Current Literature March 4 2017

Keita Takubo -Wipf group-

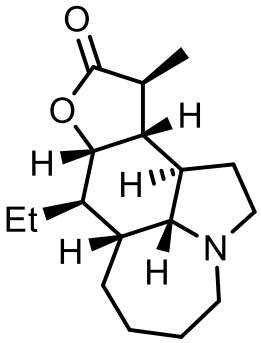
Stereocontrolled Total Synthesis of (−)-Stemaphylline

Ana Varela, Lennart K. B. Garve, Daniele Leonori,* and Varinder K. Aggarwal*

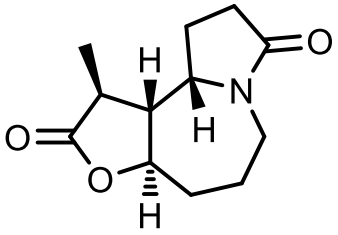
Angew. Chem. Int. Ed. **2017**, *56,* 2127–2131

Stemona alkaloids

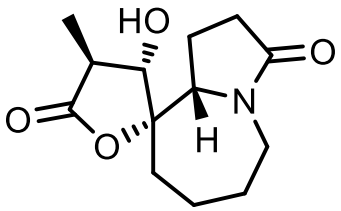
- ✓ **Isolation:** A root extract of *Stemona aphylla*.
- ✓ **Biological activity:** Insecticidal and antiparasitic properties.
- ✓ **Structure:** Pyrrolo-[1,2-*a*]azepine core as well as a γ-lactone and five stereogenic centers, three of which are contiguous.



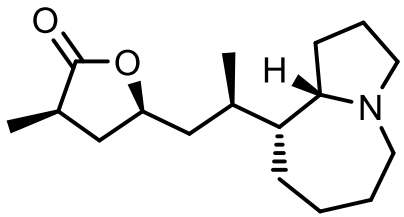
stenin



stemoamide



stemoamide

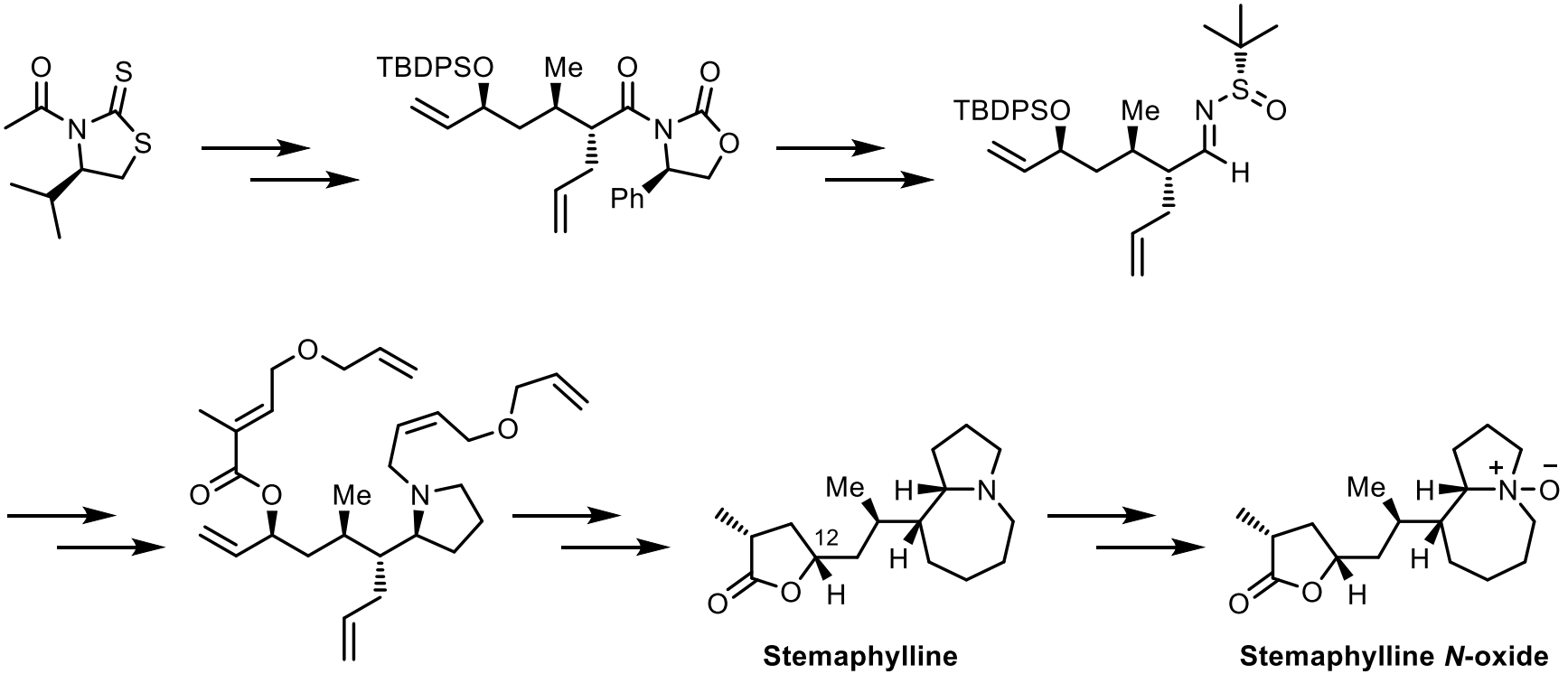


(–)-stemaphylline [(–)- **1**]

Pitchaya M. et. al., *J. Nat. Prod.* **2009,** *72,* 848–851.

