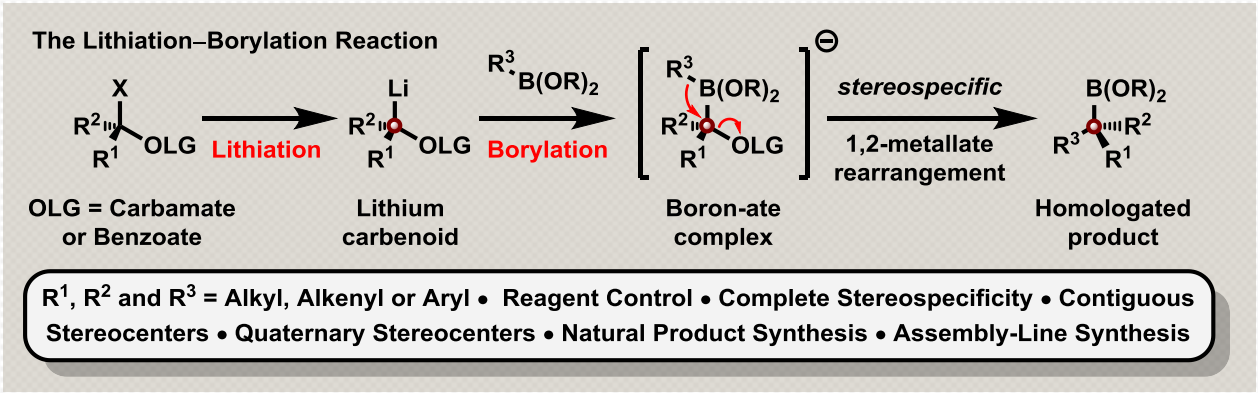
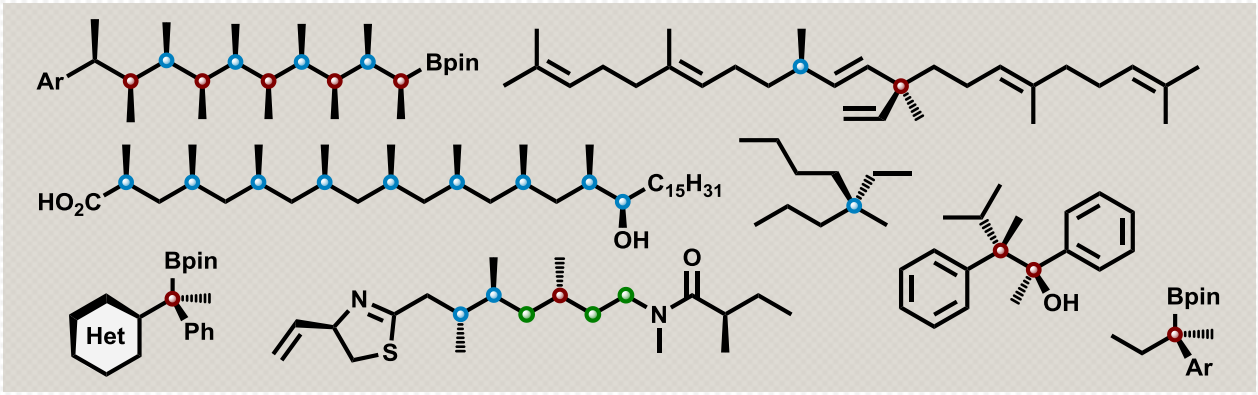
University of BRISTOL

Lithiation–Borylation in Synthesis

What can you synthesise using Lithiation–Borylation?



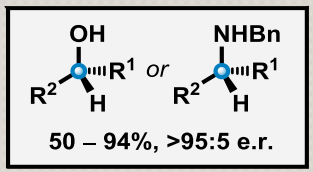


Prof. Varinder K. Aggarwal

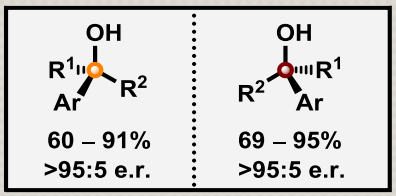
All work was performed by past and present members of the Aggarwal Group (see references for details).

Compiled and presented by Alexander Fawcett.

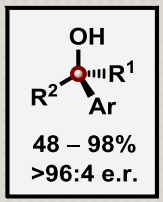
What Can You Synthesise Using Lithiation–Borylation?



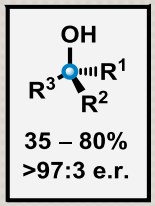
50 – 94%, >95:5 e.r.



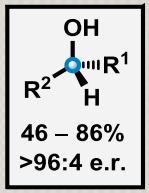
60 – 91%
>95:5 e.r.
69 – 95%
>95:5 e.r.



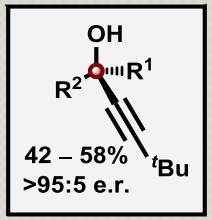
48 – 98%
>96:4 e.r.



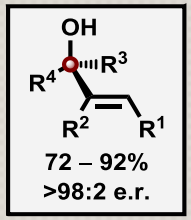
35 – 80%
>97:3 e.r.



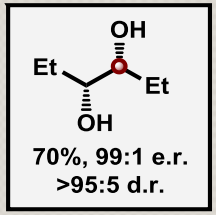
46 – 86%
>96:4 e.r.



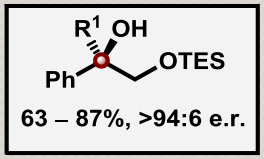
42 – 58%
>95:5 e.r.



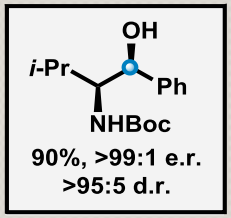
72 – 92%
>98:2 e.r.



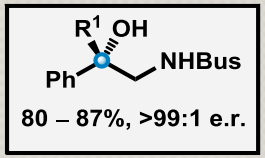
70%, 99:1 e.r.
>95:5 d.r.



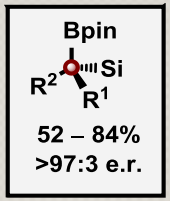
63 – 87%, >94:6 e.r.



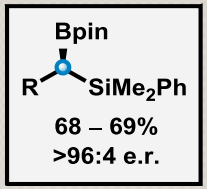
90%, >99:1 e.r.
>95:5 d.r.



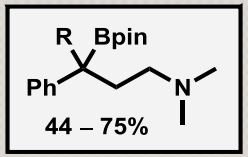
80 – 87%, >99:1 e.r.



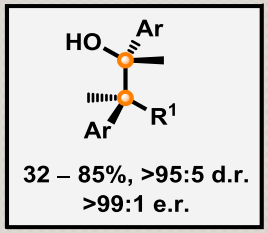
52 – 84%
>97:3 e.r.



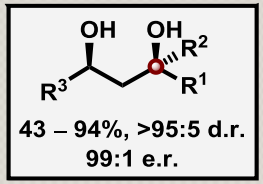
68 – 69%
>96:4 e.r.



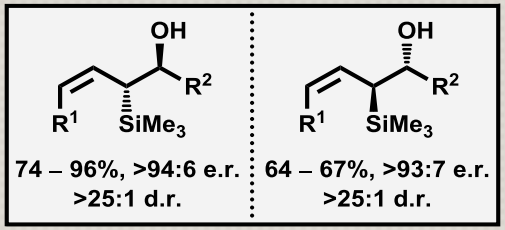
44 – 75%



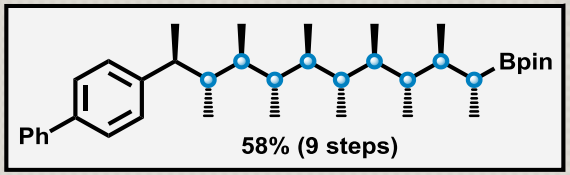
32 – 85%, >95:5 d.r.
>99:1 e.r.



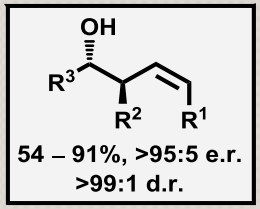
43 – 94%, >95:5 d.r.
99:1 e.r.



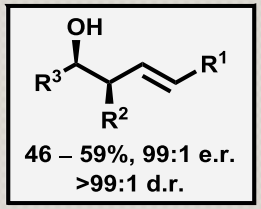
74 – 96%, >94:6 e.r.
>25:1 d.r.
64 – 67%, >93:7 e.r.
>25:1 d.r.



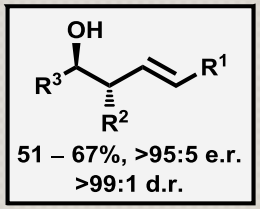
58% (9 steps)



54 – 91%, >95:5 e.r.
>99:1 d.r.

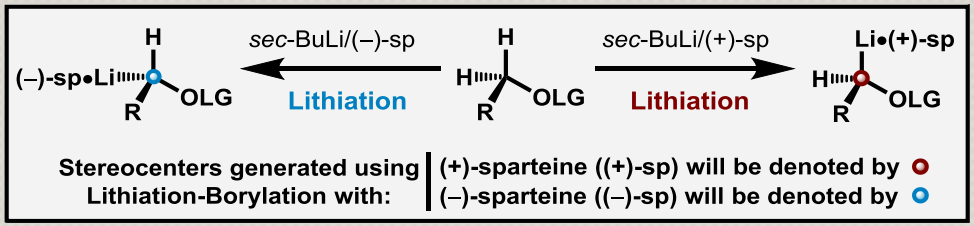


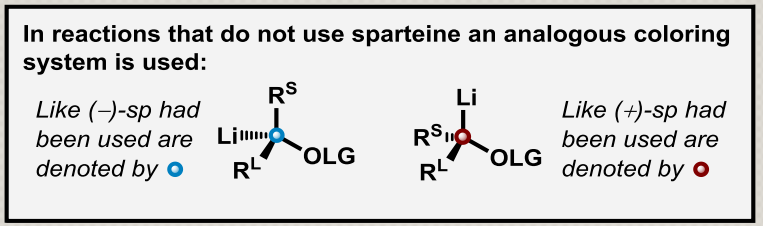
46 – 59%, 99:1 e.r.
>99:1 d.r.

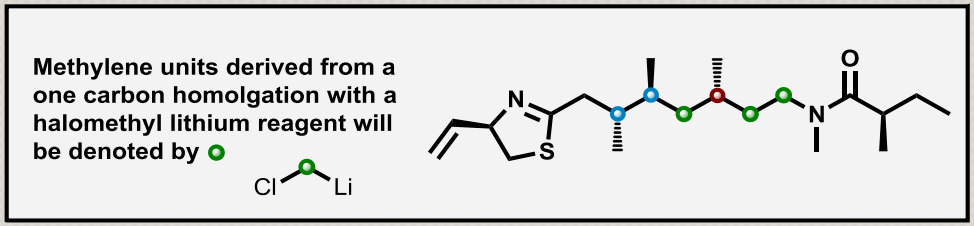


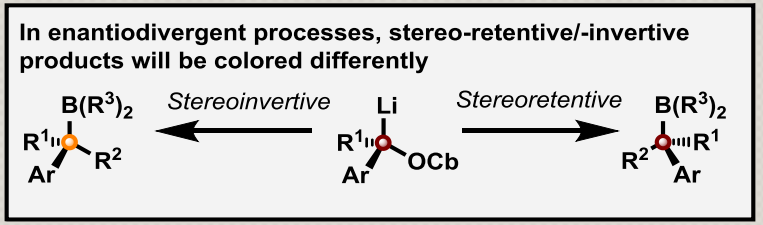
51 – 67%, >95:5 e.r.
>99:1 d.r.

