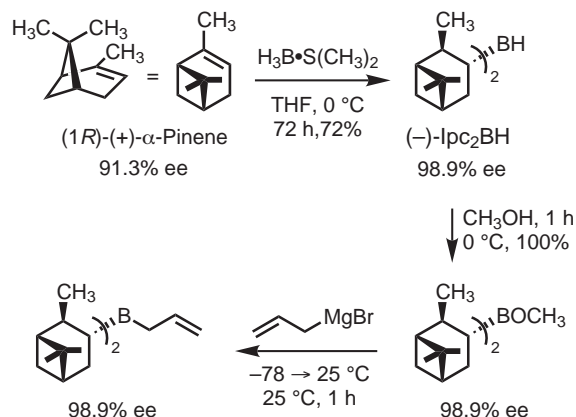


Brown Allylation and Crotylation Reactions

Reviews:

Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, 20, 9.

Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 1-53.

Synthesis of *B*-Allyldiisopinocampheylborane

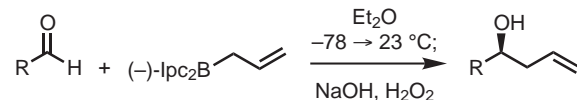
- Prolonged incubation at 0 °C affords enantiomerically enriched lpc₂BH. This is due to equilibration of tetraisopinocampheylborane with α -pinene and triisopinocampheylborane; the symmetrical dimer crystallizes preferentially.
- Both enantiomers of α -pinene are commercially available and inexpensive (Aldrich: (1*R*)-(+)- α -pinene, 91% ee, \$100/500mL; (1*S*)-(-)- α -pinene, 87% ee, \$42/100mL).
- *B*-Allyldiisopinocampheylborane can be prepared and used in situ after filtration of the magnesium salts produced during its formation.

Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, 47, 5065-5069.

Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, 49, 945-947.

Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, 51, 432-439.

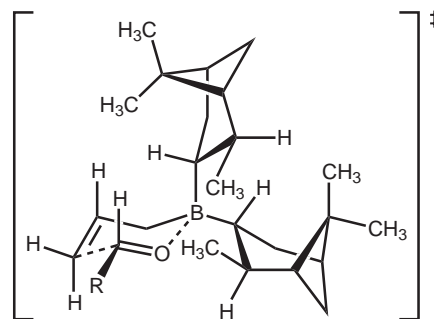
Enantioselective Allylboration



R	yield (%)	ee (%) ^a	ee (%) ^b
CH ₃	74	93	≥99
<i>n</i> -C ₃ H ₇	71	86	-
<i>n</i> -C ₄ H ₉	72	87	96
<i>t</i> -C ₄ H ₉	88	83	≥99
C ₆ H ₅	81	96	96

^aAllylboration carried out without filtration of Mg salts. ^bAllylboration carried out at -100 °C under Mg-salt free conditions.

- The reaction is quite general; the stereochemistry of the addition is the same in all cases examined.
- Lower reaction temperatures (0 → -78 → -100 °C) lead to increased enantioselectivity.
- Only Mg-salt free reagent can be used at -100 °C because the reactive borane is sequestered by ate complex formation with CH₃OMgBr at this temperature.
- Allylboration of aldehydes is essentially instantaneous at -78 or -100 °C in the absence of Mg salts.



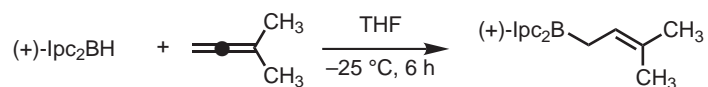
- Allylation of aldehydes proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial lpc ligand and the allyl group.

Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, 105, 2092-2093.

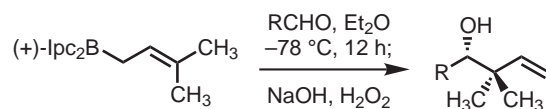
Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, 108, 5919-5923.

Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, 56, 401-404.

Asymmetric Isoprenylation of Aldehydes



- Hydroboration of allenes is an efficient method for preparing *B*-allyldiisopinocampheylboranes

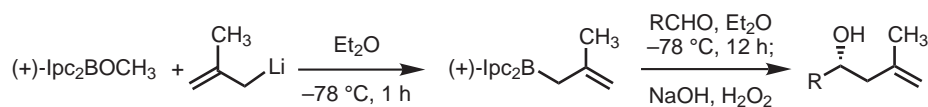


R	yield (%)	ee (%)
CH ₃	73	91
<i>n</i> -C ₄ H ₉	79	92
CH ₂ =CH	70	95
(CH ₃) ₂ C=CH	85	96

Brown, H. C.; Jadhav, P. K. *Tetrahedron Lett.* **1984**, 25, 1215-1218.

Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, 51, 432-439.

