Boron Reagents for Asymmetric Synthesis

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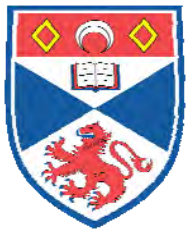


Overview

1) Hydroboration

2) Reductions

3) Aldol Reactions

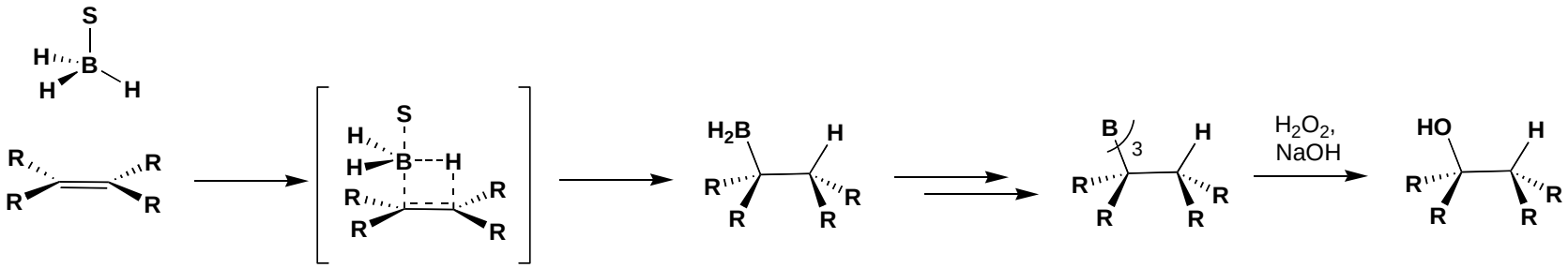
4) Allylboration Reactions

5) Vinylations and Homologations

Hydroboration

Hydroboration

The Starting Point



"In the course of investigating the facile conversion of olefins into trialkylboranes under the influence of the sodium borohydride-aluminum chloride reagent, we have discovered that in the presence of organic ethers diborane adds to olefins with remarkable ease and speed at room temperature to form the corresponding organoboranes in yields of 90-95%."

Brown and Rao, JACS 1956, 78, 5694
JOC 1957, 22, 1136
JOC 1957, 22, 1137

"At the time many individuals expressed scepticism as to the value of devoting so much research effort to this reaction. They took the position that hydroboration, while a clean, simple reaction, produces only organoboranes, compounds of no known use…… We bided our time."

Brown & Ramachandran Pure Appl. Chem, 1991, 63 307

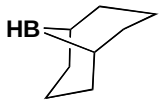
Hydroboration

Common Reagents

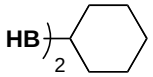
Borane complexes

BH_3•THF BH_3•DMS B_2H_6

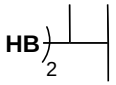
Alkylboranes



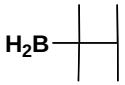
9-BBN



$cHex_2BH$

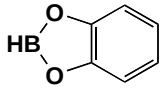


disiamylborane

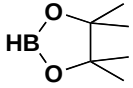


thexylborane

Dialkyloxyboranes

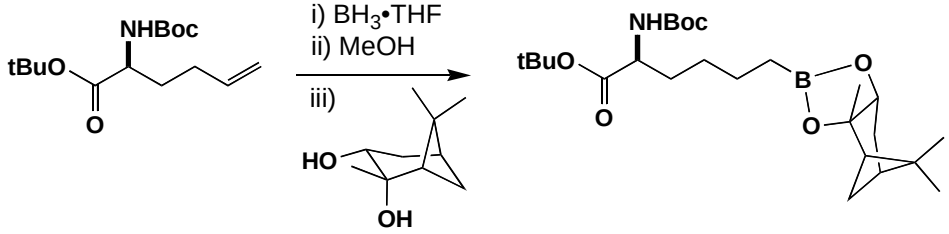


catecholborane

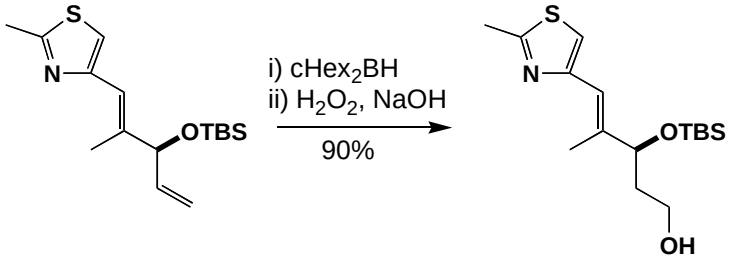


pinacolborane
pinBH

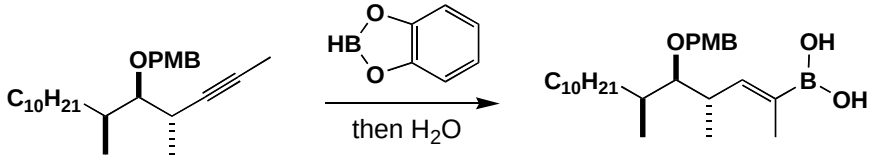
Examples



Christianson et al. JACS 1997, 119, 8107



Panek et al. OL 2000, 2, 2575



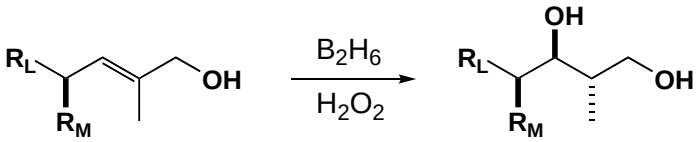
cross-coupling precursor

Kobayashi et al. JOC 2001, 66, 5580

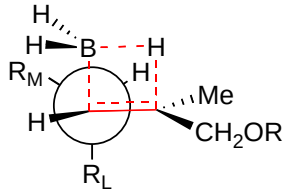
For a recent review, see: Buckhardt and Matos, Chem. Rev. 2006, 106, 2617

Diastereoselective Hydroboration - Acyclic Systems

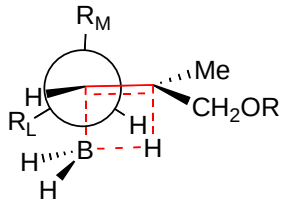
Hydroboration of trisubstituted olefins can be controlled by A(1,3) strain



- ***A(1,3) strain minimised***
- ***Staggered transition state***
- ***Sterics : R_L vs R_M***



major

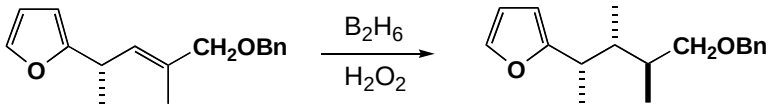


minor

For detailed TS calculations and discussion, see: Houk et al. Tetrahedron 1984, 40, 2257

Representative Applications

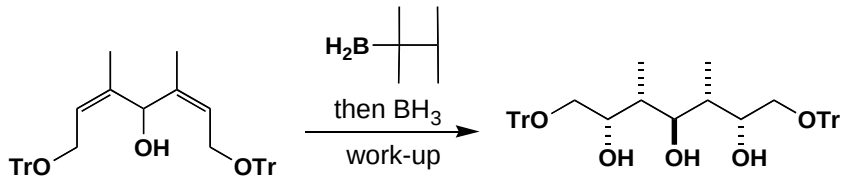
E-olefins



dr = 8 : 1

Kishi et al. JACS 1979, 101, 259

Z-olefins



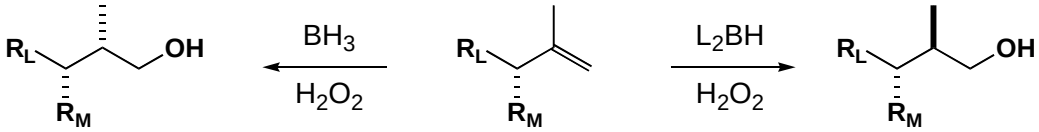
dr = 5 : 1

Still & Barrish JACS 1983, 105, 2487

Diastereoselective Hydroboration - Acyclic Systems

Hydroboration of acyclic 1,1-disubstituted olefins controlled by A(1,2) strain

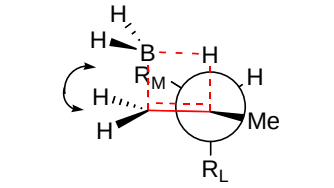
In general - Houk's rules



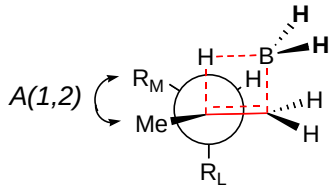
For boranes

•Small reagent

•Minimisation of A(1,2) strain favours TS1



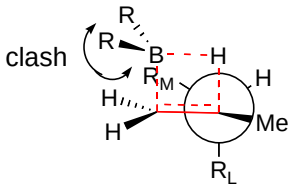
major



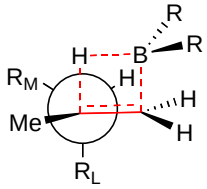
minor

TS1

TS2



minor



major

For dialkylboranes

•Bulky reagent

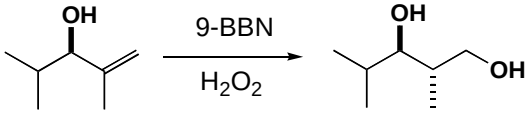
•Minimisation of steric interaction between boron ligand and R_M favours TS2

For detailed TS calculations and discussion, see: Houk et al. Tetrahedron 1984, 40, 2257

Diastereoselective Hydroboration - Acyclic Systems

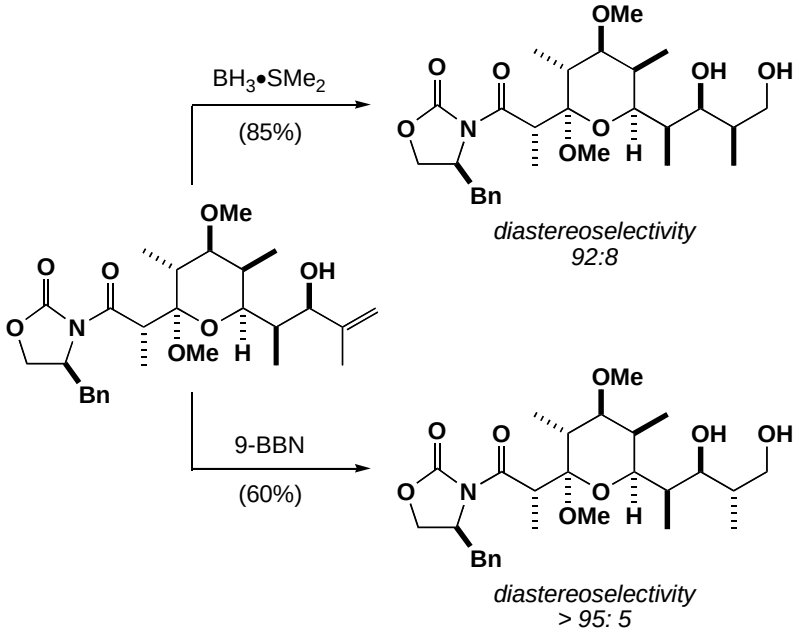
Hydroboration of acyclic 1,1-disubstituted olefins controlled by A(1,2) strain

Applications

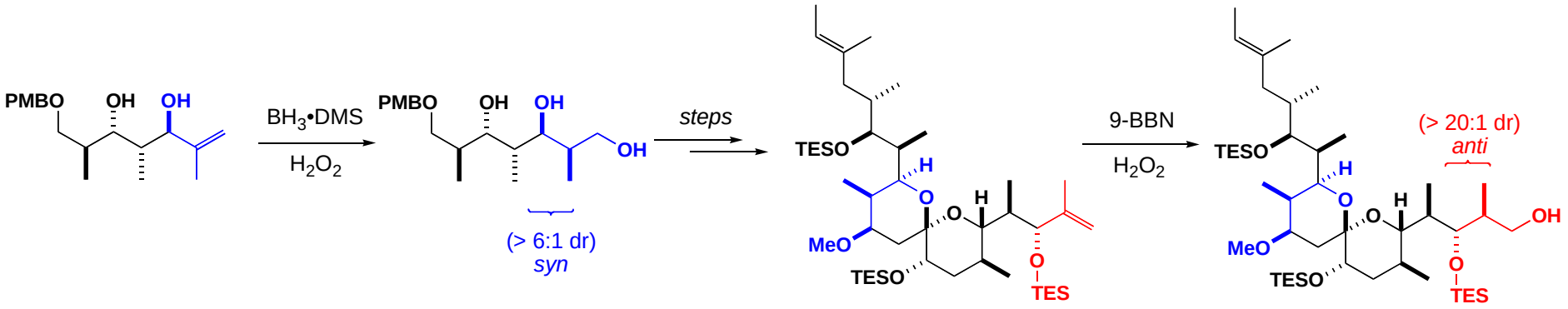


R_M = OH

Still & Barrish JACS 1983, 105, 2487



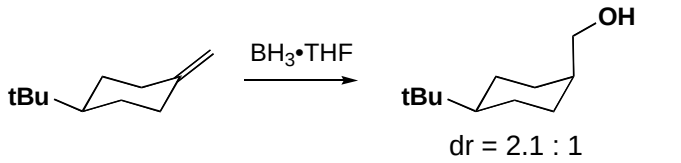
Lonomycin: Evans et al. JACS 1995, 117, 2487



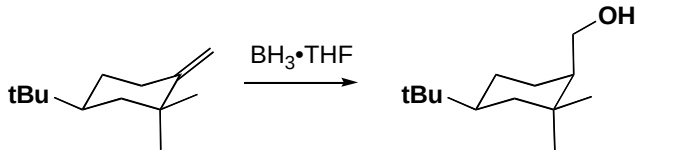
Spirangien A: Paterson et al. ACIEE 2007, 46, 6699; Chem. Comm. 2008, 6408

Diastereoselective Hydroboration - Cyclic Systems

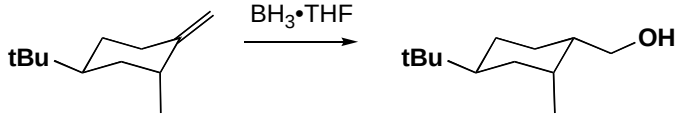
substituted methylenecyclohexanes



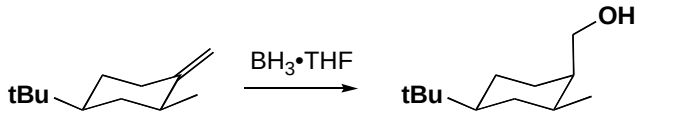
dr = 2.1 : 1



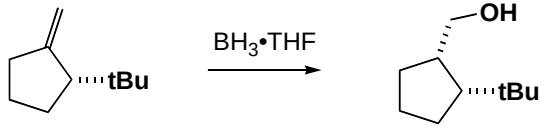
dr = 1.2 : 1



dr = 3.3 : 1



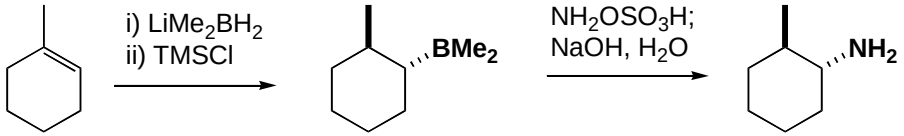
dr = 2.4 : 1



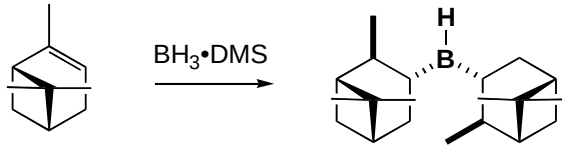
dr = 99 : 1

- ***Largely governed by steric interactions***
- ***dr greater when 2-position substituent is axial***

Senda et al. Tetrahedron 1977, 33, 2933

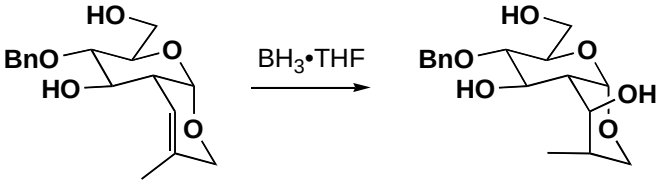


Brown et al. JACS 1966, 88, 2870
Review, see: Brown & Sinagram Pure. Appl. Chem. 1987, 59, 879



(+)-α-pinene (-)-Ipc_2BH

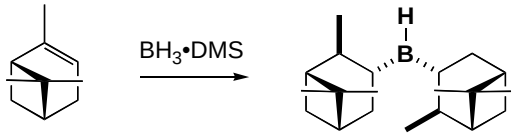
Brown & Zweifel JACS 1961, 83, 486



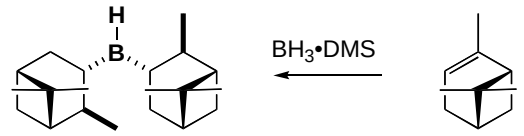
sole product

Fraser-Reid et al. JACS 1984, 106, 731

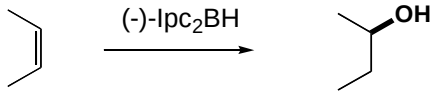
Asymmetric Hydroboration - Brown's Ipc reagents



(+)-α-pinene (-)-Ipc_2BH

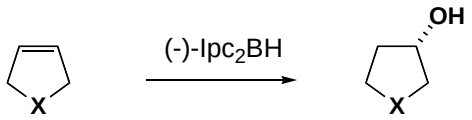


(+)-Ipc_2BH (-)-α-pinene

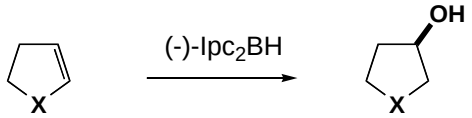


>98.4% ee

JACS 1961, 83, 486; JACS 1964, 86, 1076; JOC 1982, 47, 5065



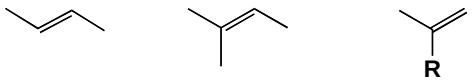
X = O, >99% ee
X = NBn, >99% ee
X = Cbz, 89% ee



X = O, >99% ee
X = S, >99% ee

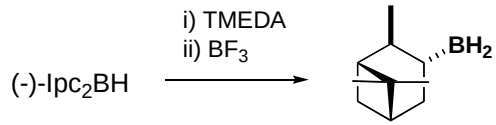
JOC 1986, 51, 4296; Heterocycles 1987, 25, 641

Limitations

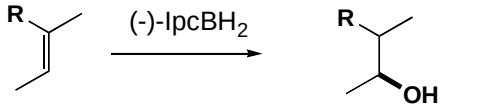


14% ee 15% ee R = iPr, 32% ee
R = Ph, -

$IpcBH_2$ - alleviates E-olefin limitation

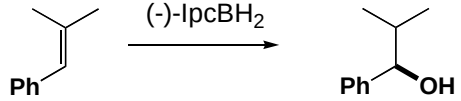


JOC 1978, 43, 4395; JOC 1982, 47, 5069



NB: reversed sense of induction

R = H, 73% ee
R = Me, 53% ee

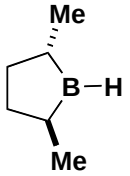


72% ee

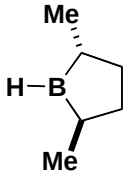
JOC 1982, 47, 5074

•For perspective reviews, see: Pure Appl. Chem. 1991, 63, 316; Pure Appl. Chem. 1987, 59, 879; Acc. Chem. Res. 1988, 21, 287
•Highlight on asymmetric hydroboration, see: Thomas & Aggarwal ACIEE 2009, 48, 1896

Asymmetric Hydroboration - Masamune's C2-symmetric borolanes

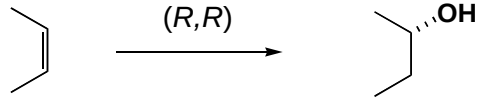


(*S*,*S*)

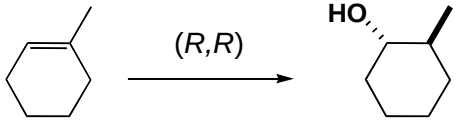


(*R*,*R*)

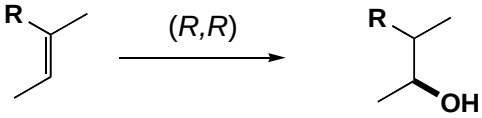
Advantages: Uniformly high enantioselectivities for all olefins apart from 1,1-disubstituted



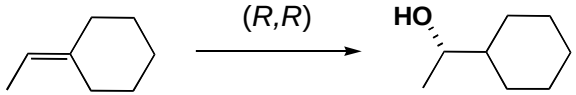
97.6% ee



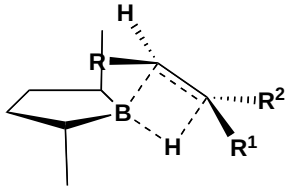
95.6% ee



R = H, 99.5% ee
R = Me, 97.6% ee



99.3% ee



Selectivity rationalised by TS model:
- ***hydrogen occupies position closest to Me group of borolane***
- ***loss of selectivity when R = H***

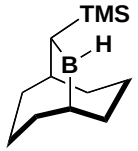
Largely ignored due to one disadvantage:

Reagent prepared in seven steps, including:

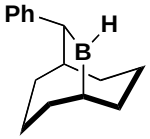
1. ***Separation of diastereomers***
2. ***Resolution of racemic trans-borolane***

Masamune et al. JACS 1985, 107, 4549

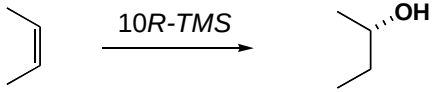
Asymmetric Hydroboration: 10-TMS-9-BBD and 10-Ph-9-BBD



