

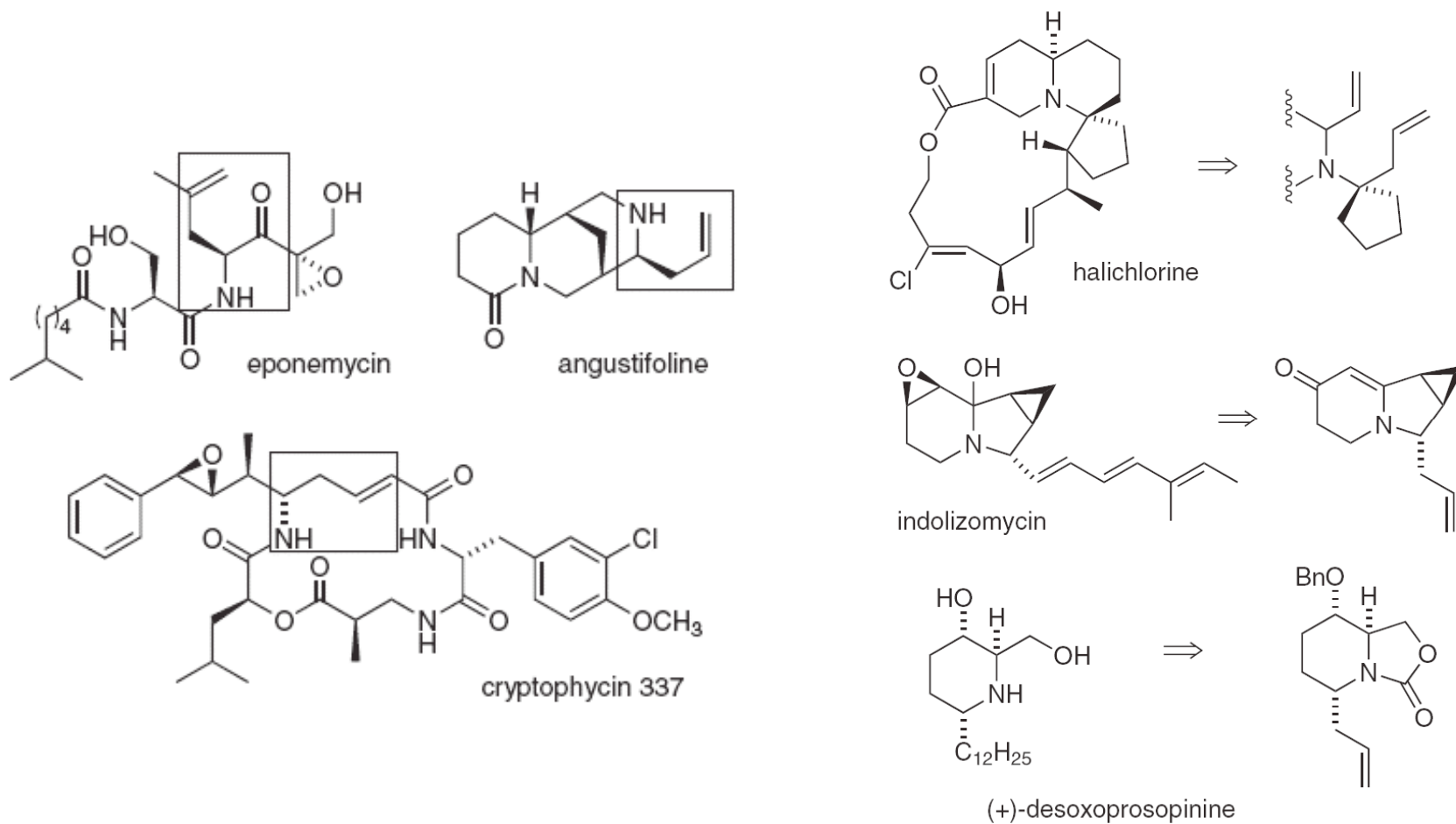
Asymmetric Allylboration of Acyl Imines Catalyzed by Chiral Diols

Sha Lou, Philip N. Moquist, Scott E. Schaus

J. Am. Chem. Soc. ASAP

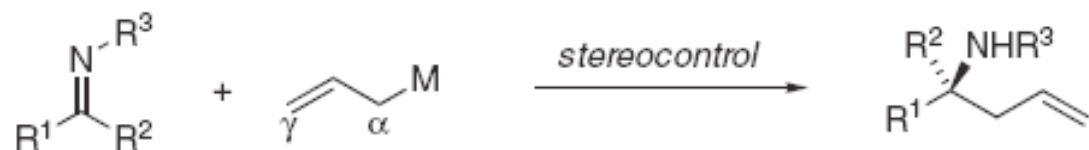
Current literature
Group Meeting
November, 24th 2007
Filip Petronijevic

Chiral homoallylic amines as building blocks in synthesis



Synthesis, **2005**, 2815.
Org. Lett. **2000**, 2(13), 1847.
J. Am. Chem. Soc. **1990**, 112.

