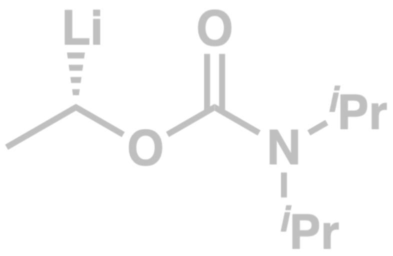
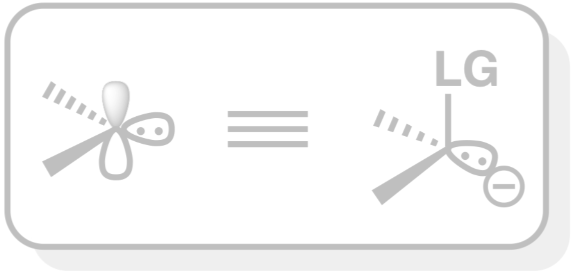
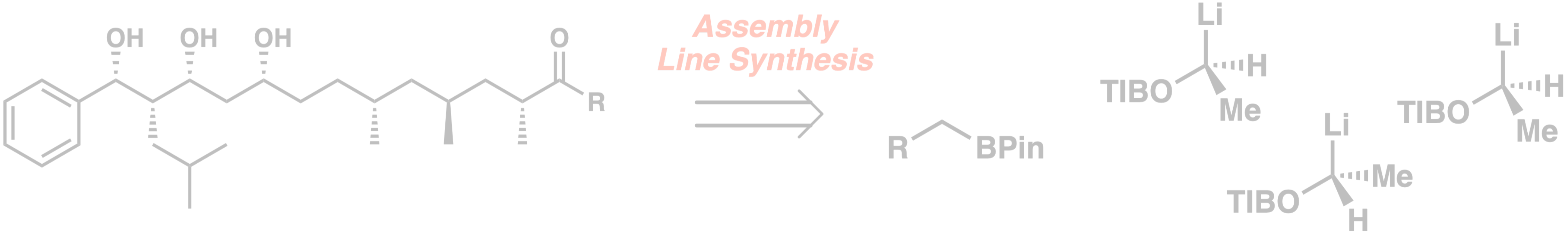




Borane/Carbenoid Homologation: Varinder Aggarwal's Contributions

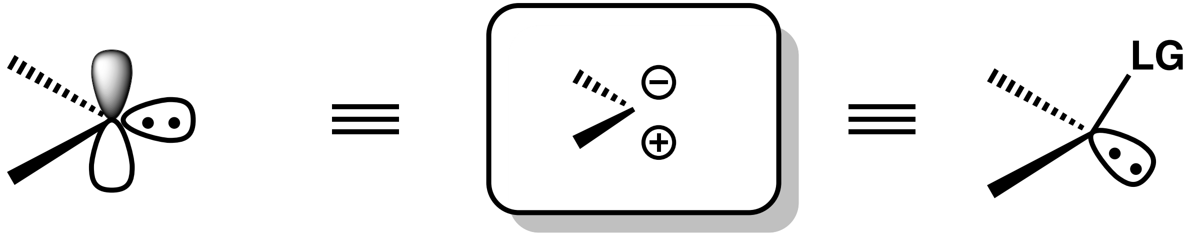
Jordan Dotson

September 29, 2021



Carbenes and Carbenoids

True Carbene

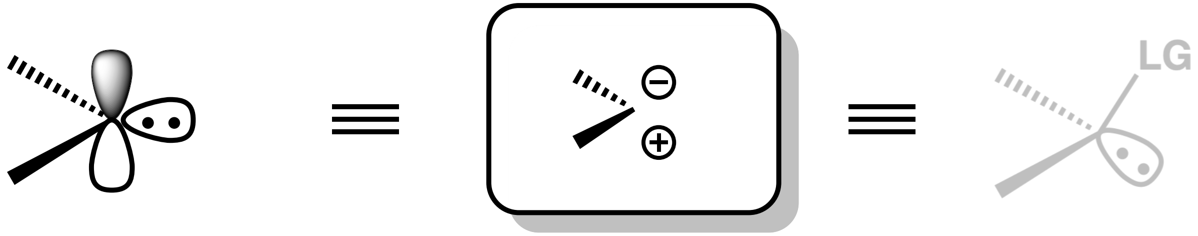


Carbenoid

A synthon with simultaneous nucleophilic and electrophilic characteristics

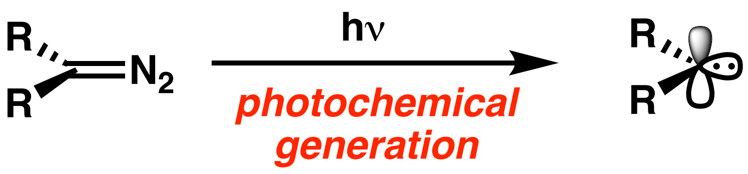
Carbenes and Carbenoids

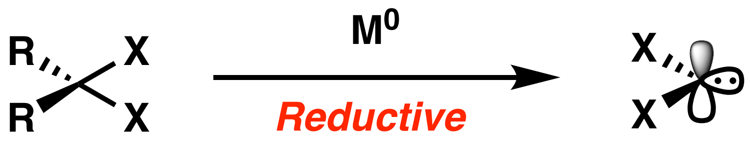
True Carbene



Carbenoid

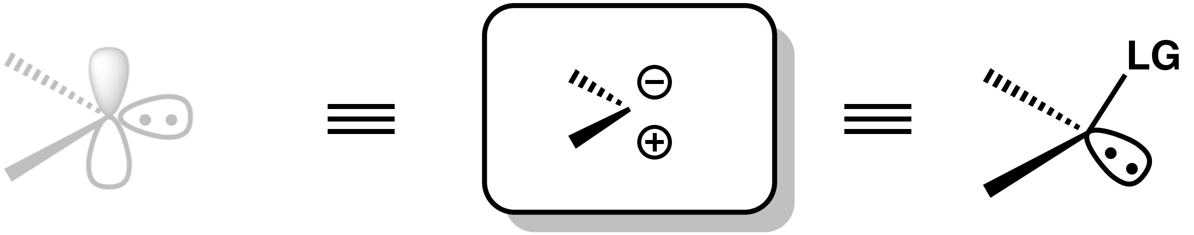
A synthon with simultaneous nucleophilic and electrophilic characteristics





Carbenes and Carbenoids

True Carbene



Carbenoid

A synthon with simultaneous nucleophilic and electrophilic characteristics

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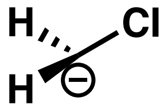
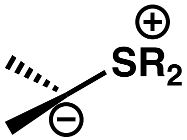
- *If leaving group is only modest, α-elimination will not take place*

- *Carbene reactivity will take place stepwise, with nucleophilic attack typically taking place first*

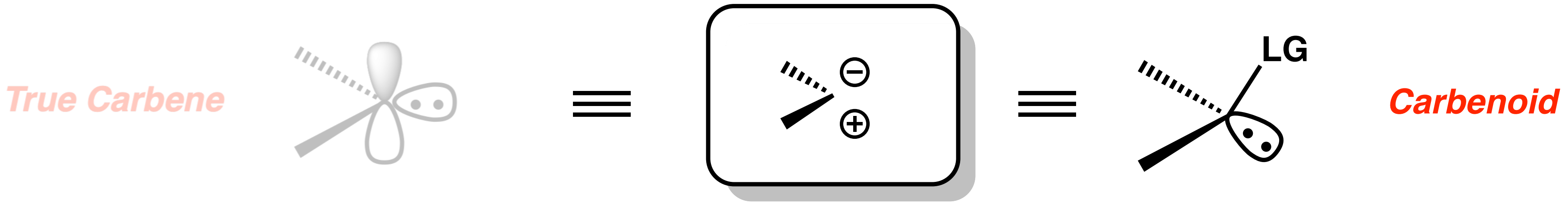


α-chloro metalates



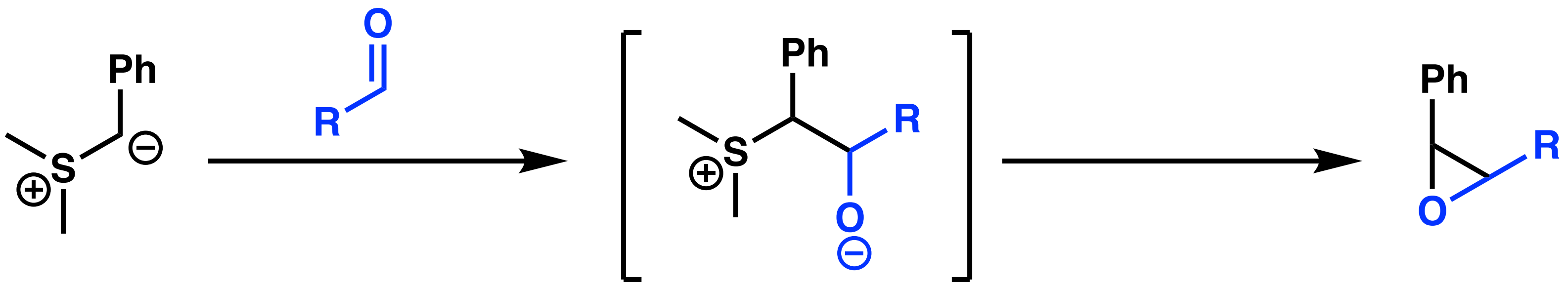
Sulfur Ylides

Carbenes and Carbenoids



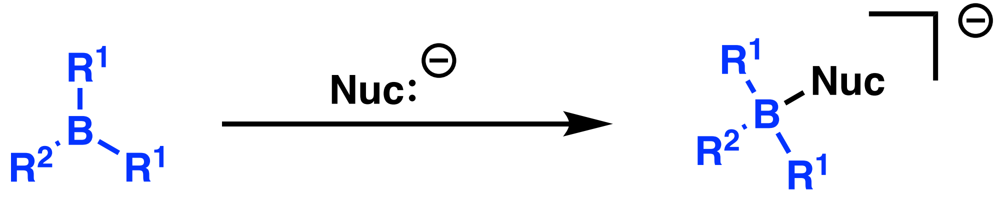
A synthon with simultaneous nucleophilic
and electrophilic characteristics

Example of stepwise reactivity: Corey-Chaykovsky epoxidation



Complimentary Reactivity: Boranes/Boronic Esters

· *Boranes/ boronic esters display Lewis acidity initially but are converted into good nucleophiles uppon addition of a nucleophile*

