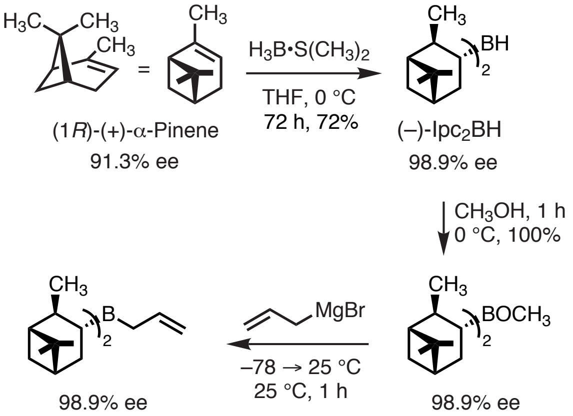
Brown Allylation and Crotylation Reactions

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



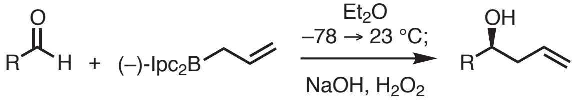
- Prolonged incubation at 0 °C affords enantiomerically enriched Ipc_2BH. This is due to equilibration of tetraisopinocampheyldiborane with α-pinene and triisopinocampheyldiborane; the symmetrical dimer crystallizes preferentially.
- Both enantiomers of α-pinene are commercially available and inexpensive.
- *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.

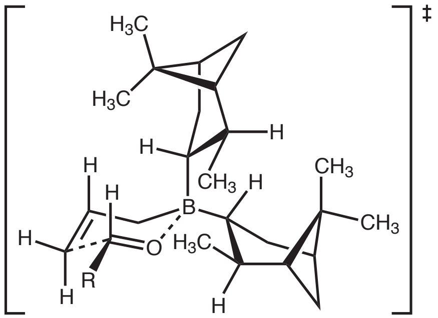
Enantioselective Allylboration



R	yield (%)	ee (%)[a]	ee (%)[b]
CH_3	74	93	≥99
n-C_3H_7	71	86	-
n-C_4H_9	72	87	96
t-C_4H_9	88	83	≥99
C_6H_5	81	96	96

[a] Allylboration carried out without filtration of Mg salts. [b] Allylboration 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 CH_3OMgBr 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 Ipc 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.

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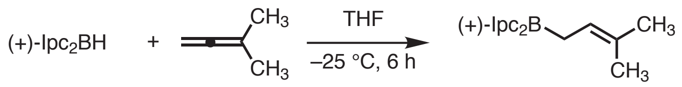
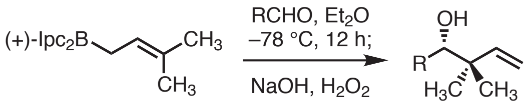
Asymmetric Isoprenylation of Aldehydes



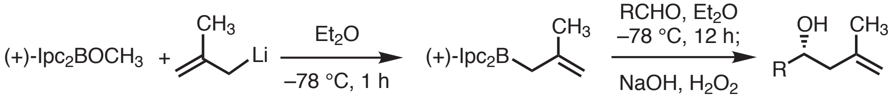
- Hydroboration of allenes is an efficient method for preparing *B*-prenyldiisopinocamphenylboranes.



R	yield (%)	ee (%)
CH_3	73	91
n-C_4H_9	79	92
$CH_2{=}CH$	70	95
$(CH_3)_2C{=}CH$	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



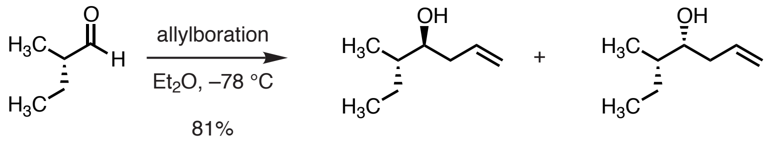
R	yield (%)	ee (%)
CH_3	56	90
n-C_3H_7	54	90
n-C_4H_9	56	91
t-C_4H_9	55	90
$CH_2{=}CH$	57	92

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

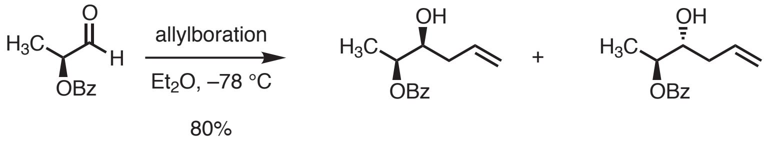
Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111-5114.
Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

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.

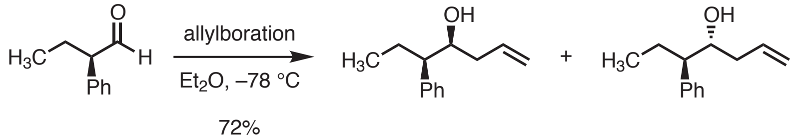


MATCHED:	(–)-$Ipc_2BCH_2CH{=}CH_2$	96	:	4	(92% de)
MISMATCHED:	(+)-$Ipc_2BCH_2CH{=}CH_2$	5	:	95	(90% de)



MISMATCHED:	(–)-$Ipc_2BCH_2CH{=}CH_2$	94	:	6	(88% de)
MATCHED:	(+)-$Ipc_2BCH_2CH{=}CH_2$	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:



MISMATCHED:	(–)-$Ipc_2BCH_2CH{=}CH_2$	67	:	33	(34% de)
MATCHED:	(+)-$Ipc_2BCH_2CH{=}CH_2$	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.

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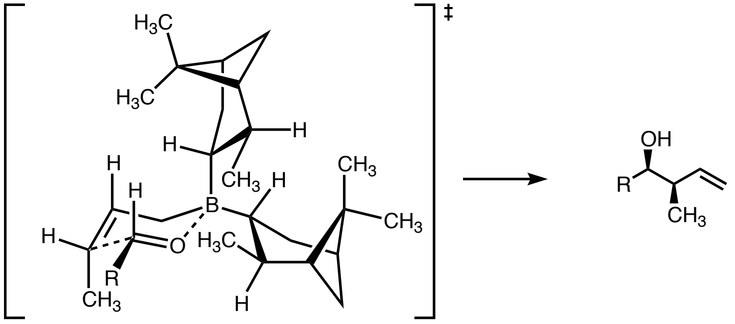
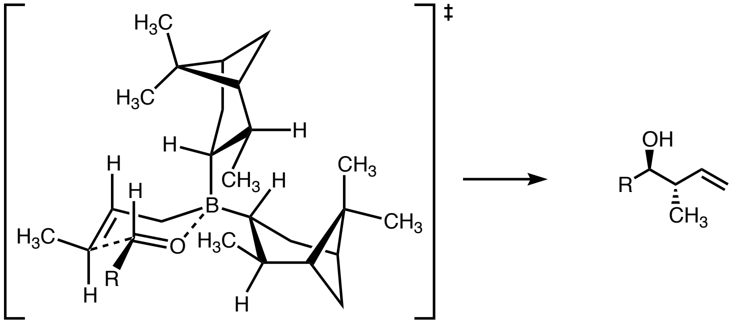
Chair TS's Produce syn Adducts from (*Z*)-Crotylboranes and anti Adducts from (*E*)-Crotylboranes.



"(*Z*)-crotylborane"

"syn adduct"



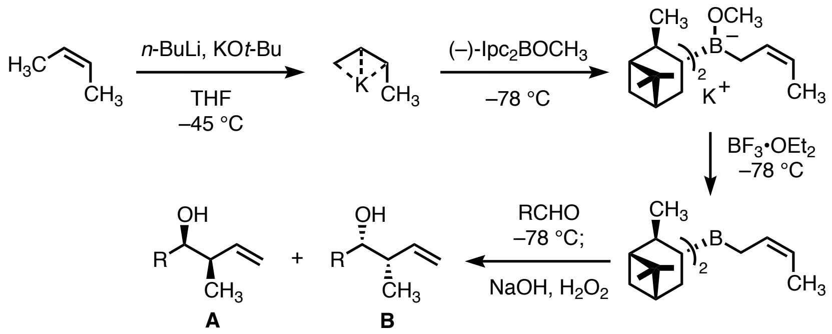
"(*E*)-crotylborane"

"anti adduct"

- 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

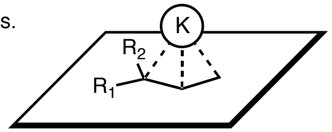


Ipc	aldehyde	yield (%)	**A**:**B**	ee (%)
–	CH_3CHO	75	95:5	90
+	CH_3CHO	72	4:96	92
–	C_2H_5CHO	70	95:5	90
+	C_2H_5CHO	78	4:96	92
–	$CH_2{=}CHCHO$	63	95:5	90
–	C_6H_5CHO	72	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by $BF_3{\cdot}OEt_2$ 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 η^3-bonding in allyl, crotyl and prenyl derivatives:

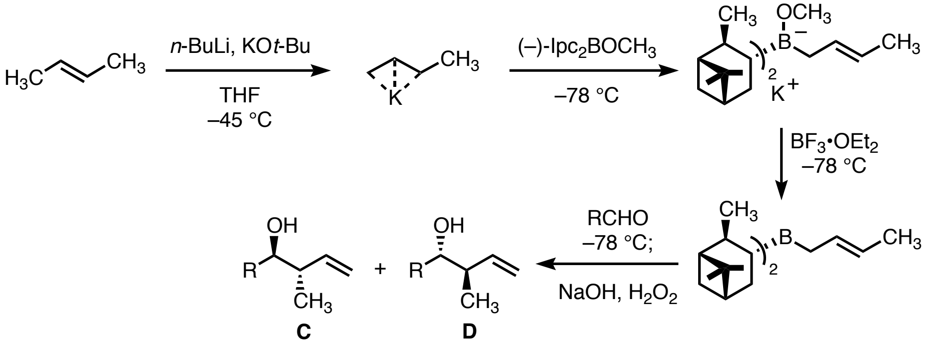


R_1, R_2 = H, CH_3

Schlosser, M. *Pure & Appl. Chem.* **1988**, *60*, 1627-1634.
Schlosser, M.; Stahle, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 487-489.

