52
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17	isobutyl	<i>n</i> -butyl	23	77	66
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▪ A partial relative migratory aptitude order: bicyclooctyl > *n*-butyl > cyclohexyl, isobutyl, *sec*-butyl > thexyl.

Generally 1° > 2° > 3° (except for bicyclo group).

▪ Inexact ordering of the cyclohexyl, isobutyl, and *sec*-butyl groups.



Can be explained by the stability of the migrating group that carries partial negative charge (factor 5).

Example 1. Iodine-Induced Rearrangement of Ethynyltrialkylborates (3)

Table II. Relative Alkyl Group Migratory Aptitudes (M) in the Iodination of Lithium Ethynyltrialkylborates

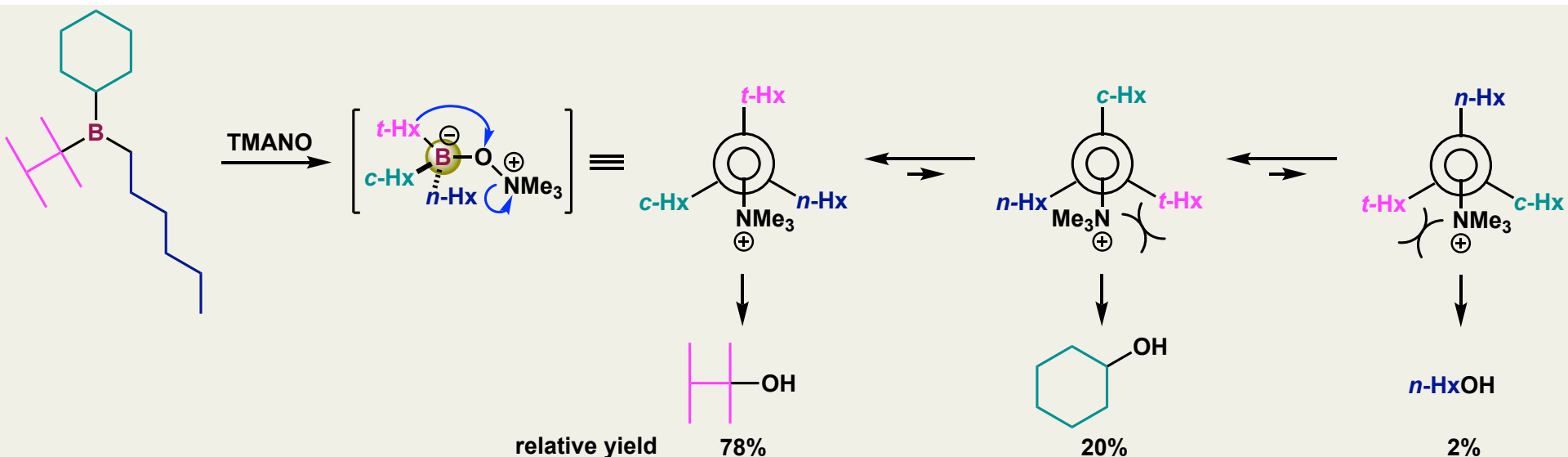
compd	trialkylborane ^a		$M (R/R')^b$
	R	R'	
For $R_{3-n}BR'_n$			
4	dicyclohexyl	<i>n</i> -butyl	0.85
5	dicyclohexyl	<i>sec</i> -butyl	1.5
6	dicyclohexyl	isobutyl	3.1
7	cyclohexyl	di- <i>n</i> -butyl	0.35
8	cyclohexyl	di- <i>sec</i> -butyl	1.4
9	cyclohexyl	diisobutyl	0.94
For $CH(CH_3)_2C(CH_3)_2BRR'$			
14	cyclohexyl	<i>n</i> -butyl	0.37
15	cyclohexyl	<i>sec</i> -butyl	1.4
16	cyclohexyl	isobutyl	0.92
17	isobutyl	<i>n</i> -butyl	0.30
18	<i>sec</i> -butyl	<i>n</i> -butyl	0.33

For 4-6, An approximate two-fold increase in M in the series n -butyl < *sec*-butyl < isobutyl but no such regularity for 7-9.

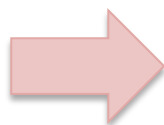


Can be explained by the steric acceleration due to B strain (factor 1).

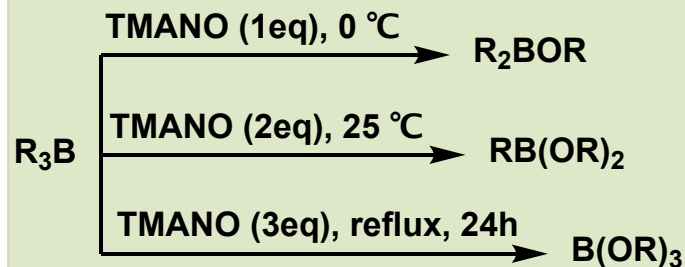
Example 3. Oxidation of Trialkylborane with TMANO



The bulkier groups are preferentially oxidized (migratory aptitude decreases in the order $3^\circ > 2^\circ > 1^\circ$).

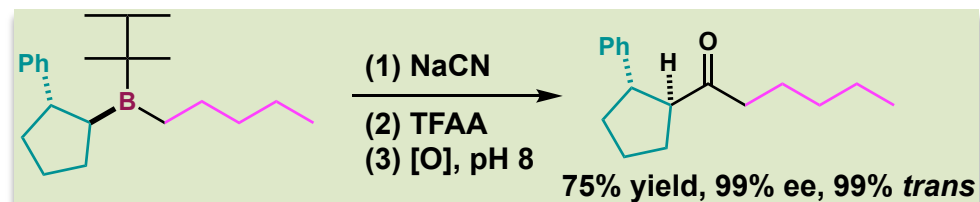
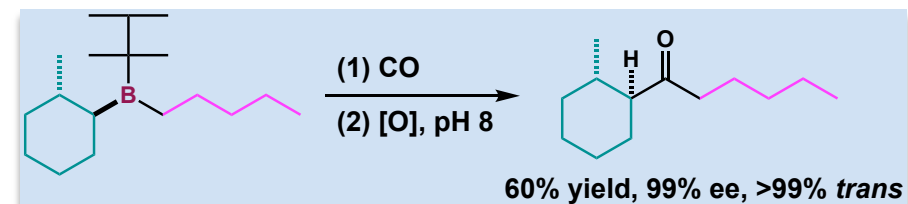
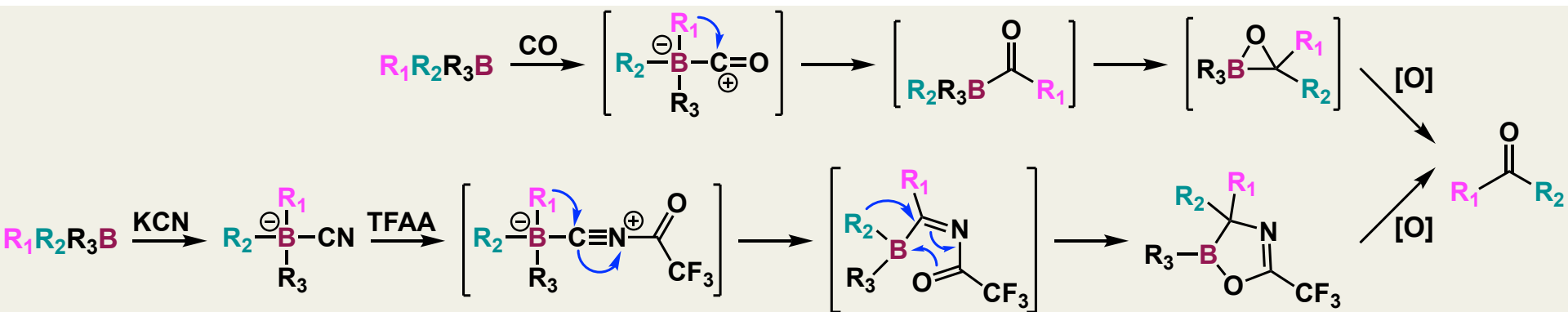


Can be accounted for the preferred conformation of the ate complex (factor 4).

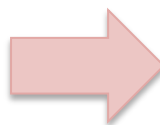


The oxidation process can be controlled depending on the stoichiometry and reaction conditions.

Example 4. Carbonylation of Organoboranes



No ketones bearing the most hindered group were isolated. The order in the migration step is $1^\circ > 2^\circ > 3^\circ$.



Suggesting that the 1,2-migration is dominated by electronic factors relating to the ability of the migrating group to carry negative charge (factor 5).

Short Summary

- Several factors should be considered when thinking about which group will migrate preferentially.
- There is no migrating / nonmigrating group absolutely.
- A consideration of the conformation required for migration of the ate complex is important.