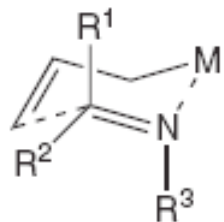
Allyl Addition to the C=N bond



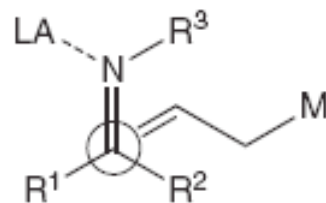
Chiral allyl metal reagents:

- allyl silanes
- allyl boronates and boranes
- diastereoselective allyl metal additions to chiral imines (Cu, Zn, Zr, Pd, In mediated additions)

Stereochemistry

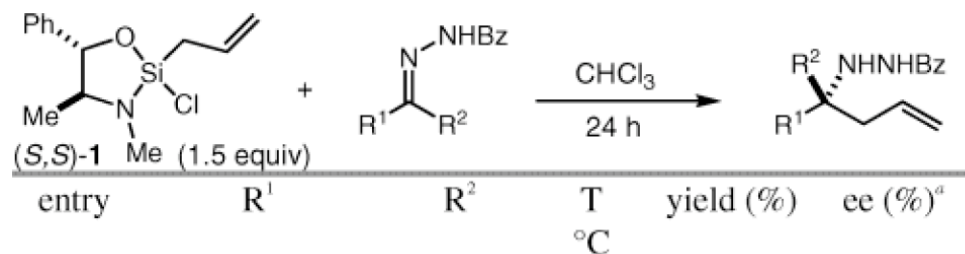


Type I TS
(Zimmerman–Traxler)

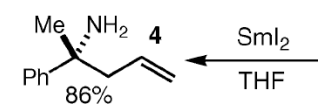
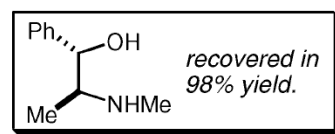
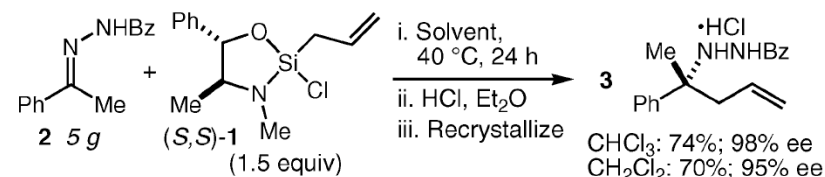


Type II TS
(open, acyclic)

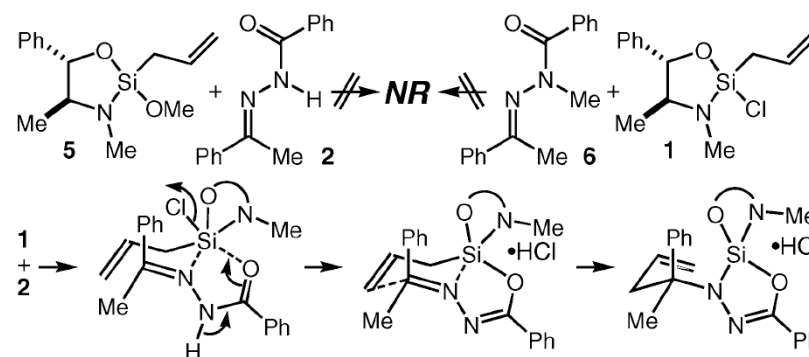
Allyl Silanes as Chiral Allylation Reagents



entry	R ¹	R ²	T °C	yield (%)	ee (%) ^a
1	Ph	Me	40	86	90
2	Ph	Et	40	91	89
3	Ph	CH ₂ Ph	40	95	84
4 ^b	Ph	CO ₂ Me	-10	76	93
5	Ph	<i>i</i> -Pr	57	80	97
6	<i>p</i> -Br-C ₆ H ₄	Me	23	92	89
7	<i>p</i> -MeO-C ₆ H ₄	Me	40	70	85
8	<i>m</i> -NO ₂ -C ₆ H ₄	Me	23	79	88
9	2-Naphthyl	Me	23	80	89
10		Me	40	46	88
11		Me	40	70	90
12		Me	40	64	86
13	PhCH ₂ CH ₂	Me	23	86	87
14 ^c	PhCH ₂ CH ₂	Me	23	87	87
15	<i>c</i> -Hex	Me	23	78	94

