Homologation of chiral boronic esters and application to 1,3-polyols synthesis

Literature Seminar #1

B4 Yuta Kasamoto

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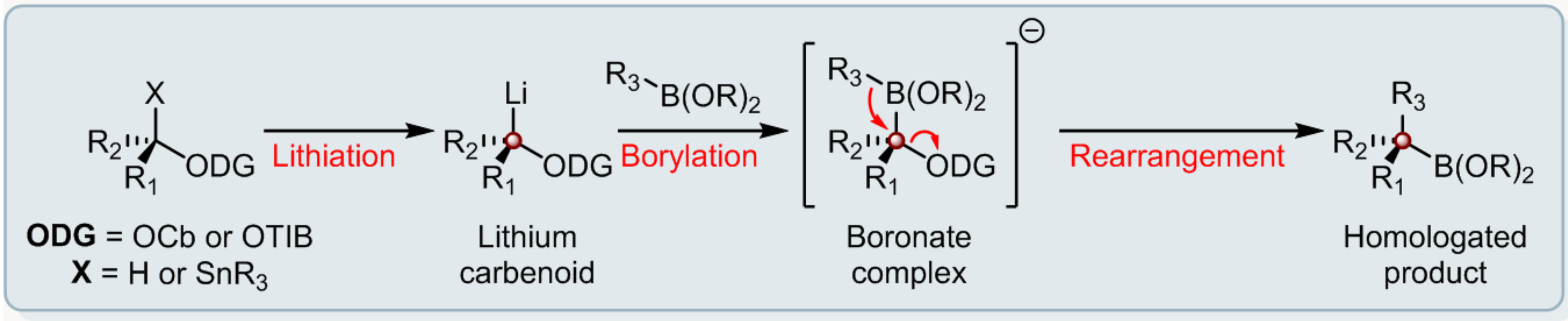
Homologation

<u>Homologation: Method for one carbon elongation</u>

Lithiation and borylation process



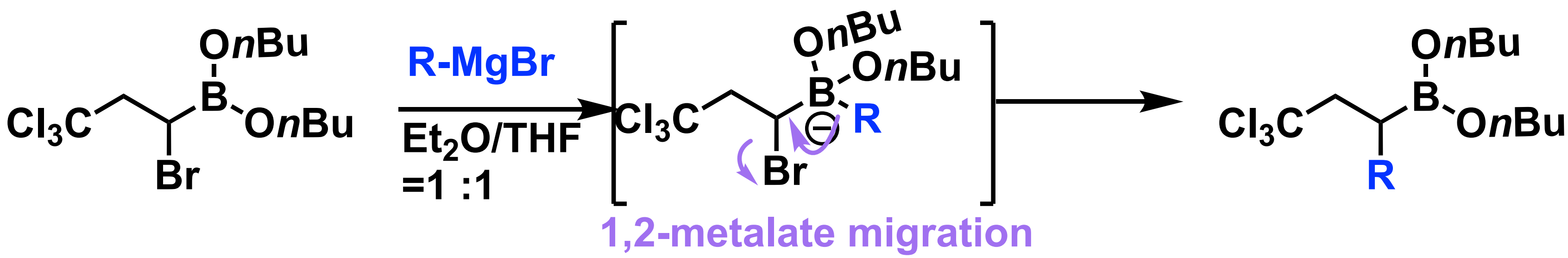
○Excellent stereocontrol

○Utilized in iterative reaction

https://www.chm.bris.ac.uk/org/aggarwal/research.php#li-b

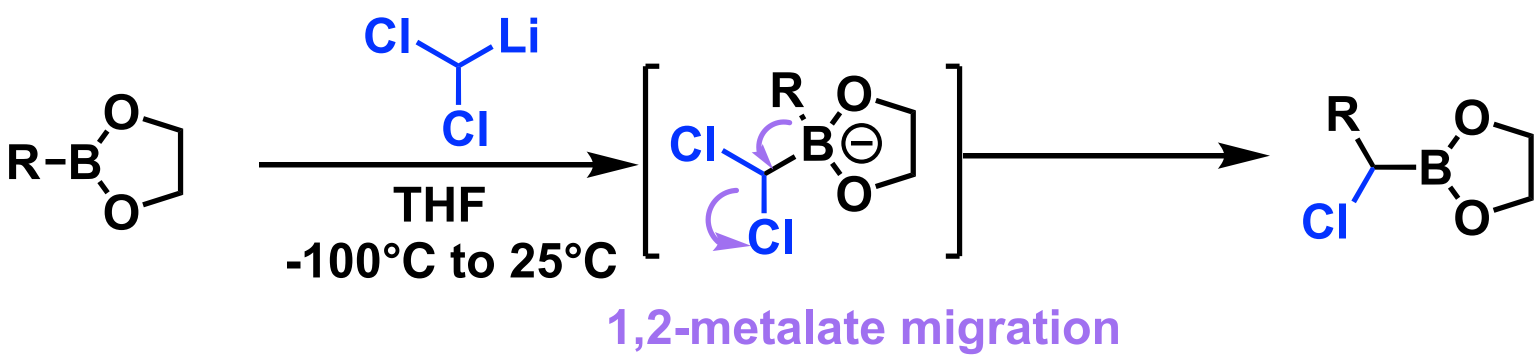
Matteson reaction

Reaction discovery of Matteson homologation



D. S. Matteson, *et al. J. Am. Chem. Soc.* ***1963***, 85, 2599.

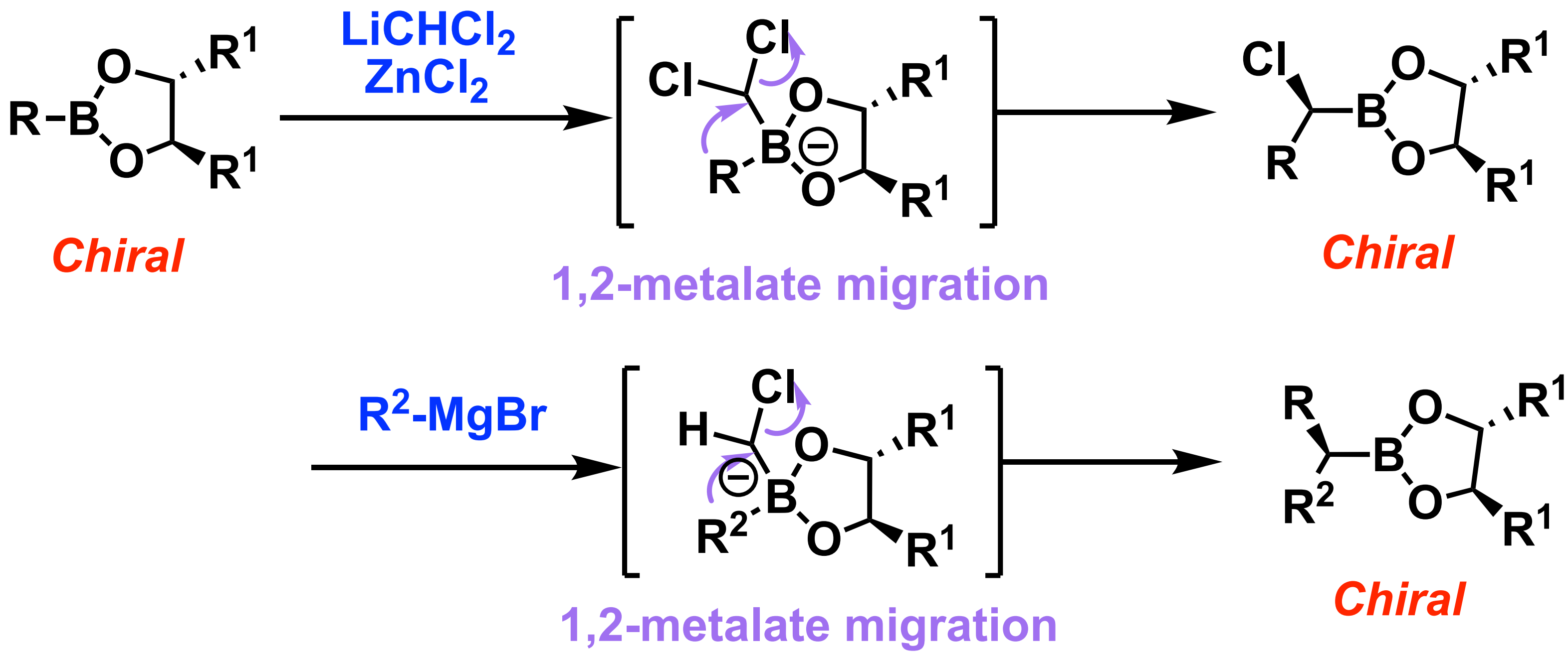
α-Chlorol alkyl lithium reagents for homologation



D. S. Matteson, *et al. J. Am. Chem. Soc.* ***1980***, 102, 7588.

Matteson reaction

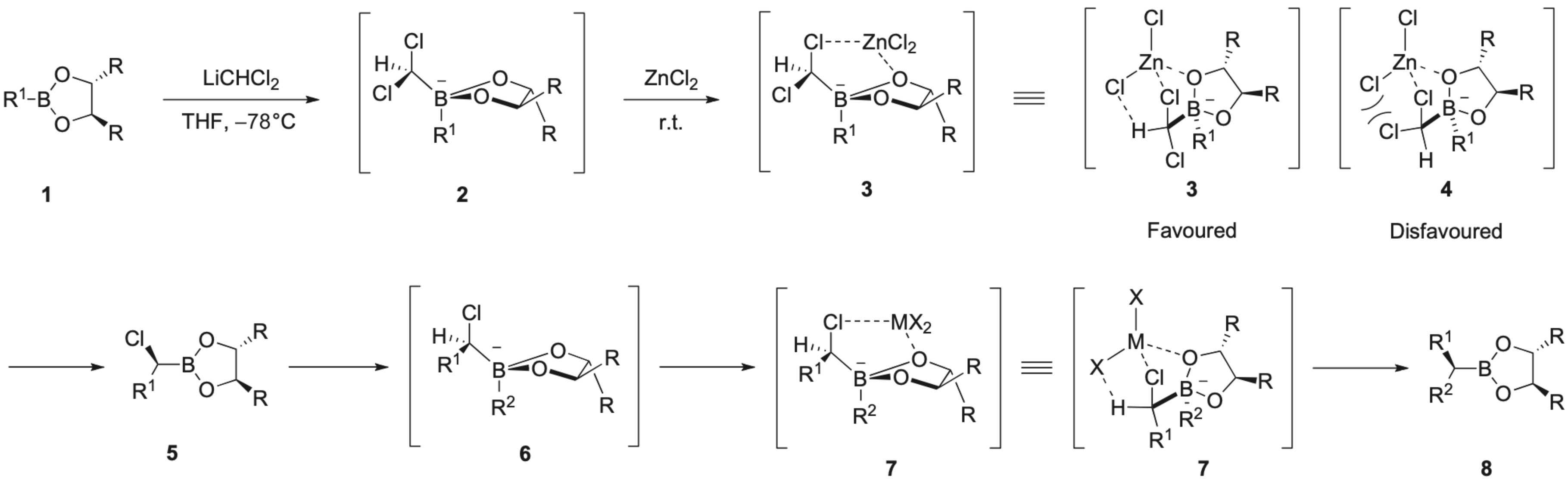
Homologation of boronic acid pinacol esters with high level of diastereoselectivity



D. S. Matteson, *et al. J. Am. Chem. Soc.* ***1980***, 102, 7590.

Matteson reaction

<u>The reason for high stereocontrol</u>



✔ 2→5: ZnCl$_2$ promotes the migration of R^1 by interaction.

→α-chloroboronic ester 5: High level of diastereroselectiyity

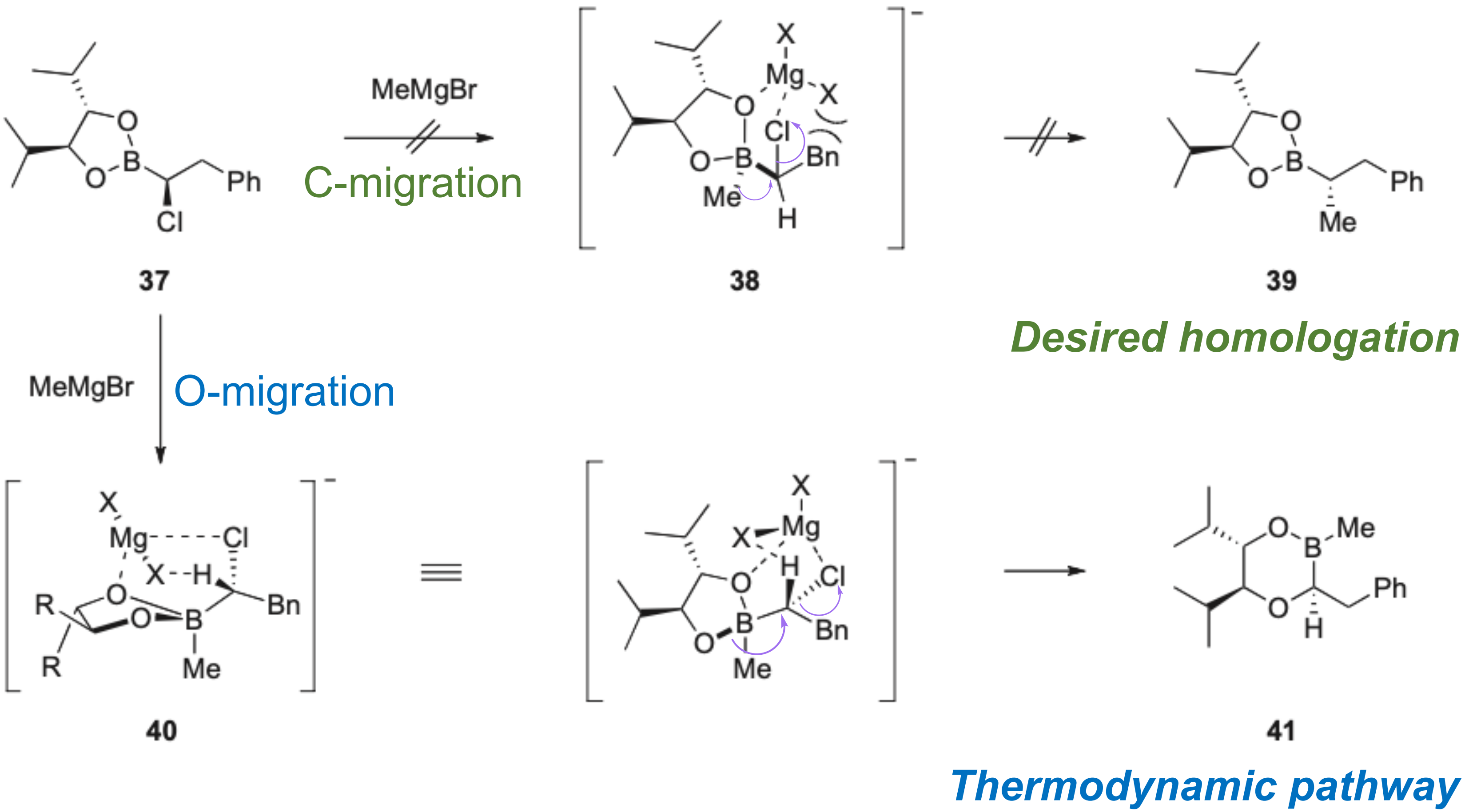
✔ 7→8: Migration group and leaving group: anti-periplanar