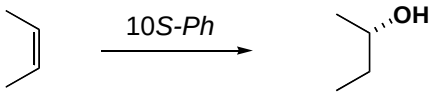
(10*R*)-9-TMS-10-BBD-H



(10*S*)-9-Ph-10-BBD-H

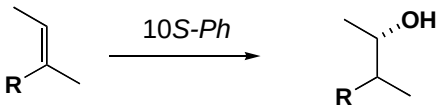


82% ee

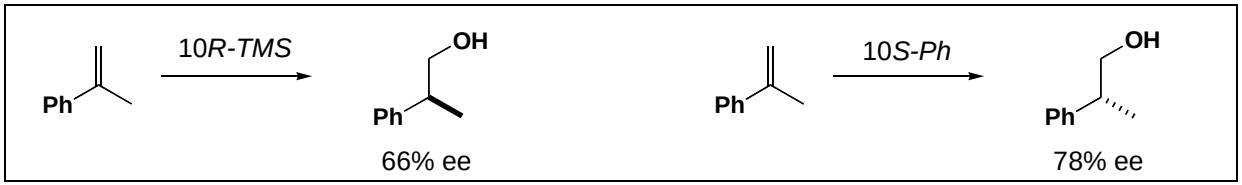


32% ee

R = H, 96% ee
R = Me, 84% ee

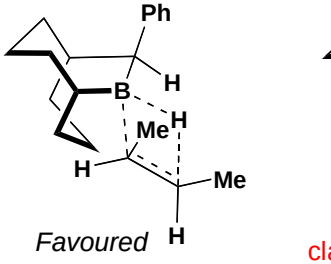


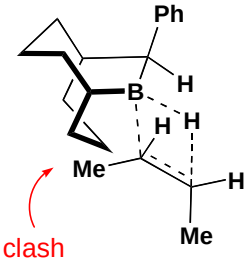
R = H, 96% ee
R = Me, 74% ee



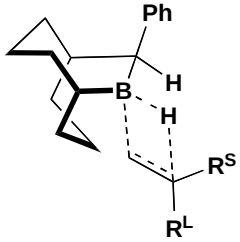
66% ee

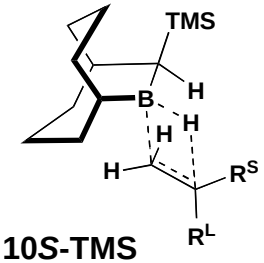
78% ee





10*S*-Ph



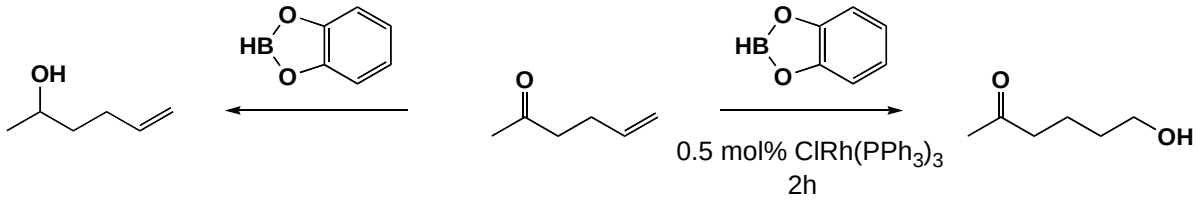


10*S*-TMS

- ***Good levels of enantioselectivity observed with 1,1-disubstituted olefins using either reagent system***
- ***First real solution to this longstanding hydroboration problem***

Initial disclosure: Soderquist et al. **ACS Symposium Series 783, Organoboranes for Synthesis, P. V. Ramachandran, H. C. Brown, Ed., Ch 13, pp 176-194, American Chemical Society, Washington, DC, 2000.**
Soderquist et al. JACS 2008, 130, 9218

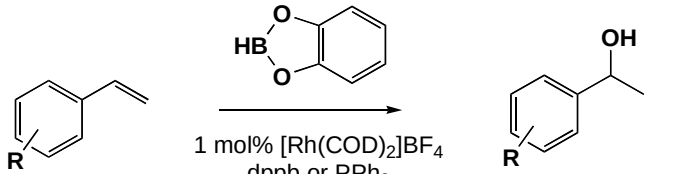
Catalytic Hydroboration



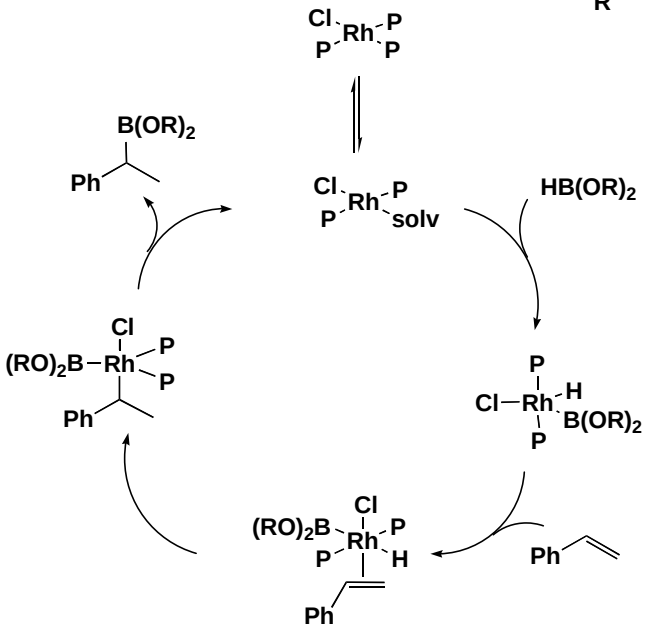
Männig & Nöth ACIEE, 1985, 24, 878

- ***need to use an unreactive dialkoxyboranes***
- ***hydroboration is achieved over ketone reduction by use of Wilkinson's catalyst***

Styrene gives reversal of selectivity



Hayashi et al. Tetrahedron Asymmetry 1991, 2, 601
Burgess et al. JACS 1992, 114, 9350



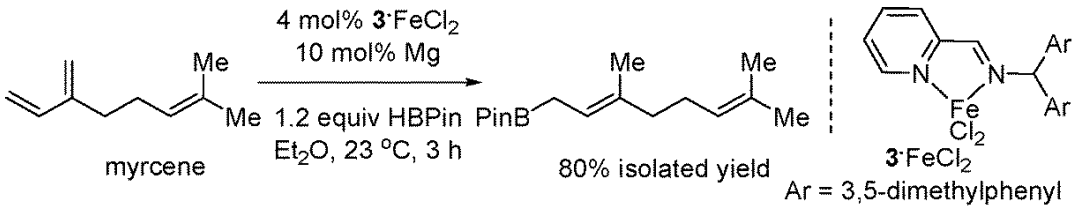
Catalytic cycle with Wilkinson's catalyst

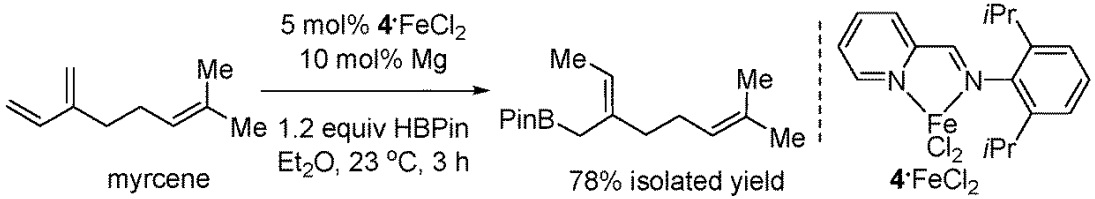
Reversal of selectivity rationalised by formation of η^3-Rh complex with Ph group after insertion of Rh-H

Wilkinson's catalyst is highly sensitive to oxygen - significant as slight variation in catalyst structure changes reaction outcome - much debate in early studies

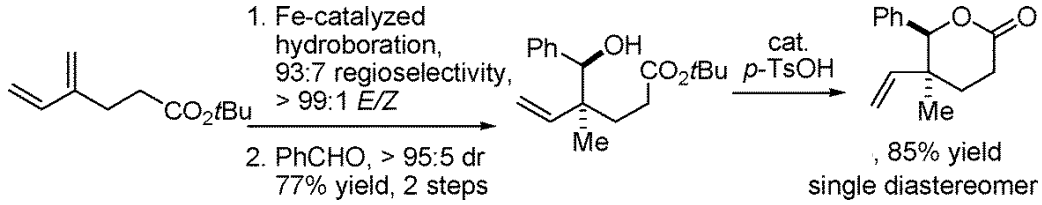
Reviews, see: Beletskaya & Pelter Tetrahedron 1997, 53, 4957; Crudden & Edwards EJOC 2003, 4695

Catalytic Hydroboration of 1,3-dienes





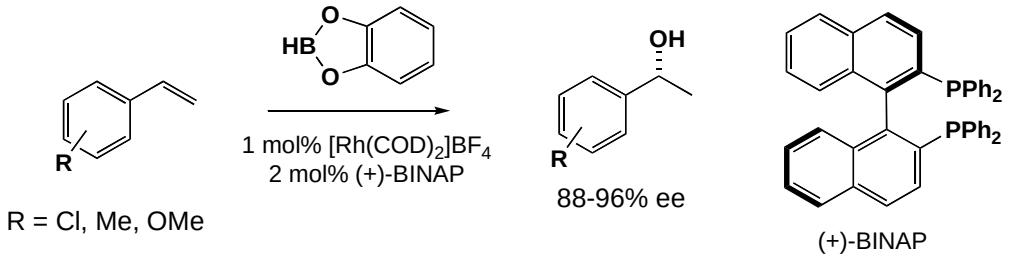
- ***Regioselective hydroboration of 1,3-diene by choice of Fe(II)-ligand***



- ***Sequential hydroboration/crotylation***

Ritter et al. JACS 2009, 131, 12915

Asymmetric Catalytic Hydroboration



R = Cl, Me, OMe

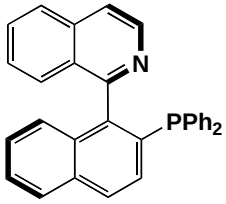
88-96% ee

(+)-BINAP

Hayashi et al. JACS 1989,111, 3426
Tetrahedron Asymmetry 1991, 2, 601

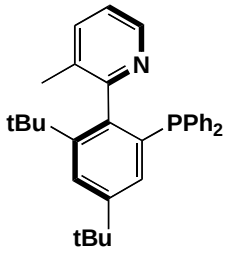
Hayashi was first to report catalytic asymmetric hydroboration of styrene with high ee
To date, BINAP remains one of the best ligand systems

Notable ligand systems



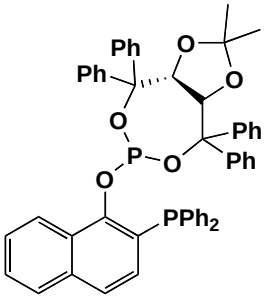
QUINAP
78-94% ee

J. M. Brown et al.
Chem. Comm. 1993, 1673



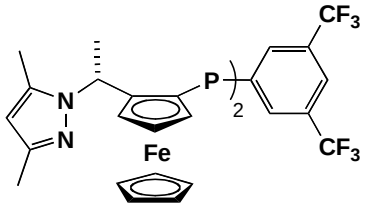
Pyphos
90% ee

Chan et al.
JOC 2002, 67, 2769



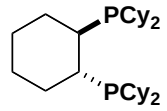
Taddol-based phosphane-phosphite
91% ee

Schmalz et al.
Adv. Synth. Catal. 2002, 344, 868



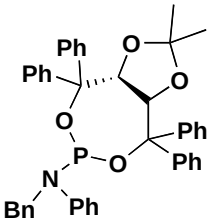
Josiphos-derivative
98.5% ee

Togni et al.
JACS 1994, 116, 4062
ACIEE, 1995, 34, 931;



C_2-diphosphane
70-93% ee

Knochel et al.
ACIEE 2001, 40, 1235

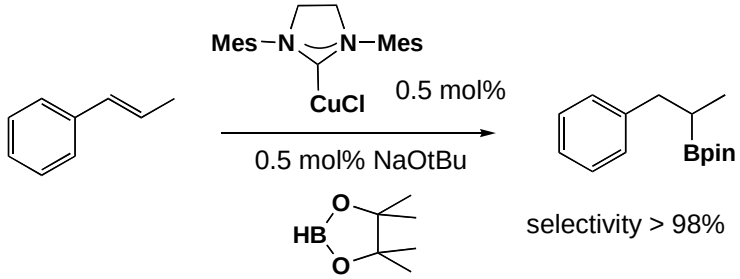


monodentate-Taddol
90-96% ee

Takacs et al.
OL 2006, 8, 3097

Reviews, see: Beletskaya & Pelter Tetrahedron 1997, 53, 4957; Crudden & Edwards EJOC 2003, 4695

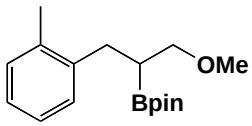
Asymmetric Catalytic Hydroboration



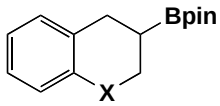
Hoveyda et al.
JACS 2009, 131, 3160

Hoveyda has recently established the catalytic hydroboration of 1,2-disubstituted olefins
Use Cu-NHC complex and pinacolborane for regioselective hydroboration

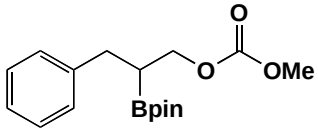
Substrate Scope



96% yield

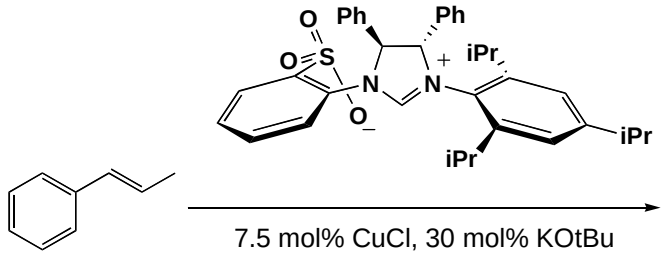


X= CH_2, 97%
X= O, >98%

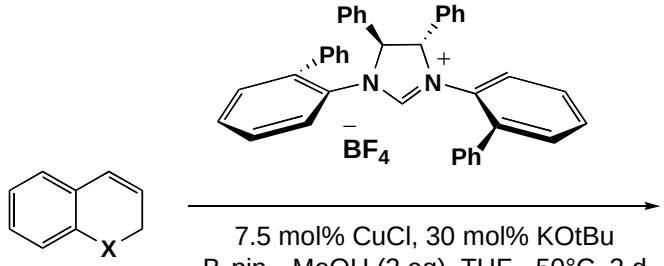


76% yield

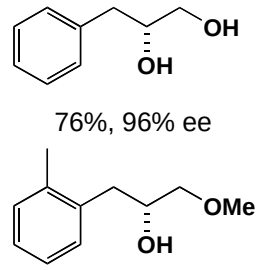
Enantioselective variant



80%, 98% ee



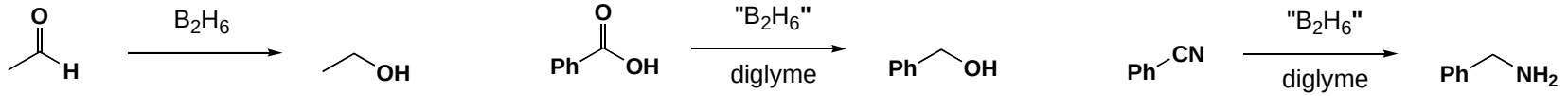
X = CH_2, 63%, 72% ee
X = O, 98%, 89% ee



Hoveyda et al. JACS 2009, 131, 3160

Reductions

Reductions with Borane Reagents



H. C. Brown PhD thesis, University of Chicago

Brown, Schlesinger & Burg JACS 1939, 61, 673

diborane generated in situ from $NaBH_4$ and BF_3•OEt_2

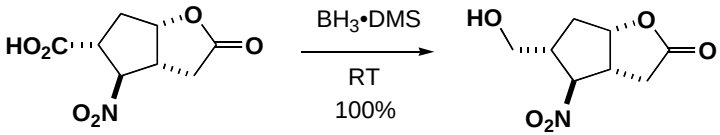
Brown & Rao JOC 1957, 22, 1135

Commercial Boranes

Primary Applications

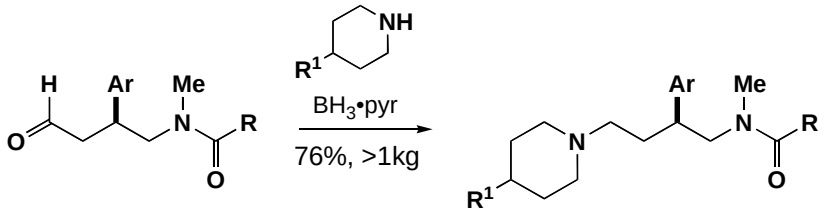
BH_3•THF **BH_3•DMS** **BH_3•pyr** **BH_3•NEt_3** **BH_3•$NH_2{}^tBu$**

Carboxylic acid reduction
Amide reduction

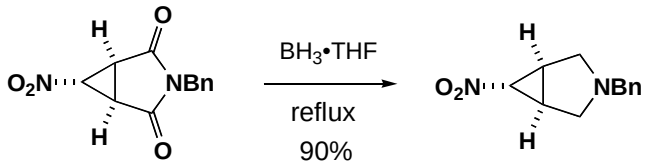


Hoffman-La Roche: US Patent 4112225, 1978

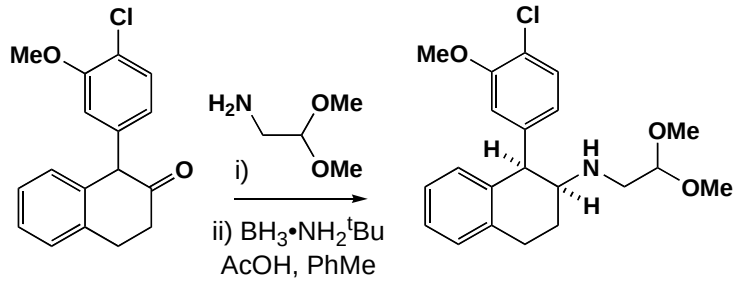
Reductive amination
enamine reduction
Oxime reduction



Parker et al. Org. Proc. Res. Dev. 2003, 7, 67



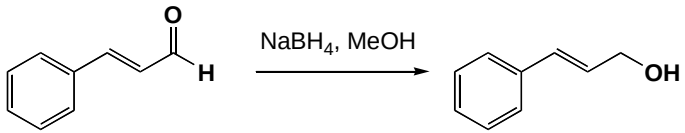
Pfizer: US Patent 5256791, 1993



Draper et al. Org. Proc. Res. Dev. 1998, 2, 175

For review, see: Buckhardt & Matos Chem. Rev. 2006, 106, 2617

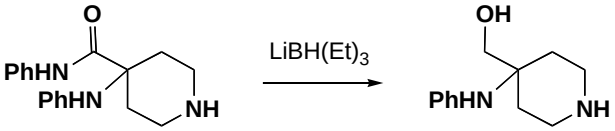
Reductions with Borohydride Reagents



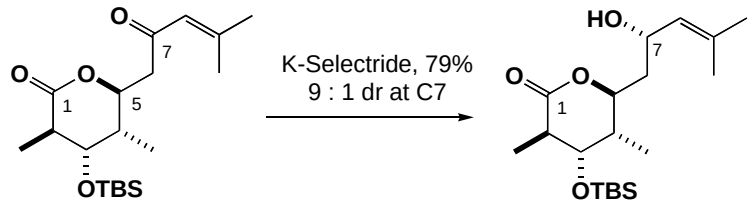
Chaikin & W. C. Brown JACS 1949, 71, 122
H.C. Brown, Mead & Rao JACS 1955, 77, 6209

A selection of some commercial borohydrides and applications

$NaBH_4$	$LiBH_4$	$LiBH(Et)_3$	$Met\text{-}BH(sBu)_3$
		Super Hydride	Met = Li, Na, K Met-Selectride
ketone/aldehydes acid chlorides	+ esters directed ketone reductions	Hindered ketones S_N2 - Ts/Ms displacement Amide to alcohol	Stereoselective reductions of ketones Enone reductions - 1,2 or 1,4 Lactones to lactols



Killigore et al. WO Appl. 0140184, 2001



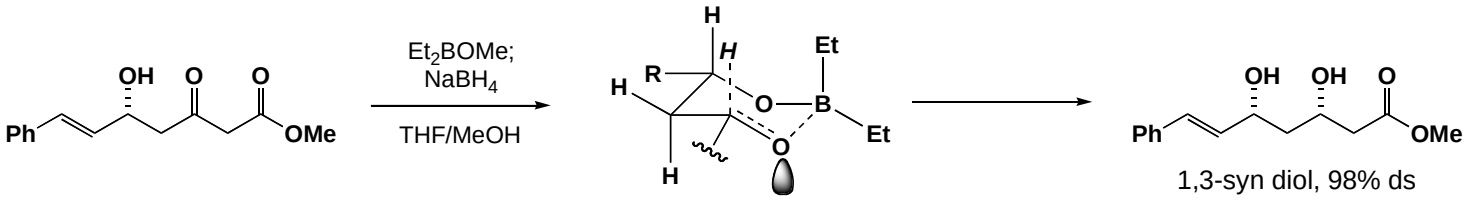
Smith et al. JACS 2000, 122, 8654

$NaBH_3(CN)$ — **$NaBH(OAc)_3$** — **$Me_4NBH(OAc)_3$**

reductive amination — directed ketone reductions

Directed Reductions of β-Hydroxy Ketones

1,3-syn reduction - Narasaka-Prasad

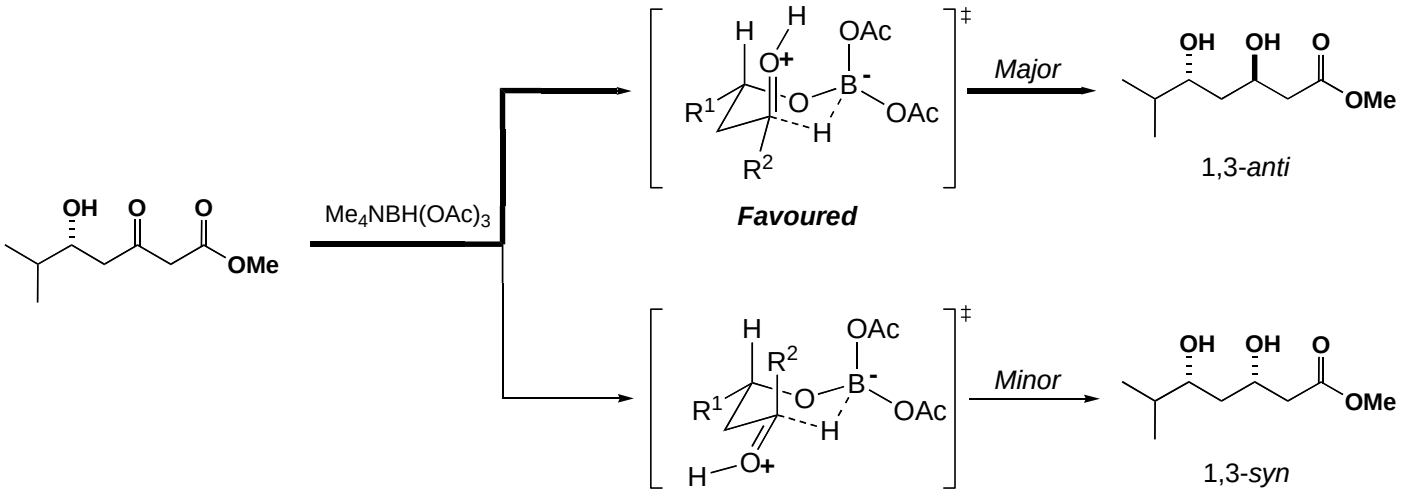


1,3-syn diol, 98% ds

- ***Formation of intermediate boron aldolate***
- ***Axial addition of hydride from lowest energy half-chair***
- ***Reaction can be done in situ following boron aldol reaction***

With trialkylboranes: Narasaka & Pai Tetrahedron 1984, 40, 2233
Modification with alkoxyboranes: Prasad et al. TL 1987, 28, 155