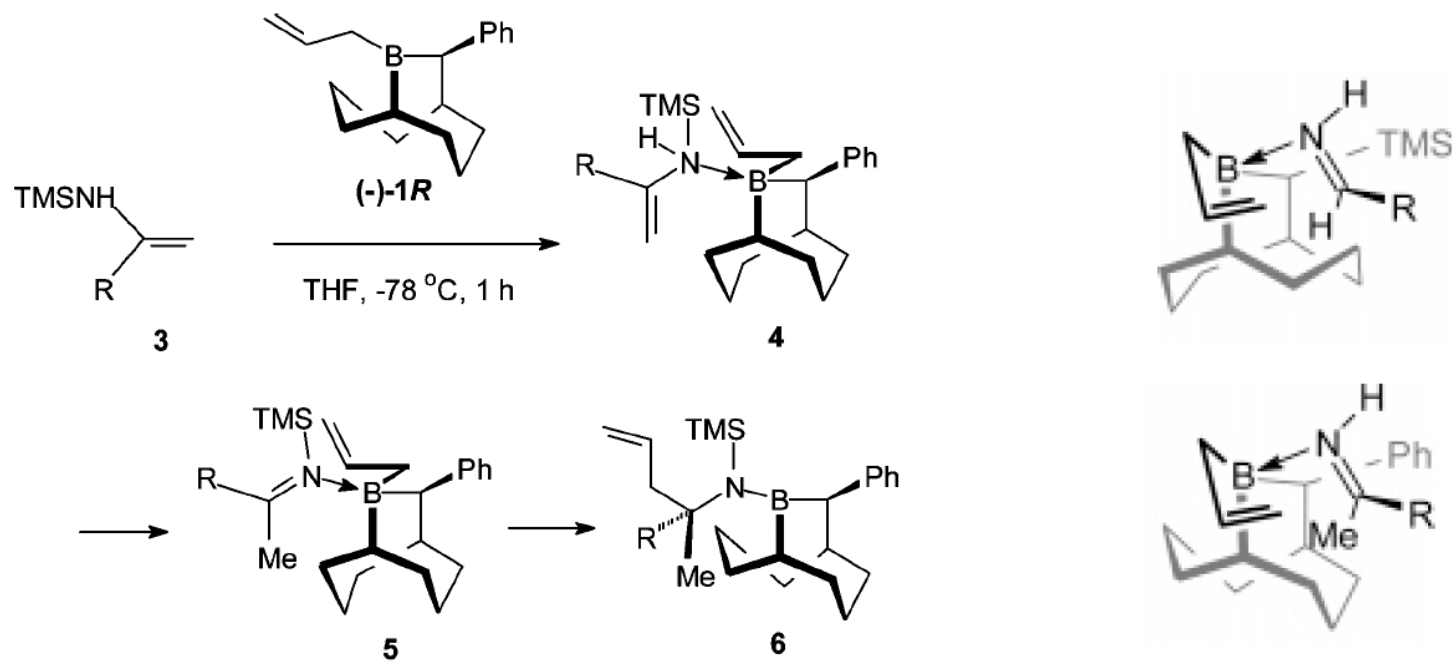


Mechanism: coordination of both imine nitrogen and acyl oxygen with Lewis Acidic silane



J. Am. Chem. Soc. **2003**, 125, 9596.
J. Am. Chem. Soc. **2004**, 126, 5686.

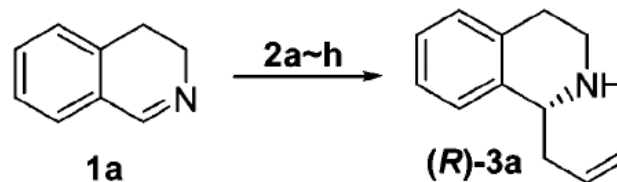
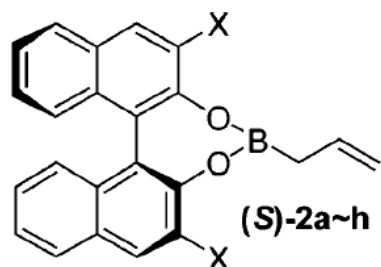
Allylboranes: Addition to C=N Bond



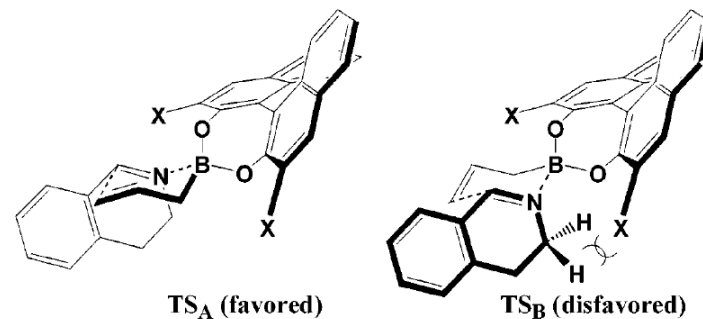
“9-BBDs contain a nearly ideal chiral pocket for the highly enantioselective allylation...”