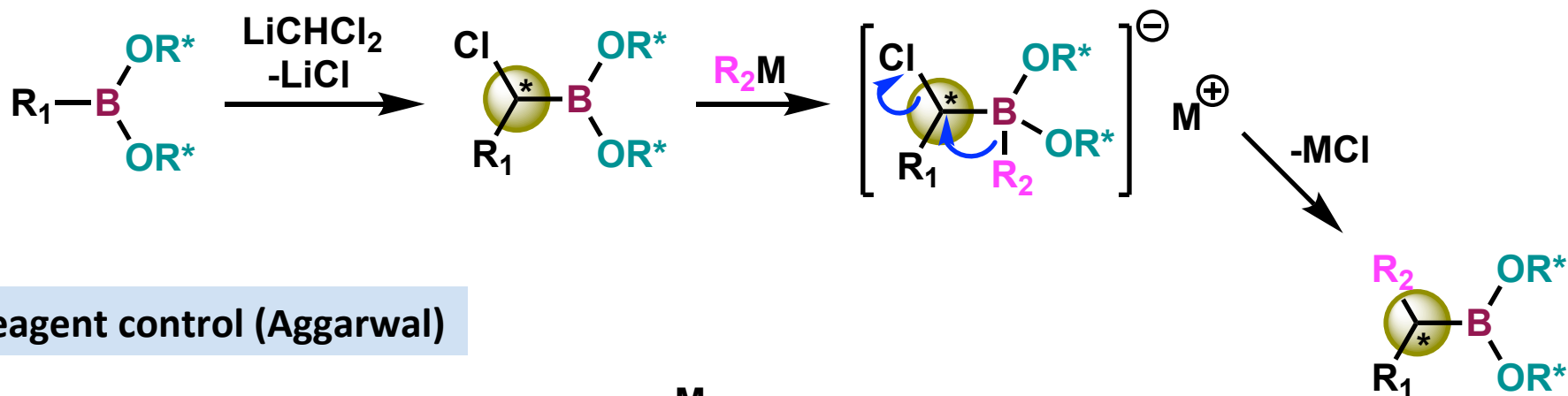
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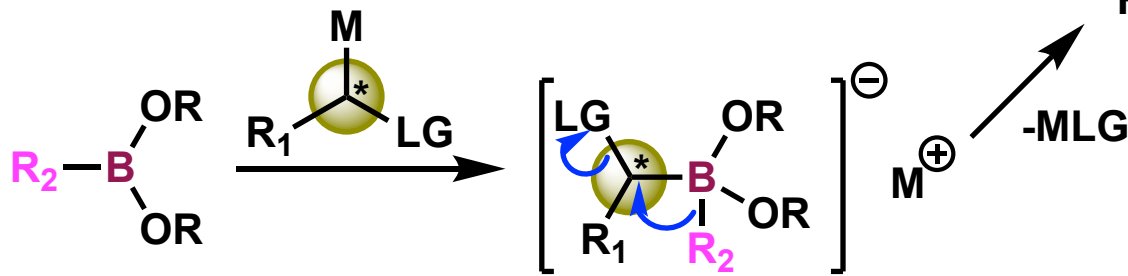
Stereocontrol: Substrate Control VS Reagent Control

Complementary routes to homochiral organoboranes involving 1,2-metallate rearrangement

Substrate control (Matteson)

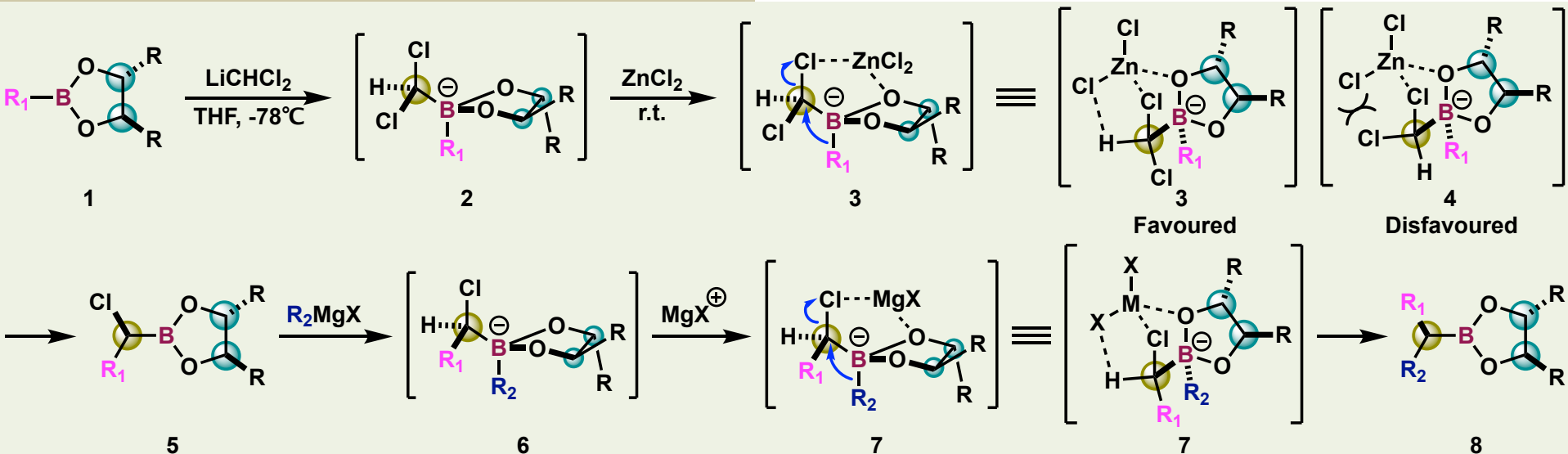


Reagent control (Aggarwal)

