Asymmetric Synthesis of α-Substituted Allyl Boranes and Their Application in the Synthesis of Iso-agatharesinol

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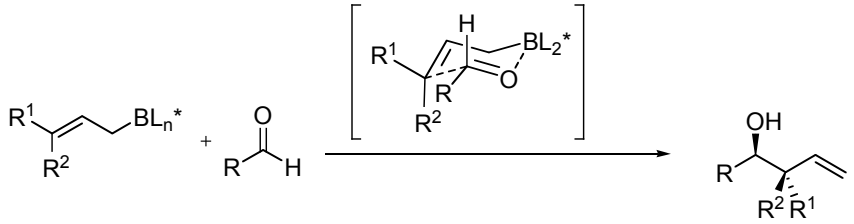
Stephan Elzner
January 06, 2007

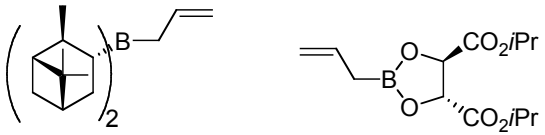
Introduction

Allyl boron reagents

- Important tool in the synthesis of natural products
- Allyl addition of organoboron reagents to carbonyl compounds are highly diastereoselective

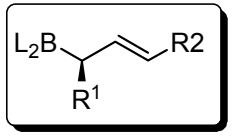


- A number of reagents for enatioselective allylation were developed with chiral ligands at the boron center



(^{l}Ipc)$_2$B

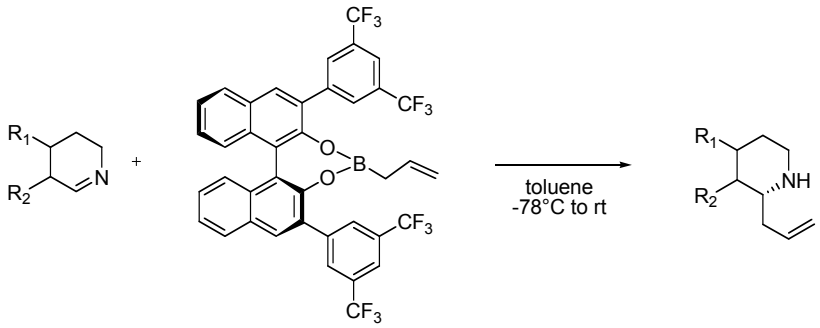
- Few protocols were developed in which the chiral center is a structural component of the allylic unit

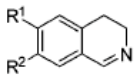
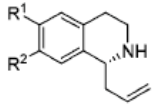
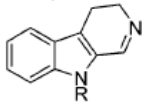
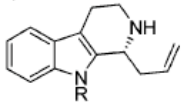
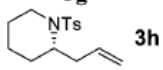
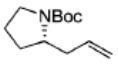


V. Aggarwal, G. Y. Feng, A. T. Schmidt, *J. Am. Chem. Soc.* **2005**, *127*, 1642-1643
Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207-2293

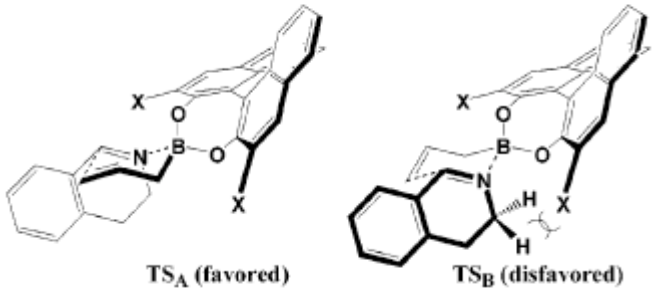
Allylboration of Imines

- Enantioselective allylation of cyclic imines



entry	imine	product	yield[a] (%)	ee (%)[c]
				
1	**1a** (R^1 = R^2 = H)	**3a**	92[b]	95
2	**1b** (R^1 = R^2 = OMe)	**3b**	78	98
3	**1c** (R^1, R^2 = OCH_2O)	**3c**	86	98
4	**1d** (R^1 = R^2 = Cl)	**3d**	88	95[d]
5	**1e** (R^1 = H, R^2 = NO_2)	**3e**	90	99
				
6	**1f** (R = H)	**3f**	80	94
7	**1g** (R = Ts)	**3g**	84	94
8	 **1h**	 **3h**	65[e]	91
9	 **1i**	 **3i**	71[e]	92