J. Am. Chem. Soc. **2006**, 128, 8712.

Asymmetric Allylboration of Cyclic Imines: BINOL Starring



Proposed transition states

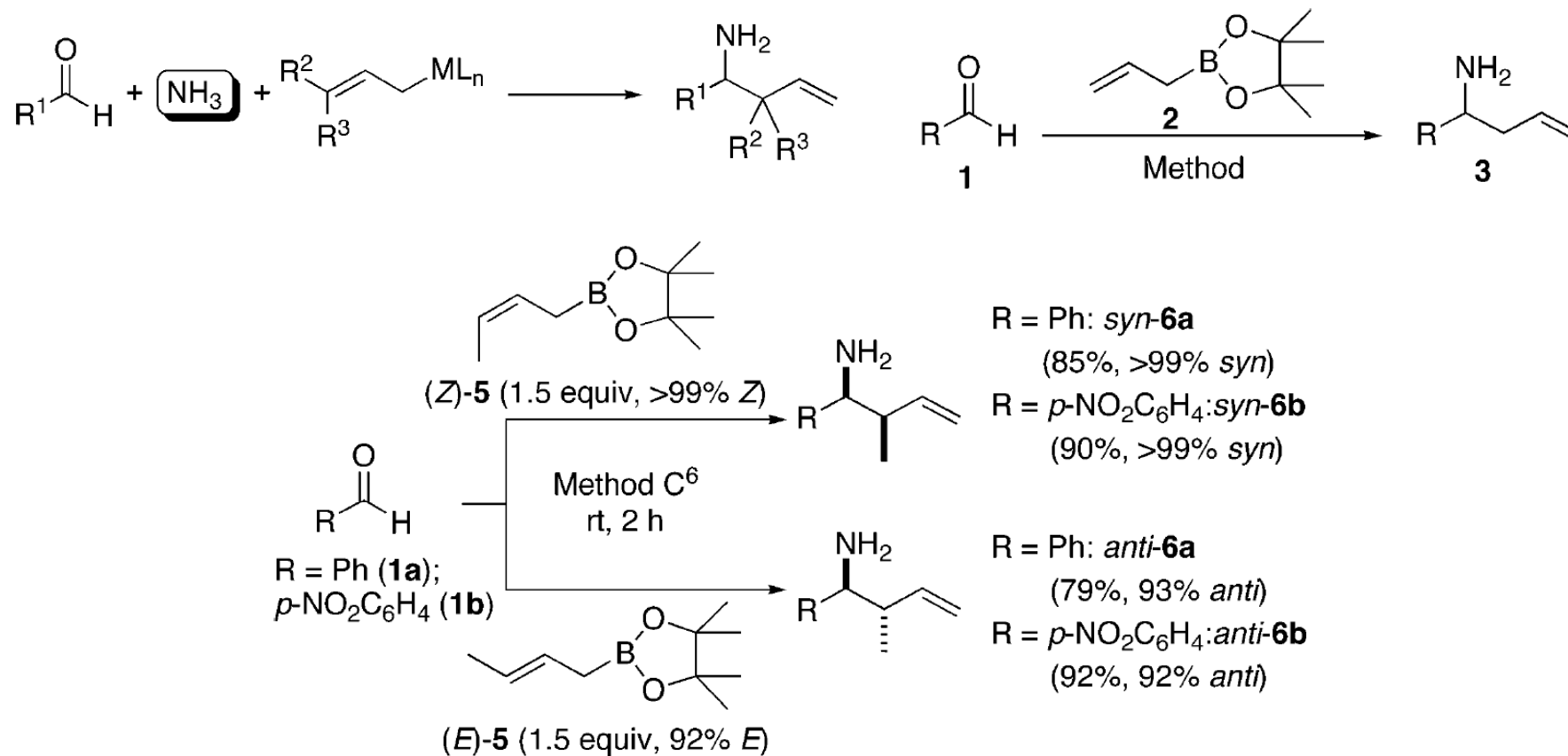


entry	X	yield ^a (%)	ee ^b (%)
1	H (2a)	<50	10
2	Me (2b)	94	75
3	I (2c)	87	77
4	CF ₃ (2d)	83	84
5	Ph (2e)	90	87
6	4-MeO-C ₆ H ₄ - (2f)	94	88
7	3,5-(CH ₃) ₂ -C ₆ H ₃ - (2g)	88	87
8	3,5-(CF ₃) ₂ -C ₆ H ₃ - (2h)	92	95

^a Isolated yields after acid–base extraction. ^b Determined by chiral HPLC analysis of the trifluoroacetamide. Absolute configuration based on rotation.⁹

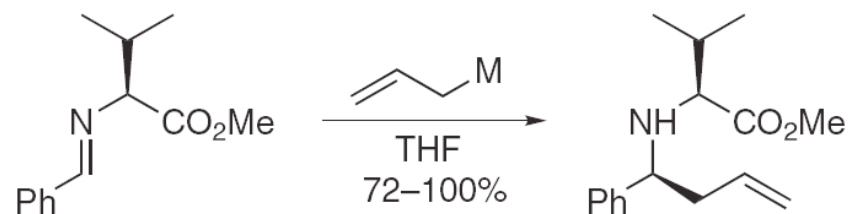
J. Amer. Chem. Soc. **2006**, *128*, 9646.

α -Aminoallylation of Aldehydes with Ammonia



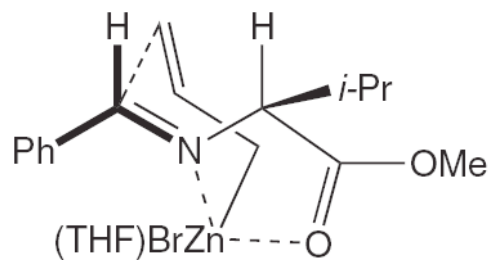
J. Am. Chem. Soc. **2004**, *126*, 7182.

Zinc vs. Boron: Opposing Modes of Stereocontrol Depending on Chelation

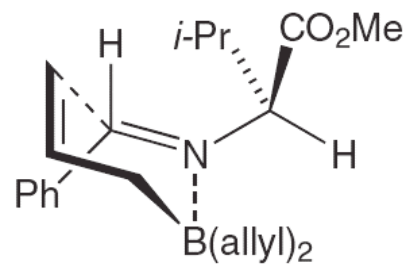


M = Pb, Bi, Cu, Al, Zn: dr 97:3 to 100:0

M = B (triallylborane): dr 8:92



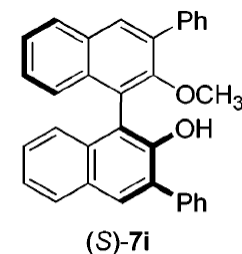
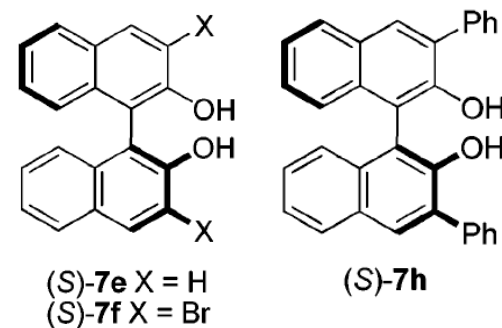
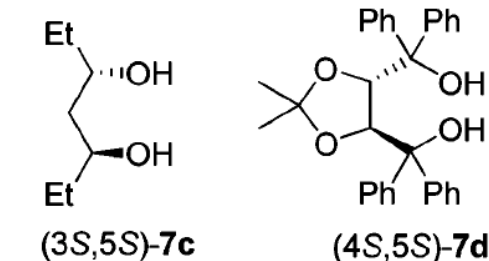
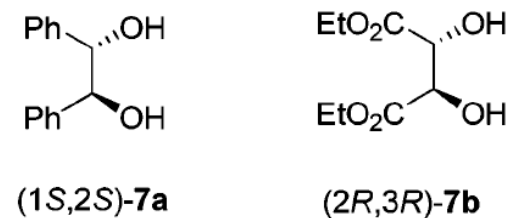
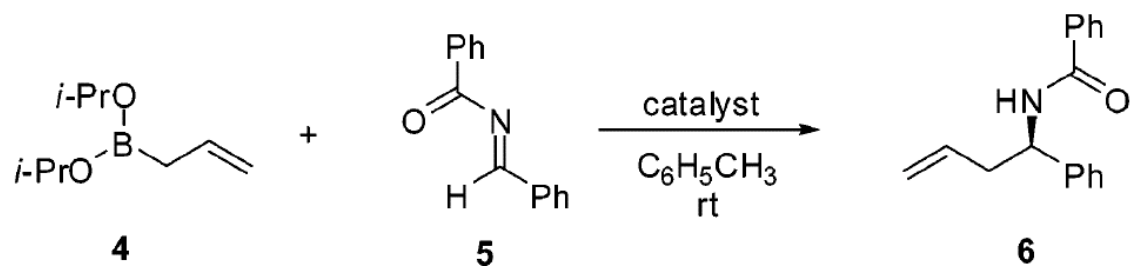
chelation,
si-face attack



free rotation,
re-face attack

Synlett, **2002**, 651.