Methallylation of Aldehydes



R	yield (%)	ee (%)
CH ₃	56	90
<i>n</i> -C ₃ H ₇	54	90
<i>n</i> -C ₄ H ₉	56	91
<i>t</i> -C ₄ H ₉	55	90
CH ₂ =CH	57	92

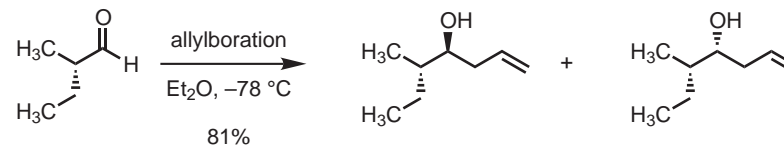
- The yields for methallylation of aldehydes are generally lower than in simple allylation reactions.

Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, 25, 5111-5114.

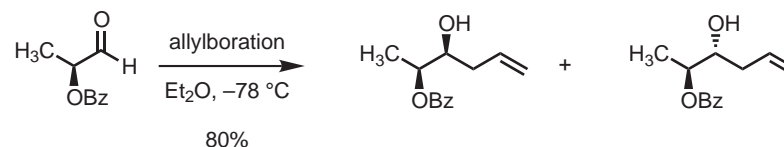
Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, 51, 432-439.

Diastereoselective Allylboration of Chiral, α -Substituted Aldehydes

- The diastereofacial selectivity of the *B*-allyldiisopinocampheylborane reagent typically overrides any facial preference of the aldehyde for nucleophilic attack.

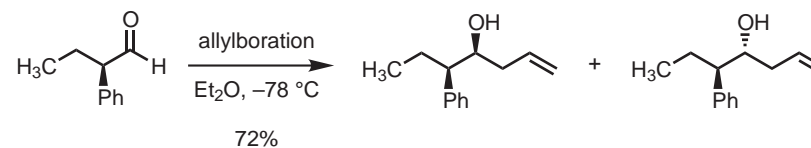


<i>MATCHED</i> :	(-)-Ipc ₂ BCH ₂ CH=CH ₂	96	:	4	(92% de)
<i>MISMATCHED</i> :	(+)-Ipc ₂ BCH ₂ CH=CH ₂	5	:	95	(90% de)



<i>MISMATCHED</i> :	(-)-Ipc ₂ BCH ₂ CH=CH ₂	94	:	6	(88% de)
<i>MATCHED</i> :	(+)-Ipc ₂ BCH ₂ CH=CH ₂	4	:	96	(92% de)

- Although the stereochemical outcome of the allylboration of aldehydes using *B*-allyldiisopinocampheylborane is typically reagent controlled, this selectivity may be challenged with certain substrates:

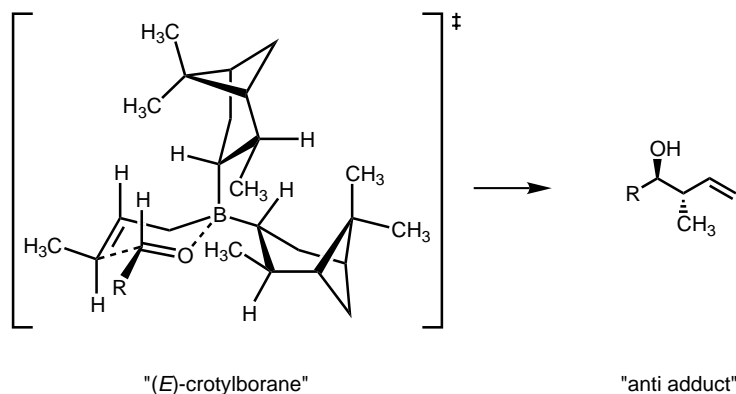
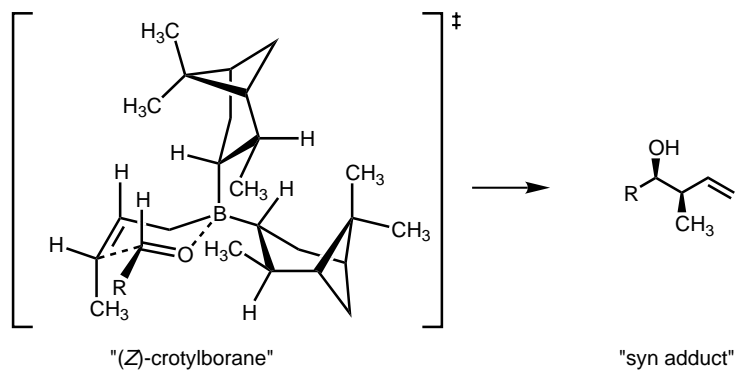


<i>MISMATCHED</i> :	(-)-Ipc ₂ BCH ₂ CH=CH ₂	67	:	33	(34% de)
<i>MATCHED</i> :	(+)-Ipc ₂ BCH ₂ CH=CH ₂	2	:	98	(96% de)

Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, 52, 319-320.

Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, 54, 1570-1576.

Chair TS's Produce syn Adducts from (Z)-Crotylboranes and anti Adducts from (E)-Crotylboranes.