→Homologation product 8: High level of diastereroselectiyity

V. K. Aggarwal, *et al. Chemical Record.* **2009,** *9,* 24.

Matteson reaction

Problems

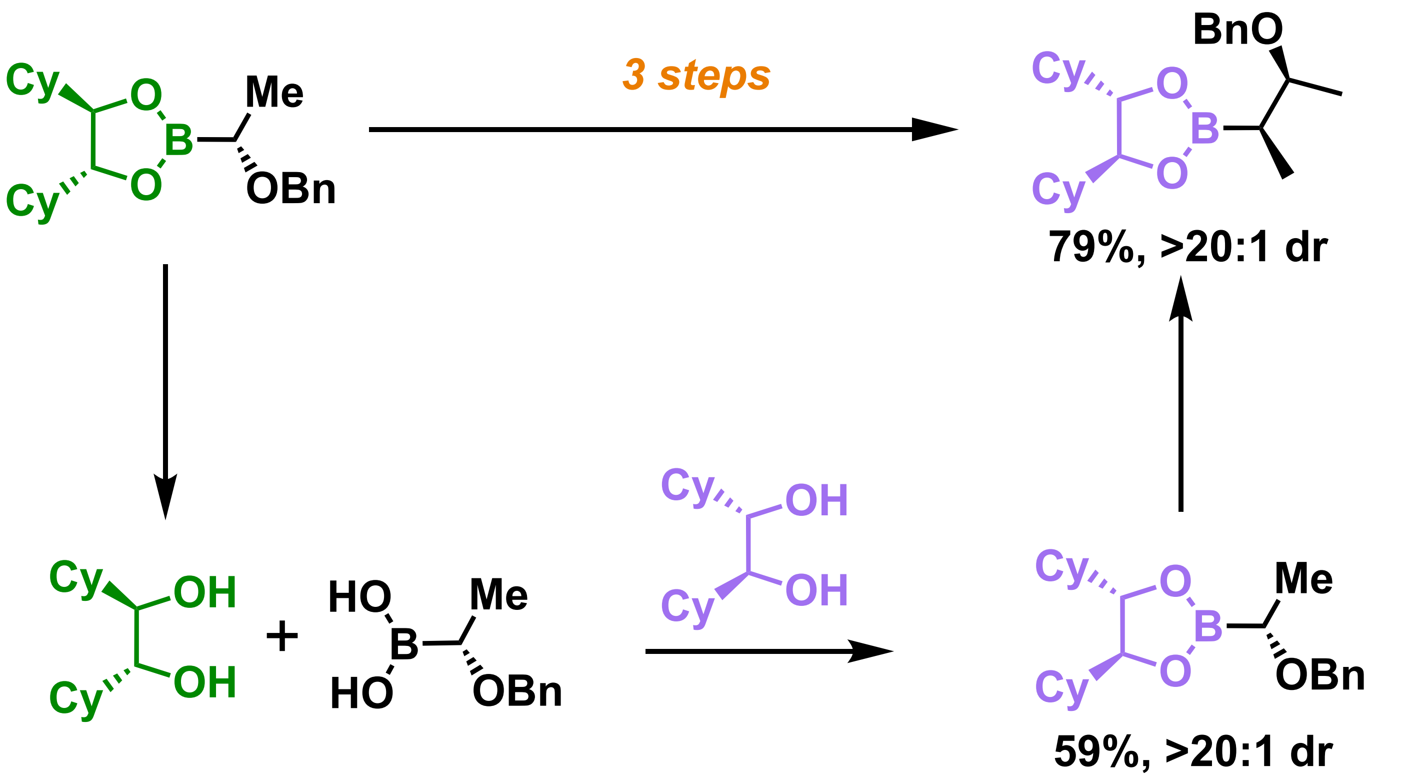


V. K. Aggarwal, *et al. Chemical Record.* **2009,** *9,* 24.

Matteson reaction

Problems

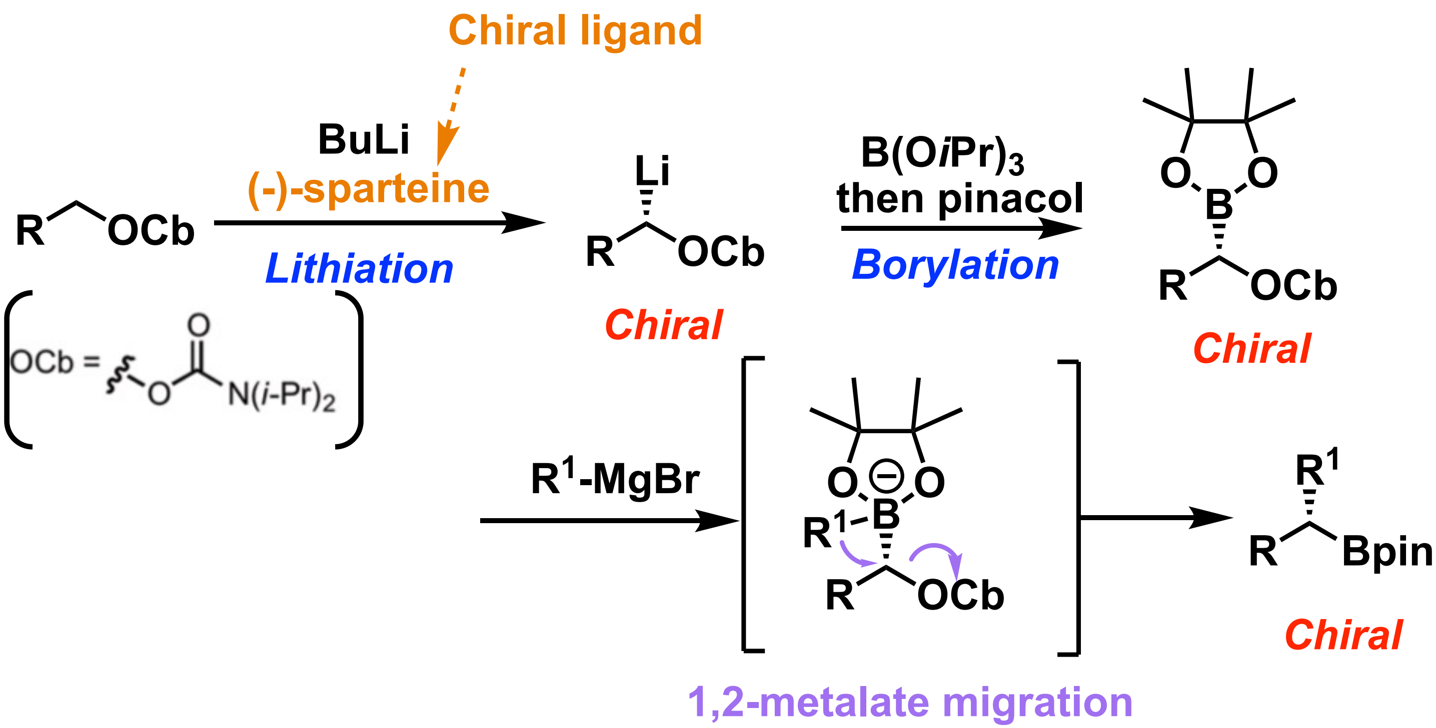
- To obtain opposite stereoisomers, 3 steps are required for changing of boronic ester stereochemistry.



V. K. Aggarwal, *et al. Chemical Record.* **2009,** *9,* 24.

Hoppe's approach

Hoppe's approach : Alternative homologation of boronic esters



✓ This lithiated carbamates homologates boronic ester with high stereocontrol.

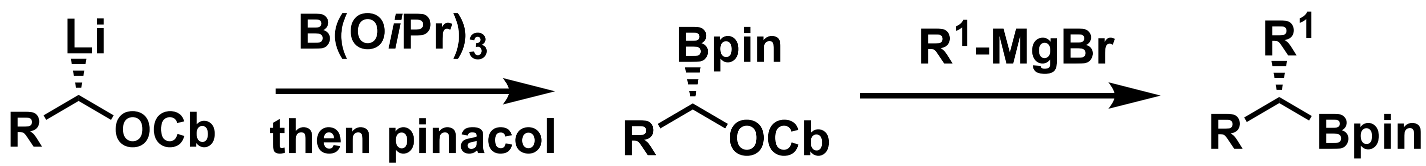
V. K. Aggarwal, *et al. Acc. Chem. Res.* **2014,** *47*, 3174.

Aggarwal's approach

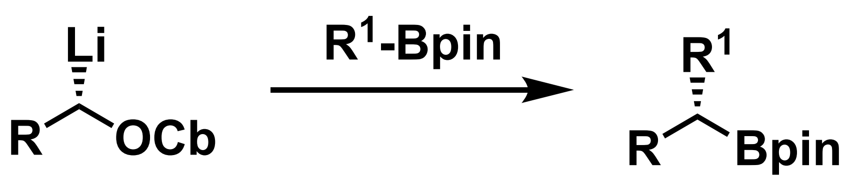
Aggarwal's approach : Improve Hoppe's homologation of boronic esters

<u>Good point</u>

Hoppe's approach: 2 steps per one homologation



Aggarwal's approach: 1 step per one homologation



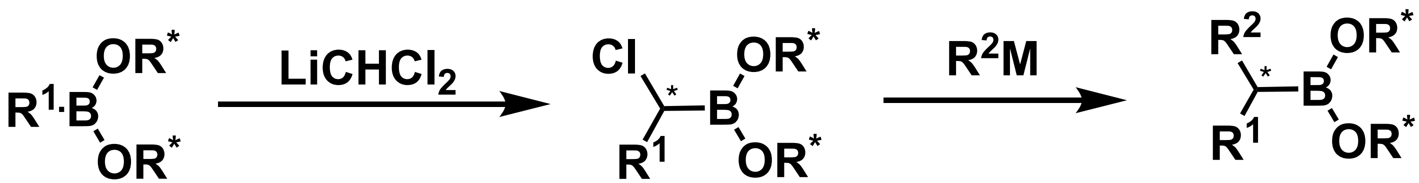
V. K. Aggarwal, *et al. Chemical Record.* **2009,** *9,* 24.

Aggarwal's approach

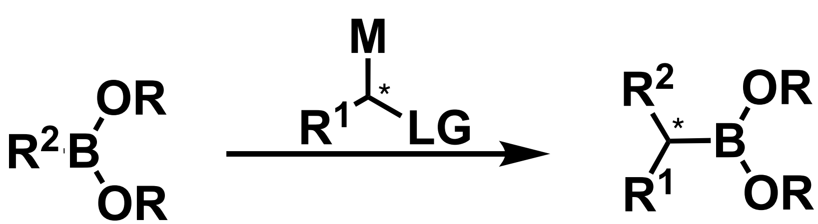
Good point

- Stereocontrol of the homologated product

Matteson's reaction: Substrate control



Aggarwal's approach: Reagent control

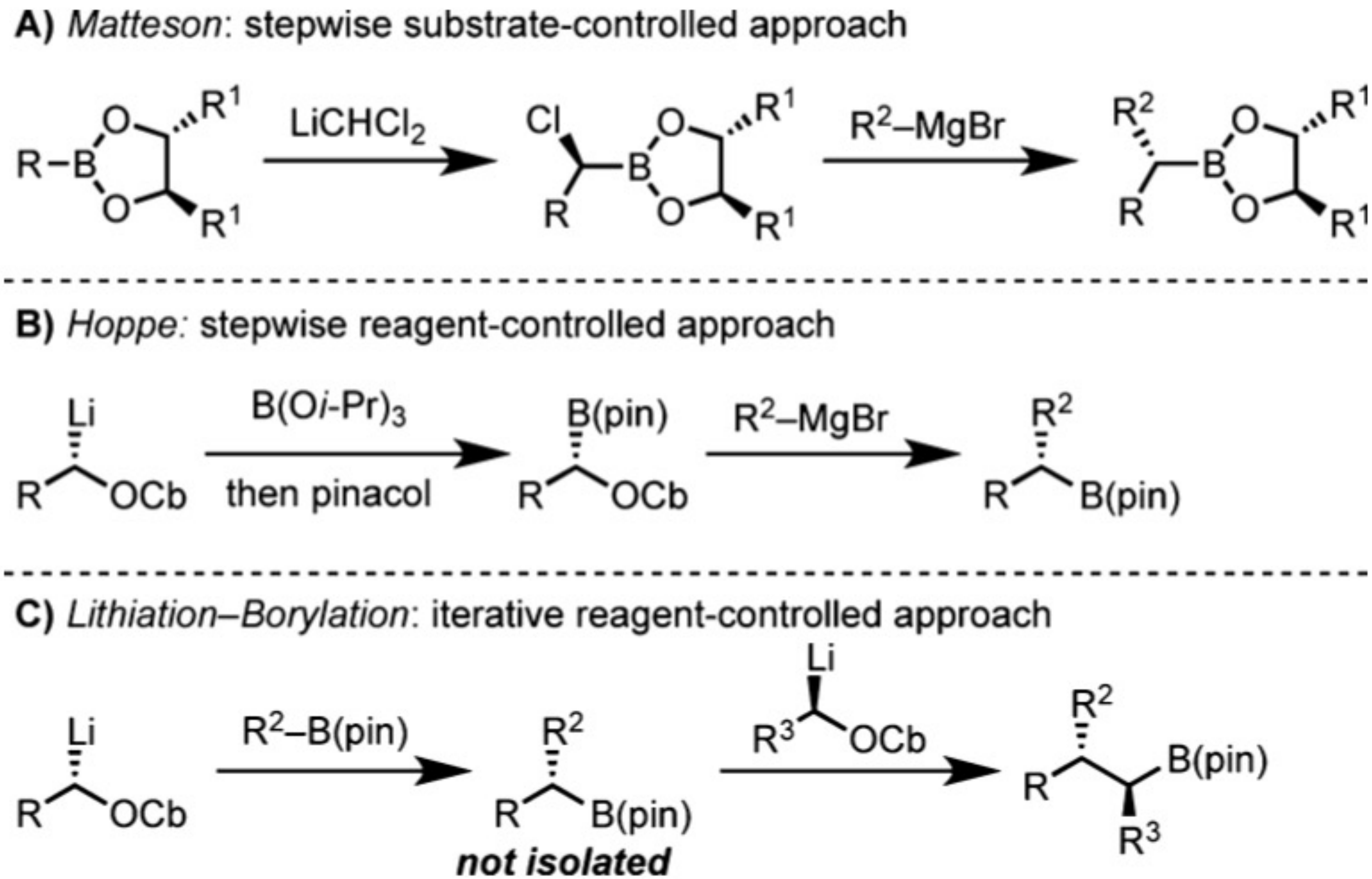


Aggarwal's approach are easy to obtain the opposite stereoisomers.

V. K. Aggarwal, *et al. Chemical Record.* **2009,** *9,* 24.

Short summary

Homologation of boronic esters with high stereocontrol was developed in various ways.



V. K. Aggarwal, *et al. Acc. Chem. Res.* **2014,** *47,* 3174.

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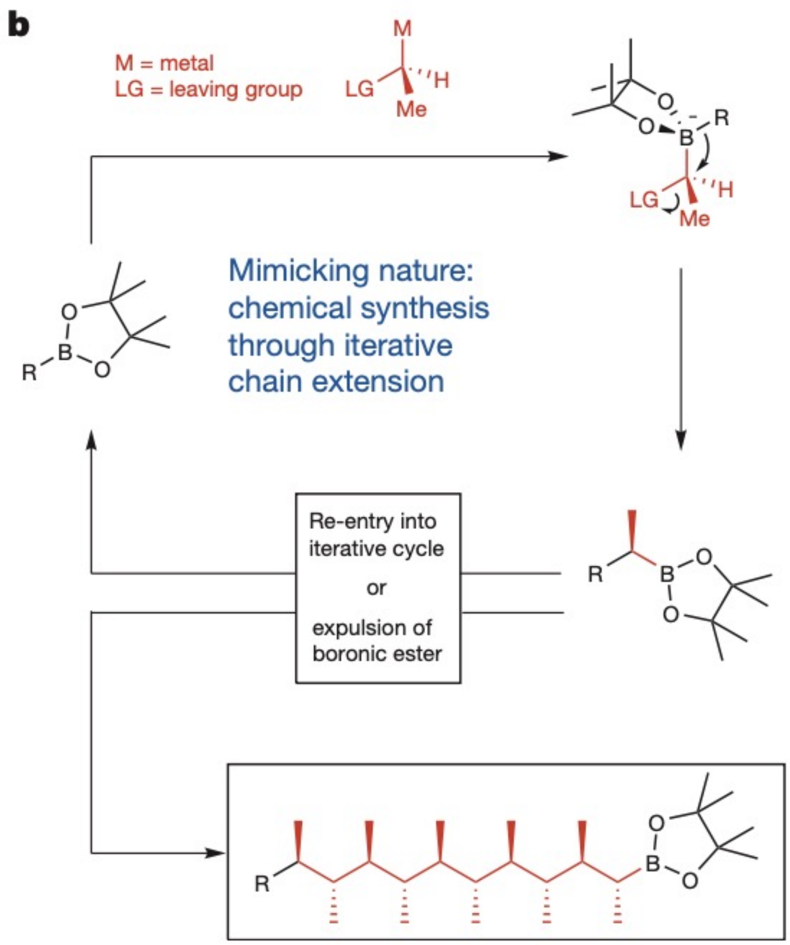
Aggarwal's iterative homologation

Aggarwal developed **iterative homologation process**.



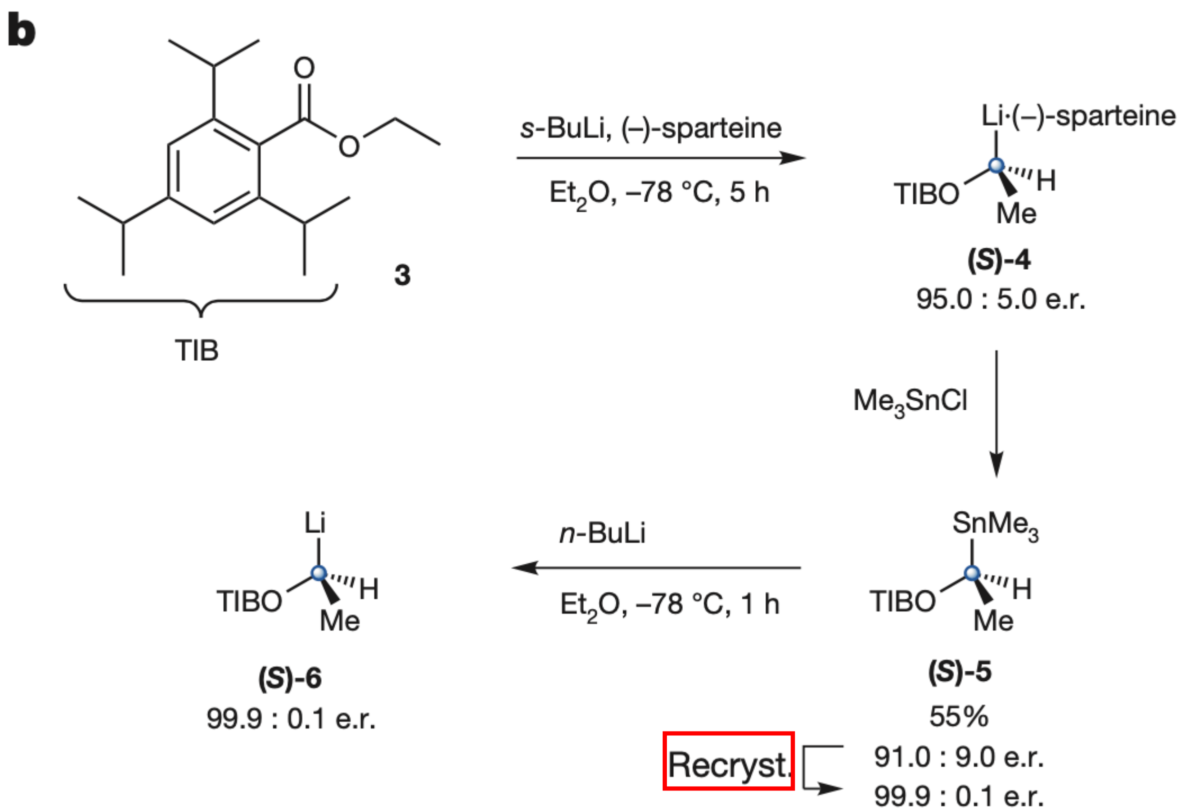
V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

Aggarwal's iterative homologation

Challenges

- Full stereocontrol to obtain pure product.