Notes on use of color





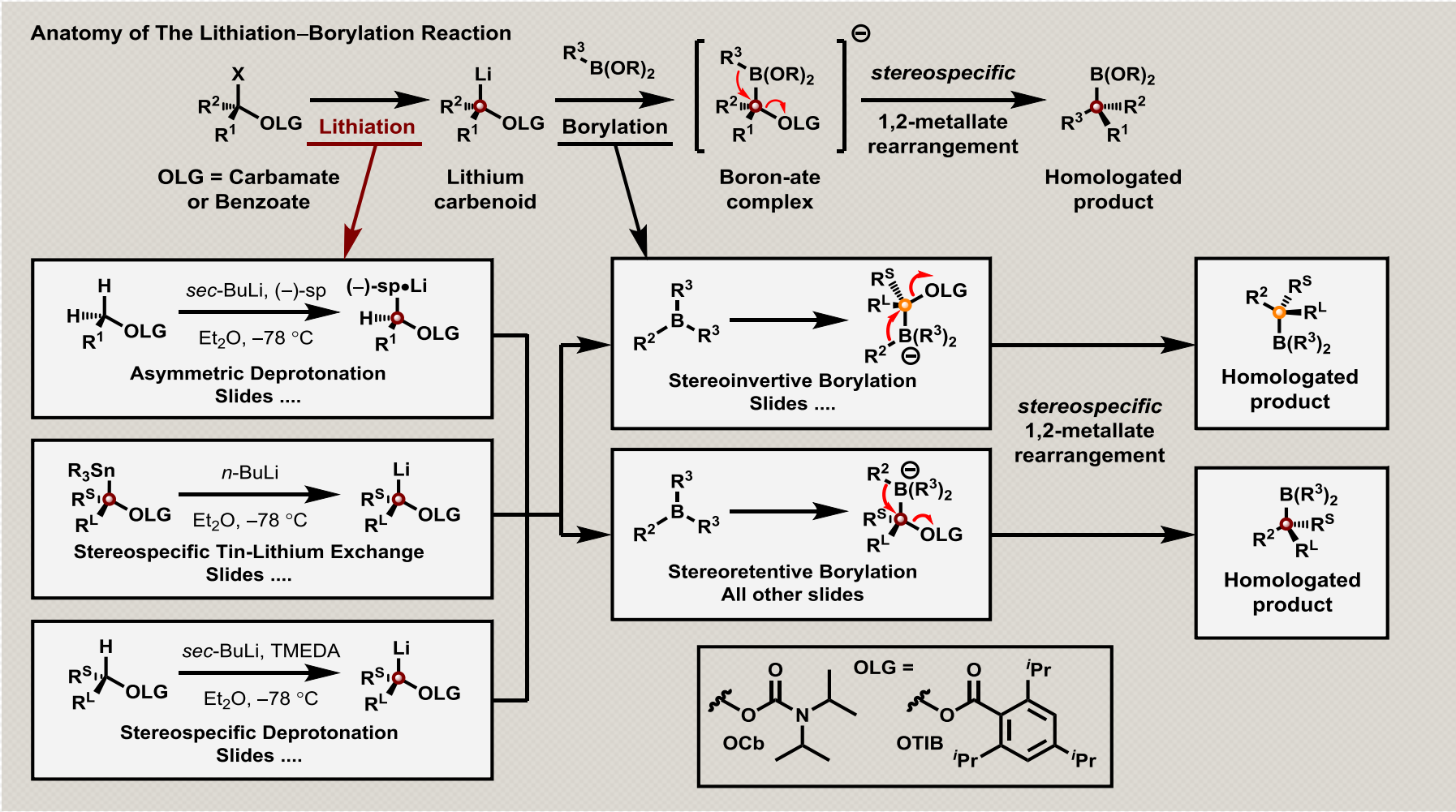




List of Reviews and Book Chapters

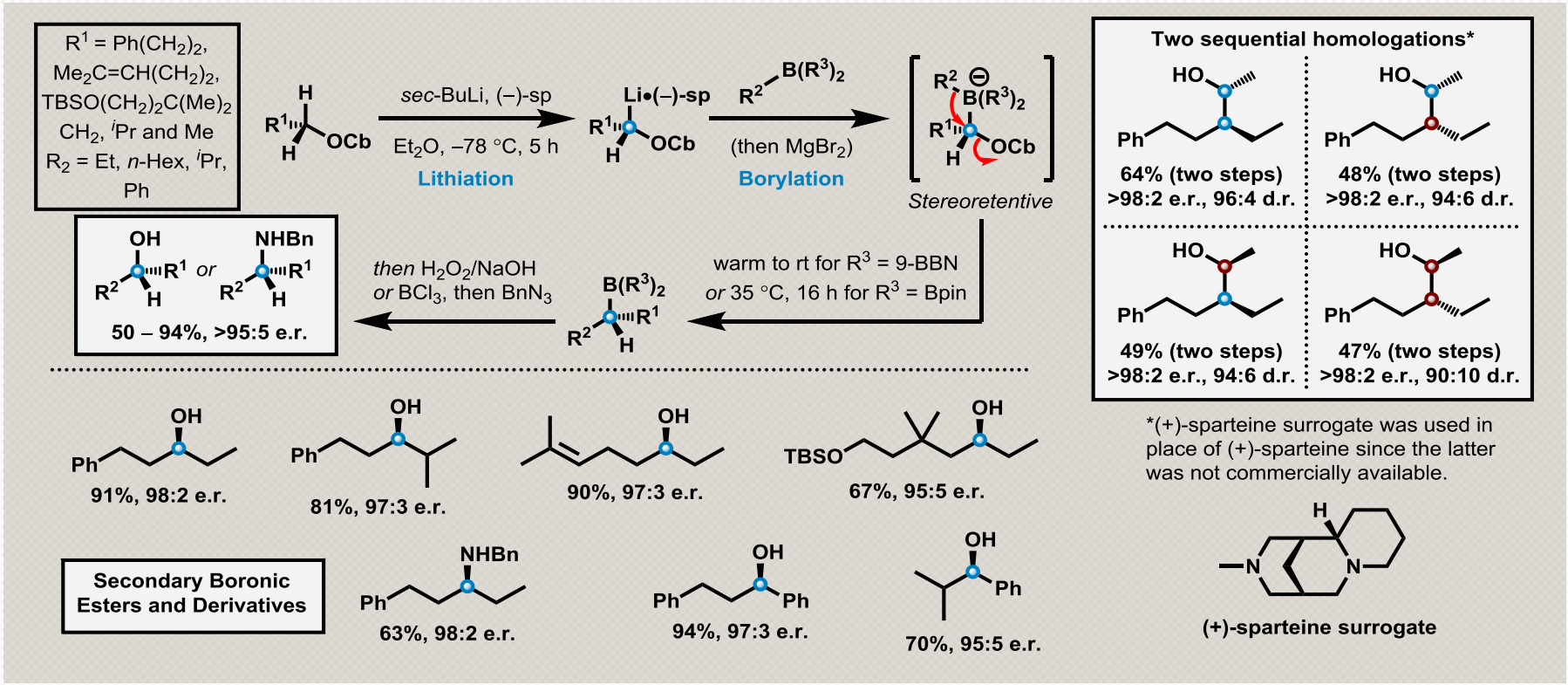
1) Reagent-Controlled Lithiation–Borylation, D. Leonori, V. K. Aggarwal, in *Synthesis and Application of Organoboron Compounds*, Topics in Organometallic Chemistry, E. Fernandez, A. Whiting (Eds), Springer International Publishing Switzerland, **2015**, *49*, pp 271-295. DOI: 10.1007/978-3-319-13054-5_9, ISBN: 978-3-319-13053-8.
2) Lithiation–Borylation Methodology and its Application in Synthesis, D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174–3183. DOI: 10.1021/ar5002473.
3) Asymmetric Homologation of Boronic Esters with Lithiated Carbamates, Epoxides and Aziridines, M. Webster, V. K. Aggarwal, in *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, Dennis G. Hall (Eds), Wiley-VCH, **2011**, pp 479-505. DOI: 10.1002/9783527639328, ISBN: 9783527325986.
4) Homologation and Alkylation of Boronic Esters and Boranes by 1,2-Metallate Rearrangement of Boron Ate Complexes, S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chemical Record*, **2009**, *9*, 24-39. DOI: 10.1002/tcr.20168.
5) 'Towards an Understanding of the Factors Responsible for the 1,2-Migration of Alkyl Groups in Borate Complexes' V. K. Aggarwal, G. Y. Fang, X. Ginesta, D. M. Howells, M. Zaja, *Pure Appl. Chem*. **2006**, 215-229. DOI: 10.1351/pac200678020215

The Lithiation–Borylation Reaction



Key Features: **Lithiation:** Three methods of generating lithium carbenoid; The organolithium is chemically and configurationally stable at cryogenic temperatures. **Borylation:** Very rapid and occurs stereospecifically, with either retention or inversion of stereochemistry. **1,2-Rearrangement:** Completely stereospecific due to requirement for antiperiplanar arrangement of migrating group and leaving group

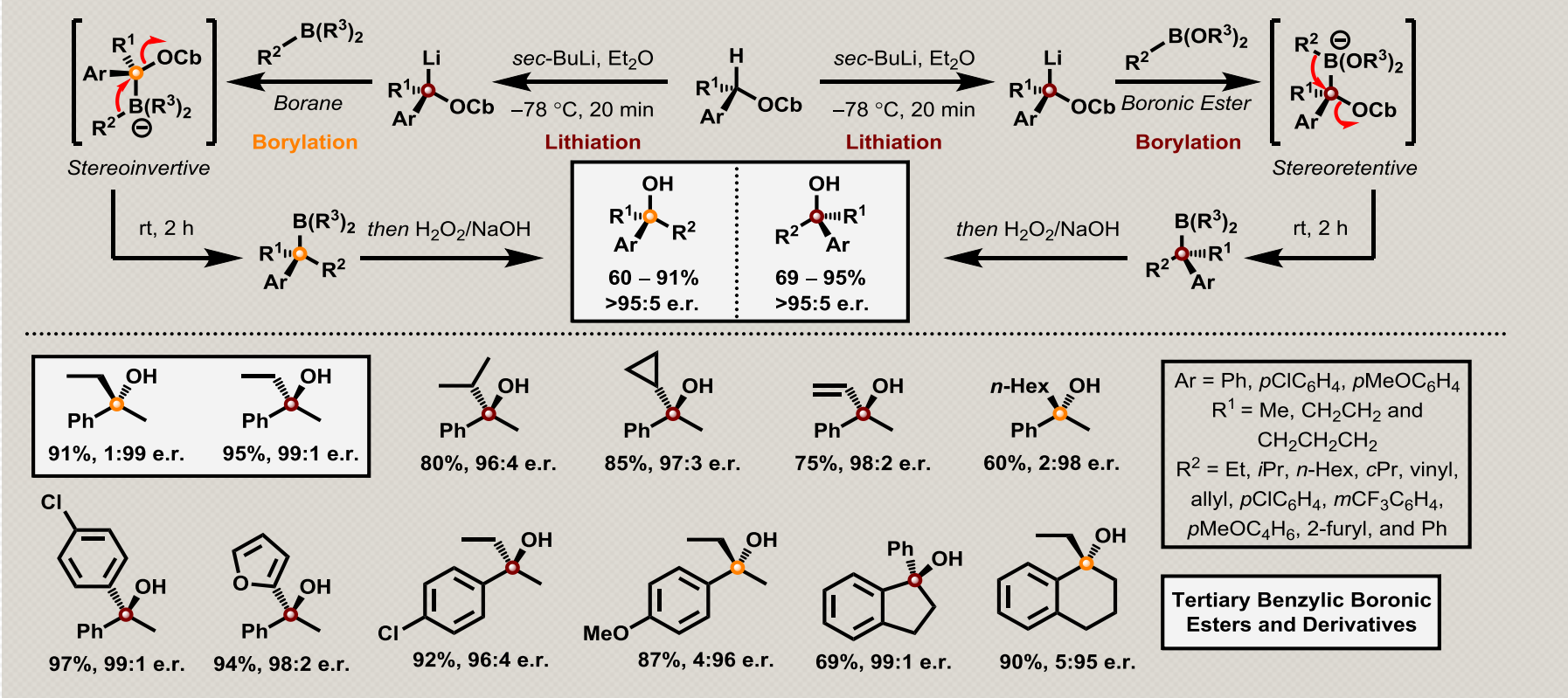
Secondary Boronic Esters and Derivatives