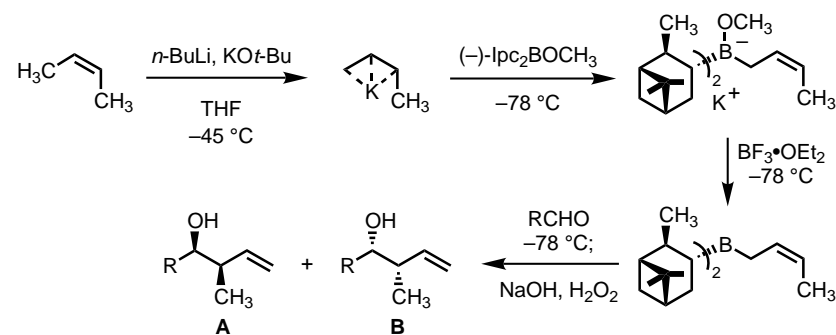
- These adducts can be viewed as protected aldol products; "deprotection" is brought about by dihydroxylation/periodate cleavage or by ozonolysis.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.

Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 1-53.

(Z)-Crotylboranes

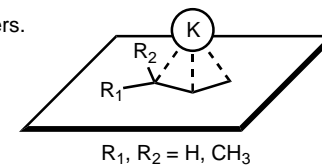


lpc	aldehyde	yield (%)	A:B	ee (%)
-	CH ₃ CHO	75	95:5	90
+	CH ₃ CHO	72	4:96	92
-	C ₂ H ₅ CHO	70	95:5	90
+	C ₂ H ₅ CHO	78	4:96	92
-	CH ₂ =CHCHO	63	95:5	90
-	C ₆ H ₅ CHO	72	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by BF₃·OEt₂ at -78 °C to avoid crotyl isomerization.

"Superbases" for Organic Synthesis

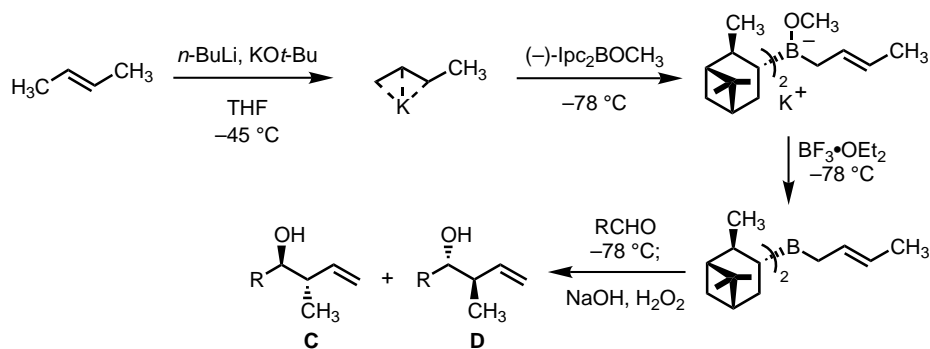
- The "superbase" prepared by mixing *n*-butyllithium and potassium *t*-butoxide (1:1) can metalate hydrocarbons of low acidity—in particular—olefins.
- Allylic methyl groups are much more readily metalated than allylic methylene or methine centers.
- *cis*-2-alkenes generally react faster than their *trans*-isomers.
- The large atomic radius of potassium favors η³-bonding in allyl, crotyl and prenyl derivatives:



Schlosser, M. *Pure & Appl. Chem.* **1988**, *60*, 1627-1634.

Schlosser, M.; Stahle, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 487-489.

(E)-Crotylboranes



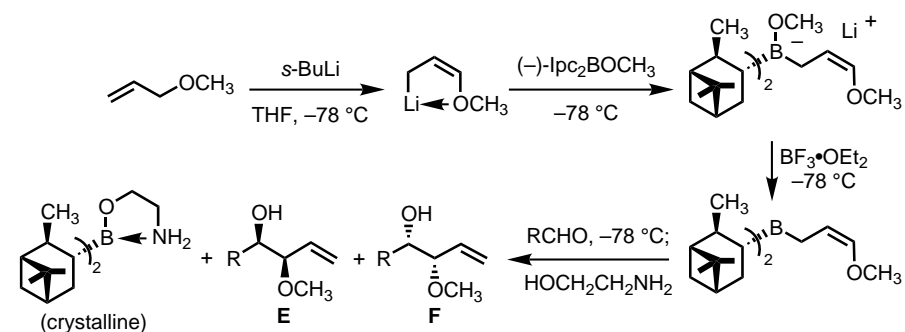
lpc	aldehyde	yield (%)	C:D	ee (%)
-	CH ₃ CHO	78	95:5	90
+	CH ₃ CHO	76	4:96	92
-	C ₂ H ₅ CHO	70	95:5	90
+	C ₂ H ₅ CHO	69	4:96	92
-	CH ₂ =CHCHO	65	95:5	90
-	C ₆ H ₅ CHO	79	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by BF₃·OEt₂ at -78 °C to avoid crotyl isomerization.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.

Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.

