# Varinder K. Aggarwal

## Homologation of Boronic Esters

Balu D. Dherange

Dec 2nd 2020

# **Varinder Kumar Aggarwal**

Date of Birth: January 1, 1961

BS in chemistry, Cambridge University 1983

PHD : Prof. Stuart Warren Cambridge University 1983-1986

Prof. Gilbert Stork, Columbia University 1986-1988.

Lecturer in Chemistry, Bath University, 1988-1991.

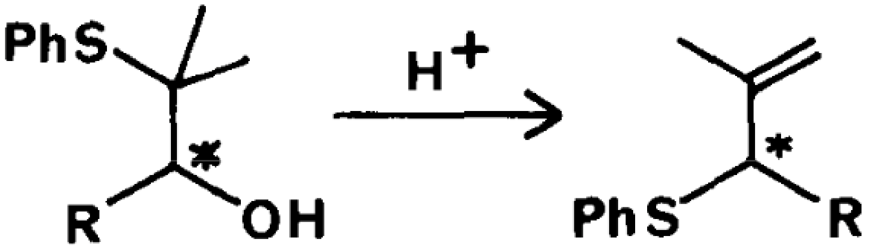
Lecturer in Chemistry, Sheffield University (1991-1995)

Reader in Chemistry, Sheffield University (1995-1997)

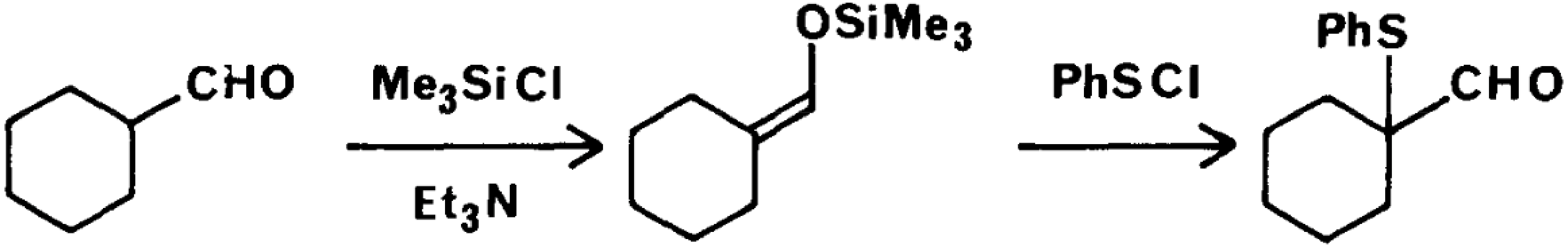
Professor in Chemistry, Sheffield University (Oct. 1997-Sept. 2000).

Professor in Synthetic Chemistry, Bristol University (Sept. 2000 - present).

# Phenylthio (PhS) Migration in the Stereocontrolled Synthesis of Allylic Alcohols with 1,4-Related Chiral Centres



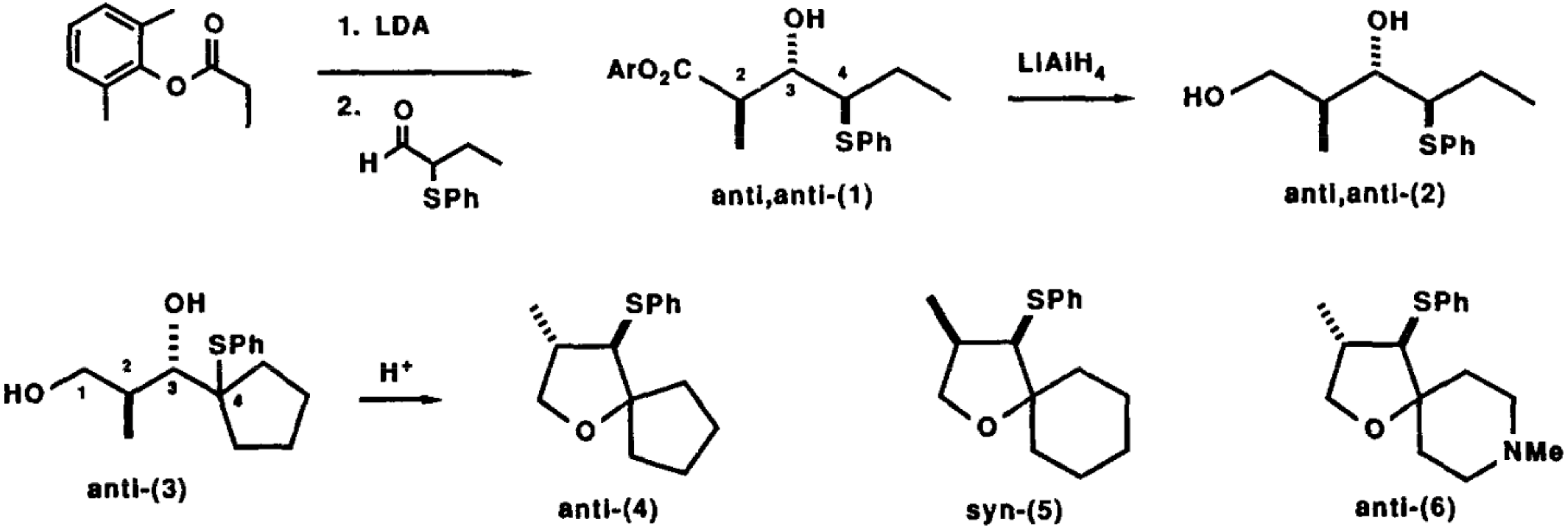
(1) (2)



(3)

V. K. Aggarwal and S. Warren, Tetrahedron Letters, **1986**, 27, 101-104.

# Stereochemical Control in the Synthesis of Tetrahydrofurans by Cyclisation of Diols with Phenylthio Migration



anti,anti-(1)

anti,anti-(2)

anti-(3)

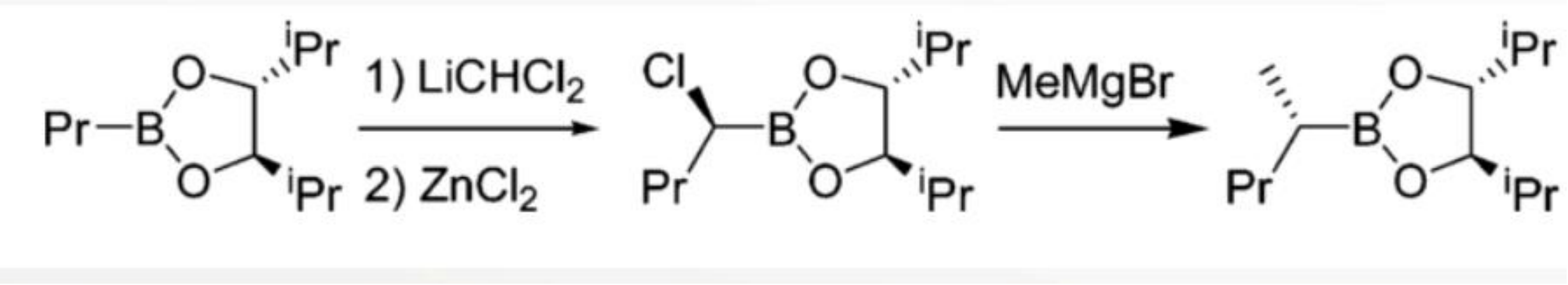
anti-(4)

syn-(5)

anti-(6)

V. K. Aggarwal, I Coldham, S. McIntre, F. H. Sansbury, M.-J. Villa and S. Warren, Tetrahedron Letters, **1988**, 29, 4885-4888

# First Homologation of Boronic Esters

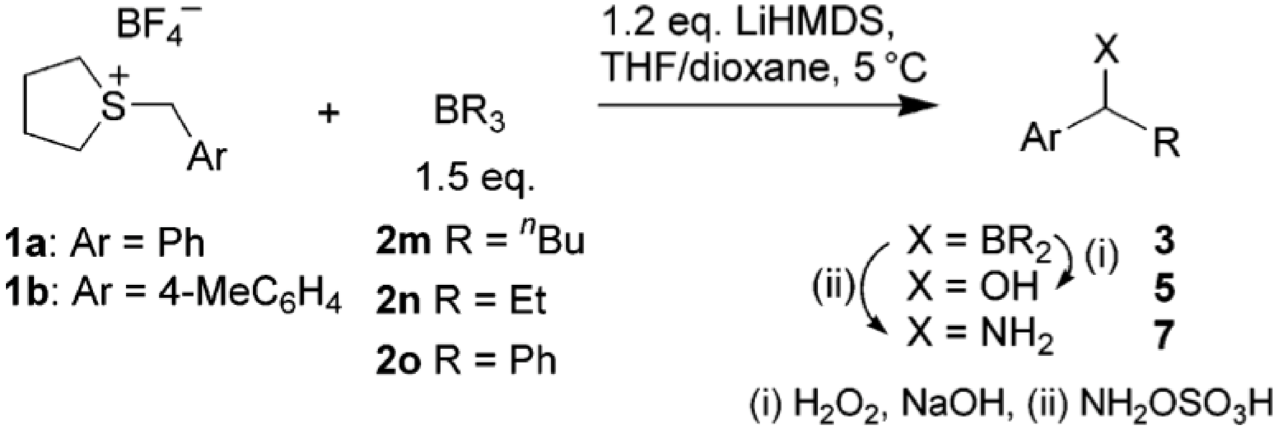


dr: 97%

dr: 92-95%

Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590

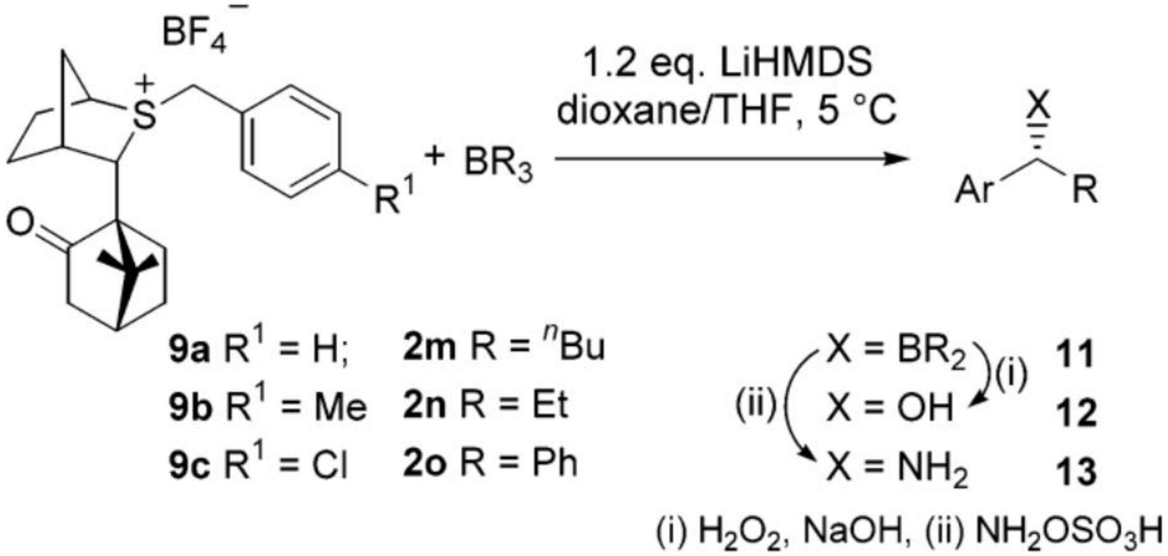
# Synthesis and Applications of Chiral Organoboranes Generated from Sulfonium Ylides



| entry | R | Ar | X | compound/yield (%)[a] |
|---|---|---|---|---|
| 1 | $^n$Bu | Ph | OH | **5am**/78 |
| 2 | $^n$Bu | Ph | NH$_2$ | **7am**/74 |
| 3 | Et | Ph | OH | **5an**/76 |
| 4 | Et | Ph | NH$_2$ | **7an**/77 |
| 5 | Ph | 4-MeC$_6$H$_4$ | OH | **5bo**/87 |
| 6 | Ph | 4-MeC$_6$H$_4$ | NH$_2$ | **7bo**/17 |