Notes and Key Features: synthesis of secondary boronic esters; stereoretentive borylation; when using Ph-9BBN $MgBr_2$ is necessary to prevent loss of e.r., which is caused by sparteine being present in the reaction mixture (or can be overcome by using the corresponding stannane); –40 °C is sufficient for borane migration; refluxing Et_2O in the presence of $MgBr_2$ is required for the migration of pinacol boronic esters; 'iterative' homologations possible by isolating the intermediate boronic ester; no match/mis-match effects observed when generating diastereomers.

Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters, J. L. Stymiest, G. Dutheuil, A. Mahmood and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2007**, *46*, 7491. DOI: 10.1002/anie.200702146

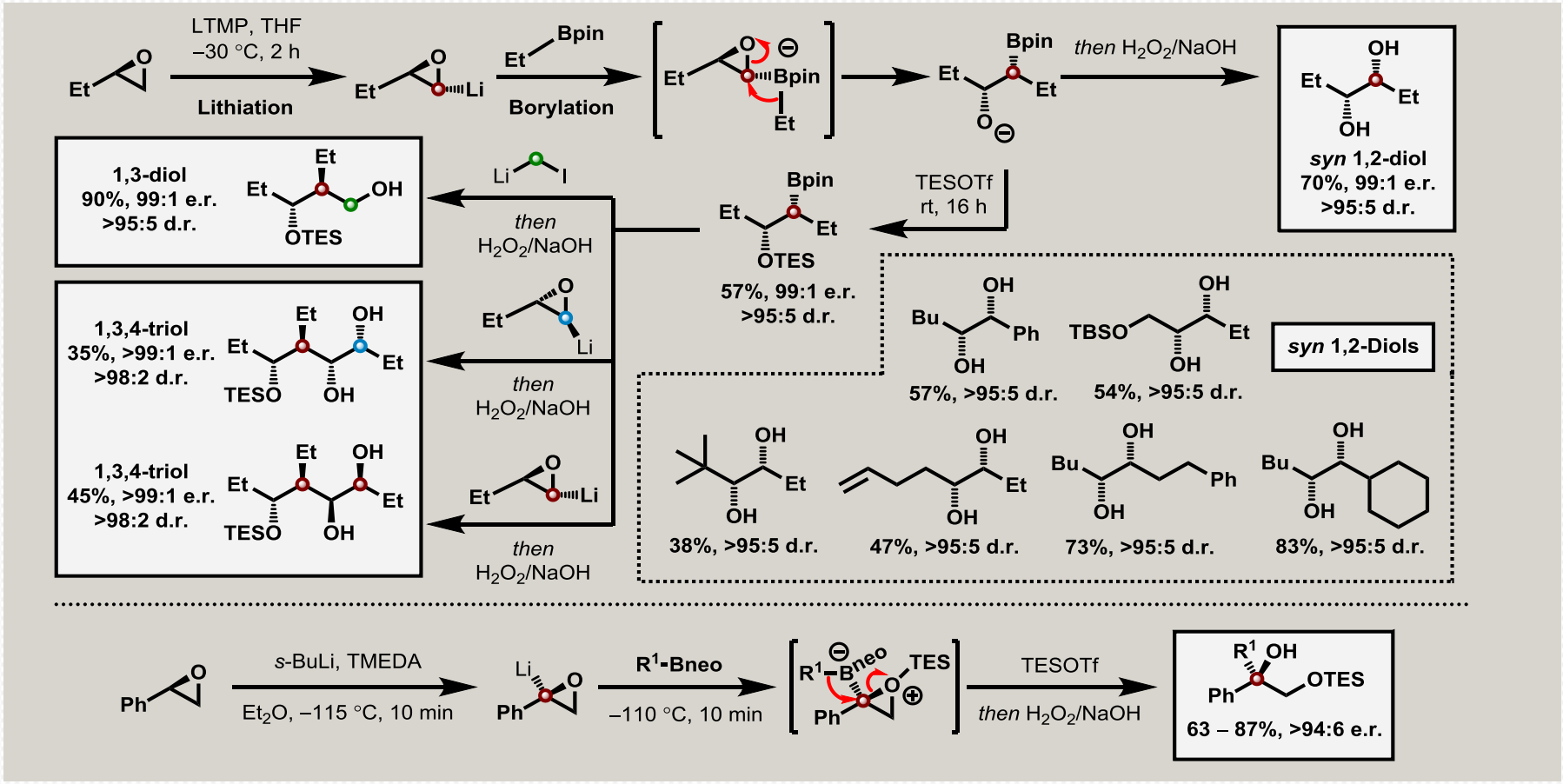
Tertiary Benzylic Boronic Esters



Notes and Key Features: synthesis of tertiary benzylic boronic esters; stereoretentive borylation with boronic esters; stereoinvertive borylation with boranes; TMEDA required for lithiation of *p*MeOC4H6, indanyl and tetrahydronapthyl carbamates; aryl boranes lead to protodeboronation products, so should not be used; indanyl carbamate leads to stereoretentive products with both borane and carbamates; add BHT and THF to ensure complete and enantiospecific oxidation

Enantiodivergent Conversion of Chiral Secondary Alcohols into Tertiary Alcohols, J. L. Stymiest, V. Bagutski, R. M. French and V. K. Aggarwal, *Nature* **2008**, *456*, 778. DOI: 10.1038/nature07592

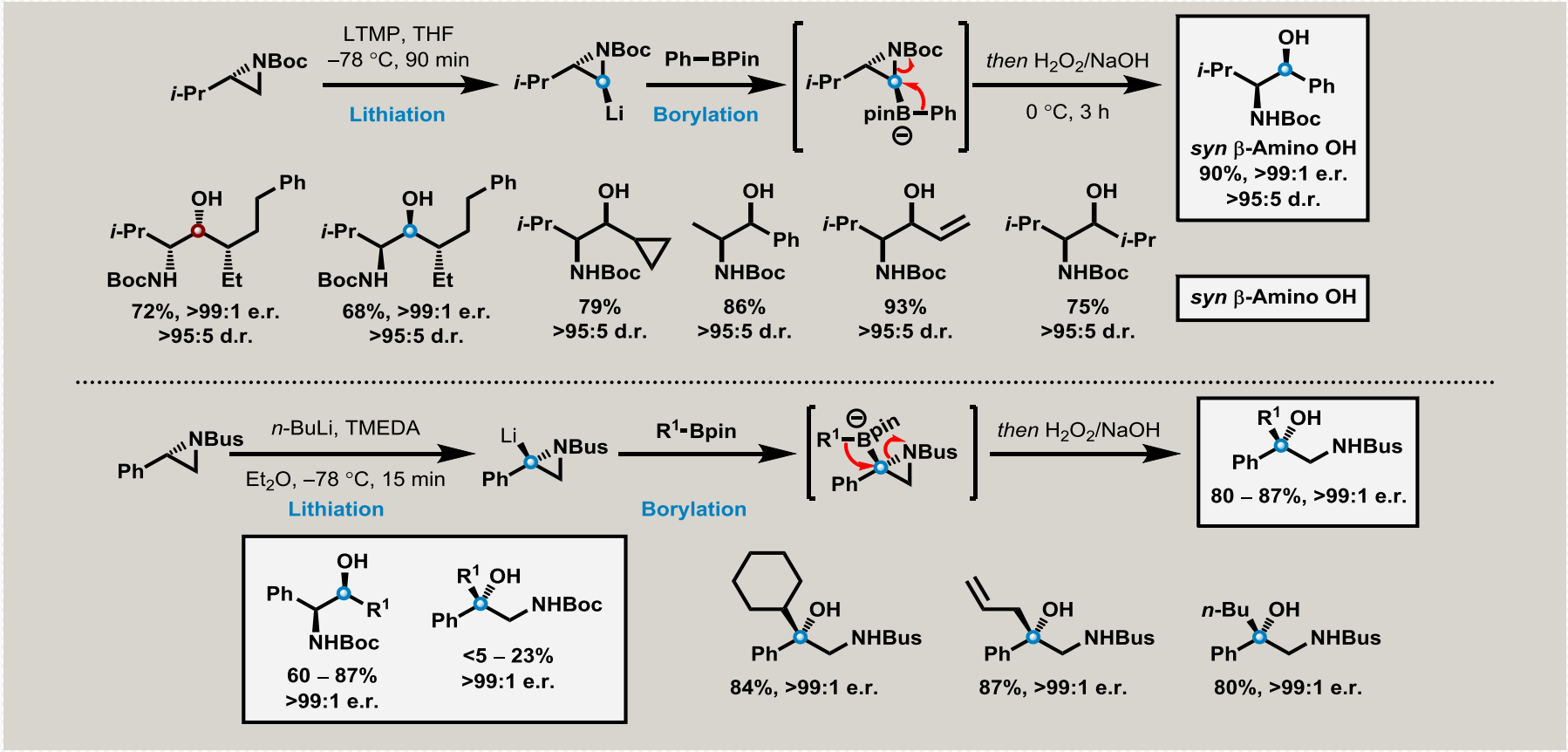
1,2- and 1,3-Diols and 1,2,4-Triols



Notes and Key Features: synthesis of 1,2- and 1,3-diols, and 1,2,4-triols; lithiation and borylation are performed in situ; use of PhBpin leads to boron-Wittig-type elimination; use of pinacol boronic esters in reaction with styrene oxides leads to products with poor e.r.