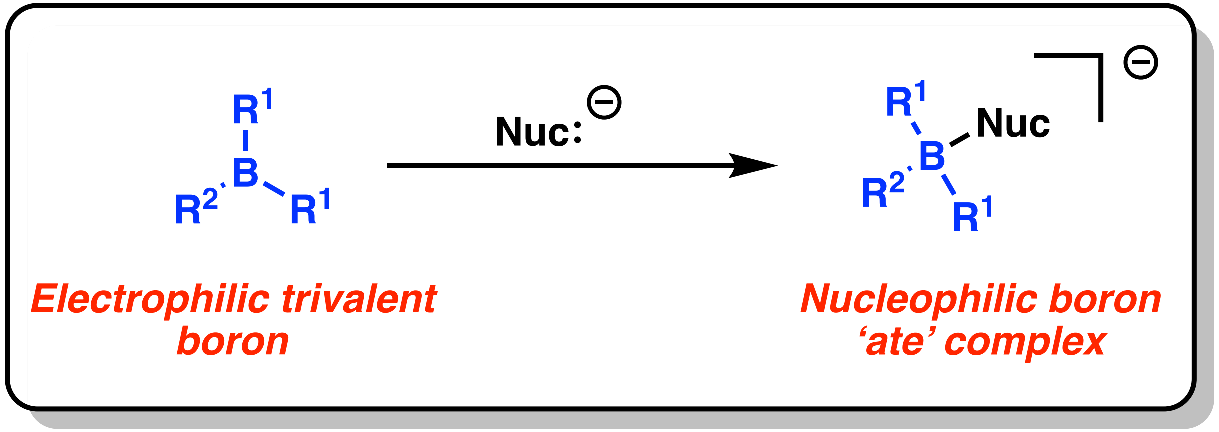


Electrophilic trivalent boron

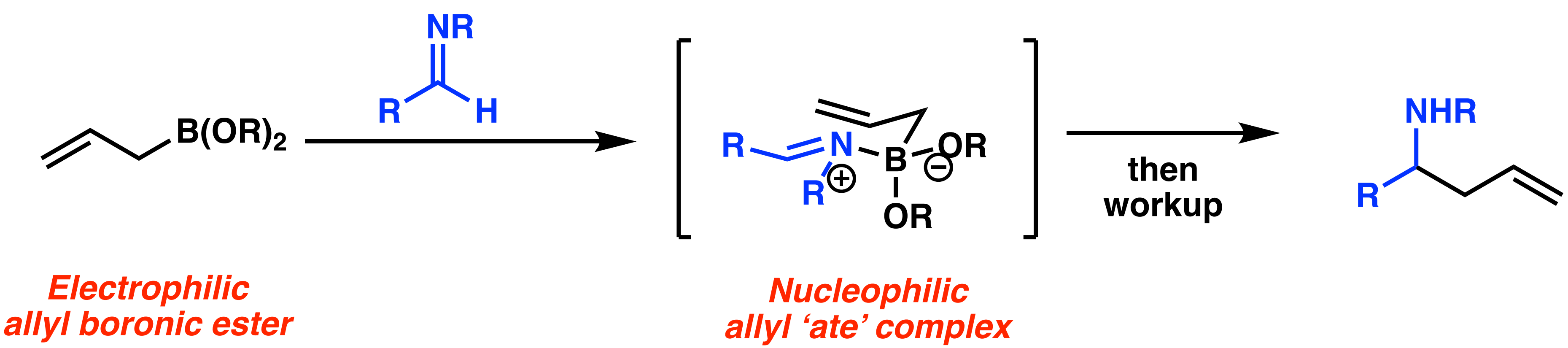
Nucleophilic boron 'ate' complex

Complimentary Reactivity: Boranes/Boronic Esters

· *Boranes/ boronic esters display Lewis acidity initially but are converted into good nucleophiles uppon addition of a nucleophile*

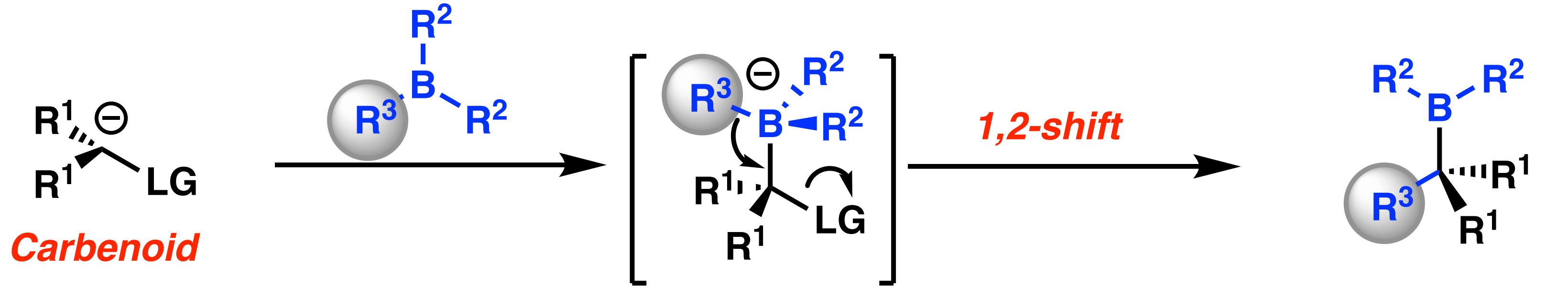


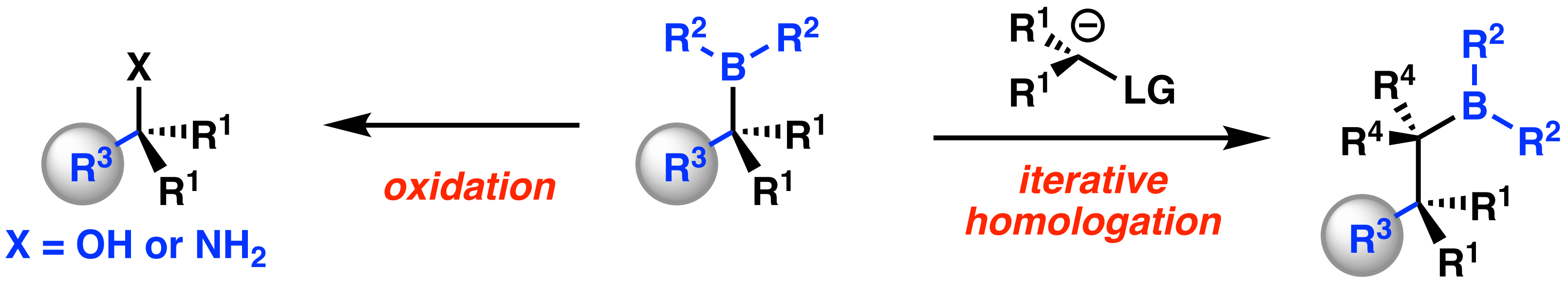
One such example: The Petasis Reaction



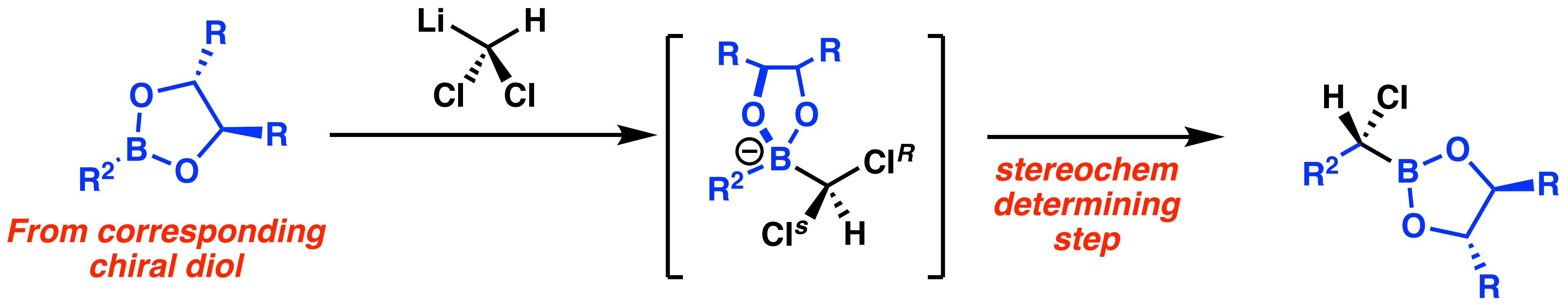
Carbenoid-Borane Synergy

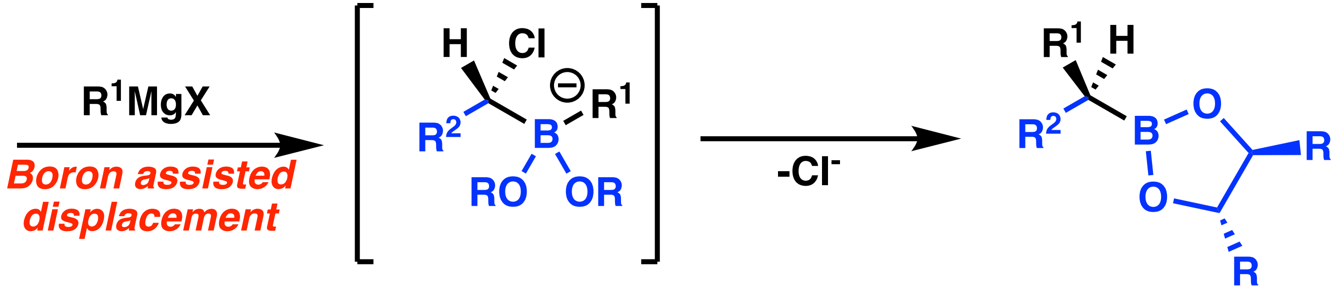
Carbenoid-Borane Synergy





Carbenoid-Borane Synergy: Matteson Homologation



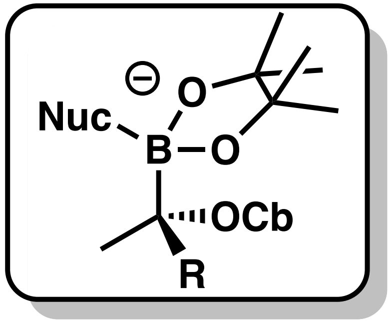


· Powerful methodology

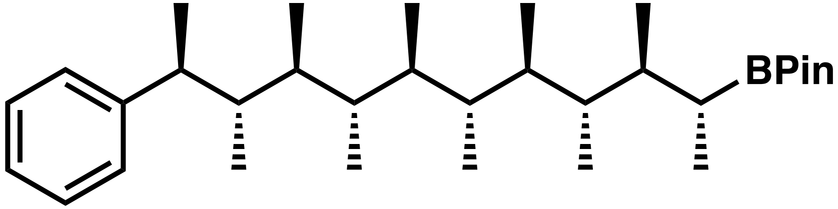
· Stereochemistry is substrate controlled

<u>Varinder Aggarwal</u>

· **Early Career**
· **Contributions to borane/carbenoid chemistry**

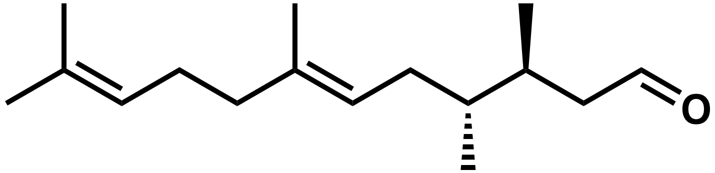


Angew. Chem. Int. Ed. **2007**, *46*, 7491.
Nature, **2008**, *456*, 778.
Org. Lett. **2017**, *19*, 2762.



Assembly Line Synthesis

Nature, **2014**, *513*, 183.



(+) Faranal

Angew. Chem. Int. Ed, **2009**, *48*, 6317.