V. K Aggarwal, G. Yu Fang, A. Schmidt, *J. Am. Chem. Soc.*, **2005**, *127*, 1642-1643

# Synthesis and Applications of Chiral Organoboranes Generated from Sulfonium Ylides



**9a** $R^1$ = H; **2m** R = $^n$Bu
**9b** $R^1$ = Me **2n** R = Et
**9c** $R^1$ = Cl **2o** R = Ph

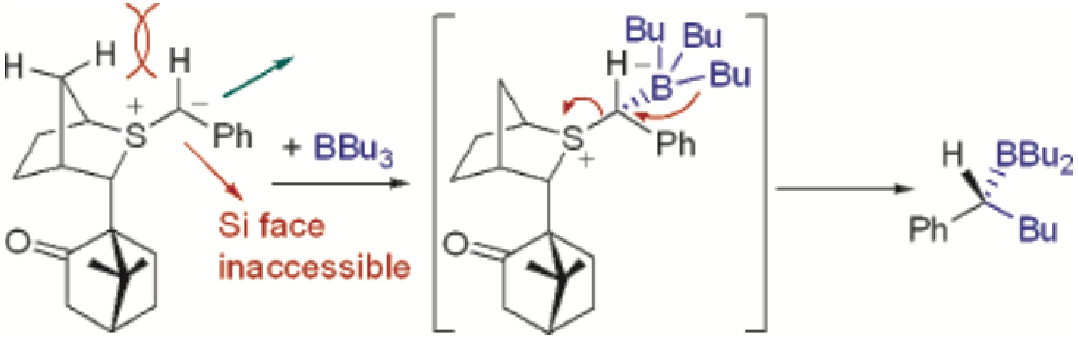
X = $BR_2$ **11**
X = OH **12**
X = $NH_2$ **13**

(i) $H_2O_2$, NaOH, (ii) $NH_2OSO_3H$

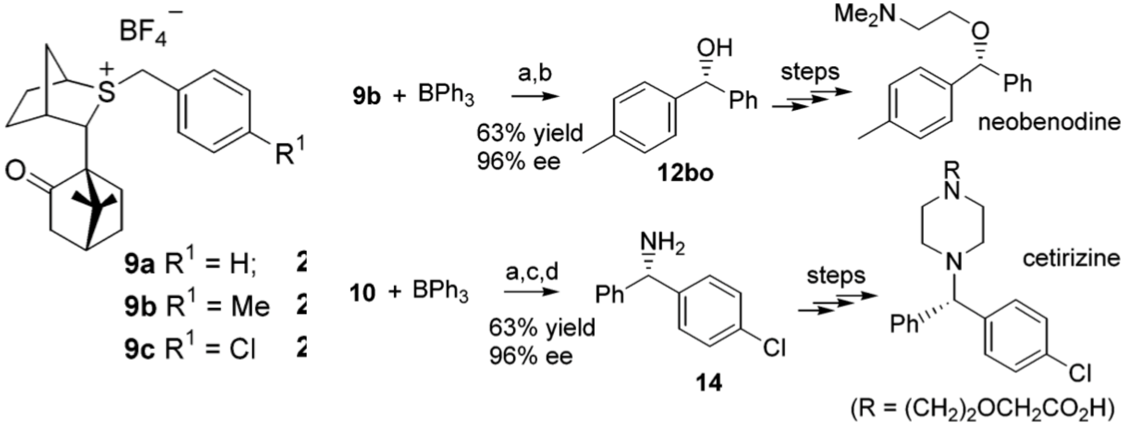
| entry | R | Ar | X | product | yield[b]/ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $^n$Bu | Ph | OH | **12am** | 70/95 |
| 2 | $^n$Bu | Ph | $NH_2$ | **13am** | 72/97[d] |
| 3 | Et | Ph | OH | **12an** | 73/96 |
| 4 | Et | Ph | $NH_2$ | **13an** | 68/97[d] |
| 5 | Ph | 4-$MeC_6H_4$ | OH | **12bo** | 87/95 |
| 6 | Ph | 4-$ClC_6H_4$ | $NH_2$ | **13co** | 68/96[d] |

V. K Aggarwal, G. Yu Fang, A. Schmidt, *J. Am. Chem. Soc*., **2005**, *127*, 1642-1643

# Synthesis and Applications of Chiral Organoboranes Generated from Sulfonium Ylides

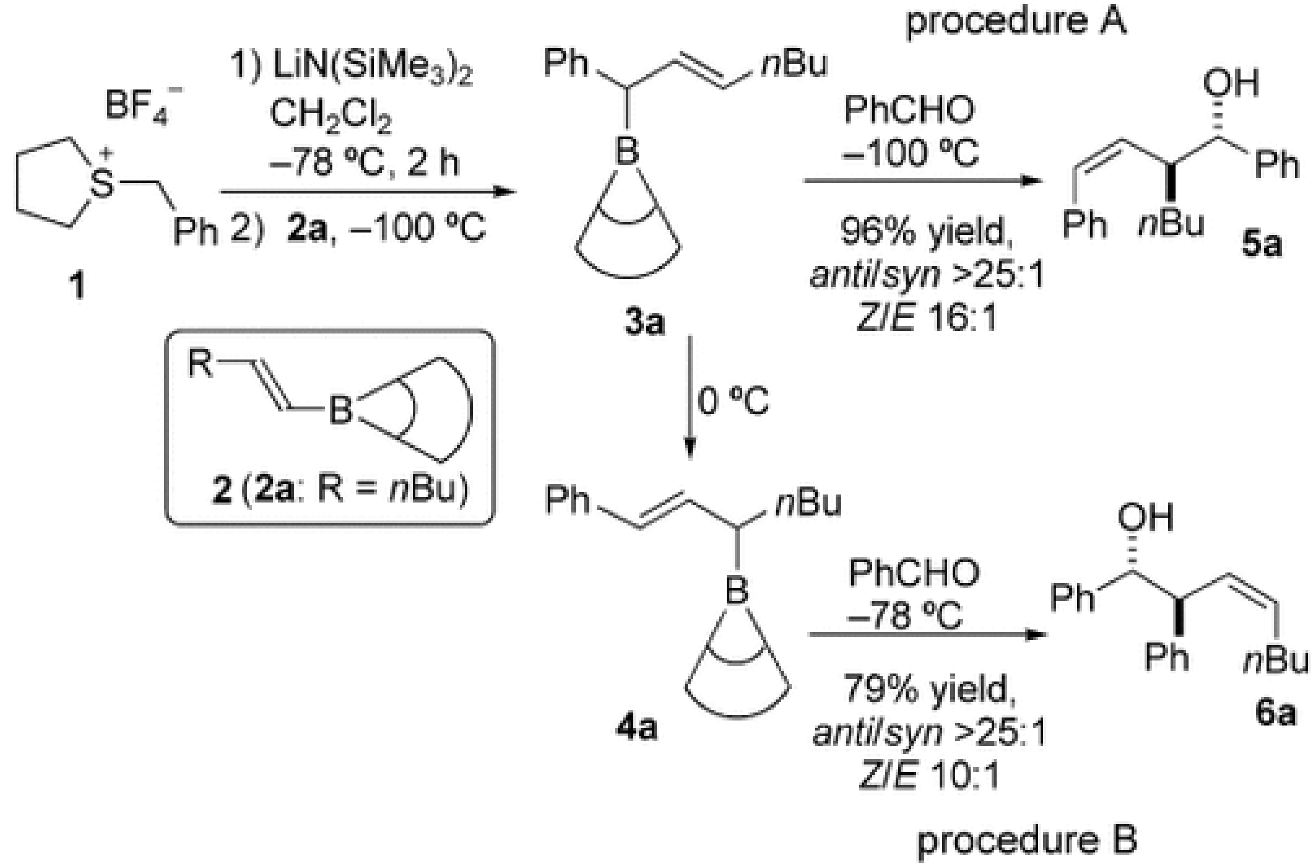


Control of Enantioselectivity



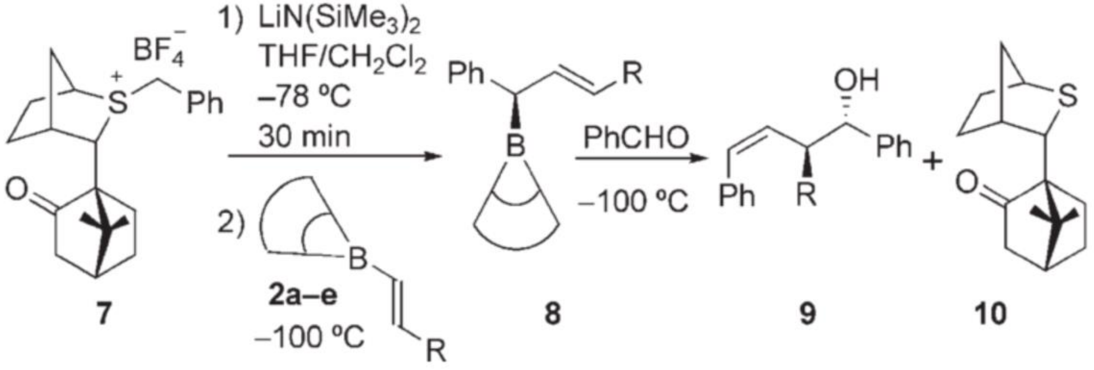
V. K Aggarwal, G. Yu Fang, A. Schmidt, *J. Am. Chem. Soc.*, **2005**, *127*, 1642-1643

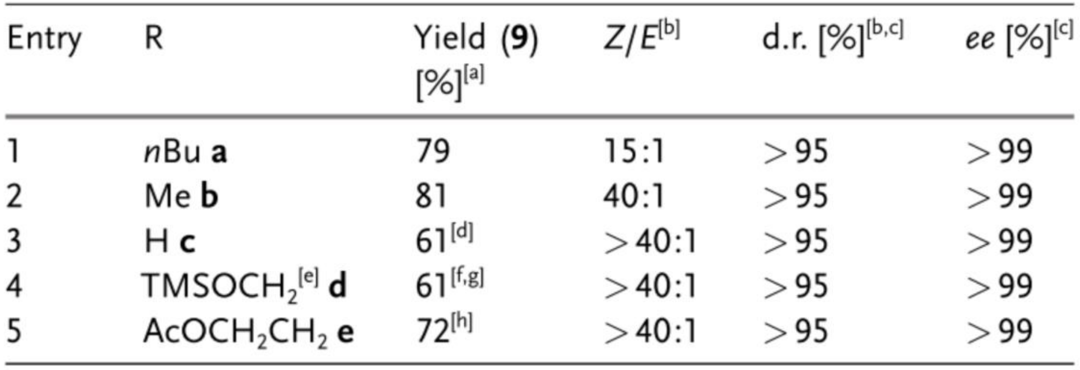
# Asymmetric Synthesis of α Substituted Allyl Boranes



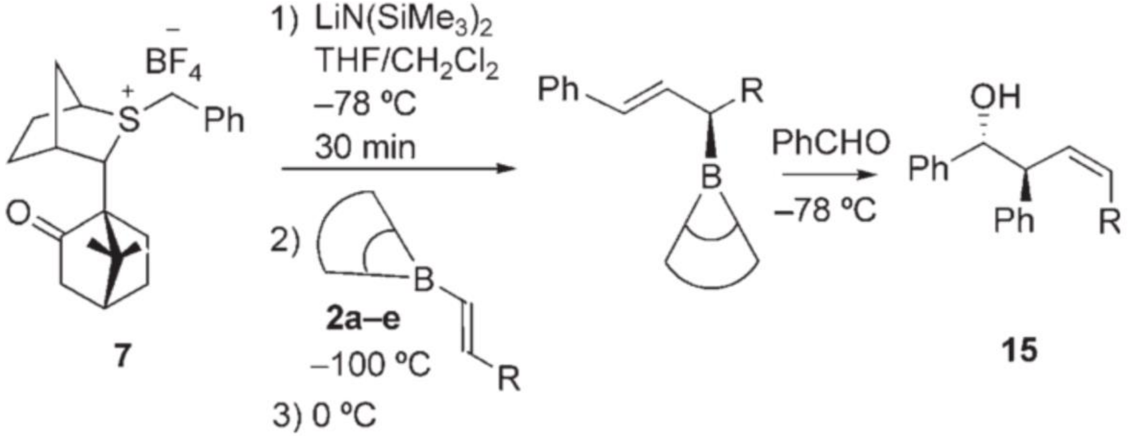
G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46*, 359-362