Proposed transition state

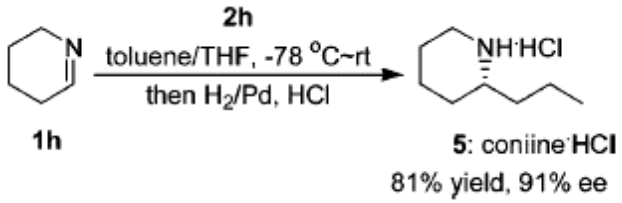


T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, 128, 9646-9647

Application: Synthesis of Alkaloids

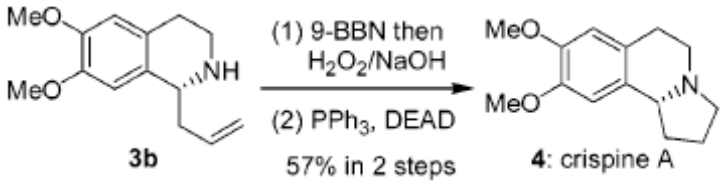
- Coniine

  Neurotoxin found in poison hemlock

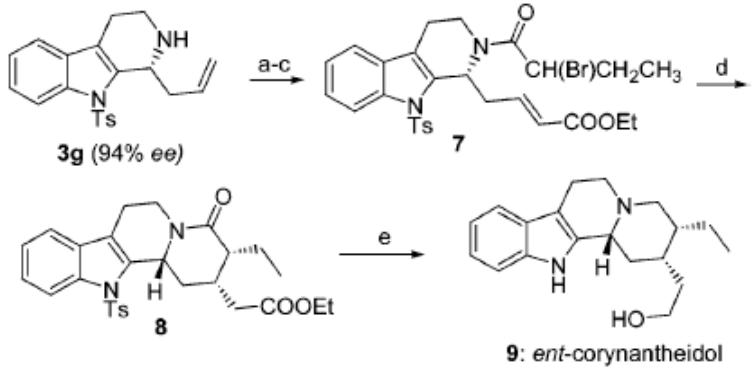


- Crispine A

  Alkaloid with antitumor activity



- *ent*-Corynantheidol

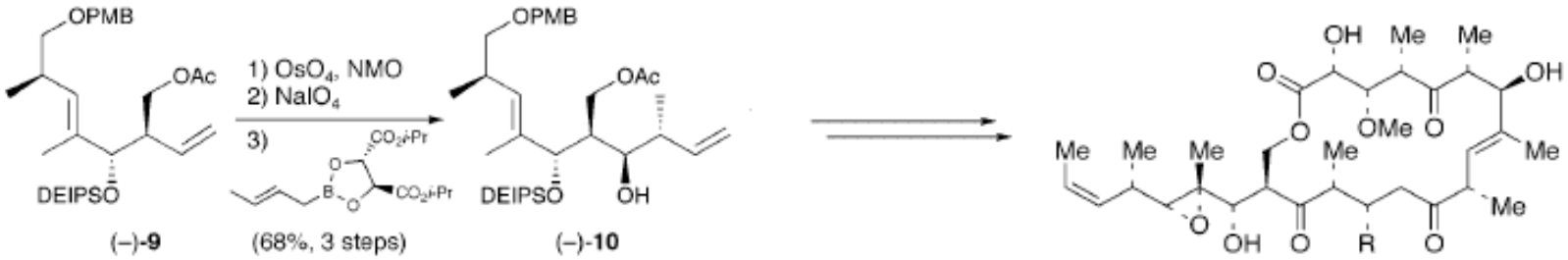


[a] Reaction conditions: (a) (±)-$HO_2CCH(Br)CH_2CH_3$, DCC, CH_2Cl_2; (b) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O; (c) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 82% for 3 steps; (d) *n*-BuLi (1.2 equiv), THF, 63%; (e) LAH (15 equiv), THF, 79%.