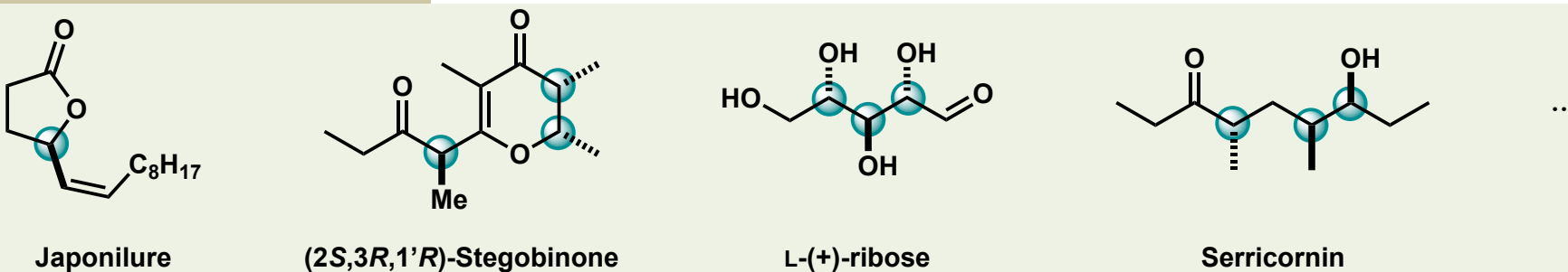


Substrate Control: Anatomy And Application

Matteson homologation-alkylation sequence

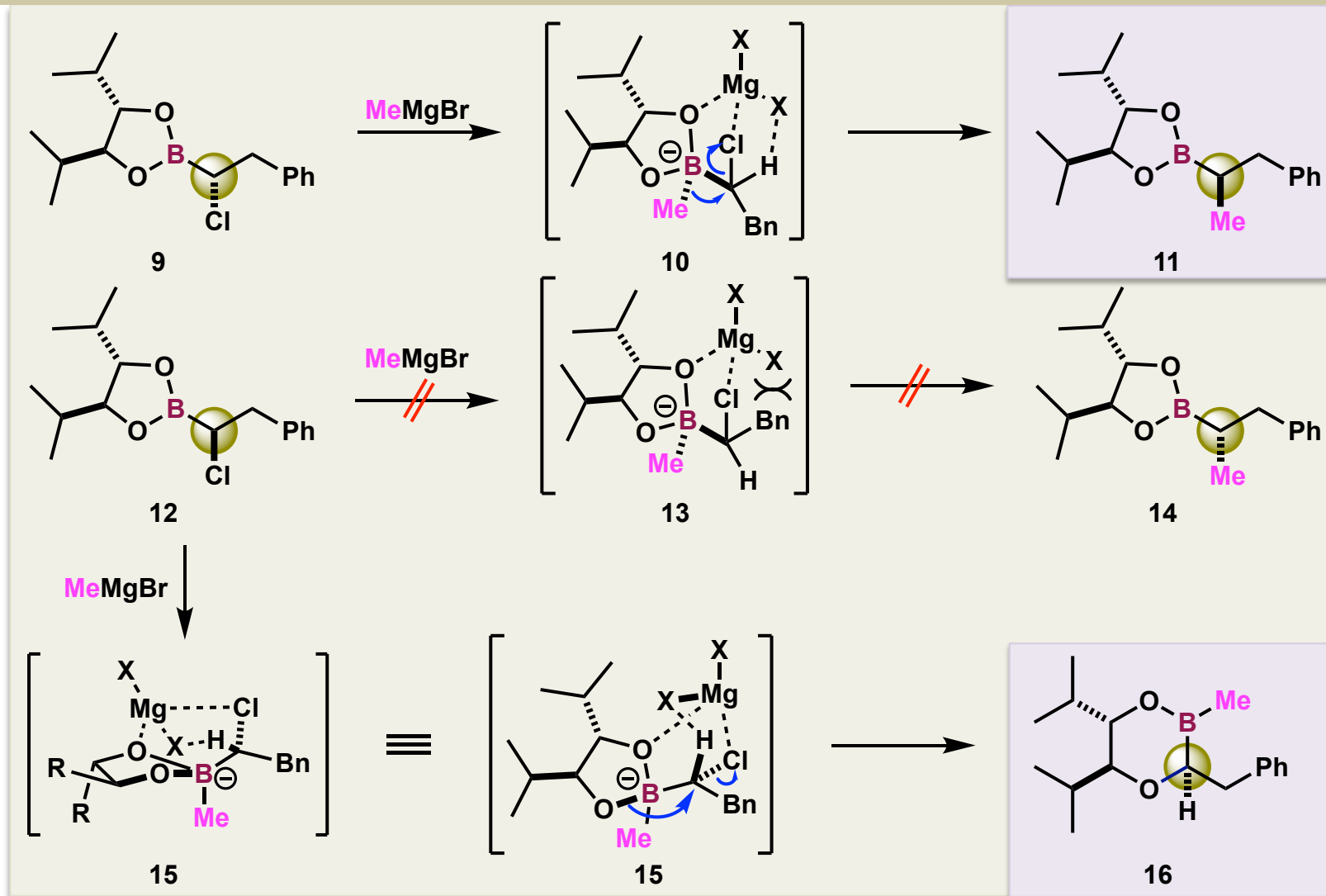


Synthetic Applications



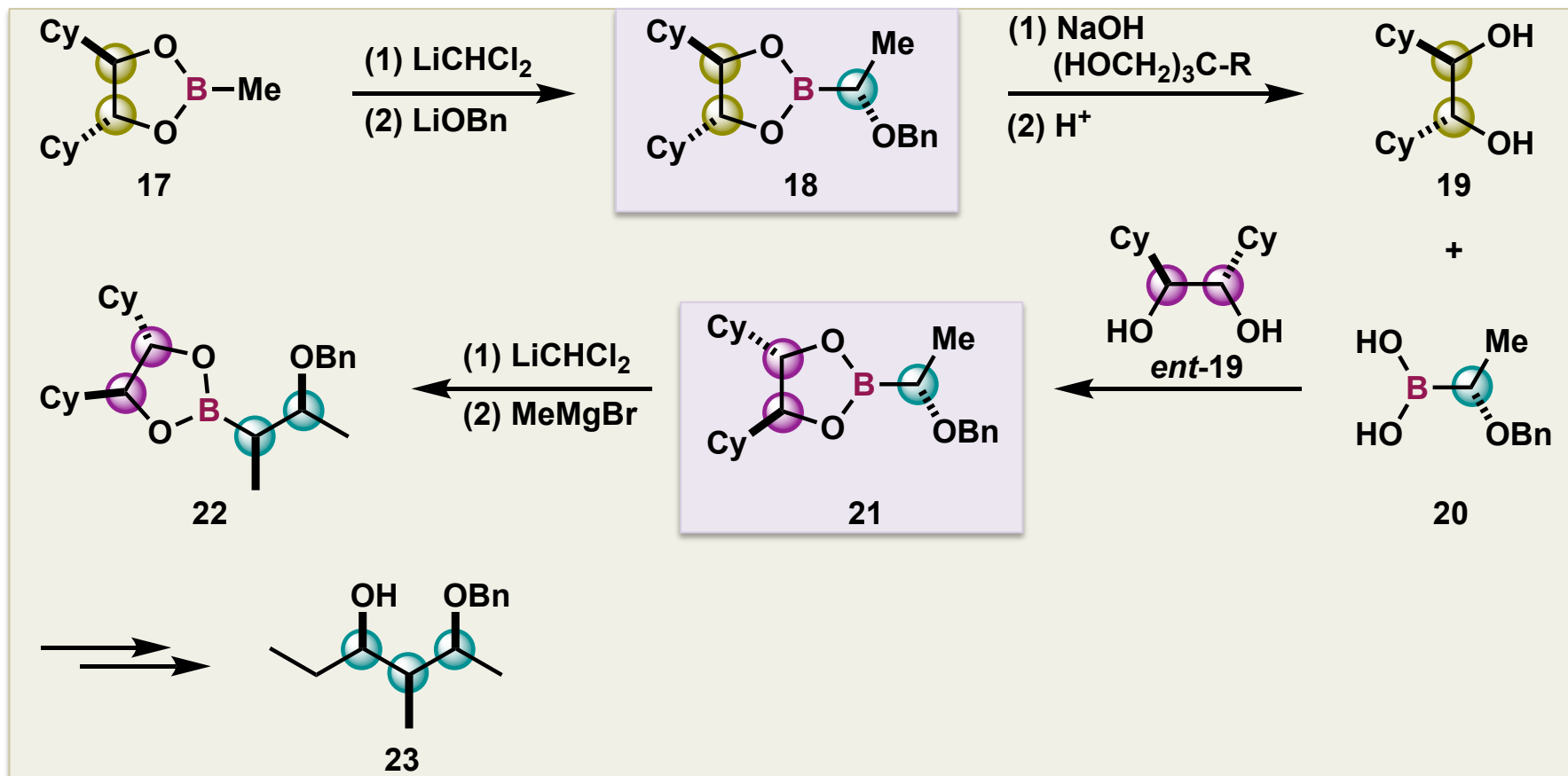
Limitations of the Matteson-type Homologation-Alkylation (1)

Reaction of diastereomeric boronic esters with grignard reagents lead to different outcome.



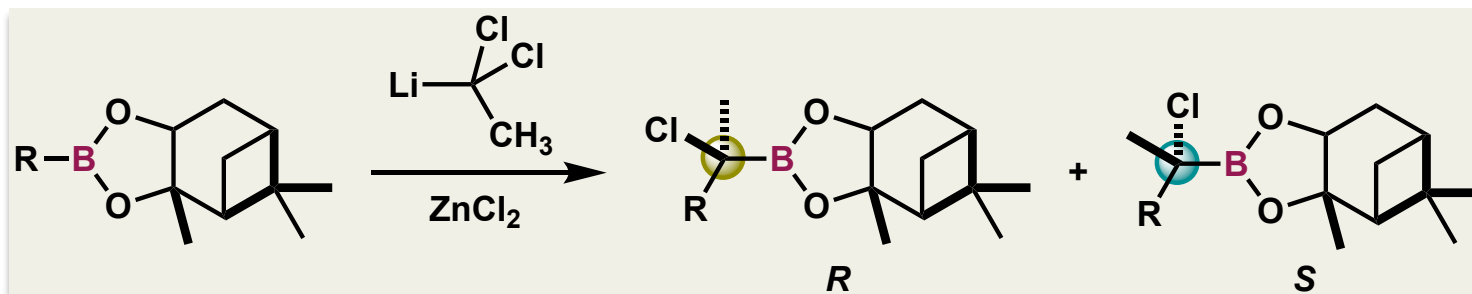
Limitations of the Matteson-type Homologation-Alkylation (2)

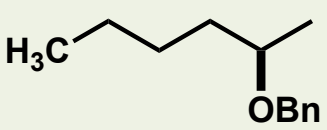
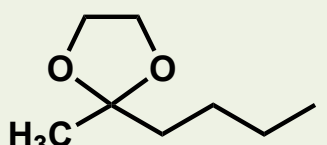
Additional steps are required when changing the stereochemistry of boronic ester.



Limitations of the Matteson-type Homologation-Alkylation (3)

Limited success for the synthesis of quaternary stereocenters.



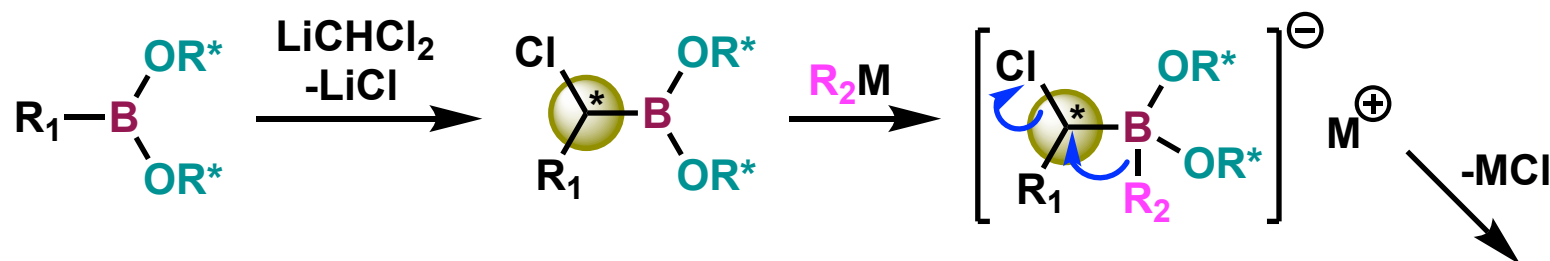
	R	dr
a	Et	<i>R/S</i> = 8
b	Ph	<i>S/R</i> = 24
c	Bu	<i>R/S</i> = 1.04
d	Cy	<i>S/R</i> = 1.5
e	<i>i</i> -Pr	?/? = 40
f		?/? = 10
g		<i>R/S</i> = 1.5

- Variable levels of selectivity were obtained.
- The sense of asymmetric induction was unpredictable.