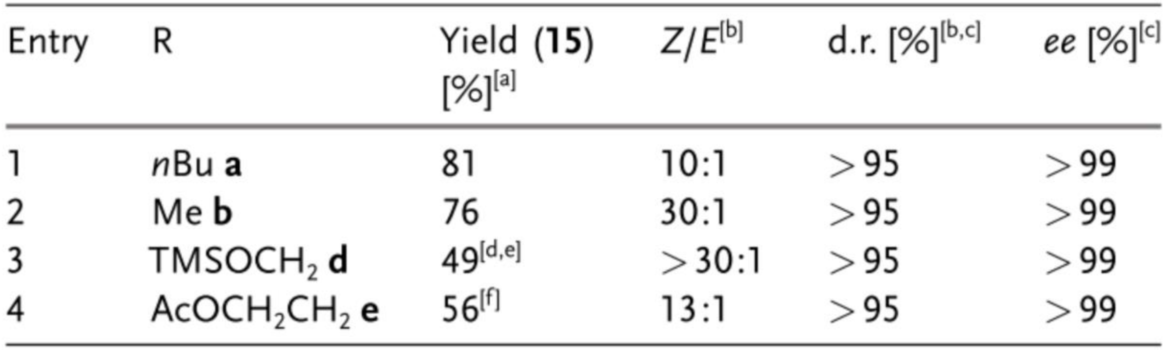
# Asymmetric Synthesis of α Substituted Allyl Boranes





| Entry | R | Yield (**9**) [%][a] | $Z/E$[b] | d.r. [%][b,c] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | *n*Bu **a** | 79 | 15:1 | >95 | >99 |
| 2 | Me **b** | 81 | 40:1 | >95 | >99 |
| 3 | H **c** | 61[d] | >40:1 | >95 | >99 |
| 4 | $TMSOCH_2$[e] **d** | 61[f,g] | >40:1 | >95 | >99 |
| 5 | $AcOCH_2CH_2$ **e** | 72[h] | >40:1 | >95 | >99 |

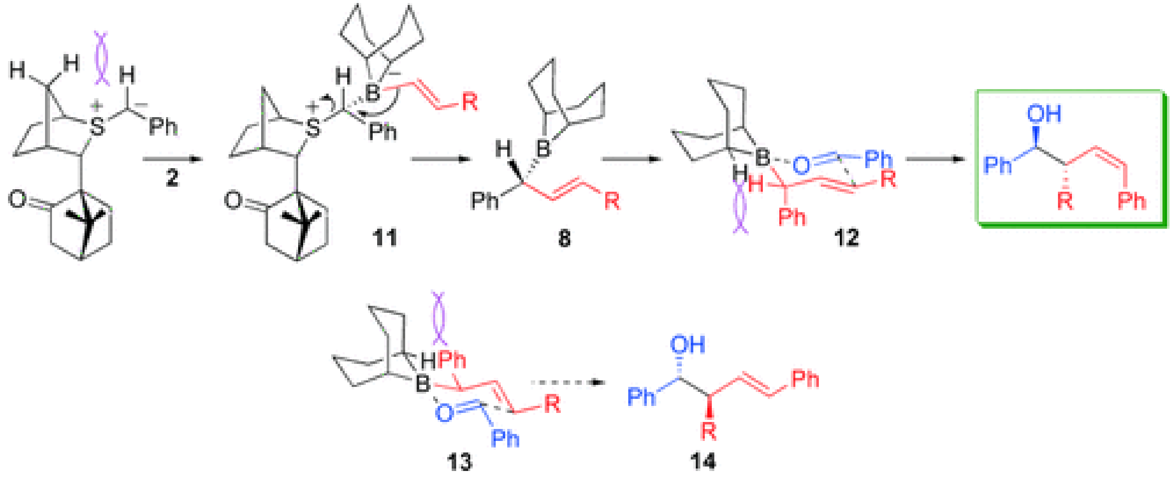




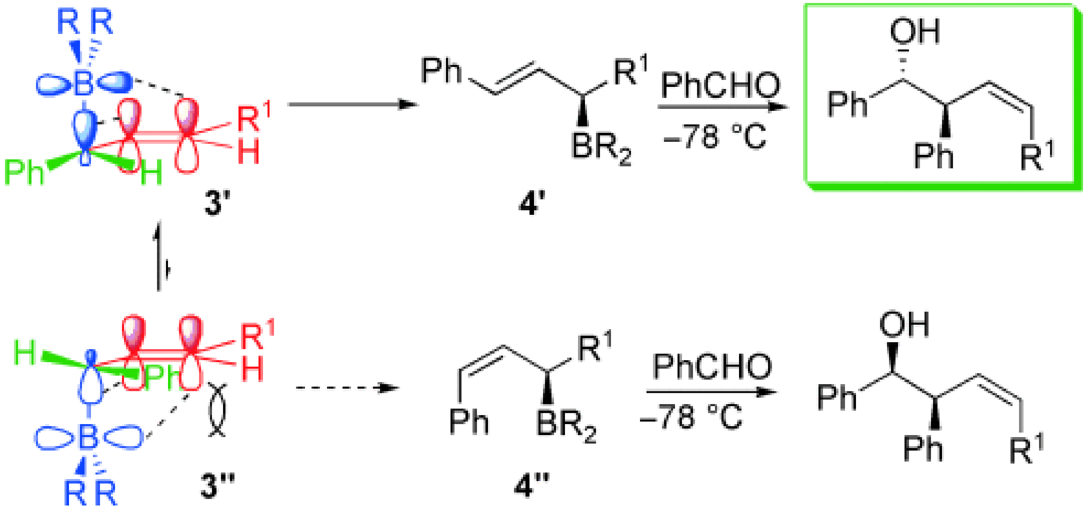
| Entry | R | Yield (**15**) [%][a] | $Z/E$[b] | d.r. [%][b,c] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | *n*Bu **a** | 81 | 10:1 | >95 | >99 |
| 2 | Me **b** | 76 | 30:1 | >95 | >99 |
| 3 | $TMSOCH_2$ **d** | 49[d,e] | >30:1 | >95 | >99 |
| 4 | $AcOCH_2CH_2$ **e** | 56[f] | 13:1 | >95 | >99 |

G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46*, 359-362

# Asymmetric Synthesis of α Substituted Allyl Boranes



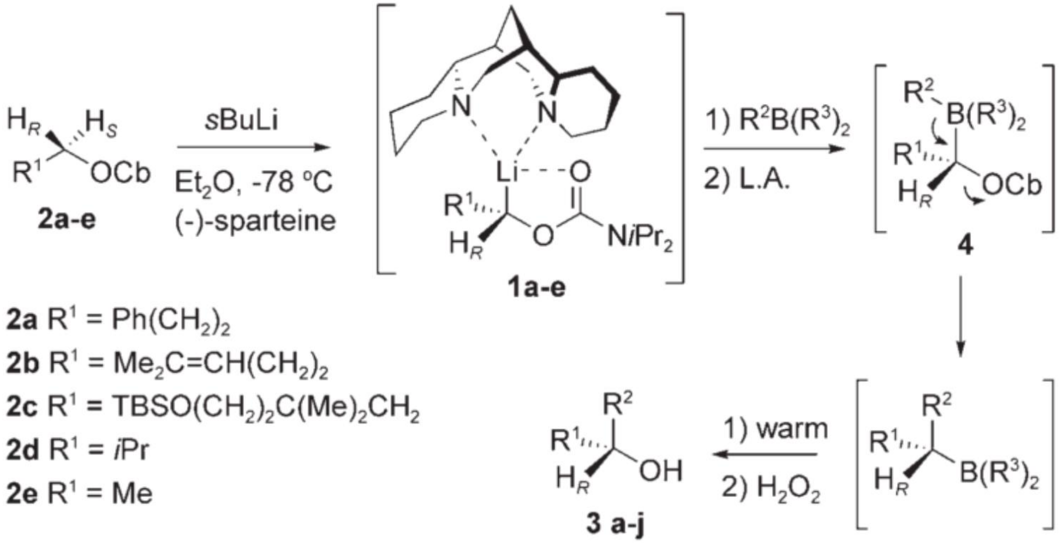
**Rationale for the observed stereochemistry**



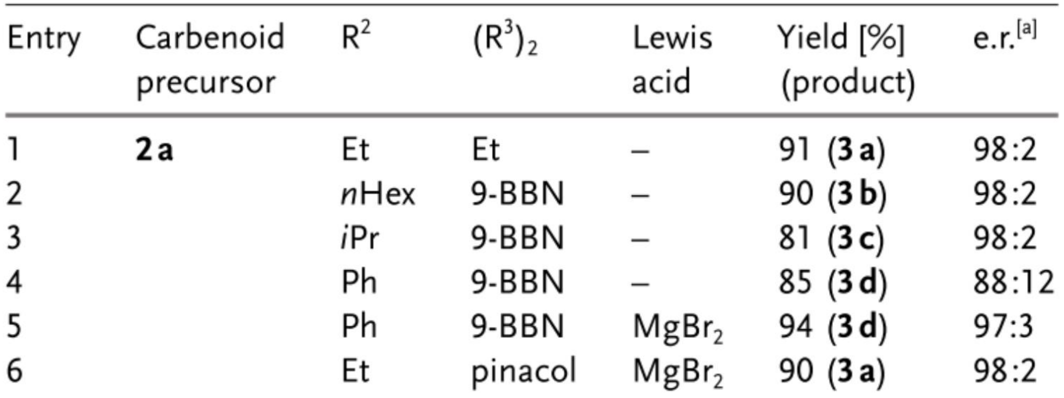
**Proposed [1,3]-borotropic rearrangement.**

G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46*, 359-362

# Lithiated Carbamates: Chiral Carbenoids for Iterative Homologationof Boranes and Boronic Esters



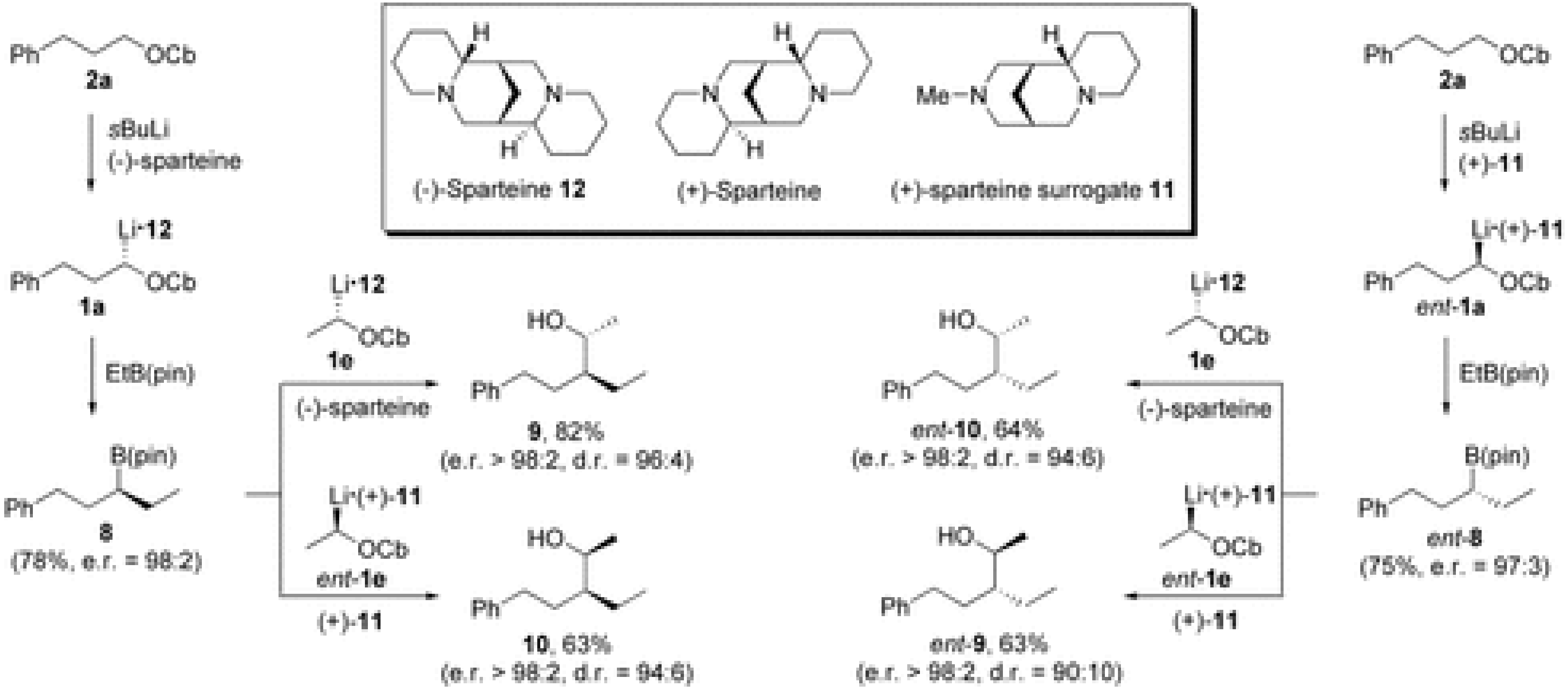
**2a** $R^1 = Ph(CH_2)_2$
**2b** $R^1 = Me_2C{=}CH(CH_2)_2$
**2c** $R^1 = TBSO(CH_2)_2C(Me)_2CH_2$
**2d** $R^1 = i$Pr
**2e** $R^1$ = Me



| Entry | Carbenoid precursor | $R^2$ | $(R^3)_2$ | Lewis acid | Yield [%] (product) | e.r.[a] |
|---|---|---|---|---|---|---|
| 1 | **2a** | Et | Et | – | 91 (**3a**) | 98:2 |
| 2 | | *n*Hex | 9-BBN | – | 90 (**3b**) | 98:2 |
| 3 | | *i*Pr | 9-BBN | – | 81 (**3c**) | 98:2 |
| 4 | | Ph | 9-BBN | – | 85 (**3d**) | 88:12 |
| 5 | | Ph | 9-BBN | $MgBr_2$ | 94 (**3d**) | 97:3 |
| 6 | | Et | pinacol | $MgBr_2$ | 90 (**3a**) | 98:2 |