Title Paper: Asymmetric Allylboration of Acyl Imines

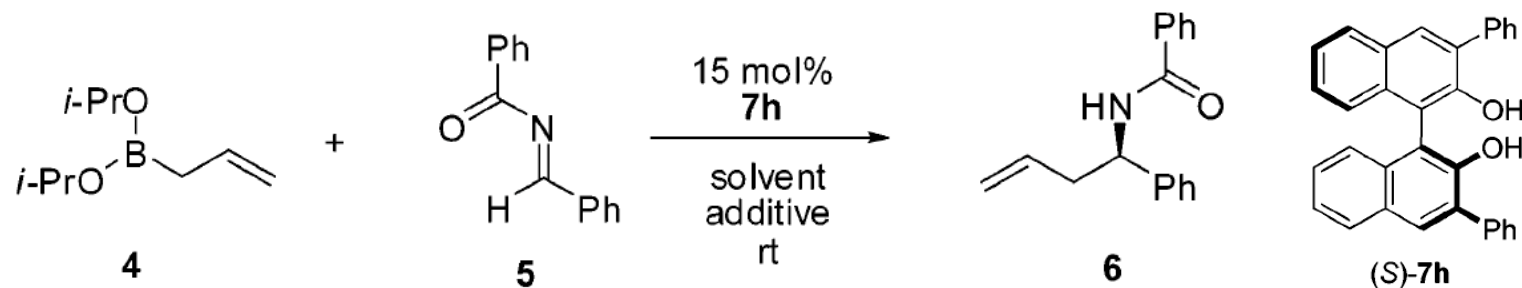


entry	catalyst	mol % ^b	% yield ^c	er ^d
1			<5	
2	7a	15	<5	50:50
3	7b	15	<5	55:45
4	7c	15	10	60:40
5	7d	15	51	50:50
6	7e	15	76	68:32
7	7f	15	81	93:7
8	7g	10	60	96.5:3.5
9	7h	15	85	96:4
10	7h	10	80	95:5
11	7h	5	60	90:10
12	7i	15	21	55:45

^a Reactions were run with 0.125 mmol of borane, 0.125 mmol of acyl imine, 15 mol % catalyst and in toluene (0.1 M) for 16 h under Ar, followed by flash chromatography on silica gel. ^b Catalyst concentration used relative to imine. ^c Isolated yield. ^d Enantiomeric ratios determined by chiral HPLC analysis.

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Asymmetric Allylboration of Acyl Imines: Solvent and Additive Effects

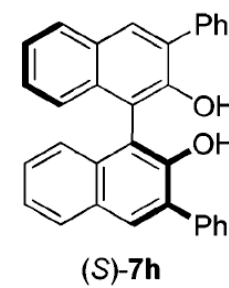
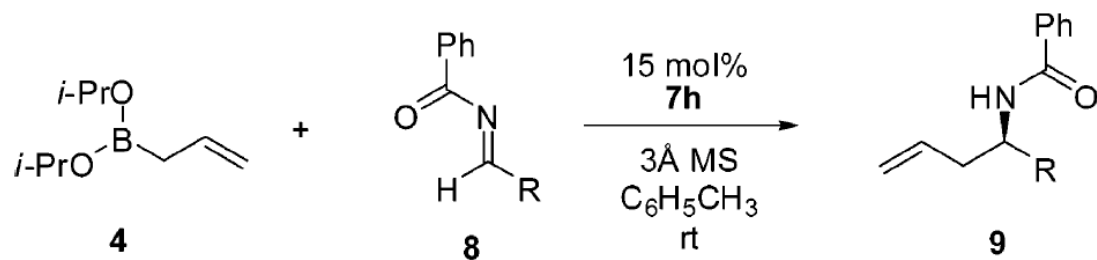


entry	solvent	additive	% yield ^b	er ^c
1	THF		32	58:42
2	Et ₂ O		28	60:20
3	CH ₂ Cl ₂		75	92:8
4	C ₆ H ₅ CH ₃ /C ₆ H ₅ CF ₃ (3:1)		77	92:8
5	C ₆ H ₅ CH ₃		81	93:7
6	C ₆ H ₅ CH ₃	3 Å molecular sieve	87	99:1
7	C ₆ H ₅ CH ₃	4 Å molecular sieve	85	97:3
8	C ₆ H ₅ CH ₃	5 Å molecular sieve	83	90:10

^a Reactions were run with 0.125 mmol of borane, 0.125 mmol of acyl imine, 15 mol % catalyst and in toluene (0.1 M) for 16 h under Ar, followed by flash chromatography on silica gel. ^b Isolated yield. ^c Enantiomeric ratios determined by chiral HPLC analysis.