  →Improving e.r. of the reagent (lithiated carbamates)



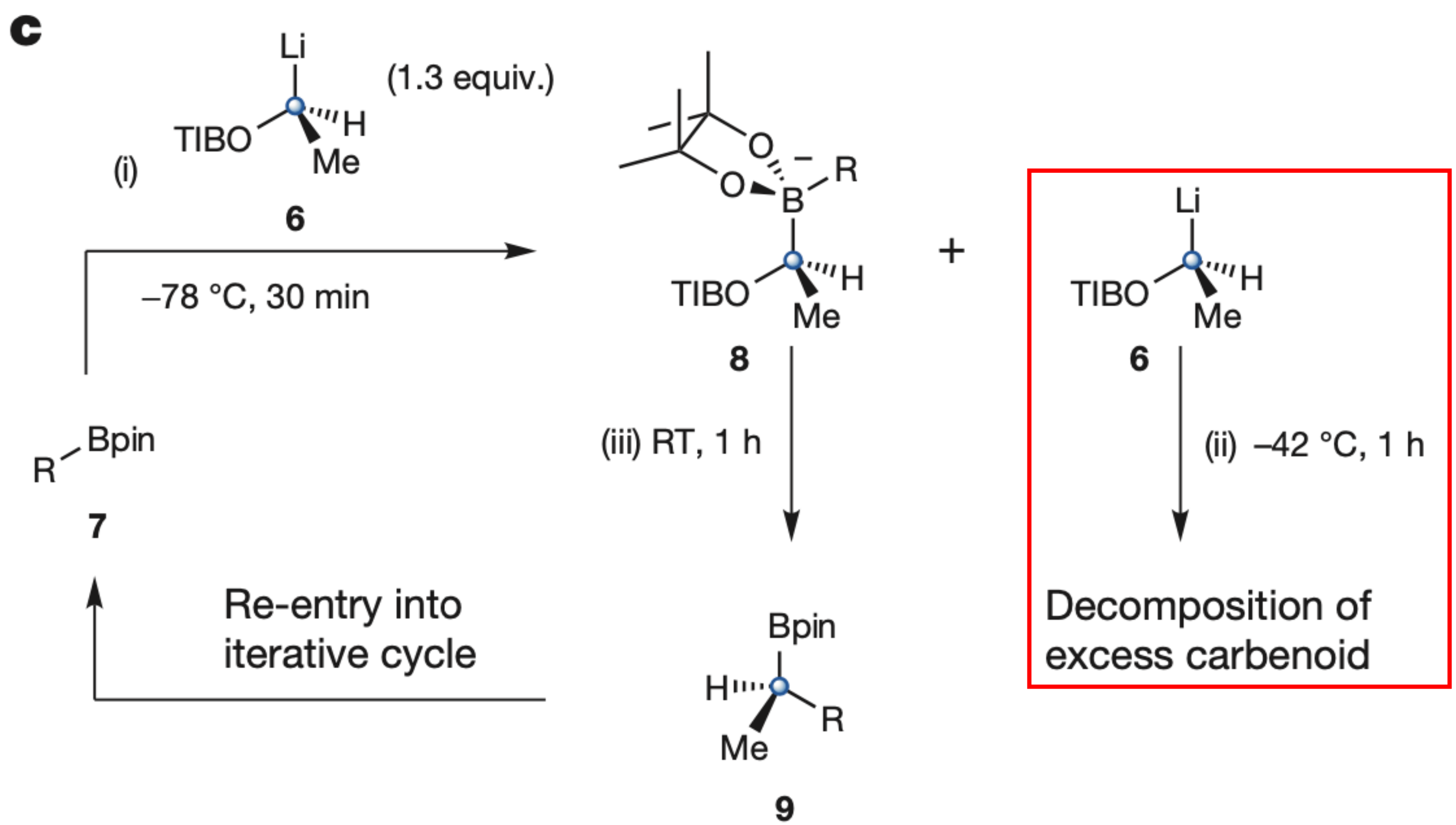
V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

Aggarwal's iterative homologation

Challenges

- Control of reactivity (over reaction)

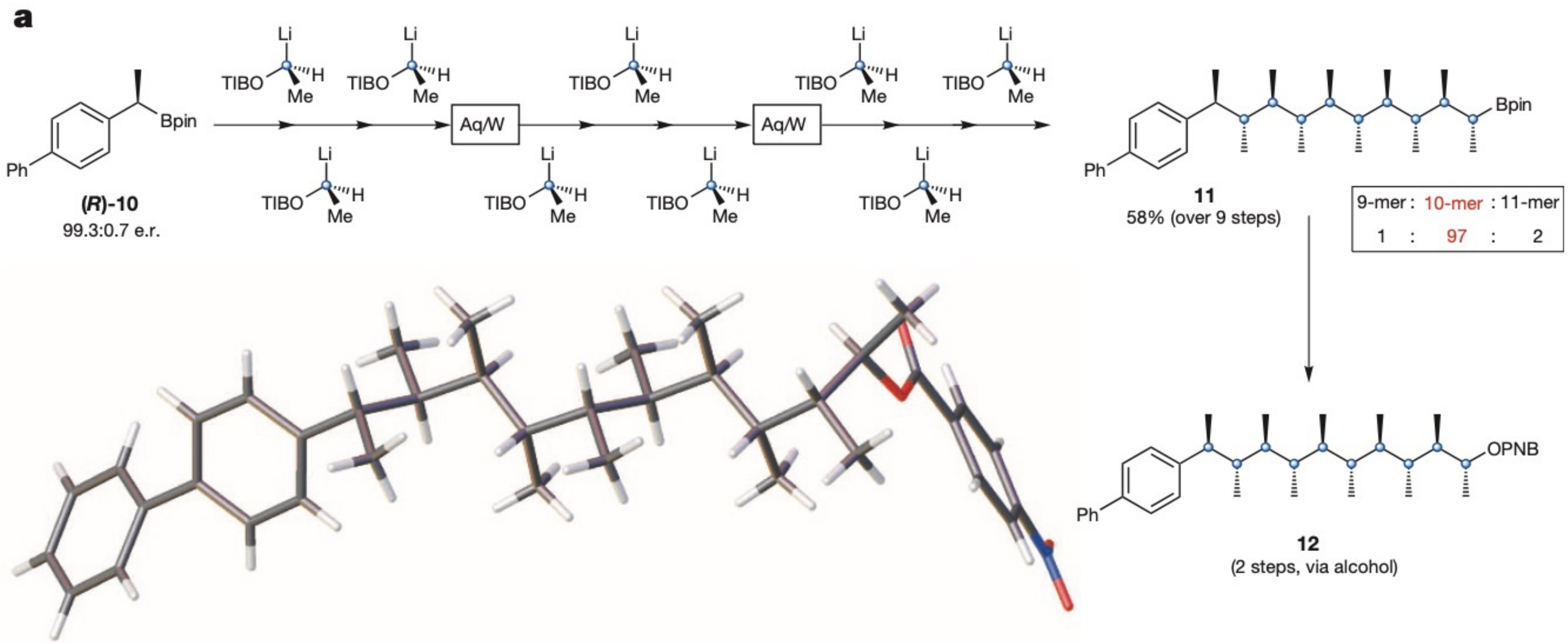
  →It was solved by temperature control during reaction.



V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

Aggarwal's iterative homologation

Apply to iterative reaction



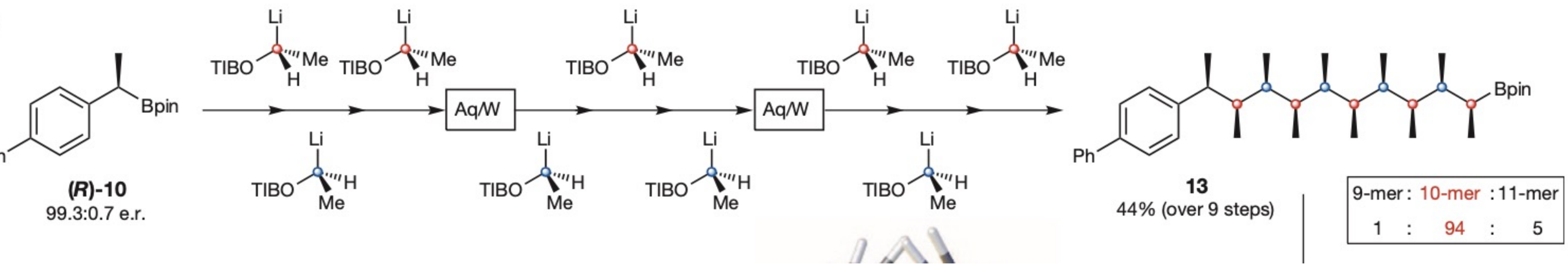
- One pot
- High stereocontrol

V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

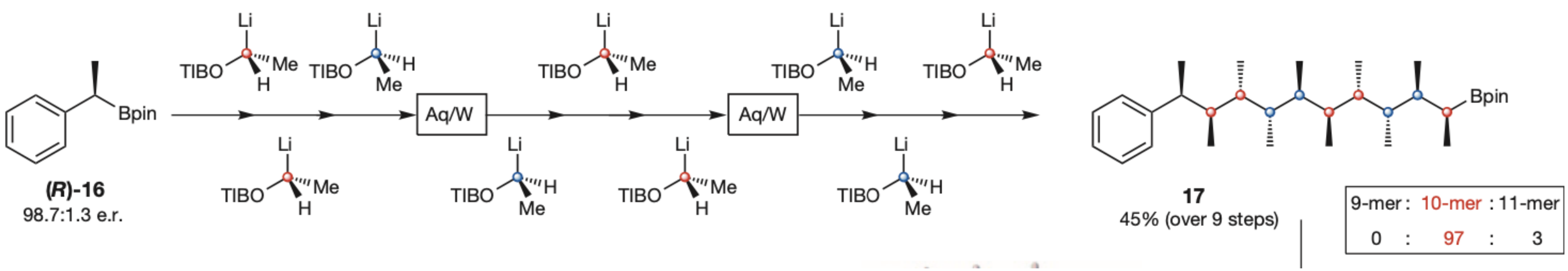
Aggarwal's iterative homologation

Similarly, alternative stereoisomer of boronic ester could be obtained.

b



c



V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

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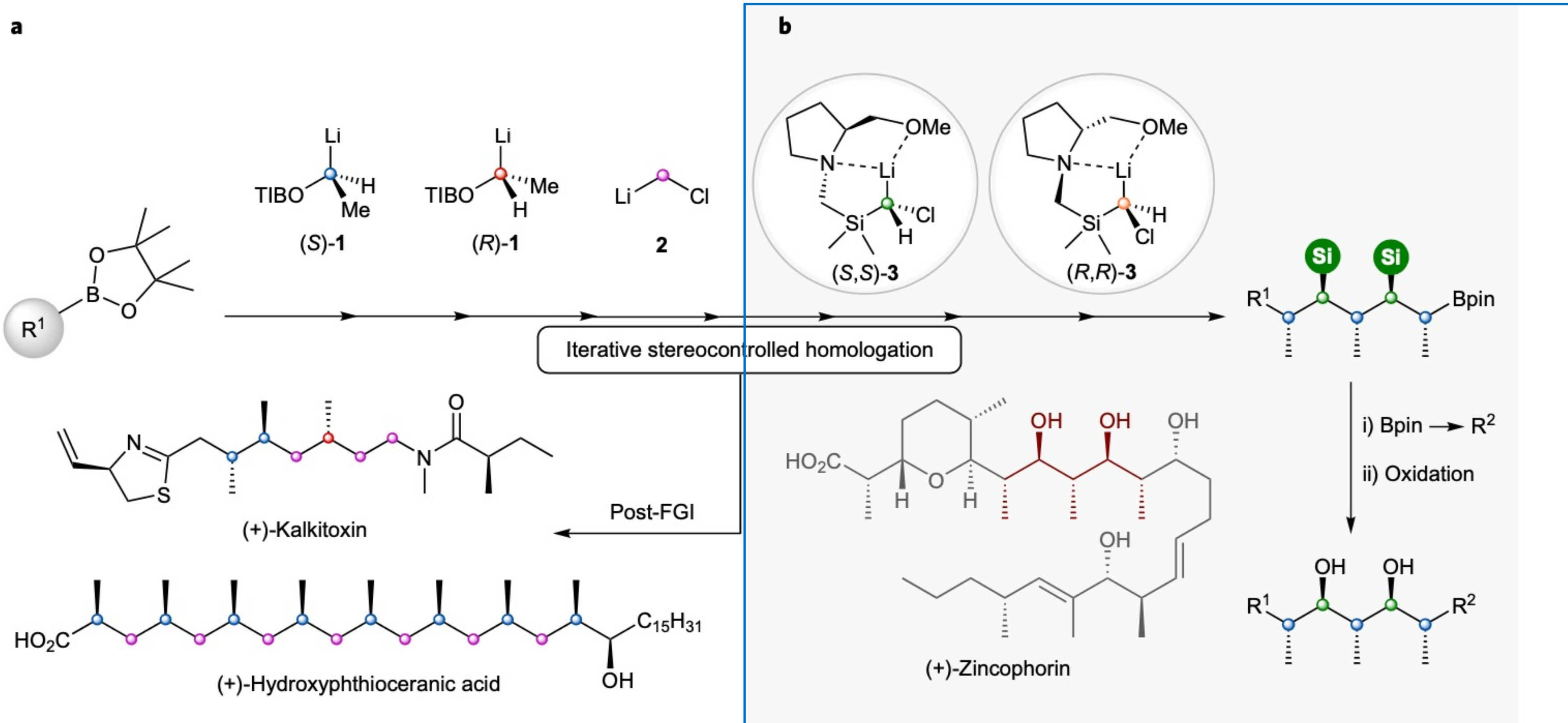
Using silyl groups for iterative homologation

Aggarwal applied their iterative homologation to 1,3-polyol synthesis.



Previous work

This work

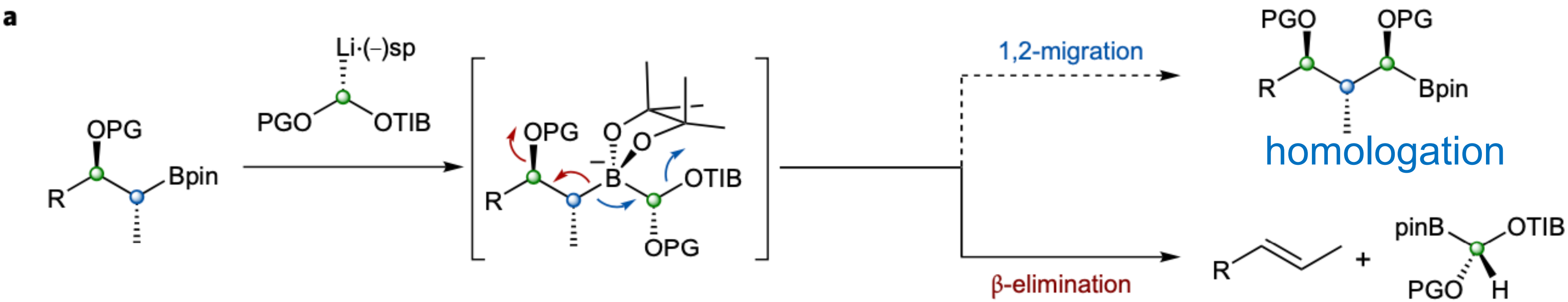
Apply to 1,3-polyols synthesis

✔ Masking the hydroxy group as a silyl group

V. K. Aggarwal, *et al. Nat. Chem.* **2017**, *9*, 896.

Using silyl groups for iterative homologation

The reason of using organosilyl lithiated reagents for iterative homologation



✖Undesired reaction could happen by application of Aggarwal's homologation.