T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2006**, 128, 9646-9647

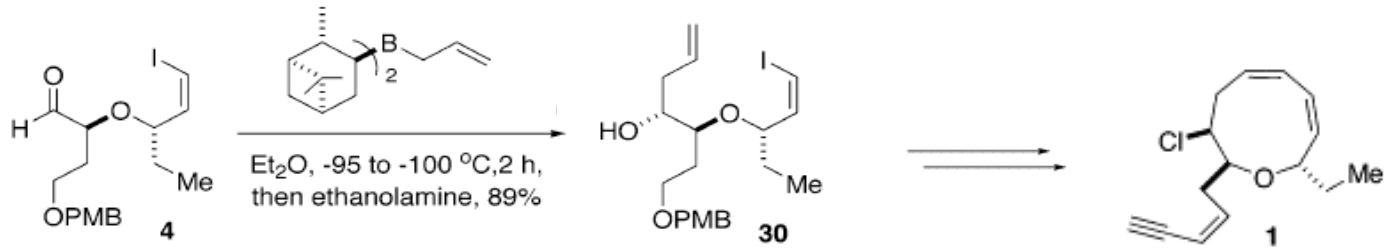
Examples for Enantioselective Allylboration in total synthesis

- (+)-13-Deoxytedanolide



A. B. Smith, C. M. Adams, S. A. Lodise, A. P. Degnan, A. B. Smith, *J. Am. Chem. Soc.* **2003,** 125, 350-351

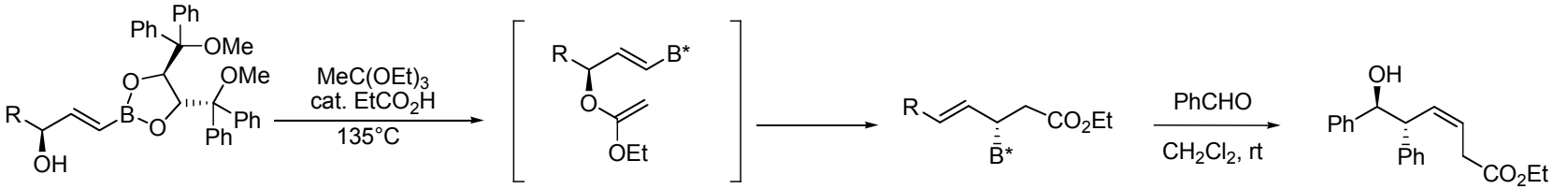
- (+)-Brasilenyne

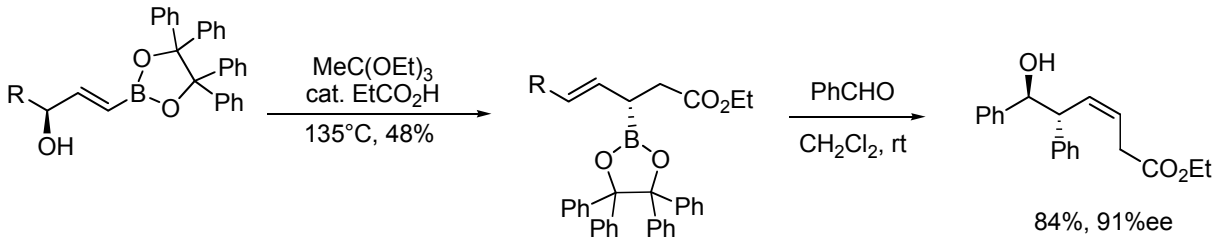


S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2004,** *126*, 12432-12440

1,3-Disubstituted Allylboronate

Aldol addition to chiral α-substituted allyl boronate compounds

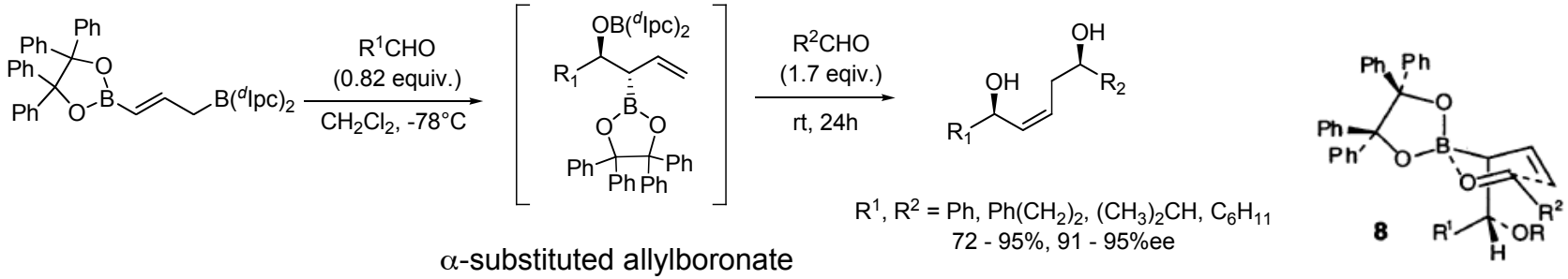