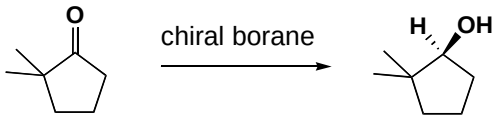
1,3-anti reduction of β-hydroxy ketones - Evans-Saksena Reduction

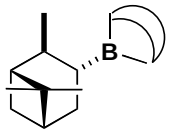


1,3-directed reductions with $NaBH_4$ / AcOH: Saksena & Mangiaracina TL 1983, 24, 273
Optimisation and utility in polyketide synthesis: Evans et al. JACS 1988, 110, 3560

Asymmetric Borane Reductions

Brown's Ipc-based Boranes





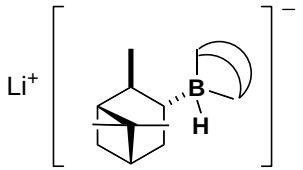
Alpine-Borane

Brown et al. JOC 1977, 42, 2534

20% ee

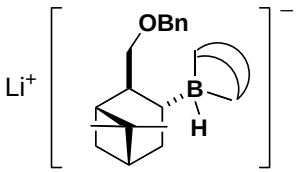
effective for ynones (99% ee)

Midland et al. JACS 1980, 102, 867



Alpine-Hydride

-

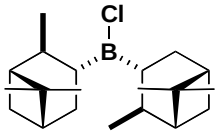


NB-Enantride

Midland et al. JOC 1982, 47, 2495

1% ee

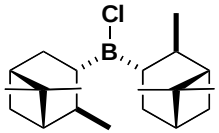
effective for straight chain ketones (68-79% ee)



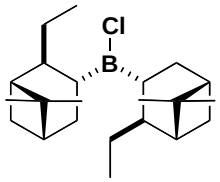
(-)-Ipc_2BCl

Brown et al. JACS 1988, 110, 1539

98% ee



(+)-Ipc_2BCl

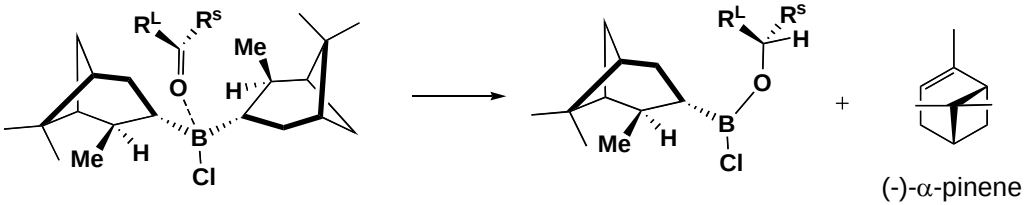


Eap_2BCl

Brown et al. Pure. Appl. Chem. 1991, 63, 307

>99% ee

(+)-Ipc_2BCl reduction



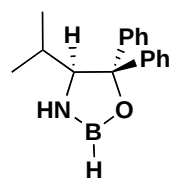
(-)-α-pinene

- ***boron chloride reagents work by de-hydroboration and loss of pinene***

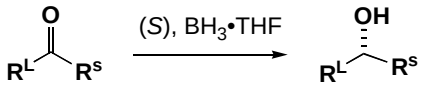
For a comparative study with various classes of ketones prior to CBS, see: Brown et al. J. Org. Chem. 1987, 52, 5406

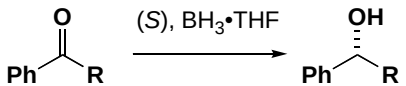
Asymmetric Borane Reductions

Itsuno's Reagent

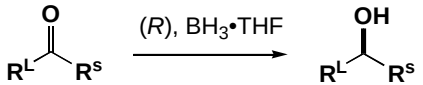


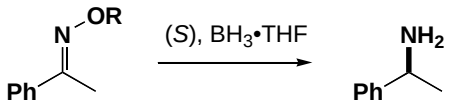
(*S*)
Itsuno's reagent





R = Me, 94% ee
R = Et, 94% ee
R = Pr, 96% ee



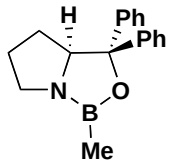


R = Me, 99% ee
R = Bn, 95% ee

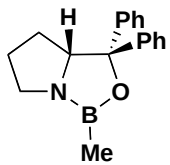
- ***reagent and BH_3•THF mixed in situ to form diborane complex***
- ***stoichiometric reagent system works well for ketones with defined large and small groups***
- ***catalytic version developed by Corey (see below)***
- ***oxime ether reduction gives reversal of facial selectivity***

Itsuno et al. J. Chem. Soc. Chem. Comm. 1983, 469
J. Chem. Soc. Perkin Trans. 1, 1985, 2039

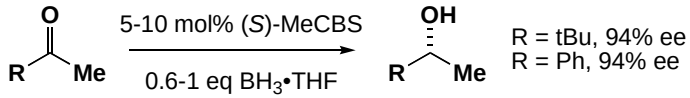
Corey's CBS Reagent



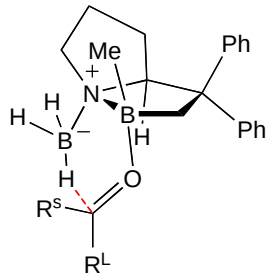
(*S*)-MeCBS



(*R*)-MeCBS

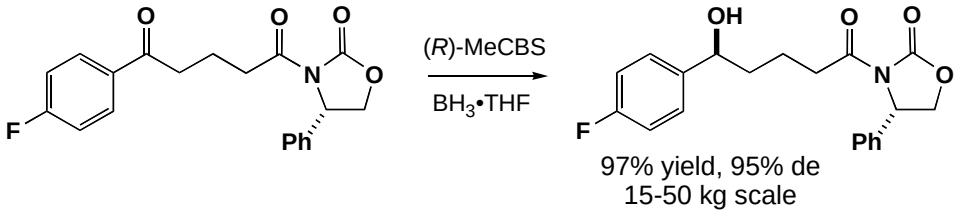


R = tBu, 94% ee
R = Ph, 94% ee



- ***Corey proposed mechanistic rationale for observed selectivity***
- ***Optimised catalytic version of reaction***
- ***Both (R)- and (S)-MeCBS commercially available***

Corey et al. JACS 1987, 109, 5551



97% yield, 95% de
15-50 kg scale

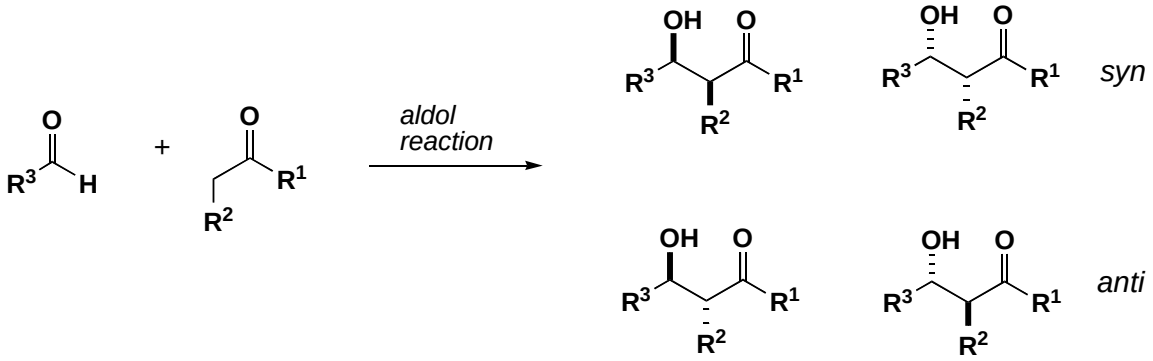
- ***Utility has been demonstrated in process chemistry - 50 kg scale***
- ***Remains a go to reagent for many total synthesis campaigns for tricky reductions***

Schering-Plough: Fu et al. TL 2003, 44, 801; Wu et al. JOC 1999, 64, 3714

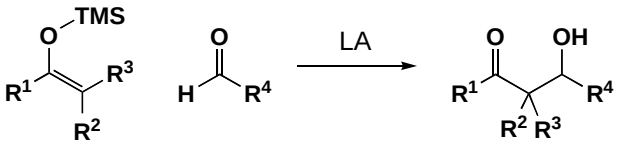
Aldol Reactions

Boron Reagents for Aldol Reactions

Focus of intense interest over last 30 or so years due to its primary utility in the synthesis of polyketide natural products

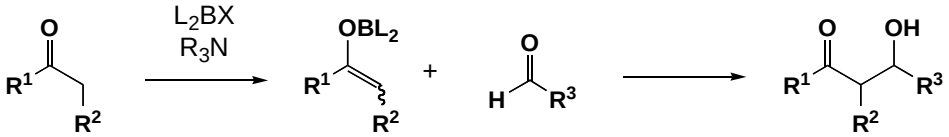


1) Mukaiyama



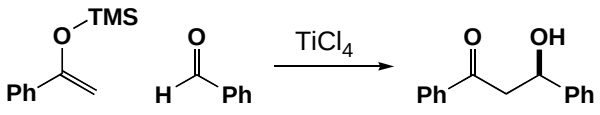
Lewis acid promoted (e.g. BF_3•OEt_2)

2) Boron-mediated



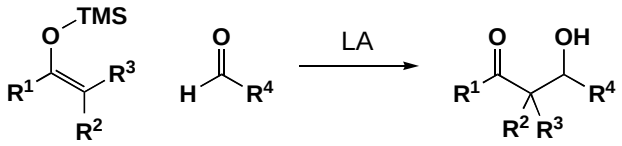
Formation of boron enolate and reaction with aldehyde

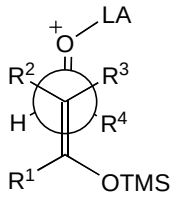
Mukaiyama Aldol Reactions



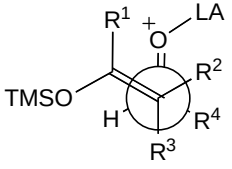
Mukaiyama et al.
Chem. Lett. 1973, 1011
JACS 1974, 96, 7503
Reviews: Org. React. 1994, 46, 1

- ***Reaction of silyl enol ether and aldehyde in presence of Lewis acid promoter (e.g. TiCl4, BF3•OEt2)***
- ***Proceeds via open transition state***





antiperiplanar
"Favoured"

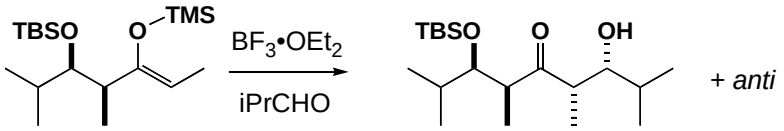


synclinal

Possible to control relative and absolute stereochemistry by use of:

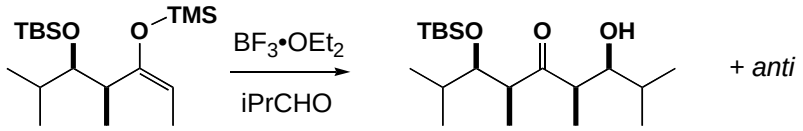
1) Chiral silyl enol ether (limited application)
2) Chiral aldehydes
3) Chiral Lewis acid

1) Chiral silyl enol ether



dr = 59 : 41
enolsilane facial selectivity = 95 : 5

Evans: JACS 1995, 117, 9598

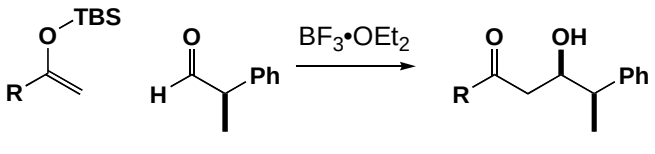


dr = 95 : 5
enolsilane facial selectivity = 90 : 10

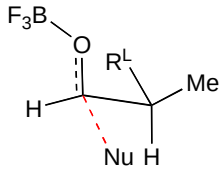
Reviews, see: Mahrwald, Chem. Rev. 1999, 99, 1095; Nelson, Tetrahedron: Asymmetry 1998, 9, 357

Mukaiyama Aldol Reaction: Chiral Aldehydes

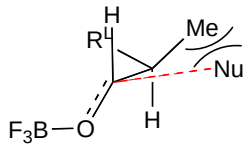
α-chiral aldehydes



R = Me, dr = 91 : 9
R = tBu, dr = 96: 4



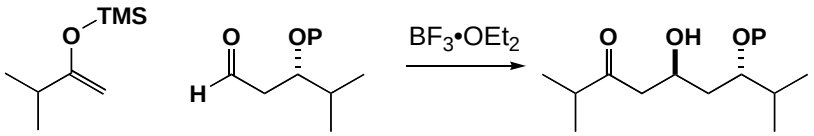
Favoured



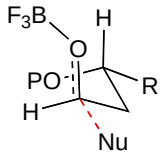
Anh & Eisenstein Noveau J. Chim. 1977,1, 61

- ***Mukaiyama aldol reactions with α-chiral aldehydes proceed with high levels of Felkin-Anh induction***
- ***Increasing size of nucleophile leads to increased selectivity for Felkin-Anh product***

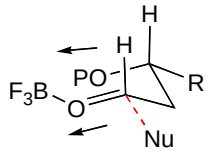
β-oxygenated aldehydes



P = PMB, dr = 92 : 8
P = TBS, dr = 80 : 20



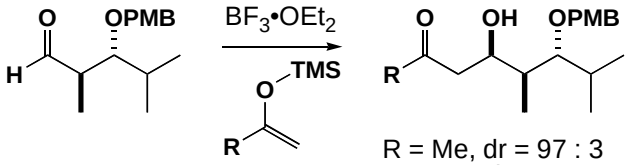
Favoured



dipole destabilization

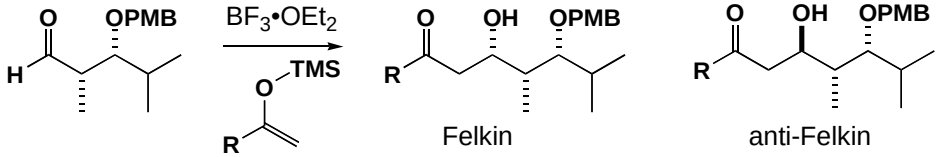
- ***Mukaiyama aldol reactions with β-OPMB proceed with high levels of 1,3-anti induction (also OBn), according to Evans' 1,3-polar model***

Merging stereochemical models



R = Me, dr = 97 : 3
R = tBu, dr = 99 : 1

anti diastereomer
α and β reinforcing



syn diastereomer
α and β non-reinforcing

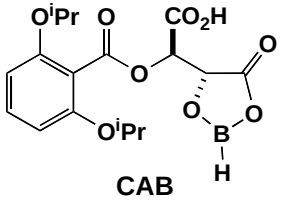
R = Me, dr = 17 : 83
R = iPr, dr = 56 : 44
R = tBu, dr = 96 : 4

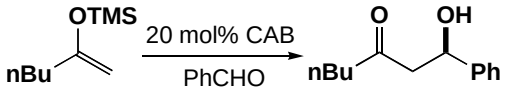
Small nuceophile - 1,3-control
Large nucleophile - Felkin control

Evans et al. JACS 1996, 118, 4322; JACS 2001, 123, 10840

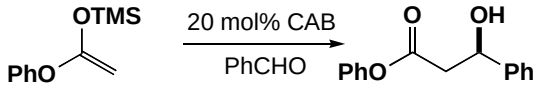
Mukaiyama Aldol Reaction: Chiral Boron Lewis Acids

Yamamoto's Chiral (Acyloxy)Boranes

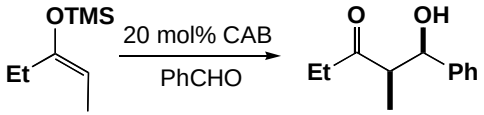




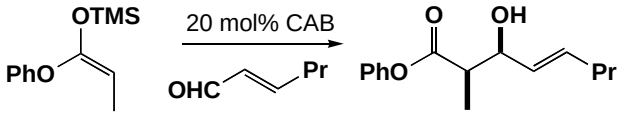
81%, 85% ee



63%, 84% ee



94%, 94% ds, 96% ee

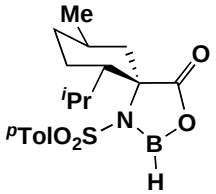


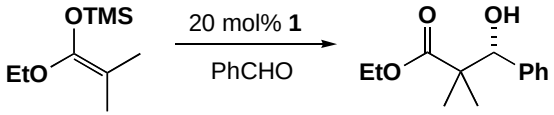
97%, 96% ds, 97% ee

- ***Yamamoto's tartrate-derived CAB give high levels of ee***
- ***substituted silyl enol ethers/ketene acetals give syn adduct regardless of starting geometry***

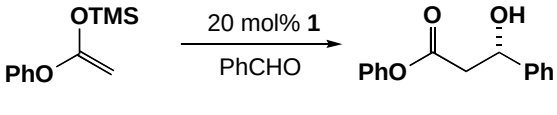
Yamamoto et al. JACS 1991, 113, 1041; Synlett 1991, 439; Bull. Chem. Soc. Jpn. 1993, 66, 3483; JACS 1993, 115, 10412

Masamune's Oxaborolidine Catalysts

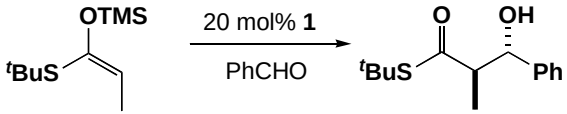




83%, 91% ee



77%, 93% ee



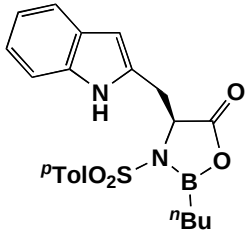
94% ds, 82% ee

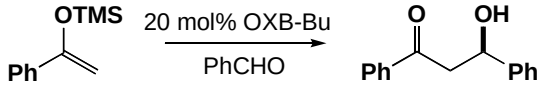
Masamune et al. JACS 1991, 113, 9365; TL 1992, 33, 1729

Reviews, see: ***Mahrwald, Chem. Rev. 1999, 99, 1095; Nelson, Tetrahedron: Asymmetry 1998, 9, 357***

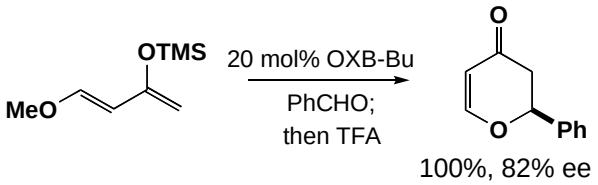
Mukaiyama Aldol Reaction: Chiral Boron Lewis Acids

Corey's Oxaborolidine Catalyst:





82%, 89% ee

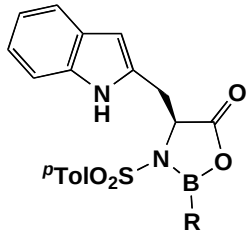


100%, 82% ee

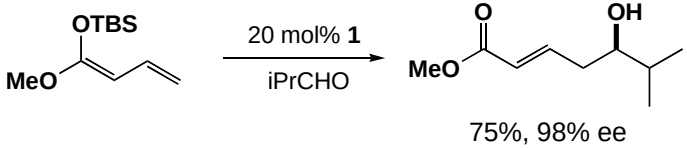
aldol - cyclisation: formal hetero-Diels Alder

Corey: TL 1992, 33, 6907

Derivatives and related applications

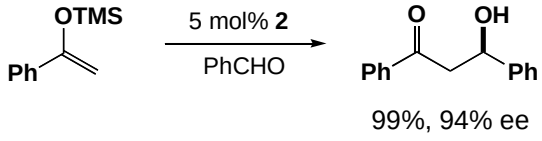


1: R = Ph,
2: R = 3,5-$(CF_3)_2C_6H_3$



75%, 98% ee

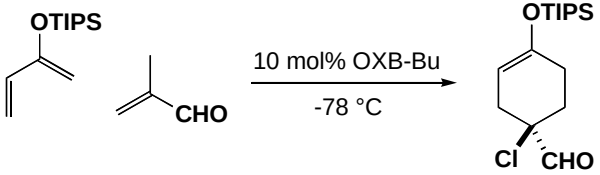
vinylogous aldol reaction:
Kalesse et al. OL 2007, 9, 5637



99%, 94% ee

Yamamoto et al. JOC, 2000, 65, 9125

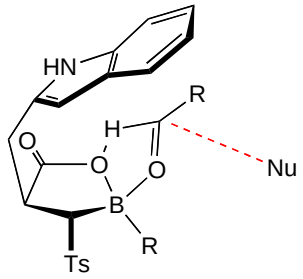
Diels-Alder reactions



94% ee

Corey: JACS 1994, 116, 3611
JACS, 1991, 113, 8966; JACS 1992, 114, 8290

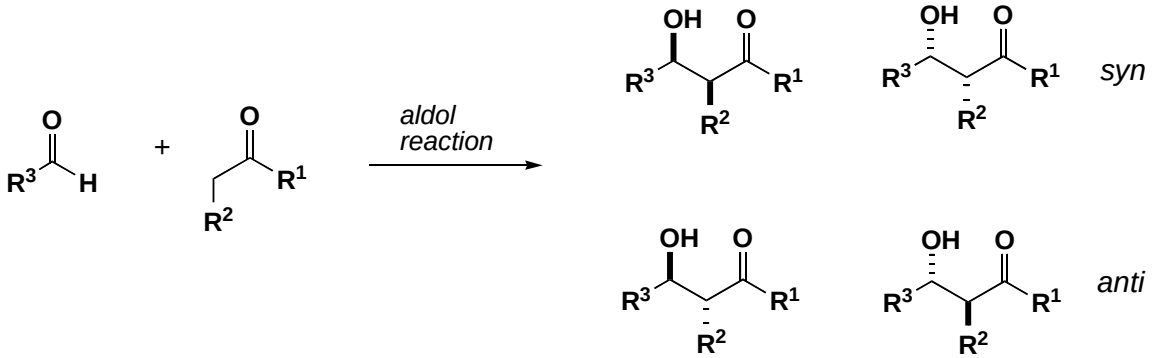
Origin of facial selectivity



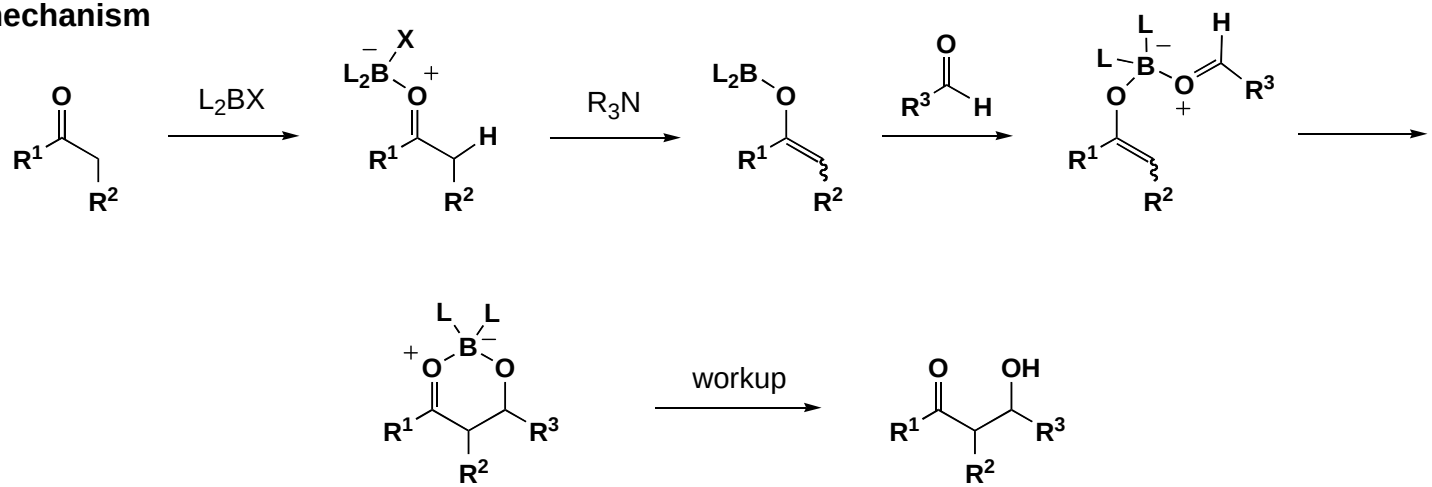
- ***π–π interaction between carbonyl of aldehyde and indole ring of catalyst***
- ***Only re-face exposed for nucleophile addition***

Boron-mediated Aldol Reaction

Focus of intense interest over last 30 or so years due to its primary utility in the synthesis of polyketide natural products



General mechanism



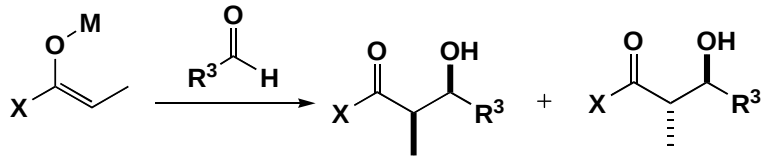
Stereochemical issues to consider:

1) relative stereocontrol - selective enolization

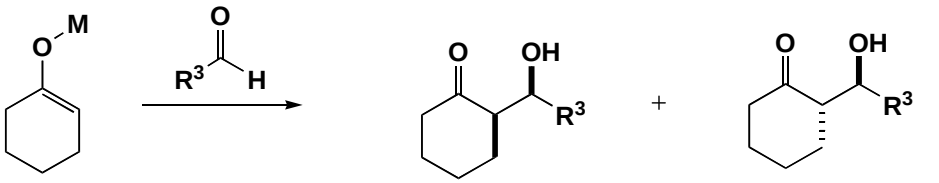
2) absolute stereocontrol - π-facial selectivity

Why Boron?