Synthesis of (-)-stemaphylline

- Previous work



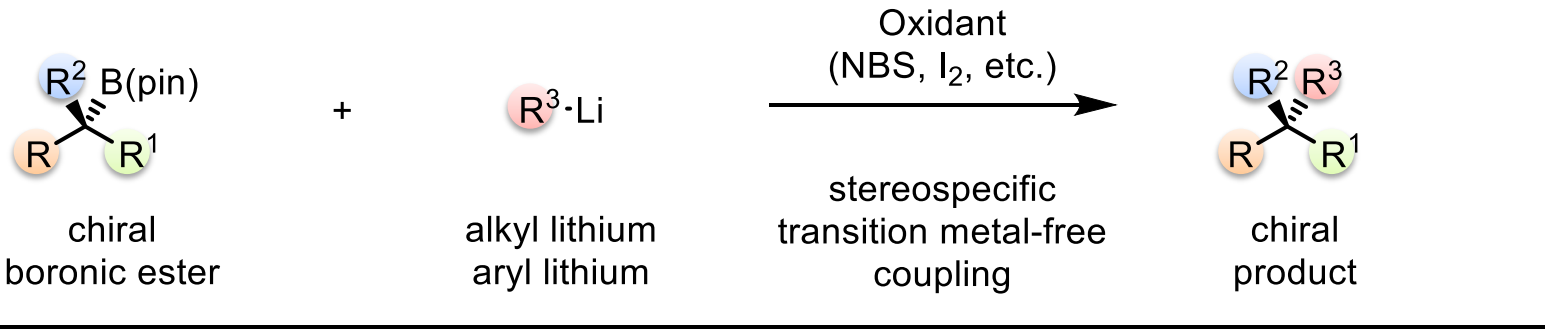
Stemaphylline
(4:1 of inseparable diasteremeric mixture at the C12)

1.9% yield over 19 steps

Stemaphylline *N*-oxide
(Isolated)

C. W. Lindsley et. al., *Chem. Eur. J.* **2013**, *19*, 11847-11852.

Homologation through lithiation-borylation

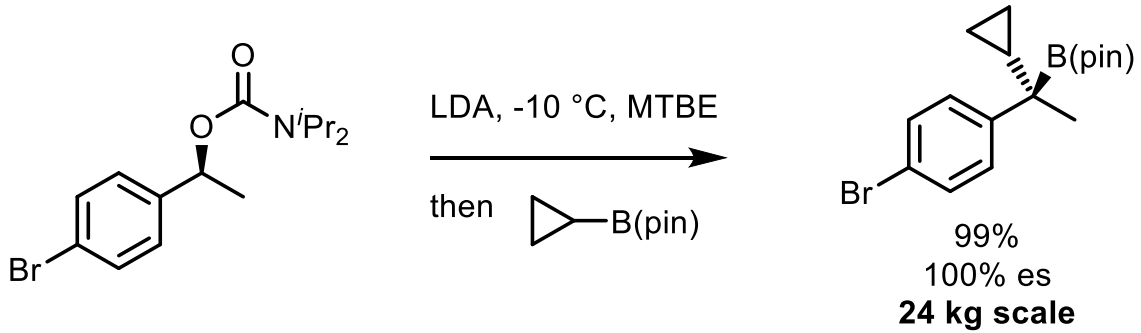


- high ee
- stable
- easy to make
- high modularity

- easy to make
- many available

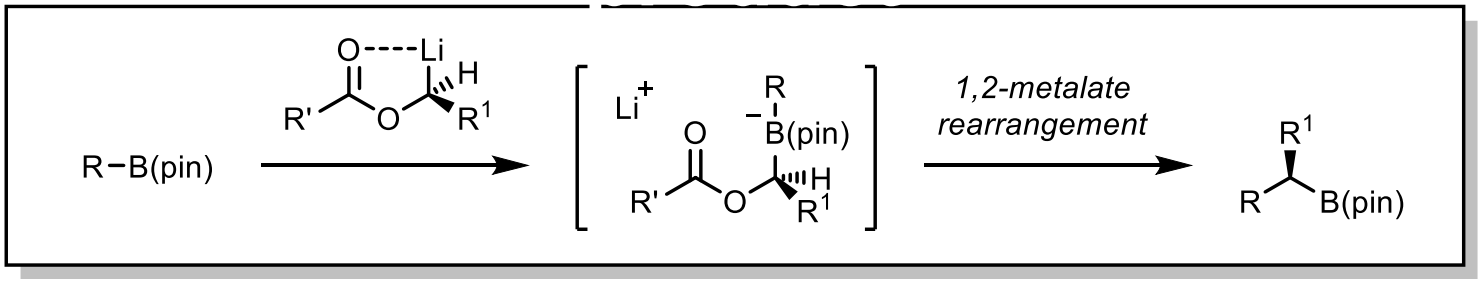
- high ee
- widespread motif
- all C-stereogenic centers

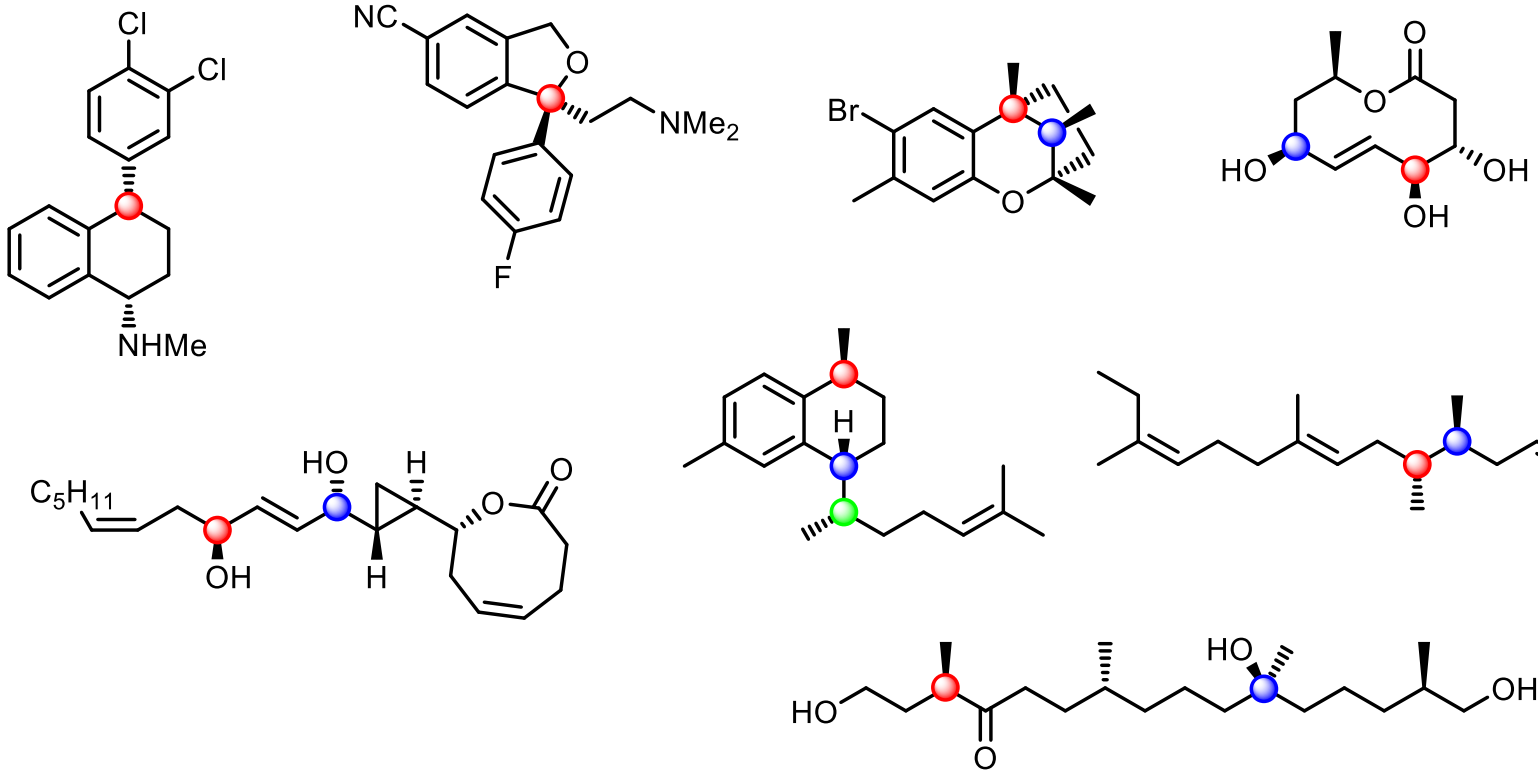
■ Large-scale lithiation-borylation reaction