J. Pietruska, N. Schöne, *Chem. Eur. J.* **2004**, 5011-5019

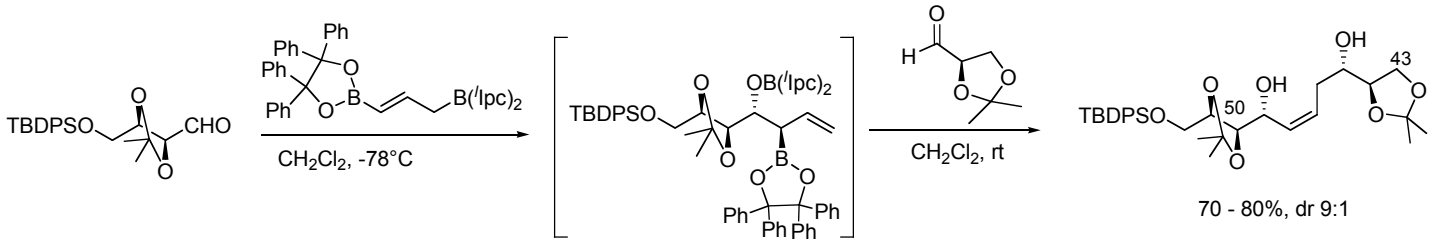
α-Substituted Allylboronates

- One-pot double allylboration with a 1,3-bifunctionalized boron reagent for the diastereo- and enantioselective synthesis of anti-1,5-diols



α-substituted allylboronate

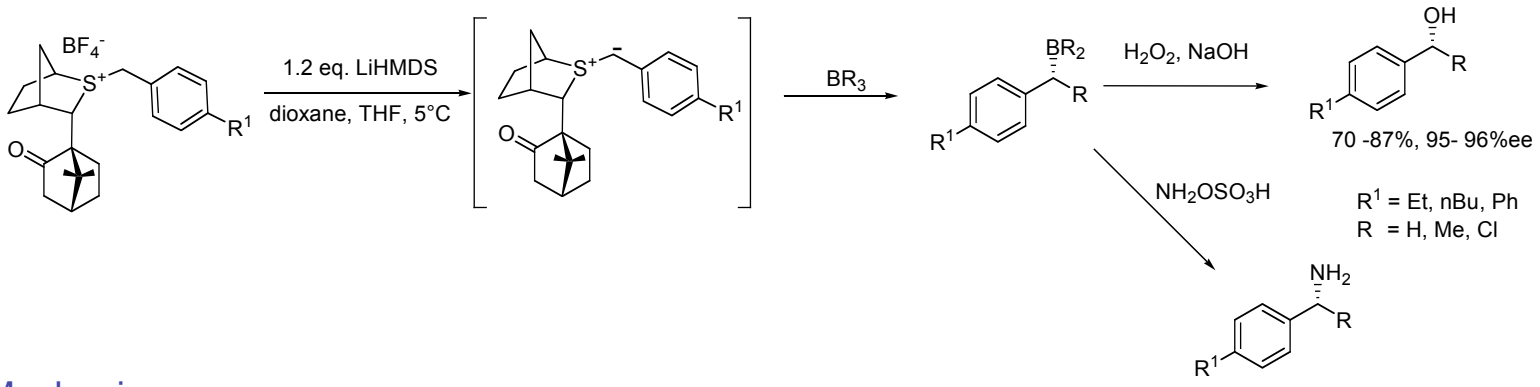
- Application: Synthesis of C(43)-C(67) fragment of Amphidinol 3



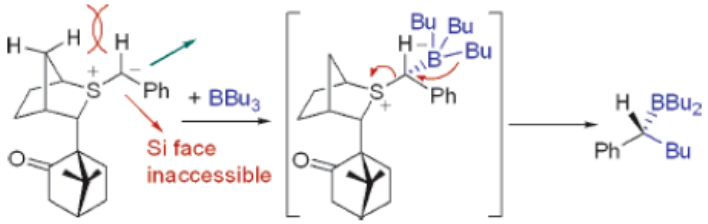
E. M. Flamme, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 13644-13645
J. D. Hicks, E. M. Flamme, W. R. Roush, Roush, *Org. Lett.* **2005**, *7*, 5509-5512