Varinder Aggarwal

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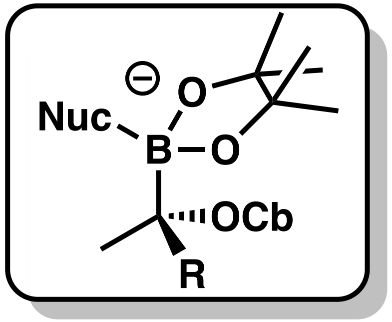
· Contributions to borane/carbenoid chemistry



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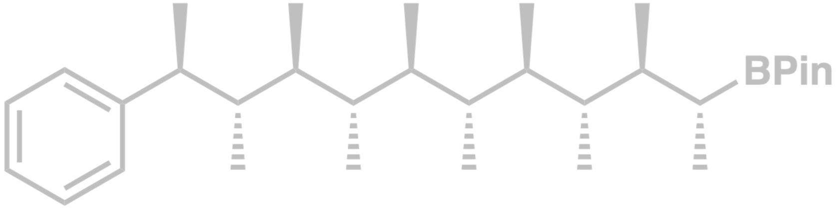

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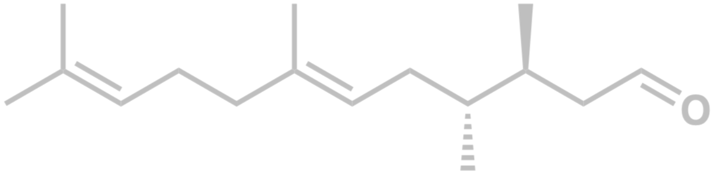
Nature, **2014**, *513*, 183.



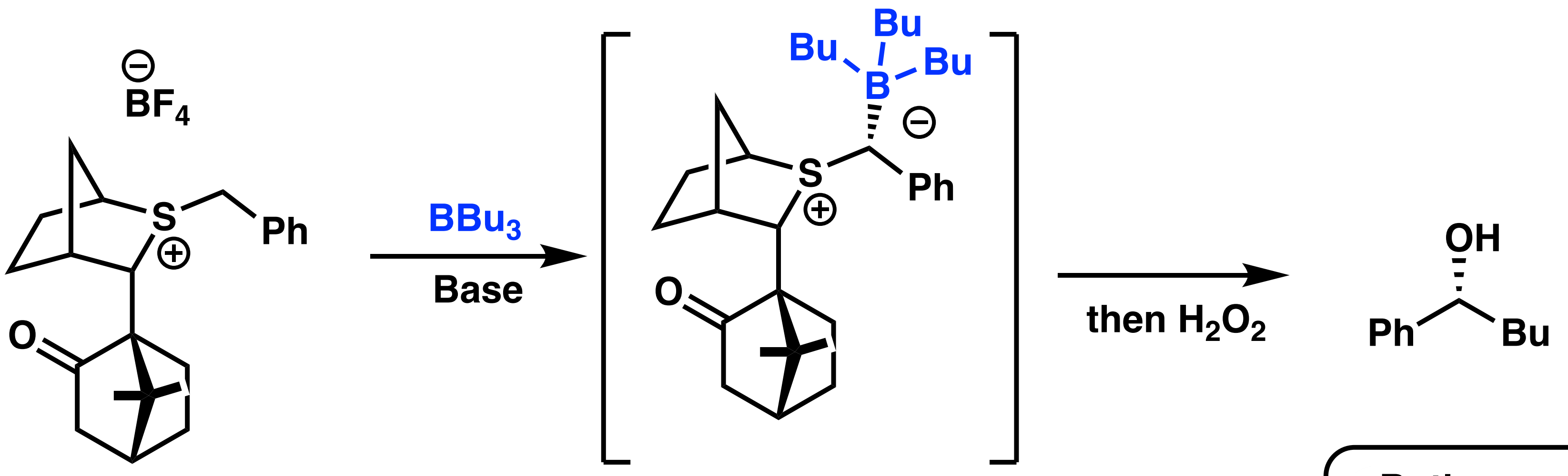
(+) Faranal

Angew. Chem. Int. Ed, **2009**, *48*, 6317.

Varinder Aggarwal

- Born in Kalyanpur, India
- B.S. (1983) University of Cambridge
- Ph.D. in Chemistry under Stuart Warren at University of Cambridge (1986)
- Post Doc under Gilbert Stork at Columbia (1986-1988)
- University of Bath (1988-91)
- University of Sheffield (1991-2000)
- University of Bristol (2000-present)

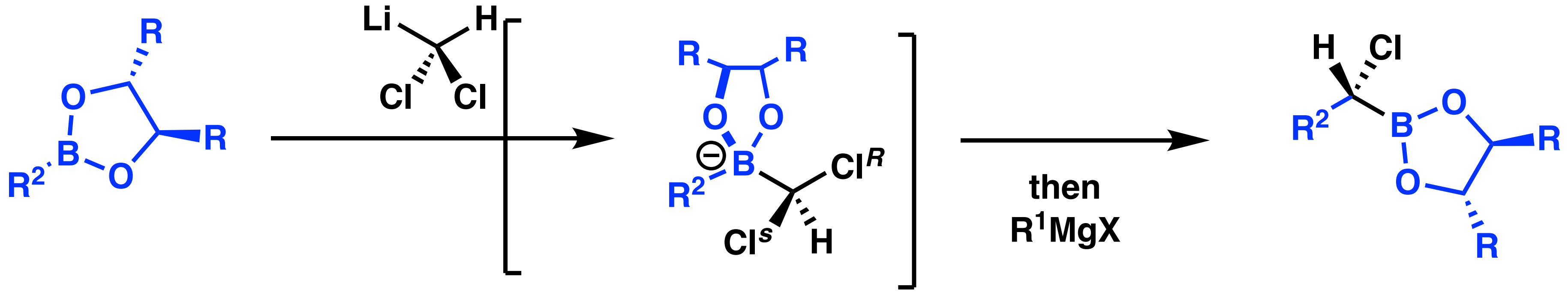
Borane homologation with carbenes



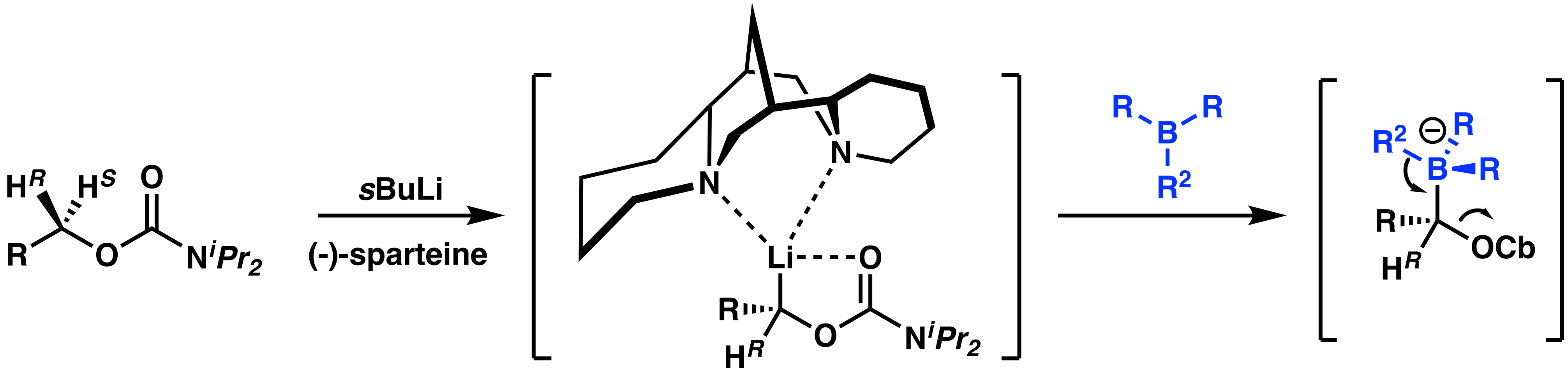
Fang, G. Y.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2005**, *127*, 1642.

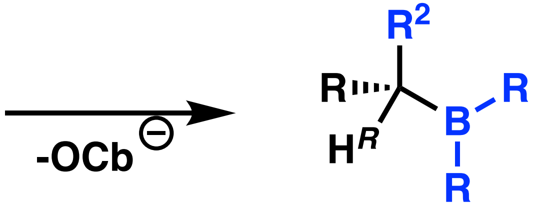
- Both use an "auxiliary" to control stereochemistry
- An alternative but not really a large improvement on Matteson's work

Remember Matteson Homologation...



Breakthrough: Noncovalent stereoinduction of carbenoid



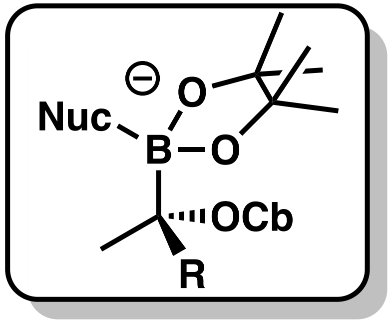


- Use of Hoppe type lithiation here is a breakthrough
- Noncovalent control allows for either configuration to be accessed reliably
- α-lithiocarbamates are exceptionally configurationally stable due to Li—O coordination

Stymiest, J. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7491.

Varinder Aggarwal

· Early Career
· Contributions to borane/carbenoid chemistry



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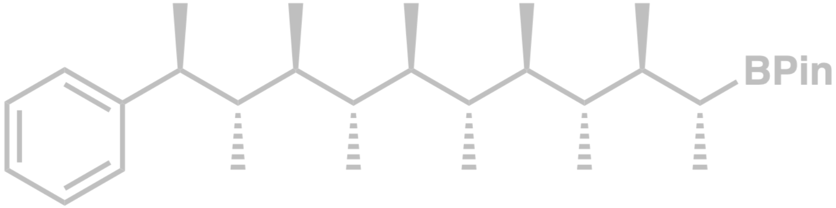

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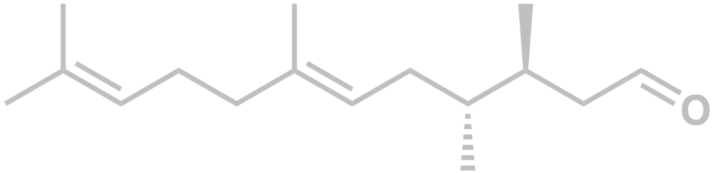

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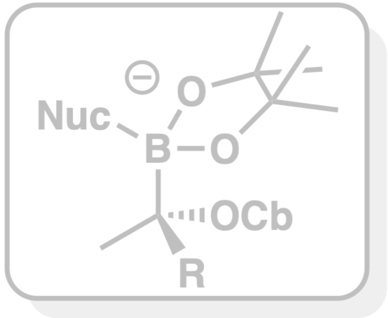

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Nature, **2008**, *456*, 778.
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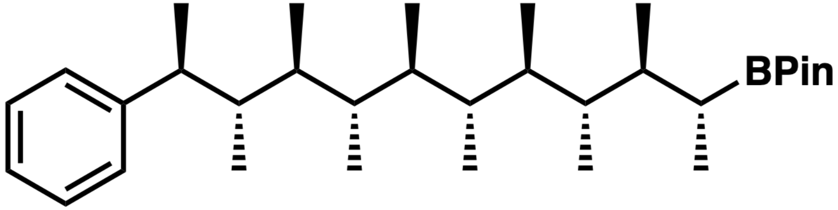

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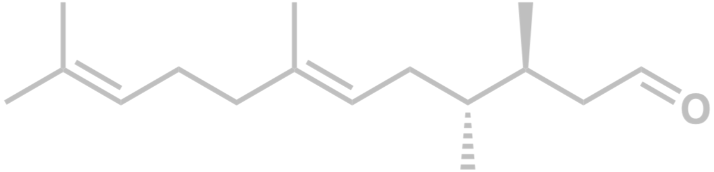
Nature, **2014**, *513*, 183.