Diastereo- and Enantioselective *vic*-Diol Synthesis



- Treatment of the crude product mixture with ethanolamine allows for easy removal of the reagent by-product as a crystalline adduct; this is an alternative to oxidative work-up.

lpc	aldehyde	yield (%)	E:F	ee (%)
-	CH ₃ CHO	57	95:5	90
+	CH ₃ CHO	59	4:96	92
-	C ₂ H ₅ CHO	65	96:4	92
+	C ₂ H ₅ CHO	68	5:95	90
-	CH ₂ =CHCHO	63	94:6	88
-	C ₆ H ₅ CHO	72	95:5	90

- Other vinyl ethers may be used, such as methoxymethyl vinyl ether (affording the MOM-protected *vic*-diol).

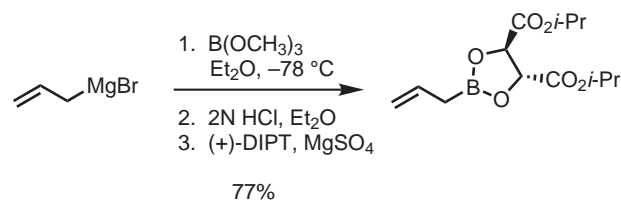
Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.

Roush Allylation and Crotylation Reactions

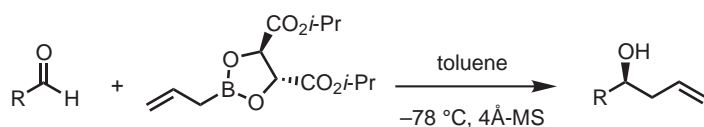
Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 1-53.

Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359.

Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294-296.



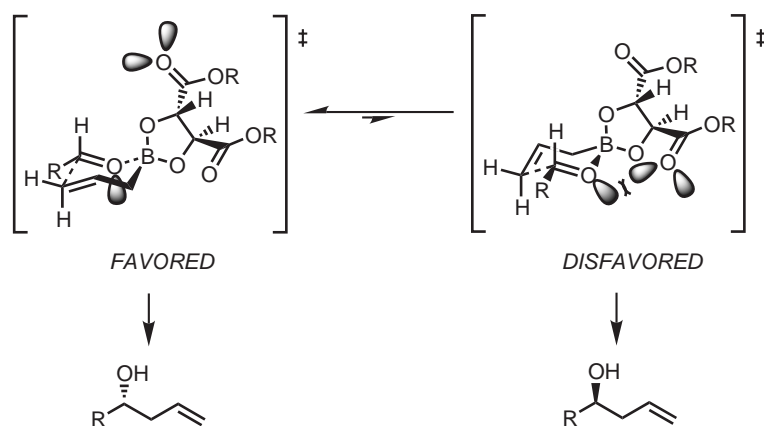
- The stability of allylboronate reagents permits their purification by distillation. Allyl diisopinocampheyl reagents cannot be distilled.



aldehyde	yield (%)	ee (%)
$n\text{-C}_9\text{H}_{19}\text{CHO}$	86	79
$c\text{-C}_6\text{H}_{11}\text{CHO}$	77	78
$\text{C}_6\text{H}_5\text{CHO}$	78	71

- Enantioselectivities are typically moderate.
- $4\text{\AA}\text{-MS}$ are necessary to achieve the highest levels of selectivity.

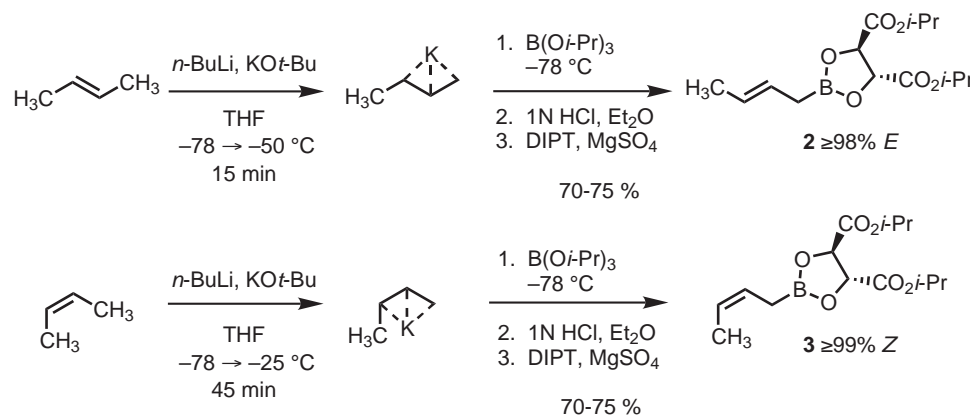
Proposed Origin of Selectivity in Tartarate Derived Allylboronate Additions



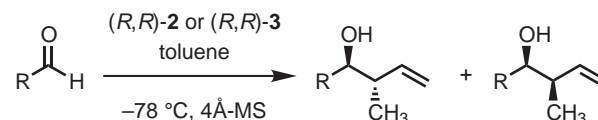
- The favored transition state is believed to minimize unfavorable lone-pair lone-pair interactions.

Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.