Fandrick, K. R. et. al., *Org. Lett.* **2014**, *16,* 4360–4363.

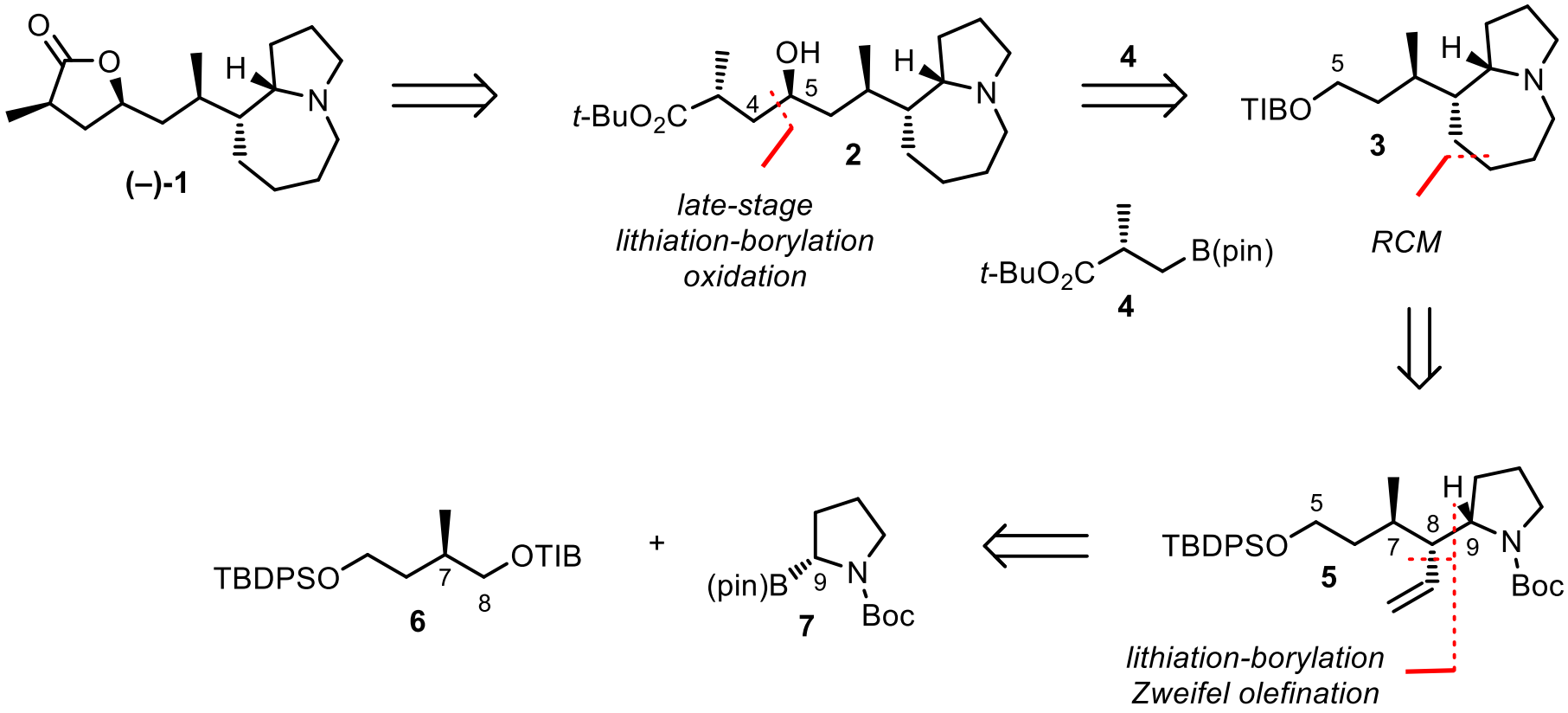
Application in the synthesis of natural product





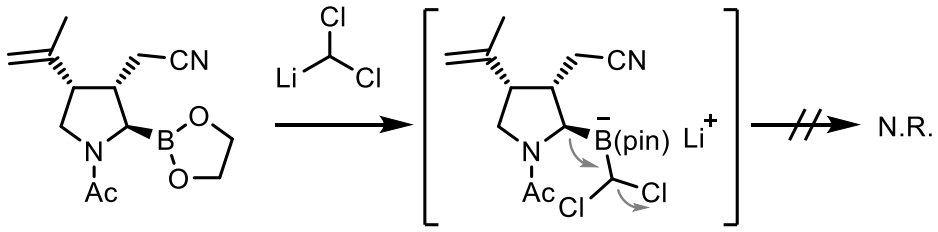
Acc. Chem. Res. **2014**, *47*, 3174−3183.