Comparison of Group I, II and III enolates

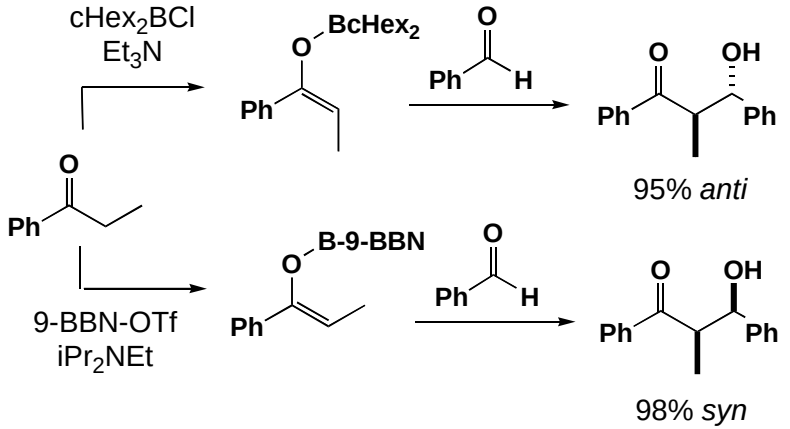


	M	*syn*	*anti*
X = CMe_3	Li	>98	2
	MgBr	>95	5
	BBu_2	>97	3
X = C_6H_5	Li	80	20
	BBu_2	>97	3
X = Et	Li	80	20
	BBu_2	>97	3



M	*syn*	*anti*
Li	48	52
$AlEt_2$	50	50
BBu_2	17	83

- **stereocontrol with Li- and Mg-enolates optimal with "large" X**
- **high levels of selectivity maintained with use of B-enolates**
- **B-O bond length < M-O bond length - tighter transition state - higher levels of stereocontrol from metal centre**



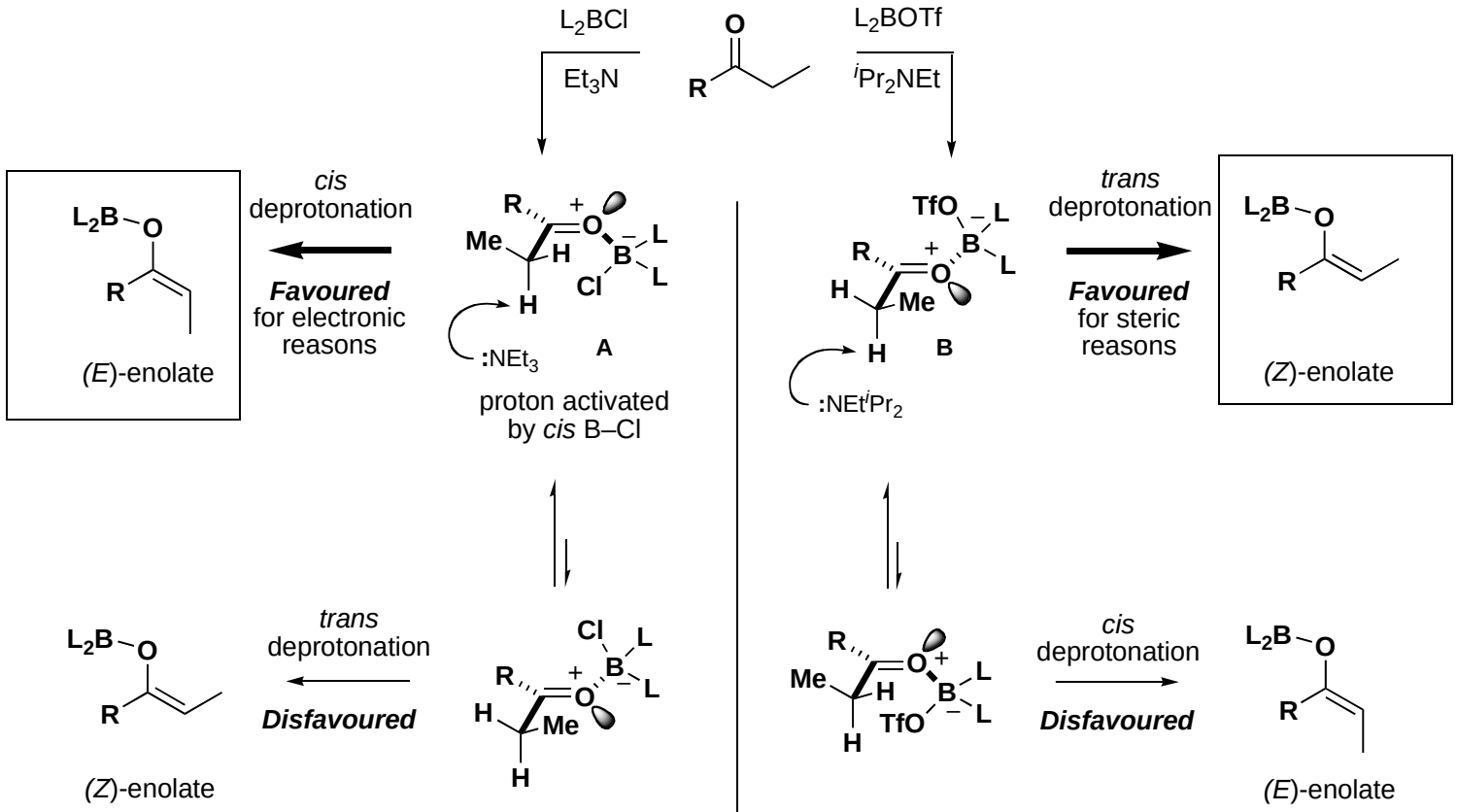
M—O	B—O	M—C	B—C
1.9-2.2 Å	1.4-1.5 Å	2.0-2.2 Å	1.5-1.6 Å

In general

Boron chloride → (*E*)-enolate → *anti aldol*

Boron triflate → (*Z*)-enolate → *syn aldol*

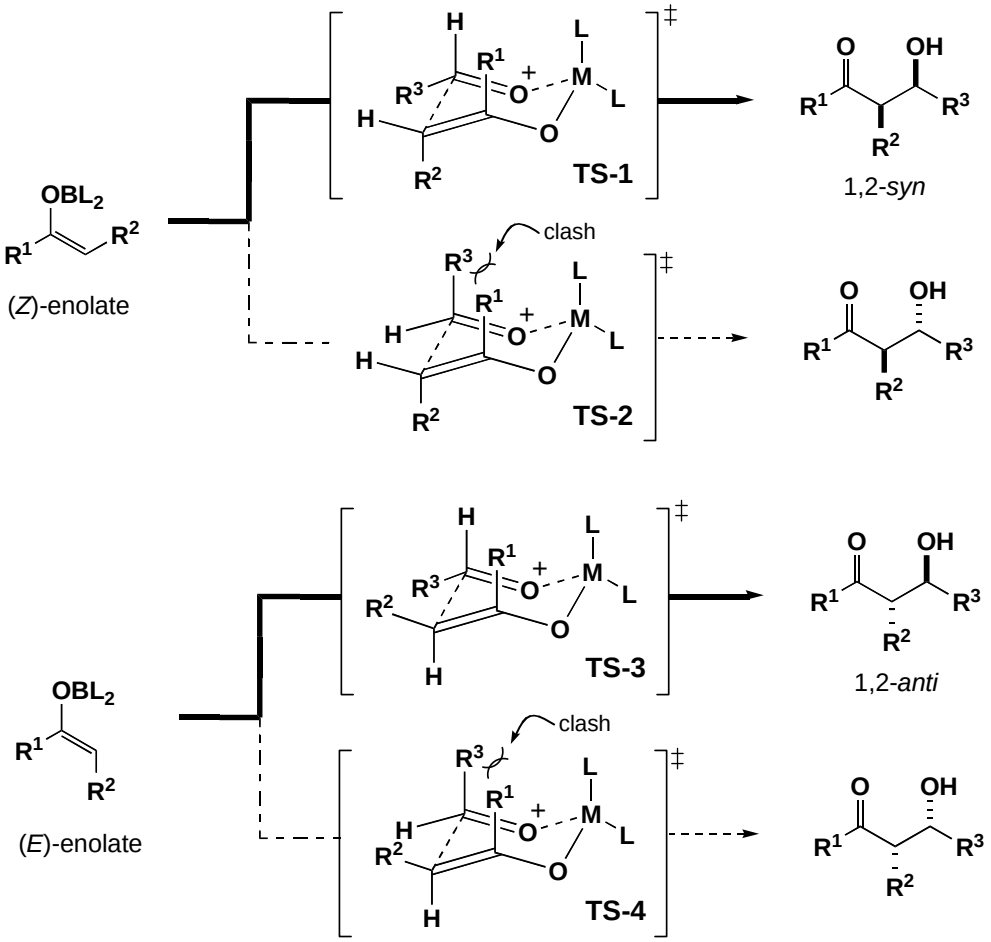
Controlling Enolate Geometry



- **sterically demanding ligands (e.g. cHex)**
- **poor leaving group (e.g. chloride)**
- **small amine base (e.g. Et_3N, Me_2NEt)**

- **small ligands (e.g. n-butyl, 9-BBN)**
- **good leaving group (e.g. triflate)**
- **bulky amine base (e.g. iPr_2NEt)**

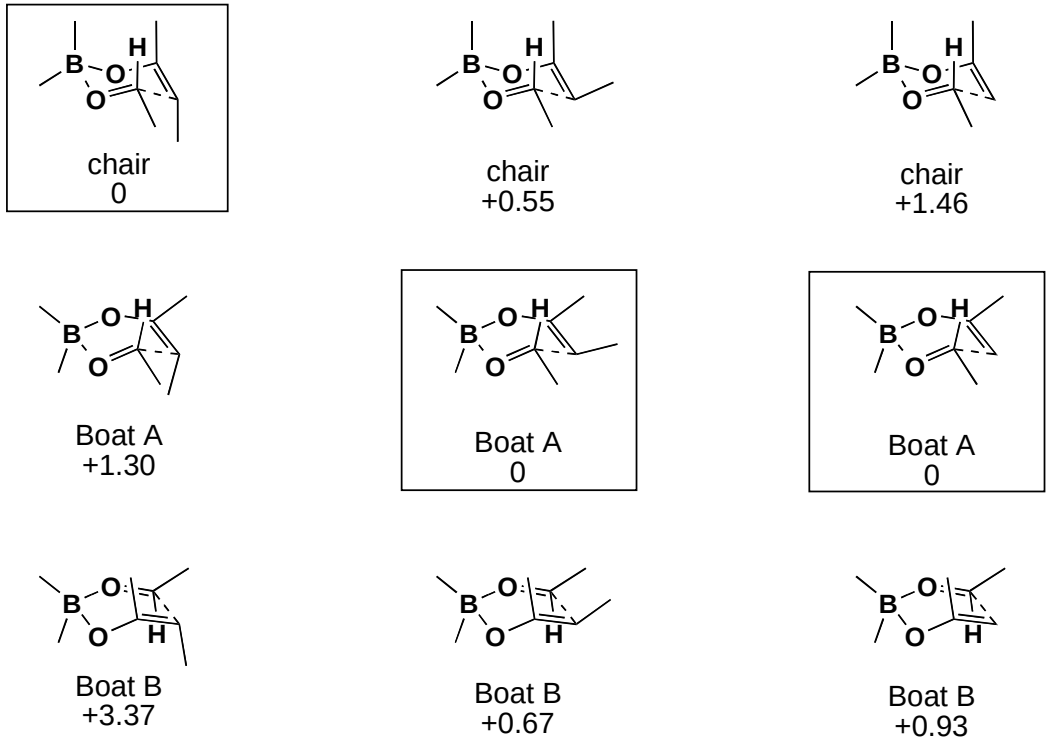
Relative Stereocontrol



- **enolate geometry faithfully transferred by 6-membered Zimmerman-Traxler TS (for $R^2 \neq H$)**
- **rationalizes observed relative stereochemistry**
- **widely accepted but is this really the case?**

Relative Stereocontrol: Revised

DFT Transition state calculations - Jaguar v4.2, 6-31G** basis set, B3LYP



relative energies in kcal mol^{-1}

For *Z*-enolborinates - boat A and B destabilized by 1,4-steric interactions between Me and ligand - Chair favoured

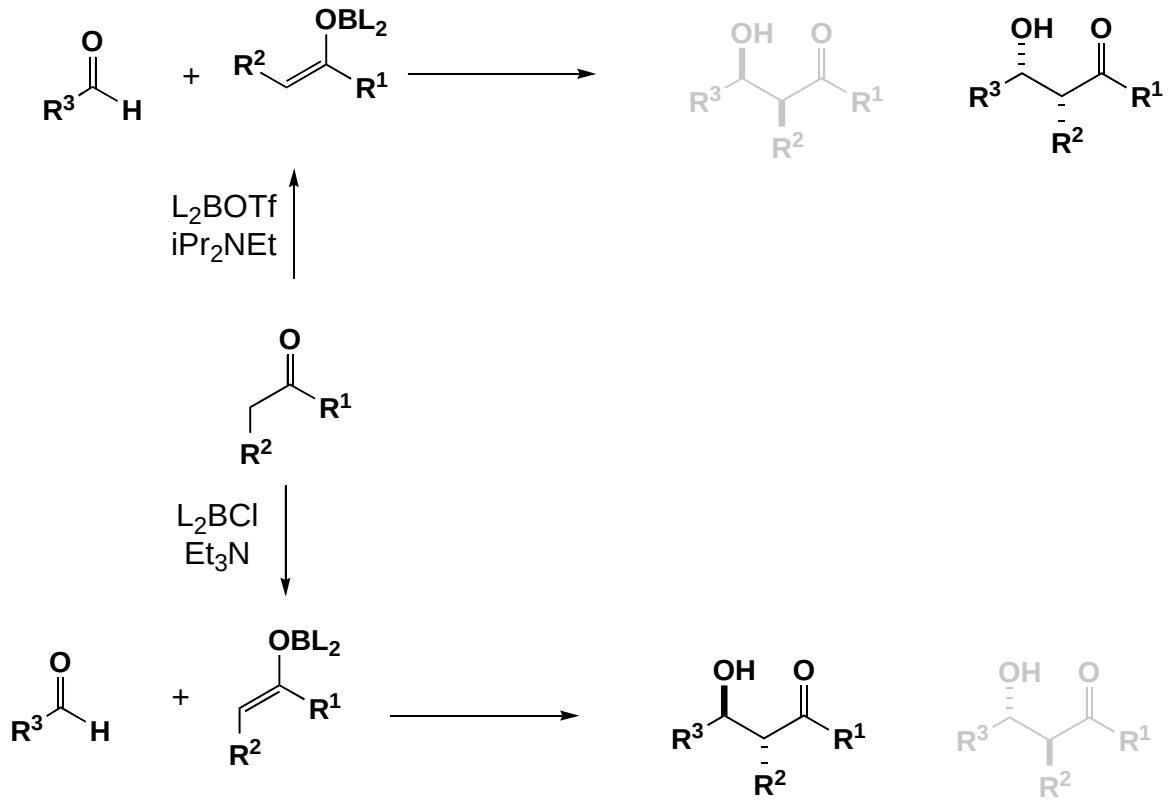
For *E*-enolborinates - chair destabilized by 1,3-diaxial repulsion (ligand ↔ enolate sidechain) - Boat A favoured

For unsubstituted enolborinate - chair disfavoured strongly (ligand ↔ enolate sidechain) - Boat A favoured

Goodman and Paton, Chem Comm 2007, 2124

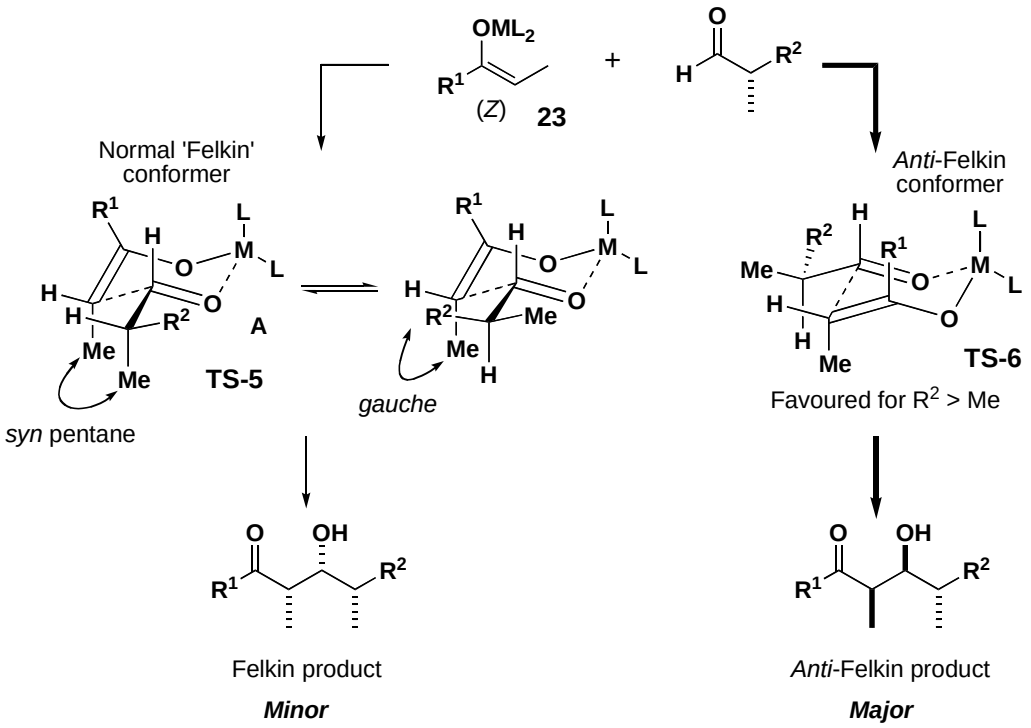
Absolute Stereocontrol in Boron Aldol Reactions

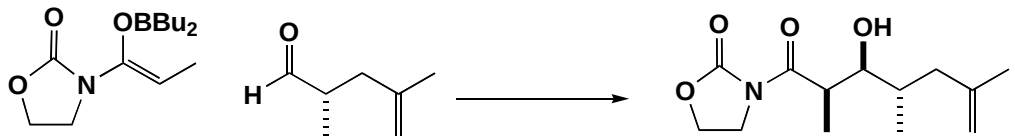
Selection of one diastereomer over an other



- **Use of chiral aldehydes where R^3 is a stereogenic group**
- **Use of auxillary control where R^1 is a stereogenic group and is subsequently removed**
- **Use of substrate control where R^1 is a stereogenic group which is retained**
- **Use of reagent control by using chiral boron reagents**