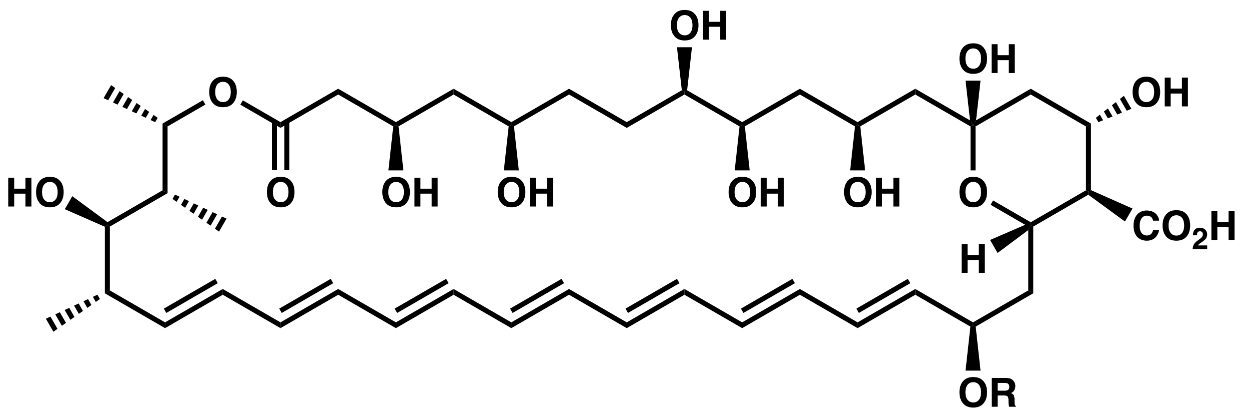


(+) Faranal

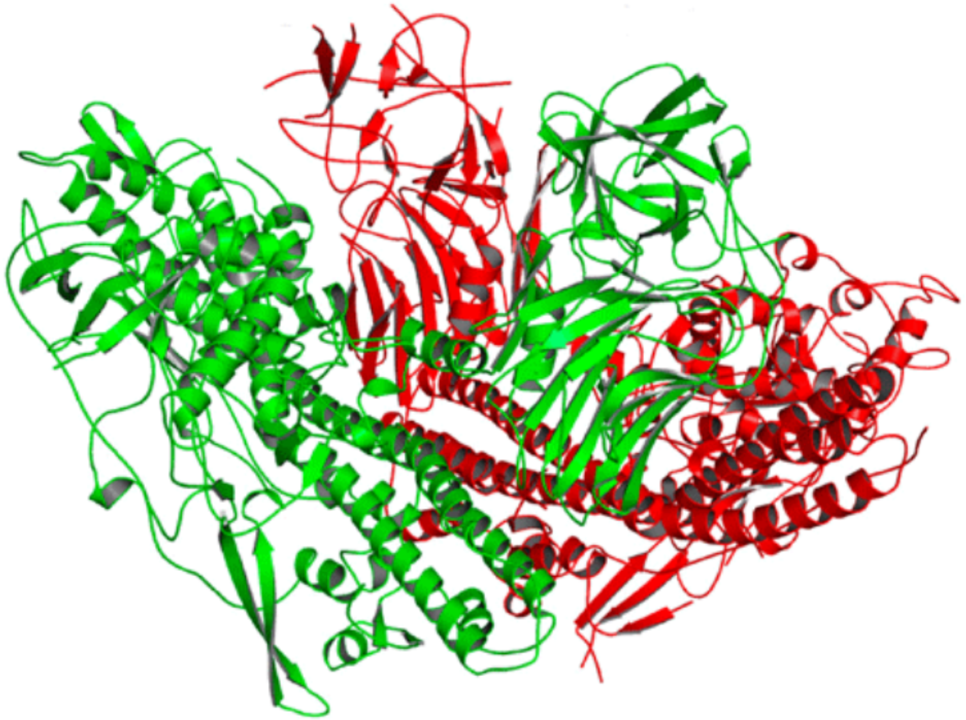
Angew. Chem. Int. Ed, **2009**, *48*, 6317.

Assembly line synthesis: Nature's Strategy

- Protein synthesis uses iterative amide bond formation
- Iterative C-C bond forming strategies are used in polyketide natural products
- Repeated structural motifs enforce conformation and function



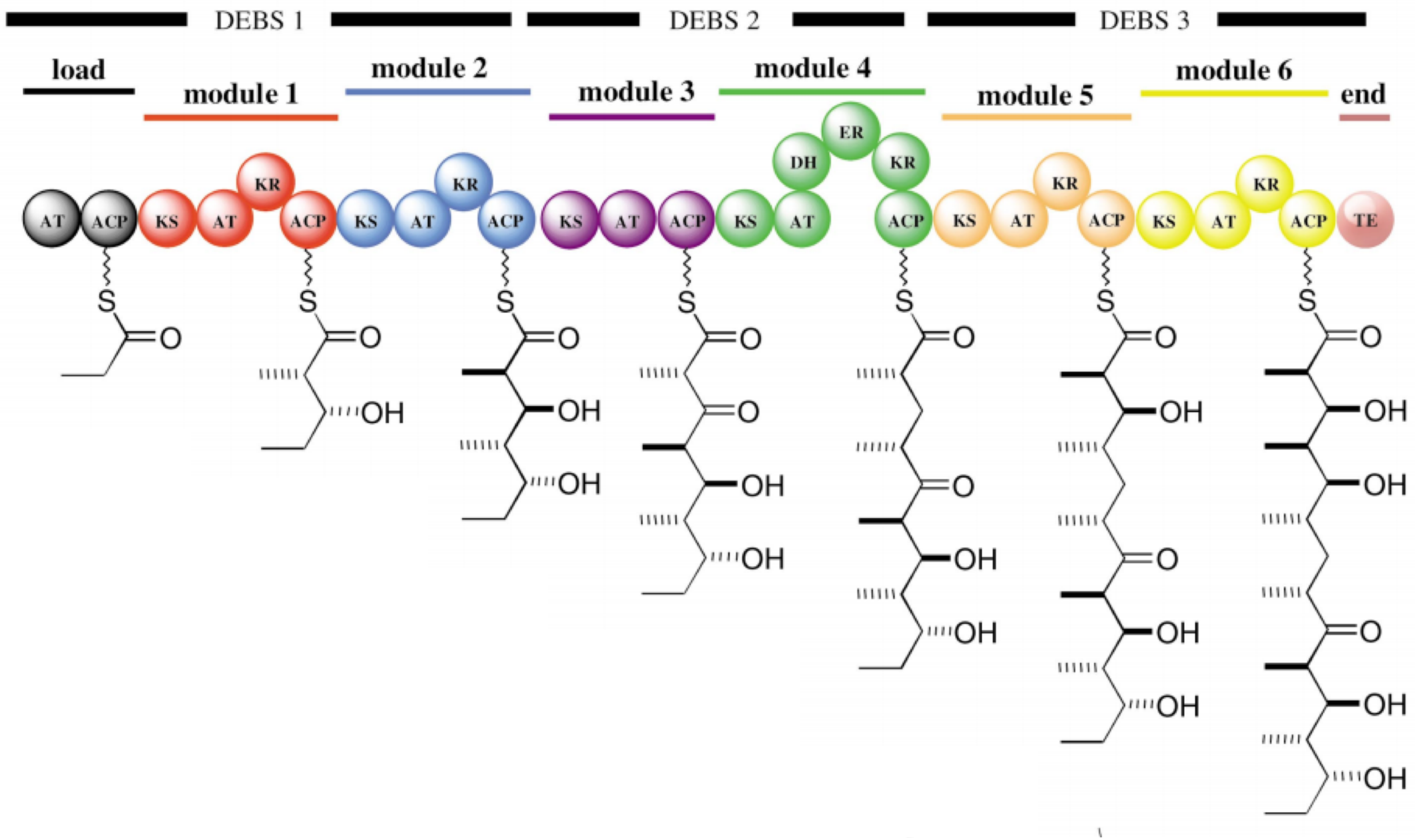
Amphotericin B
Polyketide Natural Product

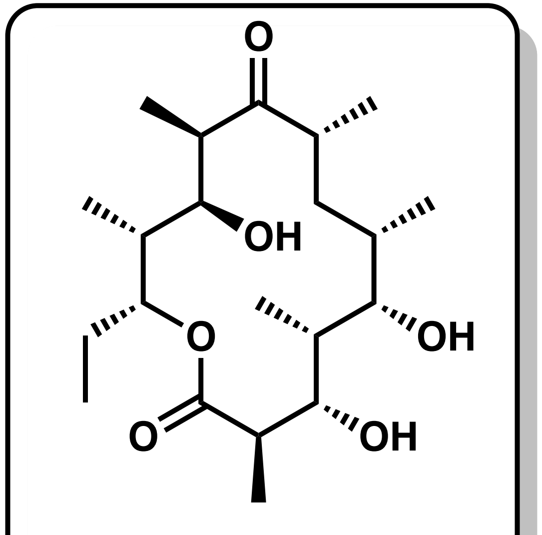


Botulinum Toxin
Polypeptide

Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.

Assembly line synthesis: Nature's Strategy

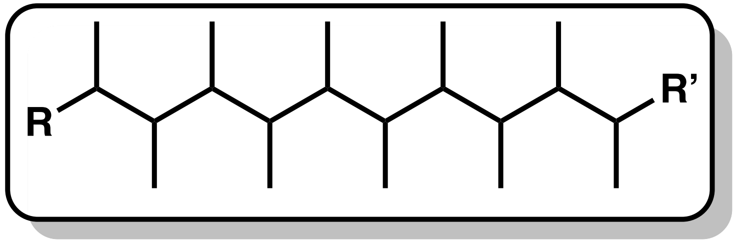




6-Deoxyerythronolide B

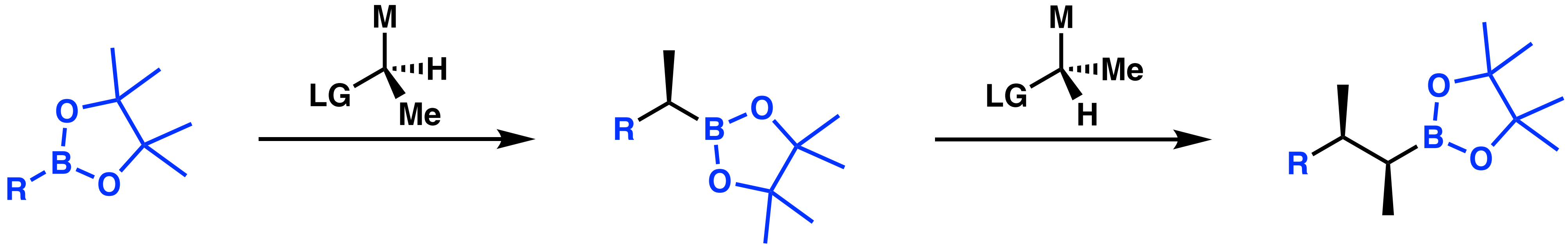
Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380.