Homologation of Boronic Esters with Lithiated Epoxides for the Stereocontrolled Synthesis of 1,2- and 1,3-Diols and 1,2,4-Triols, E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt and V. K. Aggarwal, *Org. Lett.* **2008**, *11*, 165. DOI: 10.1021/ol802651b

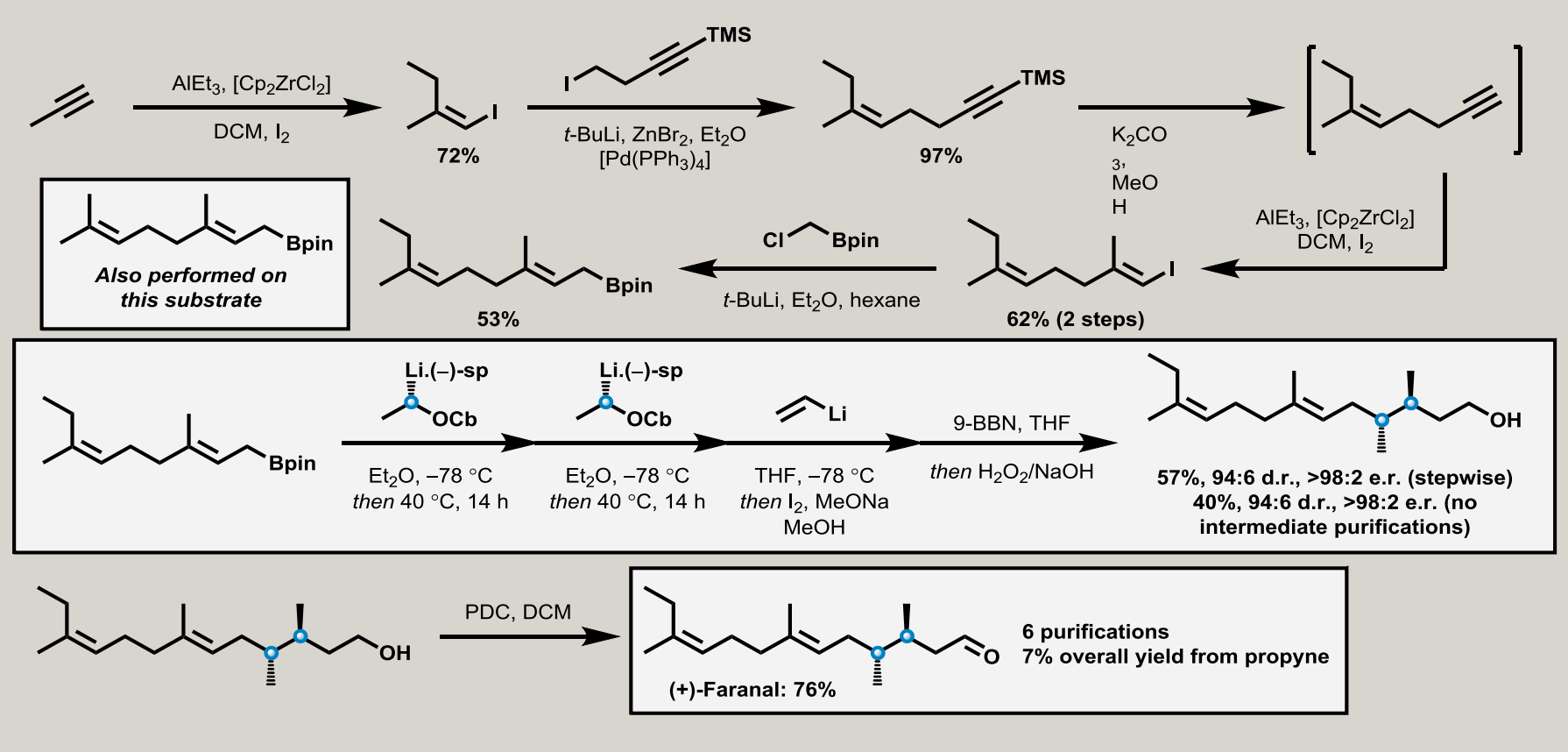
β-Amino Alcohols



Notes and Key Features: synthesis of *syn* β-amino alcohols; performed at maximum practical concentration with 3 eq. boronic ester to prevent rearrangement of lithiated aziridine; lithiating *N*-Boc phenylaziridine only gives rearranged product, so *N*-Bus used instead; lithiating with LTMP gives mixture of secondary/tertiary alcohol products; using a less hindered base gave exclusive benzylic lithiation and thus only tertiary alcohol products

Stereocontrolled Synthesis of β-Amino Alcohols from Lithiated Aziridines and Boronic Esters, F. Schmidt, F. Keller, E. Vedrenne and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2009**, *48*, 1149. DOI: 10.1002/anie.200805272

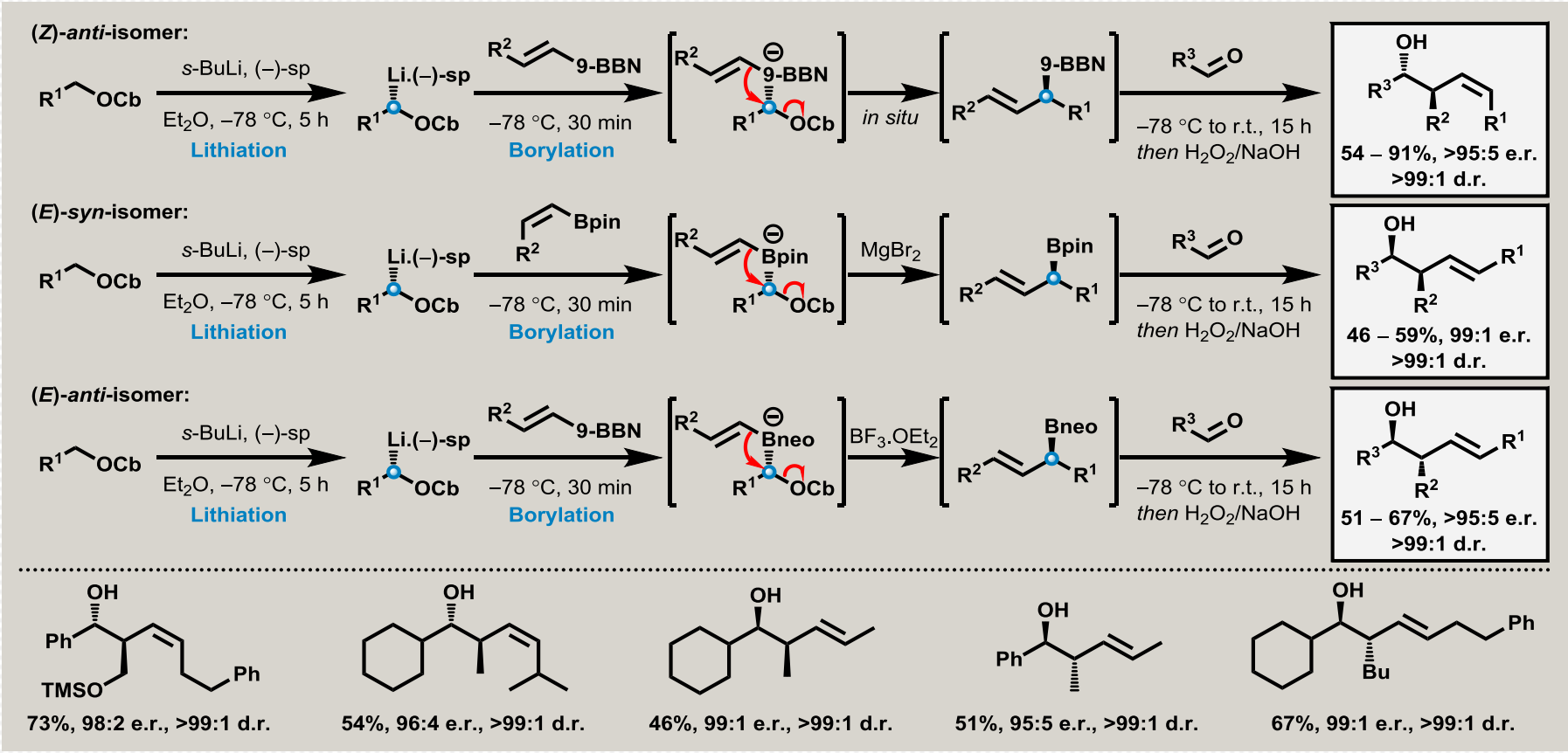
Total Synthesis: (+)-Faranal



Notes and Key Features: total synthesis of (+)-Faranal; excess carbamate used found to decompose at –20 °C; one-pot, triple-homologation sequence demonstrated; one-pot, quadruple-homologation possible (starting from second vinyl iodide); $MgBr_2$ was found to be unnecessary, but did give greater yields for the homologations

Stereocontrolled Synthesis of Carbon Chains Bearing Contiguous Methyl Groups by Iterative Boronic Ester Homologations: Application to the Total Synthesis of (+)-Faranal, G. Dutheuil, M. P. Webster, P. A. Worthington and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2009**, *48*, 6317. DOI: 10.1002/anie.200901194

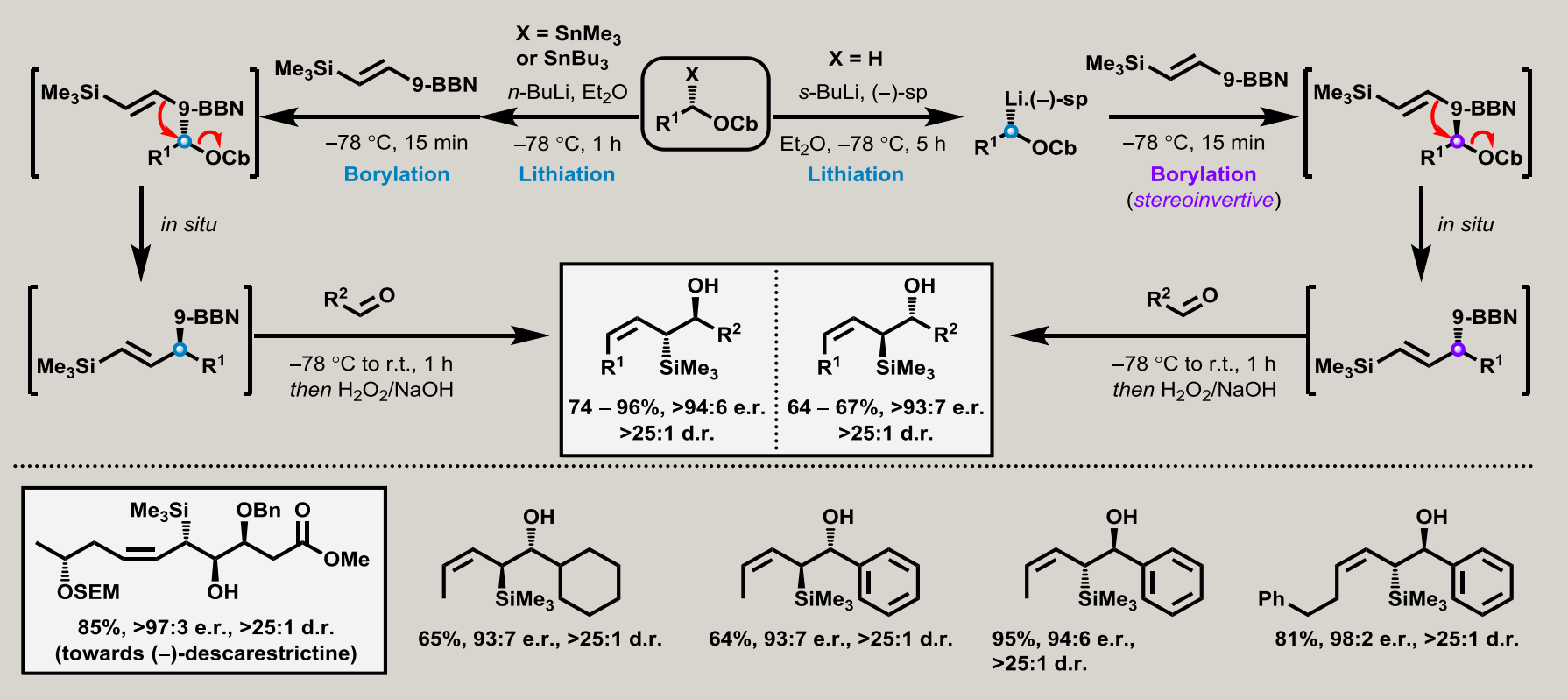
Allylic Boronic Esters (and Homoallylic Alcohols)



Notes and Key Features: synthesis of allylic boronic esters and in situ conversion to homoallylic alcohols via aldehyde allylation; adding the aldehyde to the 9-BBN ate-complex prevents isomerisation; diamine free (from stannane) was required for some 9-BBN substrates.