Aggarwal: Preliminary work

- Enantioselective synthesis of secondary alcohols and amines using chiral organoboranes generated from sulfonium ylides



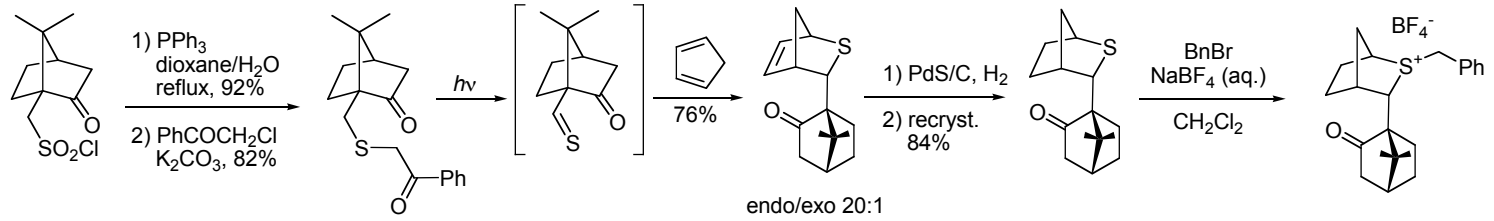
Mechanism



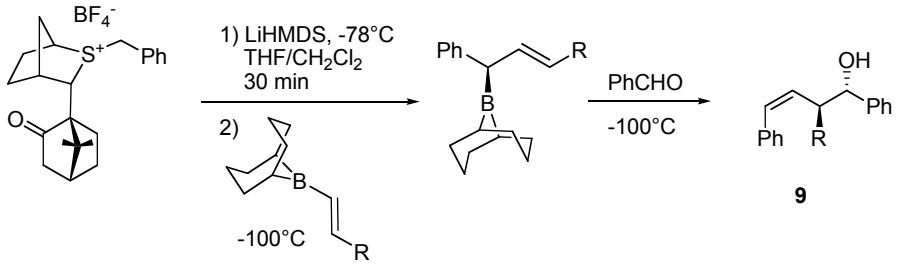
V. Aggarwal, G. Y. Feng, A. T. Schmidt, *J. Am. Chem. Soc.* **2005**, *127*, 1642-1643

Main article: Synthesis and application of α-substituted allyl boranes

- Synthesis of the sulfonium salt

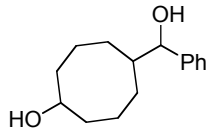


- Aldol addition to α-substituted allyl boranes



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

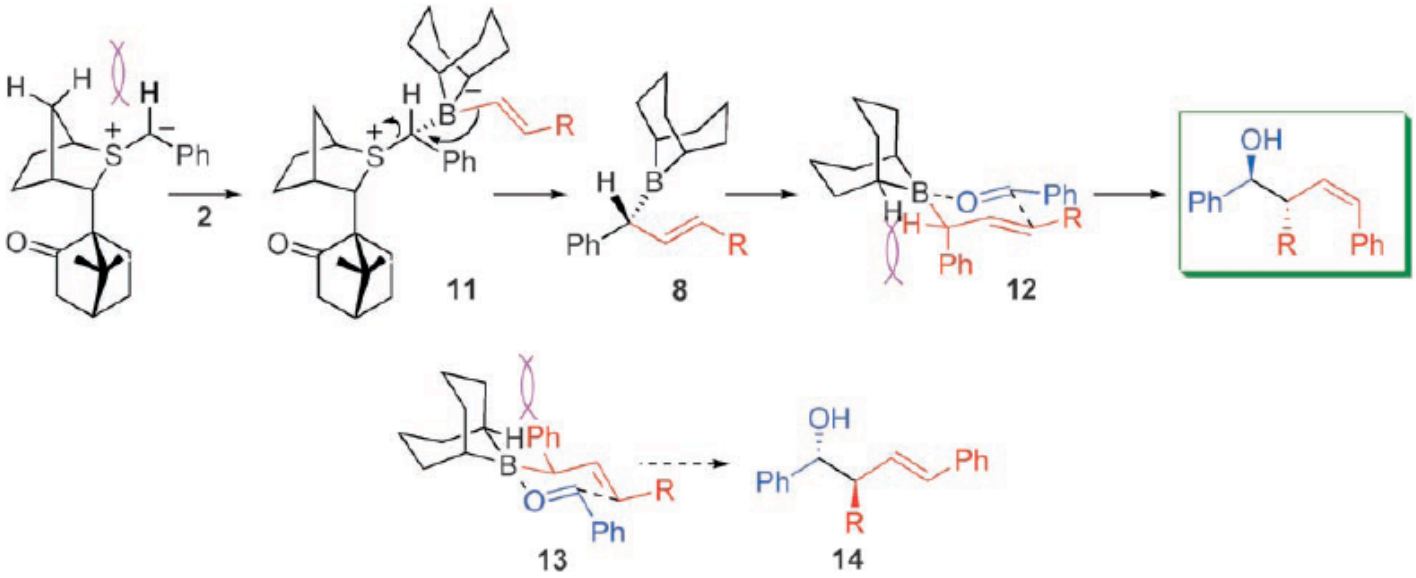
- Excellent enantio- and diastereoselectivity
- High Z selectivity
- Chiral sulfide recovered (>90%)
- Side reaction (< 20%):