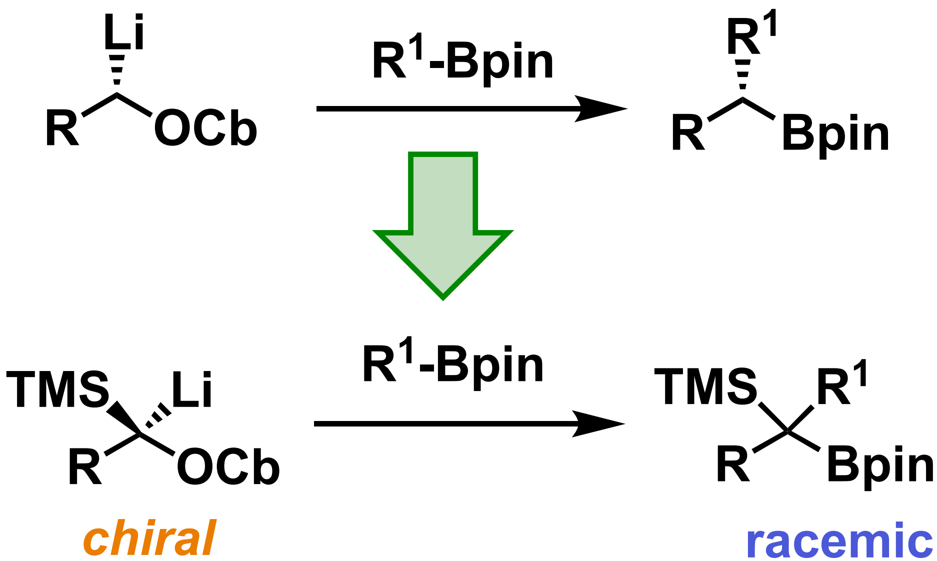
→✔Masking the hydroxy group as a silyl groups

V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9*, 896.

Using silyl groups for iterative homologation

Identifying a suitable organosilyl lithiated reagent for the homologation

- Direct application of conventional Aggarwal's homologation

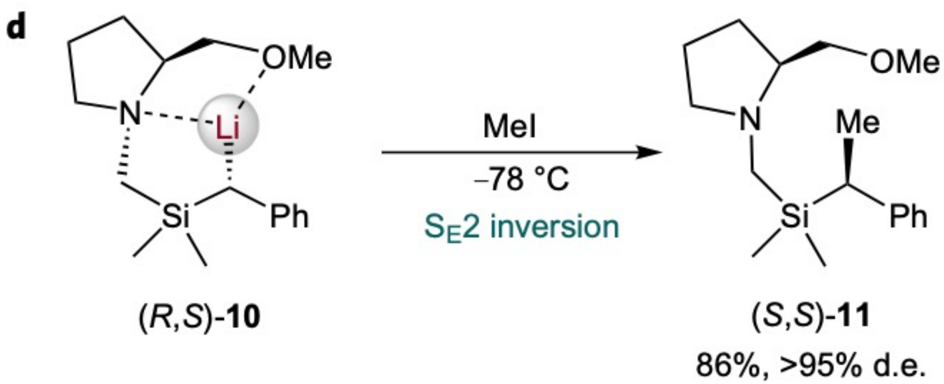


V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

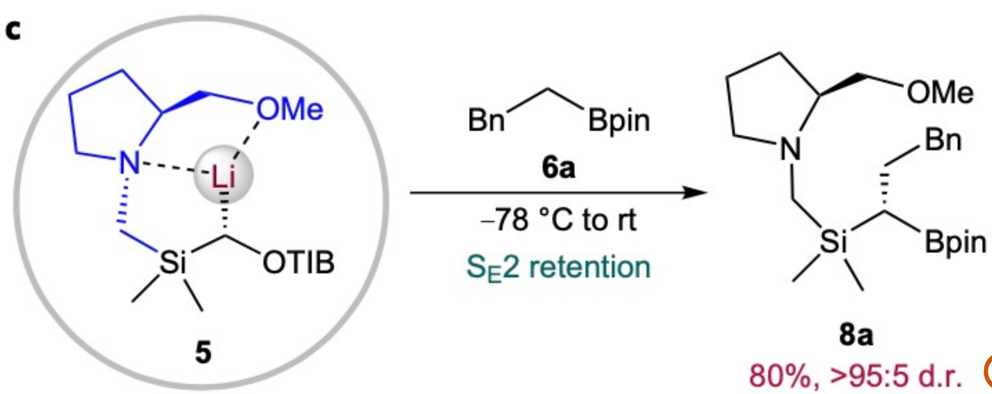
Identifying a suitable organosilyl lithiated reagent for the homologation

- Chen's lithiated benzyl silane bearing chiral pyrrolidinomethyl



○High yield and d.e.

Apply to the homologation

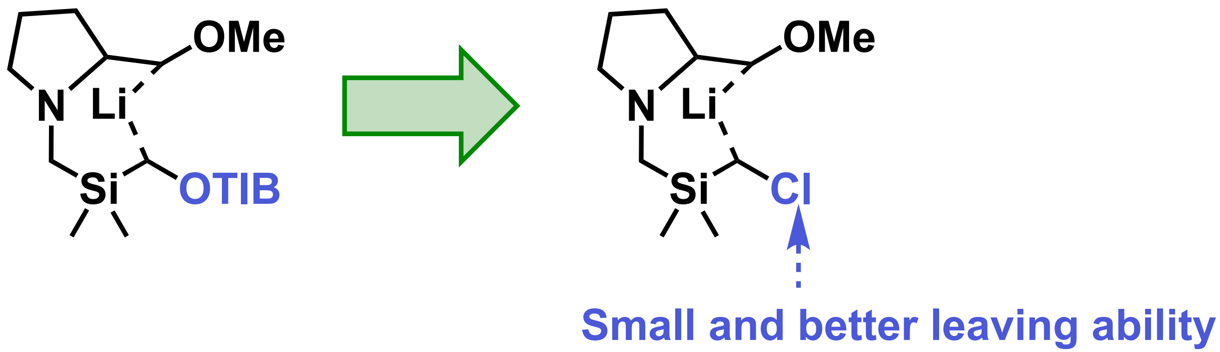


○High yield and d.r.

V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9*, 896.

Using silyl groups for iterative homologation

- Improve Chen's lithiated benzyl silane bearing chiral pyrrolidinomethyl

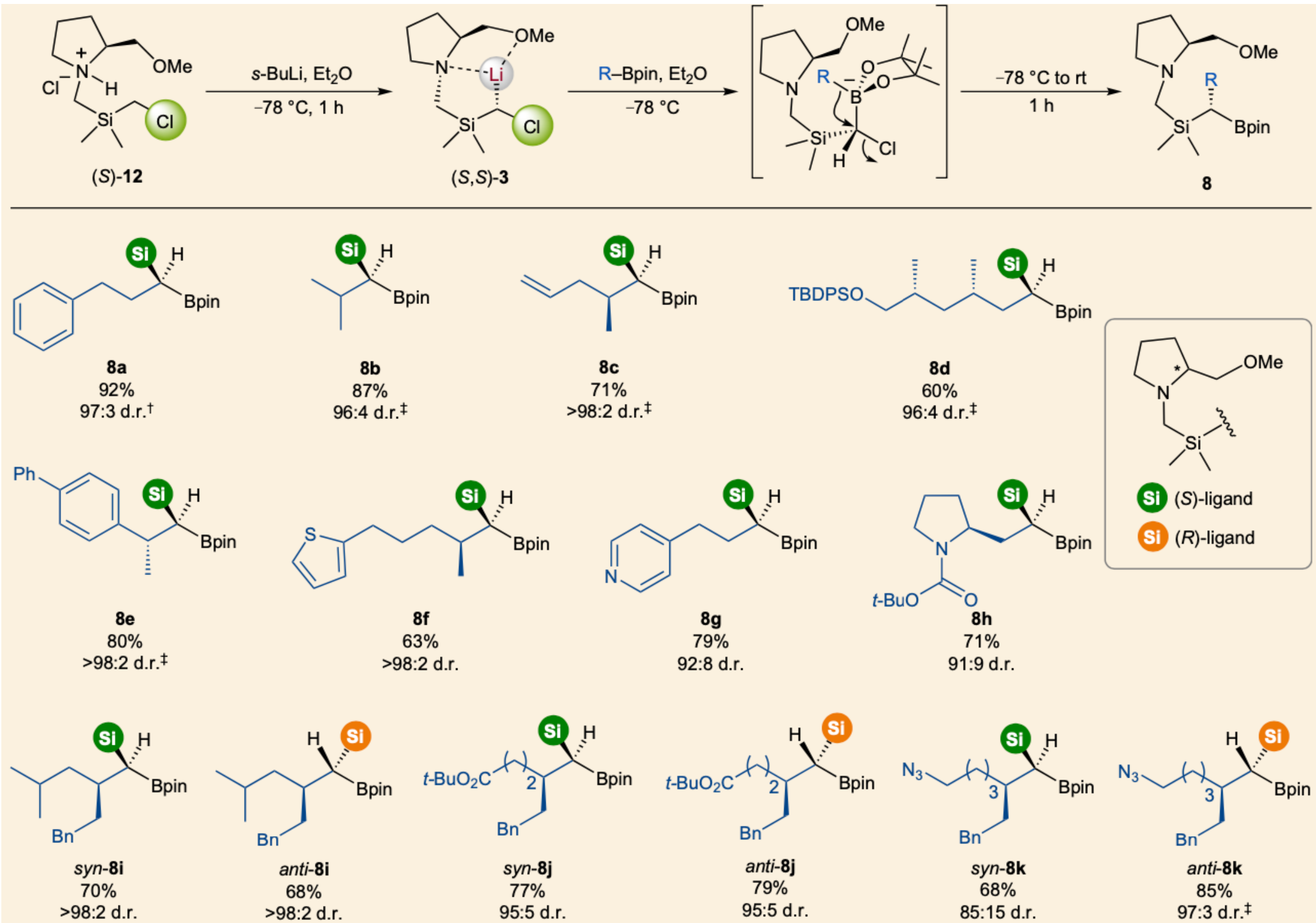


○Broader substrate scope

V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

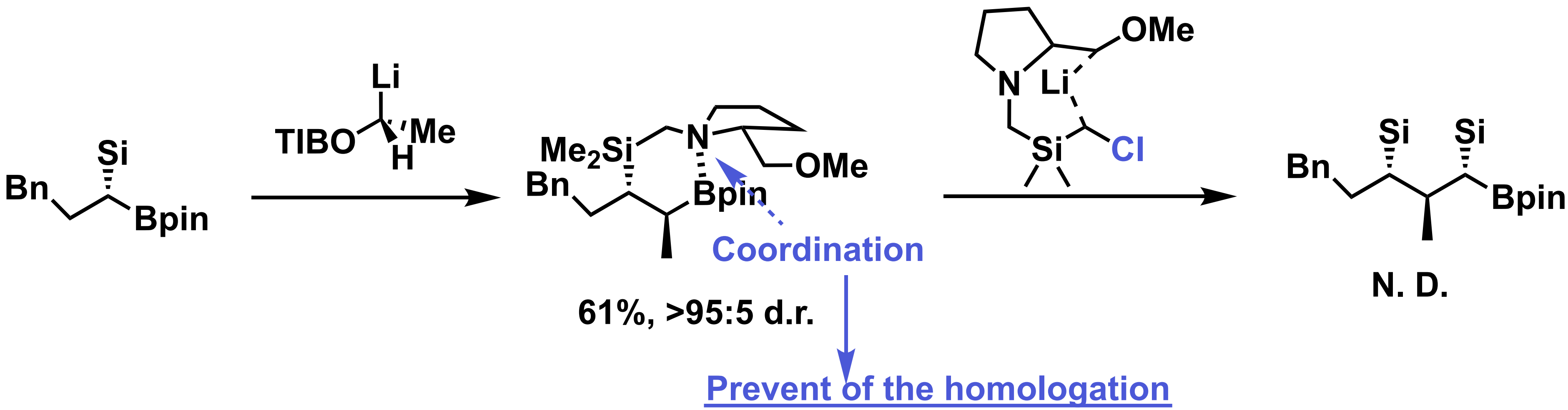
Substrate scope



V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

Subsequent homologation

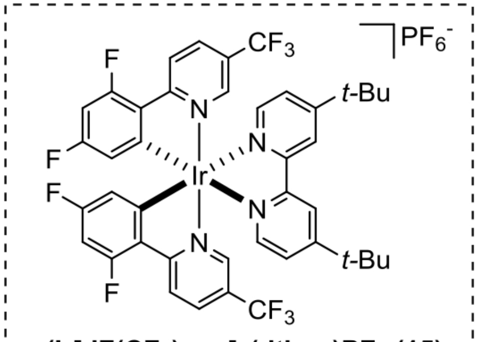


✓Need to remove amino group of the organosilyl lithiated reagents

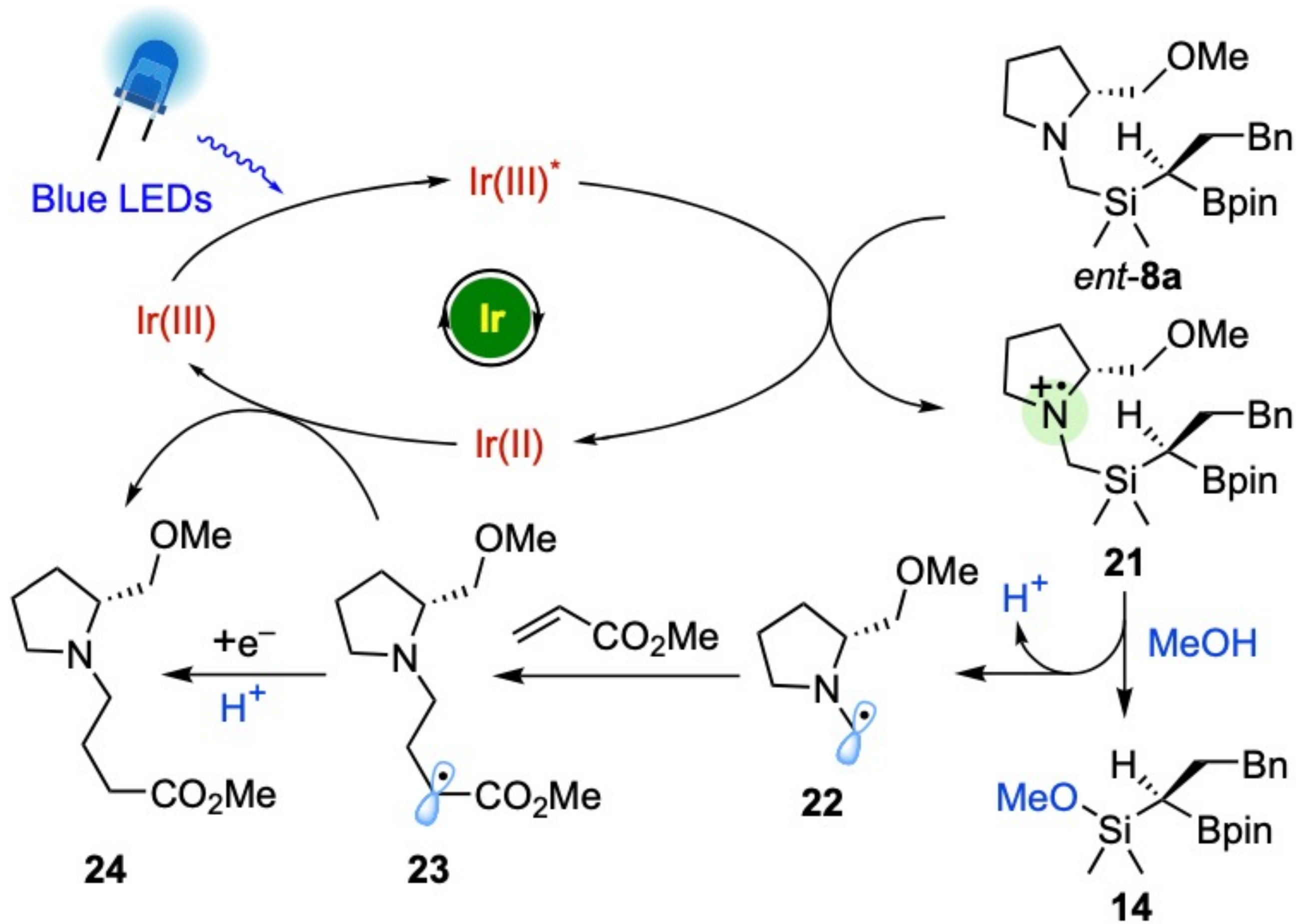
V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

Using photoredox catalysis for removing amino group from the product



(Ir[dF(CF$_3$)ppy]$_2$(dtbpy)PF$_6$ (15)



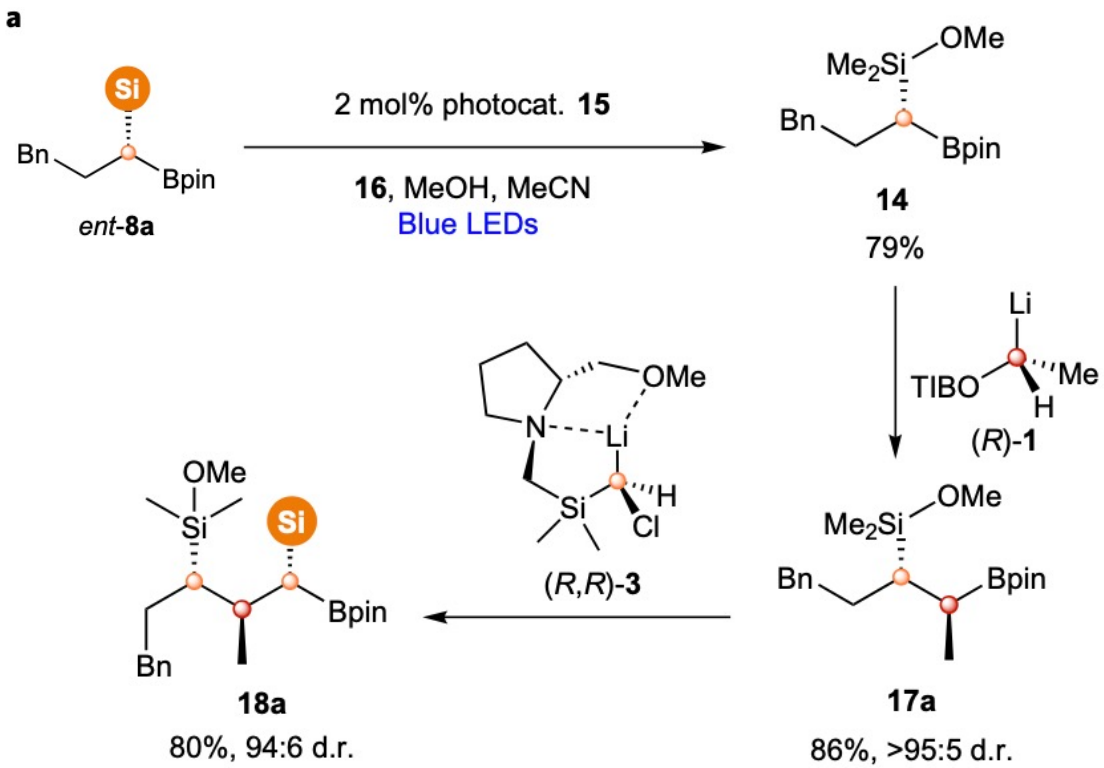
V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

Subsequent homologation

After photoredox cleavage (removing amino group),

the subsequent homologation reaction could proceed.