Preparation of (*E*)- and (*Z*)-Crotylboronate Reagents



- Crotylboronates are configurationally stable at or slightly above room temperature.
- Tartrate modified (*E*)- and (*Z*)-Crotylboronates can be stored for several months at -20°C in neat form or in solution with little noticeable deterioration.
- Competition experiments have shown that (*E*)-crotylboronates react faster with aldehydes than the corresponding (*Z*)-isomers.
- Essentially identical results are obtained with a range of commercially available tartrate esters (CH_3 , Et , $i\text{-Pr}$).



R	reagent	yield (%)	anti:syn	ee (%) ^a
$n\text{-C}_9\text{H}_{19}$	2	90	95:5	86
$n\text{-C}_9\text{H}_{19}$	3	70	1:>99	77
$c\text{-C}_6\text{H}_{11}$	2	94	>99:1	86
$c\text{-C}_6\text{H}_{11}$	3	90	2:98	83
$\text{TBSOCH}_2\text{CH}_2$	2	71	$\geq 98:2$	85
$\text{TBSOCH}_2\text{CH}_2$	3	68	$2:\geq 98$	72

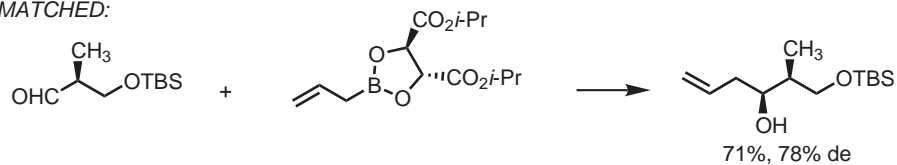
^aee of major diastereomer.

Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.

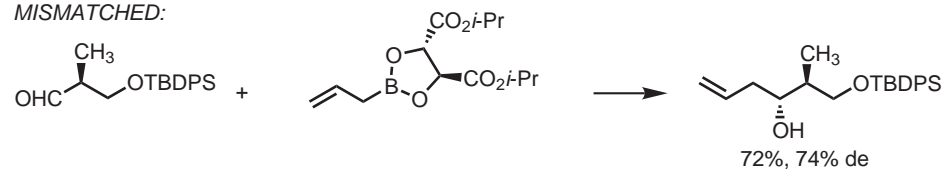
Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316-318.

Reaction of Tartrate-Derived Allyl- or Crotylboronates with Chiral Aldehydes

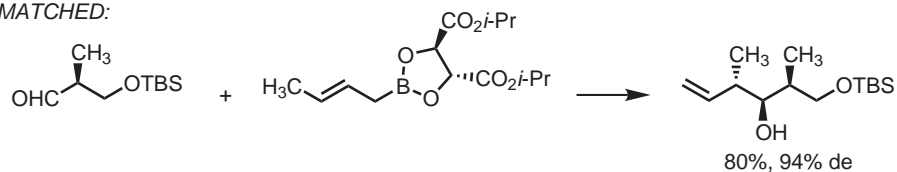
MATCHED:



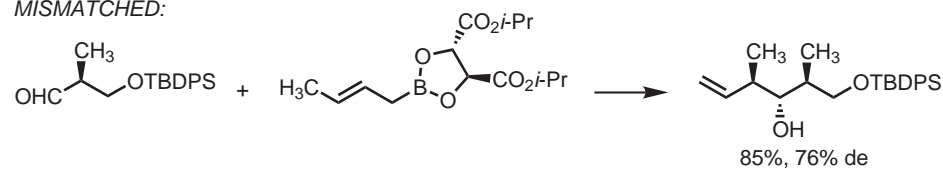
MISMATCHED:



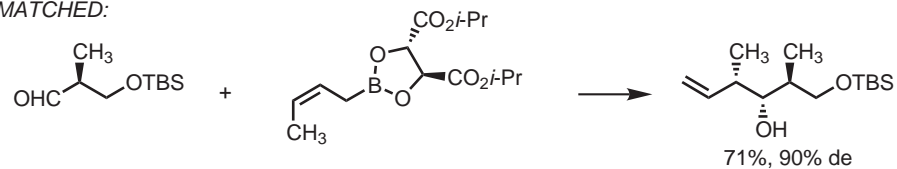
MATCHED:



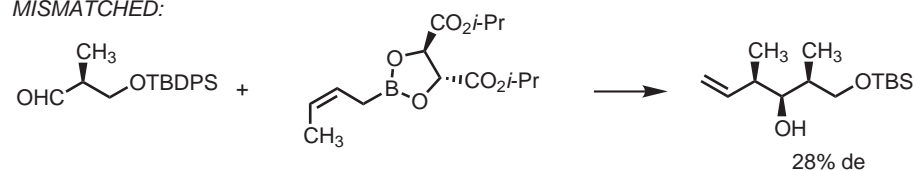
MISMATCHED:



MATCHED:



MISMATCHED:

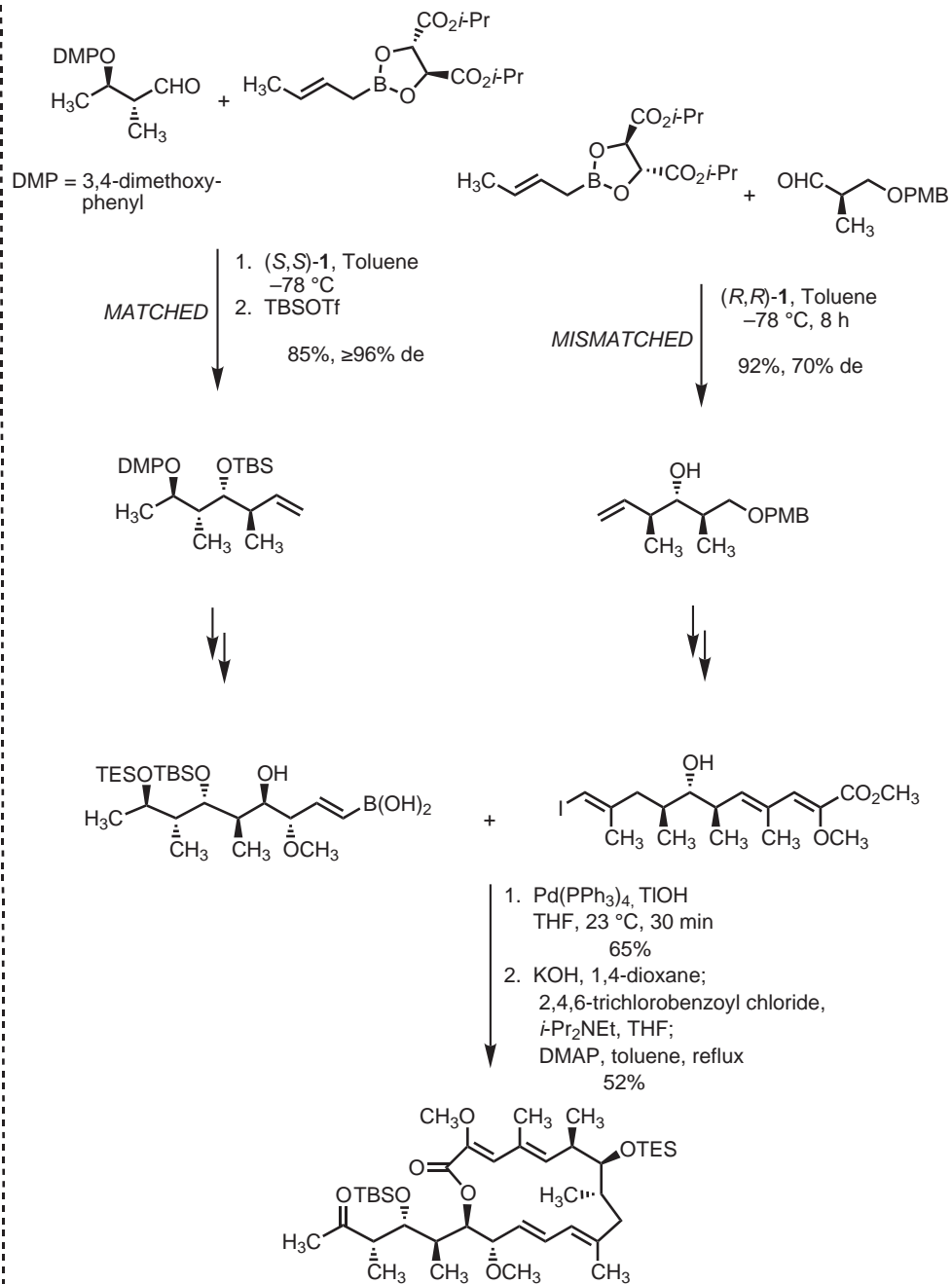


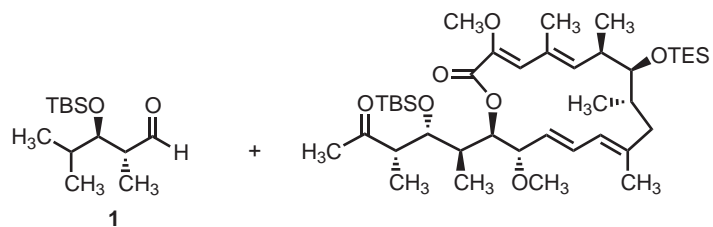
• All reactions were performed in toluene at -78°C in the presence of 4\AA -MS.

Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.

Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316-318.

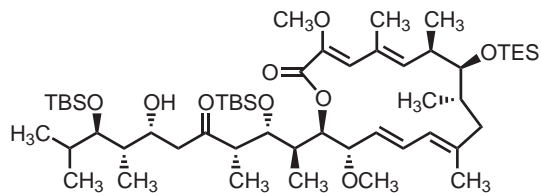
(-)-Bafilomycin A₁:





1. TMSCl, Et₃N, LHMDS
CH₂Cl₂, -78 °C, 30 min
2. 1, BF₃•OEt₂, -78 °C, 30 min

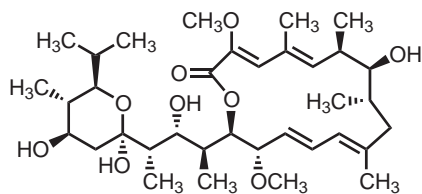
85%



TASF = [(CH₃)₂N]₃S[(CH₃)₃SiF₂]