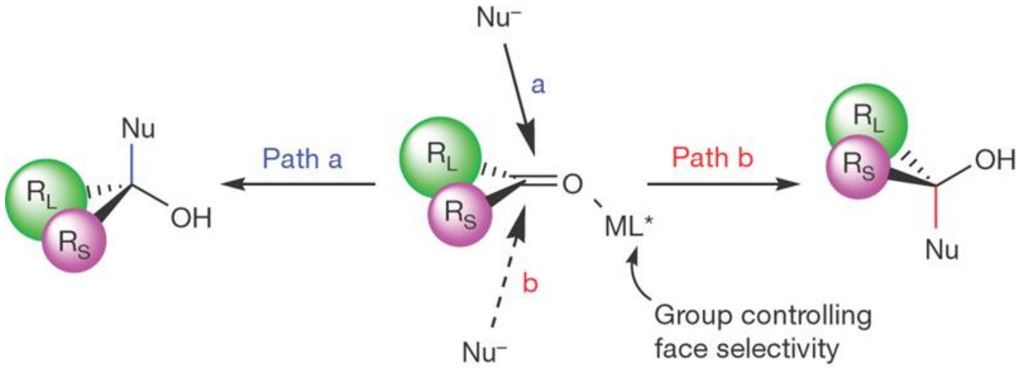
G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46,* 7491 –7494

# Lithiated Carbamates: Chiral Carbenoids for Iterative Homologationof Boranes and Boronic Esters



G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2007**, *46,* 7491 –7494

# Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols

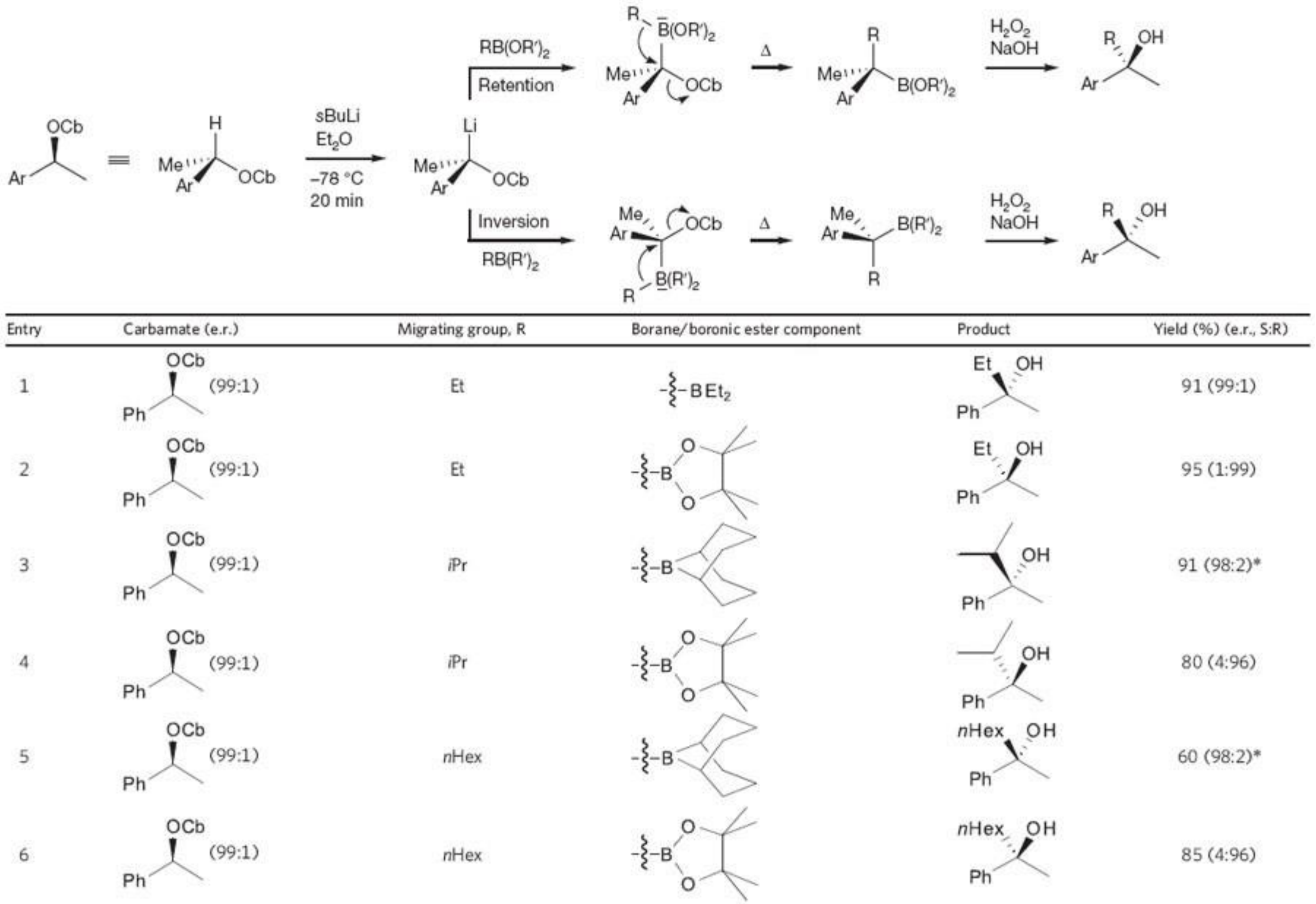


Common strategy for preparing chiral tertiary alcohols through face selective addition of nucleophiles to ketones.

JL Stymiest *et al.* *Nature* **456**, 778-782 (2008) doi:10.1038/nature07592

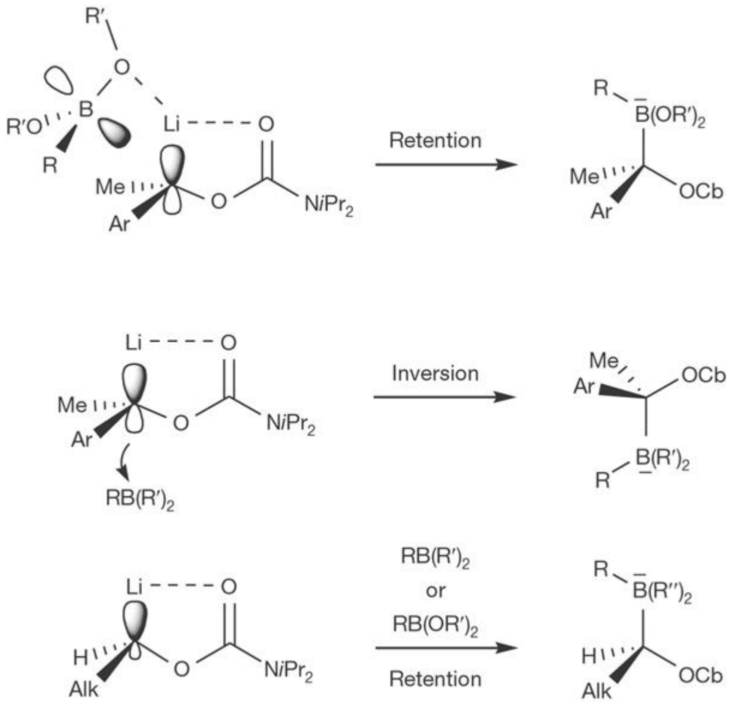
# Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols

**Table 1 | Lithiation–borylation of chiral secondary carbamates leading to tertiary alcohols**



| Entry | Carbamate (e.r.) | Migrating group, R | Borane/boronic ester component | Product | Yield (%) (e.r., S:R) |
|---|---|---|---|---|---|
| 1 | (99:1) | Et | $-BEt_2$ |  | 91 (99:1) |
| 2 | (99:1) | Et |  |  | 95 (1:99) |
| 3 | (99:1) | *i*Pr |  |  | 91 (98:2)* |
| 4 | (99:1) | *i*Pr |  |  | 80 (4:96) |
| 5 | (99:1) | *n*Hex |  |  | 60 (98:2)* |
| 6 | (99:1) | *n*Hex |  |  | 85 (4:96) |

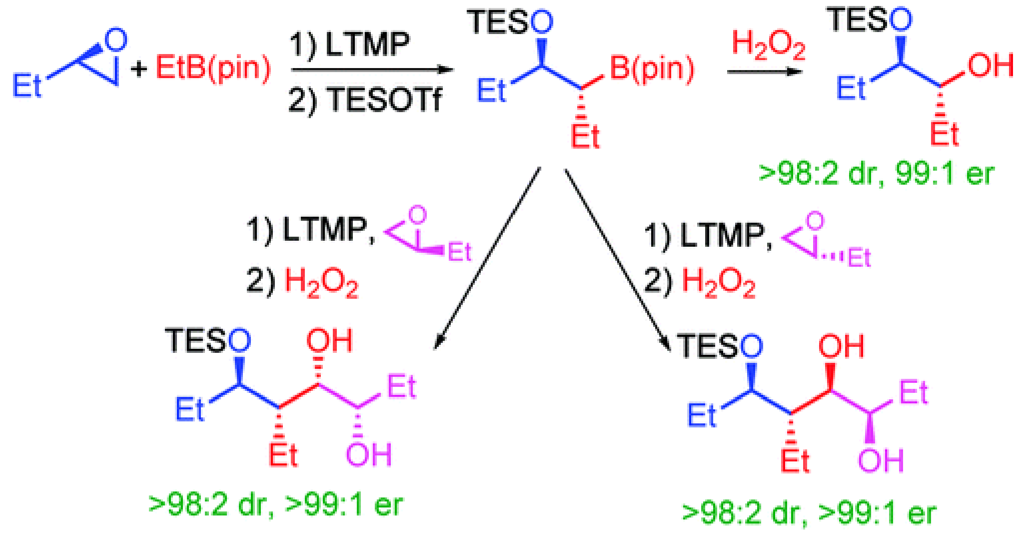
# Rationalization of the inversion versus retention of stereochemistry observed in reactions of lithiated carbamates with boranes and boronic esters respectively.

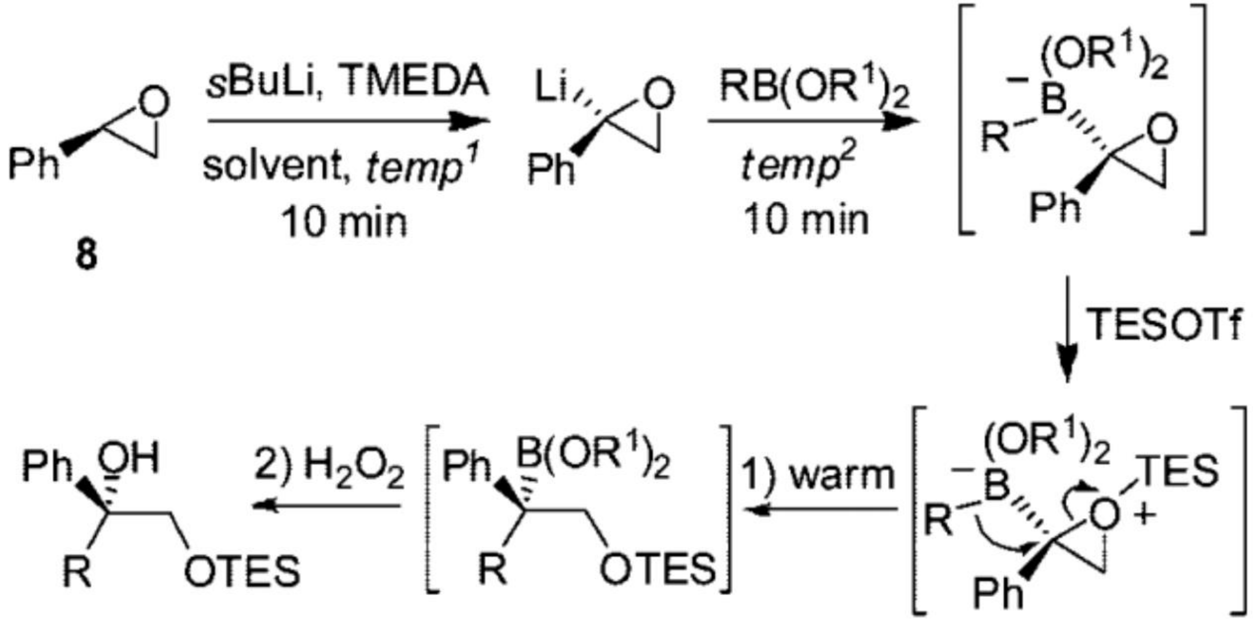


Non-mesomerically stabilized carbanion is essentially sp3 hybridized and has very little electron density opposite the metal