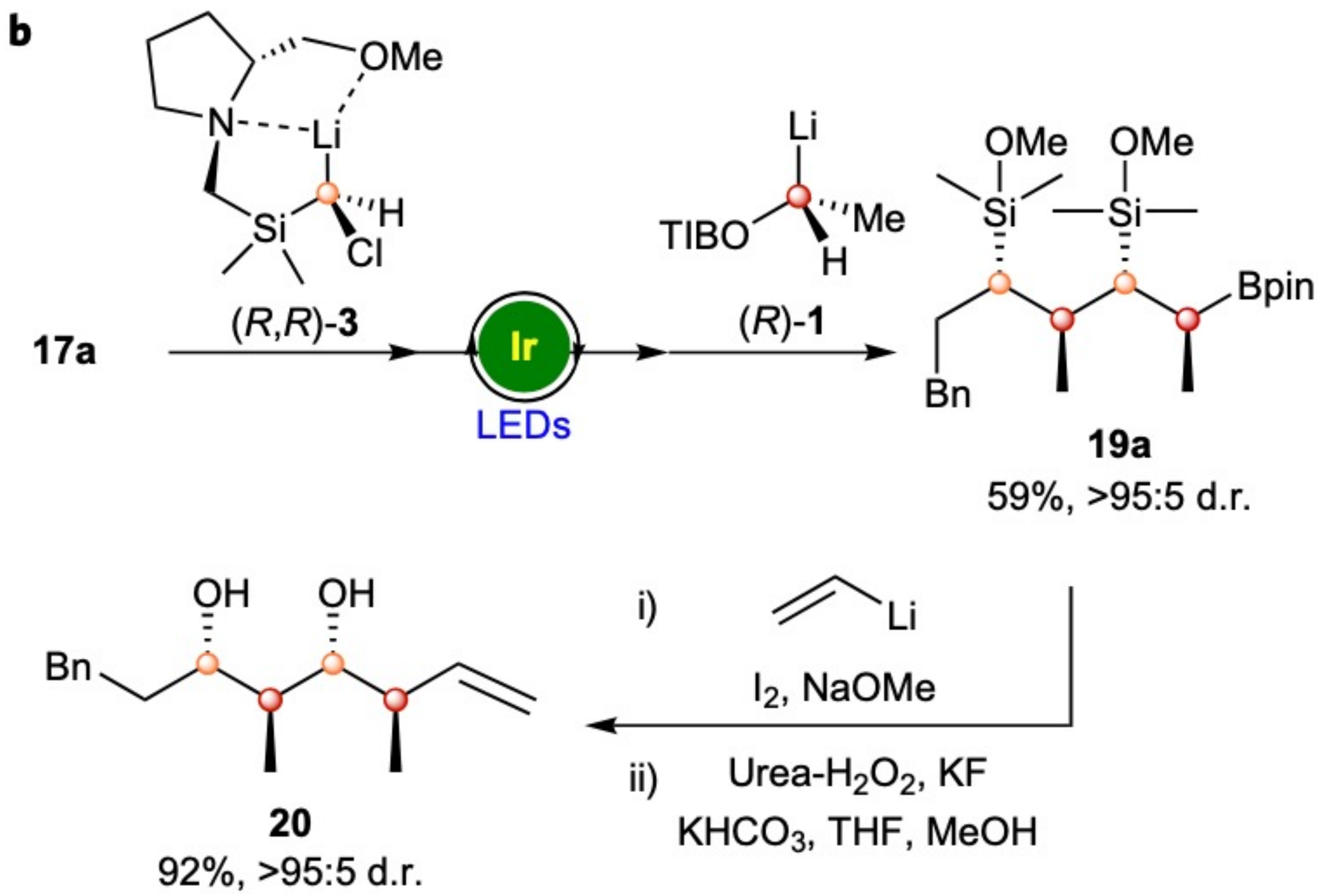


○Good yield and d. r.

V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

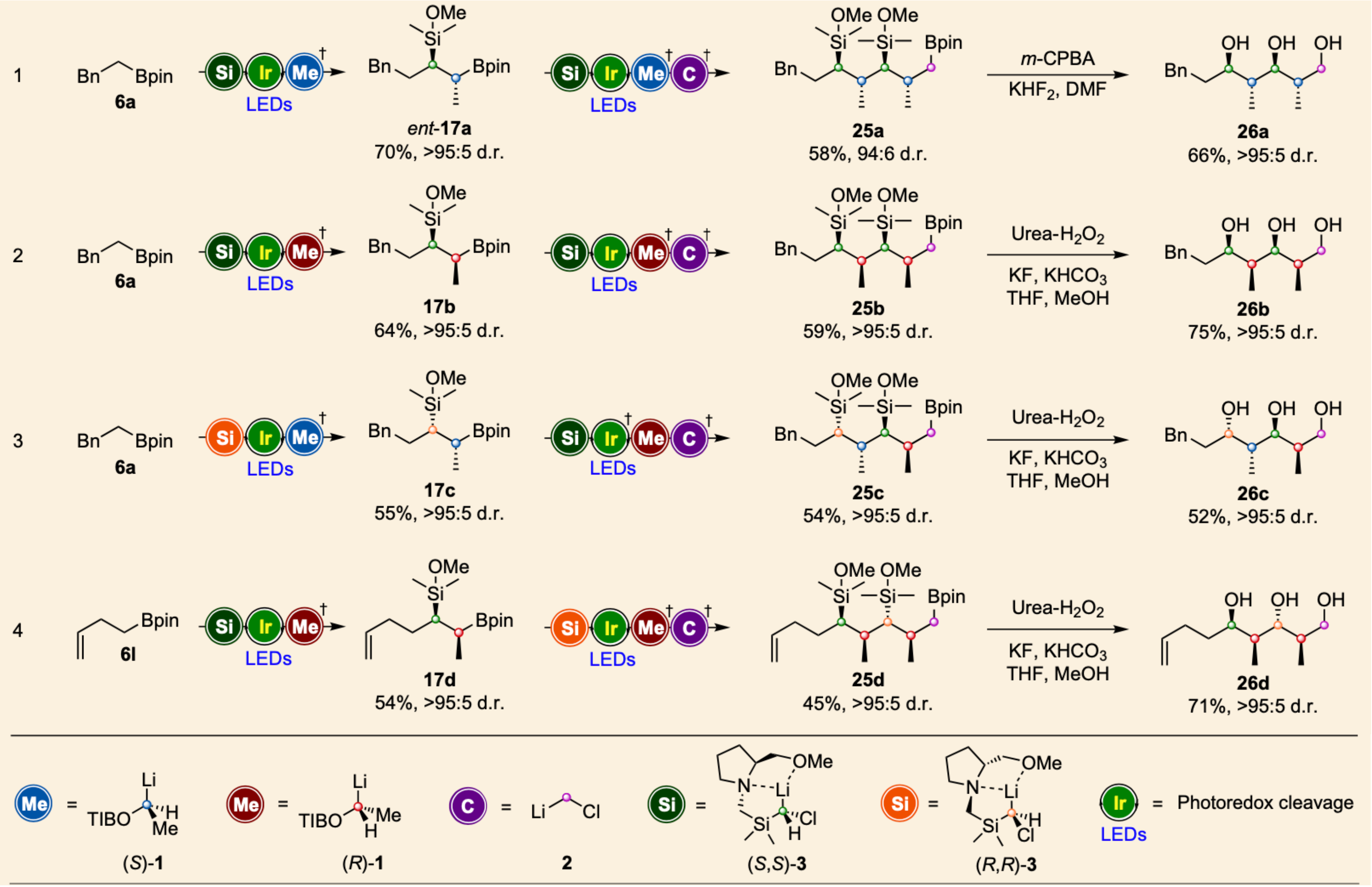
1,3-polyol motif synthesis



V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

Triol with four different stereoisomer could be obtained.



V. K. Aggarwal, *et al. Nat. Chem.* **2017**, *9*, 896.

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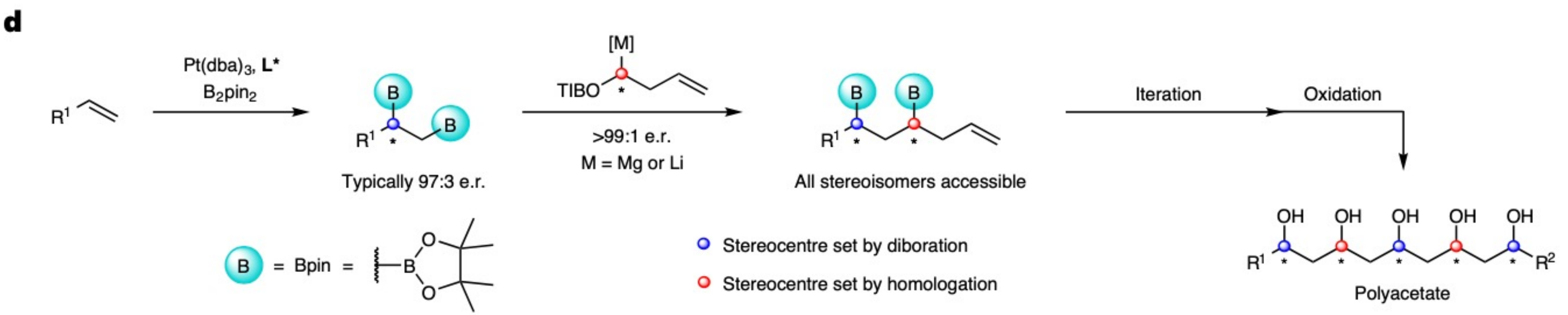
Iterative diboration and homologation

Second approach to 1,3-polyols synthesis

Iterative diboration and homologation

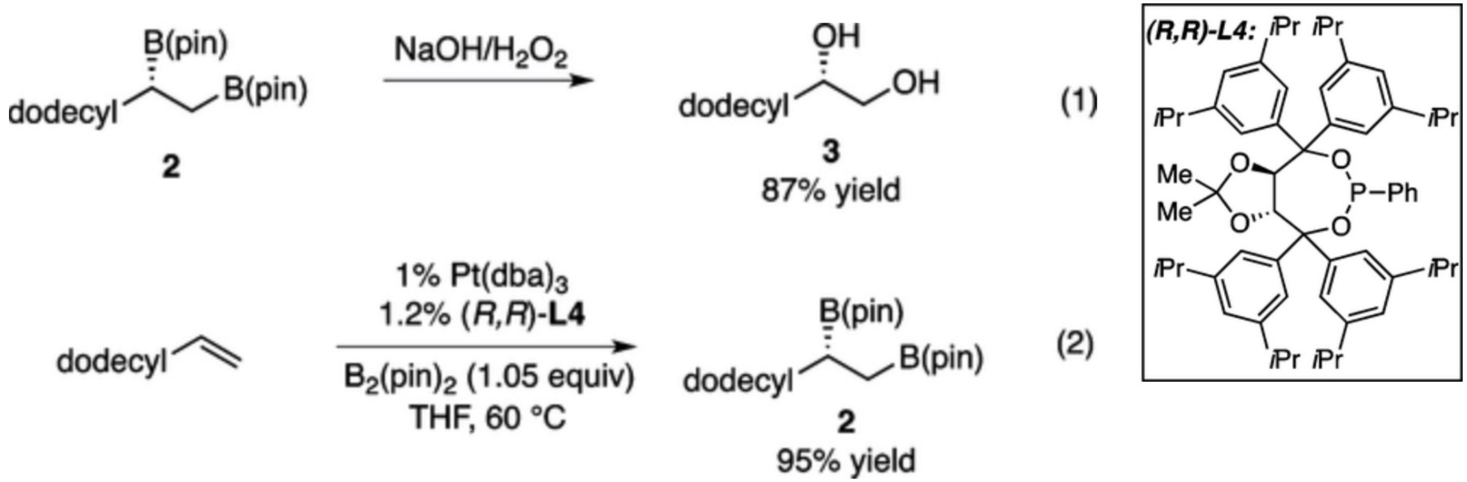


- High stereocontrol
- Fewer steps per homologation

V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15,* 248.

Iterative diboration and homologation

Diboration of terminal alkene



- ○High yield
- ○High enantioselectivity
- ○Broader substrate scope

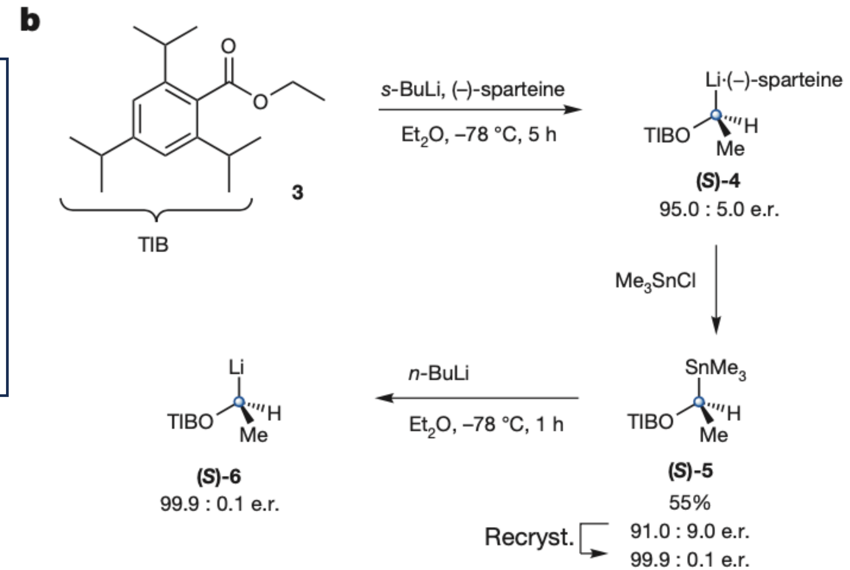
J. P. Morken, *et al. J. Am. Chem. Soc.* **2013**, 135, 11222.

Iterative diboration and homologation

Homologation

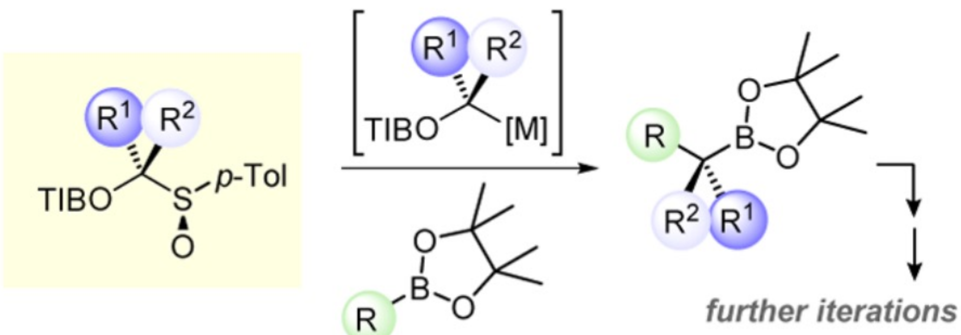
Problems of Aggarwal’s lithiated reagents

- Only the methyl substituted precursors were crystalline
- Me_3SnCl had toxic



New lithiated reagents: α-sulfinylbutenyl benzoate

- Easy to prepare with high e.e.
- Little toxic



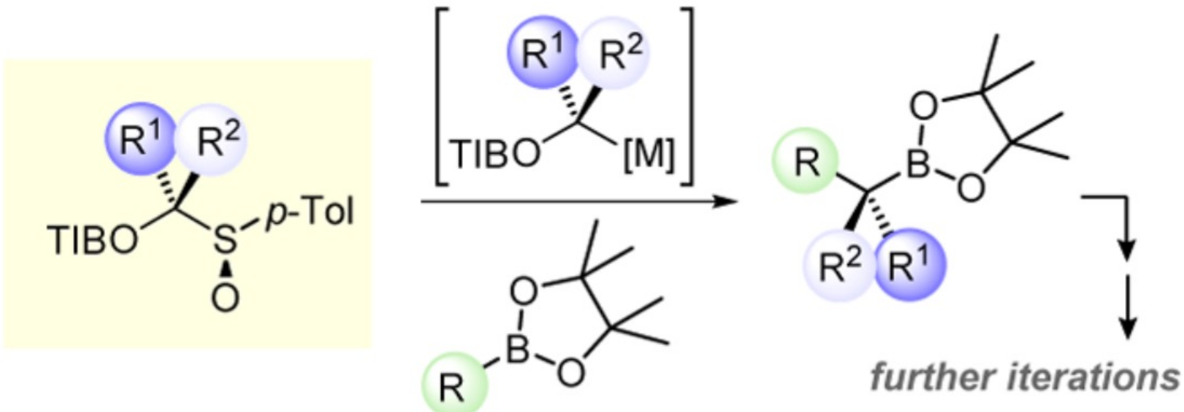
V. K. Aggarwal, *et al. J. Am. Chem. Soc.* **2017**, 139, 11877.