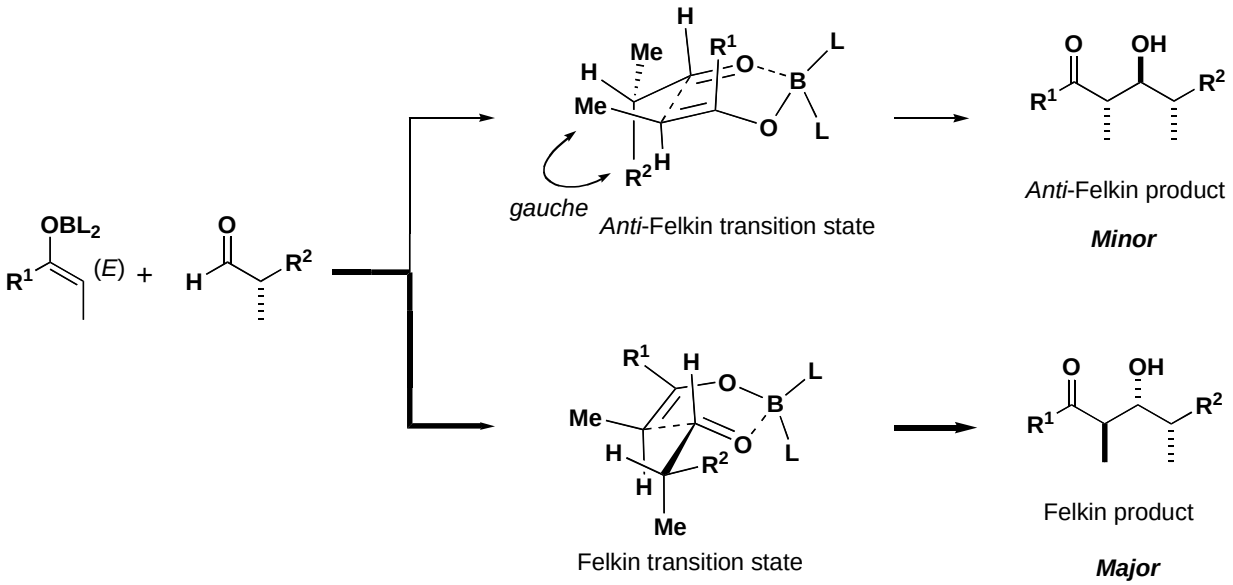
α-chiral aldehydes and (*Z*)-enolates



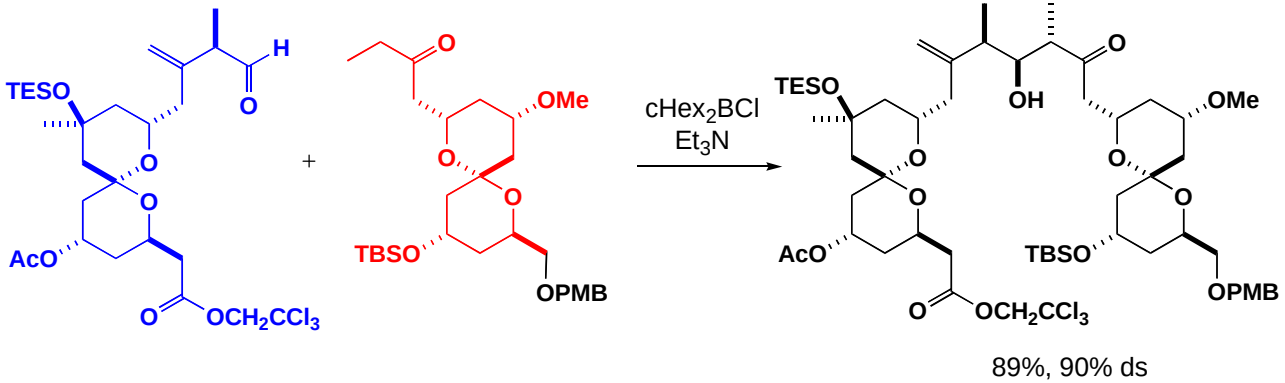


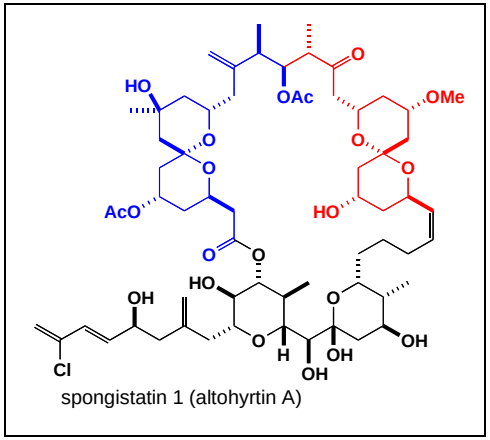
Evans & Bartoli TL 1982, 23, 807

α-chiral aldehydes and *E*-enolates



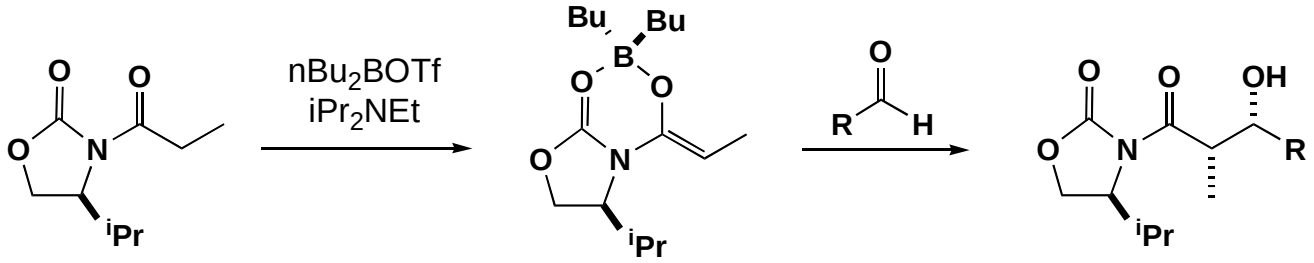
Example: Spongistatin C15-C16 bond construct





Paterson: ACIEE, 2001, 40, 4055
See also: Evans: Tetrahedron 1999, 55, 8671 (Spongistatin 2)

Chiral Auxiliaries: Evans' Oxazoladinones

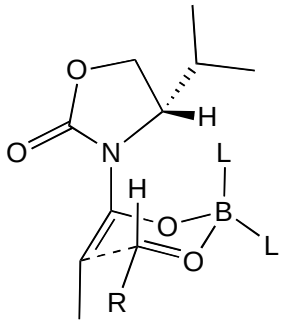


>99 : 1 for achiral aldehydes

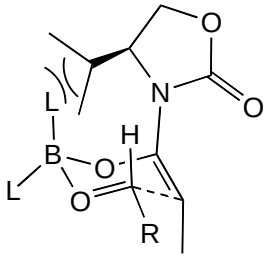
- **The benchmark** - reliable 1,2-syn aldol product via *Z*-enolate
- Facial bias of enolate overides any inherent selectivity of chiral aldehydes
- Auxillary readily available from parent amino acid (or Aldrich)
- Readily removed by hydrolysis, formation of Weinreb amide

Transition states

QuickTime™ and a
decompressor
are needed to see this picture.



Favoured



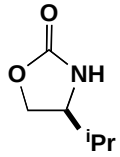
QuickTime™ and a
decompressor
are needed to see this picture.

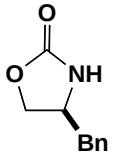
References

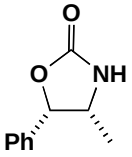
Evans et al. JACS 1981, 103, 2127; Pure Appl. Chem. 1981, 53, 1109
Calculations: Goodman and Paton, Chem Comm 2007, 2124

Chiral Auxiliaries: Evans' Oxazoladinones

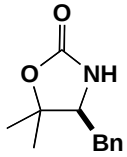
Auxiliaries





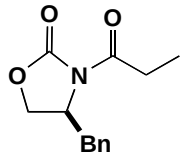


Evans et al. JACS 1981, 103, 2127; Pure Appl. Chem. 1981, 53, 1109

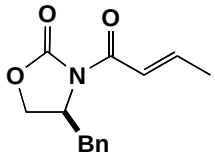


SuperQuat: Davies et al. Tetrahedron 2004, 60, 7553; OBC 2004, 2, 3385

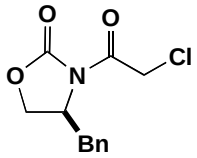
Applications



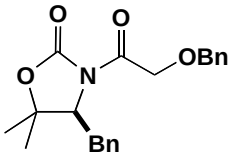
propionate



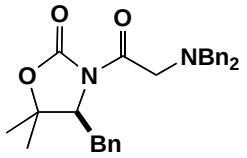
crotyl imide



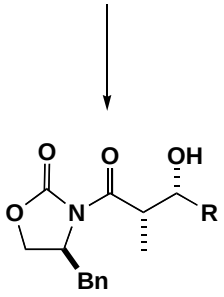
α-chloro

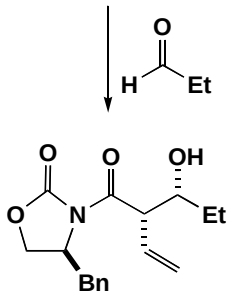


glycolate-type

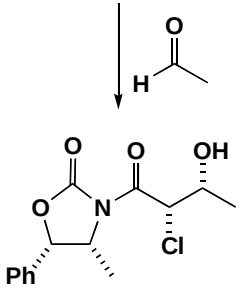


α-amino

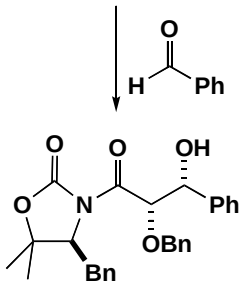


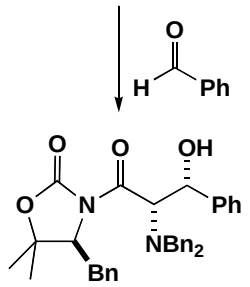


TL 1986, 27, 4957



TL 1987, 28, 39

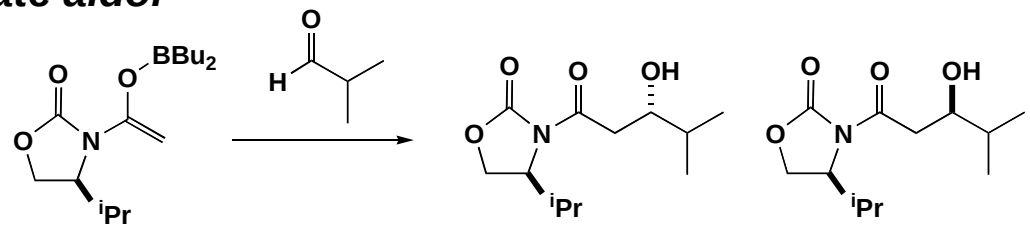




Tetrahedron 2004, 60, 7553

Chiral Auxiliaries: Evans' Oxazoladinones

Limitations - the acetate aldol



Ratio = 52 : 48

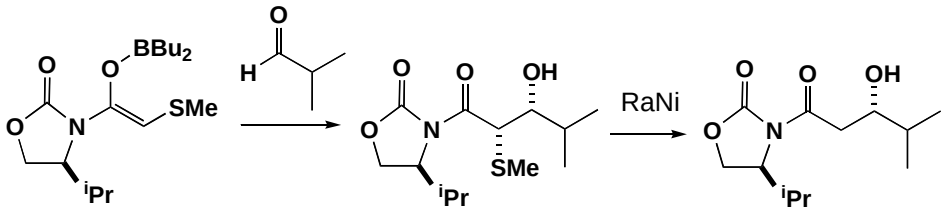
QuickTime™ and a decompressor are needed to see this picture.

QuickTime™ and a decompressor are needed to see this picture.

- ***Competing boat transition states***
- ***TS1 - iPr group occupies position pointing away from TS***
- ***TS2 - iPr group occupies position pointing towards TS***
- ***Energy difference between TSs is negligible***
- ***No selectivity***

Auxiliary-based Solutions

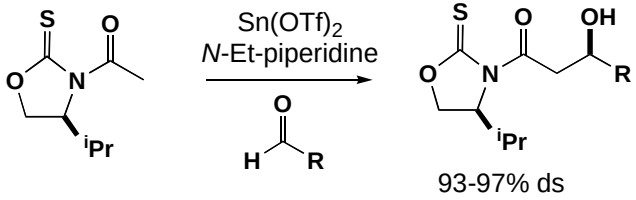
1. Introduce temporary group



98% ds

Pure Appl. Chem. 1981, 53, 1109

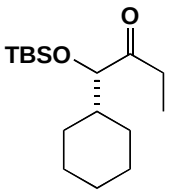
2. Nagao Sn(II) acetate aldol



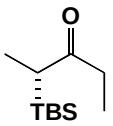
93-97% ds

Nagao et al. Chem. Soc., Chem. Commun. 1985, 1418
Nagao et al. J. Org. Chem. 1986, 51, 2391.

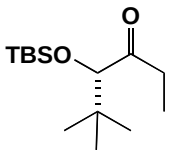
Chiral Auxiliaries: α-oxygenated ketones



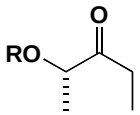
Masamune
JACS 1981, 103 1566



Enders
ACIEE 1988, 27, 581

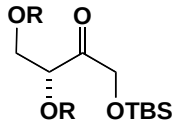


Heathcock
JOC 1991, 56, 2499



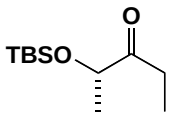
R = Bn
R = Bz

Paterson
TL 1994, 35, 9083 & 9087



R = Bn
R = Bz

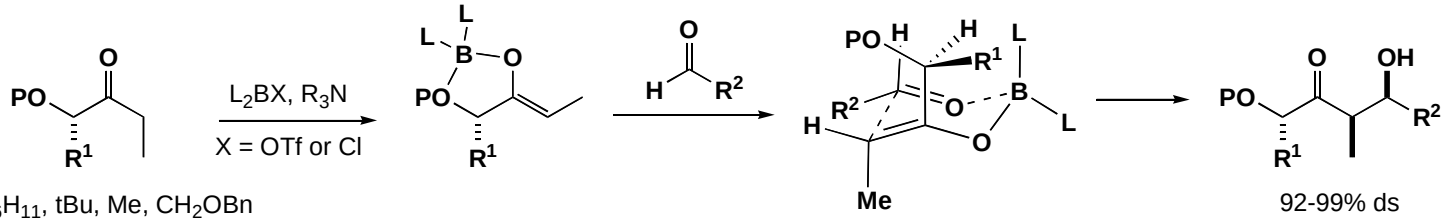
Cardo, Marco
TL 1999, 40, 6845



Romea
OL 2000, 2, 2599

- **Simple chiral ketones**
- **Use α-substituent to dictate π-facial selectivity**
- **Aldol products are the manipulated to excise directing group**

Syn aldols



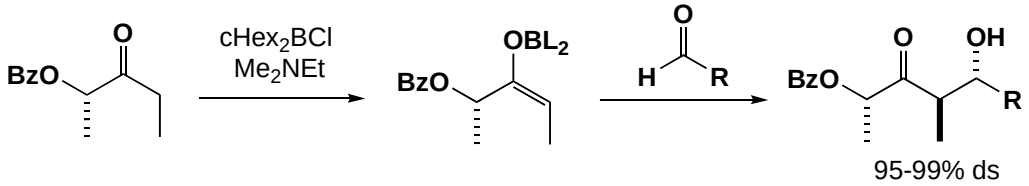
R^1 = C_6H_{11}, tBu, Me, CH_2OBn
P = TBS, TMS, Bn

92-99% ds

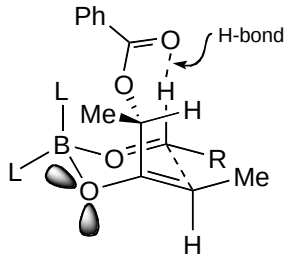
- **Preferential formation of (*Z*)-enolate due to chelation of reagent with α-alkoxy/siloxy group, independent of reagent**
- **Chair TS, in which alkoxy group aligned to oppose dipole of enolate oxygen and alkyl group is positioned to avoid steric congestion**

Chiral Auxiliaries: α-oxygenated ketones

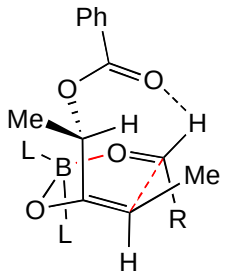
Paterson anti aldols



- **selective *E*-enolisation - α-oxygen of benzoate unable to chelate boron reagent**
- **high levels of selectivity for anti-anti diastereomer**
- **Enolate induction normally overides any other stereodifferentiating factors**



chair



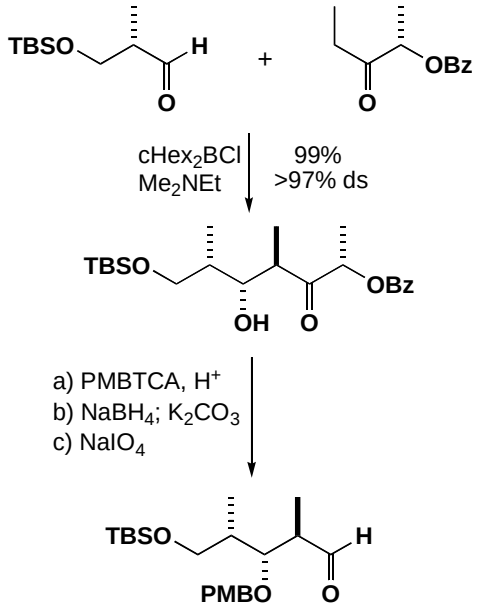
boat

- **Both chair and revised boat TSs account for π-facial selectivity**
- **Boat TS - significantly less congested**
- **A13 strain minimised between Me of enolate and α-stereocentre**
- **Contrasteric - large OBz directed in to TSs**
- **Electronic effect - lone pair repulsion between n(O) enolate and Bz group minimised and TS stabilised by H-bonding of C=O to formyl H,**

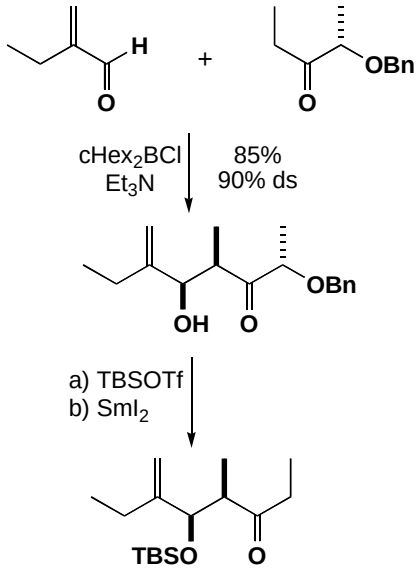
Paterson et al. Tetrahedron Lett. 1994, 35, 9083 & 9087; Synthesis 1998, 639

Chiral Auxiliaries: α-oxygenated ketones

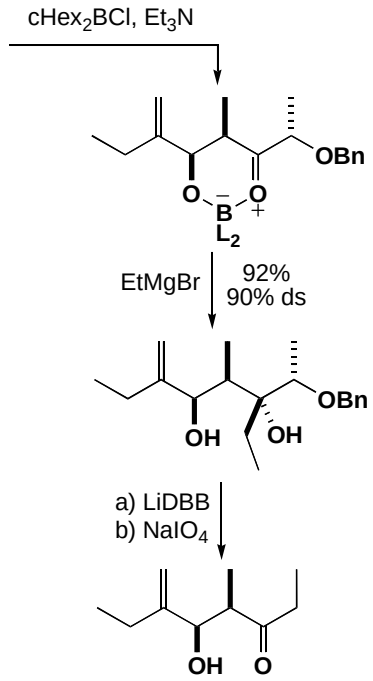
Manipulation of α-oxygenated aldol adducts



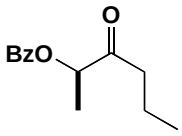
JACS 2001,123,9535



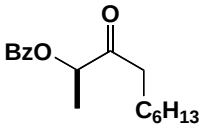
TL 1994, 35, 9087



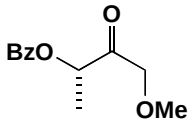
- **useful tool to incorporate *anti*-aldol motif**
- **complimentary to Evans *syn*-aldol**
- **products readily manipulated to remove superfluous stereodirecting group**
- **ketones readily available from cheap (*R*)- and (*S*)-lactate esters**
- **not limited to ethyl ketones**



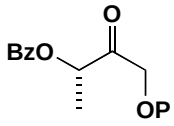
TL 1994, 35, 9083



TL 1999, 40, 393



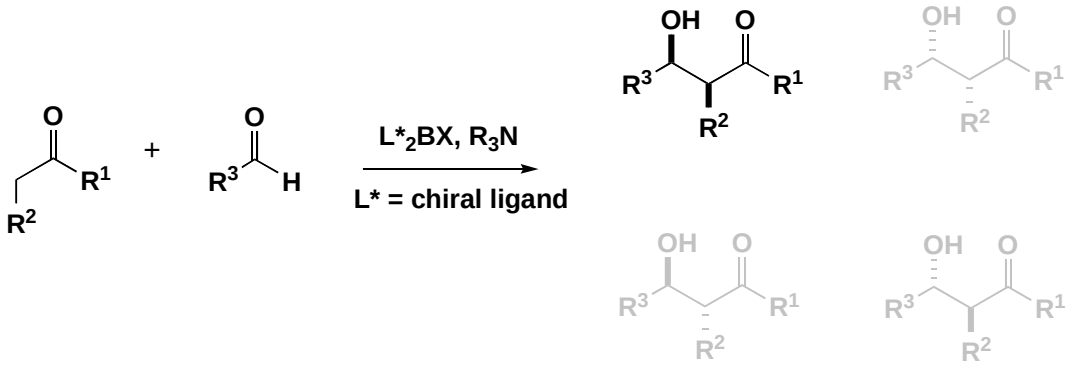
ACIEE 2000, 39, 1308



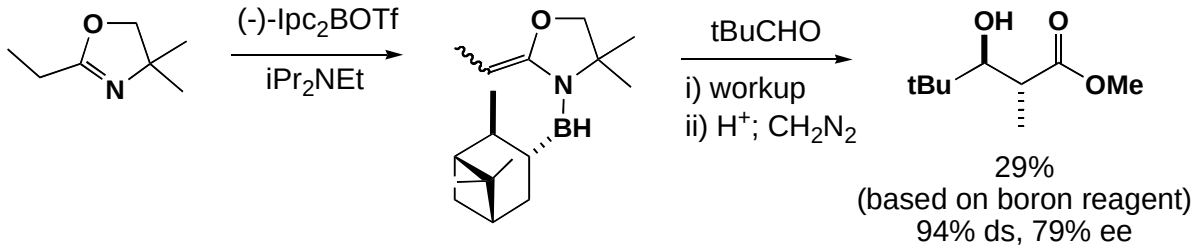
P = Bn: ***TL 1994, 35, 9087***
P = PMB: ***Shiori et al. TL* 1999, *40*, 3187**

Reagent Control

Concept : Control absolute configuration by using chiral ligands on boron

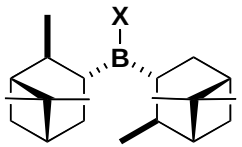


First example - Meyers and Yamamoto JACS 1981, 103, 4278

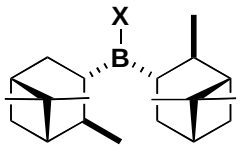


29%
(based on boron reagent)
94% ds, 79% ee

Reagent Control: Isopinocampheyl Boron Reagents



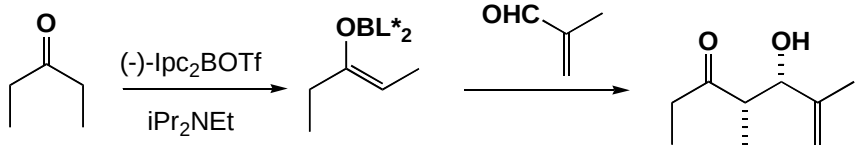
(-)-Ipc_2BX
X = Cl or OTf



(+)-Ipc_2BX
X = Cl or OTf

- **Most common chiral reagents for asymmetric boron aldols**
- **Ipc_2BCl introduced by Brown for asymmetric reduction of ketones in 1985**
- **Reagents readily prepared from (+)- or (-)-α-pinene by hydroboration**
- **Ipc_2BCl is commercially available from Aldrich, (+)- or (-)-DIPCl**
- **Ipc_2BOTf prepared *in situ* from the corresponding Ipc_2BH**