JL Stymiest *et al. Nature* **456**, 778-782 (2008) doi:10.1038/nature07592

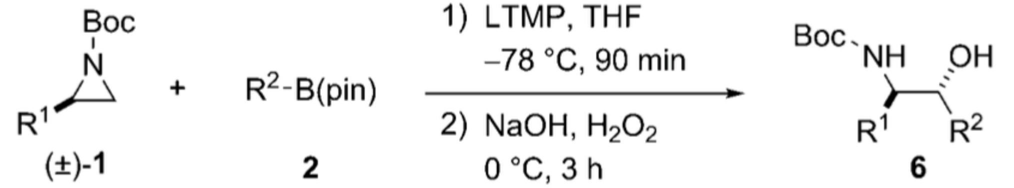
# Chiral Lithium Generated From Chiral Epoxide

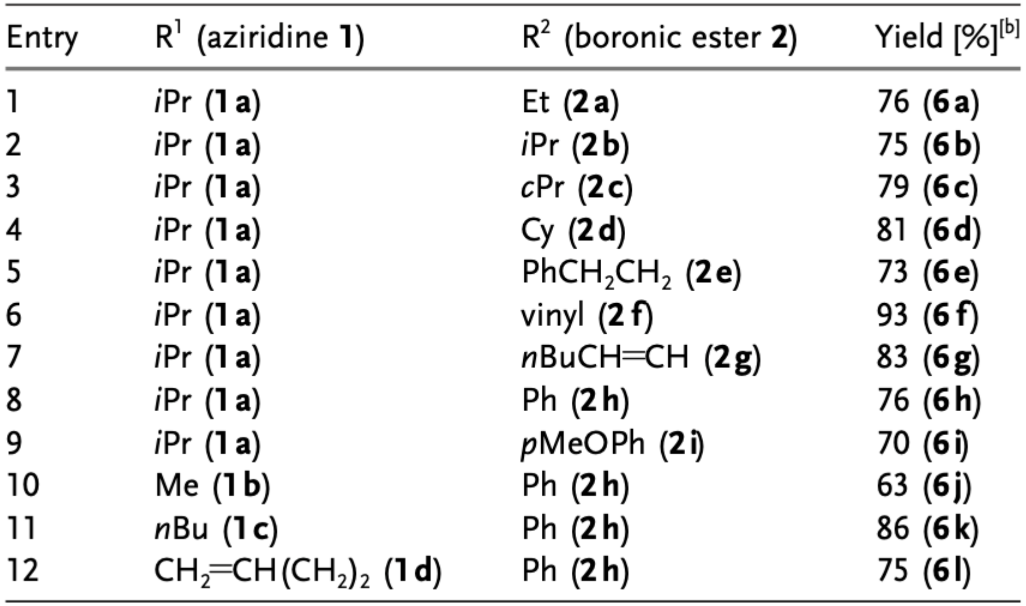




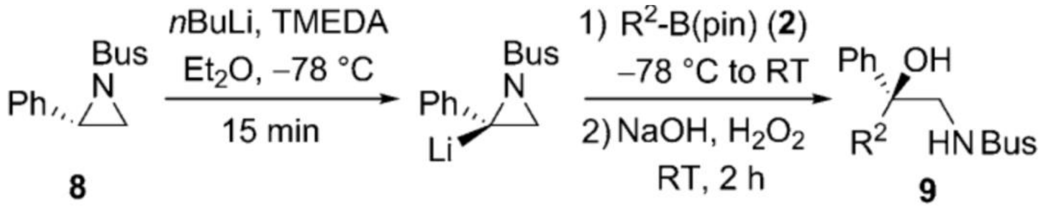
E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt, V. K. Aggarwal,*Org. Lett*. **2009**, *11*, 165-168

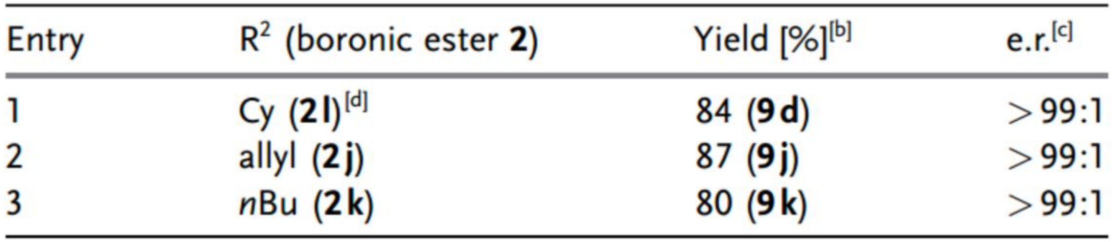
# Chiral Lithium Generated From Chiral Aziridines





| Entry | R$^1$ (aziridine **1**) | R$^2$ (boronic ester **2**) | Yield [%][b] |
|---|---|---|---|
| 1 | *i*Pr (**1a**) | Et (**2a**) | 76 (**6a**) |
| 2 | *i*Pr (**1a**) | *i*Pr (**2b**) | 75 (**6b**) |
| 3 | *i*Pr (**1a**) | *c*Pr (**2c**) | 79 (**6c**) |
| 4 | *i*Pr (**1a**) | Cy (**2d**) | 81 (**6d**) |
| 5 | *i*Pr (**1a**) | $PhCH_2CH_2$ (**2e**) | 73 (**6e**) |
| 6 | *i*Pr (**1a**) | vinyl (**2f**) | 93 (**6f**) |
| 7 | *i*Pr (**1a**) | *n*BuCH=CH (**2g**) | 83 (**6g**) |
| 8 | *i*Pr (**1a**) | Ph (**2h**) | 76 (**6h**) |
| 9 | *i*Pr (**1a**) | *p*MeOPh (**2i**) | 70 (**6i**) |
| 10 | Me (**1b**) | Ph (**2h**) | 63 (**6j**) |
| 11 | *n*Bu (**1c**) | Ph (**2h**) | 86 (**6k**) |
| 12 | $CH_2{=}CH(CH_2)_2$ (**1d**) | Ph (**2h**) | 75 (**6l**) |

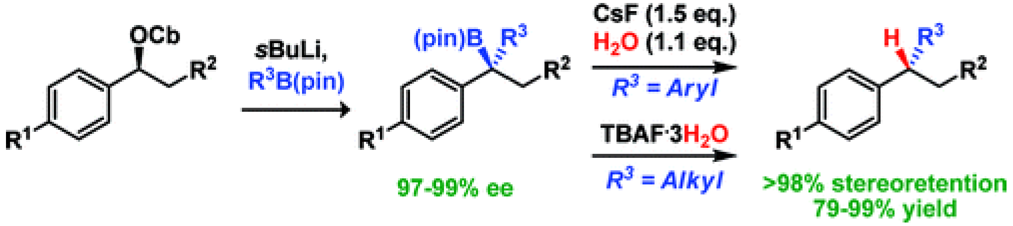


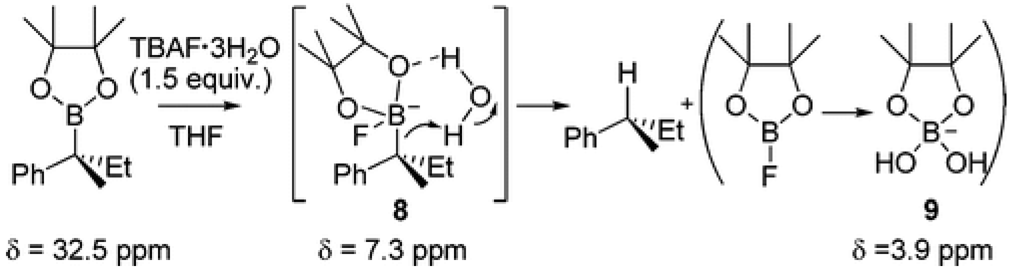


| Entry | R$^2$ (boronic ester **2**) | Yield [%][b] | e.r.[c] |
|---|---|---|---|
| 1 | Cy (**2l**)[d] | 84 (**9d**) | >99:1 |
| 2 | allyl (**2j**) | 87 (**9j**) | >99:1 |
| 3 | *n*Bu (**2k**) | 80 (**9k**) | >99:1 |

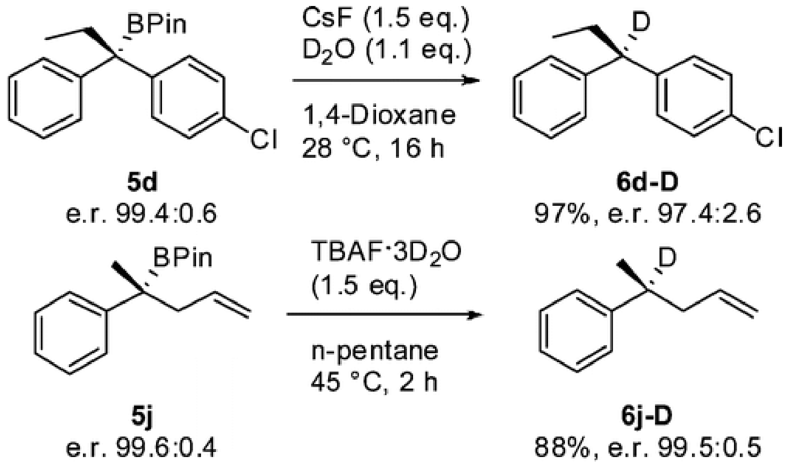
F. Schmidt, F. Keller, E. Vedrenne, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2009**, *48*, 1149-1152

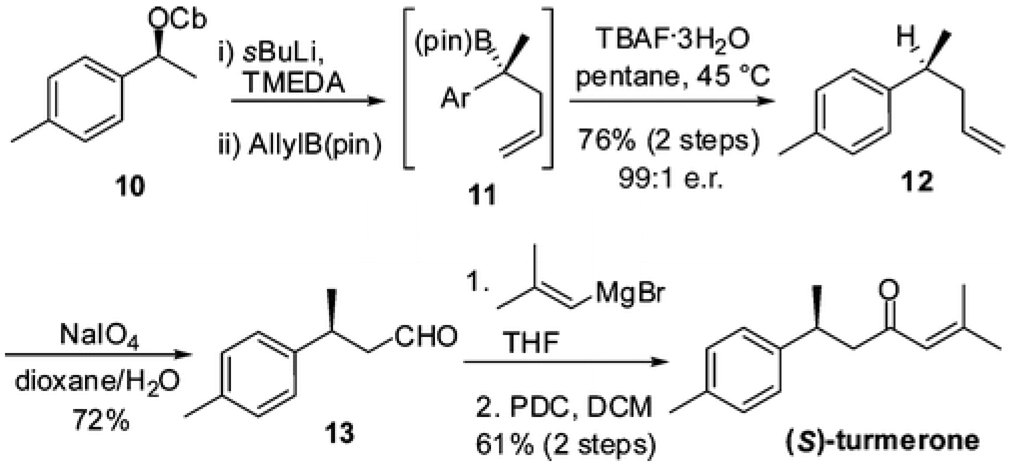
# Stereocontrolled Protodeboronation of Tertiary Boronic Esters



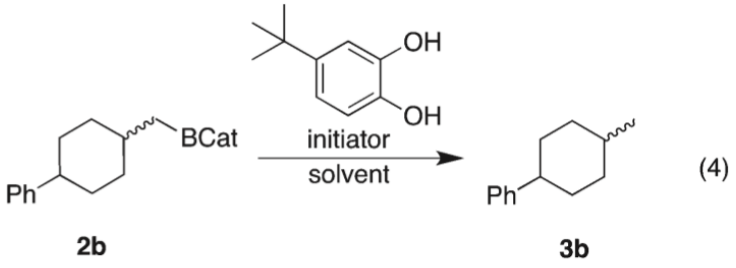


S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal.*J. Am. Chem. Soc.*, **2010**, *132*, 17096-17098