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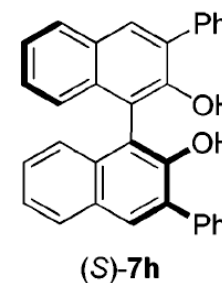
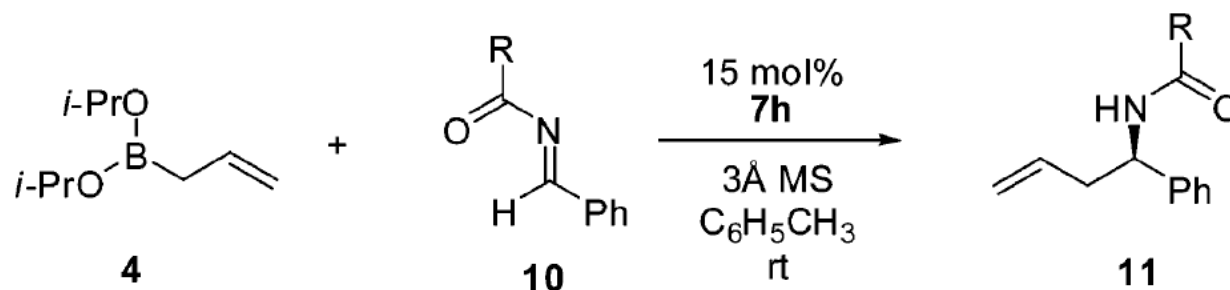
Asymmetric Allylboration of Benzoyl Imines: Scope and Limitations



entry	R	product	% yield ^b	er ^c
1	Ph	9a	87	99:1
2	<i>p</i> -CH ₃ -C ₆ H ₄	9b	83	98:2
3	<i>p</i> -Br-C ₆ H ₄	9c	86	97.5:2.5
4	<i>p</i> -CH ₃ O-C ₆ H ₄	9d	85	95:5
5 ^d	<i>p</i> -F-C ₆ H ₄	9e	94	98:2
6 ^d	<i>o</i> -F-C ₆ H ₄	9f	91	95.5:4.5
7 ^d	<i>m</i> -CF ₃ -C ₆ H ₄	9g	89	97.5:2.5
8	2-C ₄ H ₃ O	9h	83	96:4
9	2-C ₄ H ₃ S	9i	81	95:5
10	2-naphthyl	9j	88	96:4
11	(<i>E</i>)-PhCH=CH	9k	82	95.5:4.5
12	PhCH ₂ CH ₂	9l	83	99.5:0.5
13	<i>c</i> -C ₆ H ₁₁	9m	80	98:2
14	<i>t</i> -Bu	9n	81	99.5:0.5
15	BnOCH ₂	9o	84	96.5:3.5
16	(<i>Z</i>)-EtCH=CH(CH ₂) ₂	9p	82	95.5:4.5

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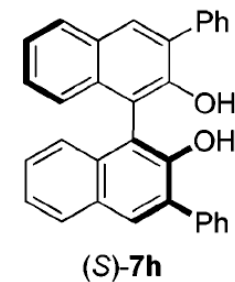
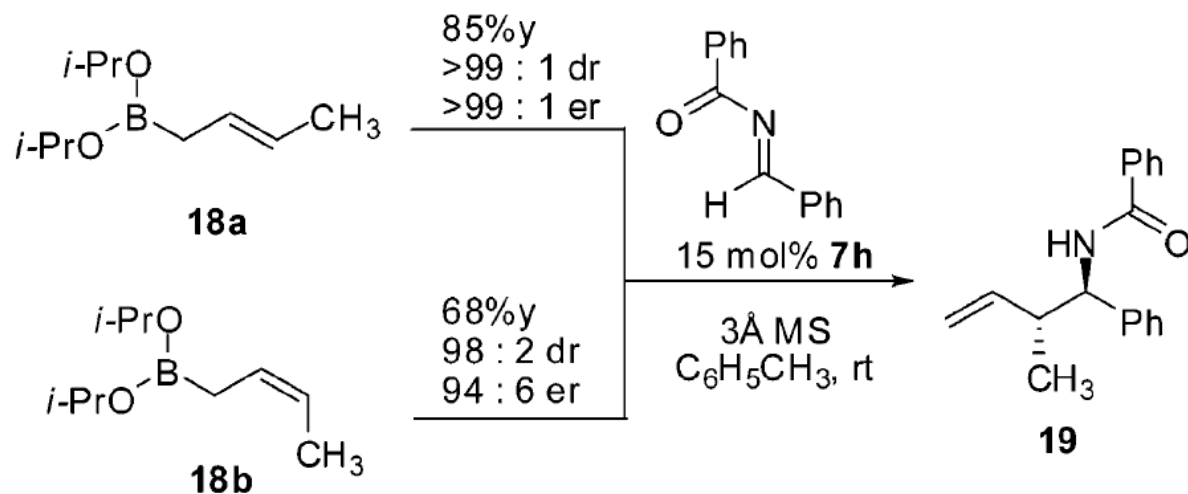
Asymmetric Allylboration of Benzoyl Imines: What About Other Types of Imines?



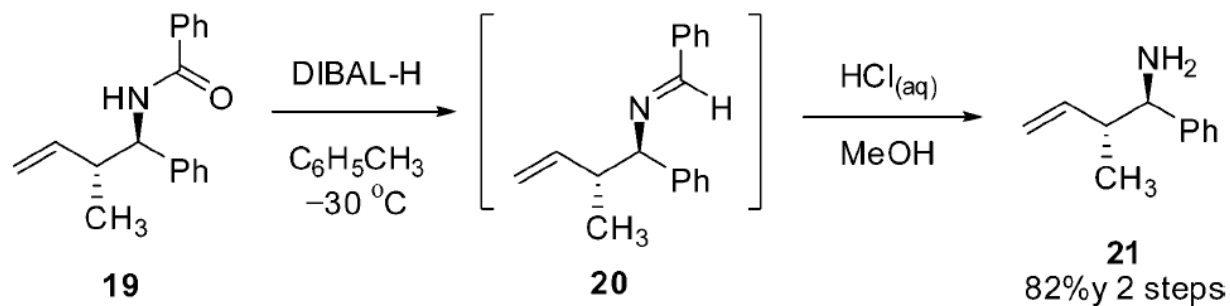
entry	R	product	% yield ^b	er ^c
1	CH ₃ O	11a	13	57:43
2	<i>t</i> -BuO	11b	25	65:35
3	CH ₂ =CHCH ₂ O	11c	41	65:35
4	CH ₃	11d	52	70:30
5	<i>p</i> -(CH ₃) ₂ N-C ₆ H ₄	11e	76	97:3
6	<i>p</i> -CH ₃ O-C ₆ H ₄	11f	80	97.5:2.5
7	<i>p</i> -Br-C ₆ H ₄	11g	83	96.5:3.5
8	<i>p</i> -F-C ₆ H ₄	11h	84	97.5:2.5
9	<i>p</i> -NO ₂ -C ₆ H ₄	11i	92	99.5:0.5
10	<i>o</i> -F-C ₆ H ₄	11j	83	69:31
11	(<i>E</i>)-PhCH=CH	11k	82	95:5
12	<i>c</i> -C ₆ H ₁₁	11l	83	97:3