M. Movassaghi

(*E*)-Crotylboranes

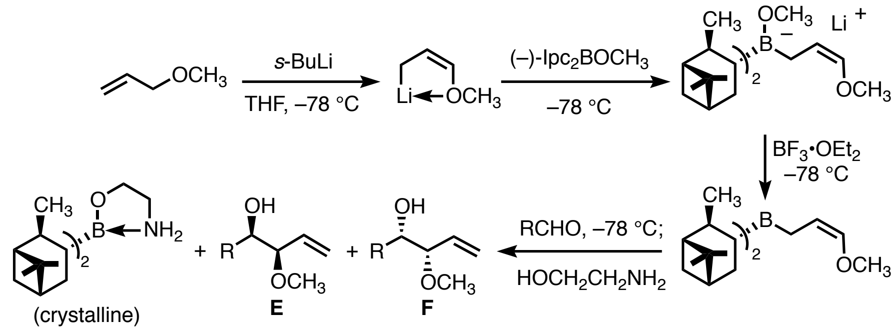


Ipc	aldehyde	yield (%)	**C**:**D**	ee (%)
–	CH_3CHO	78	95:5	90
+	CH_3CHO	76	4:96	92
–	C_2H_5CHO	70	95:5	90
+	C_2H_5CHO	69	4:96	92
–	CH_2=CHCHO	65	95:5	90
–	C_6H_5CHO	79	94:6	88

- The crotylboranes are used immediately after decomplexation of methoxide from the ate complex by BF_3•OEt_2 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.

Ipc	aldehyde	yield (%)	**E**:**F**	ee (%)
–	CH_3CHO	57	95:5	90
+	CH_3CHO	59	4:96	92
–	C_2H_5CHO	65	96:4	92
+	C_2H_5CHO	68	5:95	90
–	CH_2=CHCHO	63	94:6	88
–	C_6H_5CHO	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.

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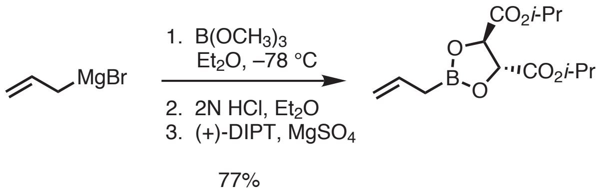
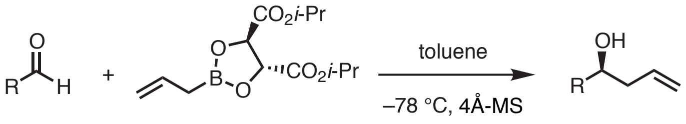
Roush Allylation and Crotylation Reactions

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.



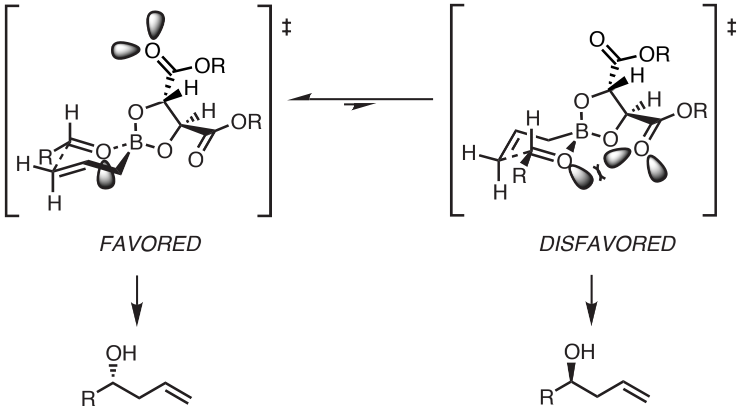
- The stability of allylboronate reagents permits their purification by distillation. Allyl diisopinocamphenyl reagents cannot be distilled.



aldehyde	yield (%)	ee (%)
n-$C_9H_{19}CHO$	86	79
c-$C_6H_{11}CHO$	77	78
C_6H_5CHO	78	71

- Enantioselectivities are typically moderate.
- 4A-MS are necessary to achieve the highest levels of selectivity.

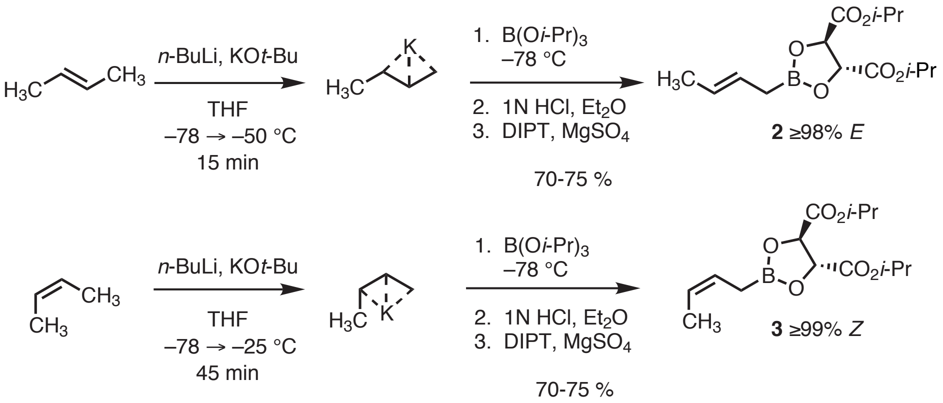
Proposed Origin of Selectivity in Tartrate Derived Allylboronate Additions



- 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

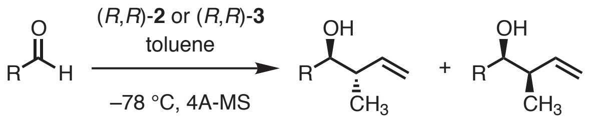


- Crotylboronates are configurationally stable at or slightly above room temperature.

- 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-Pr).



R	reagent	yield (%)	anti:syn	ee (%)[a]
n-C_9H_{19}	**2**	90	95:5	86
n-C_9H_{19}	**3**	70	1:>99	77
c-C_6H_{11}	**2**	94	>99:1	86
c-C_6H_{11}	**3**	90	2:98	83
$TBSOCH_2CH_2$	**2**	71	≥98:2	85
$TBSOCH_2CH_2$	**3**	68	2:≥98	72

[a] ee 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. *J. Org. Chem.* **1987**, *52*, 316-318.

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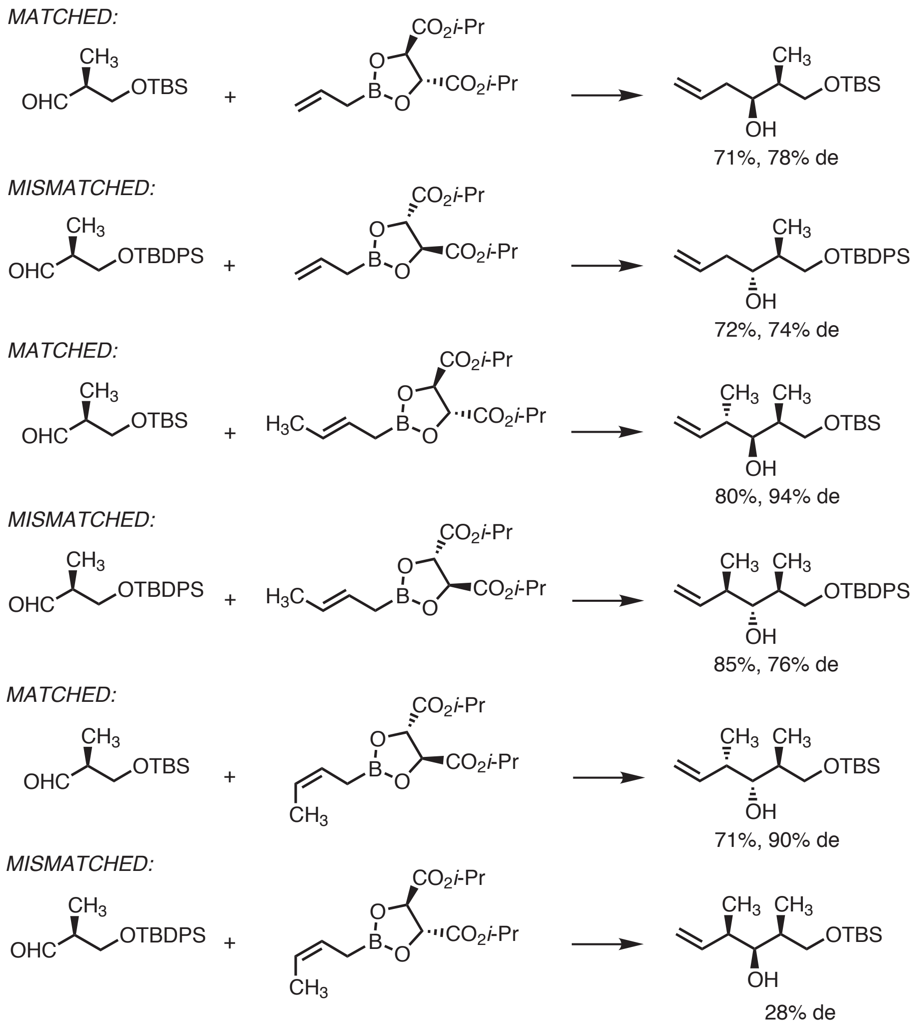
Reaction of Tartrate-Derived Allyl- or Crotylboronates with Chiral Aldehydes