V. Aggarwal *et al*, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430-1433

V. Aggarwal, G. Y. Feng, A. T. Schmidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 359-362

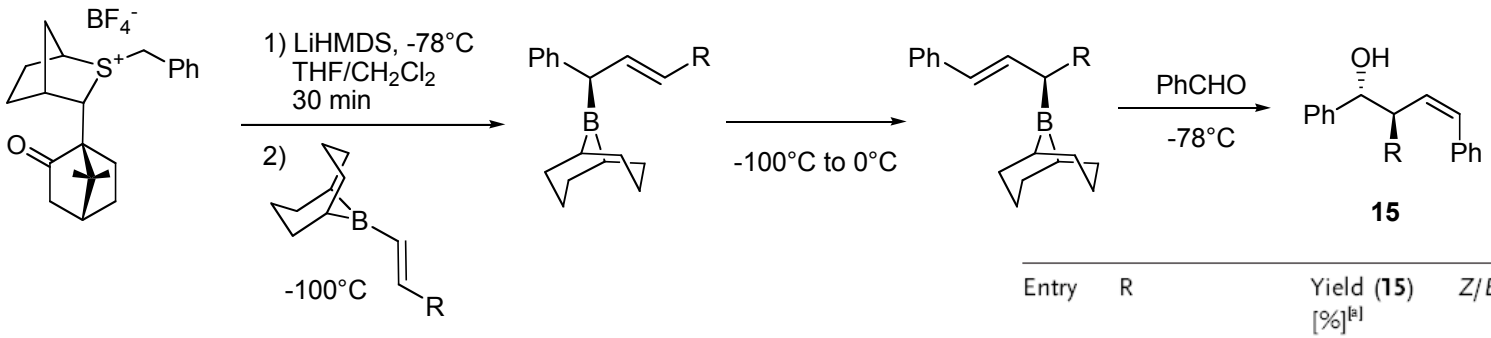
Mechanism



Aggarwal, Angew. Chem. Int. Ed. **2007**, *119*, 363-366

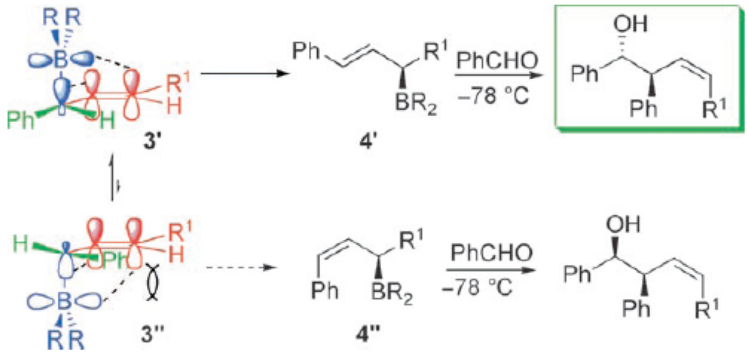
Expansion of Methodology

- Other enatiomer acessible via borane-isomerisation/aldol sequence



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

1,3 borotropic rearrangement:



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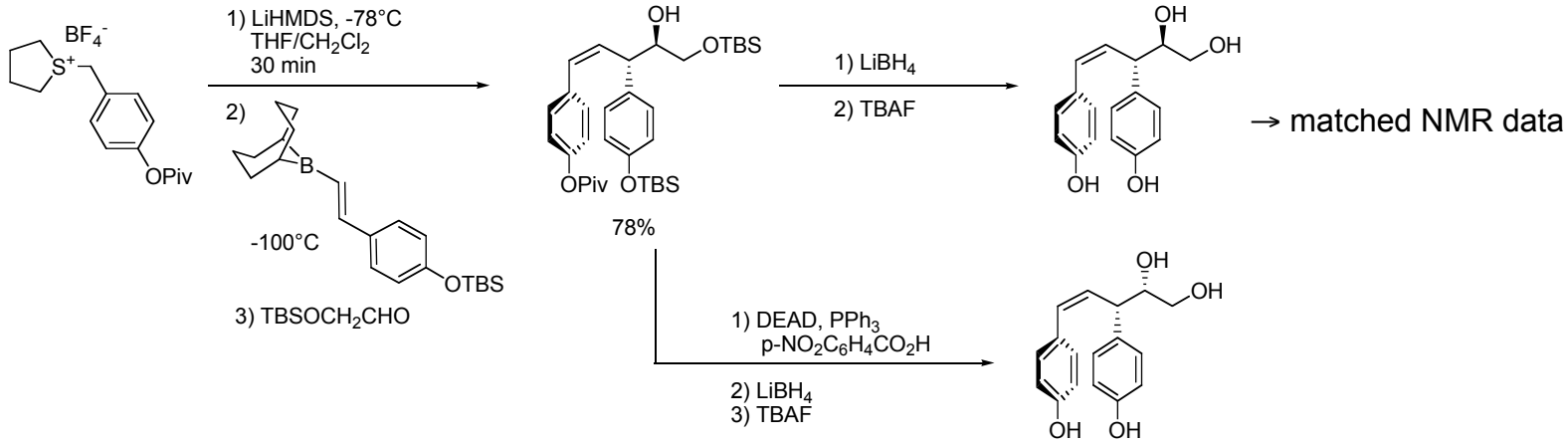
Application: Total synthesis and structural confirmation of (+)-iso-agatharesinol

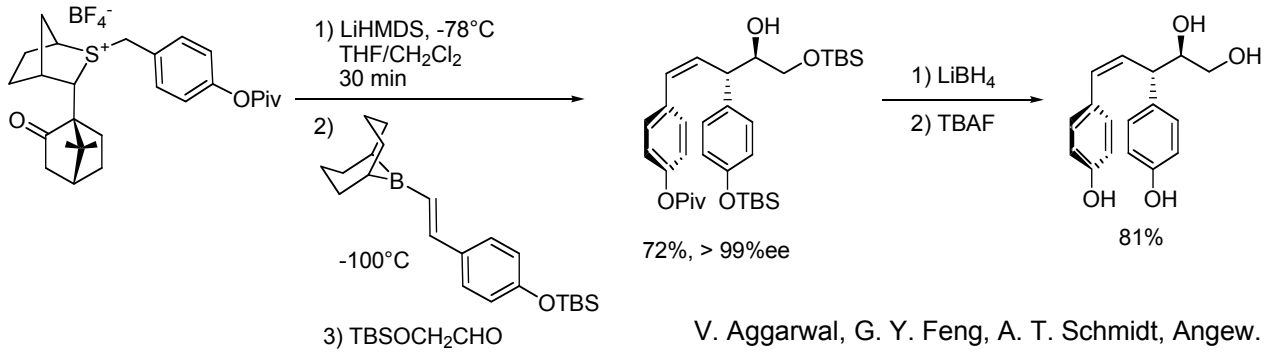
(+)-Iso-agatharesinol: Nor-lignane, isolated from *asparagus gobicus* (2004)

Confirmation of relative stereochemistry (racemic)



→ matched NMR data

Asymmetric total synthesis



V. Aggarwal, G. Y. Feng, A. T. Schmidt, Angew. Chem. Int. Ed. **2007**, *46*, 359-362

C.-X. Yang, S.-S.-Huang, X.-P. Jang, Z.-J. jia, Planta Med. **2004**, *70*, 446-451

Conclusion

- A stereocontrolled synthesis of α-substituted allyl boranes was developed
- Subsequent aldol reaction yielded *Z*-configured homoallylic alcohols in excellent enantio- and stereoselectivity
- The methodology was expanded via 1,3-borotropic rearrangement and subsequent aldol reaction
- Applied to the first total synthesis of (+)-iso-agatharesinol