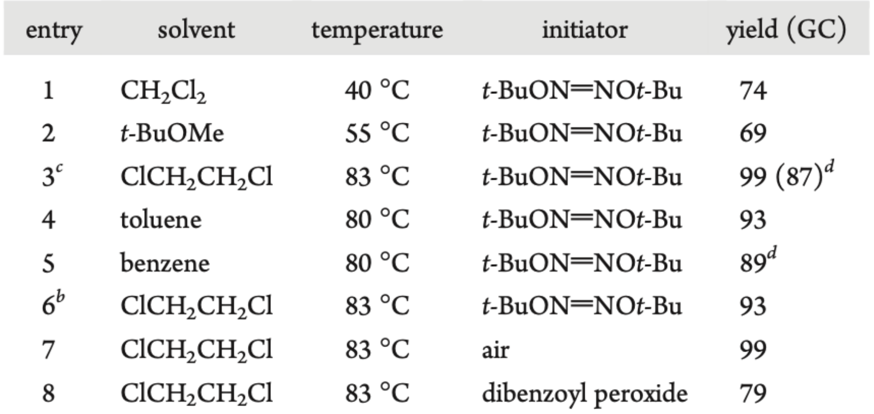


# Protodeboronation of unactivated boronic esters

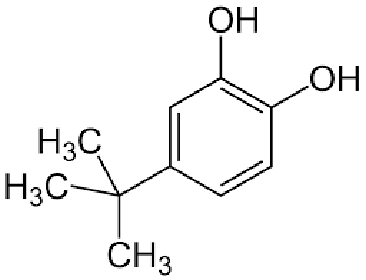


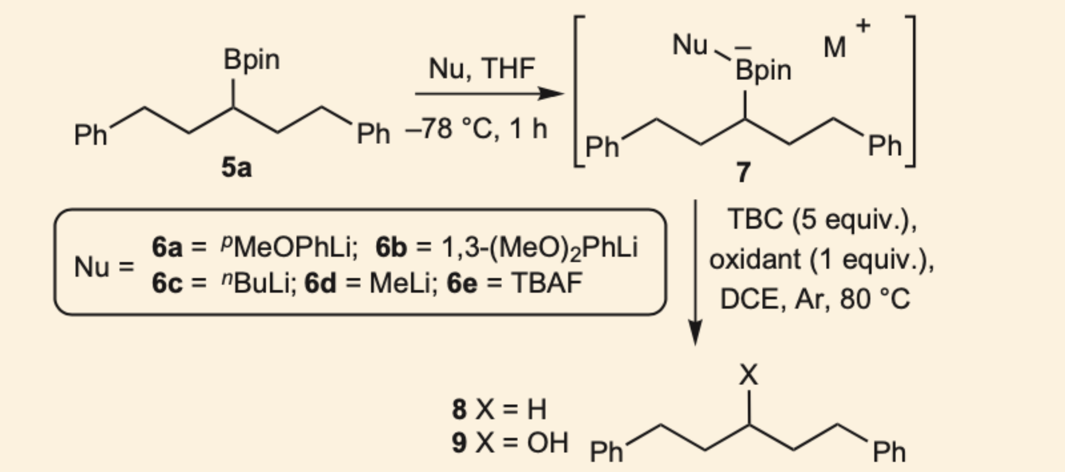
2b

3b



| entry | solvent | temperature | initiator | yield (GC) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 °C | t-BuON=NOt-Bu | 74 |
| 2 | t-BuOMe | 55 °C | t-BuON=NOt-Bu | 69 |
| 3[c] | $ClCH_2CH_2Cl$ | 83 °C | t-BuON=NOt-Bu | 99 (87)[d] |
| 4 | toluene | 80 °C | t-BuON=NOt-Bu | 93 |
| 5 | benzene | 80 °C | t-BuON=NOt-Bu | 89[d] |
| 6[b] | $ClCH_2CH_2Cl$ | 83 °C | t-BuON=NOt-Bu | 93 |
| 7 | $ClCH_2CH_2Cl$ | 83 °C | air | 99 |
| 8 | $ClCH_2CH_2Cl$ | 83 °C | dibenzoyl peroxide | 79 |

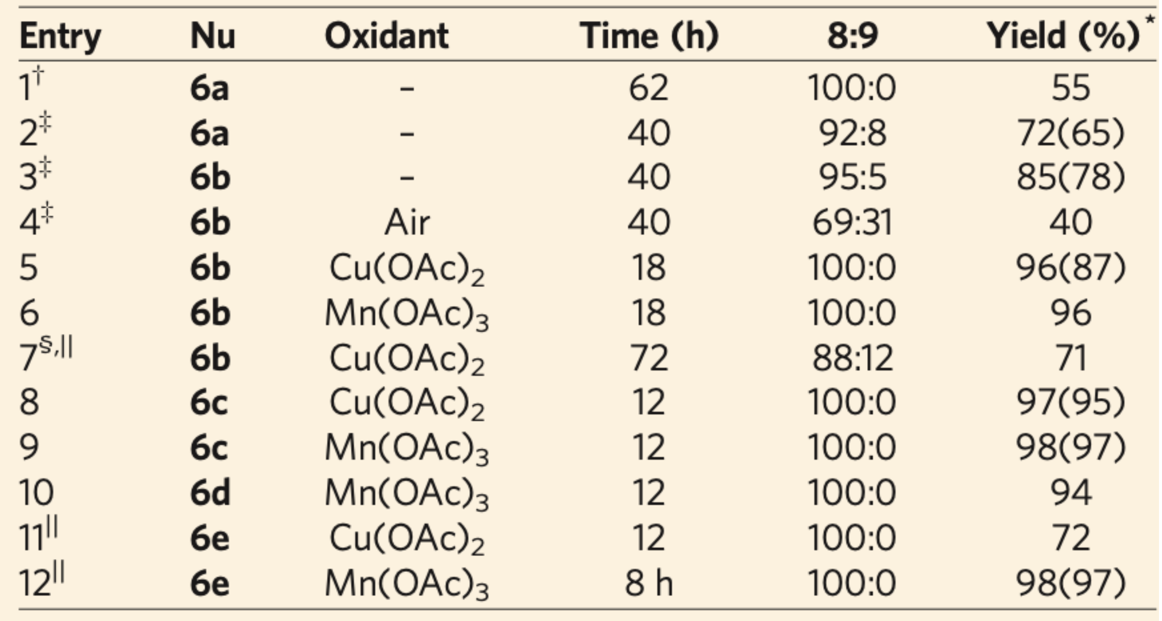




**5a**

**7**

**8** X = H
**9** X = OH

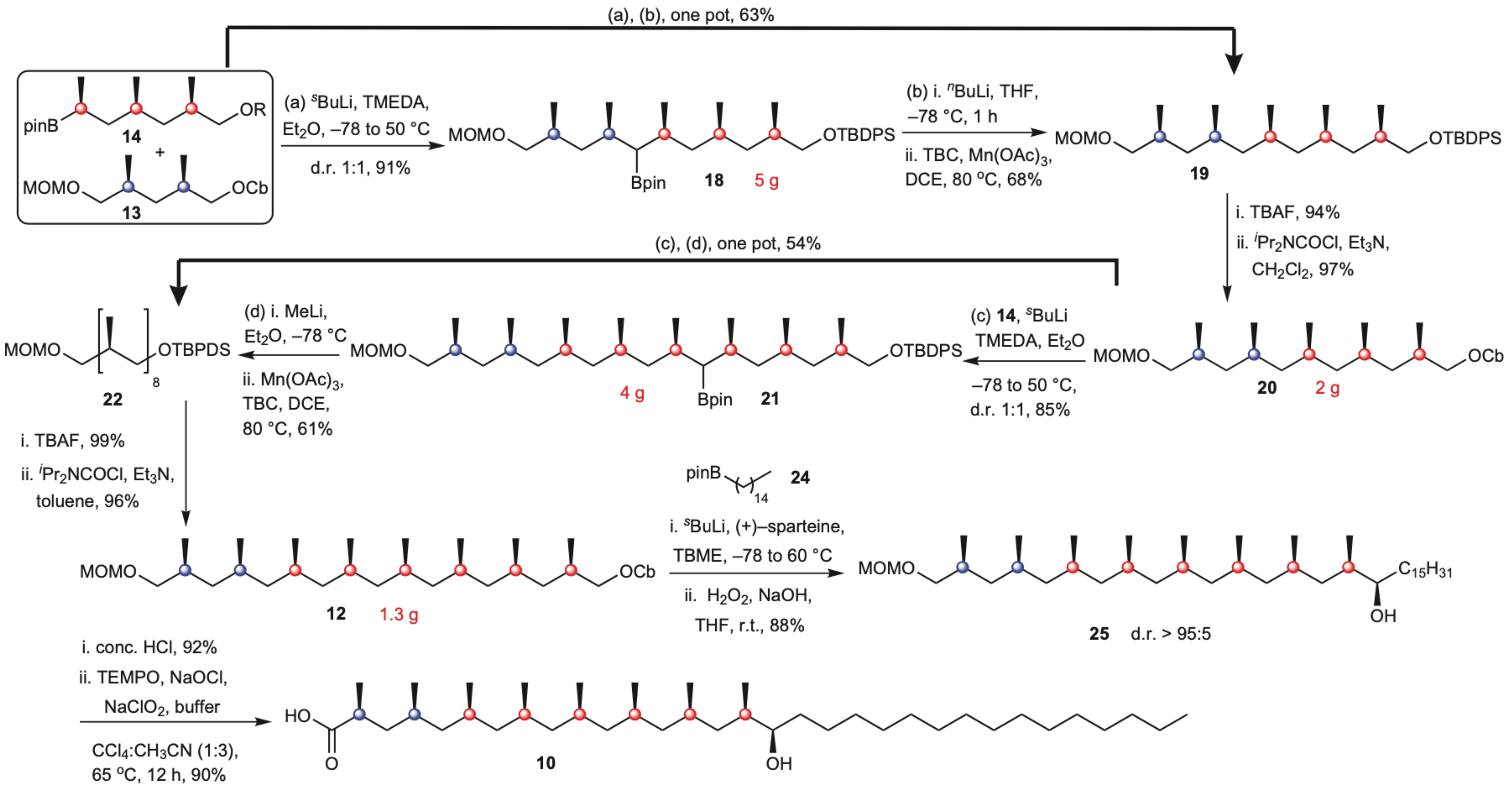


| Entry | Nu | Oxidant | Time (h) | 8:9 | Yield (%)* |
|---|---|---|---|---|---|
| 1[†] | **6a** | - | 62 | 100:0 | 55 |
| 2[‡] | **6a** | - | 40 | 92:8 | 72(65) |
| 3[‡] | **6b** | - | 40 | 95:5 | 85(78) |
| 4[‡] | **6b** | Air | 40 | 69:31 | 40 |
| 5 | **6b** | $Cu(OAc)_2$ | 18 | 100:0 | 96(87) |
| 6 | **6b** | $Mn(OAc)_3$ | 18 | 100:0 | 96 |
| 7[§,‖] | **6b** | $Cu(OAc)_2$ | 72 | 88:12 | 71 |
| 8 | **6c** | $Cu(OAc)_2$ | 12 | 100:0 | 97(95) |
| 9 | **6c** | $Mn(OAc)_3$ | 12 | 100:0 | 98(97) |
| 10 | **6d** | $Mn(OAc)_3$ | 12 | 100:0 | 94 |
| 11[‖] | **6e** | $Cu(OAc)_2$ | 12 | 100:0 | 72 |
| 12[‖] | **6e** | $Mn(OAc)_3$ | 8 h | 100:0 | 98(97) |