Application of Ipc-reagents for aldol reactions by Paterson



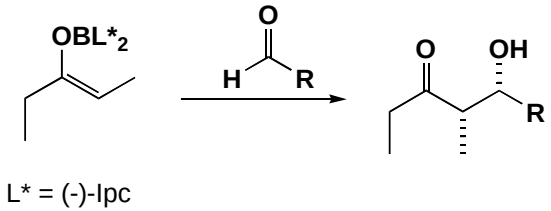
L* = (-)-Ipc

78%
98% ds, 91% ee

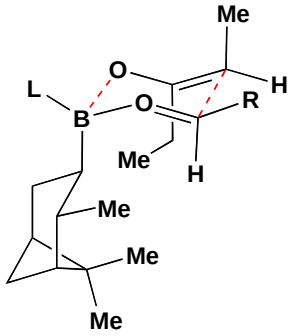
Paterson et al.
Tetrahedron Lett. 1986, 27, 4787; Tetrahedron 1990, 46, 4663; Pure Appl. Chem. 1992, 64,1821

Reagent Control: Isopinocampheyl Boron Reagents

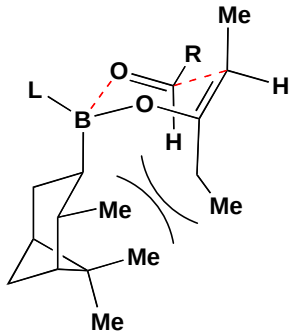
Origin of facial selectivity



L* = (-)-Ipc



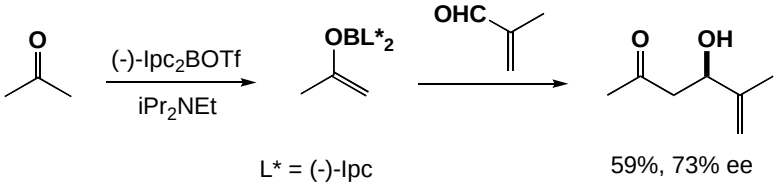
Si-face
FAVOURED



Re-face

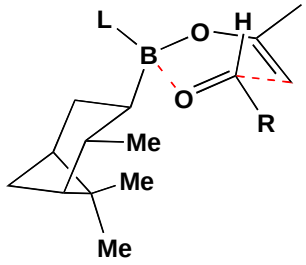
- ***Competing chair transition states***
- ***Attack on Re-face leads to unfavourable interaction between enolate sidechain and Me of pseudoaxial Ipc ligand***
- ***Calculations predict Si-face addition (88% ee) - consistent with experimental observations (66-93% ee)***

Methyl ketones

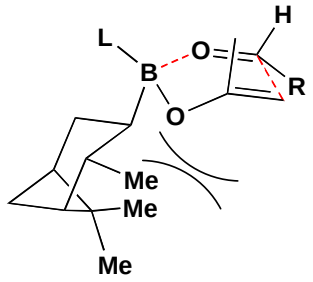


L* = (-)-Ipc

59%, 73% ee



Re-face
FAVOURED

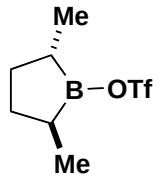


Si-face

- ***Facial selectivity is opposite***
- ***Attributed to boat-like transition state***
- ***Confirmed by calculations***

Paterson et al.
Tetrahedron Lett. 1986, 27, 4787; Tetrahedron 1990, 46, 4663; Pure Appl. Chem. 1992, 64,1821

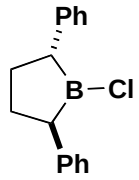
Reagent Control: C2-symmetric borolanes



Masamune

JACS 1986, 108, 8279

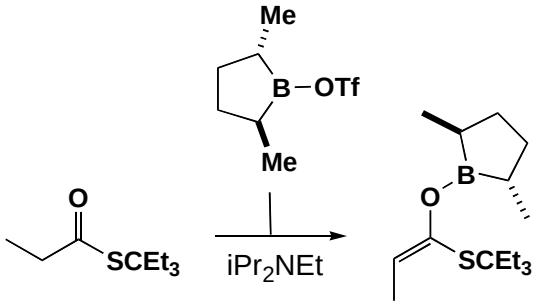
Pure Appl. Chem. 1988, 60, 1587

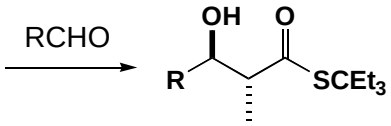


Reetz

Tetrahedron Lett. 1986, 27, 4721

Pure Appl. Chem. 1988, 60, 1607

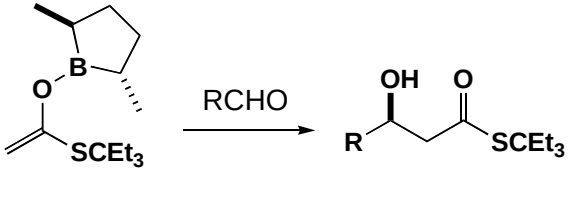




71 - 95% yield

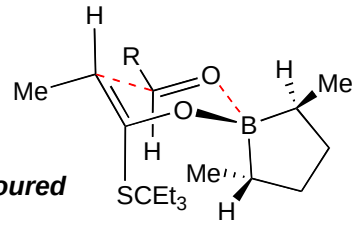
syn : anti = >30 : 1

>98% ee

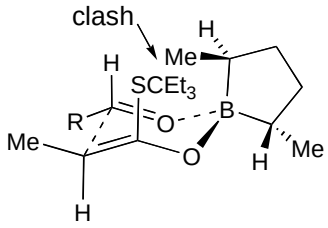


71 - 95% yield

90-98% ee



Favoured



•Enolisation of alkylthioester gives *E*-enolate, exclusively

•Selectivity rationalised by chair transition state

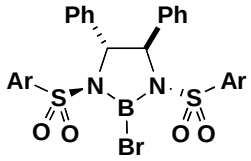
•Essentially perfect stereocontrol in *anti*-aldol products

•Comparable levels of stereocontrol are achieved in thioacetate aldol reaction

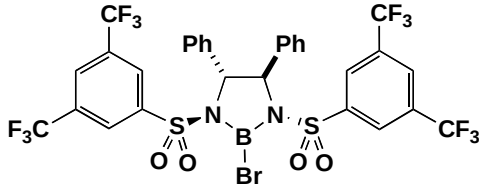
• Why is this reagent overlooked?

Practicality: Advantage of high ee outweighed by the 7-step reagent synthesis (including diastereomer separation and a resolution)

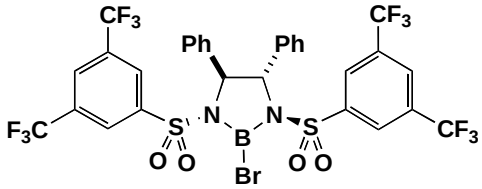
Reagent Control: C2-symmetric diazaborolidines



(*R,R*)-**2**



(*R,R*)-**1**

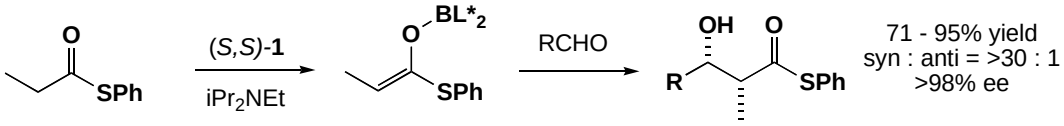


(*S,S*)-**1**

Corey

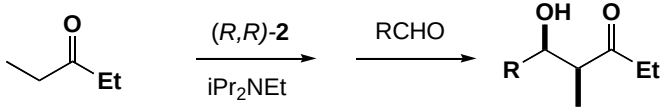
JACS 1989, 111, 5493; JACS 1990, 112, 4976;
TL. 1991, 32, 2857; TL 1993, 34, 1737

thiopropionate



71 - 95% yield
syn : anti = >30 : 1
>98% ee

diethyl ketone



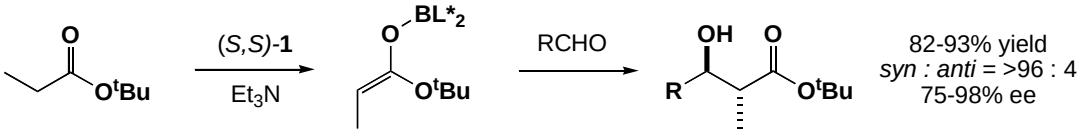
Ar = *p*-NO_2-C_6H_4

68-91% yield
syn : anti = >94 : 6
>95% ee
R= Ph, Et, iPr

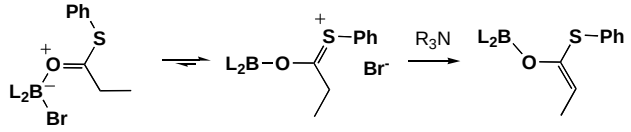
thioacetate

82-84% yield
91% ee: R = Ph
83% ee: R = iPr

t-butyl-propionate



82-93% yield
syn : anti = >96 : 4
75-98% ee



• enolisation of arylthiopropionate/ diethylketone gives *Z*-enolates, attributed to dissociation of bromide following ate formation

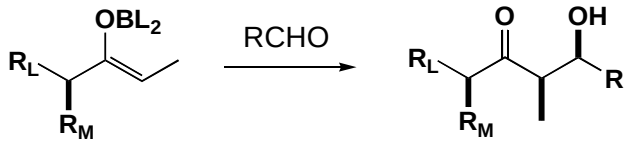
• high levels of induction
• acetate gives reverse sense of induction with high ee
• *t*-butyl propionate enolisation gives "expected" *E*-enolate

All propionate diastereomers are accessible simply by choice of starting ester and ligand

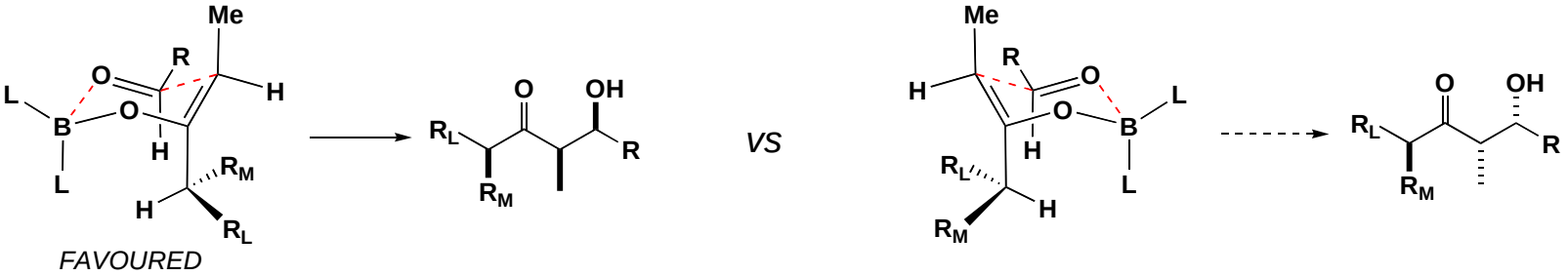
Substrate Control: Syn aldol reactions of α-chiral ethyl ketones

Substrate Control: Use stereogenic centre in a chiral ketone to control facial selectivity, which is then retained in subsequent steps

Syn aldol reactions



R_L = large group, R_M = medium group



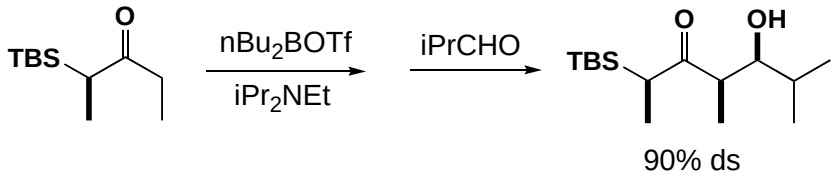
In general,

- **reaction of α-chiral (*Z*)- boron enolates governed by sterics to give *syn-syn* adduct**
- **favoured TS, A(1,3) strain and steric interactions are minimised by R_L pointing away from chair TS**
- **also applicable to titanium aldols ($TiCl_4$, Hunig's base)**

Evans, *JACS 1991, 113, 1047*

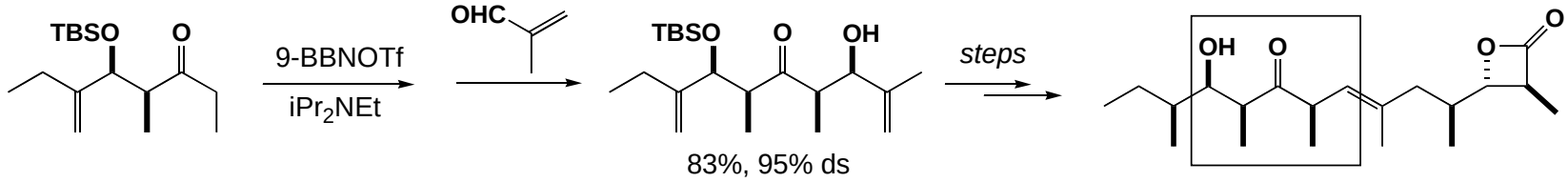
Substrate Control: Syn aldol reactions of α-chiral ethyl ketones

Examples



90% ds

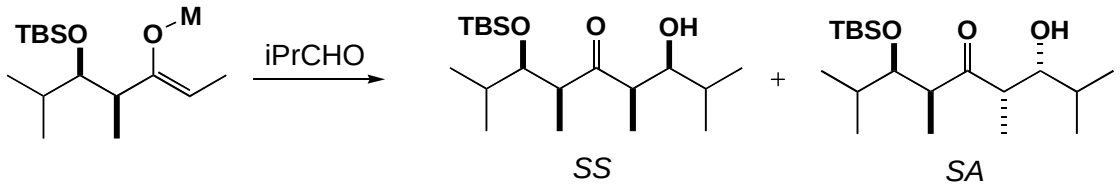
Enders
ACIEE 1988, 27, 581



83%, 95% ds

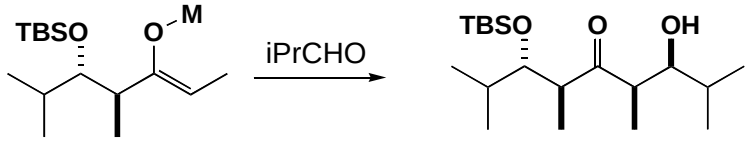
ebelactone A
Paterson and Hulme JOC, 1995, 60, 3288

Comparison of metal (Z)-enolates



SS *SA*

M	Yield (%)	*SS : SA*
$TiCl_n$	96	96 : 4
9-BBN	66	92 : 8
Li	85	17 : 76 : 7(*anti*)



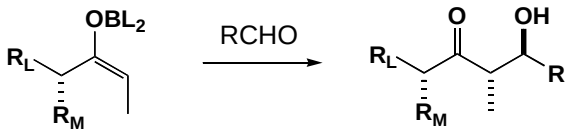
M = $TiCl_n$: 95% ds
M = 9-BBN: 92% ds

Titanium: ***Evans JACS 1991, 113, 1047***
Boron: ***Evans TL, 1995, 36, 9245***
Lithium: ***McCarthy JOC 1987, 52, 4681***

•configuration of β-silyloxy has limited effect on selectivity

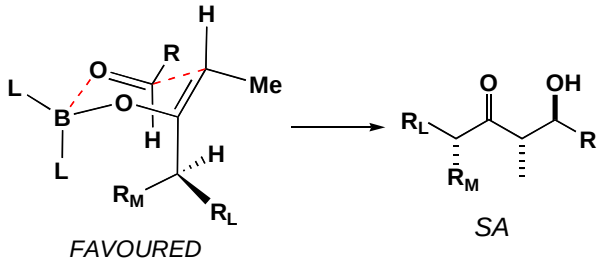
Substrate Control: Anti aldol reactions of α-chiral ethyl ketones

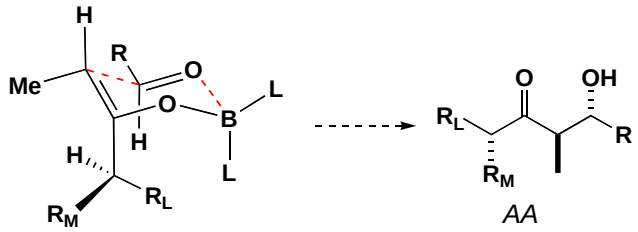
In general



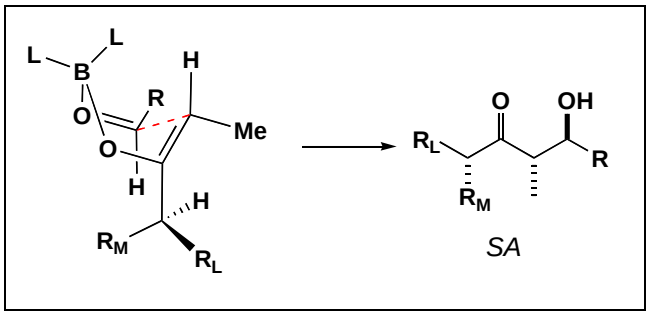
R_L = large group, R_M = medium group

Anti aldol with (*E*)-enolate under steric control gives syn-anti diastereomer





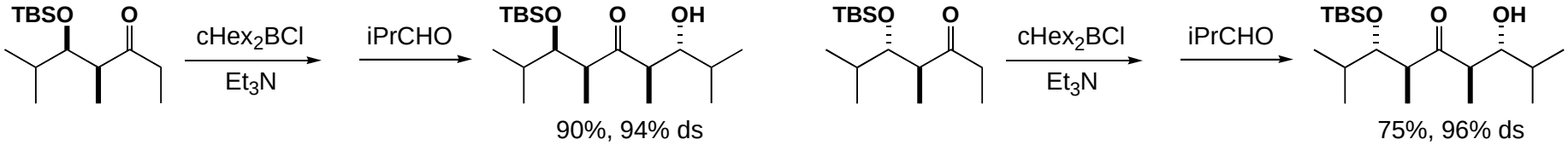
- **A(1,3) strain is minimised between α-substituent and Me group of enolate in proposed chair TSs**
- **large group orientated away in favoured TS (chair)**
- **Boat-type TS can also be envisaged - same stereochemical outcome**



Evans: Tetrahedron 1992, 48, 2127; JACS 1995, 117, 6619

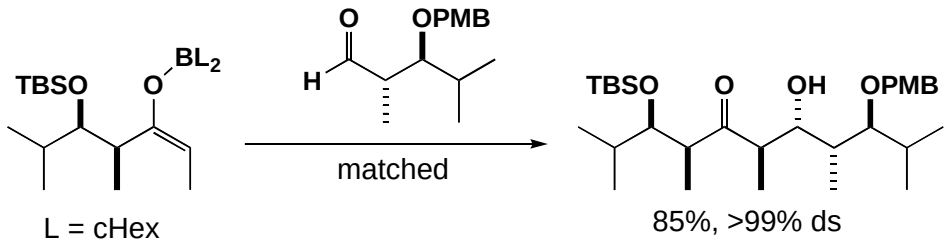
Substrate Control: Anti aldol reactions of α-chiral ethyl ketones

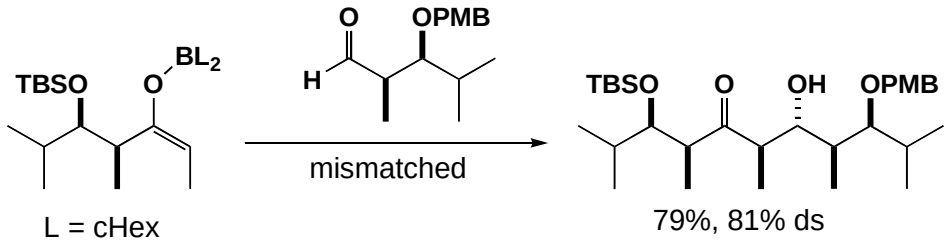
Examples: Steric Control



Evans: Tetrahedron 1992, 48, 2127

With α-chiral aldehydes

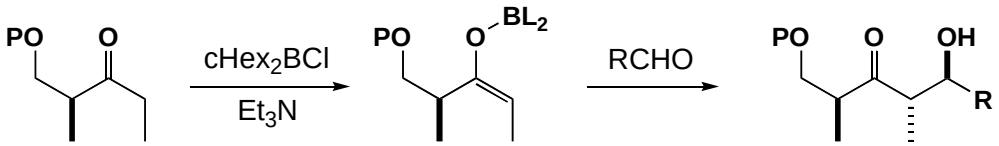




Evans: JACS 1995, 117, 6619

Substrate Control: Anti aldol reactions of α-chiral ethyl ketones

Paterson's α-chiral ethyl ketone building blocks

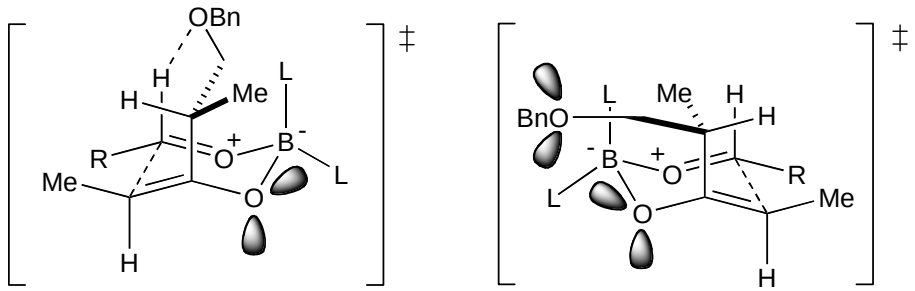


P = Bn, PMB, DMB

L = cHex

AA : >95% ds

- **Anti-anti diastereomer formed with high selectivity**
- **Proven building block for assembly of polypropionate units in natural products**
- **Both enantiomers readily available from commerical (*R*)- or (*S*)-Roche ester**
- **Does not follow steric TS model - electronic effect**



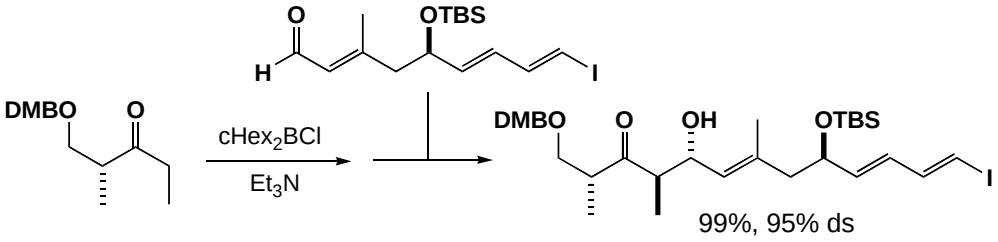
***Favoured re*-face**

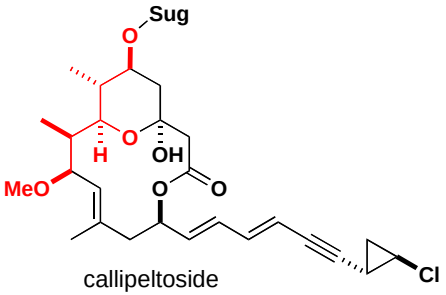
***Disfavoured si*-face**

TL 1989, 30, 7121; Pure Appl. Chem. 1992, 64,1821; JACS 1994, 116, 11287
Modeling: Tetrahedron 1993, 49, 685