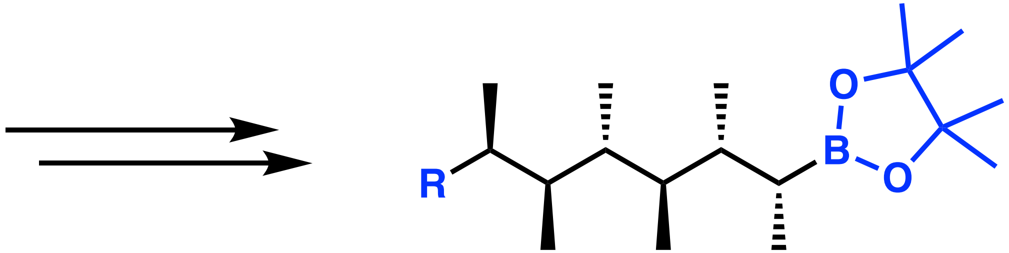
Biomimetic access to non-natural products



· What conformational behavior could be invoked in solution and in the solid state?

· This was previously thought to be an impossible motif to construct in a stereochemically controlled way

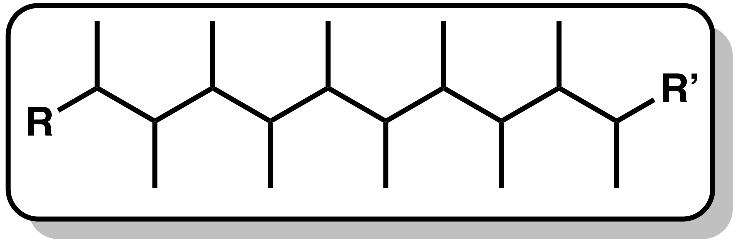




Reagent control allows complete control of the relative and absolute stereochemistry of each individual carbon

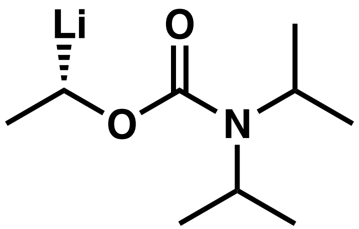
Burns, M.; Essafi, S.; Aggarwal, V. K. *Nature* **2014**, *513*, 183.

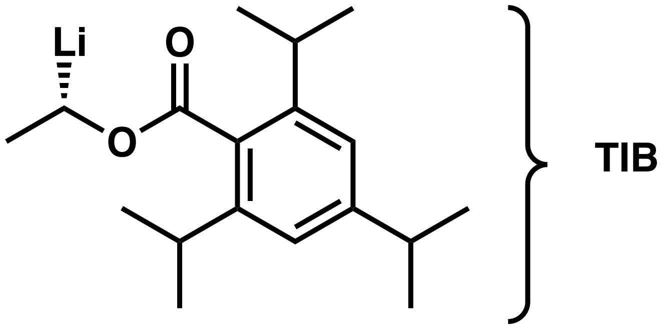
Biomimetic access to non-natural products



Problem #1: Overhomologation of boronic ester

· a 98:1:1 product: no reaction: overhomologation ratio would lead to 18% difficult to separate impurities after 10 iterations





· Carbenoid is too reactive

· 1,2-metallate shift will take place —78 °C, and allow overhomologation

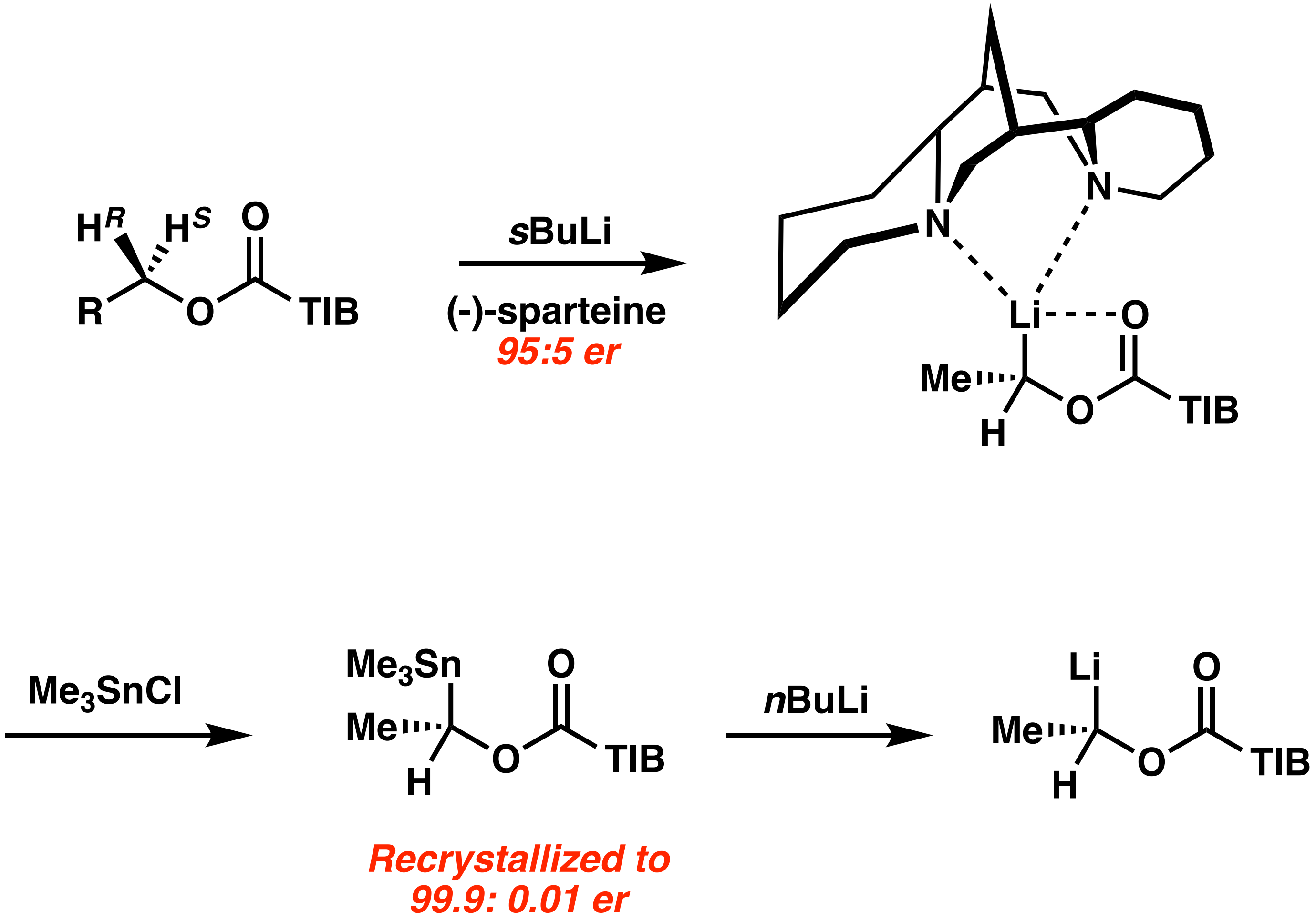
· Benzoate carbenoid has attenuated reactivity

· 1,2-metallate shift will only take place after warming to rt

Burns, M.; Essafi, S.; Aggarwal, V. K. *Nature* **2014**, *513*, 183.

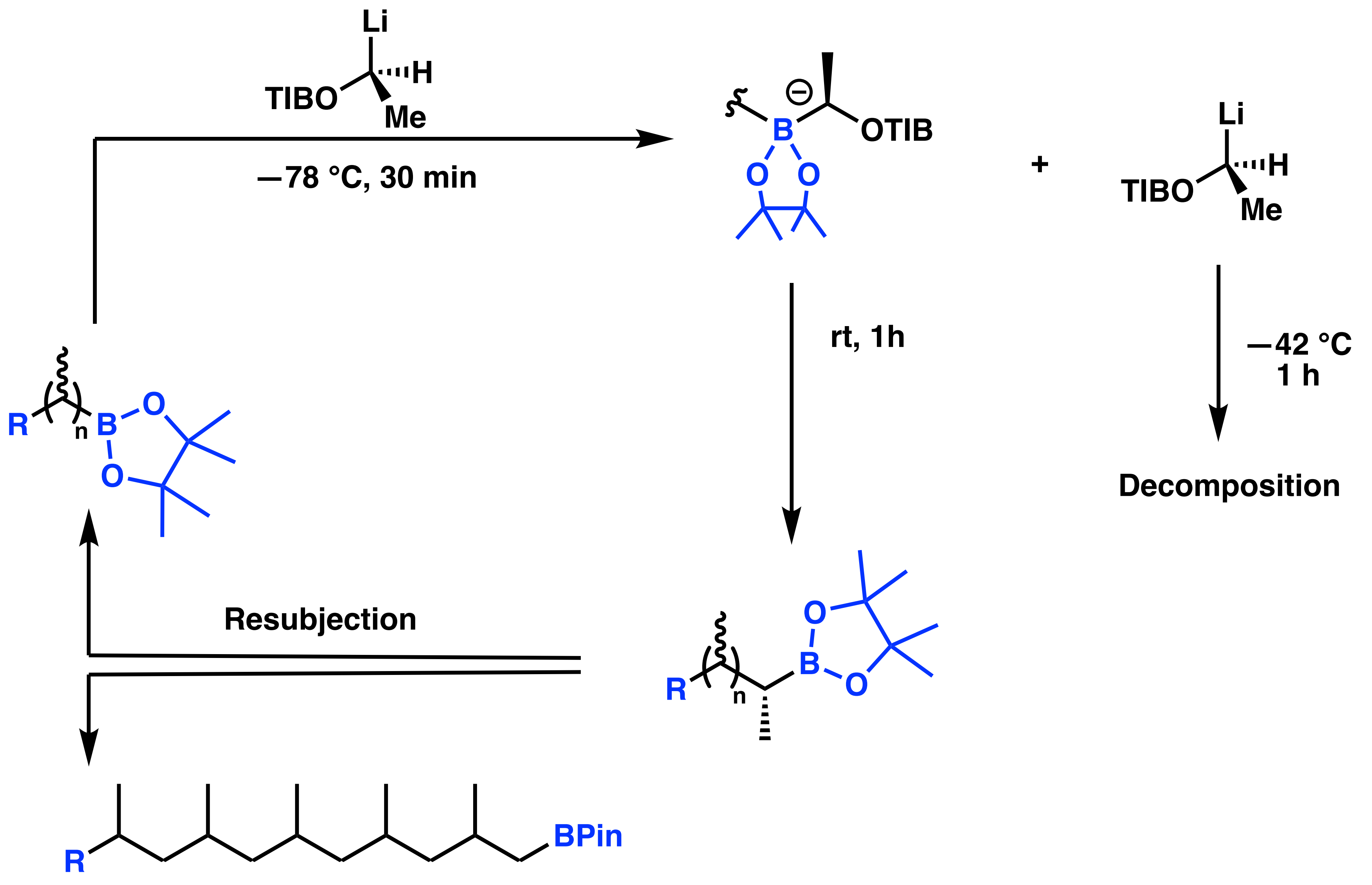
Biomimetic access to non-natural products