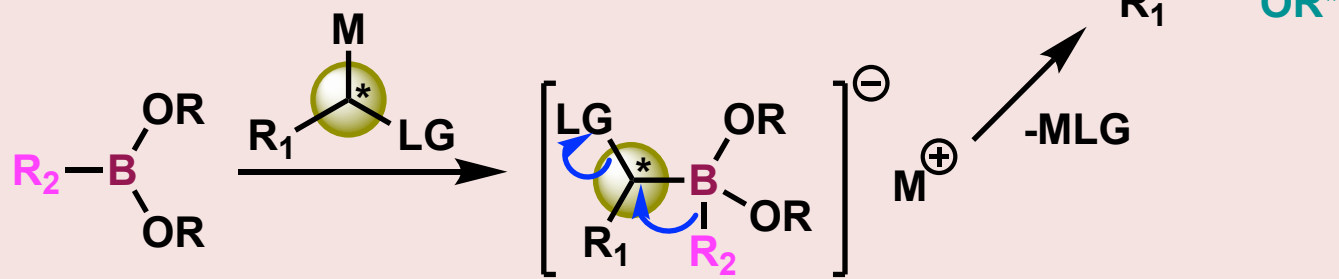
Reagent Control: Homologation-Alkylation of Boronic Esters and Boranes using Chiral Carbanions

Complementary routes to homochiral organoboranes involving 1,2-metallate rearrangement

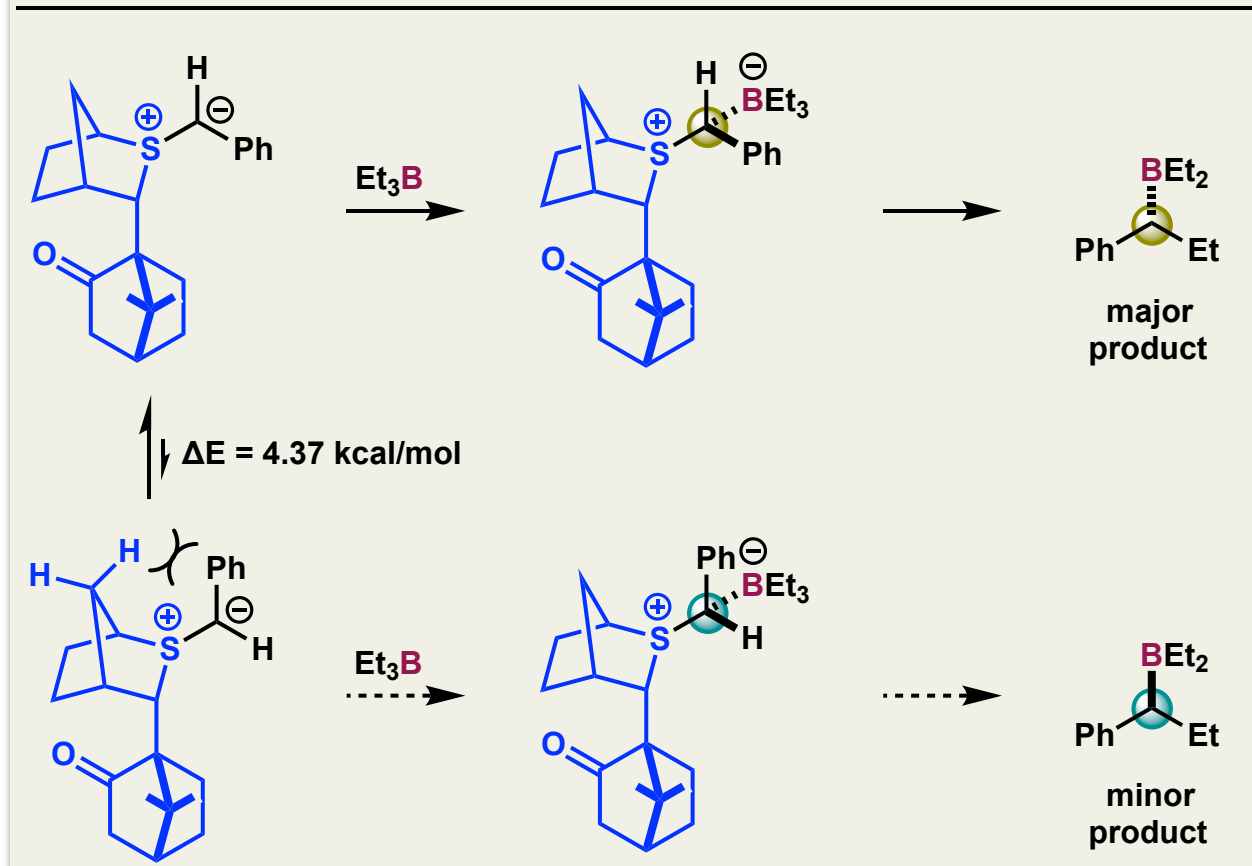
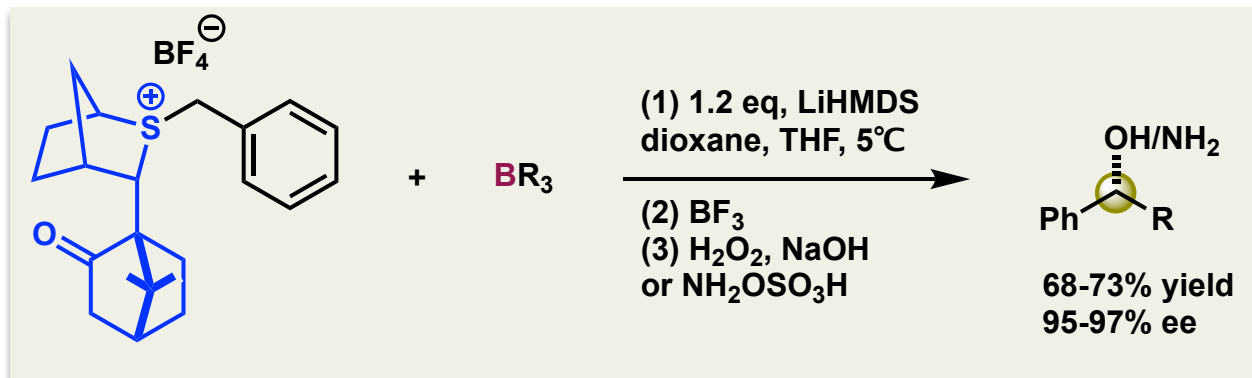
Substrate control (Matteson)



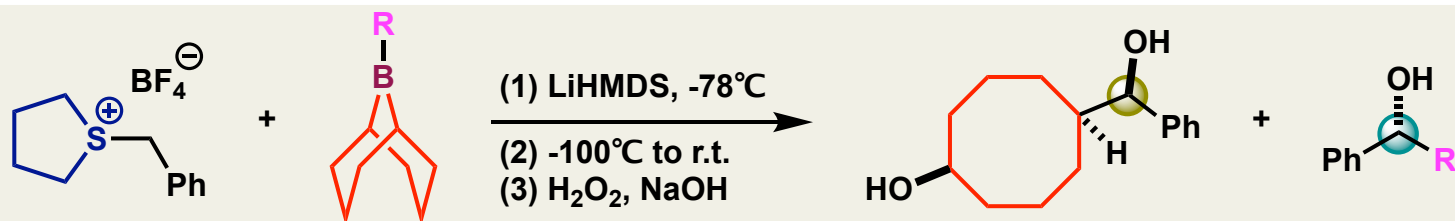
Reagent control (Aggarwal)



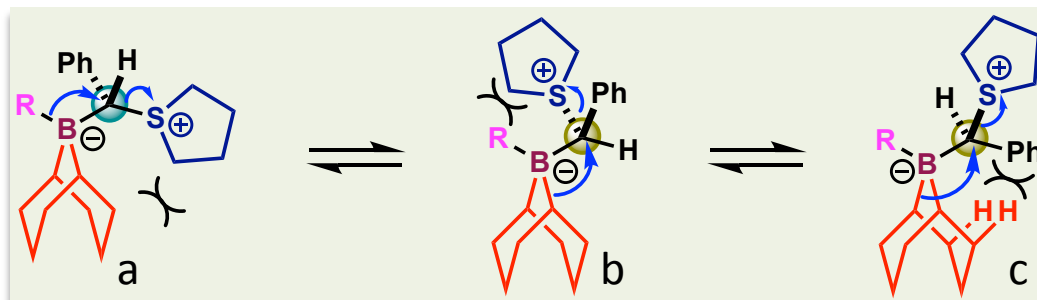
Chiral Carbanions Derived from Sulfur Ylides