Application of the Lithiation–Borylation Reaction to the Preparation of Enantioenriched Allylic Boron Reagents and Subsequent In Situ Conversion into 1,2,4-Trisubstitued Homoallylic Alcohols with Complete Control over All Elements of Stereochemistry, M. Althaus, A. Mahmood, J. R. Suárez, S. P. Thomas and V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 4025. DOI: 10.1021/ja910593w

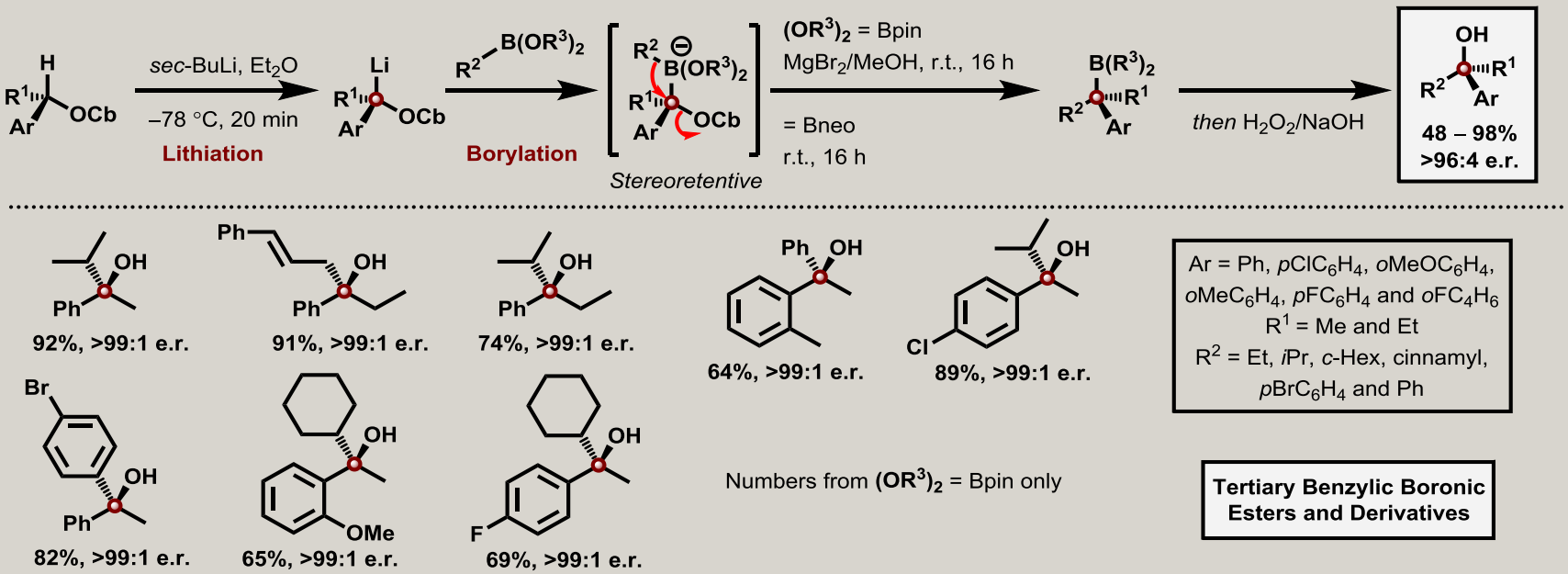
β-Hydroxy Allylsilanes



Notes and Key Features: synthesis of β-hydroxyl allylsilanes; (addition of) bulky diamines leads to stereoinvertive borylation.

Asymmetric Synthesis of Allylsilanes by the Borylation of Lithiated Carbamates: Formal Total Synthesis of (–)-Decarestrictine D, M. Binanzer, G. Y. Fang and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 4264. DOI: 10.1002/anie.201001223

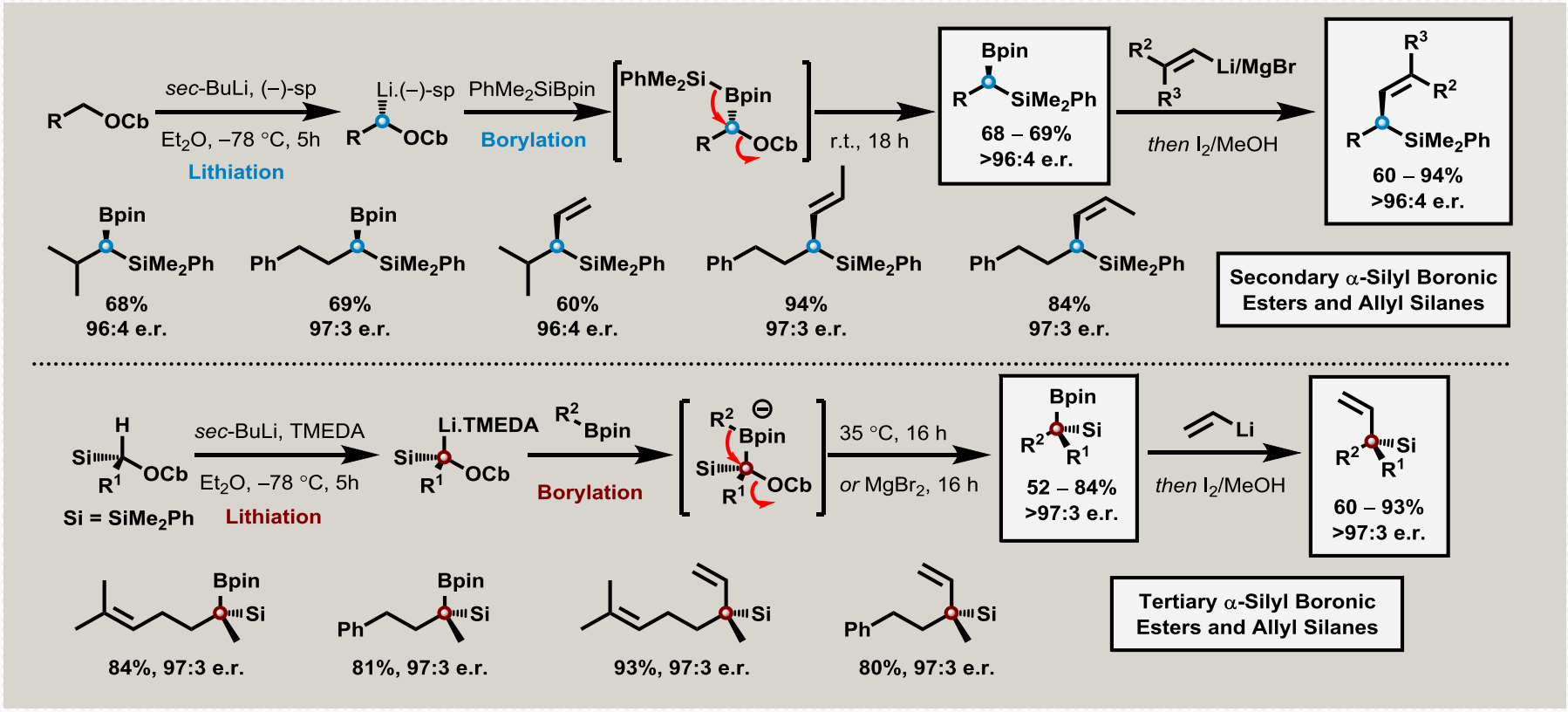
Tertiary Benzylic Boronic Esters



Notes and Key Features: synthesis of tertiary benzylic boronic esters and derivatives; reversible ate-complex identified as causing reduction in *ee* of products; two-electrophile test developed; $MgBr_2$ is required to increase rate of 1,2-migration; MeOH is required to quench any products of reversible ate-complexes; Bneo ate-complexes are less reversible than Bpin so $MgBr_2$/MeOH was not required; incomplete oxidation overcome by using THF as solvent

Full Chirality Transfer in the Conversion of Secondary Alcohols into Tertiary Boronic Esters and Alcohols Using Lithiation–Borylation Reactions, V. Bagutski, R. M. French and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 5142. DOI: 10.1002/anie.201001371

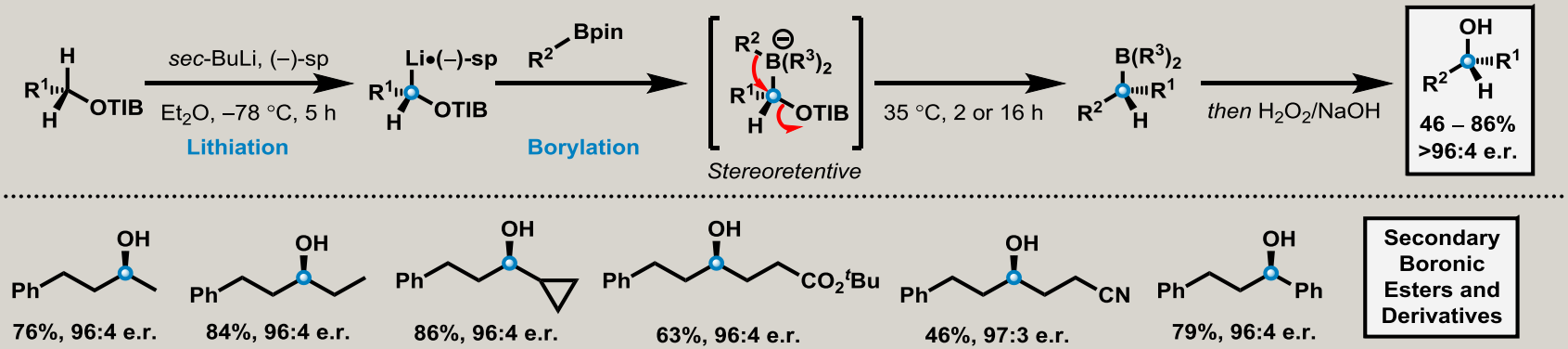
α-Silyl Boronic Esters (and Allyl Silanes)



Notes and Key Features: synthesis of α-silyl boronic esters, and allyl silanes; lithiated α-silyl carbamates are configurationally unstable, unless they are secondary; more hindered α-silyl carbamates could not be deprotonated.