Problem #2: Stereochemical control

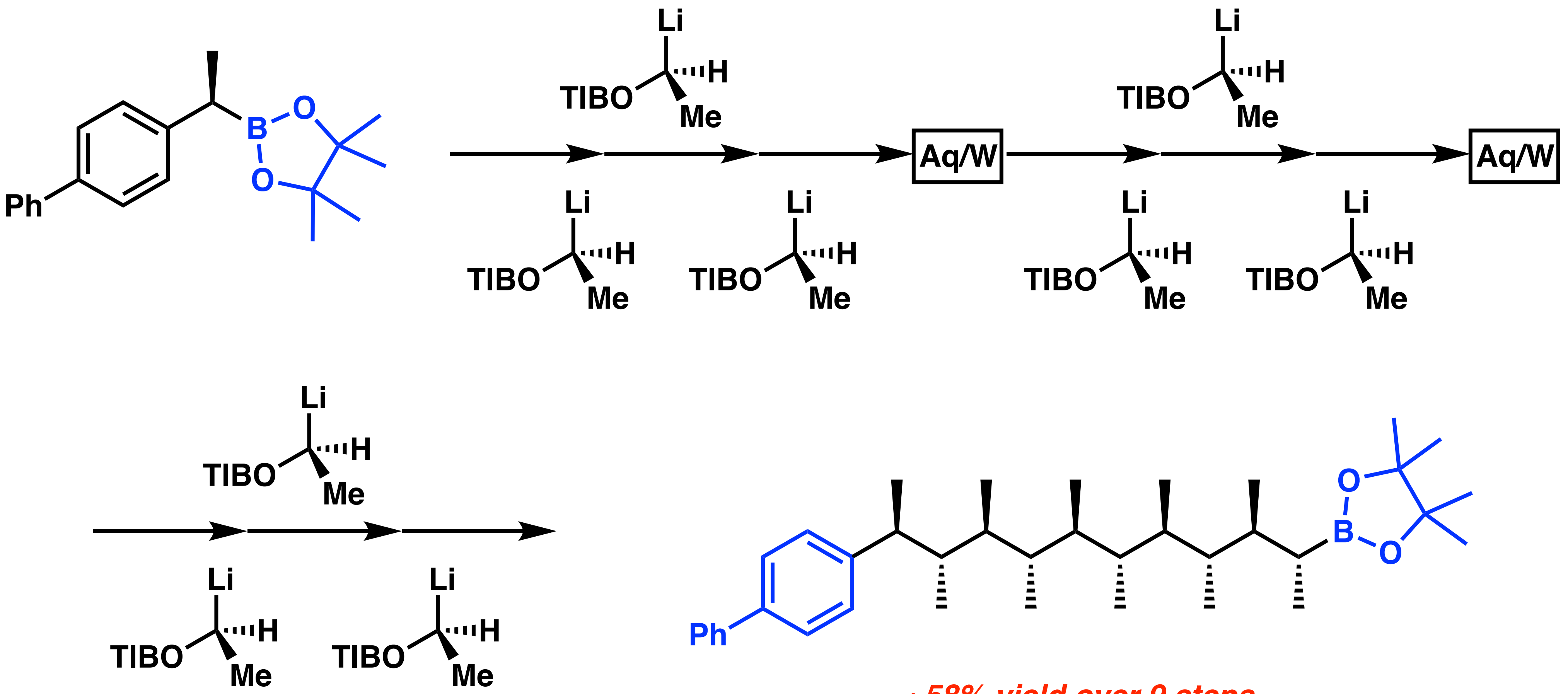


Burns, M.; Essafi, S.; Aggarwal, V. K. *Nature* **2014**, *513*, 183.