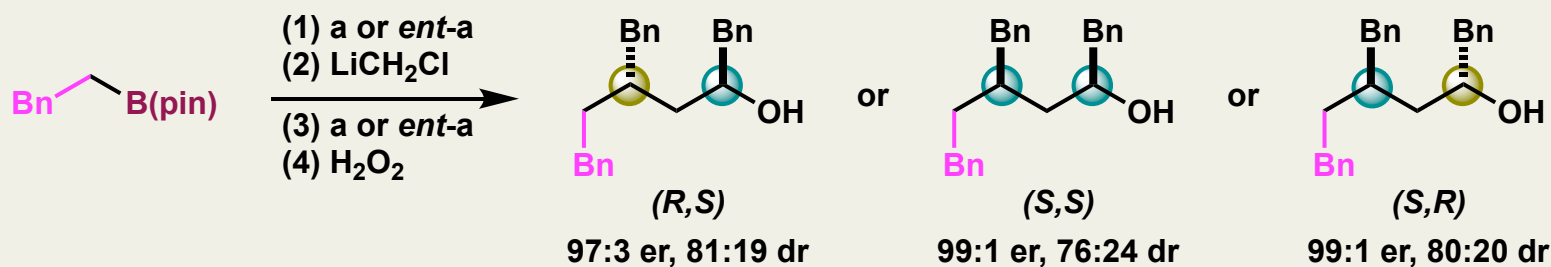
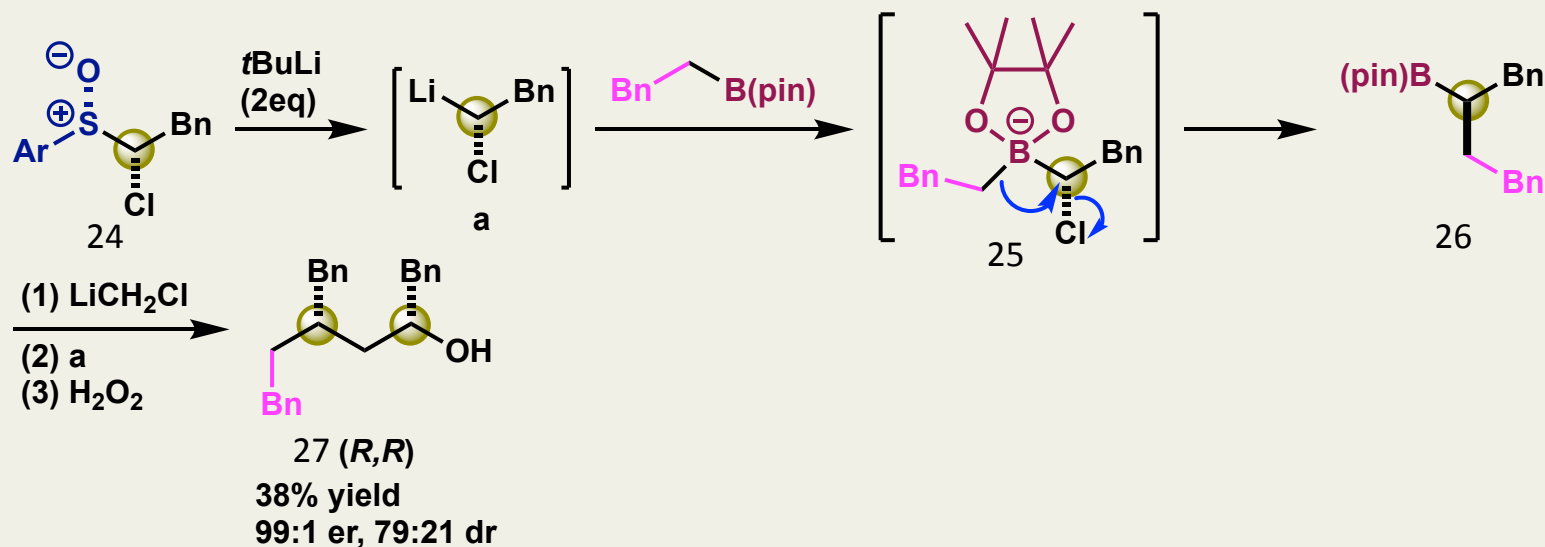
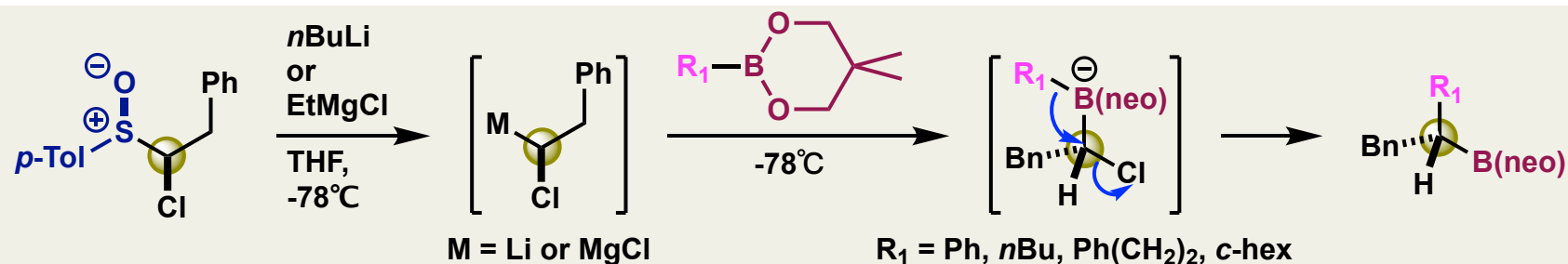
Outcome of the 1,2-Metallate Rearrangement Ate Complexes Resulting from the 9-BBN Derivatives



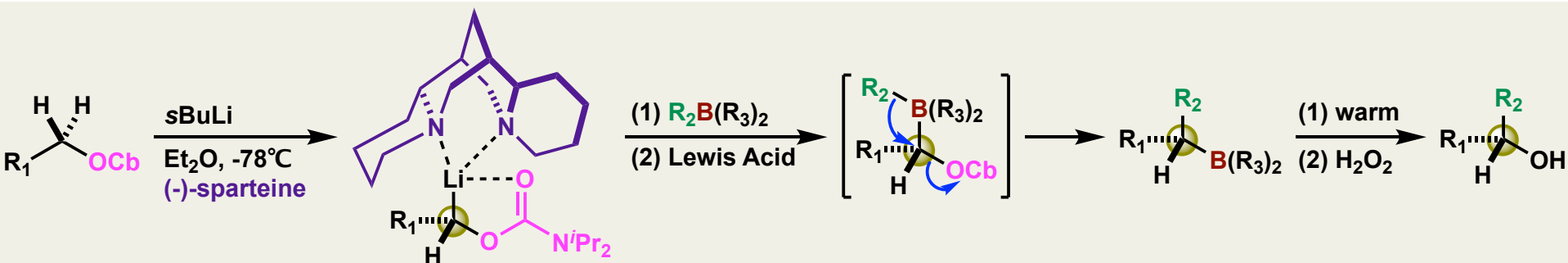
Entry	R	Yield	Yield
1	Hexyl	56%	41%
2	Allyl	51%	39%
3	Benzyl	51%	35%
4	<i>i</i> -Pr	Trace	77%
5	Cyclopropyl	89%	Trace
6	Ph	Trace	94%
7	1-Hexenyl	Trace	21%
8	1-Hexynyl	92%	Trace



Chiral Carbanions of Lithiated Alkyl Chlorides

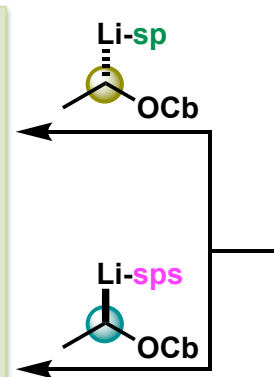
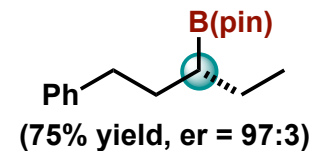
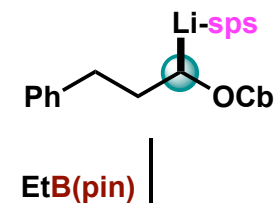
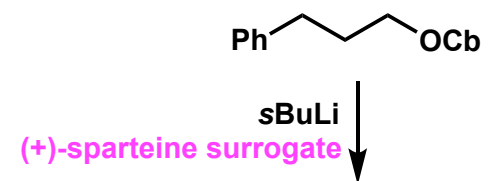
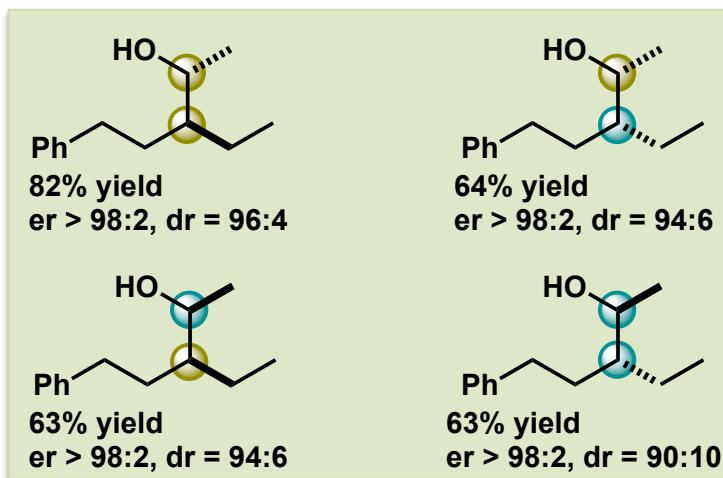
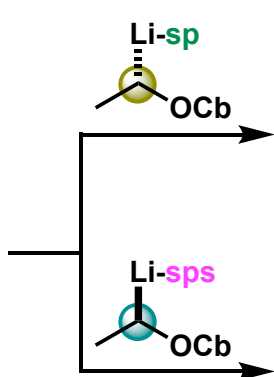
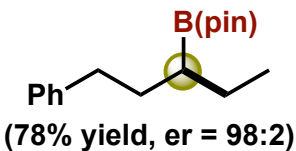
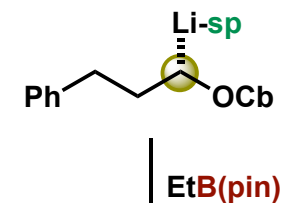
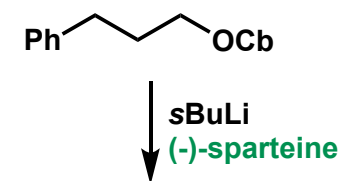
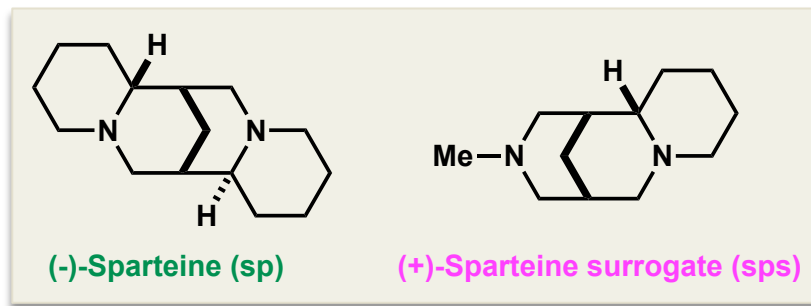