Iterative diboration and homologation

Homologation

Application of α-sulfinylbutenyl benzoate generated by MgCl

※Li carbenoid: reacting with both boronic esters



Preparation

high ee

no sparteine required

sensitive functional groups tolerated

Boronic ester homologation

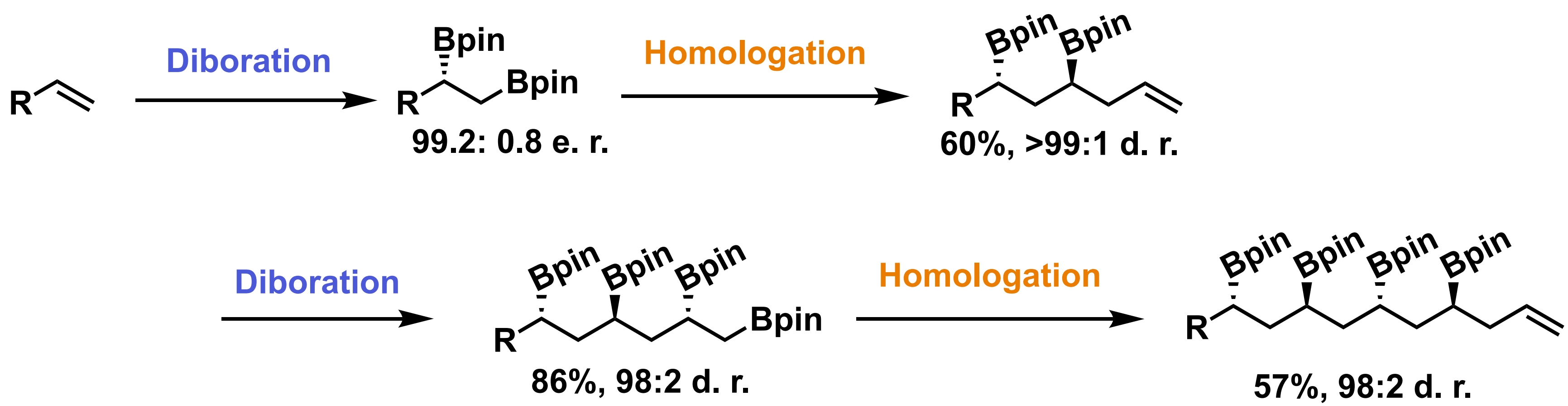
M = Li : high yields
very high enantiospecificity
enabling for forging sterically encumbered C-C bonds

M = MgCl: high yields
very high enantiospecificity
high functional-group tolerance

V. K. Aggarwal, *et al. J. Am. Chem. Soc.* **2017**, 139, 11877.

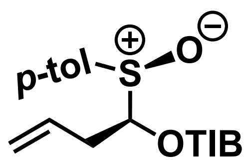
Iterative diboration and homologation

Diboration and Homologation process



Diboration: Pt(dba)$_3$, ligand, B$_2$pin$_2$, THF, 60 °C, 16 h

Homologation:



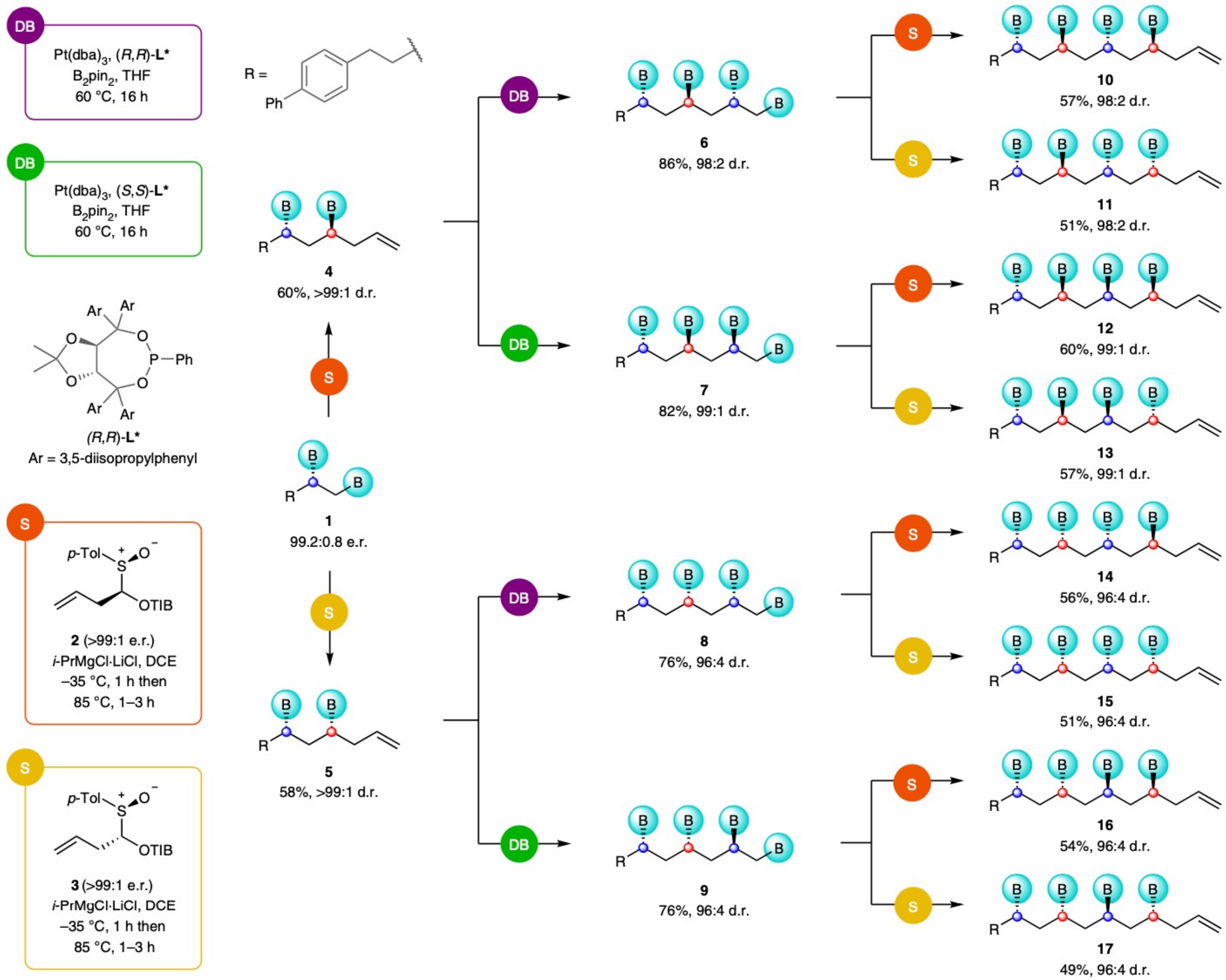
i-PrMgCl-LiCl, DCE

-35 °C, 1 h then 85 °C, 1-3 h

V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15,* 248.

Iterative diboration and homologation

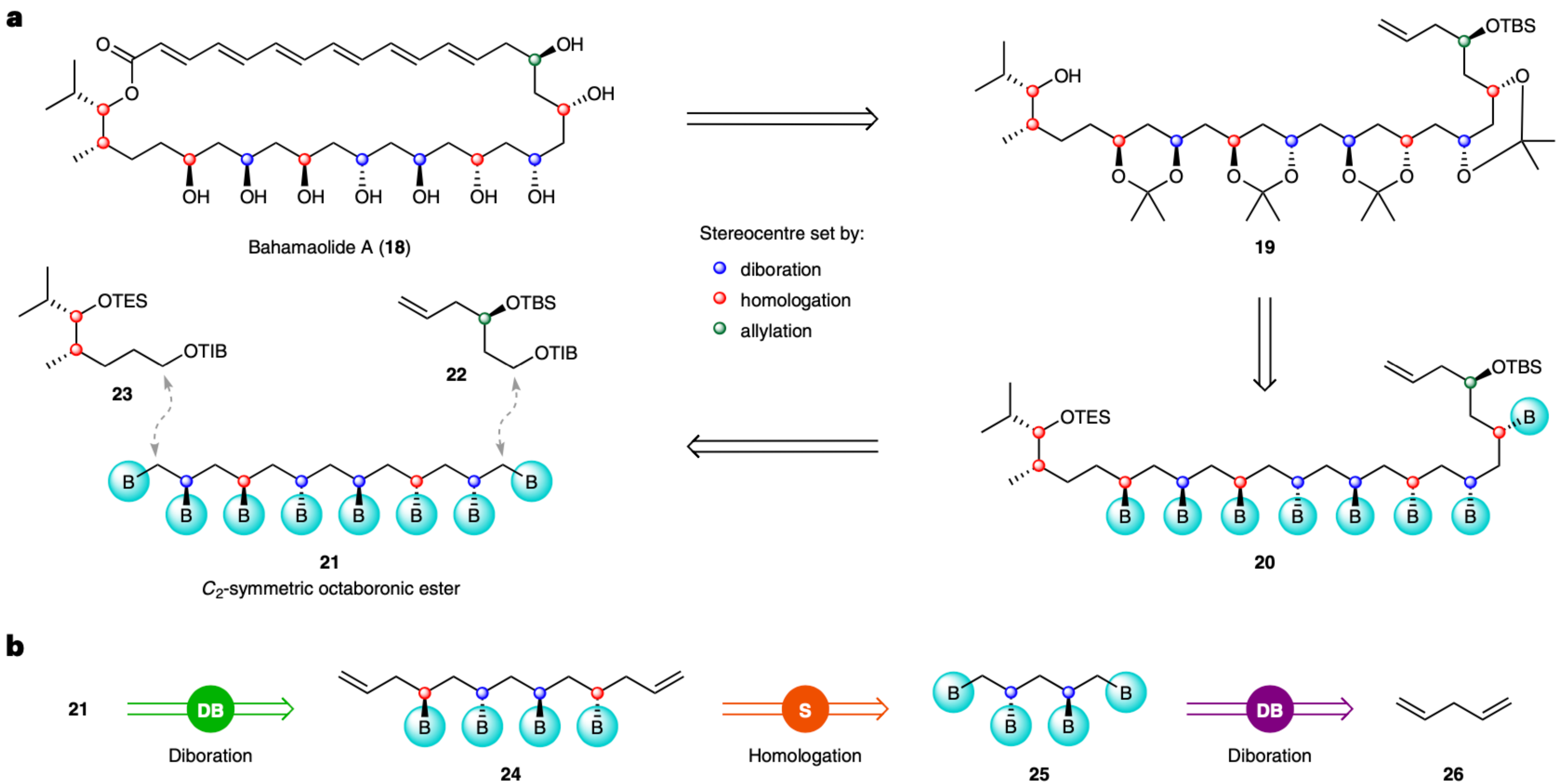
All 8 diastereomer can be formed.



V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15*, 248.

Iterative diboration and homologation

Total synthesis of bahamaolide A



V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15,* 248.

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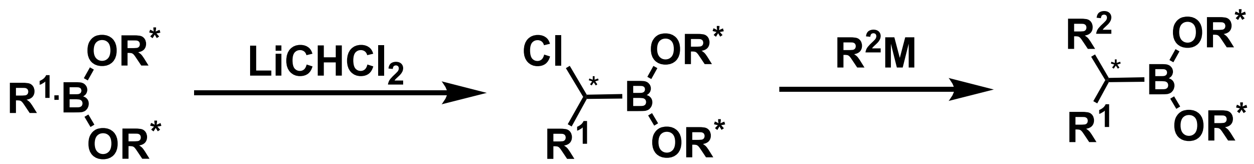
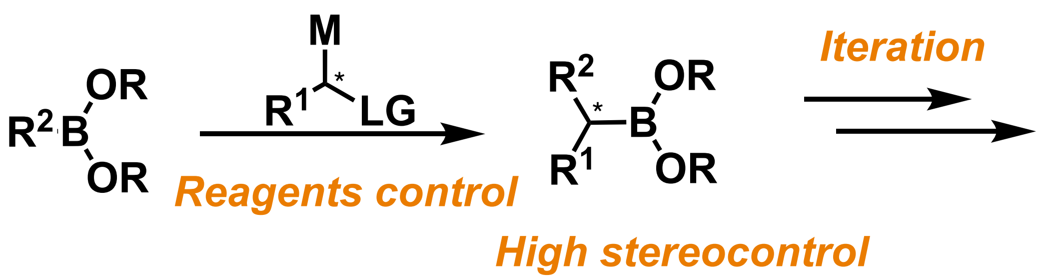
Summary

Matteson's reaction: Homologation of chiral boronic esters



Aggarwal's approach



Carbon elongation
application to 1,3-polyol etc

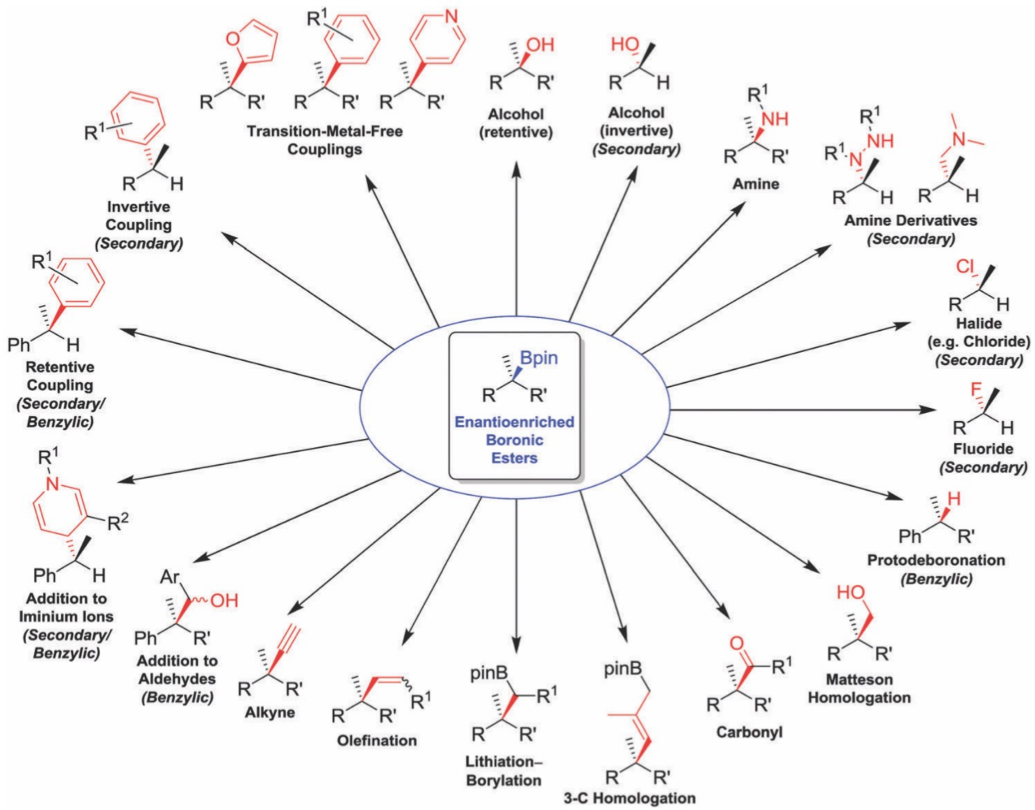
Appendix

Chiral boronic ester

Chiral boronic eater

: Significant utility in asymmetric synthesis

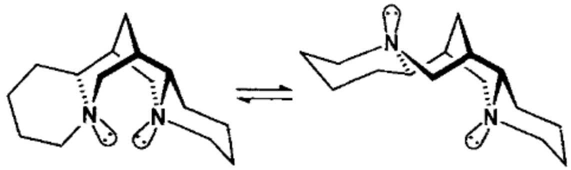
- Various ranges of stereospecific transformations into functional groups
- Easy to purify (especially; boronic acid pinacol esters)