Iterative Synthesis



Iterative Synthesis

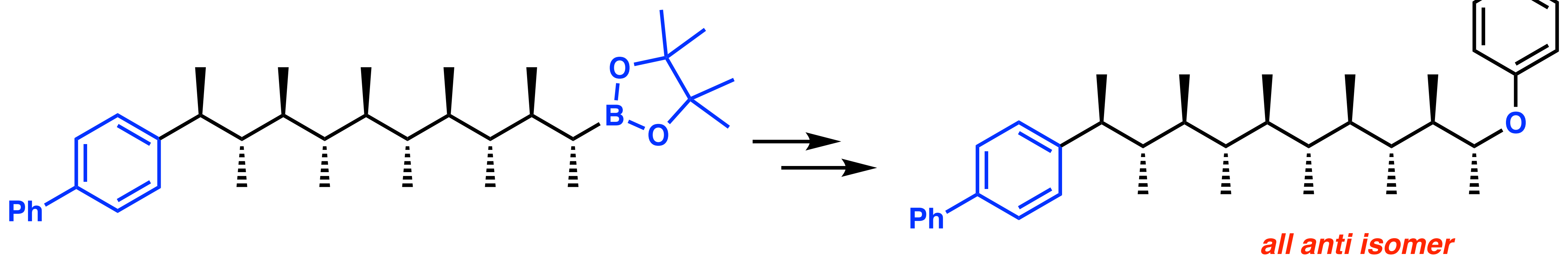


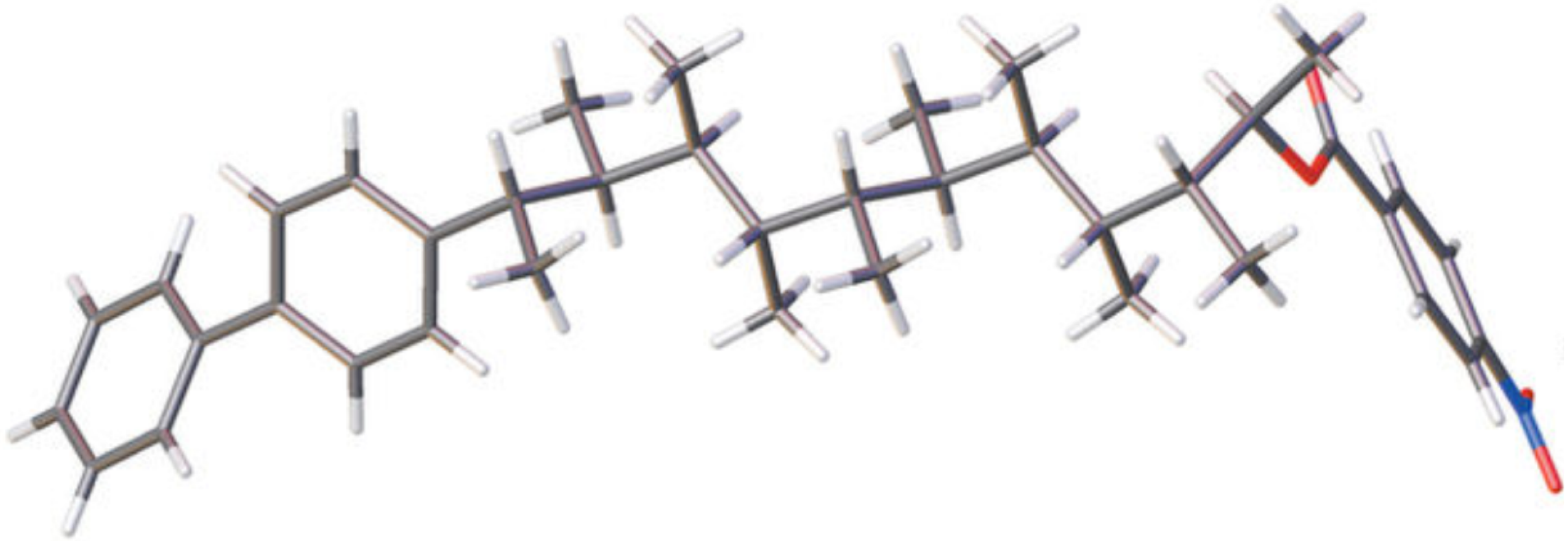
· 58% yield over 9 steps

· 9-mer : 10-mer : 11-mer
1 : 97 : 2

· 3 aqueous workups and a single column

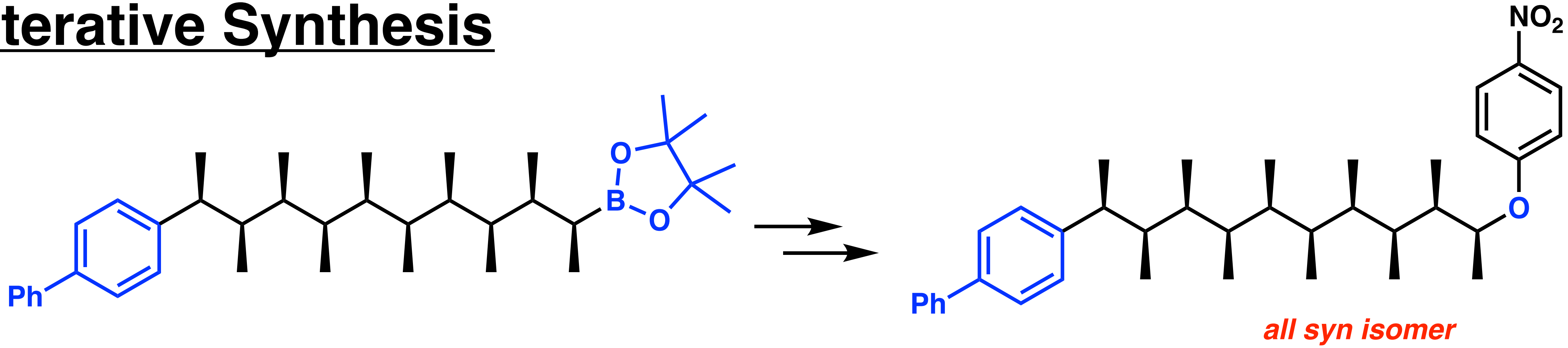
Iterative Synthesis

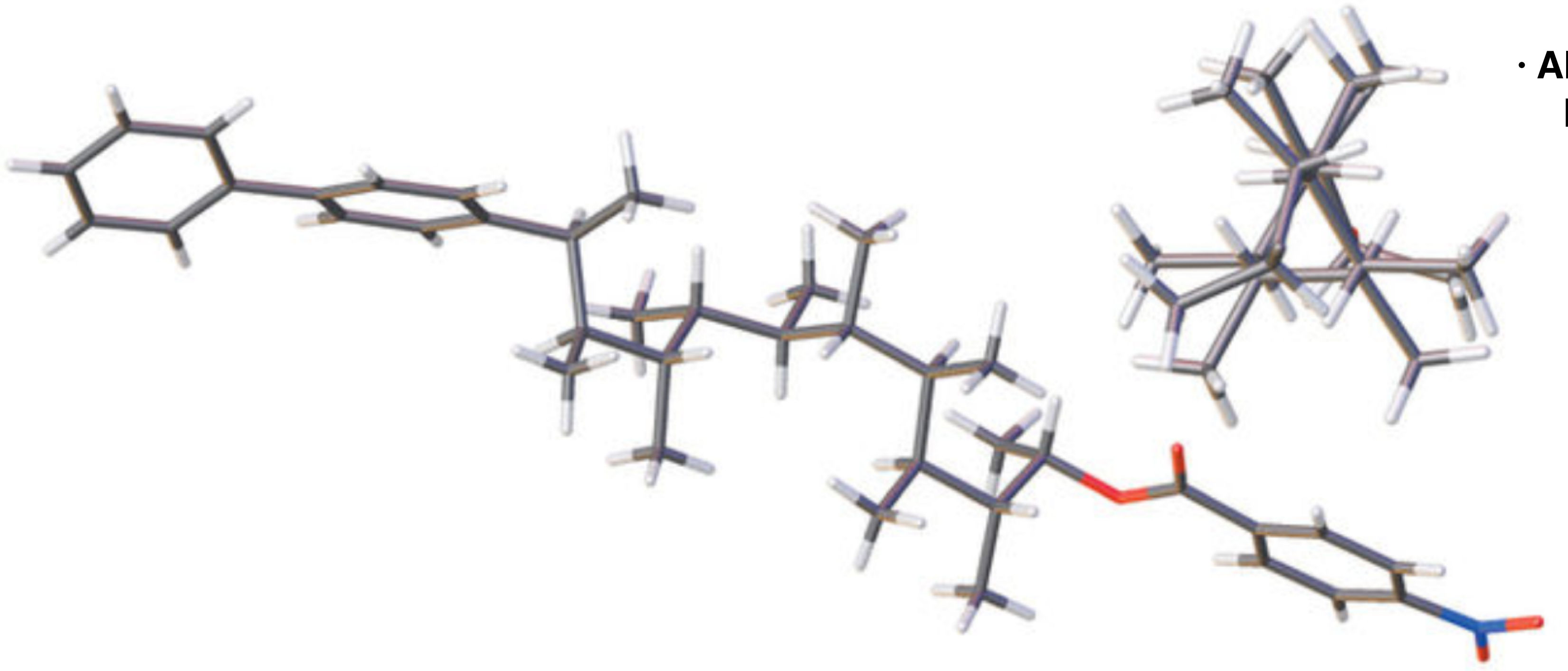




· As predicted, the all anti isomer does not adopt a regular conformation

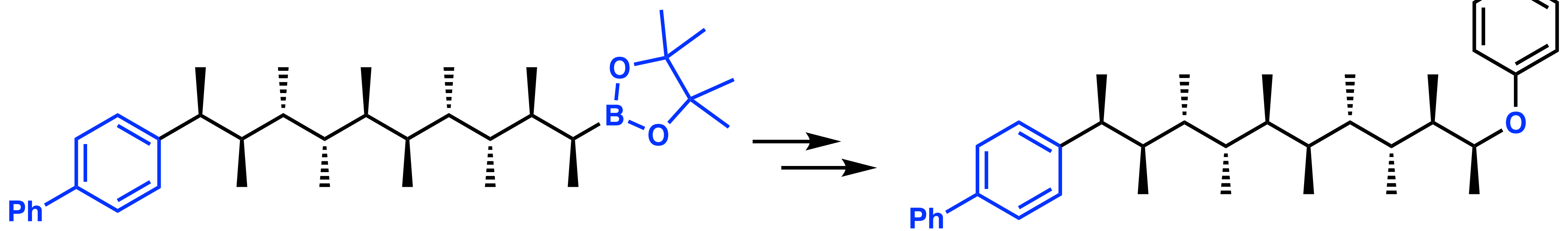
Iterative Synthesis

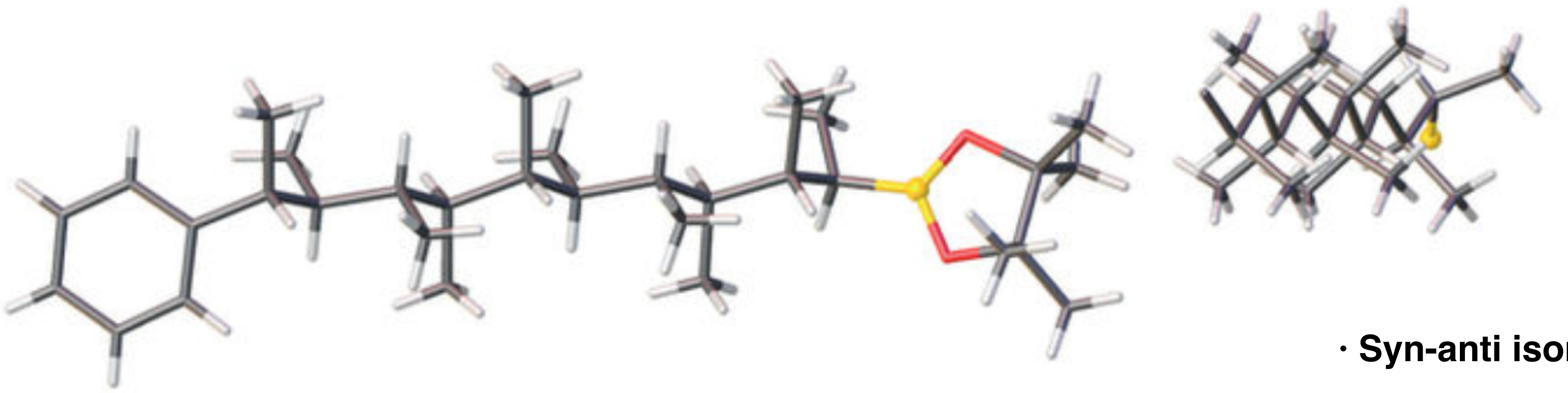




· All syn isomer prefers to adopt the predicted helical conformation

Iterative Synthesis





· Syn-anti isomer adopts a linear backbone conformation

Summary

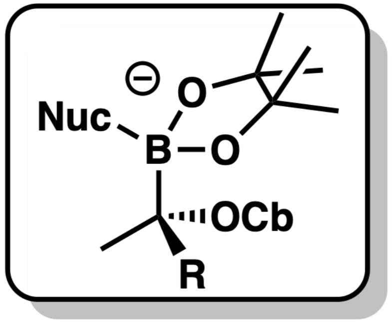
- Carbenoids provide a way to access motifs that were not previously possible

- Defined stereochemical configuration of methyl groups let to a very highly favored conformation of a seemingly flexible hydrocarbon chain

- Assembly line synthesis is a powerful synthetic methodology

<u>Varinder Aggarwal</u>

· Early Career
· Contributions to borane/carbenoid chemistry



Angew. Chem. Int. Ed. **2007**, *46*, 7491.
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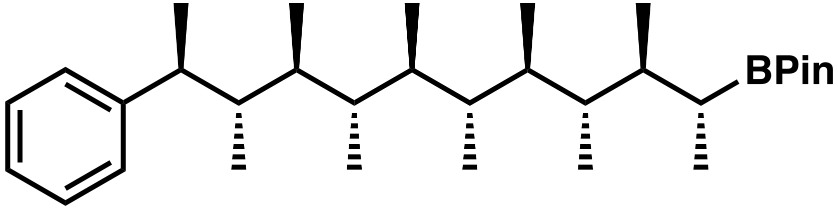

Assembly Line Synthesis

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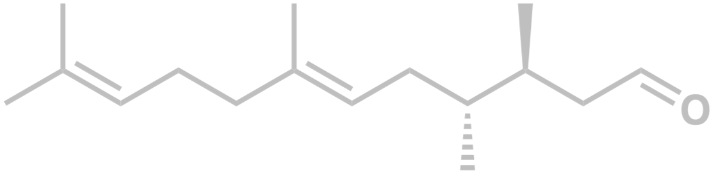

(+) Faranal

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Varinder Aggarwal

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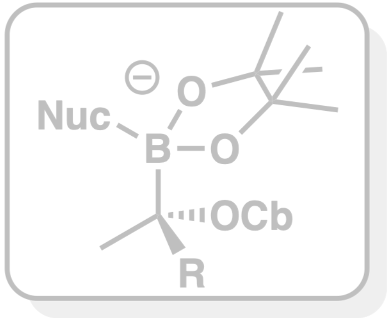

Angew. Chem. Int. Ed. **2007**, *46*, 7491.
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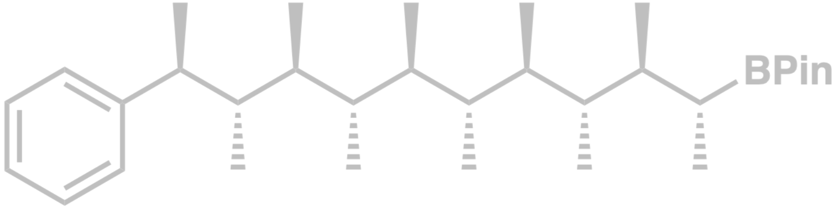
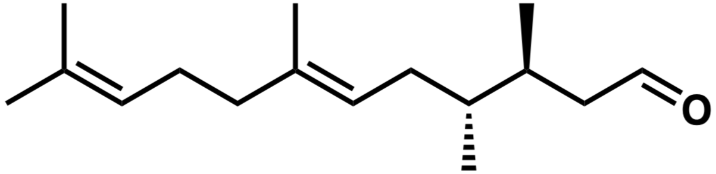


Assembly Line Synthesis

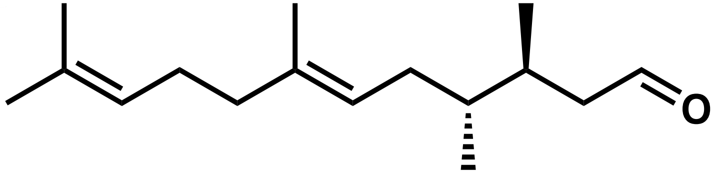
Nature, **2014**, *513*, 183.



(+) Faranal

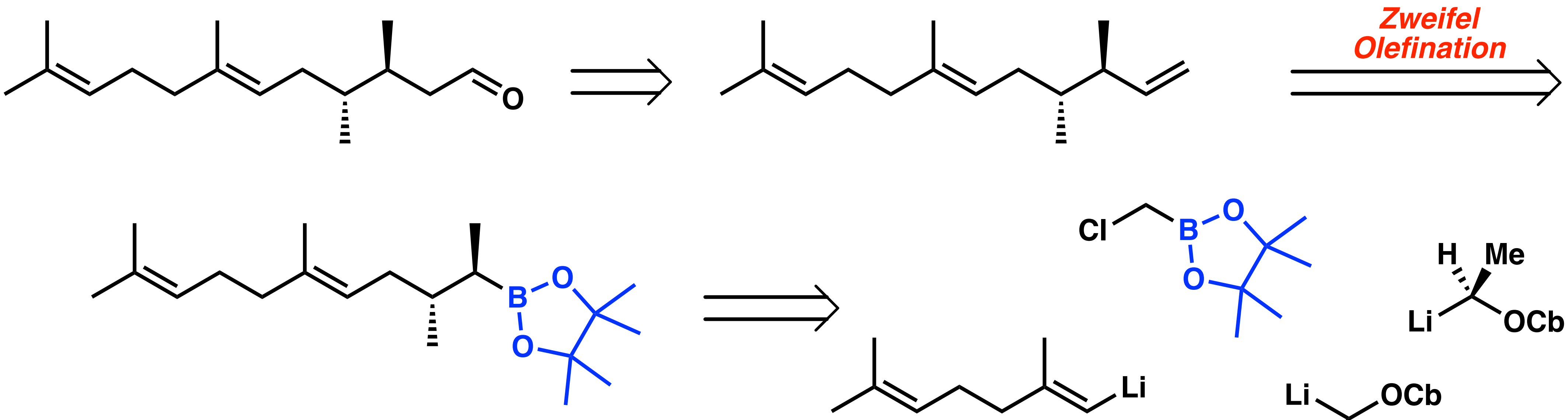
Angew. Chem. Int. Ed, **2009**, *48*, 6317.