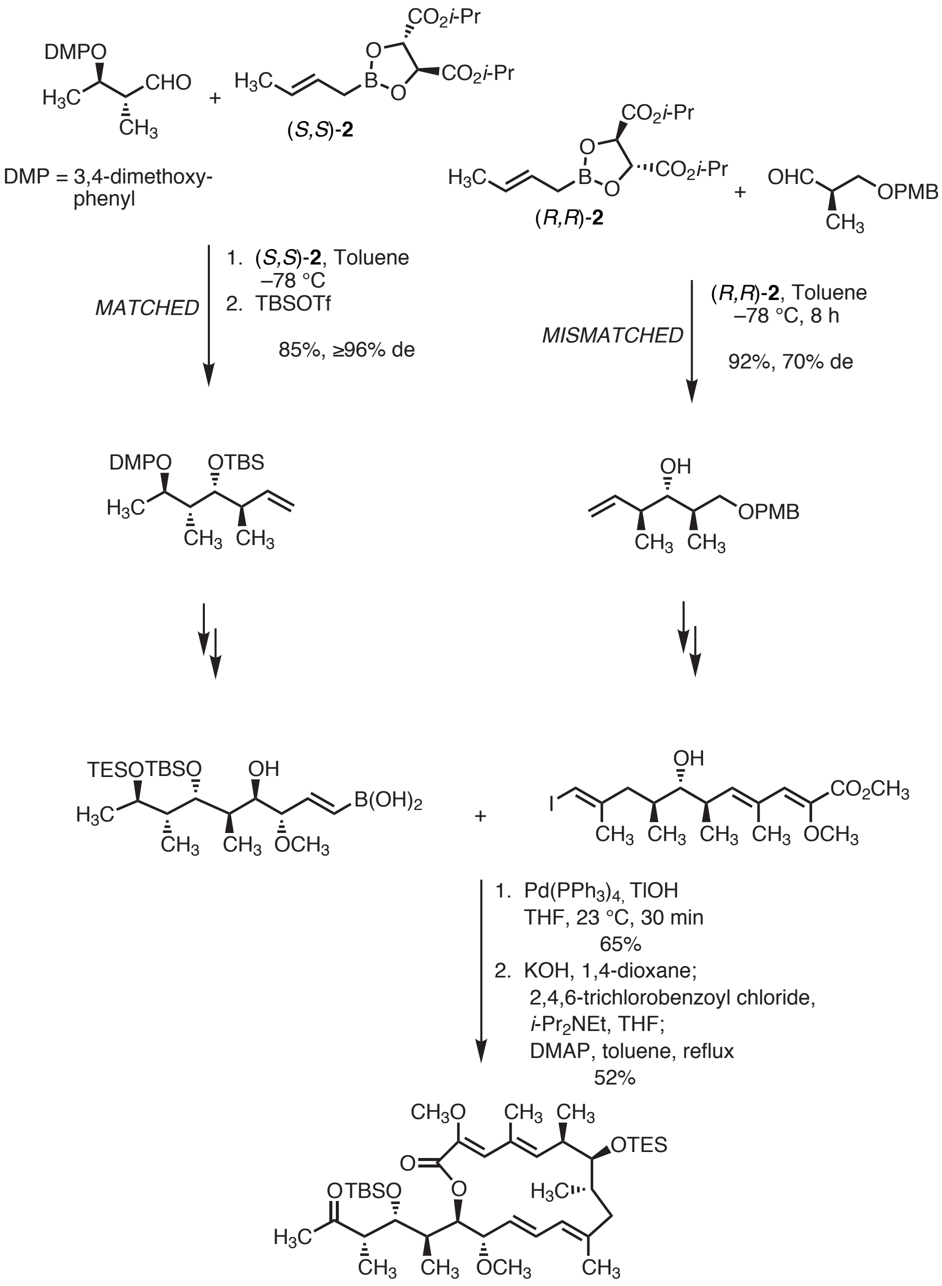


- All reactions were performed in toluene at –78 °C in the presence of 4Å-MS.

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. *J. Org. Chem.* **1987**, *52*, 316-318.

(–)-Bafilomycin A$_1$:



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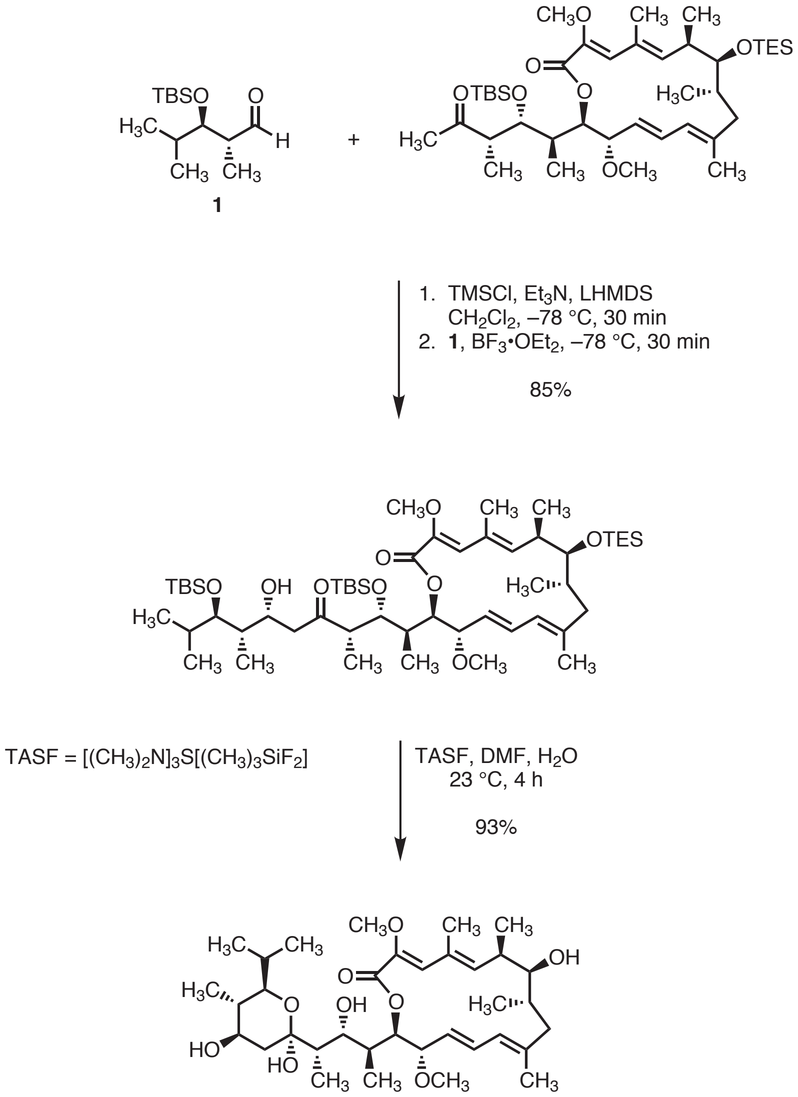
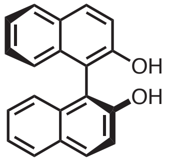


(–)-Bafilomycin A$_1$

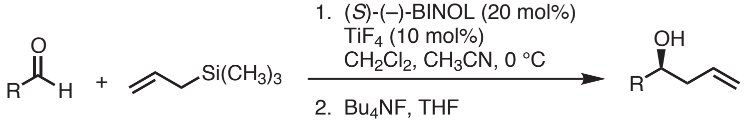
Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1652-1655.

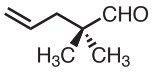
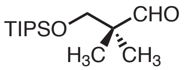
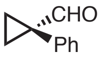
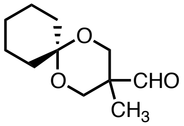
Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587-3590.

Catalytic, Enantioselective Addition of Allylsilanes to Aldehydes



(*S*)-(–)-BINOL



aldehyde	time (h)	yield (%)	ee (%)
	4	90	94
	20	93	84
$(CH_3)_3CCHO$	4	91	94
	20	92	93
	20	81[a]	74
PhCHO	4	85	80
c-$C_6H_{11}CHO$	4	72	60
$PhCH_2CH_2CHO$	4	69	61

[a] Based on 25% recovered aldehyde.

- Allyltrimethylsilane initially reacts with the HF produced during catalyst preparation to give propene and $(CH_3)_3SiF$.
- It is important that the reaction be conducted in the presence of small amounts of CH_3CN to solubilize the polymeric TiF_4.
- α,α-Disubstituted aldehydes afford the highest enantioselectivities.

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

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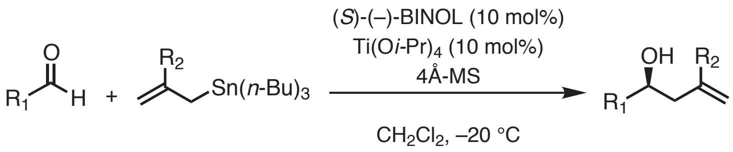
Catalytic, Enantioselective Addition of Allyltin Reagents to Aldehydes



R_1	R_2	time (h)	yield (%)	ee (%)
C_6H_5	H	70	88	95
C_6H_5	CH_3	60	75	91
$c\text{-}C_6H_{11}$	H	70	66	94
$c\text{-}C_6H_{11}$	CH_3	48	50	84
(E)-$C_6H_5CH{=}CH$	H	70	42	89
(E)-$C_6H_5CH{=}CH$	CH_3	12	68	87
$C_6H_5CH_2CH_2$	H	70	93	96
$C_6H_5CH_2CH_2$	CH_3	40	97	98
$i\text{-}C_3H_7$	H	70	89	96
furyl	H	70	73	96
furyl	CH_3	12	99	99
$p\text{-}CH_3OC_6H_4$	CH_3	48	61	93
$p\text{-}CH_3OC_6H_4CH_2OCH_2$	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.