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Crotylboration of Acyl Imines



Removal of the *N*-Benzoyl Group:

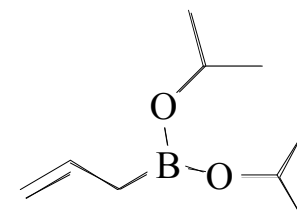
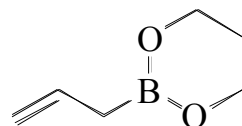
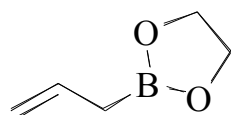
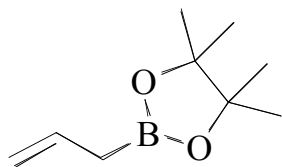


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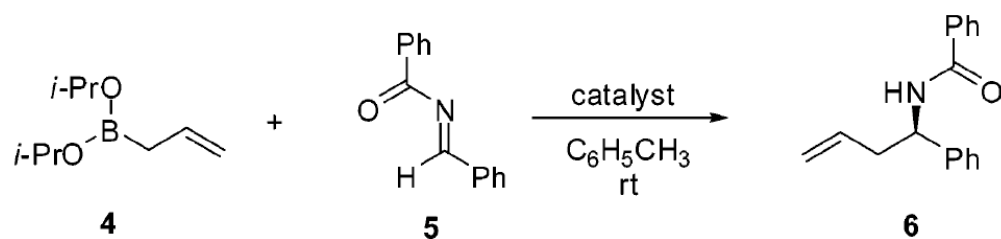
Mechanistic Studies: Boronate Ligand Exchange

Allylboronates are activated via exchange of the alkoxy boronate ligands:

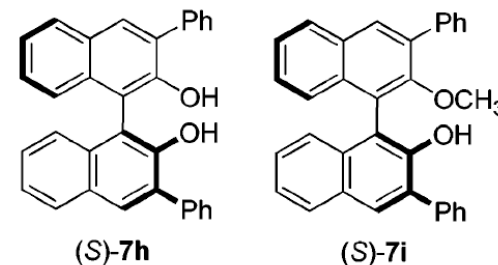
- Using pinacol, ethylene glycol and 1,3-propanediol suffers from very slow reaction, low yields and stereoselectivity
- Diisopropoxy boronate gave best results



- The diol functionality of the catalyst is essential

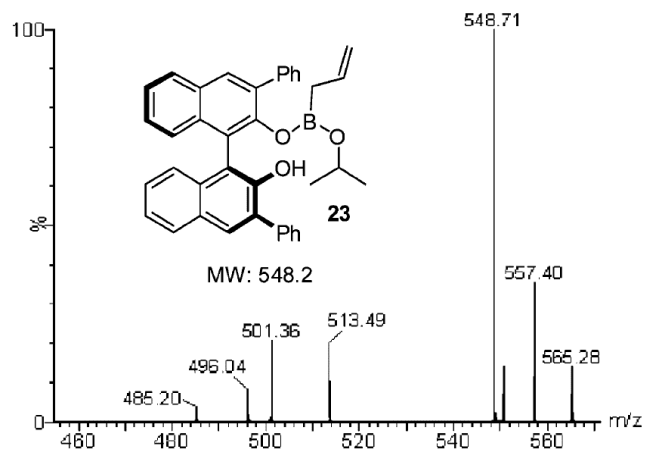
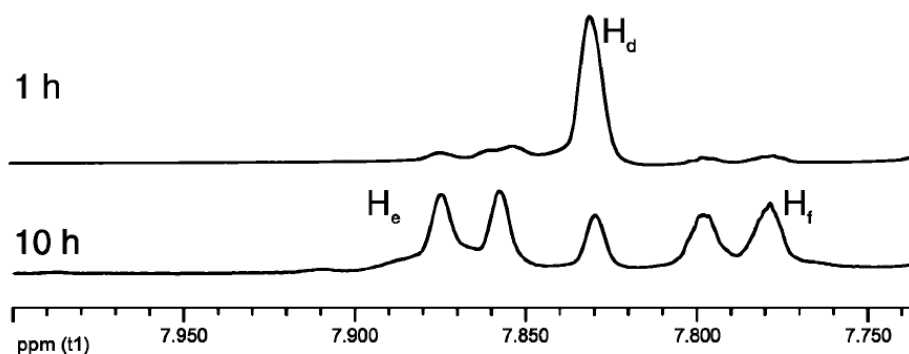
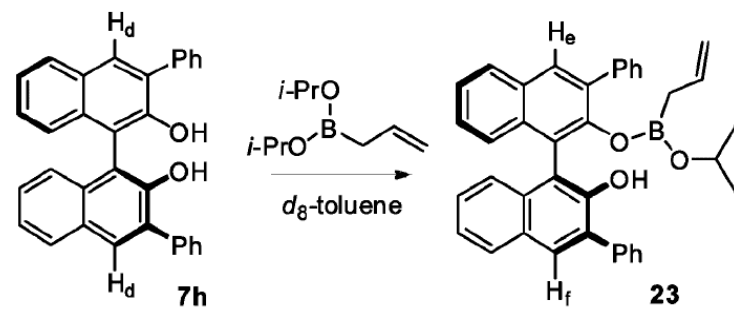
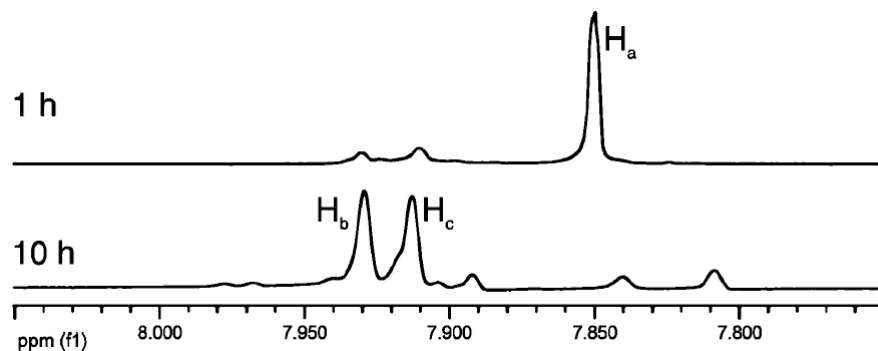
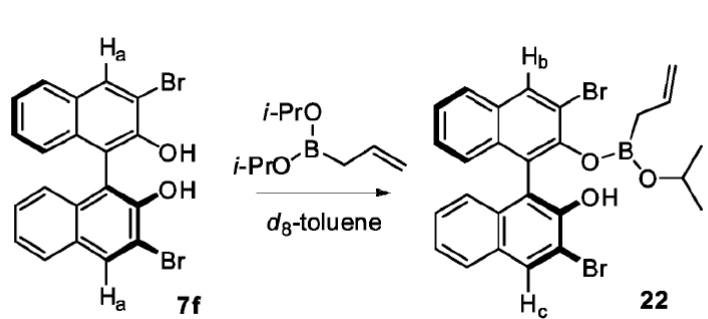