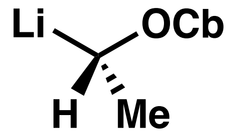
The total synthesis of (+)-Faranal



(+) Faranal

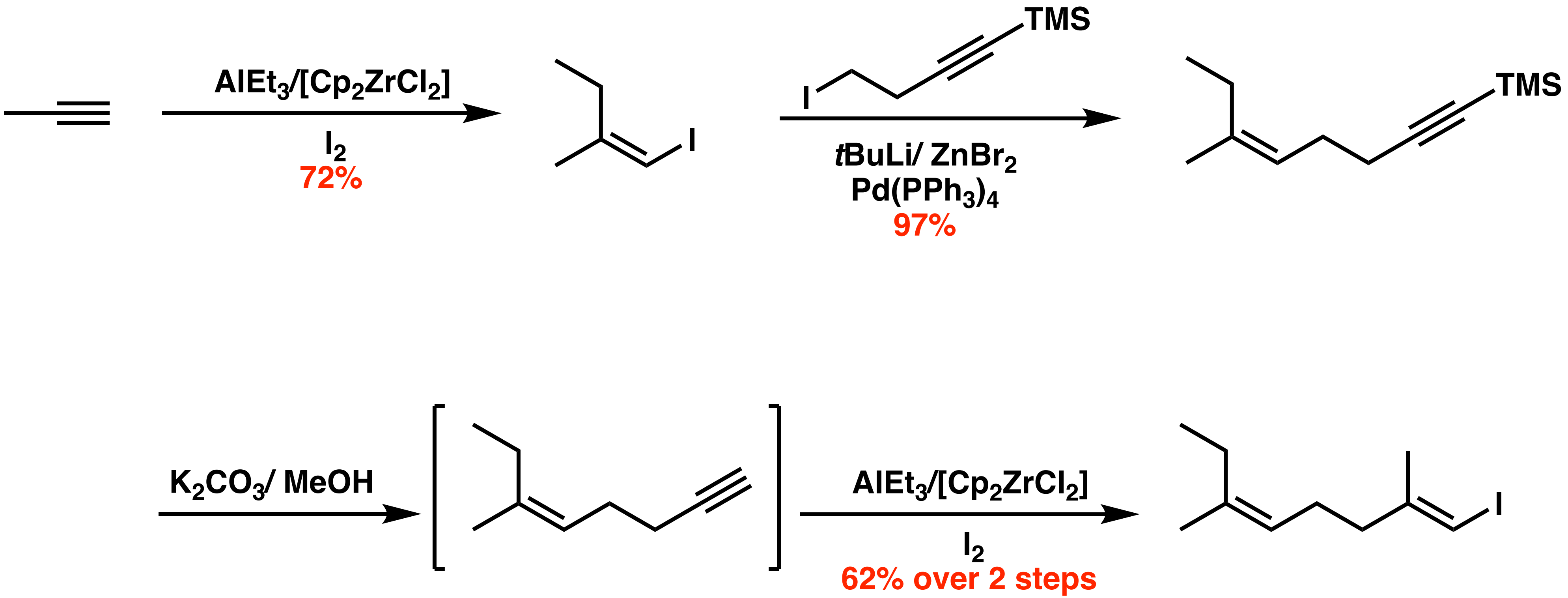
- Insect pheremon
- Syntheses prior to the inception of this work were >19 steps
- Challenging 1,2-*anti* methyl groups





Dutheuil, G.; Aggarwal, V. K. *Angew. Chem. Int. Ed*, **2009**, *48*, 6317.

The total synthesis of (+)-Faranal



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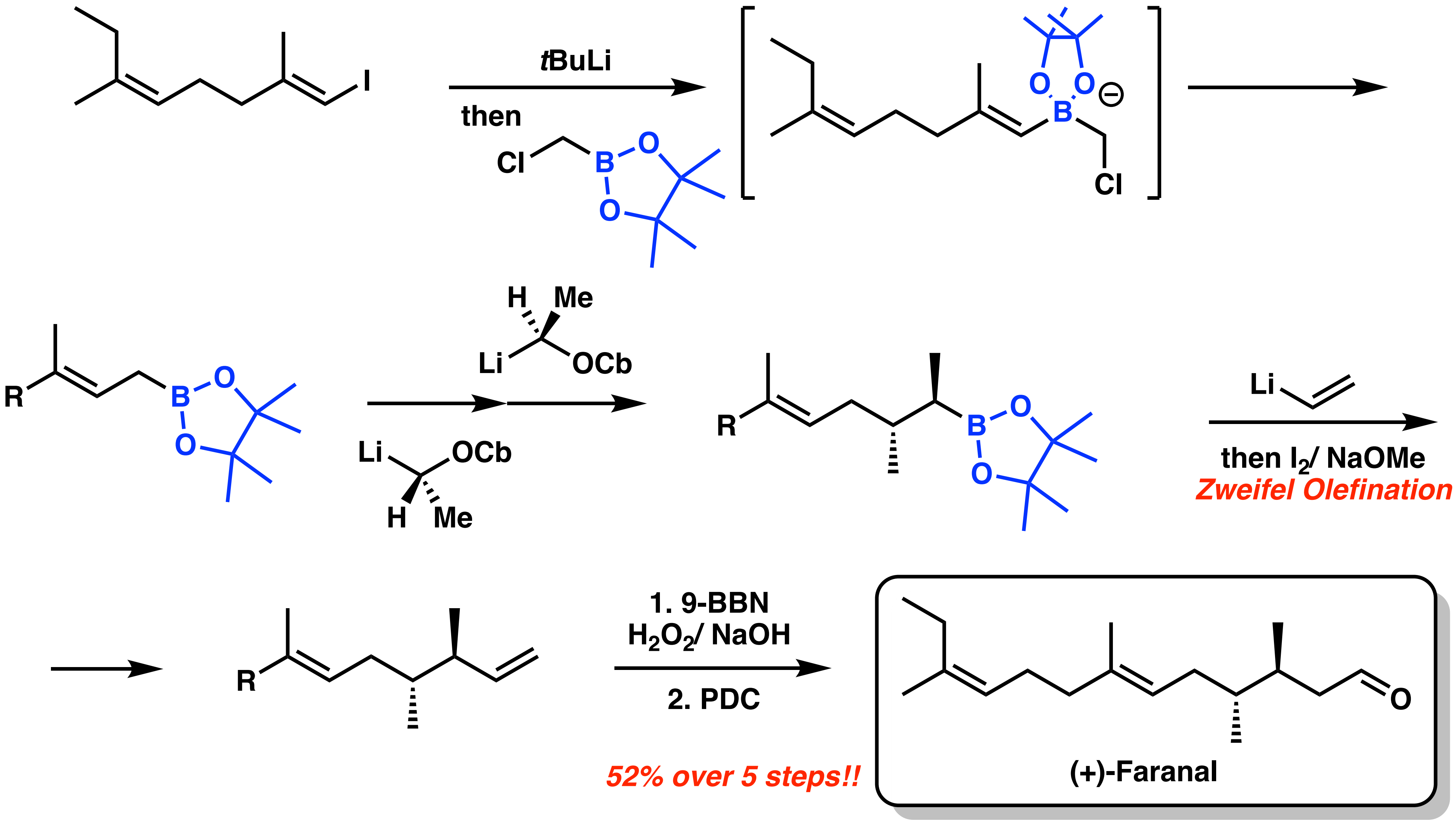
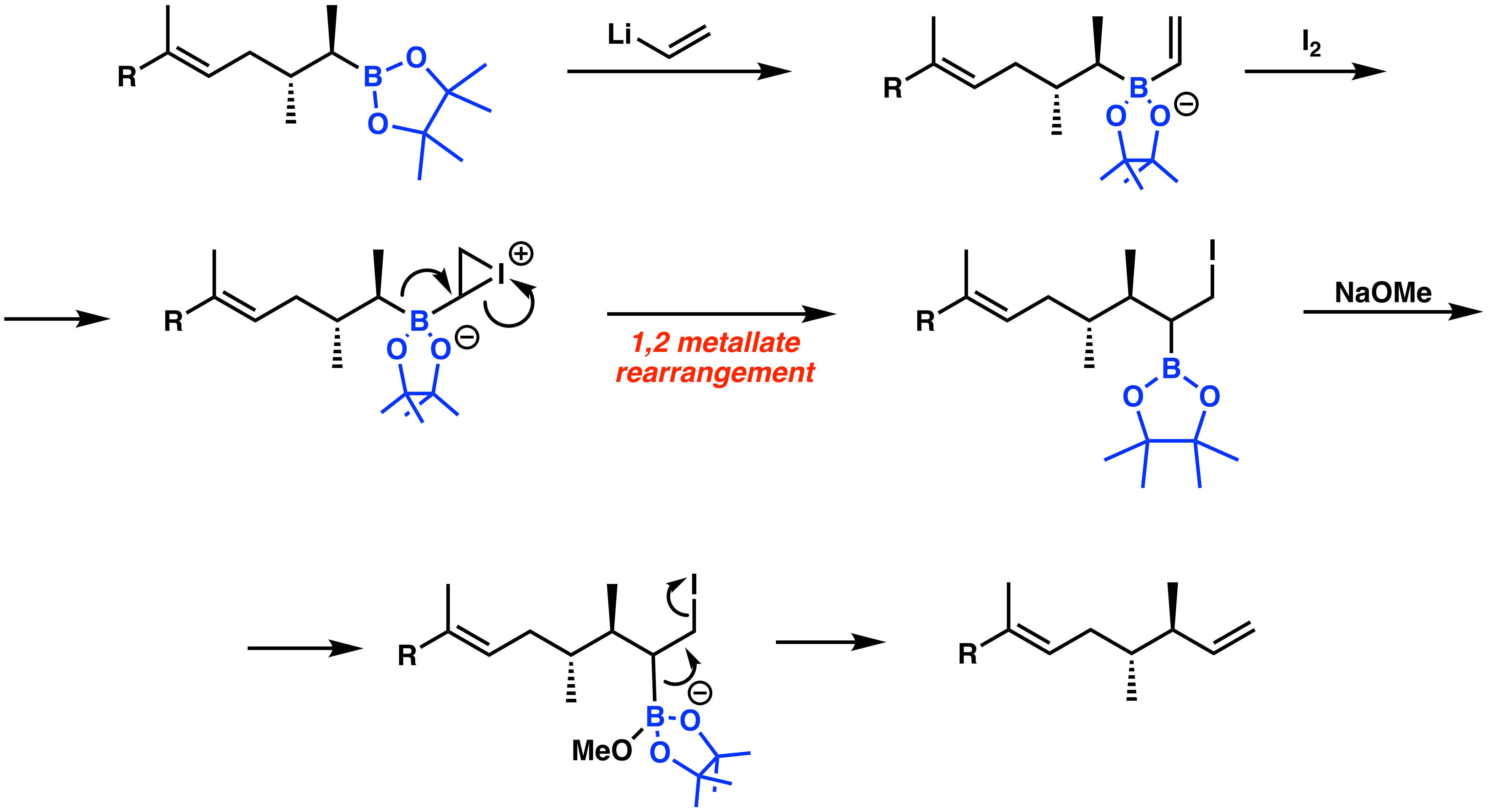
The total synthesis of (+)-Faranal



Zweifel Olefination Mechanism



Conclusion

- Carbenoids and boronic esters have unconventional but powerful reactivity

- Hoppe type lithiation allows for reagent controlled asymmetric homologations that can be done iteratively

- Biomimetic assembly line synthesis gave rapid access to interesting non-natural product

- Asymmetric boronic ester/carbenoid homologation allowed for the concise total synthesis of (+)-Faranal