Renaud et al *J. Am. Chem. Soc*. **2011**, *133*, 5913–5920

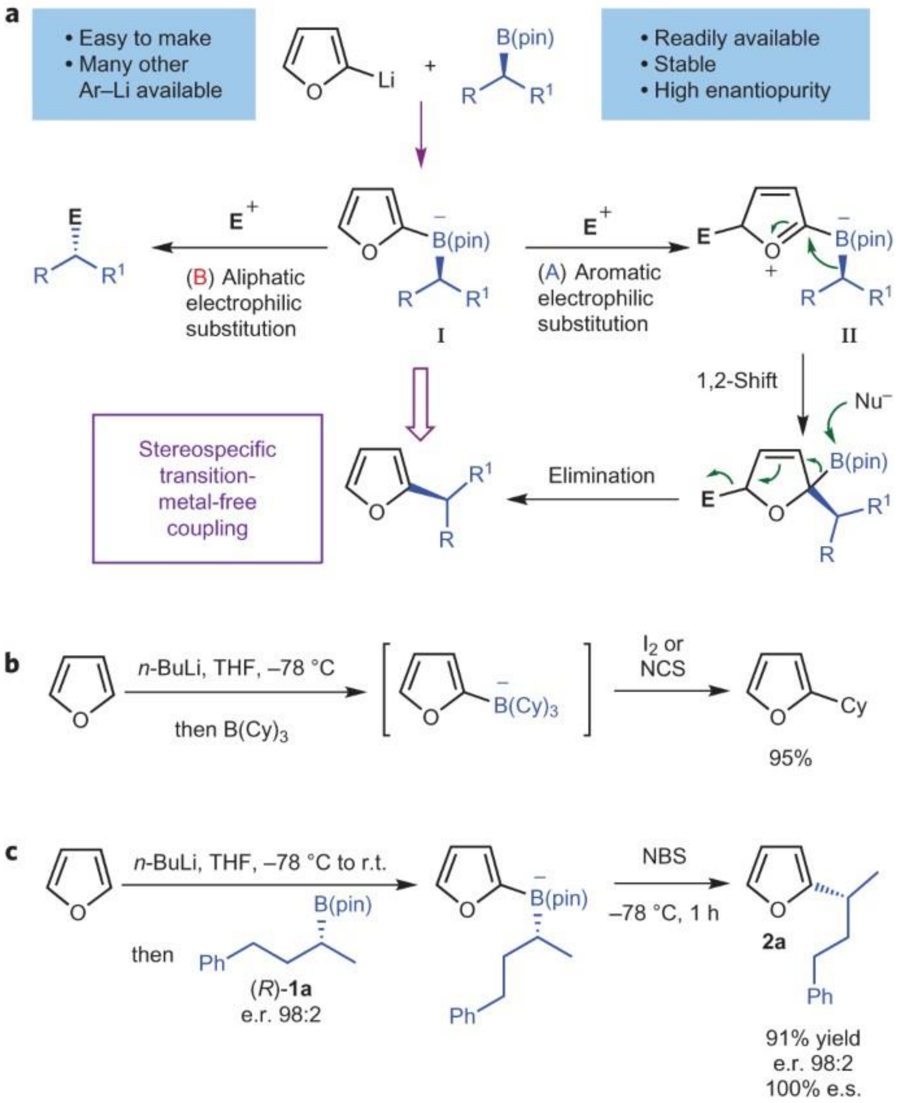
Ramesh Rasappan, Varinder Aggarwal. *Nat. Chem.*, **2014**, *6*, 810–814

# Application to total synthesis of hydroxyphthioceranic acid



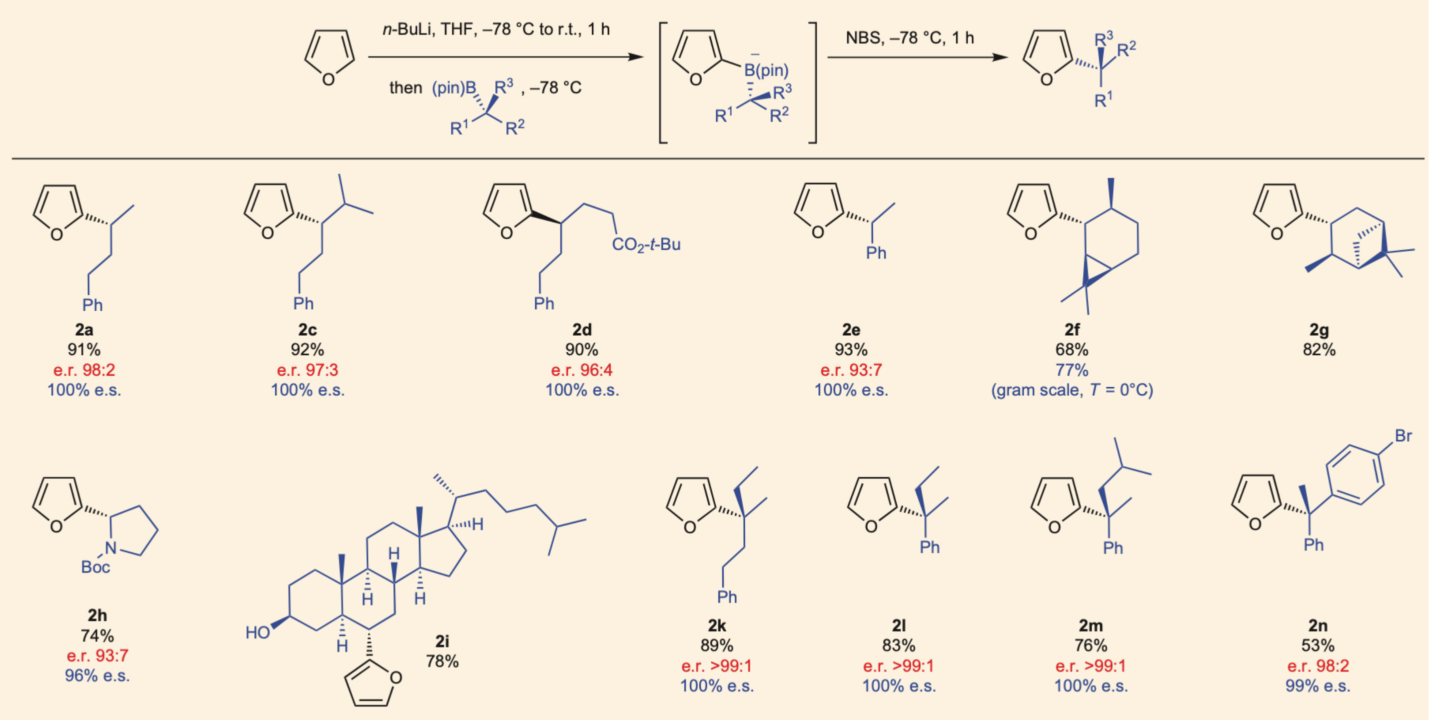
Ramesh Rasappan, Varinder Aggarwal. *Nat. Chem.*, **2014**, *6*, 810–814

# Enantiospecific sp2–sp3 coupling of secondary and tertiary boronic esters

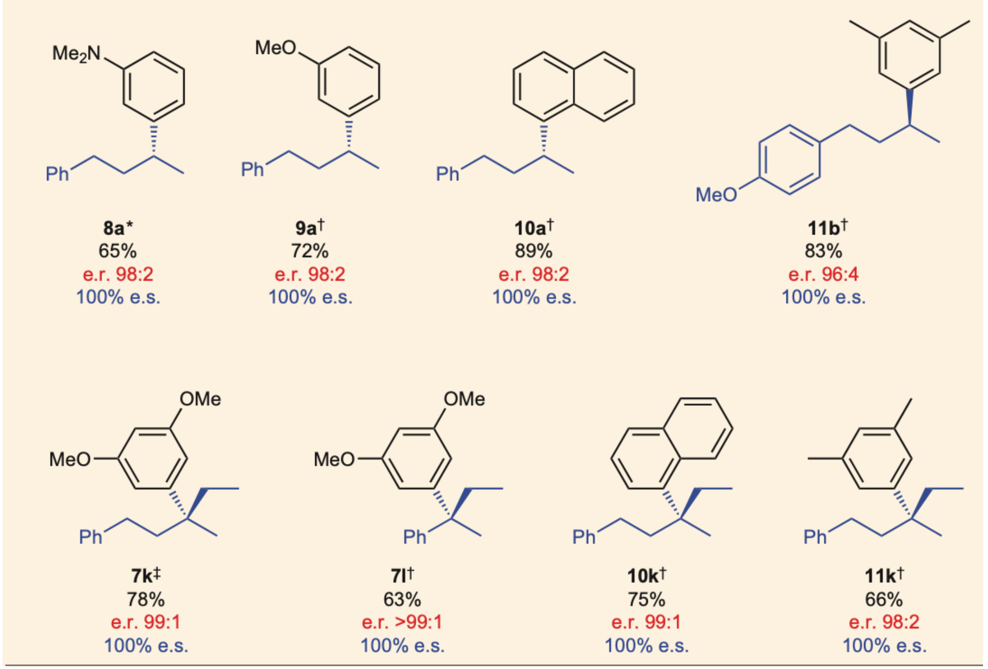


Amadeu Bonet, Marcin Odachowski, Daniele Leonori, Stephanie Essafi, Varinder Aggarwal. *Nat. Chem.*, **2014**, *6*, 584–589

# Scope



**2a** 91% e.r. 98:2 100% e.s.
**2c** 92% e.r. 97:3 100% e.s.
**2d** 90% e.r. 96:4 100% e.s.
**2e** 93% e.r. 93:7 100% e.s.
**2f** 68% 77% (gram scale, *T* = 0°C)
**2g** 82%
**2h** 74% e.r. 93:7 96% e.s.
**2i** 78%
**2k** 89% e.r. >99:1 100% e.s.
**2l** 83% e.r. >99:1 100% e.s.
**2m** 76% e.r. >99:1 100% e.s.
**2n** 53% e.r. 98:2 99% e.s.



**8a*** 65% e.r. 98:2 100% e.s.
**9a**† 72% e.r. 98:2 100% e.s.
**10a**† 89% e.r. 98:2 100% e.s.
**11b**† 83% e.r. 96:4 100% e.s.
**7k**‡ 78% e.r. 99:1 100% e.s.
**7l**† 63% e.r. >99:1 100% e.s.
**10k**† 75% e.r. 99:1 100% e.s.
**11k**† 66% e.r. 98:2 100% e.s.

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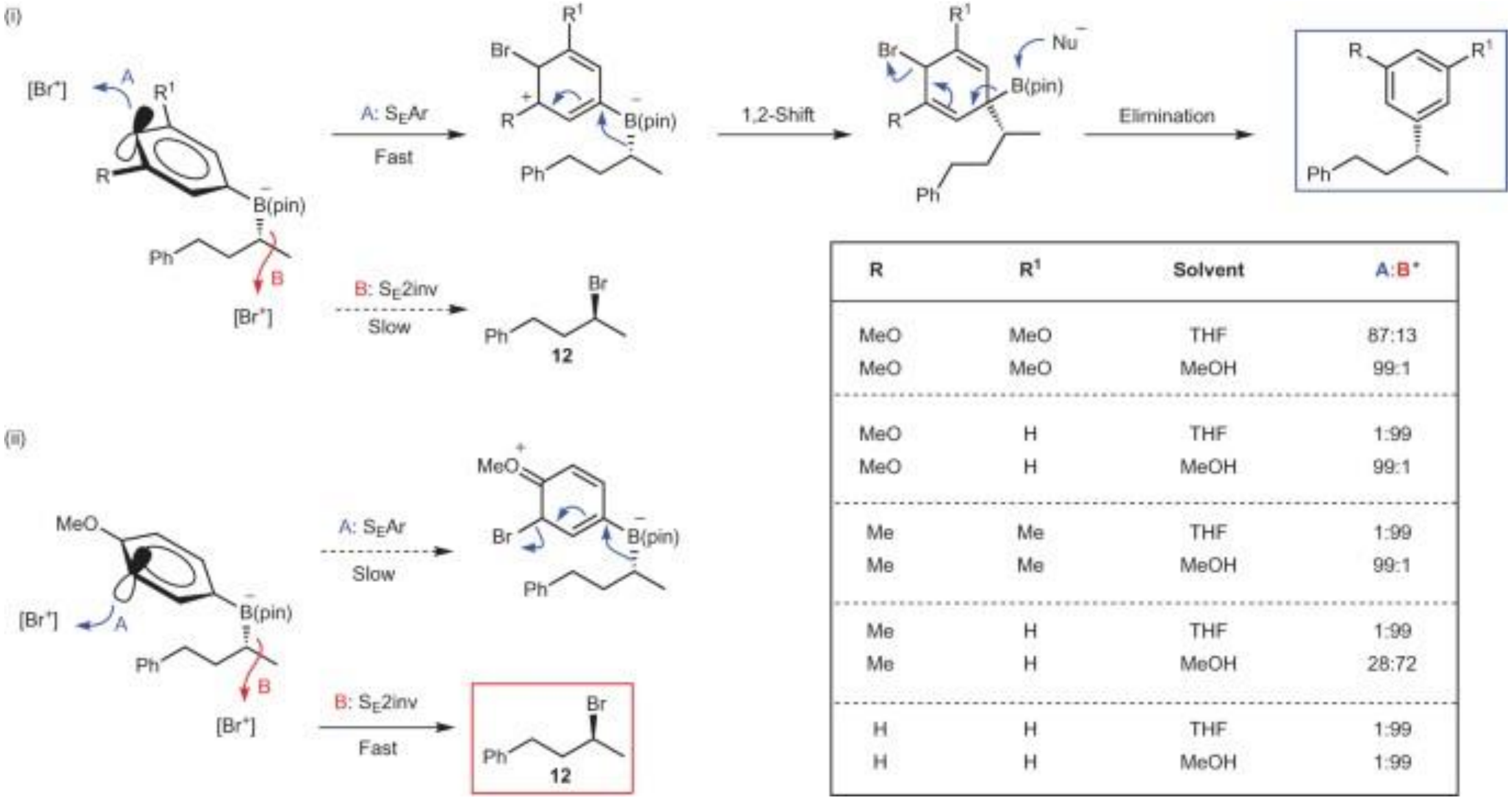
# Possible reaction pathways



| R | R¹ | Solvent | A:B* |
|---|---|---|---|
| MeO | MeO | THF | 87:13 |
| MeO | MeO | MeOH | 99:1 |
| MeO | H | THF | 1:99 |
| MeO | H | MeOH | 99:1 |
| Me | Me | THF | 1:99 |
| Me | Me | MeOH | 99:1 |
| Me | H | THF | 1:99 |
| Me | H | MeOH | 28:72 |
| H | H | THF | 1:99 |
| H | H | MeOH | 1:99 |