Chiral Carbanions of Lithiated Carbamates (1)



Entry	R^1	R^2	$(\text{R}^3)_2$	Lewis acid	Yield 89 (%)	er
1	$\text{Ph}(\text{CH}_2)_2$	Et	Et_2	—	91	98:2
2		<i>n</i> Hex	9BBN	—	90	98:2
3		<i>i</i> Pr	9BBN	—	81	98:2
4		Ph	9BBN	—	85	88:12
5		Ph	9BBN	MgBr_2	94	97:3
6		Et	Pinacol	MgBr_2	90	98:2
7	$\text{Me}_2\text{C}=\text{CH}(\text{CH}_2)_2$	Et	Et_2	—	90	97:3
8		Ph	9BBN	MgBr_2	71	95:5
9		Et	Pinacol	MgBr_2	75	97:3
10		Ph	Pinacol	MgBr_2	73	98:2
11	$\text{TBSO}(\text{CH}_2)_2\text{C}(\text{Me})_2$	Et	Et_2	—	67	95:5
12	CH_2	Ph	9BBN	MgBr_2	65	97:3
13		Ph	Pinacol	MgBr_2	64	98:2
14	<i>i</i> Pr	Ph	9BBN	MgBr_2	68	96:4
15		Ph	Pinacol	MgBr_2	70	98:2
16	Me	Ph	Pinacol	MgBr_2	70	97:3

Chiral Carbanions of Lithiated Carbamates (2)



Short Summary

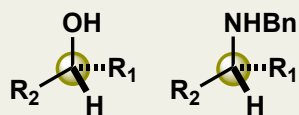
- Substrate control and reagent control are two routes to homochiral organoboranes involving 1,2-metallate rearrangement.
- Although a powerful transformation, Matteson's homologation-alkylation sequence (substrate control) suffers from a number of drawbacks (limitation 1-3).
- The reactions between chiral carbanions bearing potential leaving groups with achiral boronic esters (reagent control) is complementary to the Matteson approach.

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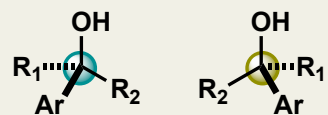
Wide Application of Lithiation-Borylation Reaction

Secondary boronic esters and derivatives



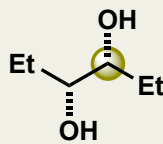
50-94% yield, >95:5 er

Tertiary benzylic boronic esters and derivatives



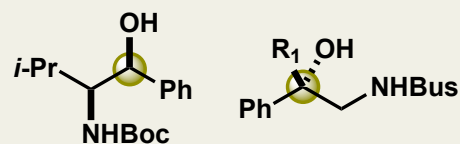
60-91% yield, >95:5 er
69-95% yield, >95:5 er

1,2-diols



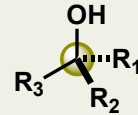
70% yield, 99:1 er,
>95:5 dr

β -Amino alcohols



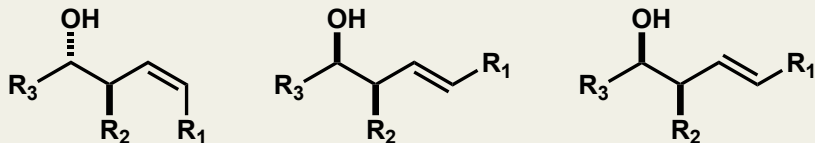
90% yield, >99:1 er, >95:5 dr
80-87% yield, >99:1 er

Tertiary alkyl boronic esters and derivatives



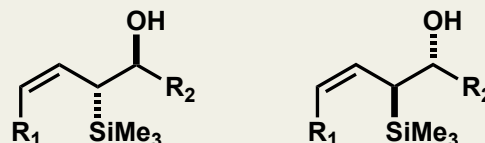
35-80% yield,
>97:3 er

Allylic boronic esters and homoallylic alcohols



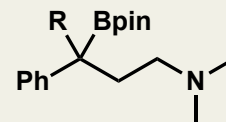
54-91% yield, >95:5 er, >99:1 dr
46-59% yield, 99:1 er, >99:1 dr
51-67% yield, >95:5 er, >99:1 dr

β -Hydroxy allylsilanes



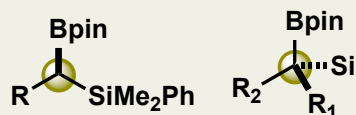
74-96% yield, >94:6 er, >25:1 dr
64-67% yield, >93:7 er, >25:1 dr

Acyclic γ -dimethylamino tertiary boronic esters



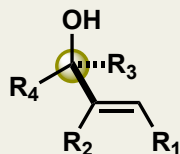
44-75% yield

α -Silyl boronic esters



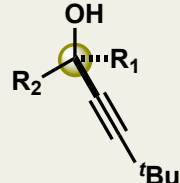
68-69% yield, >96:4 er
52-84% yield, >97:3 er

Tertiary allylic boronic esters and derivatives



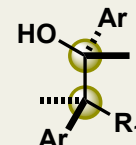
72-92% yield,
>98:2 er

Tertiary propargylic boronic esters and derivatives



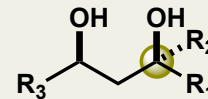
42-58% yield,
>95:5 er

Contiguous quaternary stereocenters



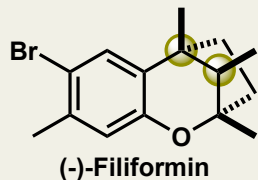
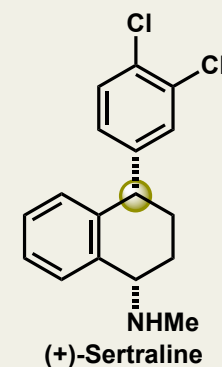
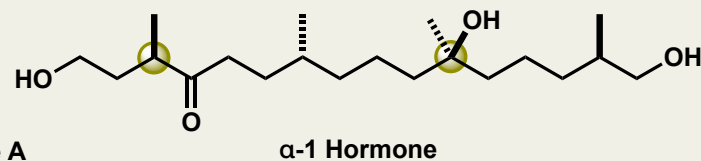
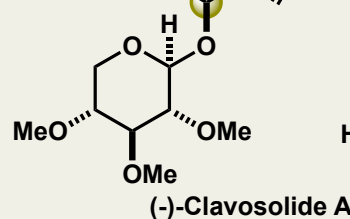
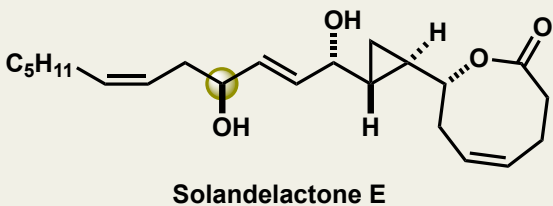
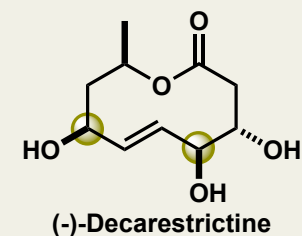
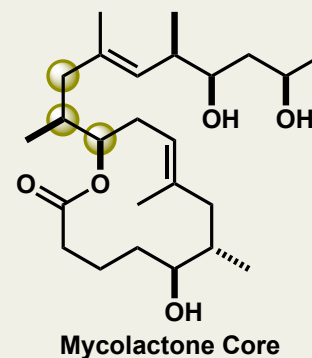
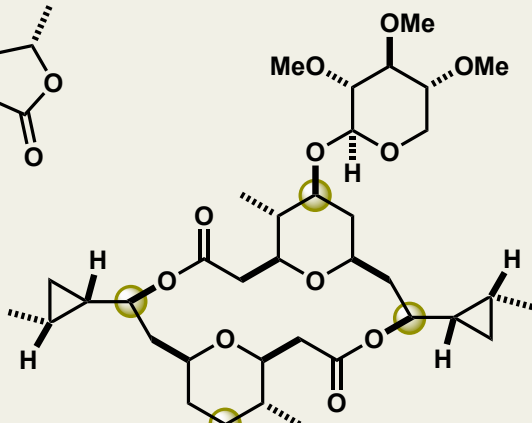
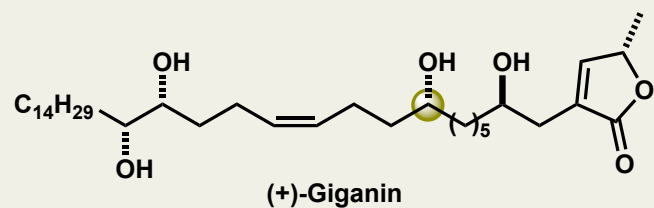
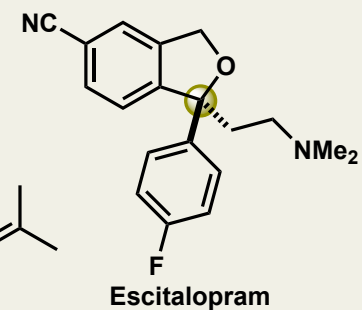
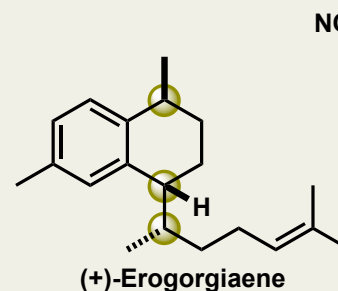
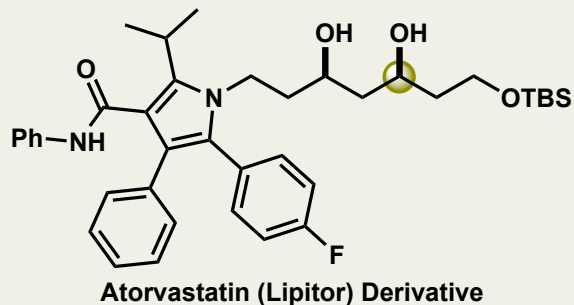
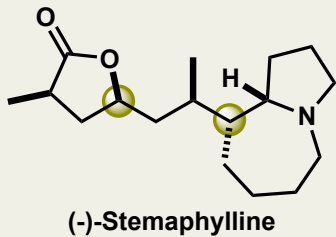
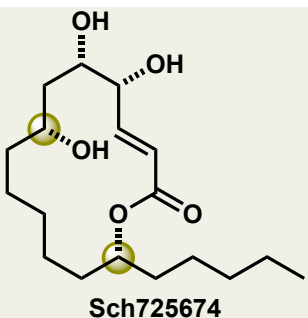
32-85% yield, >95:5 dr,
>99:1 er