entry	catalyst	mol % ^b	% yield ^c	er ^d
11	7h	5	60	90:10
12	7i	15	21	55:45



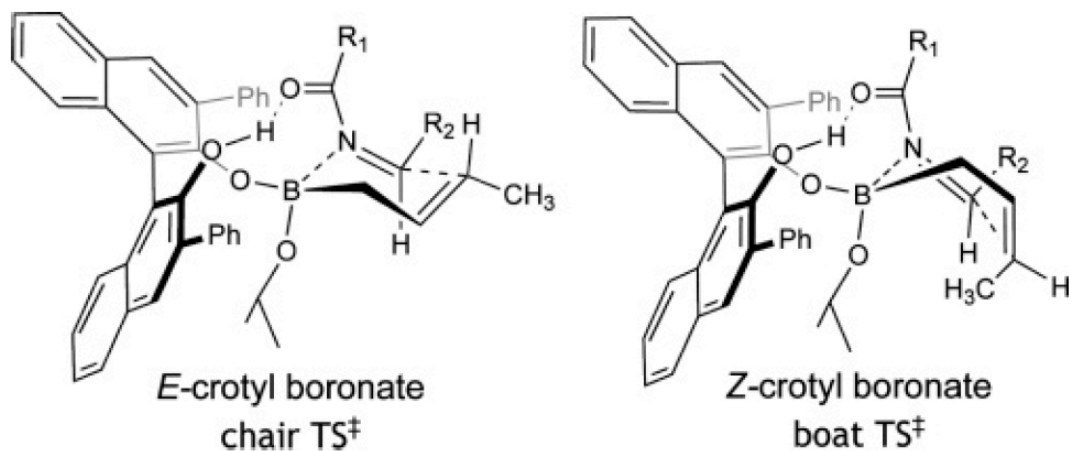
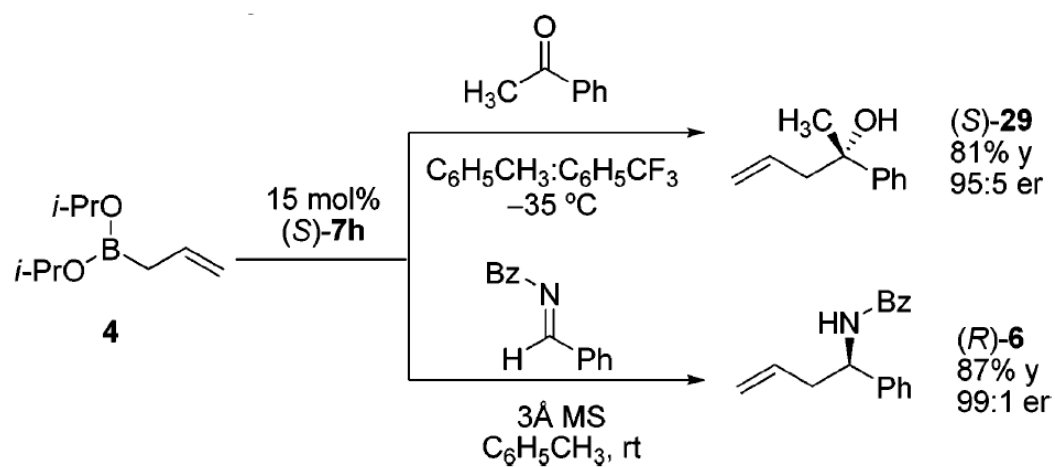
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Mechanistic Studies: Spectroscopic Characterization of the Reaction



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Enantiofacial Selectivity in Asymmetric Allylboration: Proposed Transition States



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Conclusions

- Highly enantioselective allylboration of acyl imines catalysed by chiral BINOL-derived catalysts has developed
- The reaction is highly selective for both aryl and aliphatic acyl imines
- Crotyl boronates give the corresponding *anti*-products in high diastereoselectivity
- Mechanistic studies confirm ligand exchange between boronate and catalyst