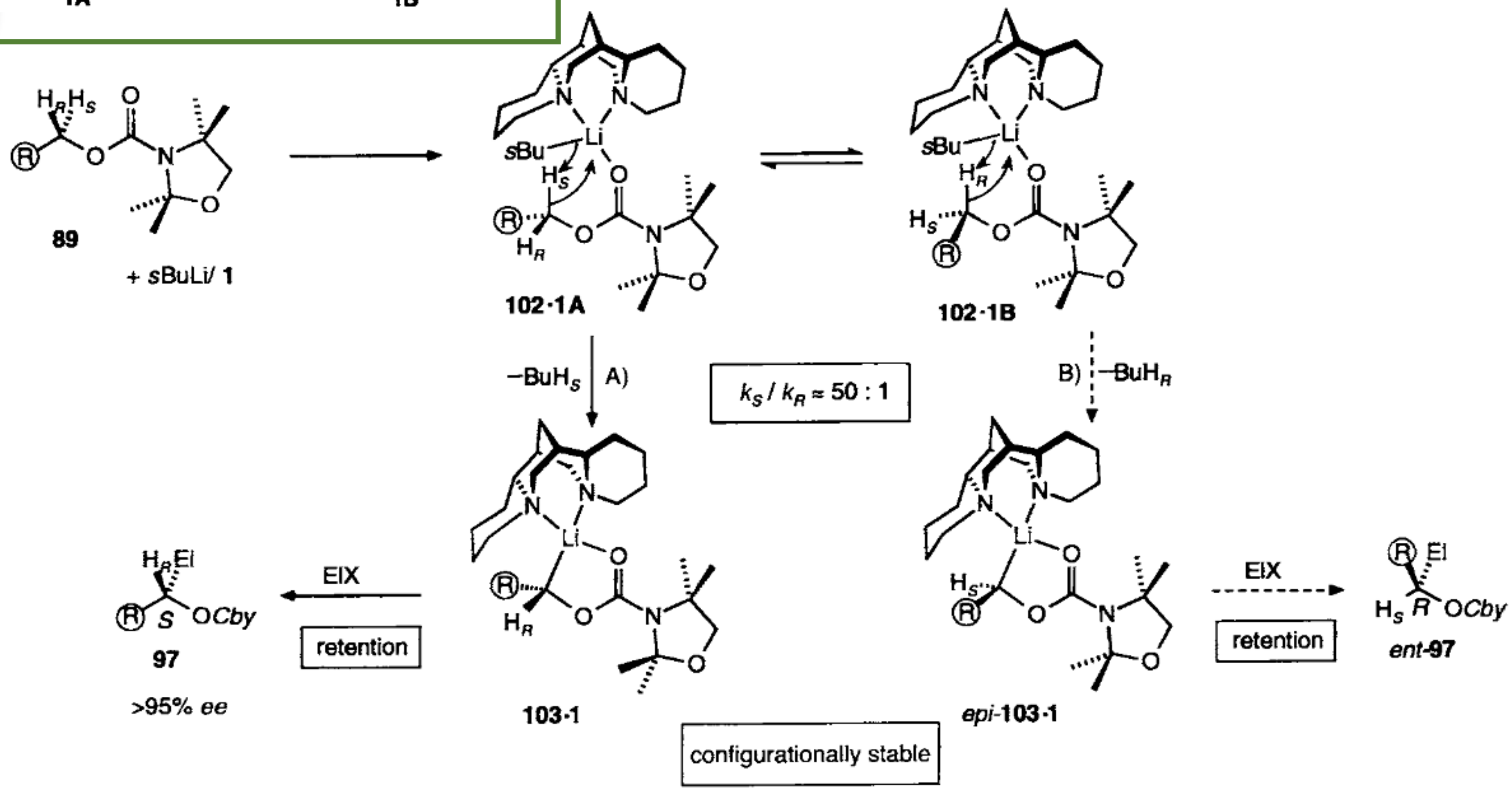


V. K. Aggarwal, *et al. Chem. Commun.* **2017**, *53*, 5481.

Chiral base

(-)-Sparteine

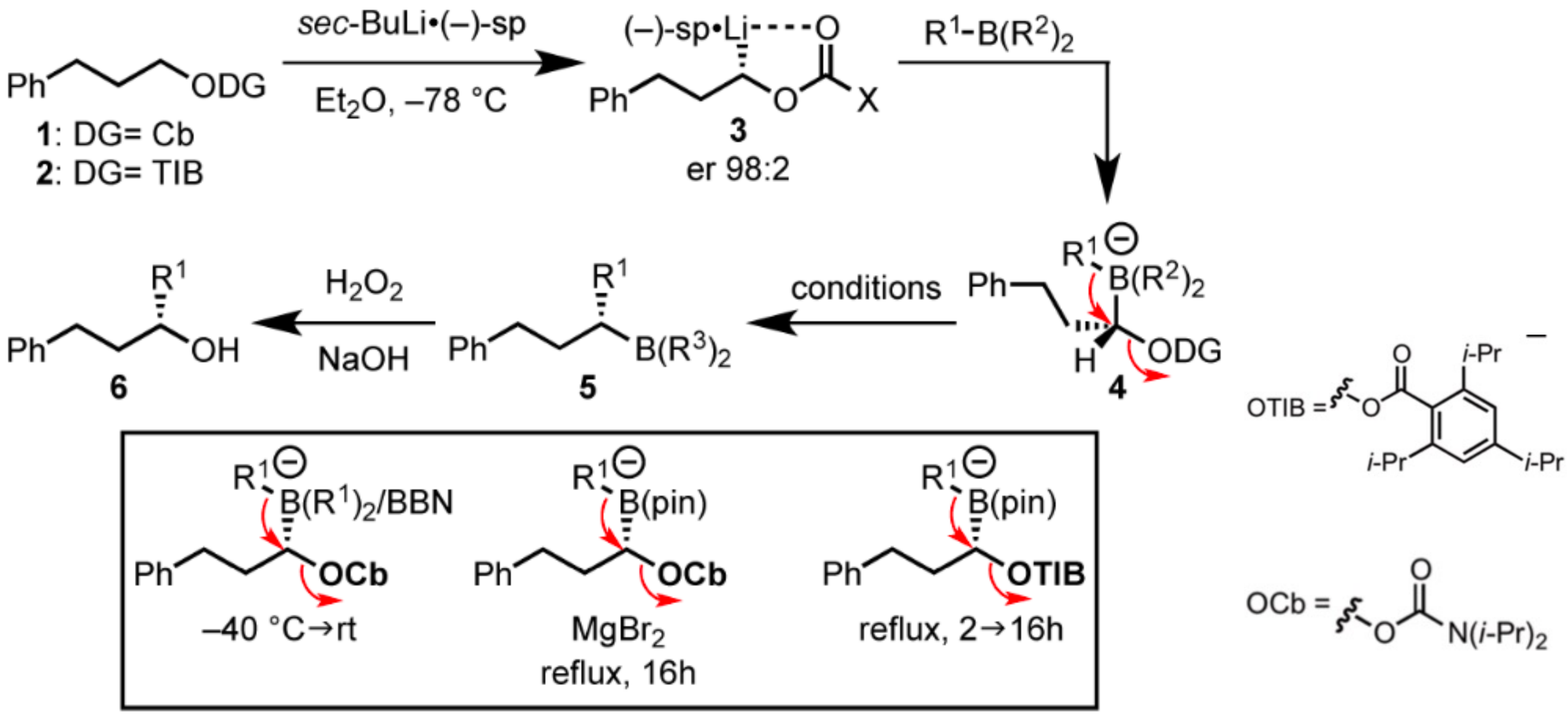




D. Hoppe, *et al. Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2282

Aggarwal's approach

Aggarwal's approach : Improve Hoppe's homologation of boronic esters



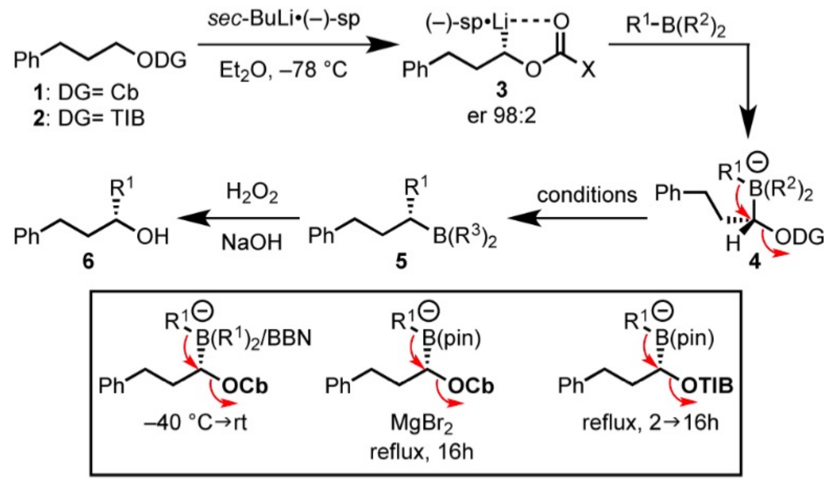
✔Improved leaving groups (OTIB)

→In fewer times under reflux without the need for Lewis acid($MgBr_2$).

V. K. Aggarwal, *et al. Acc. Chem. Res*. **2014,** *47*, 3174.

Aggarwal's approach

Aggarwal's improvement



entry	ODG	R^1	$B(R^2)_2$	T (°C), time (h)	Lewis acid	yield (%)	er
1	OCB	Et	BEt_2	−40 → rt		91	98:2
2	OCb	*i*-Pr	BBN	−40 → rt		81	98:2
3	OCb	Ph	BBN	−40 → rt		85	88:12
4	OCb	Ph	BBN	−40 → rt	$MgBr_2$	94	97:3
5	OCb	Ph	B(pin)	reflux, 16	$MgBr_2$	90	98:2
6	OCb	Et	B(pin)	reflux, 16		75	97:3
7	OCb	Me	B(pin)	reflux, 16	$MgBr_2$	50	95:5
8	OTIB	Me	B(pin)	reflux, 2		76	96:4
9	OCb	$(CH_2)_2CN$	B(pin)	reflux, 16	$MgBr_2$	0	
10	OTIB	$(CH_2)_2CN$	B(pin)	reflux, 2		46	97:3

V. K. Aggarwal, *et al. Acc. Chem. Res.* **2014,** *47,* 3174.

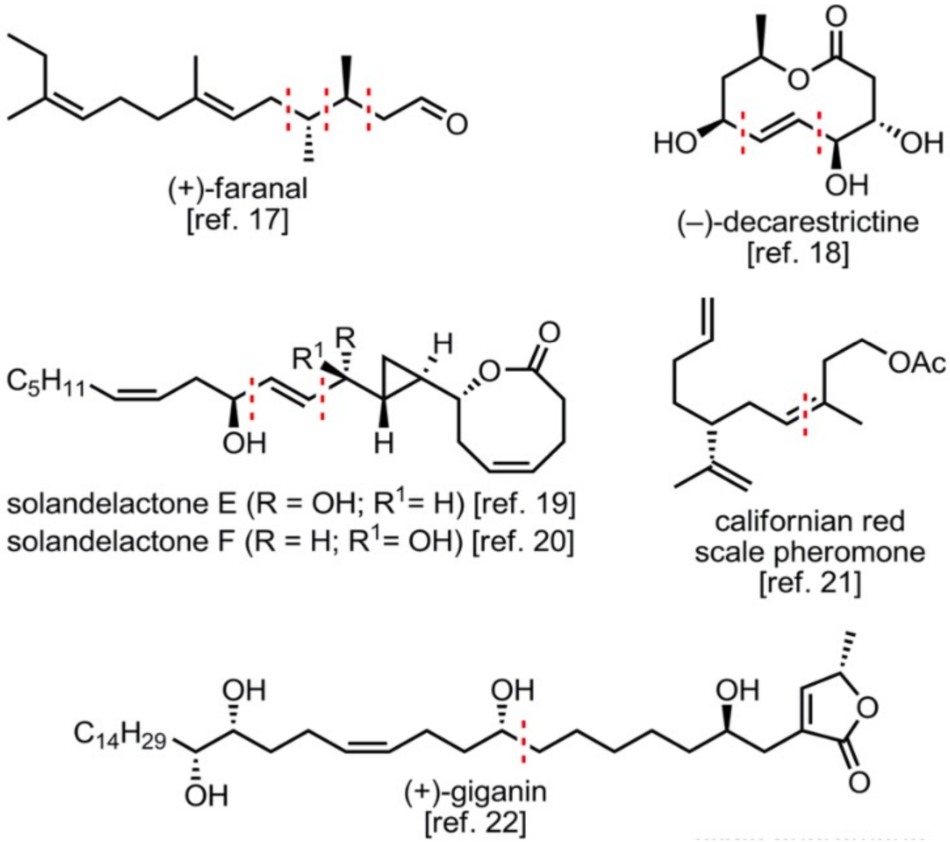
Aggarwal's approach

Application

They applied this approach to synthesis of natural products.

※ (+)-faranal challenges: Its carbon chain containing adjacent methyl groups

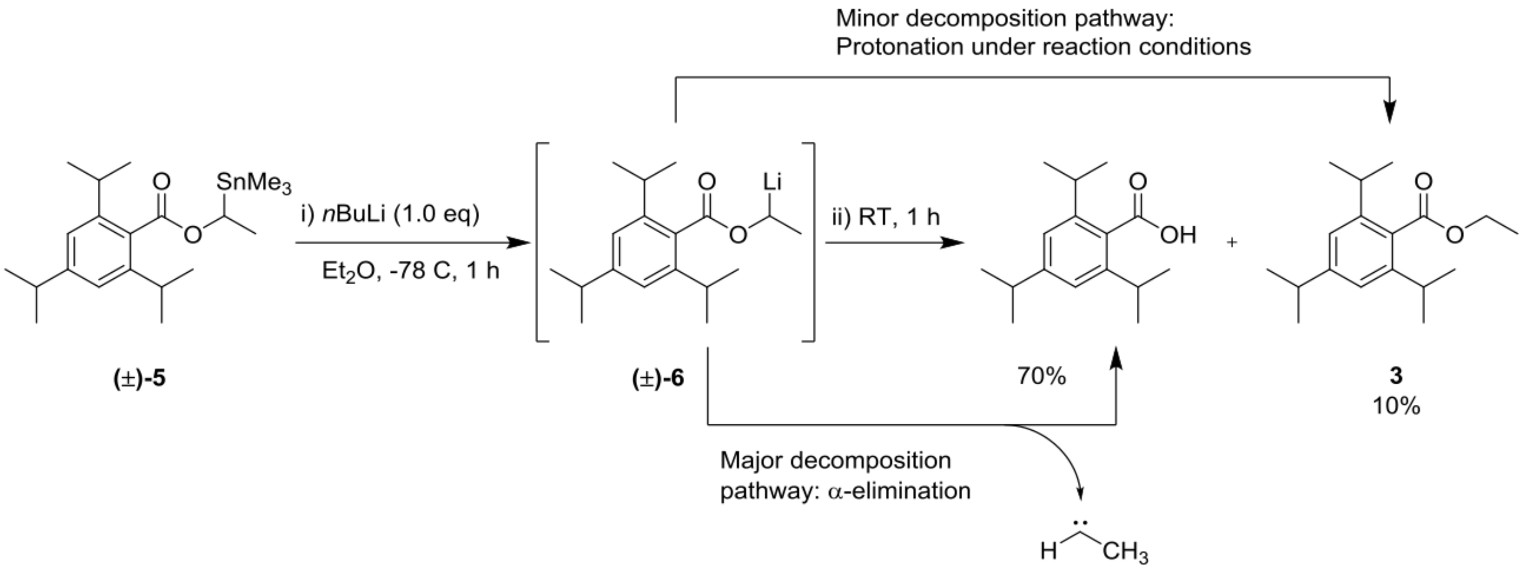
→only 6 steps.



V. K. Aggarwal, *et al. Acc. Chem. Res.* **2014,** *47,* 3174.

Aggarwal's iterative homologation

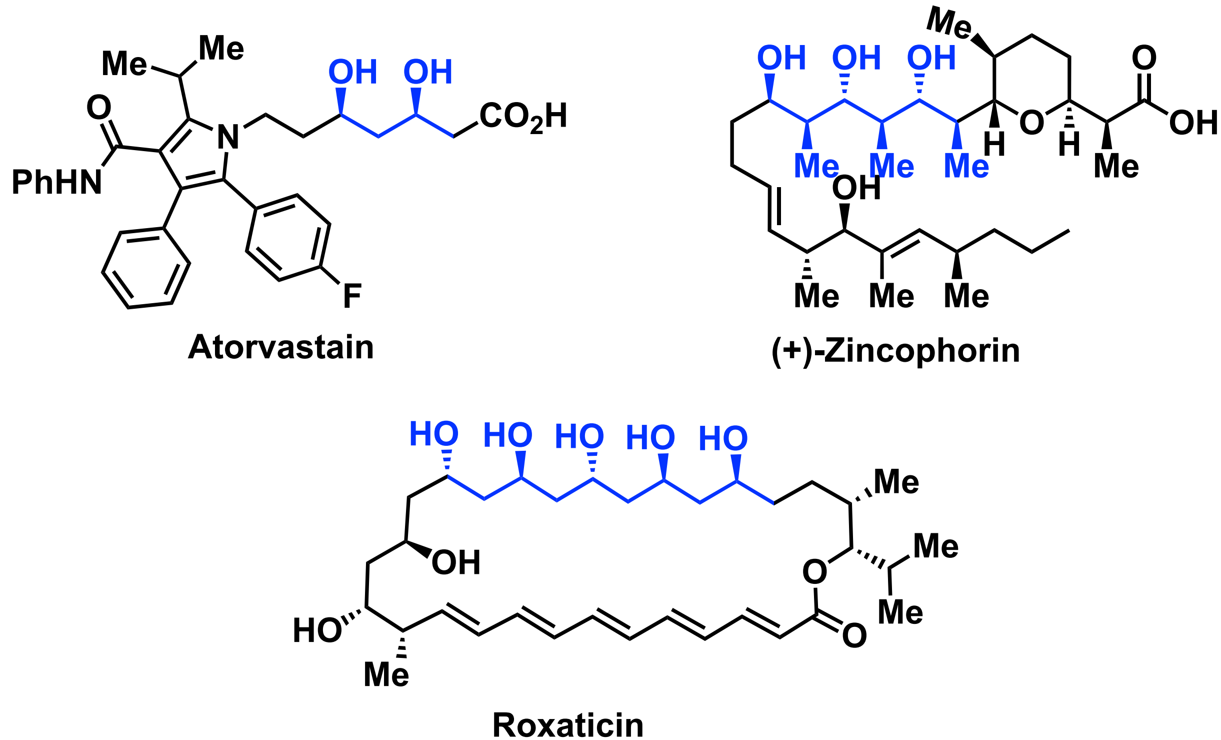
Decomposition of lithiated carbenoid



V. K. Aggarwal, *et al. Nature* **2014,** *513,* 183.

1,3-polyols

1,3-polyols are common structure in polyketides.