Asymmetric Synthesis of Tertiary and Quaternary Allyl- and Crotylsilanes via the Borylation of Lithiated Carbamates, V. K. Aggarwal, M. Binanzer, M. C. de Ceglie, M. Gallanti, B. W. Glasspoole, S. J. F. Kendrick, R. P. Sonawane, A. Vázquez-Romero and M. P. Webster, *Org. Lett.* **2011**, *13*, 1490. DOI: 10.1021/ol200177f

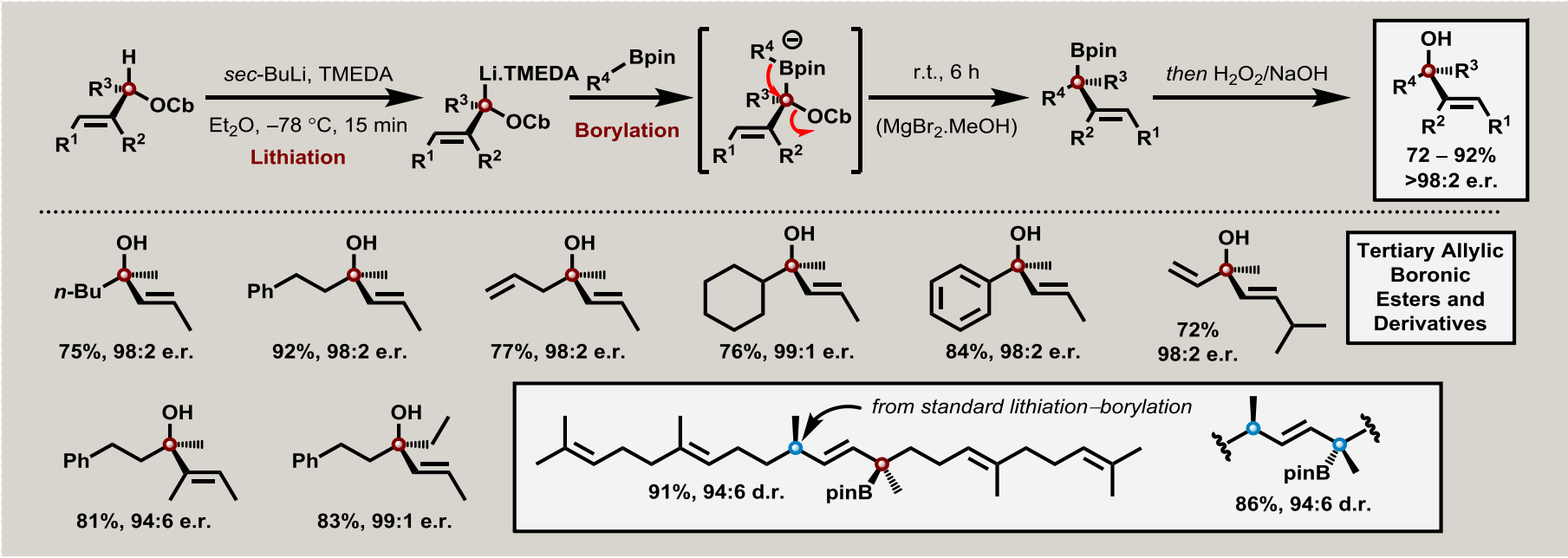
Secondary Boronic Esters



Notes and Key Features: synthesis of secondary boronic esters and derivatives; allows facile migration of challenging groups (Me, Ph, (CH2)2COOtBu and (CH2)2CN); slightly lower e.r. compared to corresponding carbamate; migration times are significantly shorter compared to carbamates.

Use of 2,4,6-triisopropylbenzoates in the asymmetric homologation of challenging boronic esters, R. Larouche-Gautier, C. J. Fletcher, I. Couto and V. K. Aggarwal, *Chem. Commun.* **2011**, *47*, 12592. DOI: 10.1039/C1CC14469C

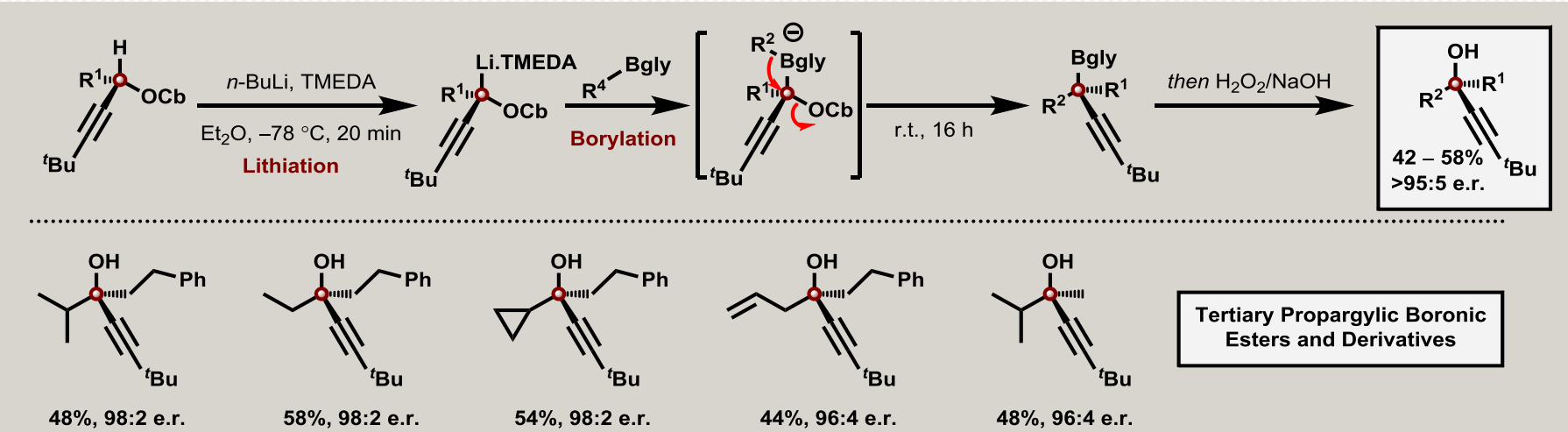
Tertiary Allylic Boronic Esters



Notes and Key Features: synthesis of tertiary allylic boronic esters; secondary dialkyl carbamates cannot be deprotonated; some issues with α/γ selectivity; addition on MgBr2.MeOH prevents racemization due to ate-complex reversibility; standard Zweifel olefination conditions cannot be used for tertiary allylic substrates.

Synthesis of Enantioenriched Tertiary Boronic Esters from Secondary Allylic Carbamates. Application to the Synthesis of C30 Botryococcene, A. P. Pulis and V. K. Aggarwal, *J. Am. Chem. Soc.* **2012**, *134*, 7570. DOI: 10.1021/ja303022d

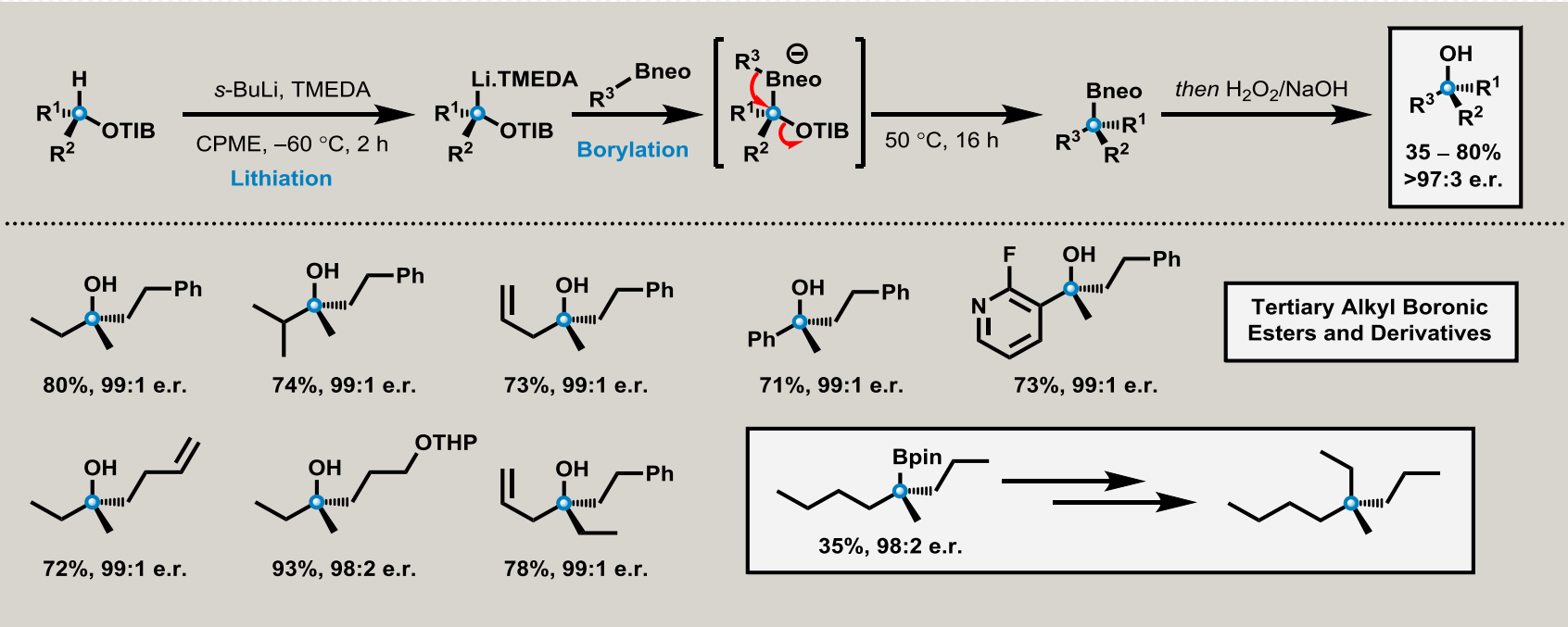
Tertiary Propargylic Boronic Esters



Notes and Key Features: synthesis of tertiary propargylic boronic esters; terminal tBu is essential for configurational stability; ethylene glycol boronic esters are required for complete enantiospecificity; protodeboronation leads to chiral allenes in with e.r.; Suzuki cross-coupling leads to all-carbon tetrasubstituted allenes with high e.r..