TASF, DMF, H₂O
23 °C, 4 h

93%

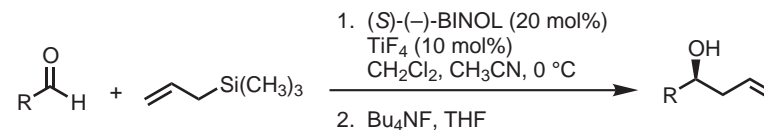
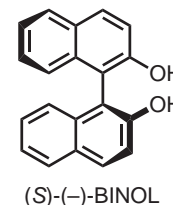


(-)-Bafilomycin A₁

Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1652-1655.

Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587-3590.

Catalytic, Enantioselective Addition of Allylsilanes to Aldehydes



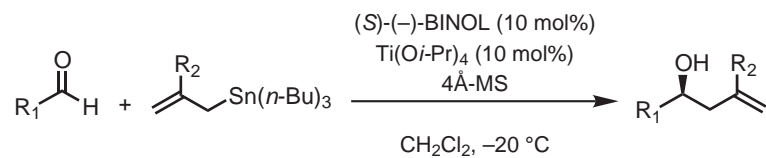
aldehyde	time (h)	yield (%)	ee (%)
	4	90	94
	20	93	84
(CH ₃) ₃ CCHO	4	91	94
	20	92	93
	20	81 ^a	74
PhCHO	4	85	80
c-C ₆ H ₁₁ CHO	4	72	60
PhCH ₂ CH ₂ CHO	4	69	61

^aBased on 25% recovered aldehyde.

- Allyltrimethylsilane initially reacts with the HF produced during catalyst preparation to give propene and (CH₃)₃SiF.
- It is important that the reaction be conducted in the presence of small amounts of CH₃CN to solubilize the polymeric TiF₄.
- α,α-Disubstituted aldehydes afford the highest enantioselectivities.

Gauthier, D. R. Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363-2365.

Catalytic, Enantioselective Addition of Allyltin Reagents to Aldehydes



R ₁	R ₂	time (h)	yield (%)	ee (%)
C ₆ H ₅	H	70	88	95
C ₆ H ₅	CH ₃	60	75	91
<i>c</i> -C ₆ H ₁₁	H	70	66	94
<i>c</i> -C ₆ H ₁₁	CH ₃	48	50	84
(<i>E</i>)-C ₆ H ₅ CH=CH	H	70	42	89
(<i>E</i>)-C ₆ H ₅ CH=CH	CH ₃	12	68	87
C ₆ H ₅ CH ₂ CH ₂	H	70	93	96
C ₆ H ₅ CH ₂ CH ₂	CH ₃	40	97	98
<i>i</i> -C ₃ H ₇	H	70	89	96
furyl	H	70	73	96
furyl	CH ₃	12	99	99
<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	48	61	93
<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ OCH ₂	H	70	81	96
BnOCH ₂	H	60	84	95

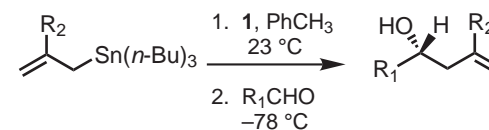
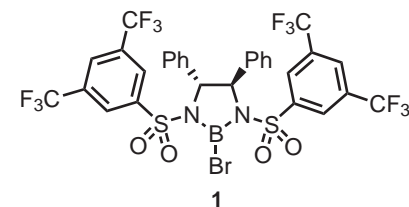
- Addition occurs to the *re* face of the aldehyde with the catalyst prepared from (*R*)-(+)-BINOL.
- This procedure allows for the efficient asymmetric methallylation of aldehydes, typically a difficult transformation.

Keck, G. E.; Krishnamurthy, D. *Org. Syn.* **1998**, *75*, 12-18.

Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467-8468.

Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543-6544.

Enantioselective Allylation Using a Stoichiometric Chiral Controller Group

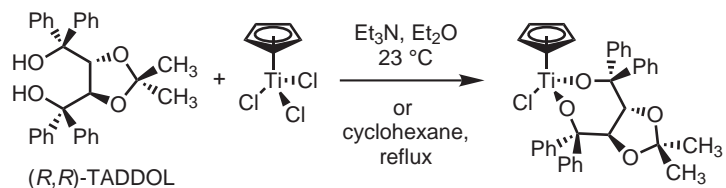


aldehyde	R ₂	yield (%)	ee (%)
PhCHO	H	92	96
PhCHO	Cl	80	90
<i>c</i> -C ₆ H ₁₁ CHO	H	84	92
<i>c</i> -C ₆ H ₁₁ CHO	Cl	76	88

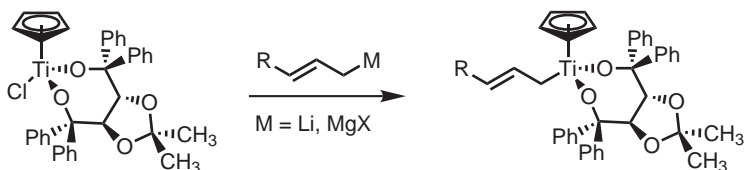
- Reagent **1** is produced from the corresponding (*R,R*)-bis-sulfonamide by reaction with BBr₃ in CH₂Cl₂.
- Transmetalation of allyltin reagents with the chiral *B*-Bromoboron reagent **1** in toluene is complete in 3-20 h.
- The (*R,R*)-bis-sulfonamide can be recovered from the reaction mixture.

Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715-3718.

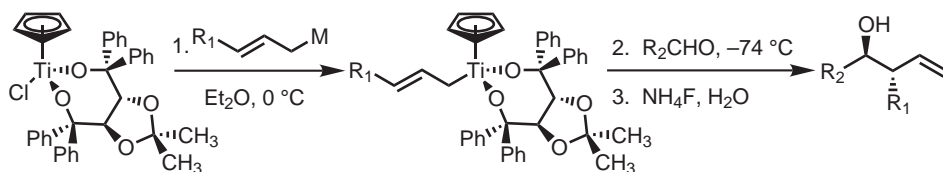
Enantioselective Allyltitanation of Aldehydes



- The chiral diol is readily available in both enantiomeric forms from the corresponding tartrate esters.
- Complex formation is driven to completion by neutralization of HCl with Et₃N, or by removal of HCl by heating.
- The complex may be used in crude form, as prepared in solution, or the complex may be crystallized and isolated.



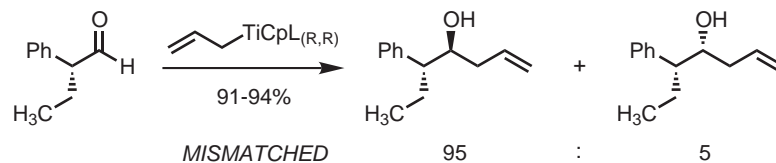
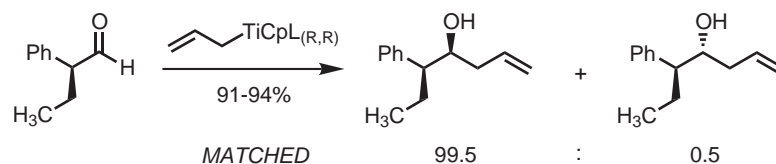
- (*E*)-Crotyltitanium reagents are produced from (*E*)- or (*Z*)-crotyl anion precursors.



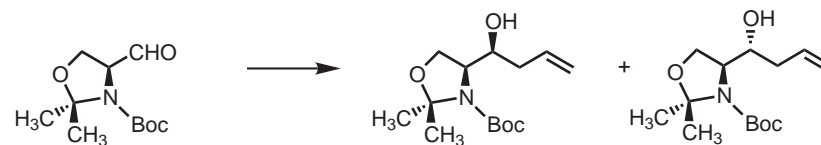
R ₁	R ₂	ee (%)	de (%)	yield (%)
H	Ph	95		93
H	(CH ₃) ₂ CH	97		88
H	CH ₂ =CH	95		79
CH ₃	Ph	98	97	89
Ph	Ph	97	≥98	54
(CH ₃) ₃ Si	Ph	≥98	≥98	68
EtO	Ph	95	75	77
CH ₃	CH ₃ (CH ₂) ₈	≥98	≥98	86
(CH ₃) ₃ Si	CH ₃ (CH ₂) ₈	≥98	≥98	69

- (*E*)-Crotyltitanation of aldehydes affords anti products, presumably by a chair-like TS.

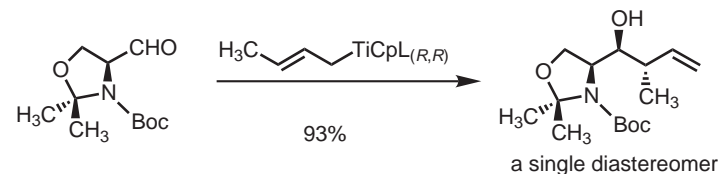
Diastereoselective Allyltitanation of Chiral Aldehydes



- Exceptionally high reagent selectivity is observed in the mismatched allylation of (*R*)-2-phenylbutyraldehyde (90% de) (cf., (-)-lpc₂BCH₂CH=CH₂: 34% de).



reagent	yield	ee (%)	de (%)
$\text{CH}_2=\text{CH}-\text{TiCpL}_{(R,R)}$	93	98.1	1.9
$\text{CH}_2=\text{CH}-\text{TiCpL}_{(S,S)}$	95	0.5	99.5
$\text{CH}_2=\text{CH}-\text{TiCp}(\text{O}i\text{-Pr})_2$	89	37.3	62.7
$\text{CH}_2=\text{CH}-\text{MgCl}$	86	55.1	44.9



Hafner, A.; Duthaler, R. O; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

Duthaler, R. O.; Hafner, A.; Riediker, M. *Pure & Appl. Chem.* **1990**, *62*, 631-642.