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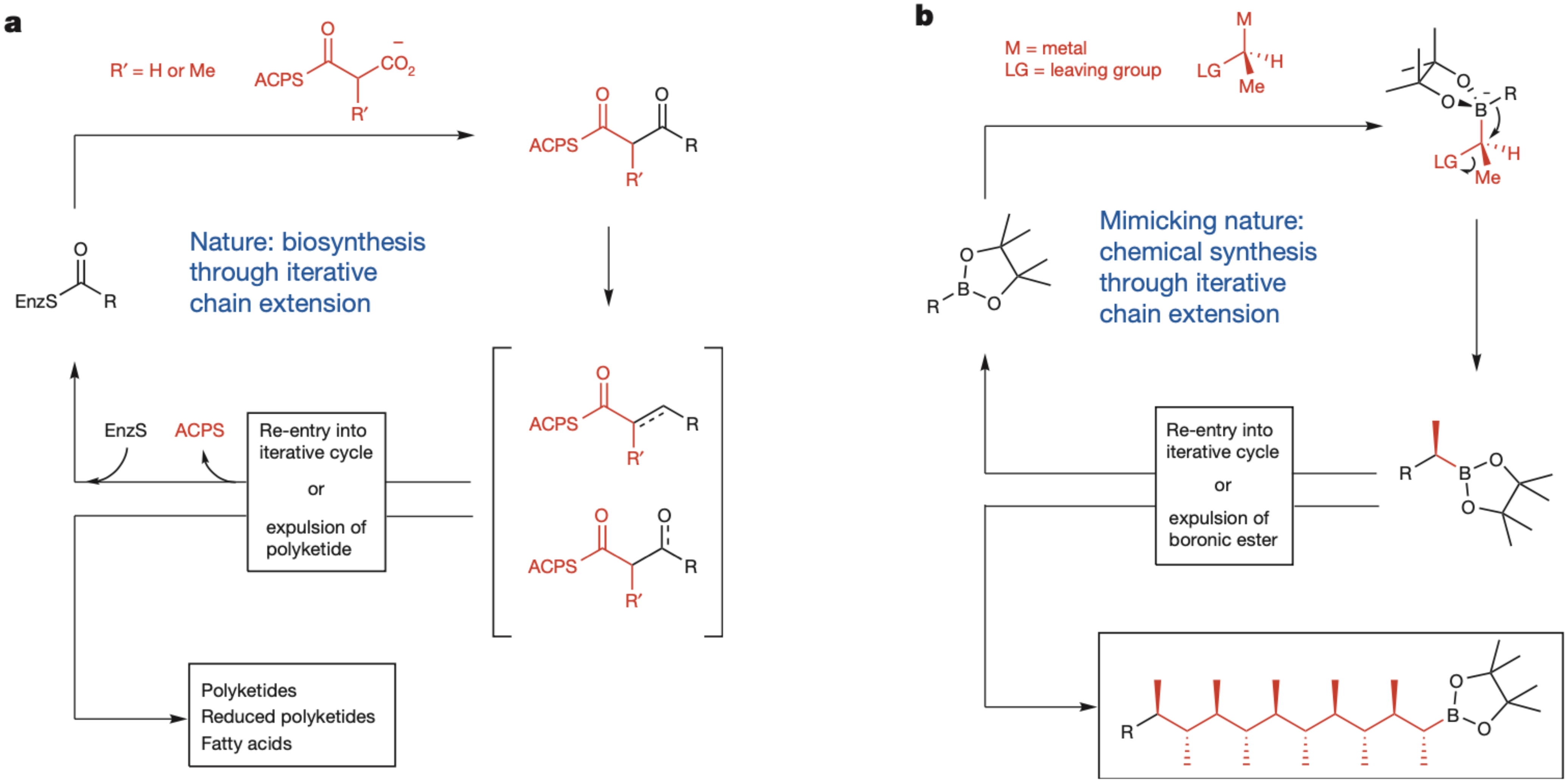
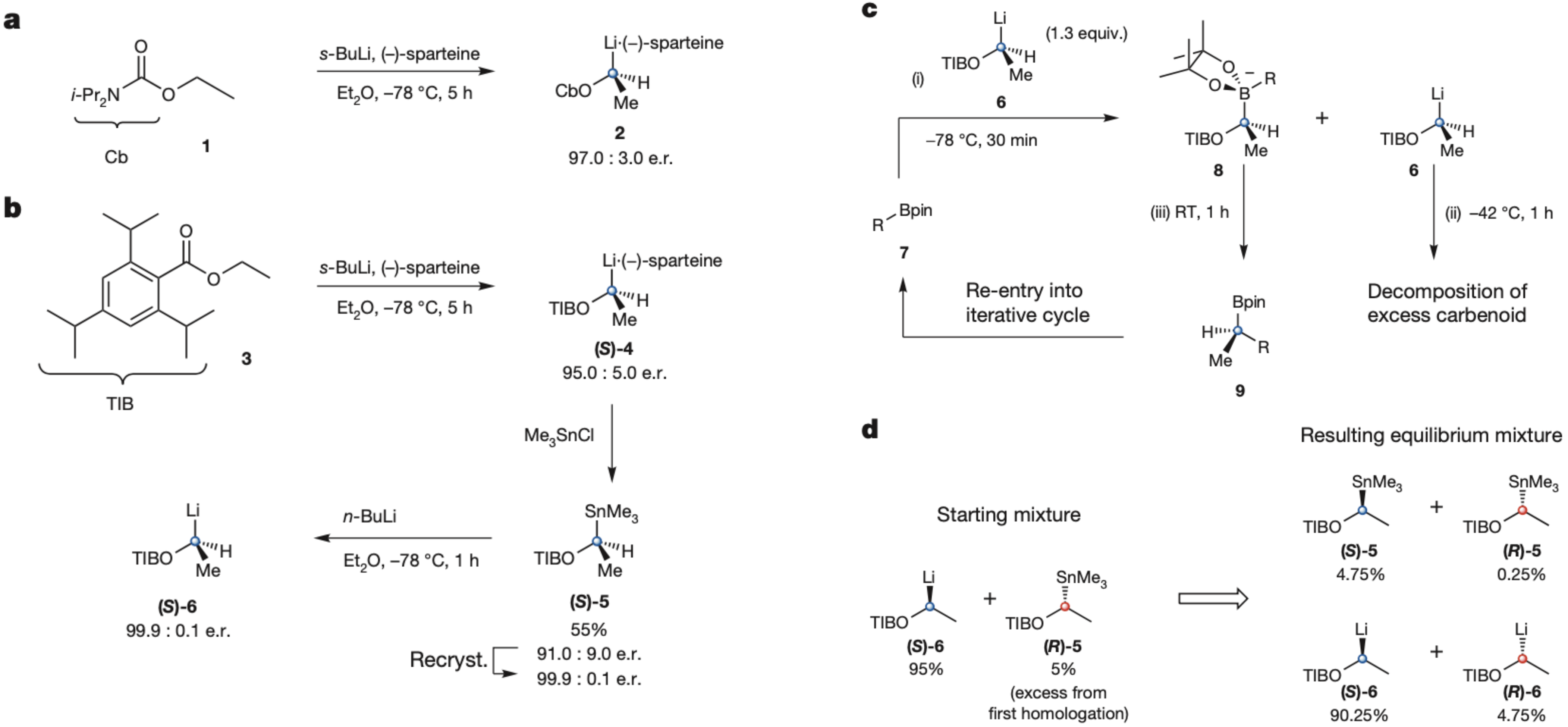
# Assembly-line synthesis of organic molecules with tailored shapes

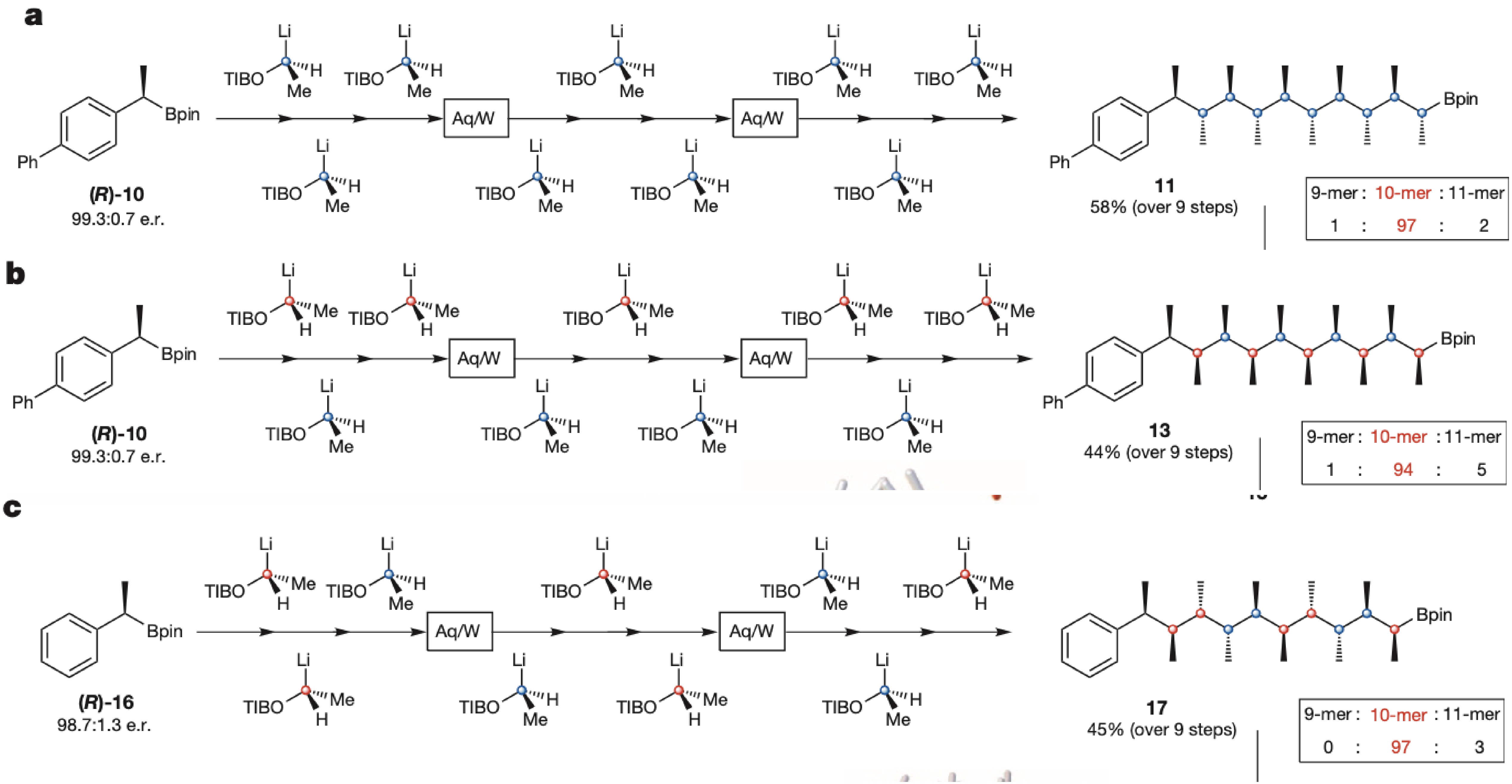


Matthew Burns, Stéphanie Essafi, Jessica R. Bame, Stephanie P. Bull, Matthew P. Webster, Sébastien Balieu, James W. Dale, Craig P. Butts, Jeremy N. Harvey, Varinder K. Aggarwal.

*Nature*, **2014**, *513*, 183-188

# Building blocks synthesis





**(*R*)-10**
99.3:0.7 e.r.

**11**
58% (over 9 steps)

| 9-mer | 10-mer | 11-mer |
|---|---|---|
| 1 | 97 | 2 |

**(*R*)-10**
99.3:0.7 e.r.

**13**
44% (over 9 steps)

| 9-mer | 10-mer | 11-mer |
|---|---|---|
| 1 | 94 | 5 |

**(*R*)-16**
98.7:1.3 e.r.

**17**
45% (over 9 steps)

| 9-mer | 10-mer | 11-mer |
|---|---|---|
| 0 | 97 | 3 |