1,3-Bis(boronic esters) and derivatives

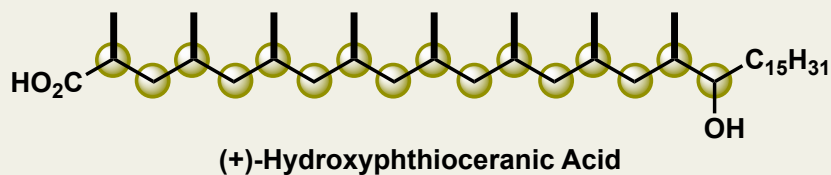
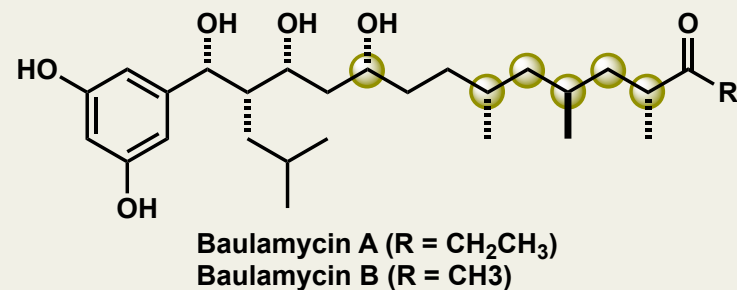
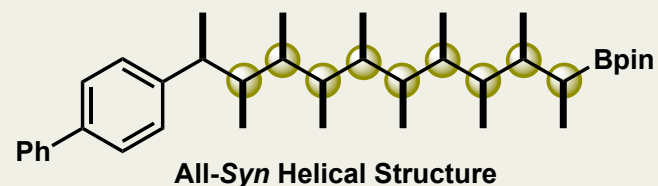
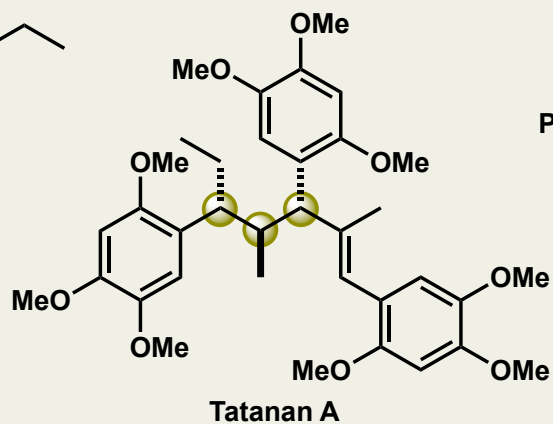
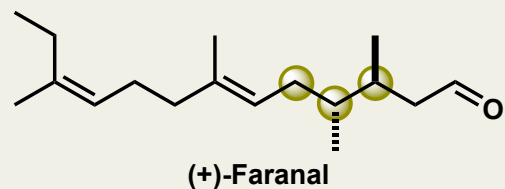
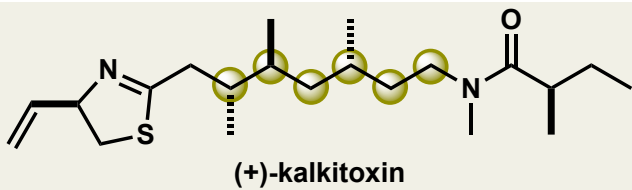


43-94% yield, >95:5 dr,
99:1 er

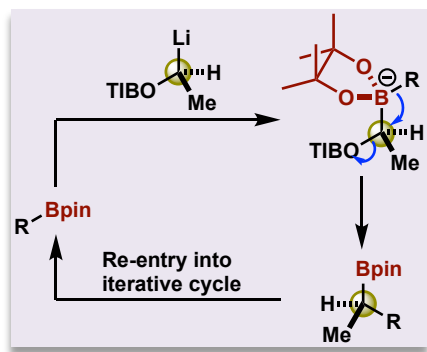
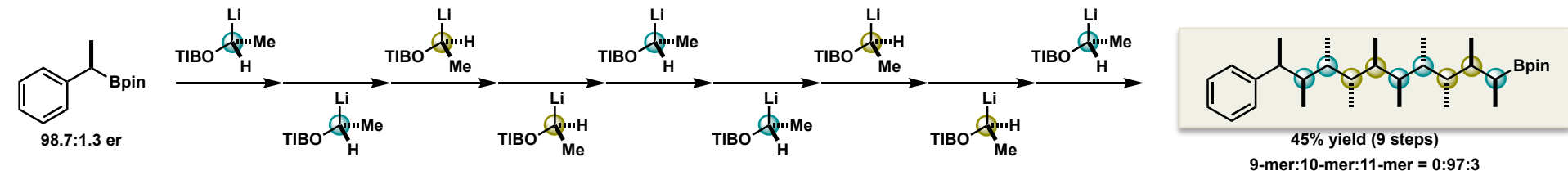
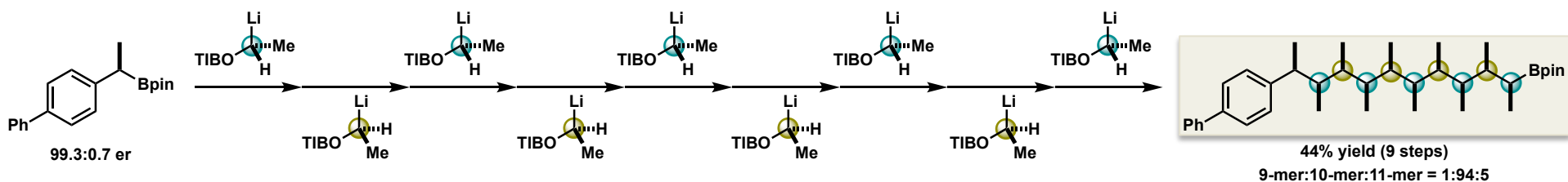
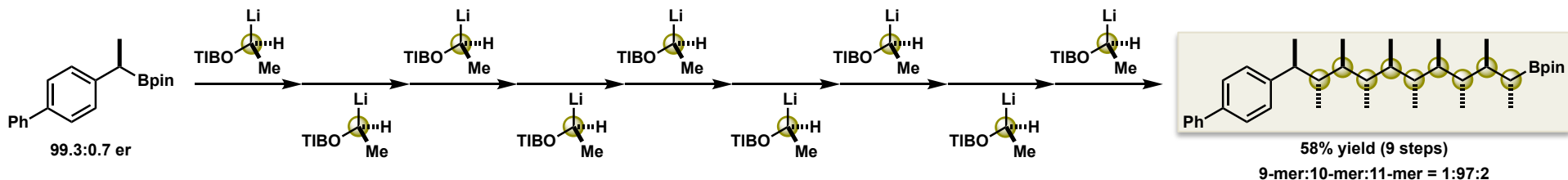
Lithiation-Borylation in Total Synthesis