Retrosynthetic analysis

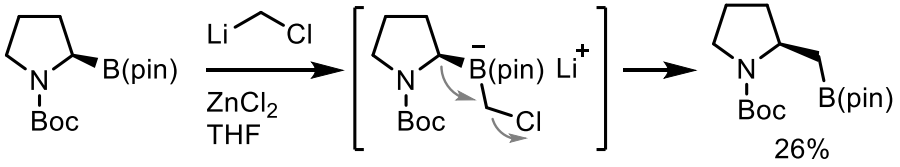


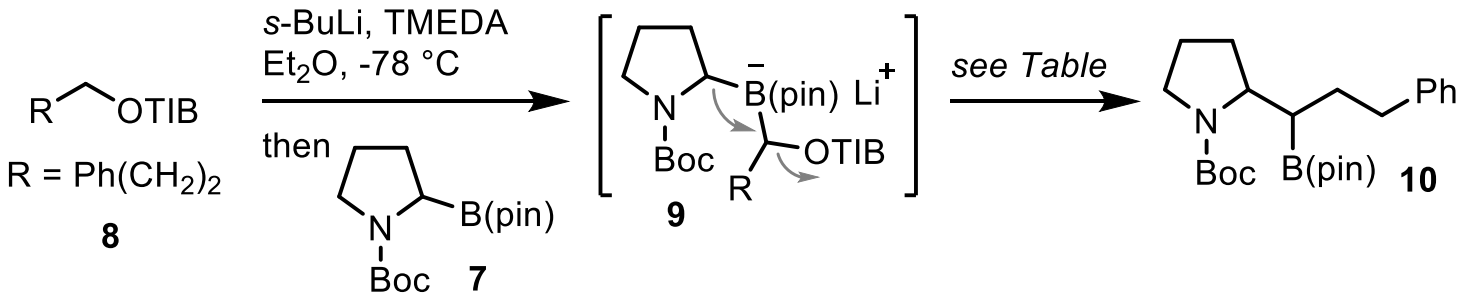
Optimization of the 1,2-migration

• Matteson (1998)



• Whiting (2008)

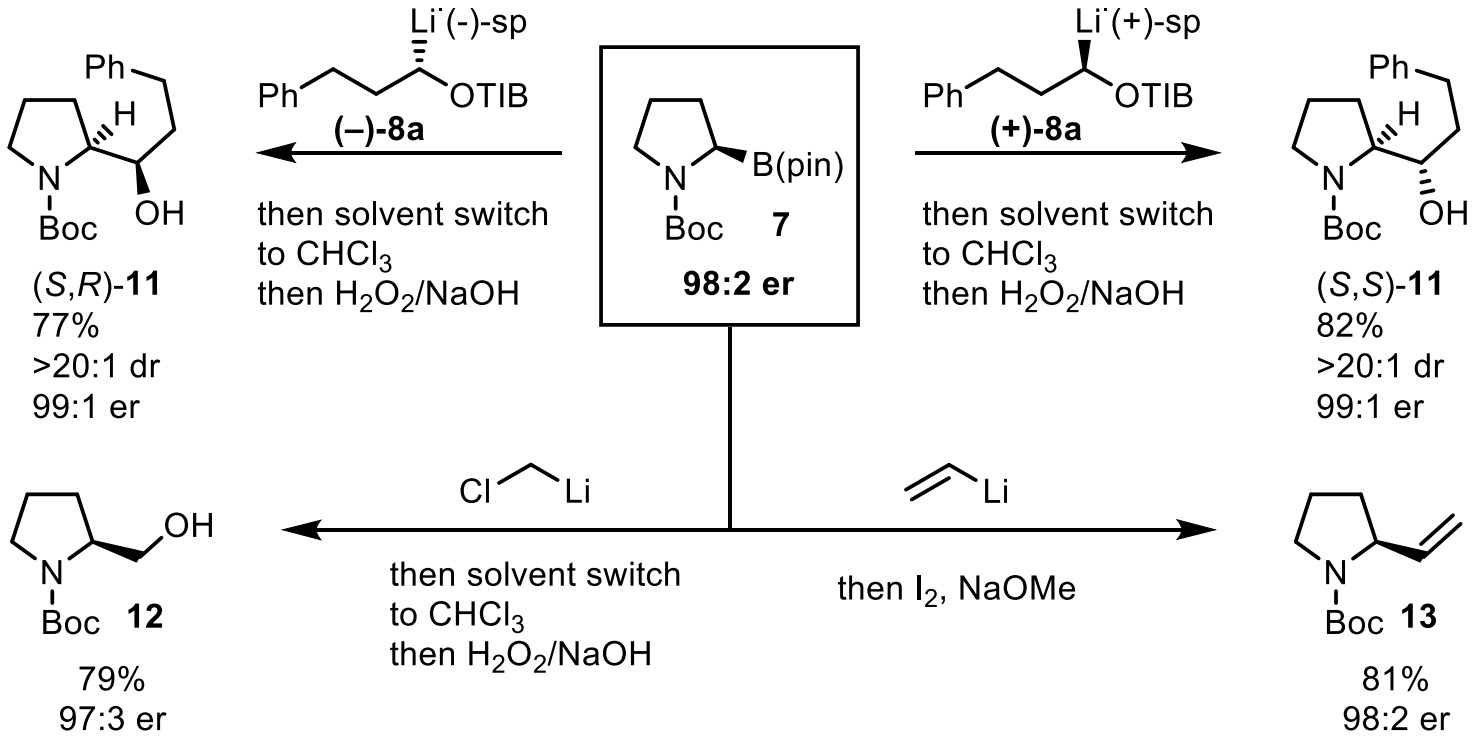


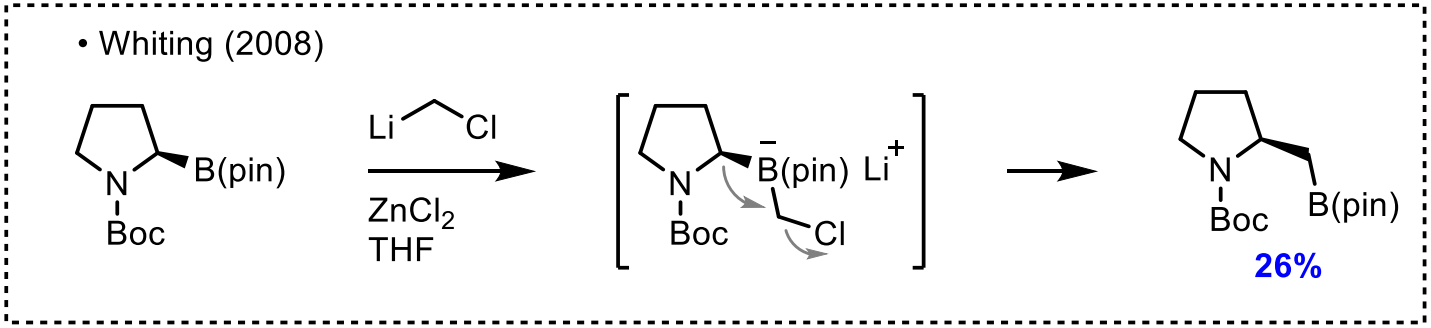


Entry	Solvent	Lewis acid	Temp. (°C)	Yield (%)
1	Et_2O	–	38	–
2	Et_2O	$MgBr_2 \cdot Et_2O$	25	–
3	Et_2O	$MgBr_2 \cdot Et_2O$	38	19
4	toluene	–	110	67
5	**$CHCl_3$**	**–**	**62**	**85**