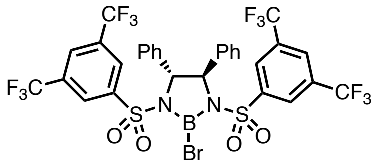
- This procedure allows for the efficient asymmetric methallylation of aldehydes, typically a difficult transformation.

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

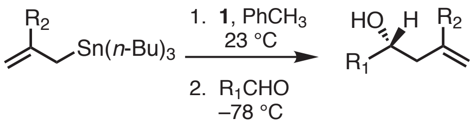
Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467-8468.

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

Enantioselective Allylation Using a Stoichiometric Chiral Controller Group



1



aldehyde	R_2	yield (%)	ee (%)
PhCHO	H	92	96
PhCHO	Cl	80	90
$c\text{-}C_6H_{11}CHO$	H	84	92
$c\text{-}C_6H_{11}CHO$	Cl	76	88

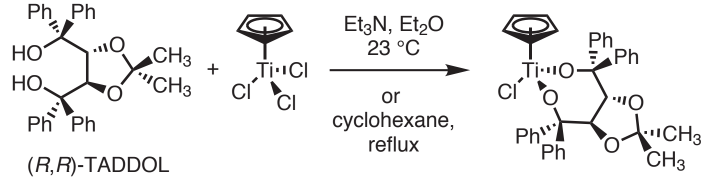
- Reagent **1** is produced from the corresponding (*R*,*R*)-bis-sulfonamide by reaction with BBr_3 in CH_2Cl_2.

- Transmetallation 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.

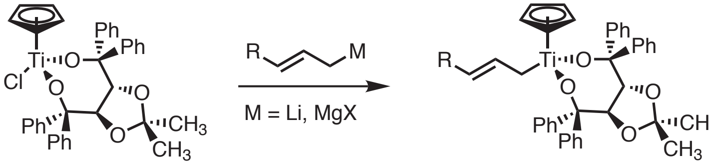
Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715-3718.

Enantioselective Allyltitanation of Aldehydes

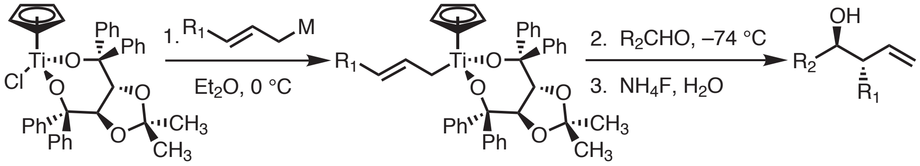


(*R*,*R*)-TADDOL

- 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 Et$_3$N, 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.



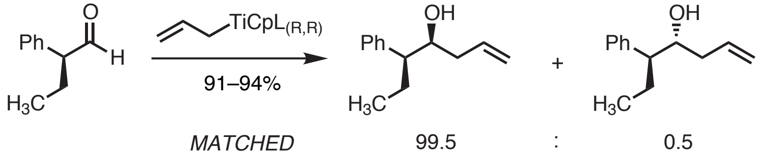
- (E)-Crotyltitanium reagents are produced from (*E*)- or (*Z*)-crotyl anion precursors.

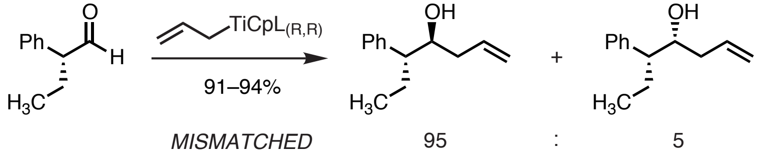


R_1	R_2	ee (%)	de (%)	yield (%)
H	Ph	95		93
H	$(CH_3)_2CH$	97		88
H	$CH_2=CH$	95		79
CH_3	Ph	98	97	89
Ph	Ph	97	≥98	54
$(CH_3)_3Si$	Ph	≥98	≥98	68
EtO	Ph	95	75	77
CH_3	$CH_3(CH_2)_8$	≥98	≥98	86
$(CH_3)_3Si$	$CH_3(CH_2)_8$	≥98	≥98	69

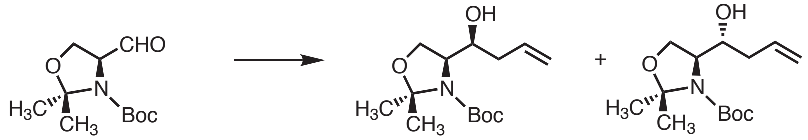
- (*E*)-Crotyltitanation of aldehydes affords anti products, presumably by a chair-like TS.

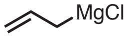
Diastereoselective Allyltitanation of Chiral Aldehydes

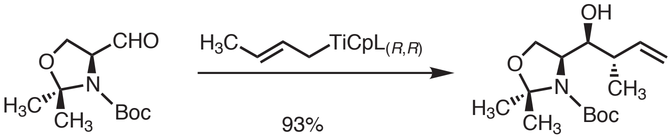




- Exceptionally high reagent selectivity is observed in the mismatched allylation of (*R*)-2-phenylbutyraldehyde (90% de) (cf., (–)-Ipc$_2$BCH$_2$CH=CH$_2$: 34% de).



reagent	yield		
 TiCpL$_{(R,R)}$	93	98.1	1.9
 TiCpL$_{(S,S)}$	95	0.5	99.5
 TiCp(O*i*-Pr)$_2$	89	37.3	62.7
 MgCl	86	55.1	44.9



a single diastereomer

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

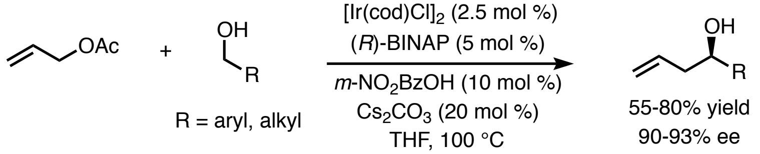
Duthaler, R. O.; Hafner, A.; Riediker, M. *Pure & Appl. Chem.* **1990**, *62*, 631-642.

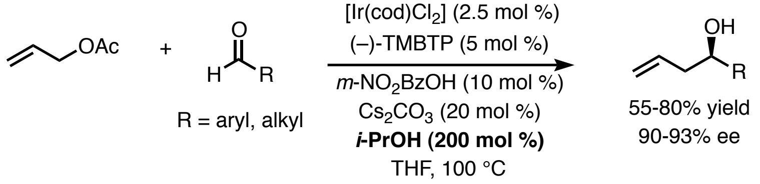
M. Movassaghi

Krische Allylation and Crotylation Reactions:

Hassan, A.; Krische, M. J. *Org. Proc. Res. Devel.* **2011**, *15*, 1236.
Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009,** 7278.

General Allylation Reaction:

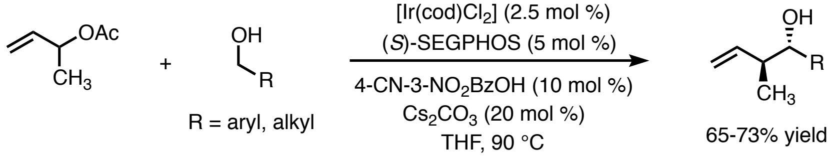




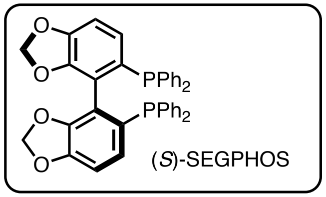
TMBTP = 2,2',5,5'-Tetramethyl-4,4'-bis(diphenylphoshino)-3,3'-bithiophene

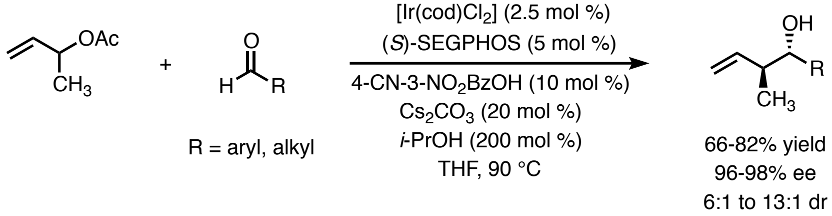
- Couplings of primary alcohols or aldehydes with allyl acetate utilizing Ir catalysts generate allylation products without the use of stoichiometric allyl-metal(oid) reagents.