Enantioselective Synthesis and Cross-Coupling of Tertiary Propargylic Boronic Esters Using Lithiation–Borylation of Propargylic Carbamates, B. M. Partridge, L. Chausset-Boissarie, M. Burns, A. P. Pulis and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2012**, *51*, 11795. DOI: 10.1002/anie.201203198

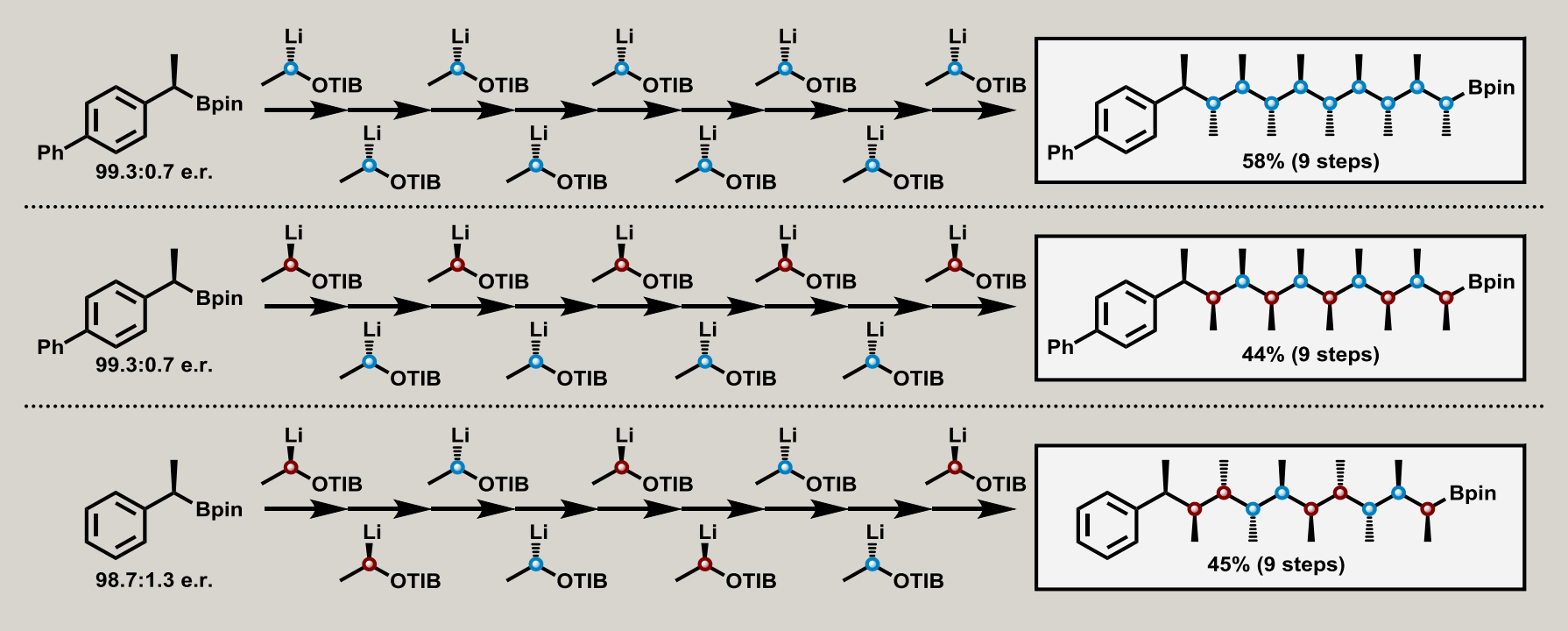
Tertiary Alkyl Boronic Esters



Notes and Key Features: synthesis of tertiary alkyl boronic esters; lithiation conditions optimized for secondary dialkyl benzoates; Bneo is essential to obtain complete stereospecificity; addition of MeOH or TMSCl required to good yield and e.r. for some substrates; 'directing' groups are required to ensure good lithiation.

Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates, A. P. Pulis, D. J. Blair, E. Torres and V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 16054. DOI: 10.1021/ja409100y

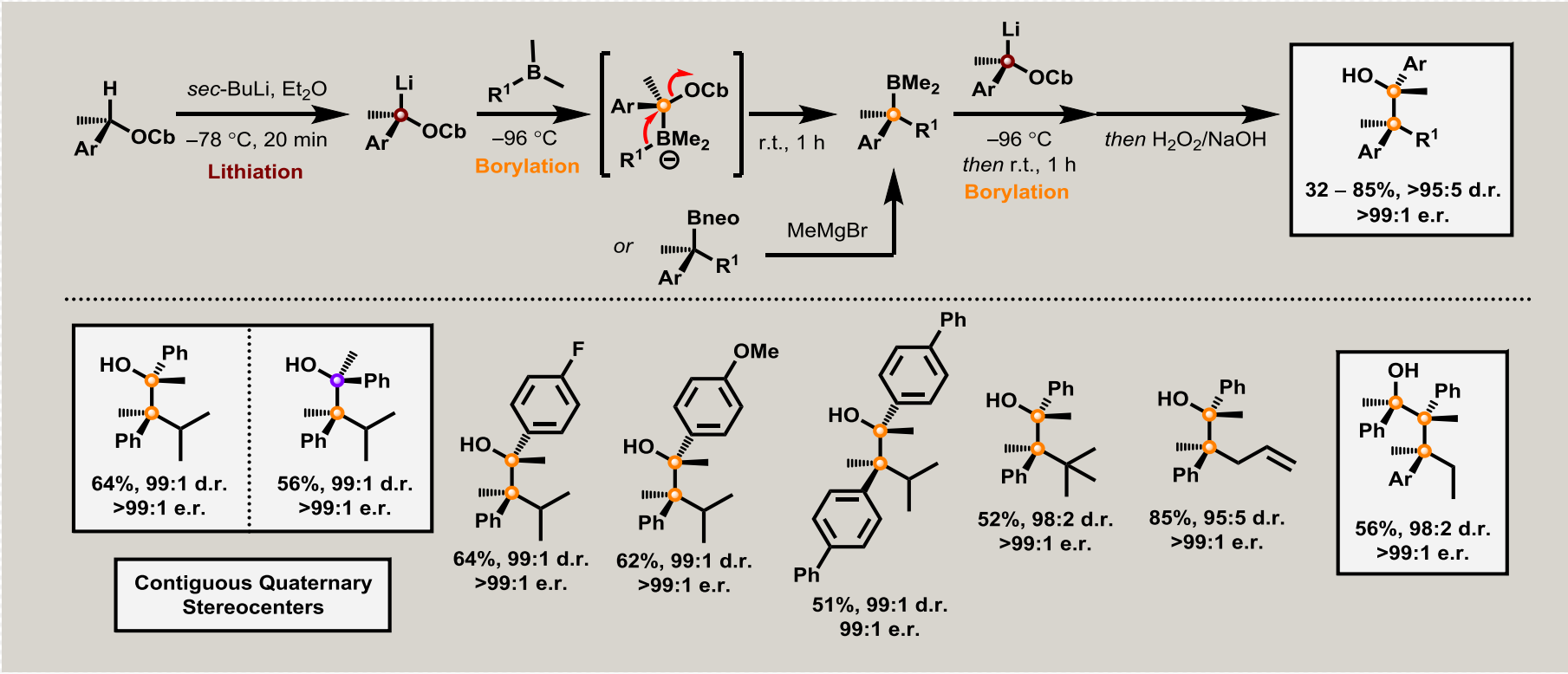
Contiguous, Methyl Bearing Stereocenters



Notes and Key Features: synthesis of contiguous, methyl bearing stereocenters; aqueous work-up required between every three homologations; care must be taken over equivalents and conditions to ensure high conversion; each isomer adopts a different 3D structure.

Assemly-Line synthesis of organic molecules with tailored shapes, M. Burns, S. Essafi, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey and V. K. Aggarwal, *Nature* **2014**, *513*, 183. DOI: 10.1038/nature13711

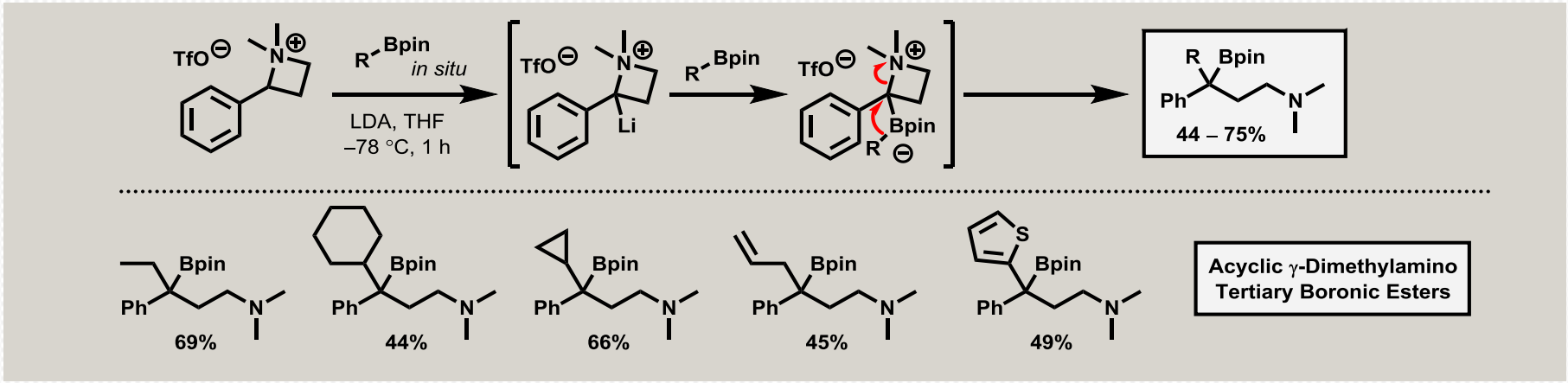
Contiguous Quaternary Stereocenters



Notes and Key Features: synthesis of contiguous quaternary stereocenters; boranes were essential for ate-complex formations and 1,2-migration; Me acts as a non-migrating group; transesterification must be done from Bneo and not Bpin (in the case of enantioenriched boronic esters); primary substituents do not migrate preferentially over Me.

Construction of Multiple, Contiguous Quaternary Stereocenters in Acyclic Molecules by Lithiation–Borylation, C. G. Watson, A. Balanta, T. G. Elford, S. Essafi, J. N. Harvey and V. K. Aggarwal, *J. Am. Chem. Soc.* **2014**, *136*, 17370. DOI: 10.1021/ja509029h