Substrate Control: Anti aldol reactions of α-chiral ethyl ketones

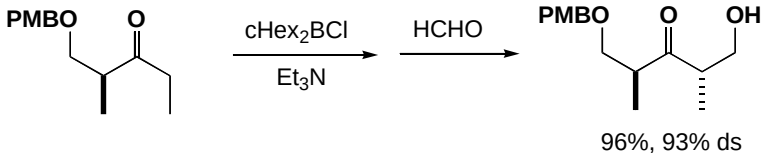
Applications in synthesis





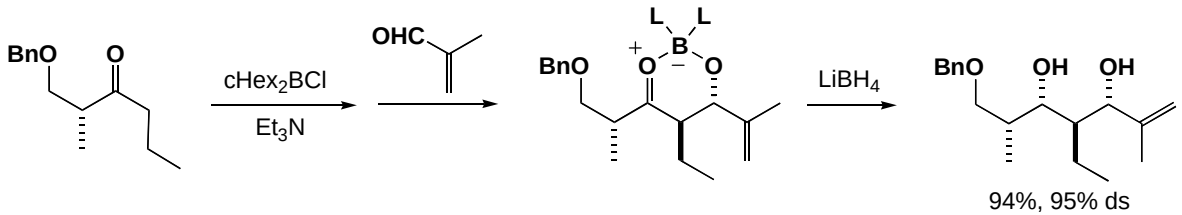
OL 2003, 5, 4477
Pure Appl. Chem. 2008, 80, 1773

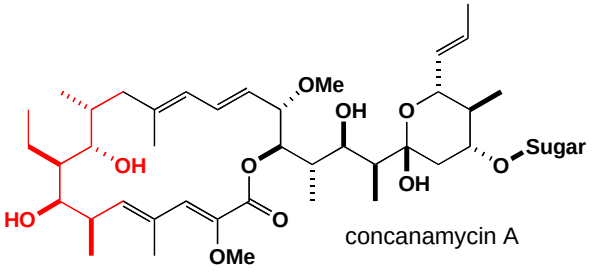
Formaldehyde aldol



discodermolide
OL, 2003, 5, 35;
JOC 2005, 70, 150

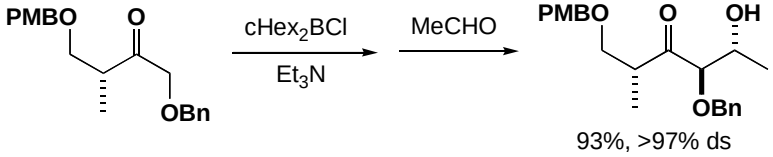
Propyl ketone with in-situ reduction





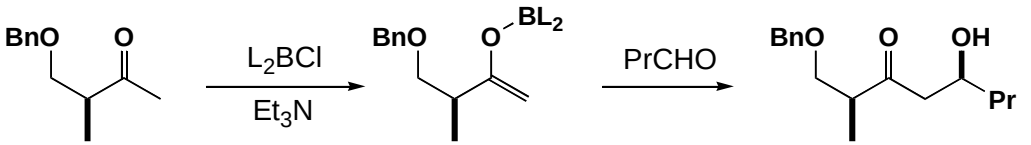
TL 1997, 38, 4183
ACIEE 2000, 39,1308
In situ reduction: TL 1992, 33,801; Tetrahedron 1996, 52, 811

Benzyloxymethyl-ketone

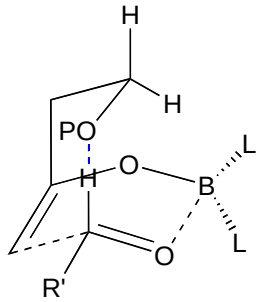


spongistatin 1
TL **1997**, *38*, **5727**
ACIEE, 2001, 40, 4055

Substrate Control: Aldol reactions of α-chiral methyl ketones



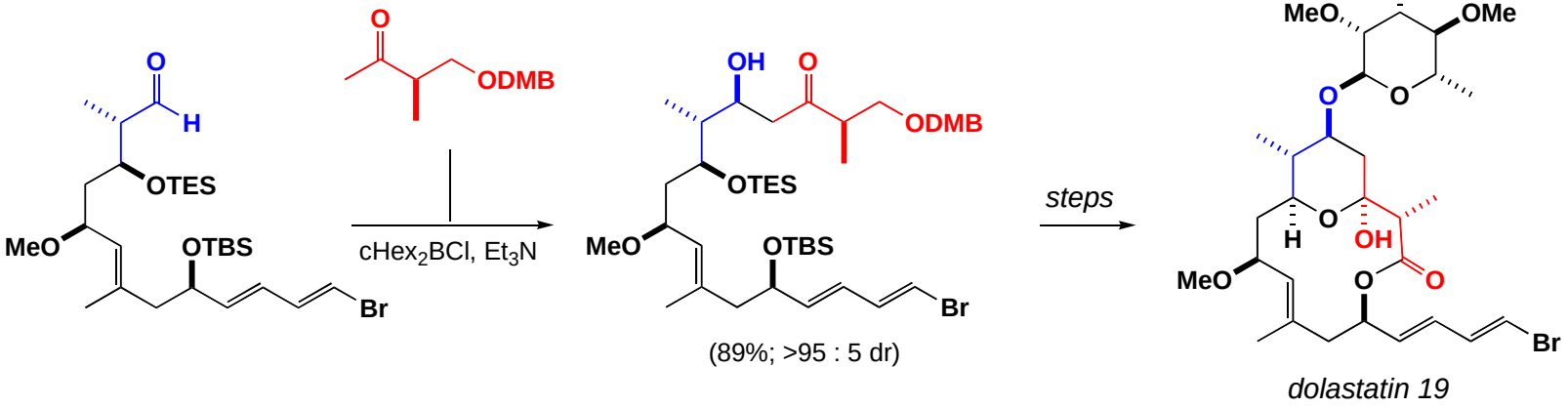
1,4-syn
L = cHex: 88% ds
L = (-)-Ipc: 92% ds



- ***Boron aldol reaction of methyl ketone gives 1,4-syn adduct***
- ***Level of selectivity can be increased by using chiral ligand system***
- ***Sense of induction in line with analogous ethyl ketone***
- ***Rationalised by boat TS- formyl H-bond stabilises favoured TS***

Paterson, Goodman, Isaka, TL 1989, 30, 7121
TS Calculations: Goodman and Paton OL, 2006,8, 4299

Application



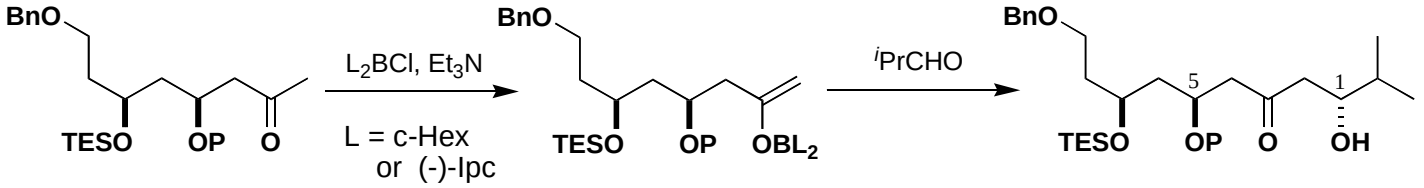
(89%; >95 : 5 dr)

dolastatin 19

OL, 2006, 8, 2131; Tetrahedron 2007, 63,5806
Pure Appl. Chem. 2008, 80, 1773

Substrate Control - β-oxygenated methyl ketones

1,5-anti induction

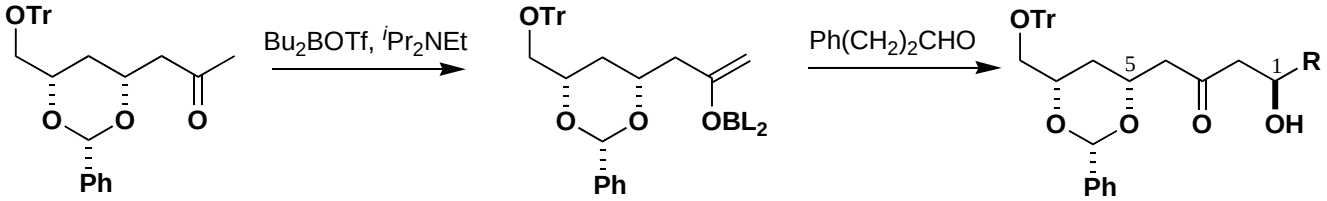


1 : P = PMB
2 : P = TBS

P = PMB
P = TBS

entry	ketone	L	ds[a] (yield)
1	**1**	c-Hex	92 (78)
2	**1**	(-)-Ipc	96 (71)
3	**2**	c-Hex	77 (80)
4	**2**	(-)-Ipc	95 (84)

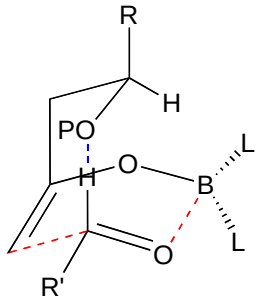
Paterson et al. TL 1996 37, 8585



R = $(CH_2)_2Ph$

(70%, >95% ds)

Evans et al. JOC 1997, 62, 788; JACS 2003, 125, 10893



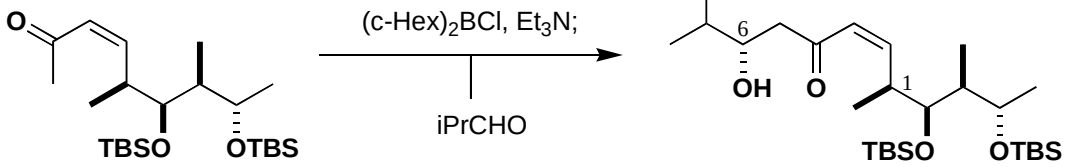
1,5-Anti‡
Favoured

- ***High levels of 1,5-anti induction from methyl ketones with bearing β-alkoxy group***
- ***Numerous applications in polyacetate natural products since discovery***
- ***Rationalised by boat TS - formyl H-bond and R group points away***

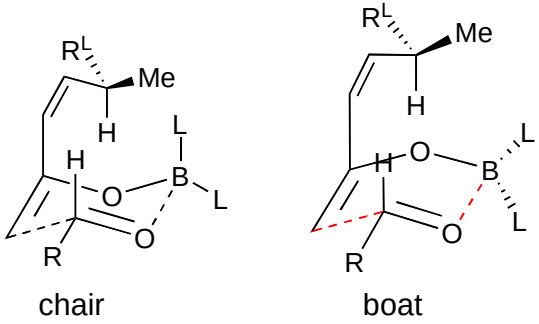
Goodman and Paton OL, 2006, 8, 4299

Substrate Control: 1,6-induction - the limit of induction?

γ–methyl-(Z)-enones



99%, 81% ds



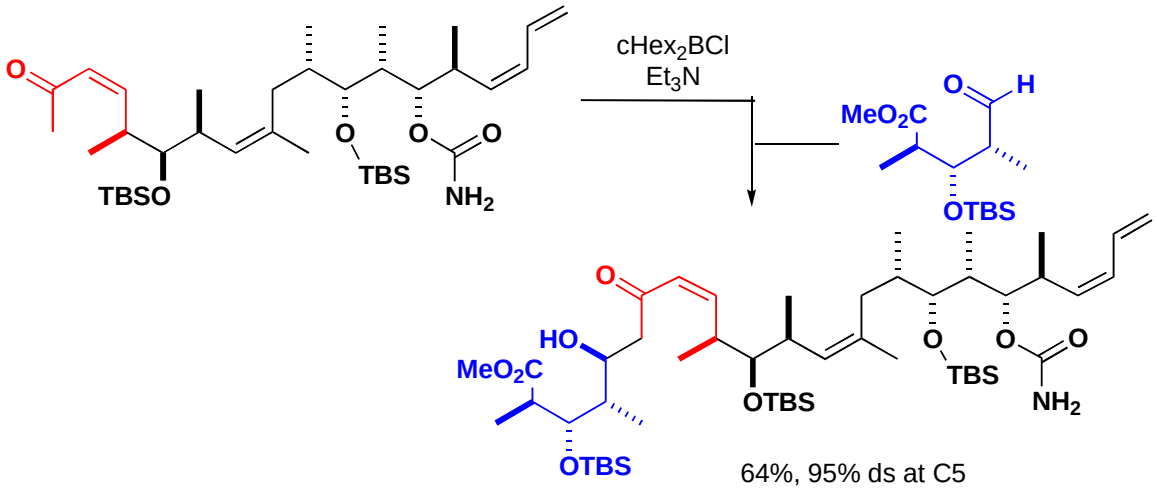
working models

dienolate in s-trans conformation

A(1,3) strain minimised

sterics control facial selectivity

Application



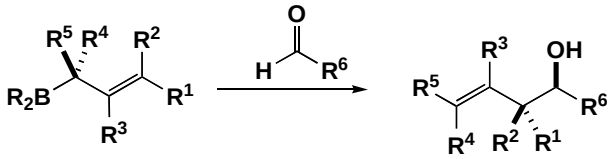
64%, 95% ds at C5

Paterson et al. OL 2003, 5, 35; JOC, 2005, 70, 160

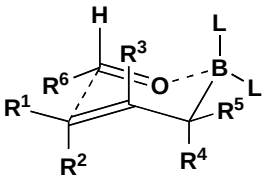
Allylboration Reactions

Allylboration and Crotylboration: Introduction

General process



via



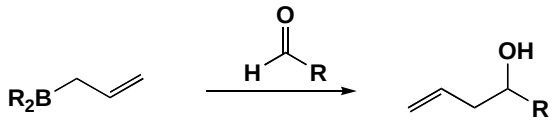
M—C → B—C

2.0-2.2 Å 1.5-1.6 Å

- ***Transfer of allyl group to an aldehyde via highly ordered cyclic TS***
- ***Reaction proceeds via 6-membered Zimmerman-Traxler transition state***
- ***High levels of relative stereocontrol from tight TS - short B-C bonds***
- ***Control of absolute stereochemistry typically by using chiral boron ligands***

Typical applications

Allylation



Crotylation

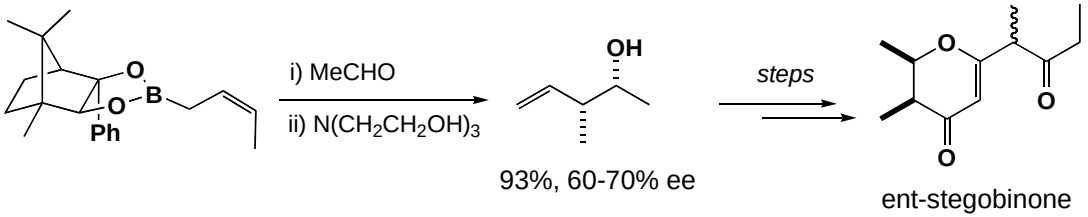
(*E*)-crotylborane *anti*-product (*Z*)-crotylborane *syn*-product

First examples reported by R. W. Hoffmann in late 70's
Developments through 80's - 90's paralleled those in asymmetric aldol methodology and continue today
Resulting terminal olefin can then be elaborated or retained as a masked functionality to be revealed at a later point

Using pinacol-based reagents: Hoffmann & Zeiß ACIEE 1979, 18, 306; JOC 1981, 46, 1309

Asymmetric Allylboration: Chiral Boronic Esters

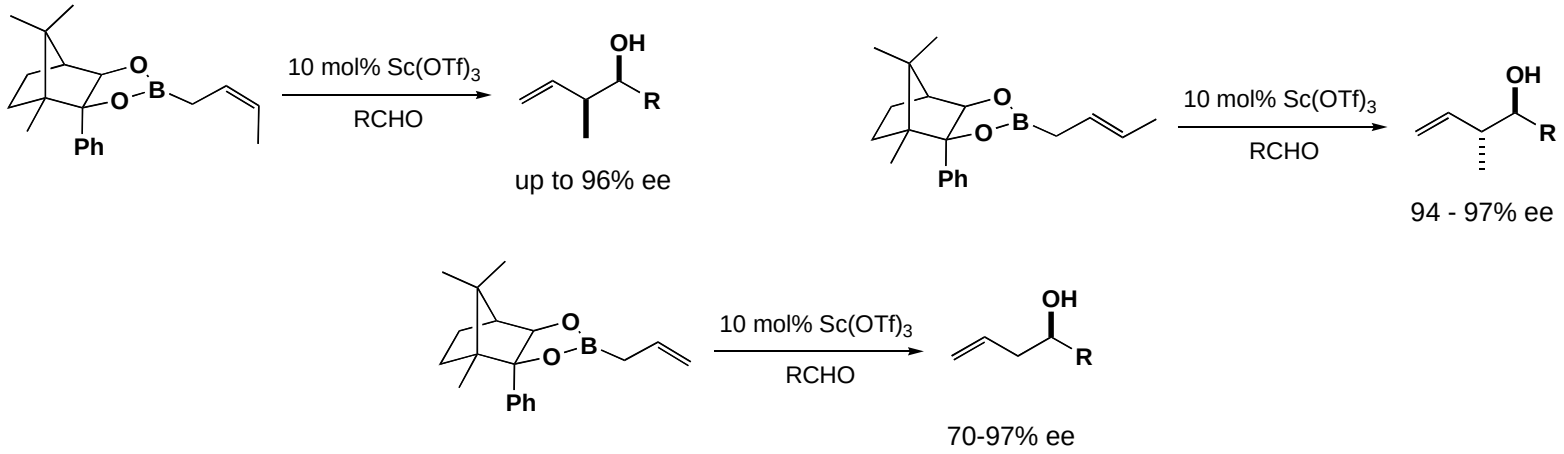
Hoffmann - 1979



First example of asymmetric allylboration using camphor-based scaffold

Hoffmann et al. ACIEE 1978, 17, 768; TL 1979, 48, 4653

Hall redesign - 2003

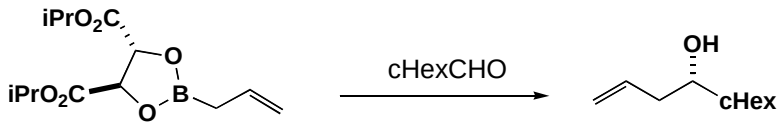


- ***Subtle redesign of original Hoffmann system***
- ***Movement of Ph-group and use of catalytic scandium triflate boosts ee***

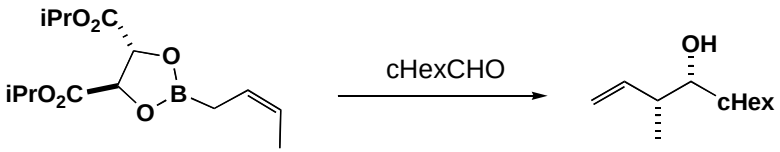
Hall et al. JACS 2003, 125, 10160; Synthesis 2004, 1290

Asymmetric Allylboration: Chiral Boronic Esters

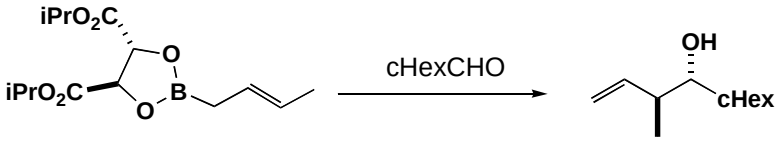
Roush's tartrate-derived systems - 1985



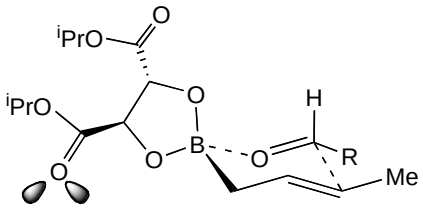
72%, 87% ee



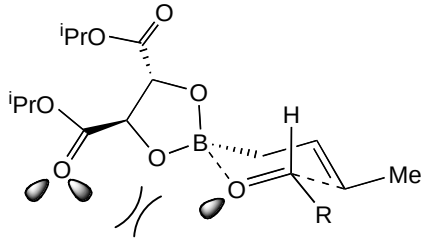
90%, 83% ee



>99%, 91% ee



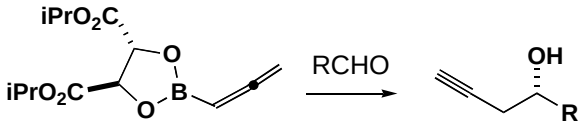
Favoured



- *Practical and predictable system using tartrate ester derivatives*
- *available in either enantiomeric form*
- *Favoured transiton state minimises interaction of aldehyde and ester lone pairs*

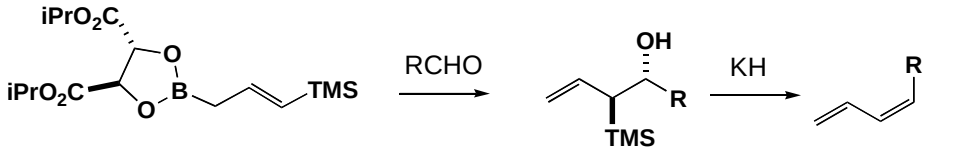
Roush et al. JACS 1985, 107, 8186; TL 1988, 29, 5579

Variations



56%, 92% ee

Yamamoto et al. JACS 1982, 104, 7667

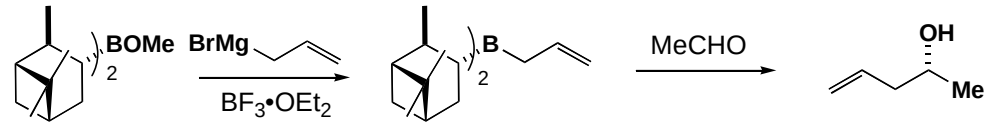


Z-diene >20:1

Roush et al. TL 1990, 31, 7563; TL 1992, 48, 1981
Myles et al. JOC 2003, 68, 6646

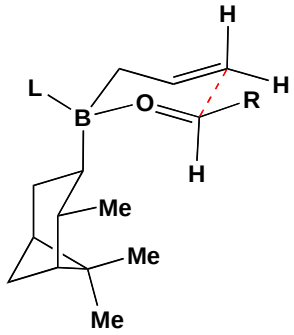
Asymmetric Allylboration: Brown's Ipc-Reagents