General Crotylation Reaction:

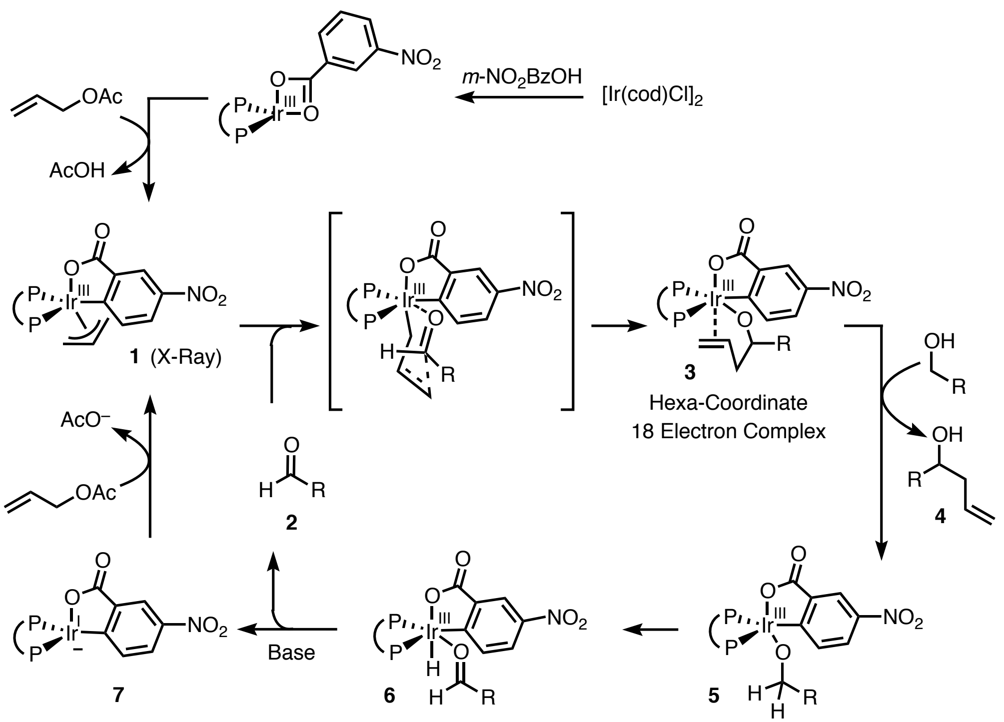


86-97% ee
4:1 to 8:1 dr





Proposed Catalytic Cycle:



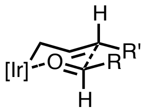
- The Ir catalyst **1** (generated *in situ*) undergoes addition to aldehyde **2** via a 6-membered chair-like transition state to generate the Ir^{III} alkoxide **3**. This does not undergo further dehydrogenation as the olefin is thought to occupy a coordination site, blocking β-hydride elimination.
- Ligand exchange with the reactant alcohol (or isopropanol) generates the homoallylic alcohol **4**.
- The Ir alkoxide **5** undergoes β-hydride elimination to produce the Ir^{III} hydride **6**. Dissociation of the aldehyde **2** produces an Ir^{III} hydride which undergoes deprotonation by the base to provide the Ir^{I} anion **7**.
- Oxidative addition of allyl acetate to **7** regenerates π-allyl Ir^{III} catalyst **1**.
- To use aldehydes as substrates in lieu of an alcohol, the use of a terminal reductant (isopropanol) is necessary for the catalytic cycle to proceed.
- Enantioselectivites are high for both alcohol and aldehyde reactants.

Kim, I. S.; Ngai, M, -Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130,* 6340-6341.
Kim, I. S.; Nagi, M. -Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130,* 14891-14899.

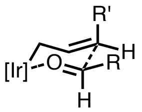
Anne-Marie Schmitt, Fan Liu

Stereochemical Model in Asymmetric Crotolation Reactions:

- Couplings of aldehydes display higher diastereoselectivities than with alcohols, as higher concentrations of aldehyde promote rapid capture of the kinetically formed *trans*-crotyl iridium complex.



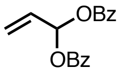
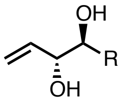
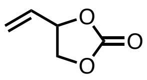
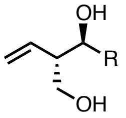
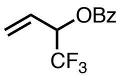
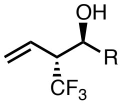
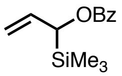
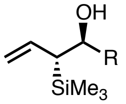
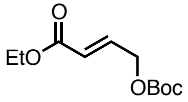
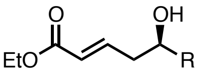
- Kinetically formed *trans*-crotyl iridium complex generates the *anti* diastereomer.



- Equilibration to the *cis*-crotyl iridium complex causes erosion in diastereoselectivity.

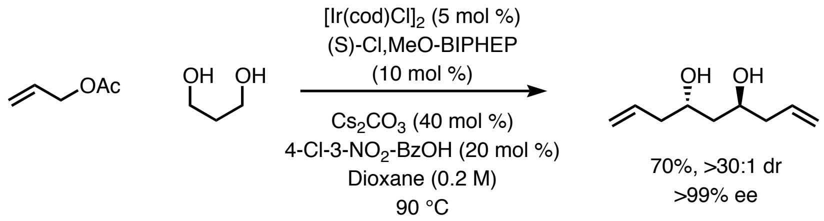
Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514–2520.

Other allyl donors have been used with alcohols and aldehydes as reactants:

Allyl Donor	Products Generated	
		R = aryl, alkyl 62-77% Yield 96-99% ee
		R = aryl, alkyl 58-74% Yield 93-99% ee
		R = aryl, alkyl 57-80% Yield 87-99% ee
		R = aryl, alkyl 58-78% Yield 90-99% ee
		R = aryl, alkyl 58-79% Yield 92-99% ee

Han, S. B.; Han, H. Krische, M. J. *J. Am. Chem Soc.* **2010**, *132*, 1760–1761.
Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *J. Am. Chem Soc.* **2010**, *132*, 4562–4563.
Gao, X.; Zhang, Y. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173–4175.
Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 9153–9156.
Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3493–3496.

Bis Allylation and Crotylation of Glycols

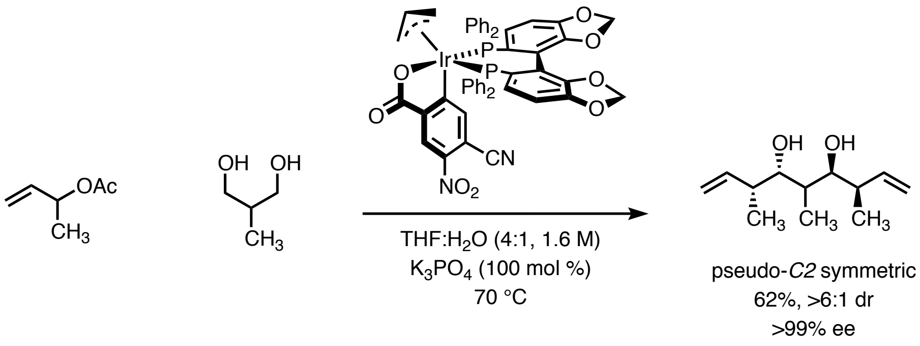


$[Ir(cod)Cl]_2$ (5 mol %)
(S)-Cl,MeO-BIPHEP
(10 mol %)

Cs_2CO_3 (40 mol %)
4-Cl-3-NO_2-BzOH (20 mol %)
Dioxane (0.2 M)
90 °C

70%, >30:1 dr
>99% ee

- Equivalent bis aldehyde counterparts are unstable or unknown.



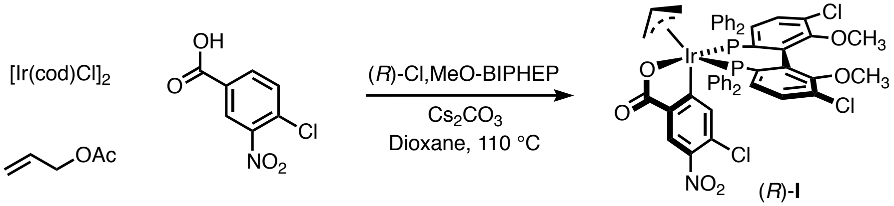
THF:H_2O (4:1, 1.6 M)
K_3PO_4 (100 mol %)
70 °C

pseudo-*C2* symmetric
62%, >6:1 dr
>99% ee

- Predominantly 1 of 16 possible stereoisomers was formed.
- Chromatographic isolation of the pre-formed iridium catalyst allows crotylations to be run at lower temperatures.

Application to the Total Synthesis of Roxaticin

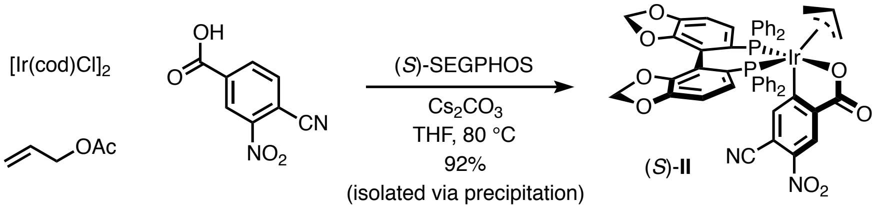
- Catalyst Generation:



(R)-Cl,MeO-BIPHEP

Cs_2CO_3
Dioxane, 110 °C

(R)-**I**
Generated *in situ*



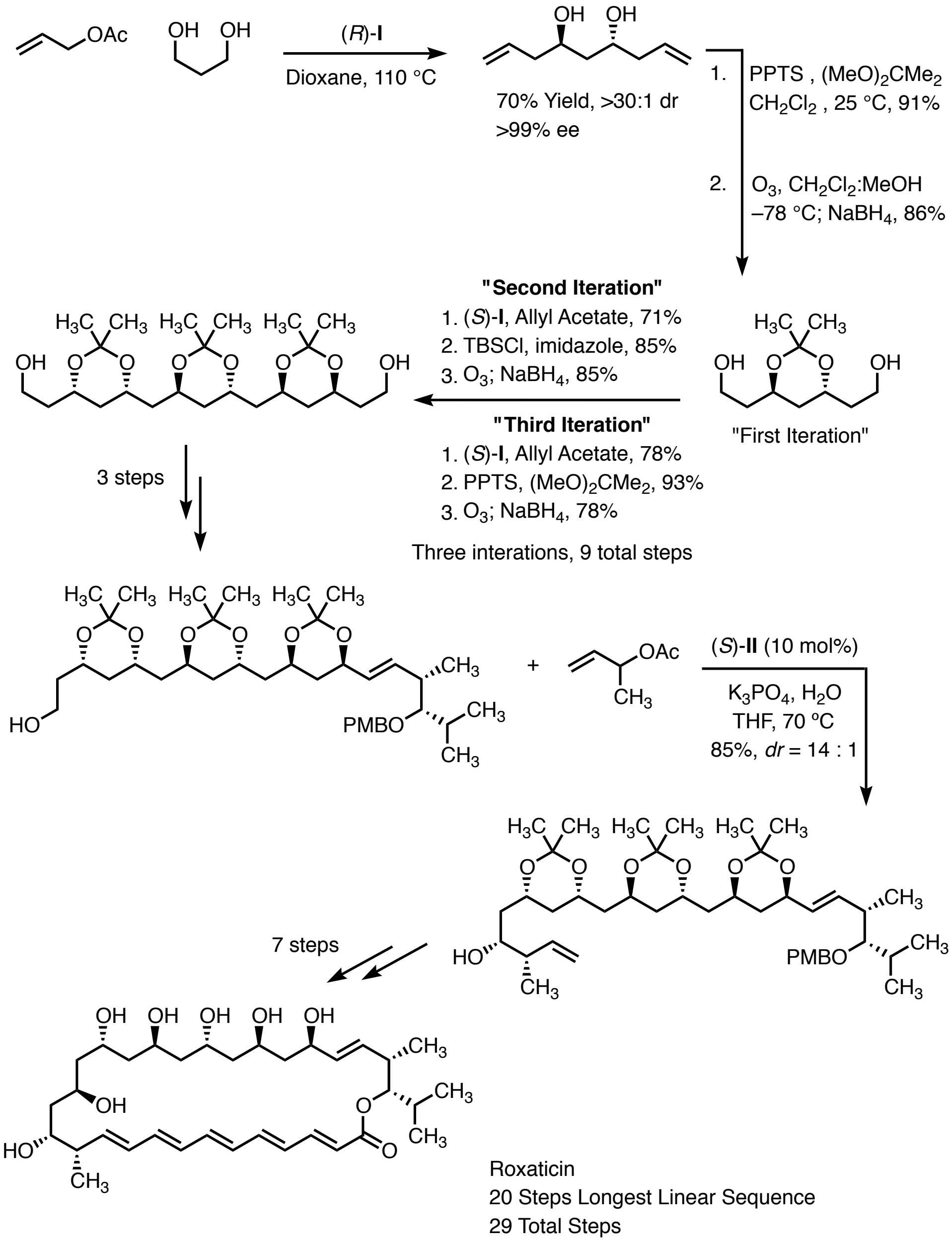
(S)-SEGPHOS

Cs_2CO_3
THF, 80 °C
92%
(isolated via precipitation)

(S)-**II**

Anne-Marie Schmitt, Fan Liu

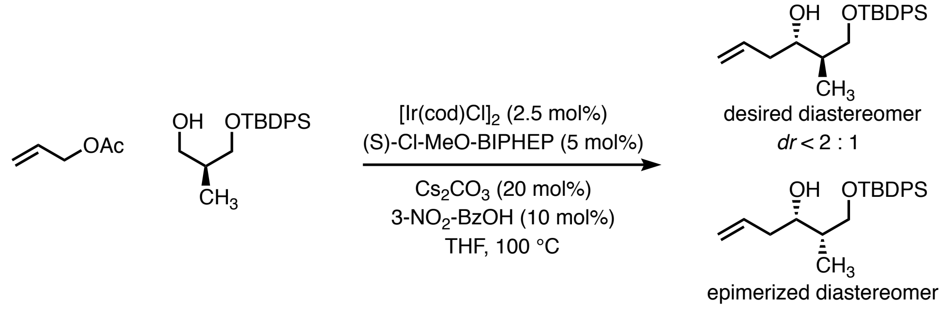
Application to the Synthesis of Roxaticin, *continued.*



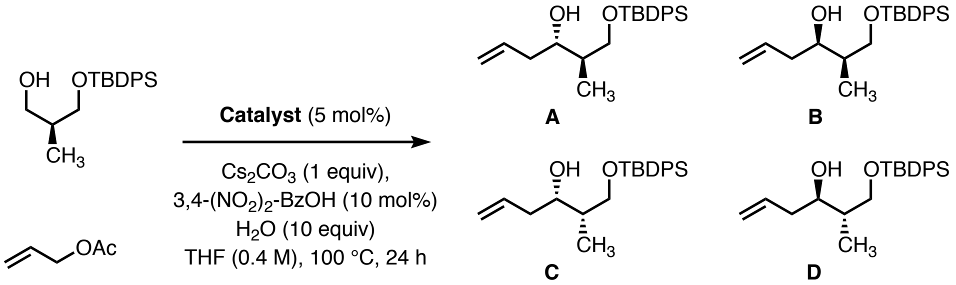
Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559–15561.

Allylation of Epimerizable Aldehydes from the Alcohol Oxidation Level:

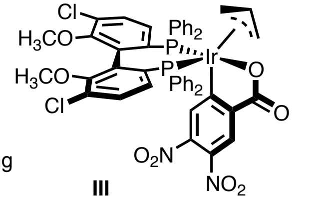
- Allylation of α-chiral aldehydes and β-chiral alcohols: the transiently generated aldehyde is prone to epimerization under the reaction conditions:



- Optimized Reaction Conditions:



Catalyst	**Yield (A : B : C : D)**
III	79% (97 : 2 : 1 : 0)
ent-**III**	80% (4 : 94 : 0 : 2)



III

- Increased loadings of base improve the yield of **A** while suppressing epimerization of the transient α-chiral aldehyde.
- Water improves the yield of **A**, possibly by facilitating the exchange between product and reactant alkoxide and by increasing the amount of Cs_2CO_3 in solution.
- The enhanced Lewis acidity at iridium may strengthen the agostic interaction between the iridium center and the carbinol C-H bond, facilitating alcohol dehydrogenation. It may also accelerate carbonyl addition with respect to aldehyde epimerization.
- Inductive electron withdrawal by the 3,4-dinitro benzoate ligand may facilitate deprotonation of the Ir(III) hydride intermediate, allowing for faster catalyst turnover.

Schmitt, D. C.; Dechert-Schmitt, A.-M. R.; Krische, M. J. *Org. Lett.* **2012**, *14*, 6302–6305.

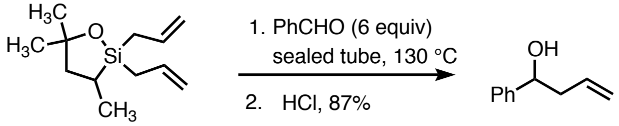
Anne-Marie Schmitt, Fan Liu

Leighton Silicon Allylation Chemistry:

Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3–14.

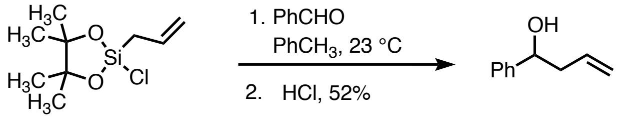
Background:

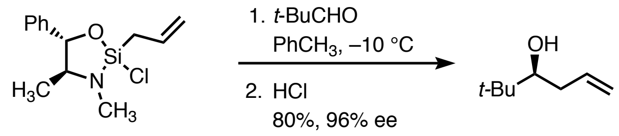
- In 2000, Leighton reported an allylation reaction where a Lewis acidic silicon atom is embedded in a strained five-membered ring:



Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587–8588.

- By incorporating another electronegative element bound to silicon, the reaction takes place at room temperature. With a chiral ligand, the reaction becomes enantioselective:

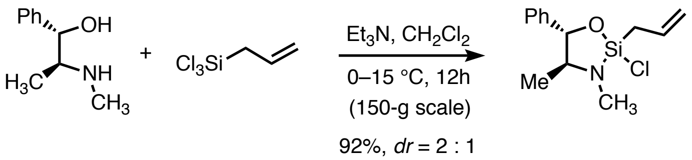




Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921.

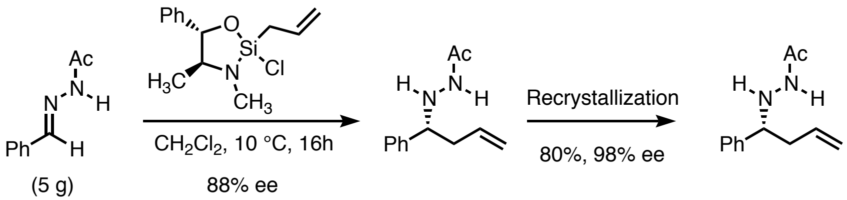
Preparation of Allylsilane

- Two diastereomers are generated upon complexation with pseudoephedrine, which converge on a common complex prior to allyl transfer:

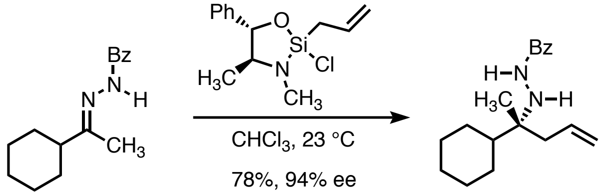


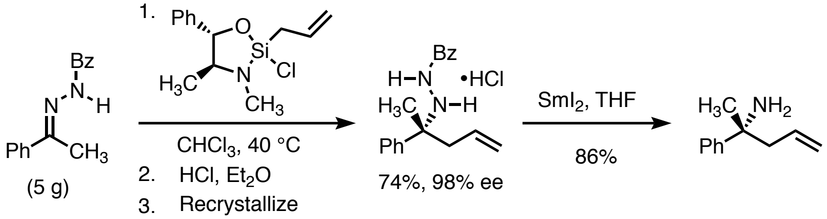
Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596–9597.

Enantioselective Addition to Acylhydrazones:



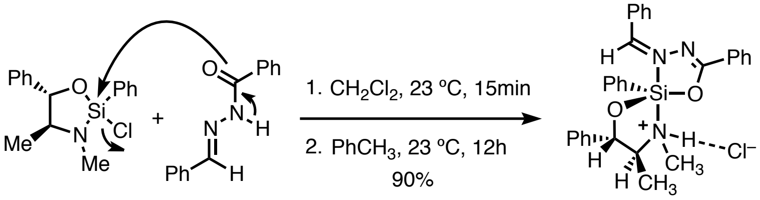
Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596–9597.





Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687.

Mechanism:

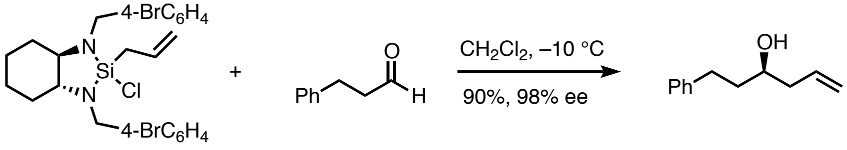


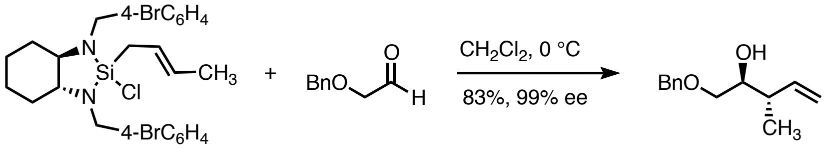
- A 5-coordinate trigonal bipyramidal silicon species is proposed.
- The strained silacyclopentane increases the Lewis acidity of silicon.
- Aldehydes and acylhydrazones react, but not ketones, aldimines, or ketimines.

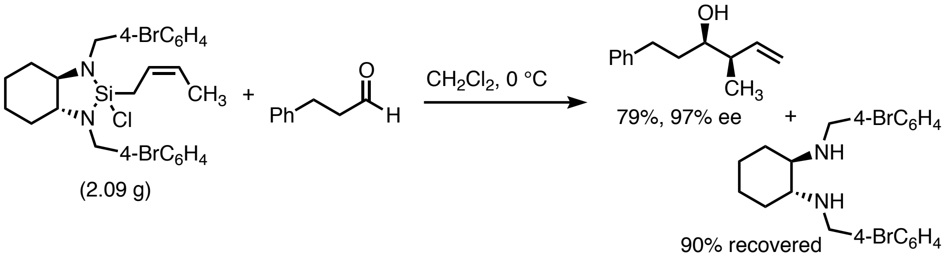
Angela Puchlopek-Dermenci, Fan Liu

A C_2-symmetric Chiral Controller for Aldehyde Allylation and Crotylation:

- The C_2-symmetric *N,N'*-dialkylcyclohexanediamine silane shown below shows improved selectivites in the allylation and crotylation of aldehydes:

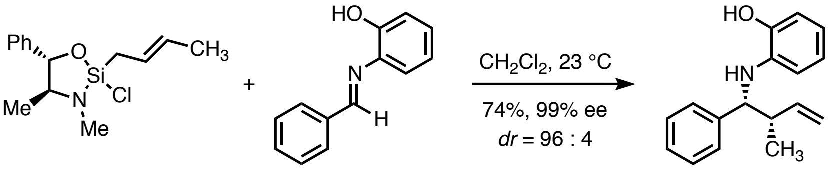






Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948.
Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375–4377.

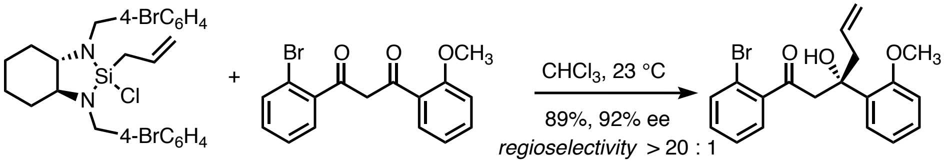
- Using 2-hydroxybenzene as an activating group, imines can be allylated or crotylated with high selectivity:

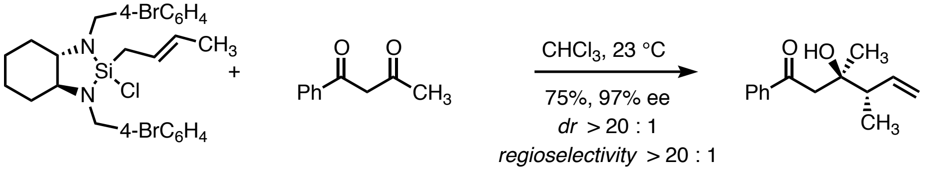


Rabbat, P. M. A.; Valdez, S. C.; Leighton, J. L. *Org. Lett.* **2006**, *8*, 6119–6121.

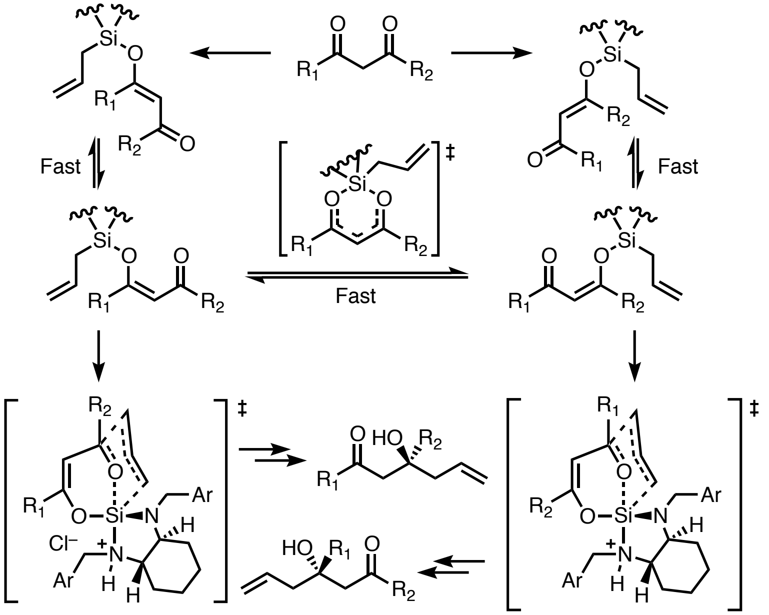
Allylation and Crotylation of β-Diketones:

- The first example of enantioselective nucleophilic addition to β-diketones was achieved using the C_2-symmetric *N,N'*-dialkylcyclohexanediamine silane reagent:





Allylation and Crotylation of β-Diketones:



- Four possible diastereomers undergo fast interconversion.
- Regioselectivity is determined by Curtin-Hammett kinetics. Steric interactions are minimized and conjugation is maximized in the lower energy transition state.

Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86–89.

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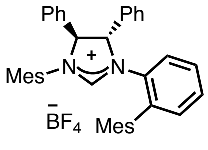
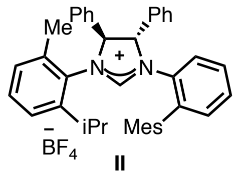
Hoveyda Boron Allylation Chemistry:

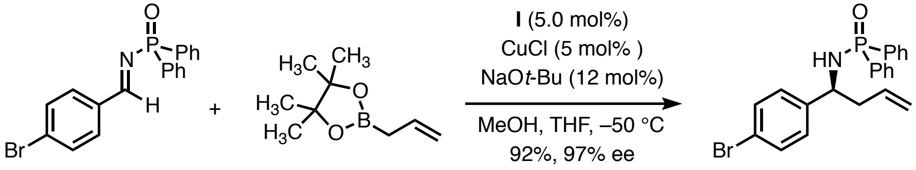
- The Hoveyda group demonstrated that Cu-complexed C_1-symmetric ligands **I** and **II**, can effect enantioselective allylation of phosphinoylimines:



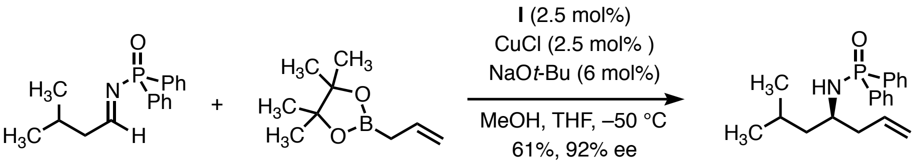
I



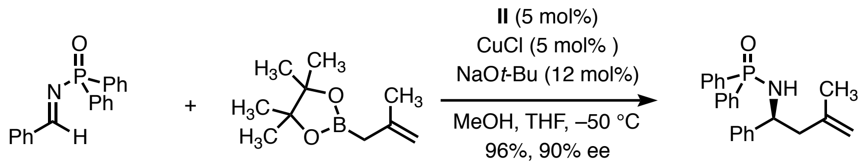
II



I (5.0 mol%)
CuCl (5 mol%)
NaO*t*-Bu (12 mol%)
MeOH, THF, –50 °C
92%, 97% ee



I (2.5 mol%)
CuCl (2.5 mol%)
NaO*t*-Bu (6 mol%)
MeOH, THF, –50 °C
61%, 92% ee

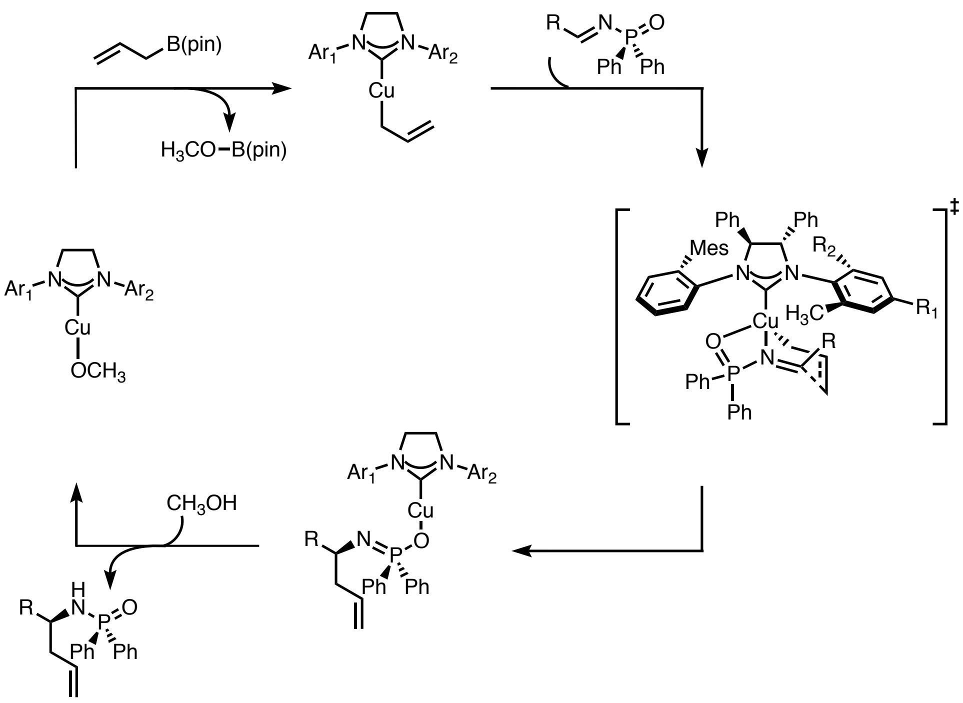


II (5 mol%)
CuCl (5 mol%)
NaO*t*-Bu (12 mol%)
MeOH, THF, –50 °C
96%, 90% ee

- The product phosphinoylamides can be convered to free amines under aqueous acidic conditions.
- High selectivity is observed with aromatic, heteroaromatic, conjugated, and some aliphatic phosphinoylimines. Crotylation reactions proceed with modest yield and enantioselectivity but low diastereoselectivity.

Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332–3335.

Mechanism:



- Allylation is driven by the formation of an energetically favorable B–O bond.
- Methanol releases the product alkoxide from the NHC–Cu complex. <5% conversion was observed in the absence of methanol.

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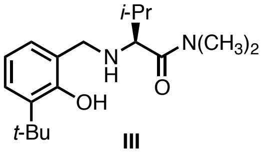
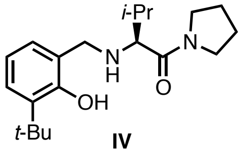
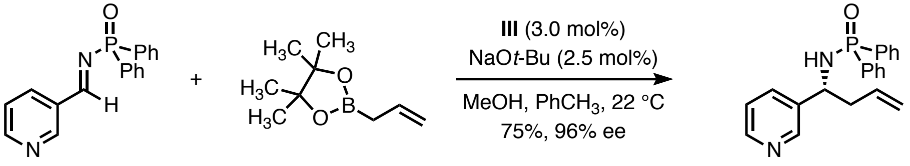
- Simple amino alcohol catalysts **III** and **IV** were found to promote stereoselective boron allylation of phospinoyl imines and isatins:



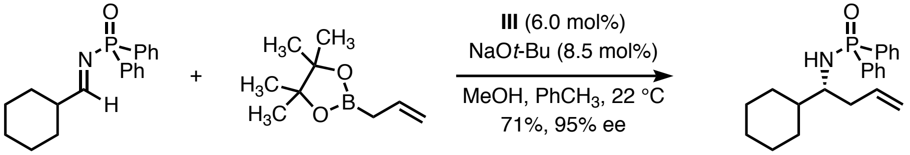
III



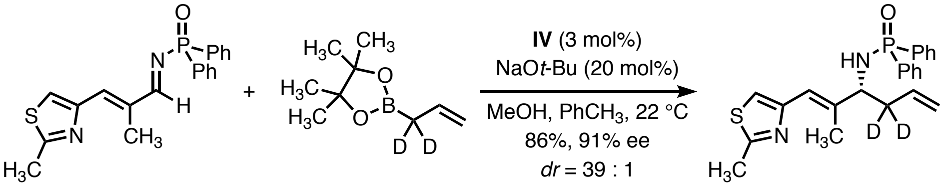
IV



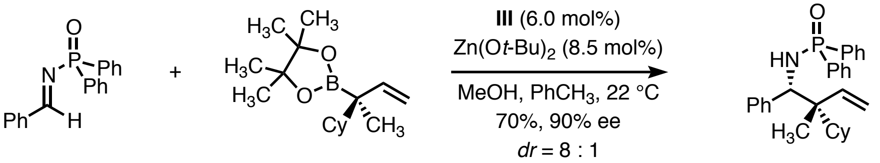
III (3.0 mol%)
NaO*t*-Bu (2.5 mol%)
MeOH, $PhCH_3$, 22 °C
75%, 96% ee



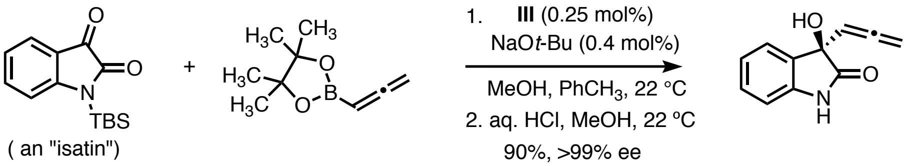
III (6.0 mol%)
NaO*t*-Bu (8.5 mol%)
MeOH, $PhCH_3$, 22 °C
71%, 95% ee



IV (3 mol%)
NaO*t*-Bu (20 mol%)
MeOH, $PhCH_3$, 22 °C
86%, 91% ee
dr = 39 : 1



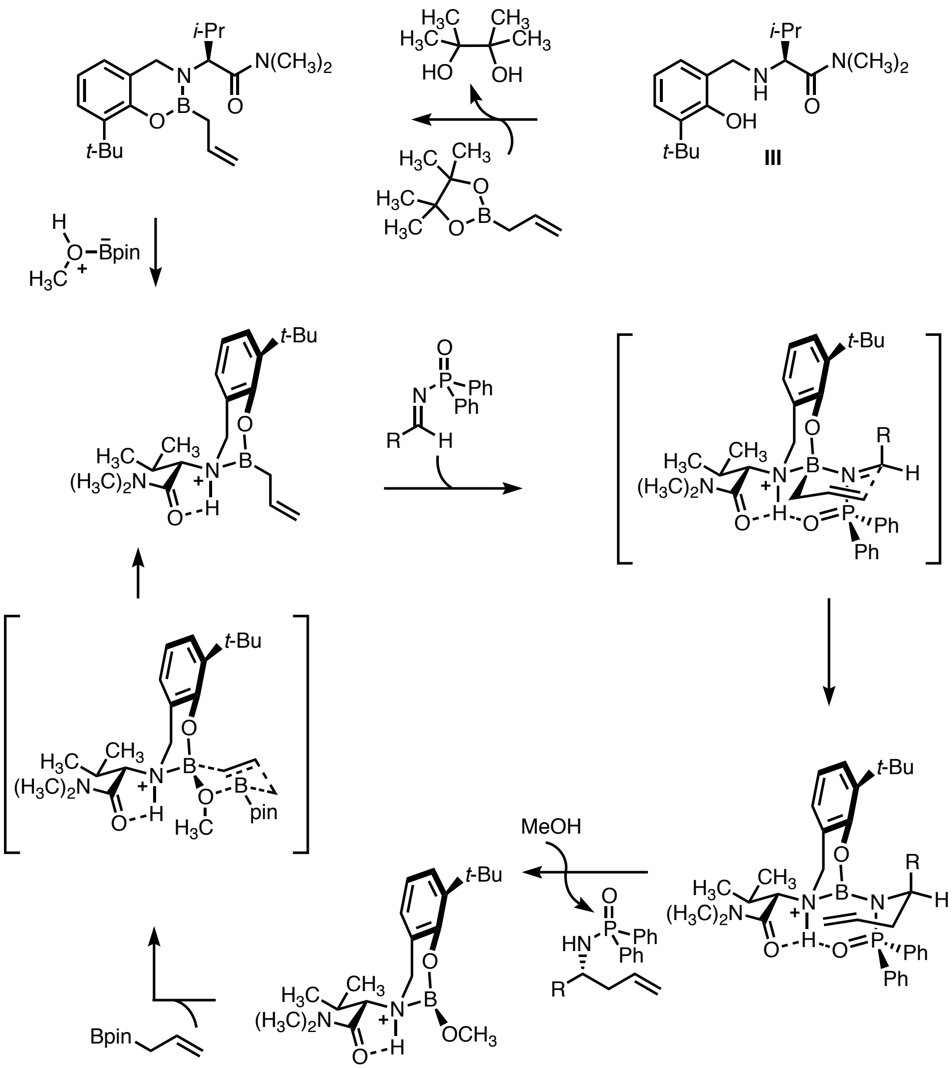
III (6.0 mol%)
$Zn(Ot\text{-}Bu)_2$ (8.5 mol%)
MeOH, $PhCH_3$, 22 °C
70%, 90% ee
dr = 8 : 1



1. **III** (0.25 mol%)
NaO*t*-Bu (0.4 mol%)
MeOH, $PhCH_3$, 22 °C
2. aq. HCl, MeOH, 22 ºC
90%, >99% ee

(an "isatin")

Mechanism:



- <2% conversion was observed in the absence of methanol.
- The internal hydrogen bond between the protonated amine and the amide carbonyl rigidifies the complex and increases the Lewis acidity of the boron center to facilitate substrate binding.
- Substrate release is accelerated by intramolecular protonation.

Silverio, D. L.; Torker, S.; Pilyugina, T.; Vieira, E.; Snapper, M. L.; Haeffner, F.; Hoveyda, A. H. *Nature* **2013**, *494*, 216–221.

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