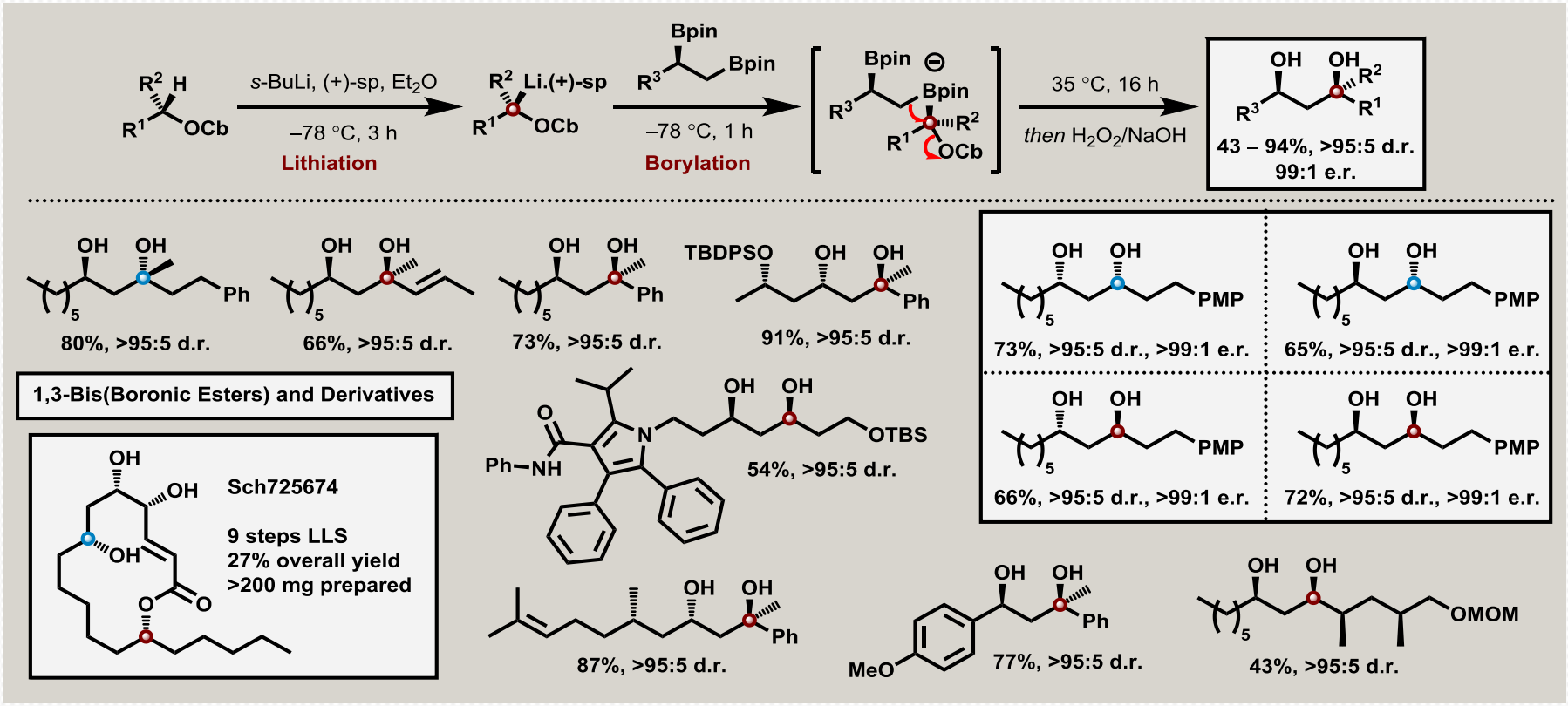
Acyclic γ-Dimethylamino Tertiary Boronic Esters



Notes and Key Features: synthesis acyclic γ-dimethylamino tertiary boronic esters; some boronic ester products underwent protodeboronation, so had to be isolated as the corresponding alcohol; azetidinium ylides are configurationally and chemically unstable.

Synthesis of 3-Aryl-1-aminopropane Derivatives: Lithiation–Borylation–Ring-Opening of Azetidinium Ions, G. Casoni, E. L. Myers and V. K. Aggarwal, *Synthesis* **2016**, *48*, 3241. DOI: 10.1055/s-0035-1562447

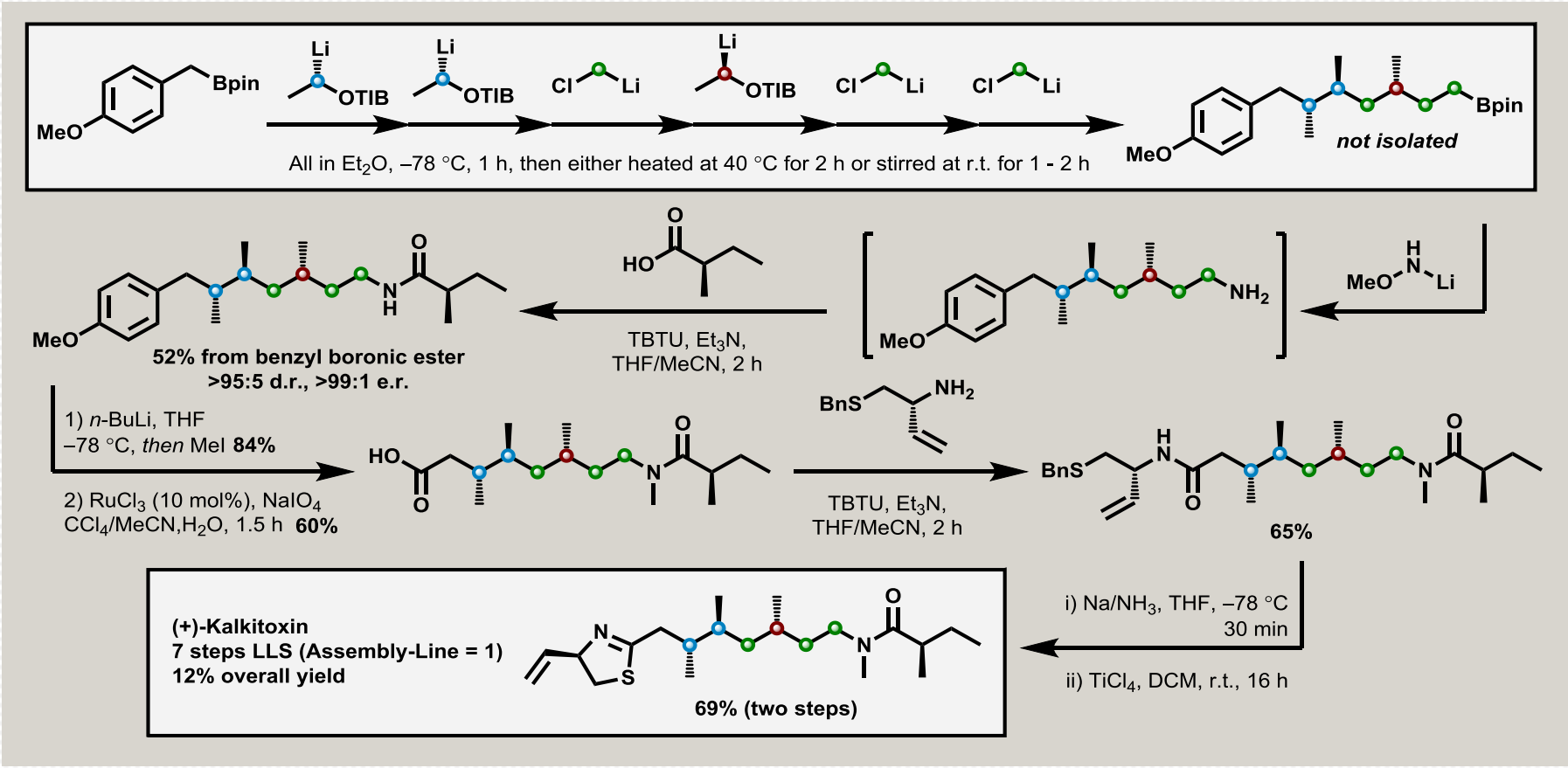
Secondary-Secondary/Tertiary 1,3-Bis(Boronic Esters)



Notes and Key Features: synthesis of secondary/secondary and secondary/tertiary 1,3-bis(boronic esters); total synthesis of Sch725674; good-excellent selectivity for primary boronic ester; only sparteine-ligated carbenoids lead to good selectivity; excess 1,2-bis(boronic ester) required for primary selectivity; or (with TIB esters) an excess of carbenoid can be used but a MeOH quench is required.

Regio- and Stereoselective Homologation of 1,2-Bis(Boronic Esters): Stereocontrolled Synthesis of 1,3-Diols and Sch725674, A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman and V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 14663. DOI: 10.1002/anie.201608406

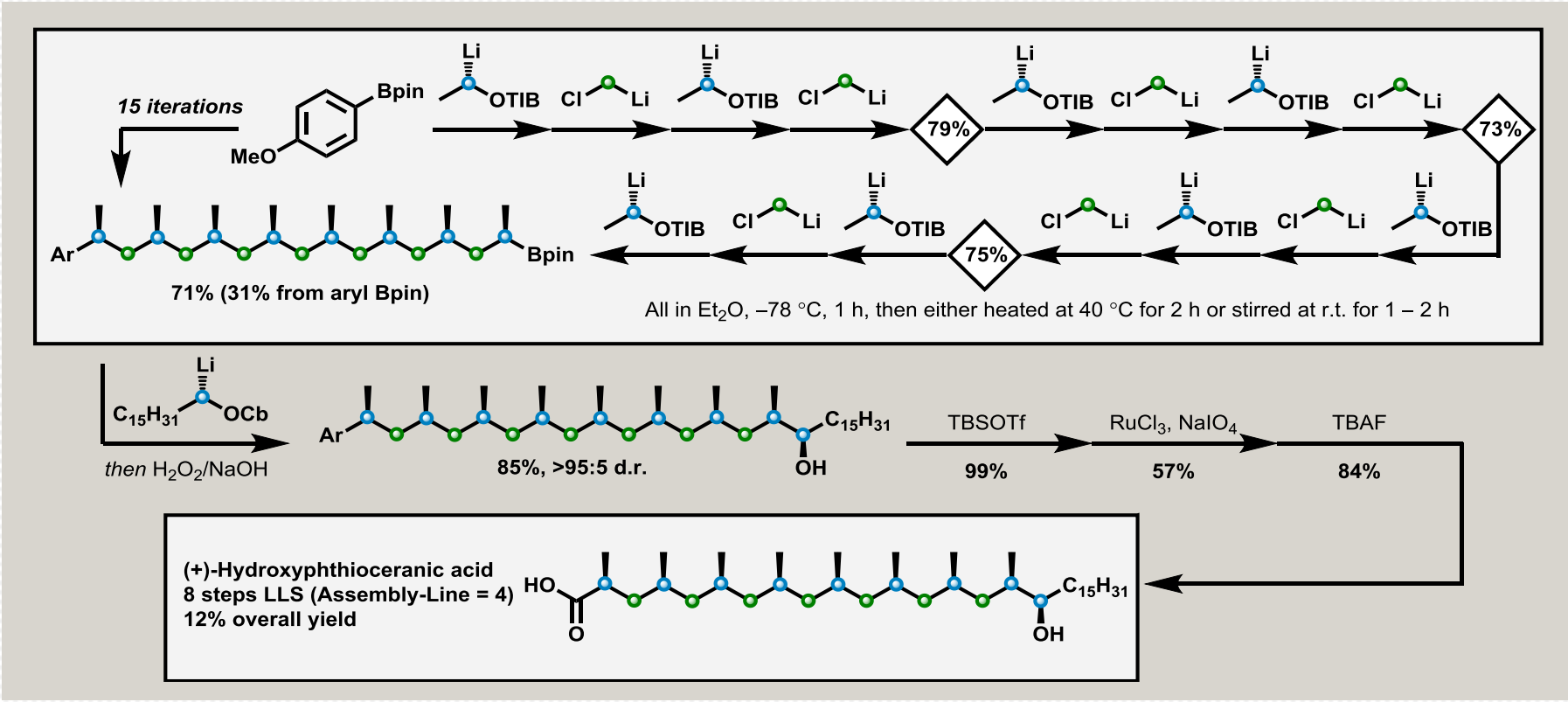
Total Synthesis: (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid



Notes and Key Features: total synthesis of (+)-kalkitoxin; assembly-line process, including amination and amide coupling only required a single purification; assembling-line process only takes 4 days.

Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis, S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley and V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398. DOI: 10.1021/ja512875g

Total Synthesis: (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid



Notes and Key Features: total synthesis of (+)-hydroxyphthioceranic acid; 15 consecutive homologations with column-chromatography after every four homologations; long chain carbamate required alternative conditions for its use due to poor solubility;

Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis, S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley and V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398. DOI: 10.1021/ja512875g