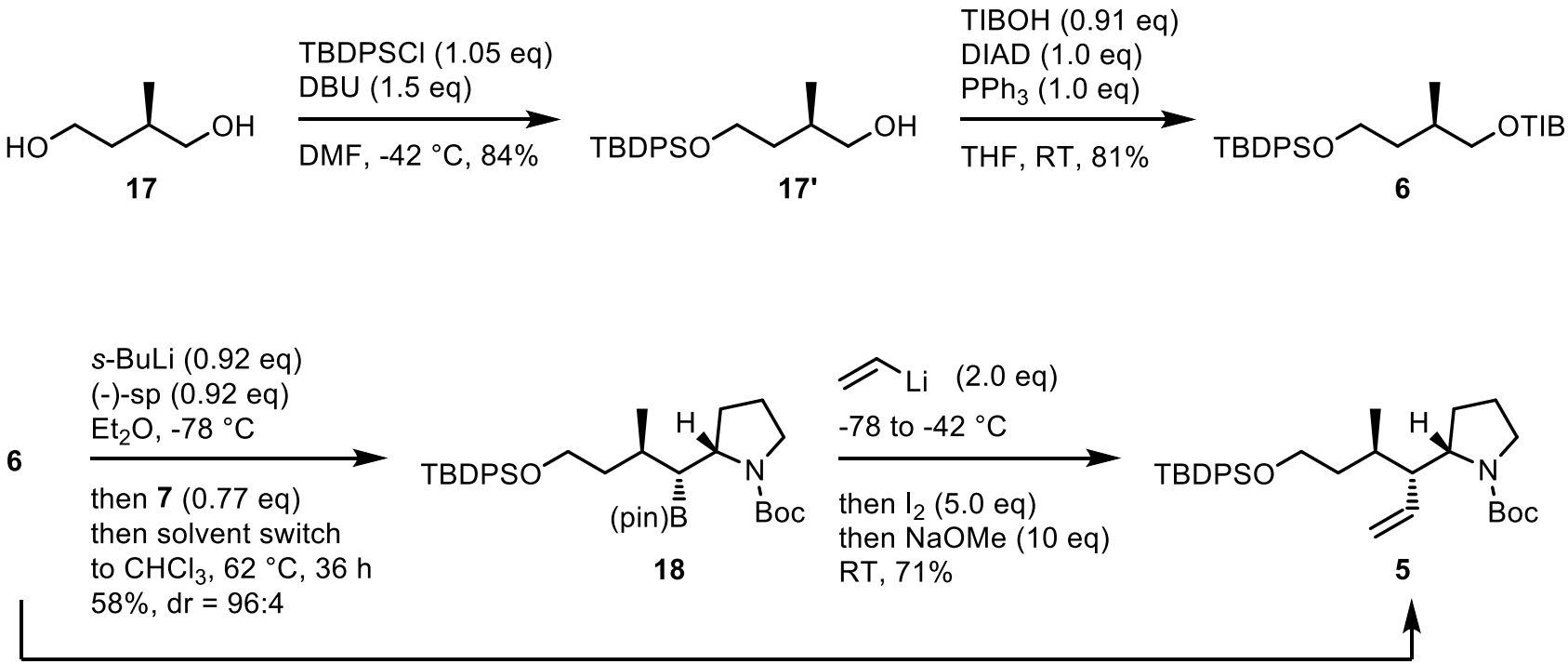
TIB = triisopropylbenzoyl

Homologation of chiral boronic ester

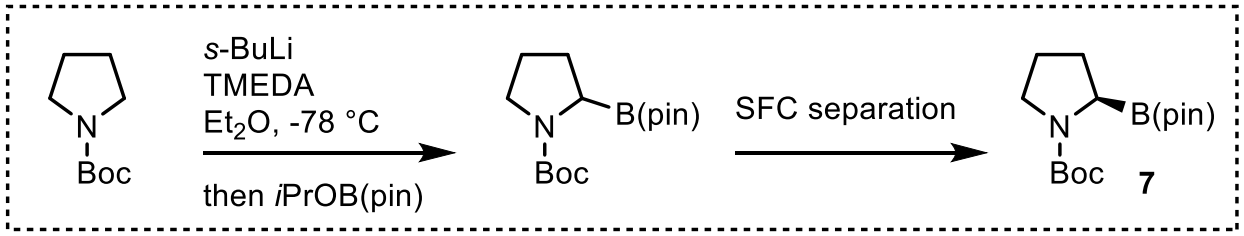


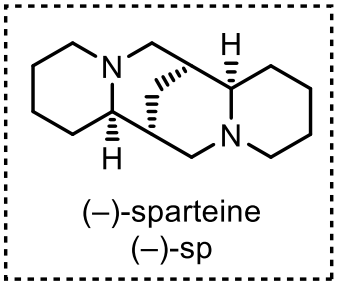


Synthesis of Allyl Pyrroridine

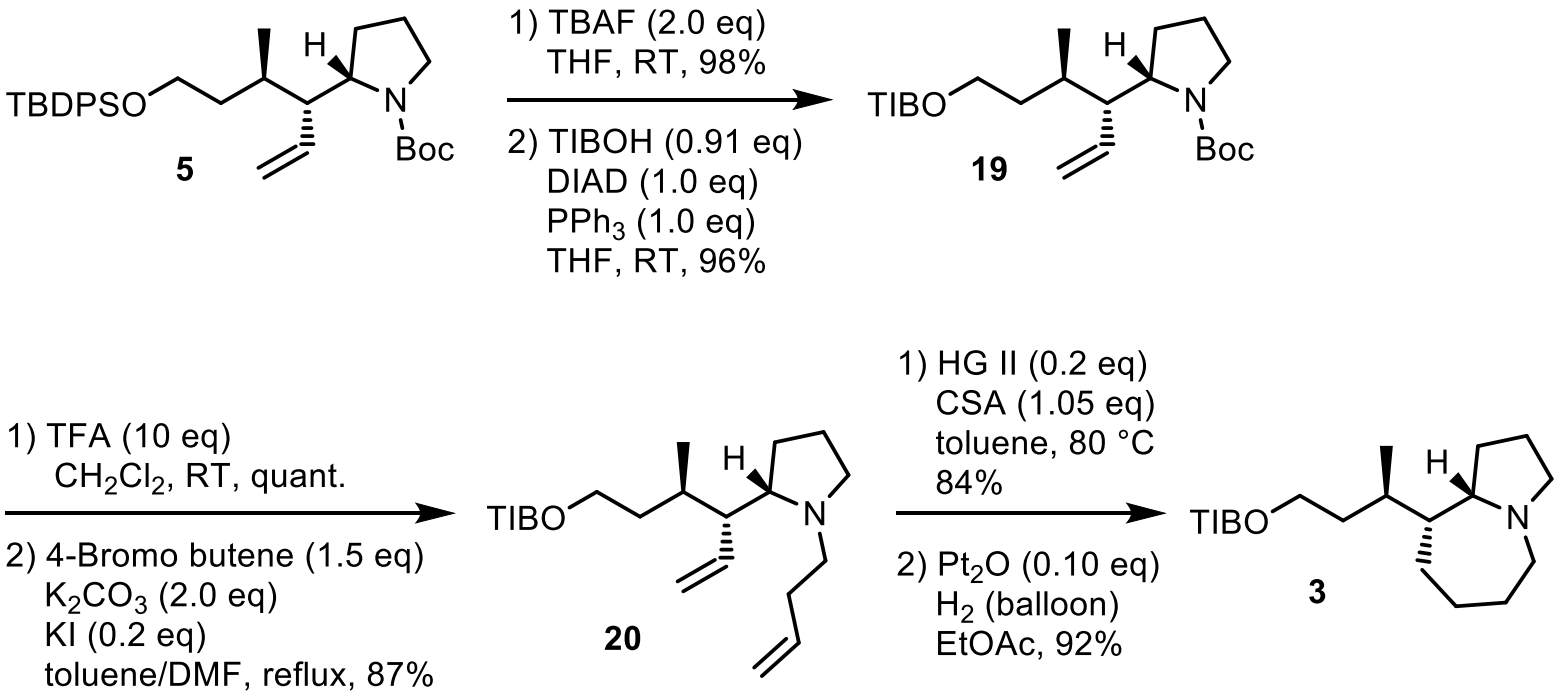


one-pot, gram scale lithiation-borylation-Zweifel olefination = 70%

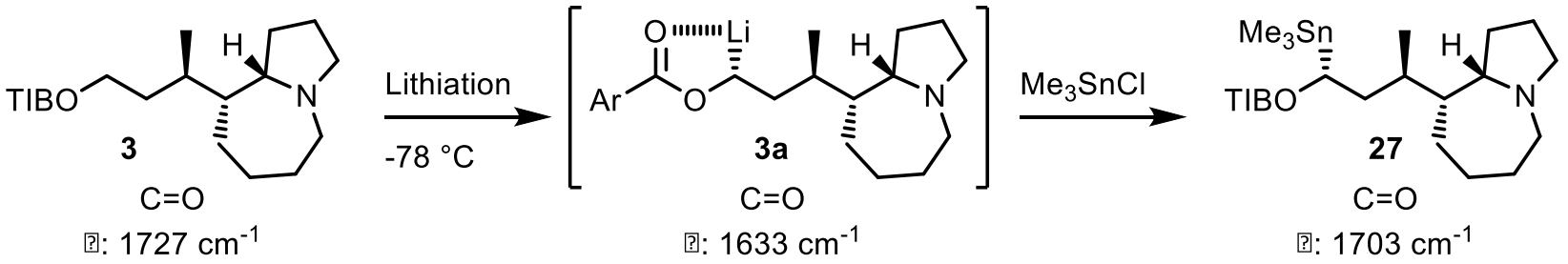




Construction of pyrrolo-[1, 2a]azepine core



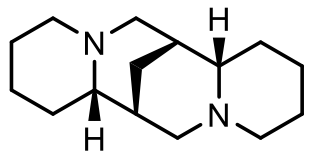
Optimization of lithiation of TIB ester



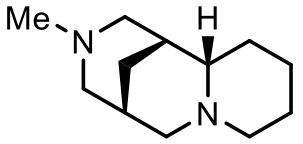
Entry	Solvent	*s*-BuLi·(+)-sps (equiv)	Ratio **3** : **27** (Yield %)[a]
1	Et_2O	2.0	100 : 0
2	Toluene	2.0	100 : 0
3	TBME	2.0	49 : 51
4	CPME	2.0	35 : 65
5	**CPME**	**3.0**	**0 : 100 (92)**
6[b]	CPME	3.0	65 : 35

[a] NMR ratio of **3** vs **27** (isolated yield of **27** after chromatography)