Polyketides are top-selling of small molecule drugs and have strong drug activity.

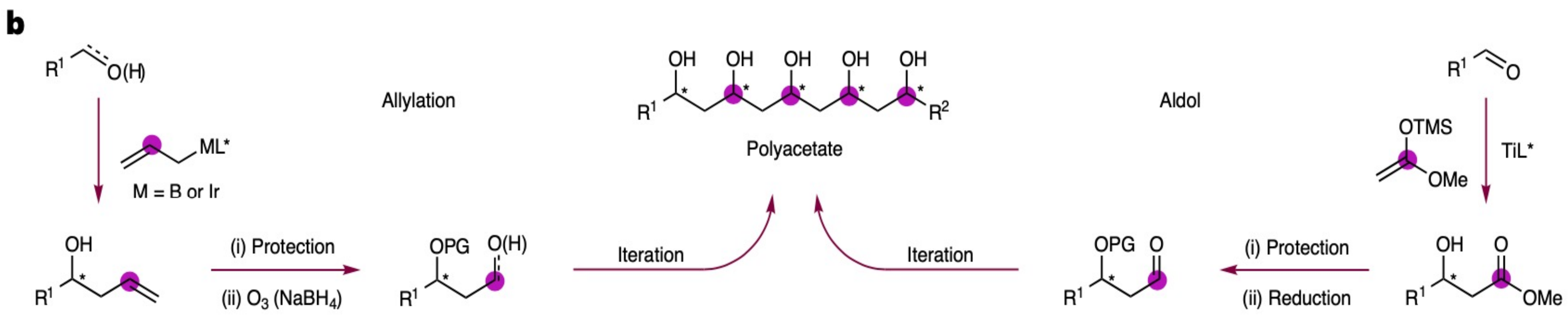
→1,3-polyols synthesis is important.

A. M. P. Koskinen, *et al. Chem. Soc. Rev.* **2005**, *34,* 677.

1,3-polyols

Conventional 1,3-polyols synthesis

Aldol reaction and allylation



✖ Require protection and deprotection

→Take multiple steps for carbon unit elongation and much waste.

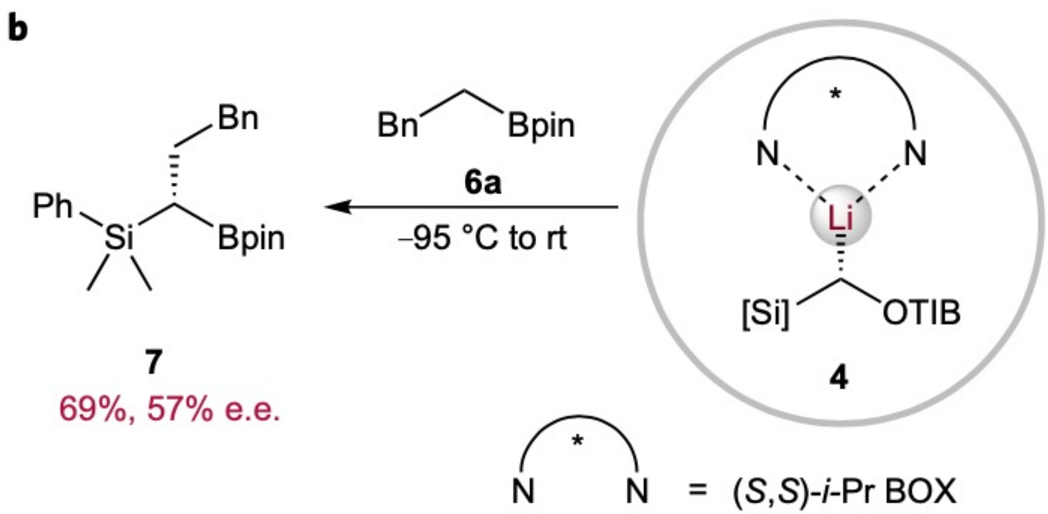
V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15,* 248.

Using silyl groups for iterative homologation

<u>Identifying a suitable organosilyl lithiated reagent for the homologation</u>

- Blackmore's silylmethyllithium carbenoid bearing chiral ligand

(chiral ligand: isopropyl-substituted bis(oxazoline)(BOX)ligand)



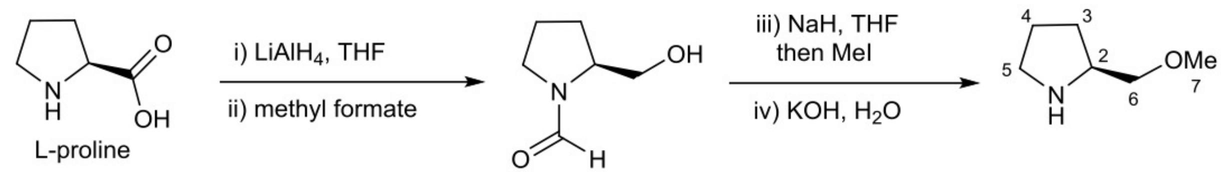
✖ Moderate e. e. & yields

V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

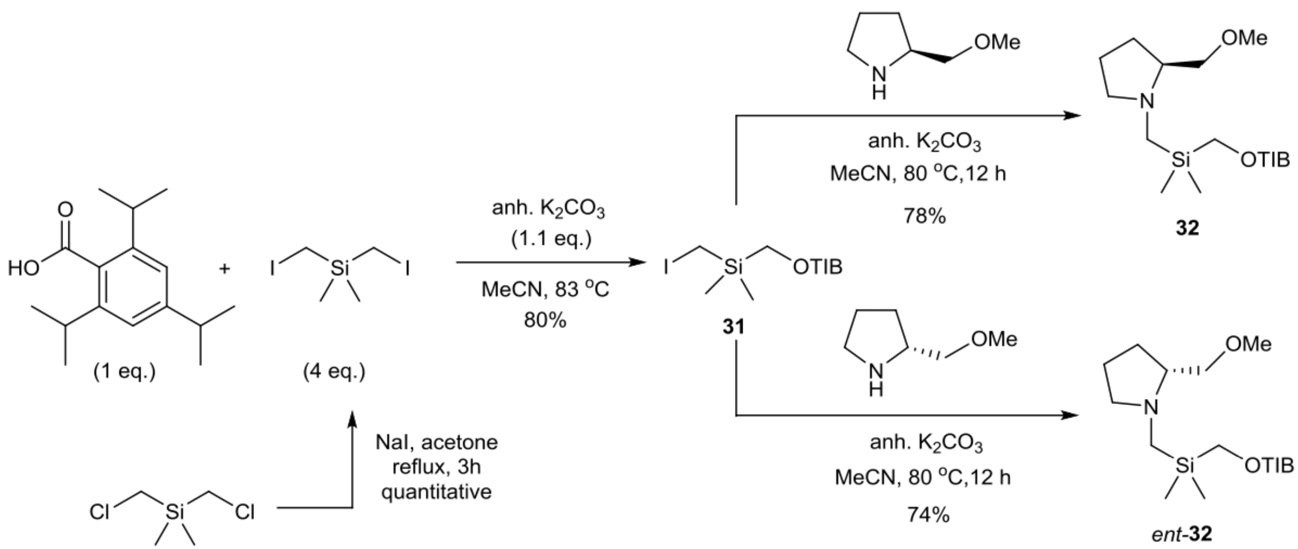
Using silyl groups for iterative homologation

<u>Generating Chen's lithiated benzyl silane bearing chiral pyrrolidinomethyl</u>

4.1 Synthesis of (*S*)-2-(methoxymethyl)pyrrolidine[13,14]



4.2 Synthesis of chiral α-silyl benzoate ester (32)

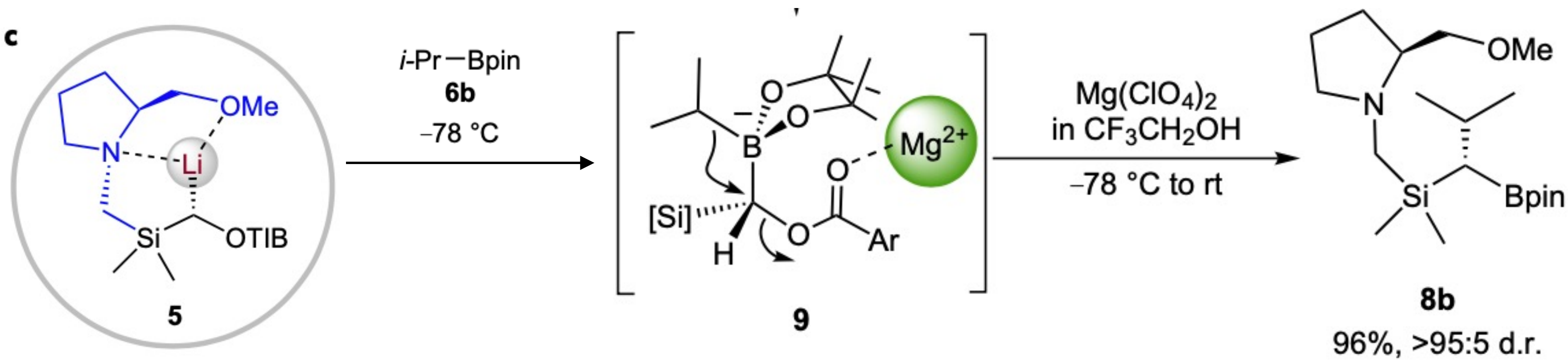


V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

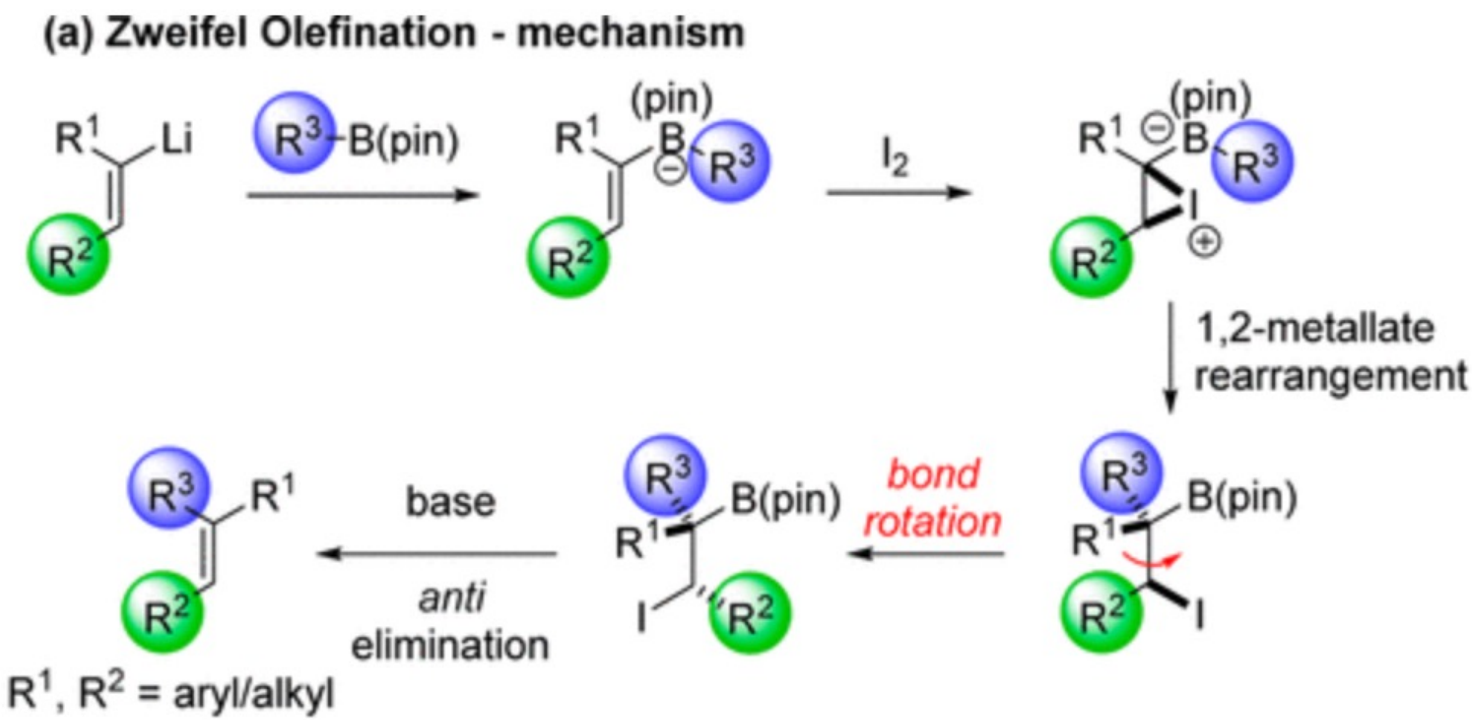
lithiation-borylation homologation didn't proceed with the more hindered boronic ester under the same conditions.

→Additives $Mg(ClO_4)_2$ in CF_3CH_2OH promote the reaction.



V. K. Aggarwal, *et al. Nat. Chem.* **2017,** *9,* 896.

Using silyl groups for iterative homologation

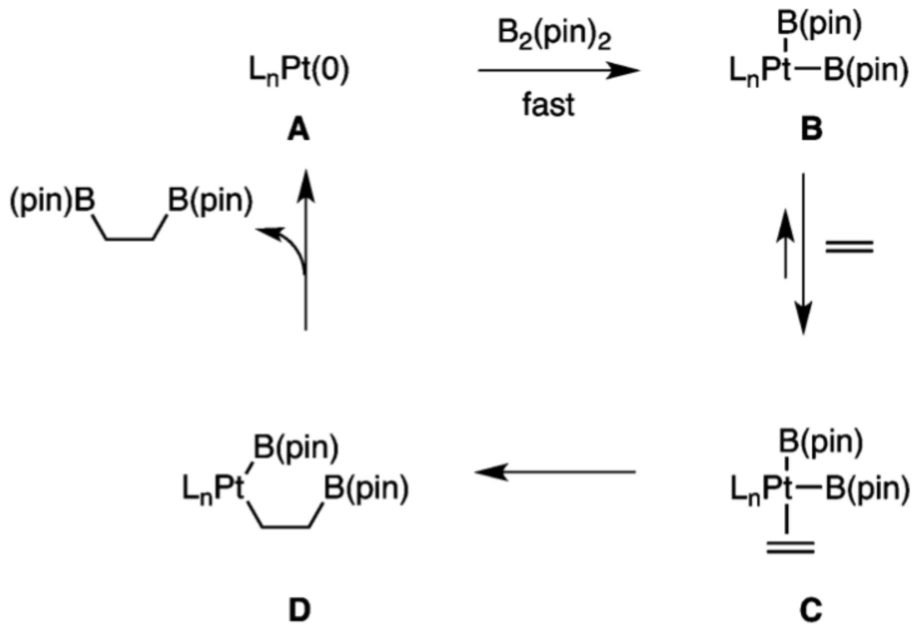


V. K. Aggarwal, *et al. Org. Lett.* **2017**, *19, 10*, 2762

Iterative diboration and homologation

Diboration of terminal alkene

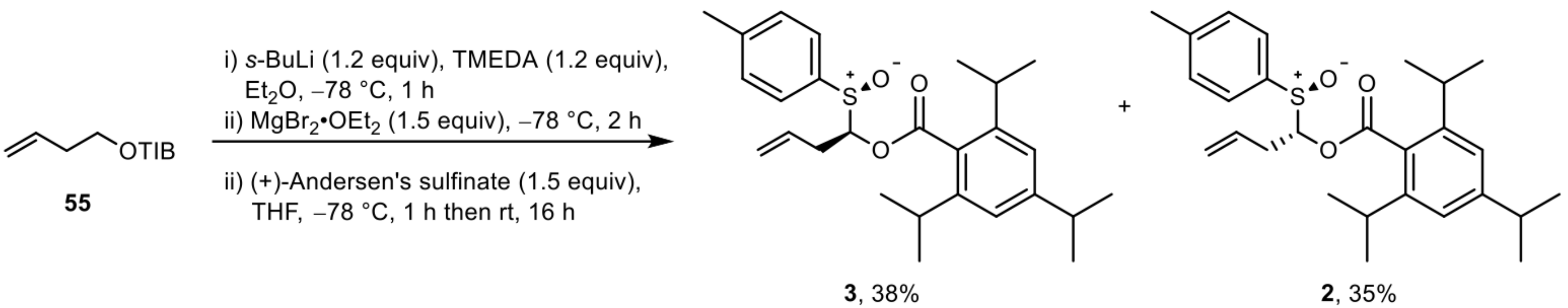
Scheme 4



J. P. Morken, *et al. J. Am. Chem. Soc.* **2013**, 135, 11222.

Iterative diboration and homologation

Preparation of α-sulfinylbutenyl benzoate



V. K. Aggarwal, *et al. Nat. Chem.* **2023,** *15,* 248.