Assembly-Line Synthesis Examples

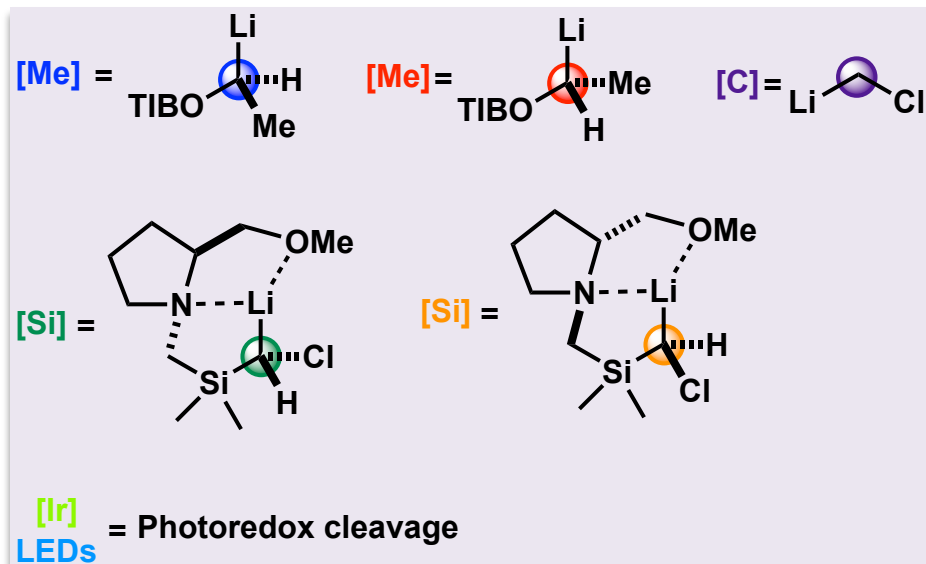
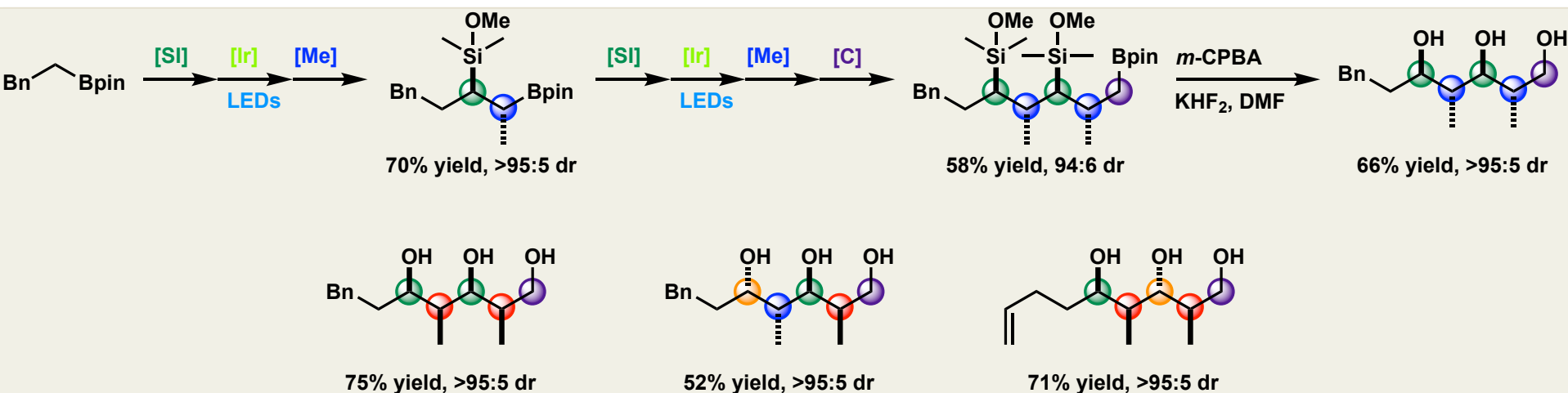


Iterative Assembly-Line Synthesis



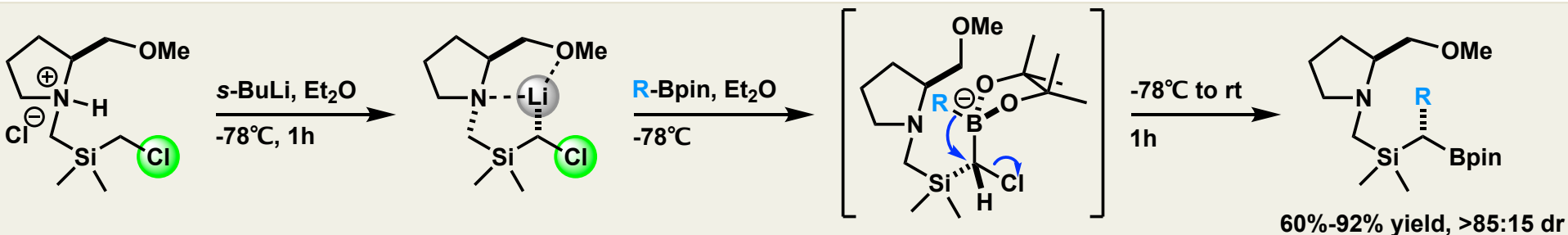
- Ten contiguous, stereochemically defined methyl groups.
- Total stereocontrol.
- No extra manipulation required.

Iterative Assembly Line Synthesis of Polypropionates



- Five contiguous stereocenters.
- Full stereocontrol in an effectively 'one-pot' process.
- Purification of intermediates is not required.

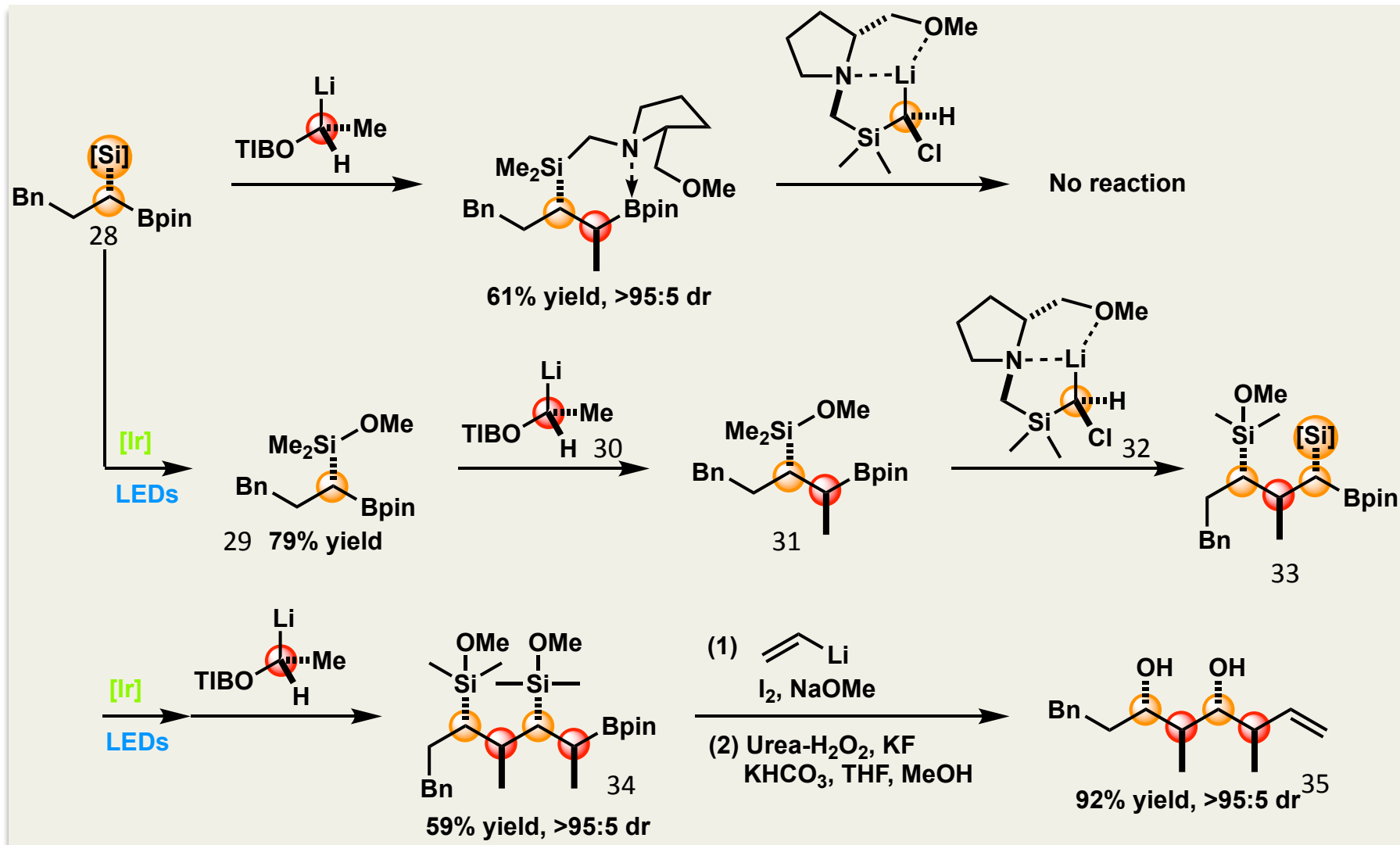
Stereocontrolled Homologation of Lithiated α -chloromethyl silane with boronic esters



R = alkanes, aromatic substituted alkanes, alkenes, protected alcohols, *tert*-butyl esters, azides

- Since the boronate complex is prone to undergo β -elimination rather than the desired 1,2-migration, the oxygen functionality is masked as a silyl group.
- The silyl group renders an adjacent carbanion configurationally unstable even at low temperature, lithiated benzylsilane bearing a tethered chiral methoxymethyl pyrrolidinomethyl moiety is used.
- The pronounced tetrahedral nature of organolithium together with its potential to complex with the oxygen atoms of the boronic ester directs the reagent to the same face as the lithium atom, accounts for the origin of the retention of configuration observed.
- A good leaving group Cl^- is used to improve the reactivity of the 1,2-migration instead of utilizing additives such as $\text{Mg}(\text{ClO}_4)_2$.

Assembly Line Synthesis Protocol for the construction of polypropionates



Contents

- Introduction
- Part 1 : Factors responsible for the 1,2-migration
- Part 2 : Factors responsible for stereocontrol
- Part 3 : Application of lithiation-borylation reaction in synthesis
- **Summary**

Summary

- Several factors should be considered when thinking about 1,2-migration and stereoselectivity of lithiation-borylation reaction.
- Lithiation-Borylation is a powerful method in assembly-line synthesis.

Thank You !

Appendix

Proposed catalytic cycle for photoredox cleavage of aminosilane