[b] (+)-sp was used instead of (+)-sps

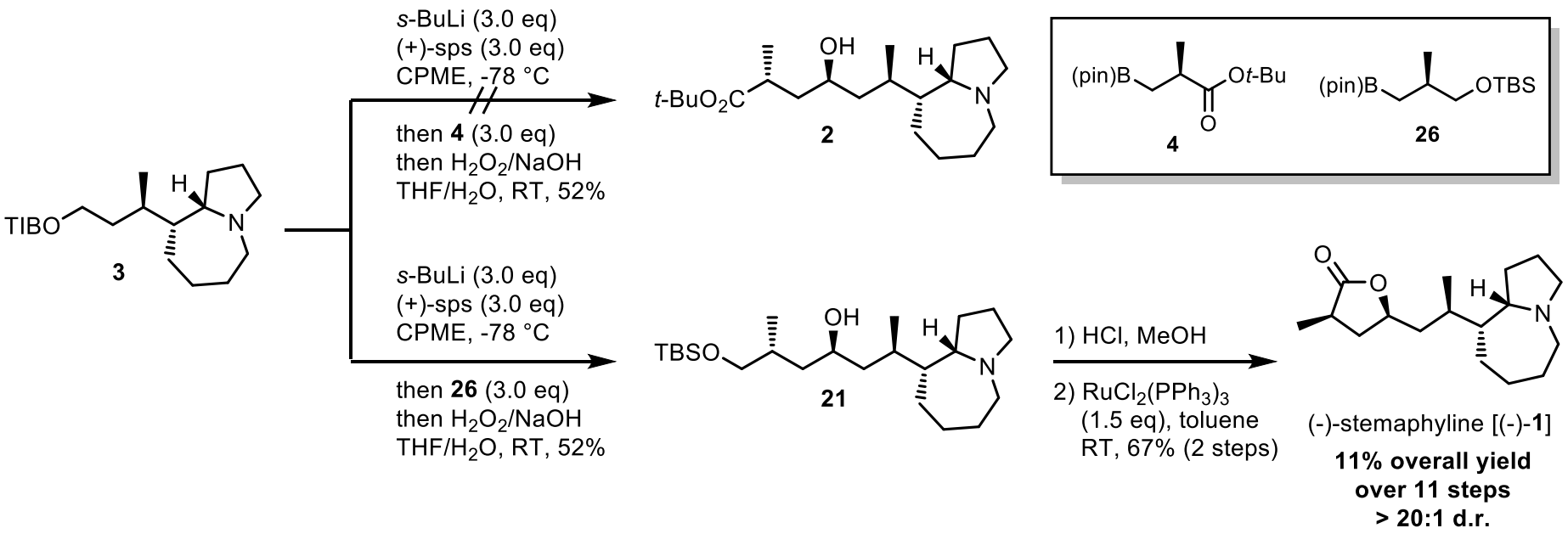


(+)-sparteine
(+)-sp

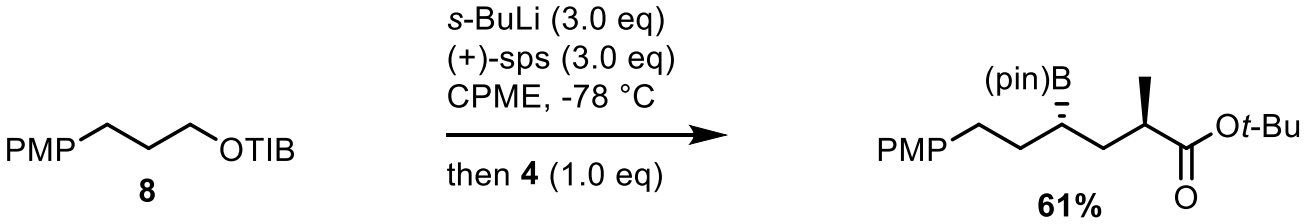


(+)-sparteine surrogate
(+)-sps

Endgame



Model study



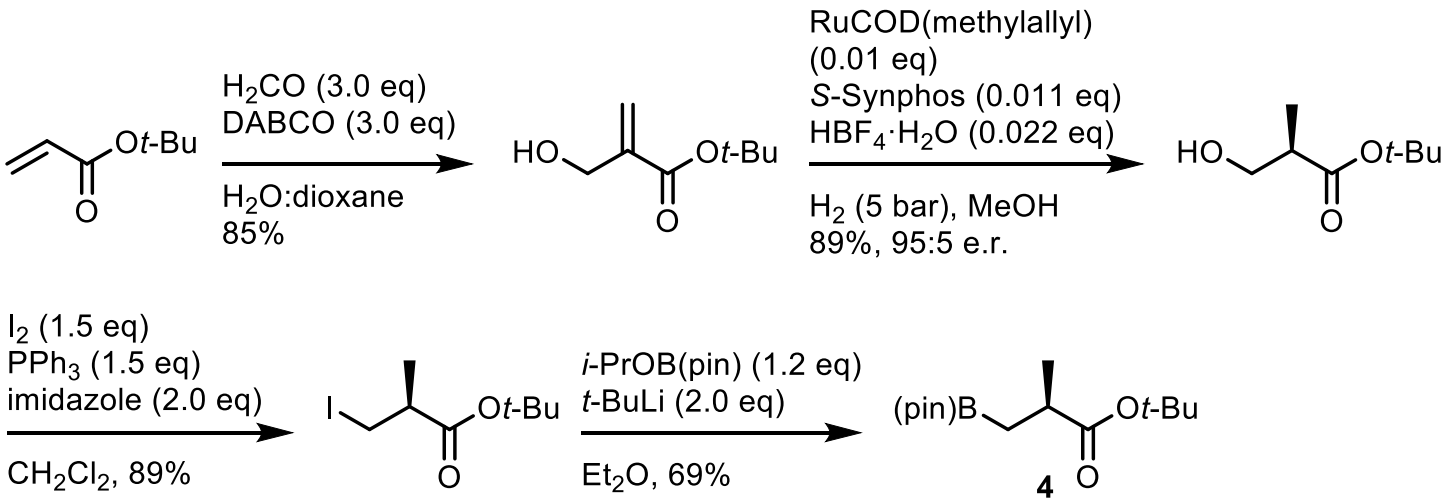
Conclusion

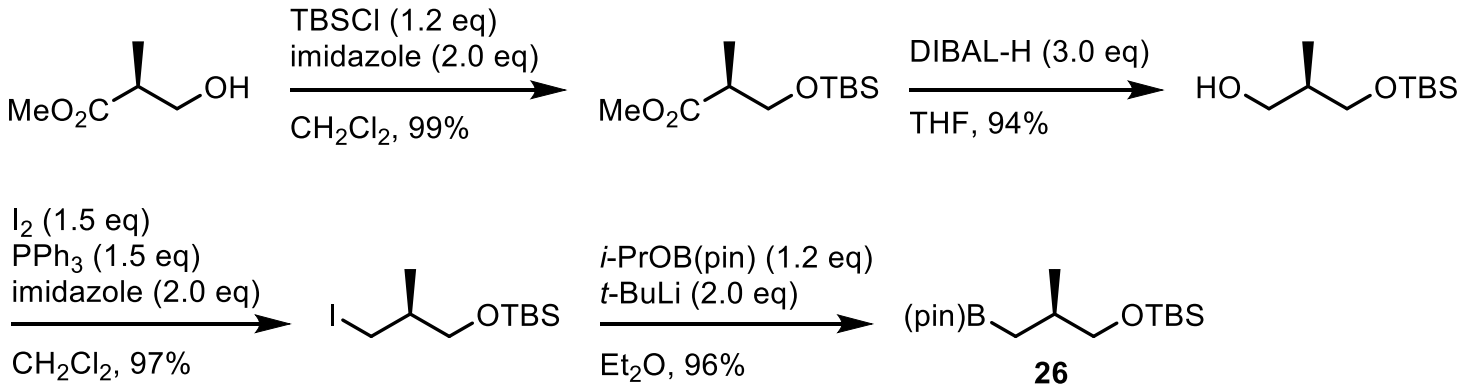
- They completed the total synthesis of (–)-stemaphylline in 11 steps, with high stereocontrol (>20:1 d.r.) and 11% overall yield.

- The synthesis features a late-stage lithiation–borylation reaction with a tertiary amine containing carbenoid.

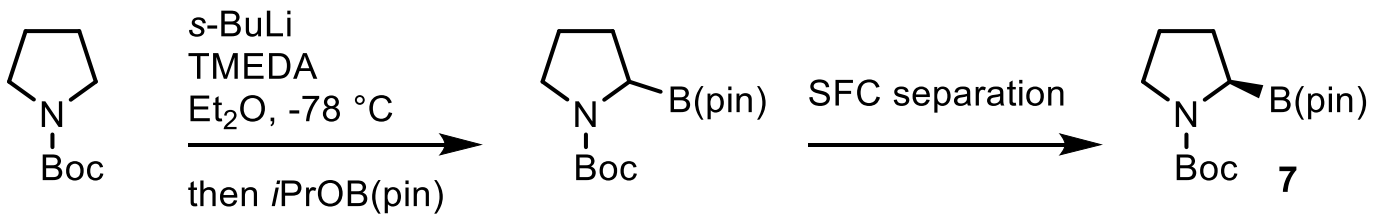
- By performing a solvent switch from Et_2O to $CHCl_3$, efficient 1,2-metalate rearrangement of the intermediate boronate occurs with both halide and ester leaving groups.

Synthesis of Boronic esters 4 and 26

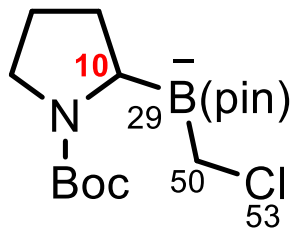


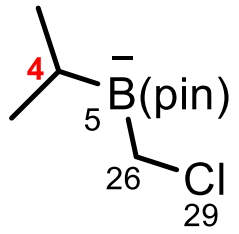


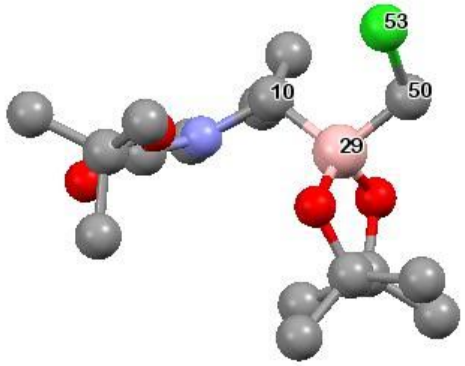
Synthesis of Boronic ester 7

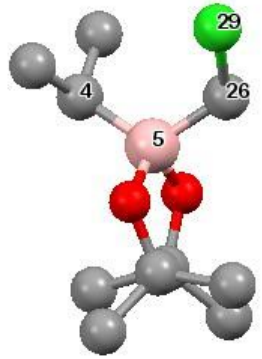


Natural charge (NBO) calculations





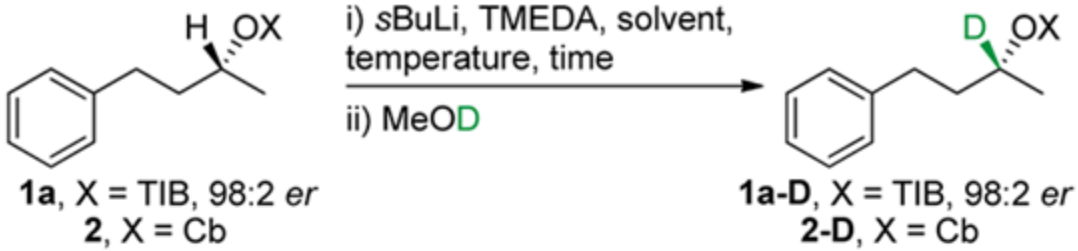




B3LYP/6-31+G* - NBO Charges

	C_{10}	B_{29}	C_{50}	Cl_{53}	**OBO fragm.**	**CH_2Cl fragm.**
Pyrrolidine	–0.363	0.949	–0.680	–0.196	–0.154	–0.421
	C_4	B_5	C_{26}	Cl_{29}	OBO fragm.	CH_2Cl fragm.
Isopropyl	–0.594	0.967	–0.680	–0.206	–0.162	–0.429

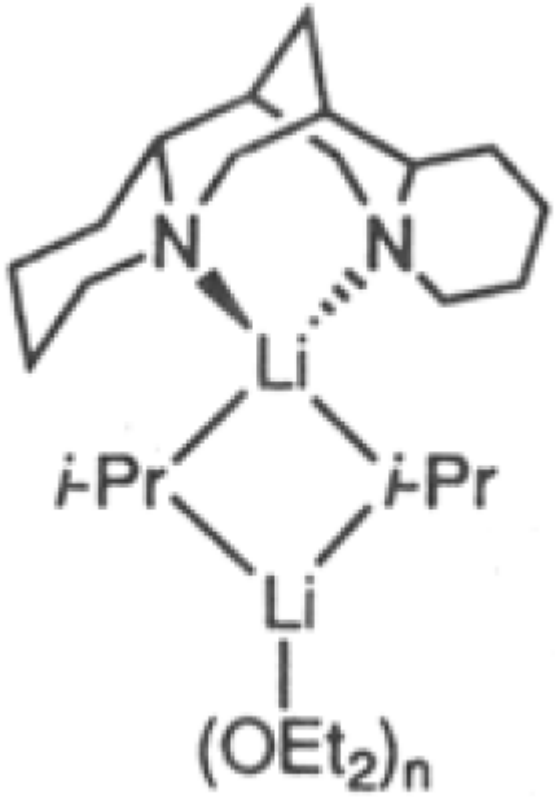
Optimization of Deprotonation Condition



entry	X	temp (°C)	solv	*s*BuLi/TMEDA (equiv)	time (h)	**1a**[a]/**2-D** (%D)
1	TIB	−78	THF	2/2	4	10
2	Cb	−78	Et_2O	2/2	4	<5
3	TIB	−78	Et_2O	2/2	4	60
4	TIB	−78	CPME	2/2	4	70
5	TIB	−50	CPME	2/2	1	74
6	TIB	−50	CPME	2/6	1	92
7	TIB	−50	CPME	1.6/6	1	89
8	TIB	−60	CPME	1.6/6	2	87
9	Cb	−50	CPME	1.6/6	1	10

J. Am. Chem. Soc. **2013**, *135*, 16054−16057.

Solution structure of i-PrLi2/(-)-sparteine



J. *Am. Chem. Soc*. **1994**, *116*, 3231-3239.