Allylation

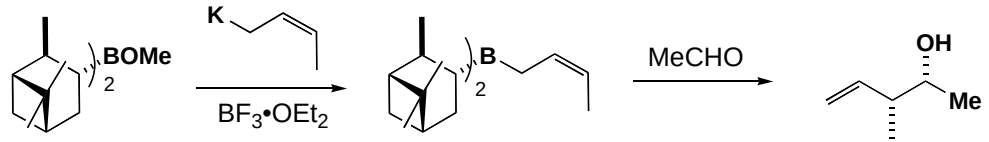


(-)-Ipc$_2$BOMe

>99% ee

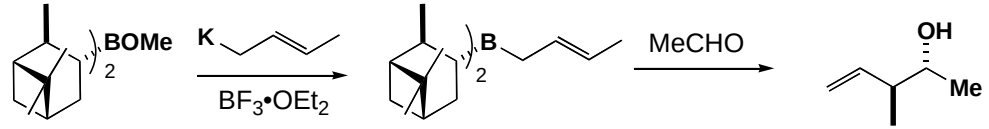


Crotylation



(-)-Ipc$_2$BOMe

99% ds, 96% ee



(-)-Ipc$_2$BOMe

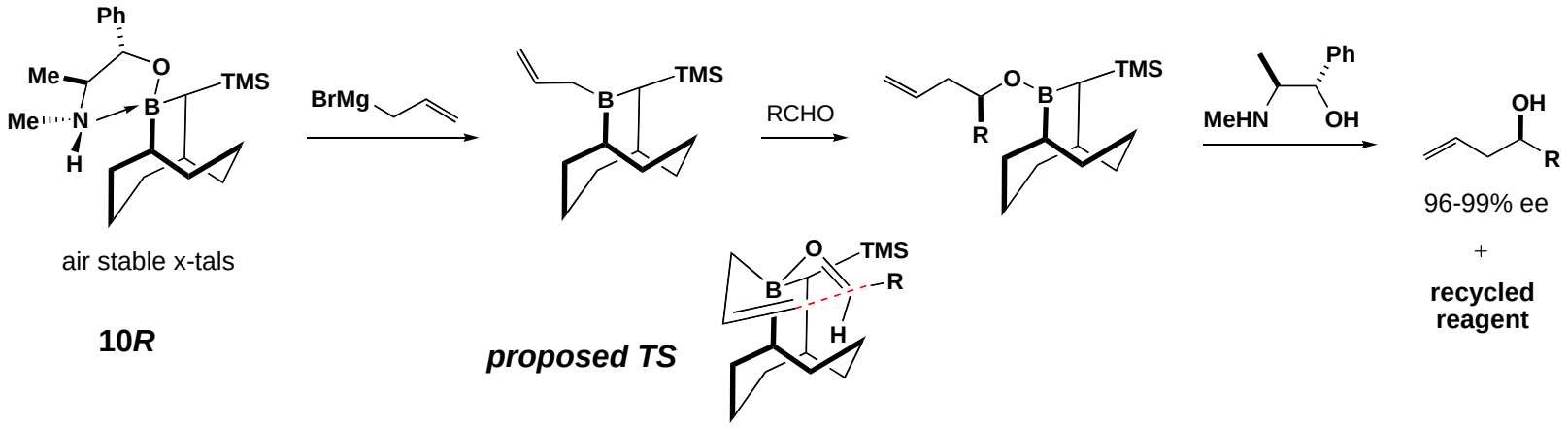
99% ds, 96% ee

- ***Deprotonation of (Z)- or (E)-2-butene with Schlosser's base at -78 °C gives respective anion***
- ***Formation of reagent by addition of Ipc$_2$BOMe, followed by BF$_3$•OEt$_2$ to break-up ate complex***
- ***Reaction with aldehydes proceeds with high selectivities***
- ***Ipc$_2$BOMe commercially available from Aldrich in either enantiomeric form***

Brown et al.
Allylation: JACS 1983, 105, 2092; JOC 1991, 56, 401
Crotlyation: JACS 1986, 108, 293; JACS 1988, 110, 1535
Full paper: JOC 1986, 51, 432

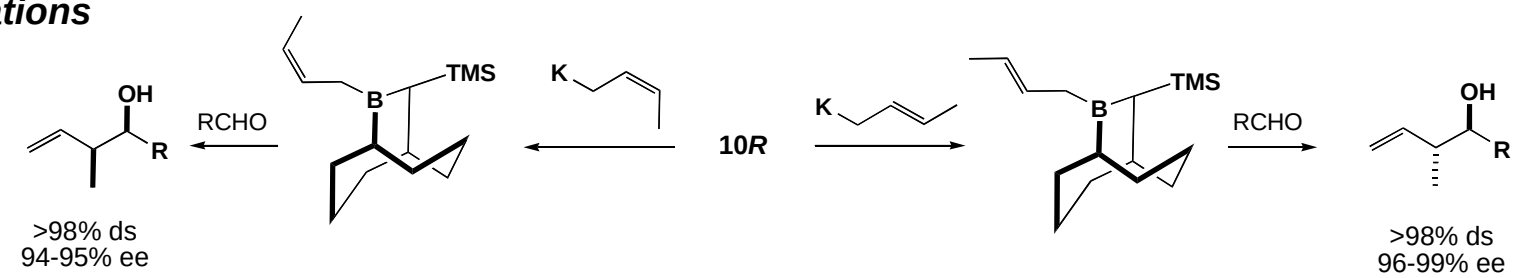
Asymmetric Allylboration: Soderquist's 10-TMS-9-BBD Reagents

Allylations



- ***Treatment of precursor 10R with allylMgBr generates allylborane reagent in situ***
- ***allylation of aldehyde proceeds through proposed TS***
- ***allyl group points away from 10-TMS group***
- ***R group of aldehyde minimises steric interaction with BBD ring system***
- ***10R recovered by refluxing with (S,S)-pseudoephedrine***

Crotylations



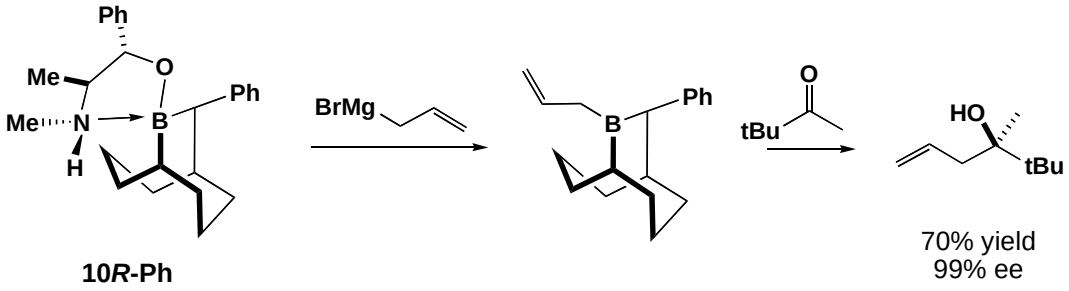
Using (S,S)-pseudoephedrine reagent recovery

Initial disclosure: Soderquist et al. **ACS Symposium Series 783, Organoboranes for Synthesis, P. V. Ramachandran, H. C. Brown, Ed., Ch 13, pp 176-194, American Chemical Society, Washington, DC, 2000.**

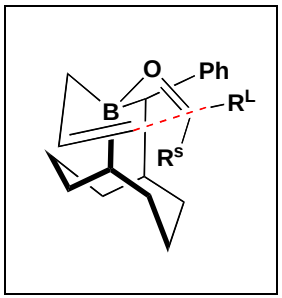
Soderquist et al. JACS 2005, 127,8044

Asymmetric Allylboration: Soderquist's 10-Ph-9-BBD Reagents

Ketone Allylations



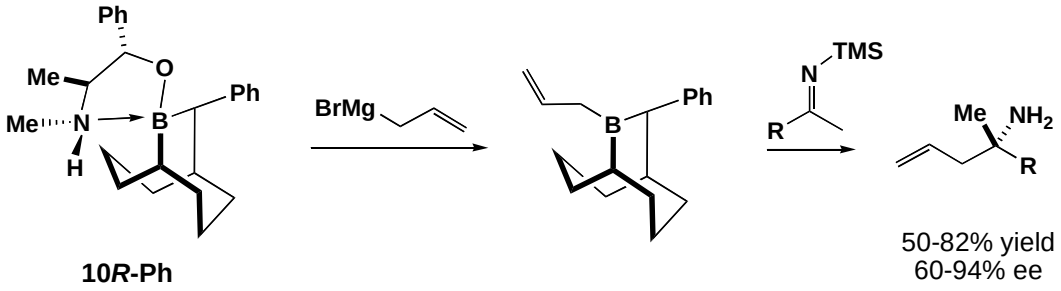
10*R*-Ph



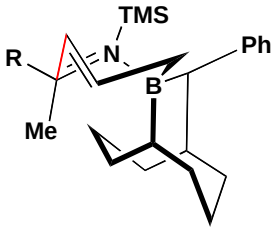
- *10R-Ph adopts chair-like conformation on side of Ph-group - larger chiral pocket for small group of ketone*
- *Allows ketone allylation- phenyl group is smaller than corresponding 10R-TMS*
- *10R recovered by refluxing with (S,S)-pseudoephedrine*

Soderquist et al. JACS 2005, 127,11572

Ketimine allylation



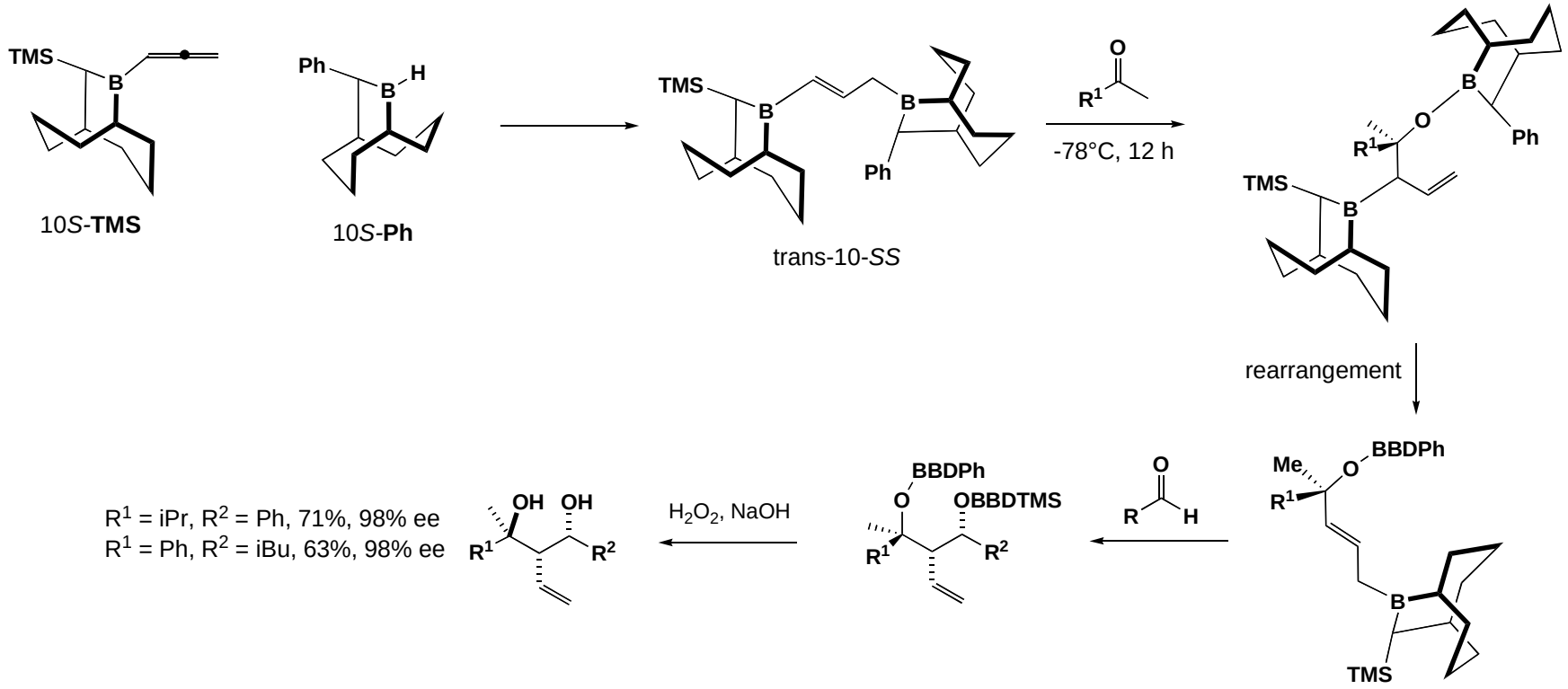
10*R*-Ph



- *10R-Ph allylation used to prepare series of enantiomeric enriched 3° carbamines*
- *Powerful solution to access rare motif*
- *NB - sense of induction opposite to carbonyl additions*
- *Ketimine approaches trans to Ph group*

Soderquist et al. JACS 2006, 128, 8712

Asymmetric Allylboration: Soderquist's Double Allylation



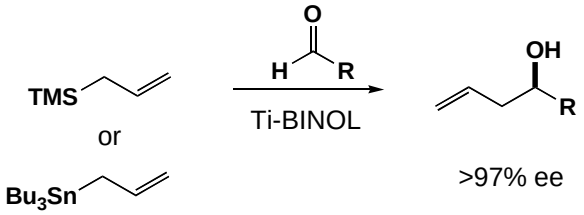
- ***Hydroboration of 10S-TMS with 10S-Ph gives diboron reagent***
- ***Ketone allylation followed by borotropic rearrangent***
- ***Subsequent aldehyde allylation and oxidative work-up gves 1,3-diols with essentially complete ds and ee***
- ***Variation of reagent configuration gives access to further diastereomers by design***

Soderquist et al. JACS 2009, 131, 1269

Catalytic Asymmetric Ketone Allylboration

Last decade has seen significant advances in catalytic asymmetric protocols

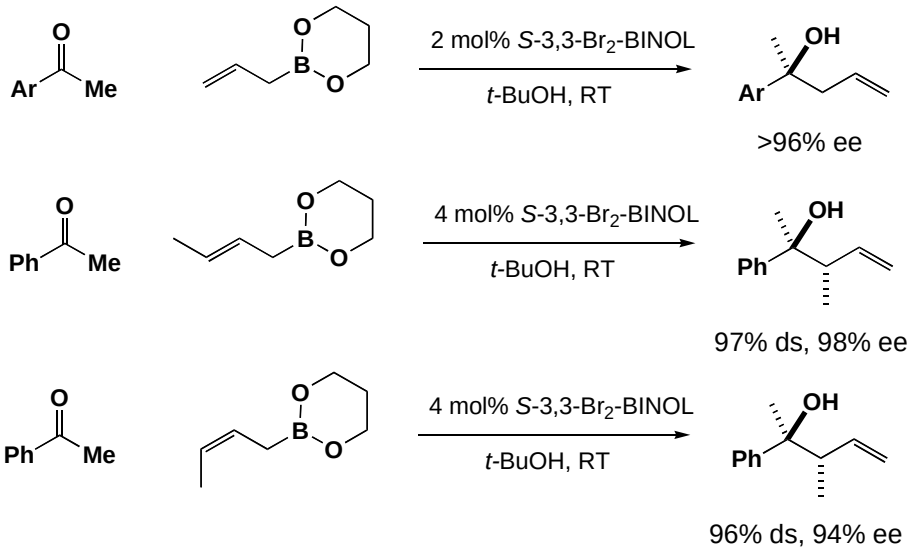
Aldehyde allylation dominated by use of Ti-BINOL-type catalysis with allylsilanes or allylstannanes

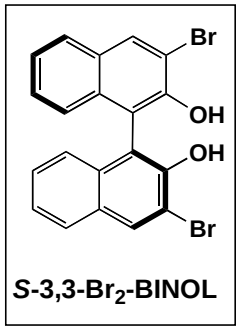


Tagliavini et al. Org Lett 1999,1,1061
Maruoka et al. TL 2001, 42,1935

Ketone allylation remained a significant hurdle until 2006:

Schaus's organocatalytic allylboration



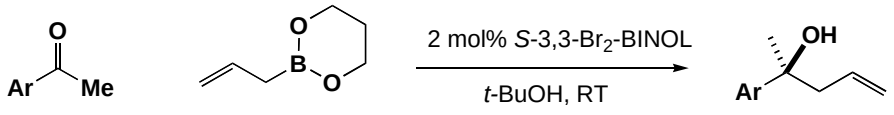


Shibasaki reported CuF_2-DUPHOS system in 2004 (~80% ee)
JACS 2004, 126, 8910; For review, see: Chem. Rev. 2008, 108, 2853

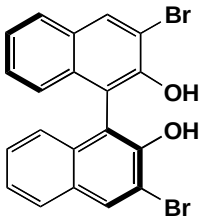
Schaus et al.
Original report: JACS 2006, 128, 12660
Optimised reaction: ACIEE, 2009, 48, 1

Schaus's organocatalytic allylboration

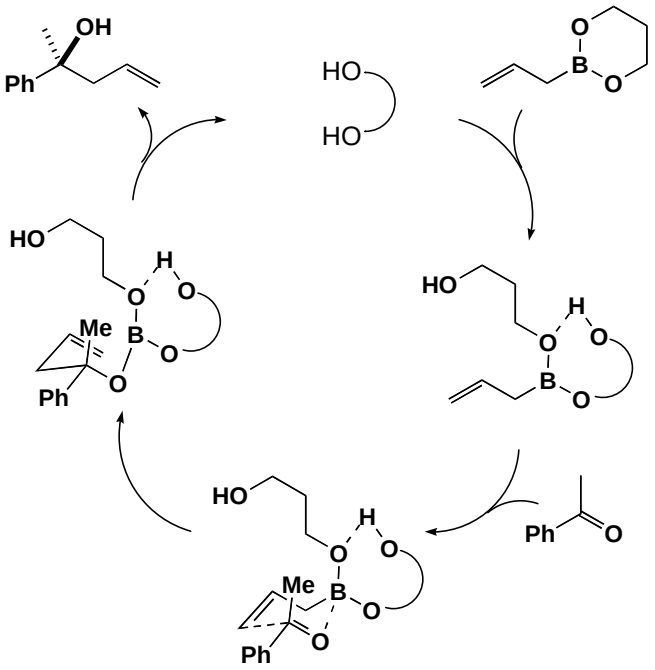
Catalytic Cycle

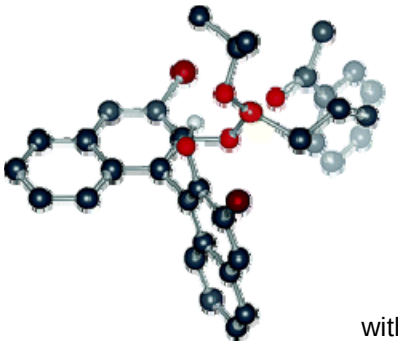


>96% ee

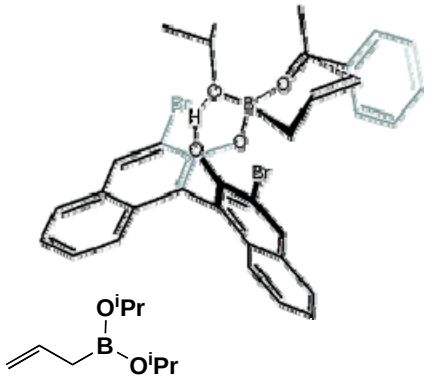


***S*-3,3-Br$_2$-BINOL**



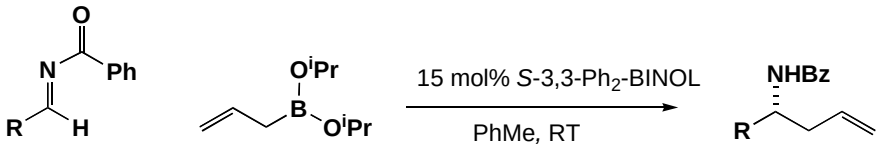


with



Schaus et al.
Original report: JACS 2006, 128, 12660
Optimised reaction: ACIEE, 2009, 48, 1

With acyl imines



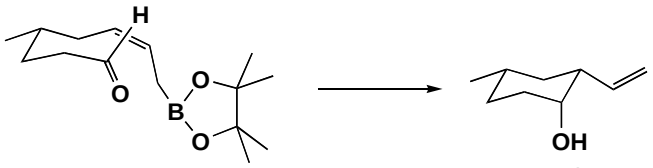
R= alkyl, aryl
91-98% ee

- ***NB - reversal of facial selectivity***
- ***High ee's***
- ***Crotylations also very efficient***

Original report: JACS 2007, 129, 15398

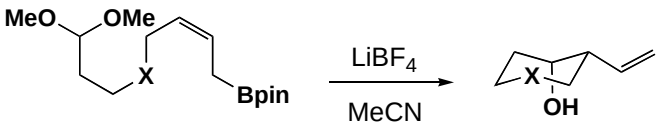
Substrate-directed allylborations

R. W. Hoffmann intramolecular allylations



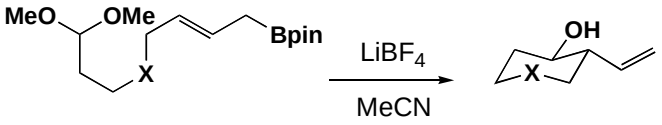
>98% ds

Liebigs Ann. Chem. 1993, 1185



X = O
X = NCO_2Me

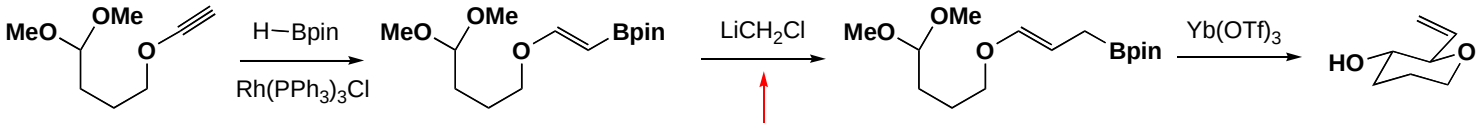
X = O, >98% ds
X = NCO_2Me, >98% ds



X = O
X = NBoc

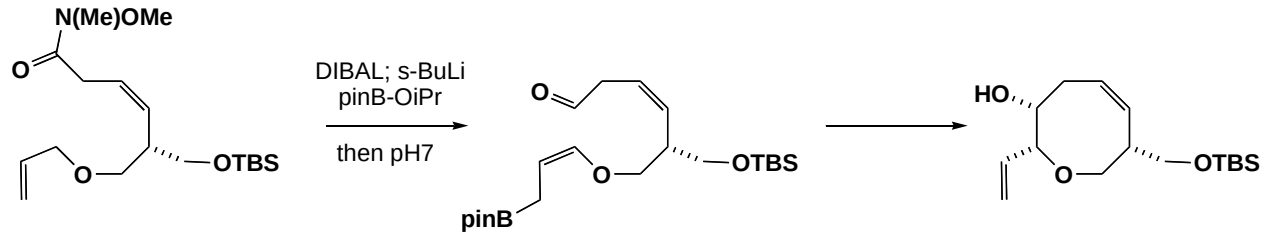
X = O, 94% ds
X = NBoc, >98% ds

Liebigs Ann. Chem. 1996, 1283



Matteson: Organometallics 1985, 4, 1687
Brown: JOC 1986, 51, 3150

Synthesis of medium ring ethers

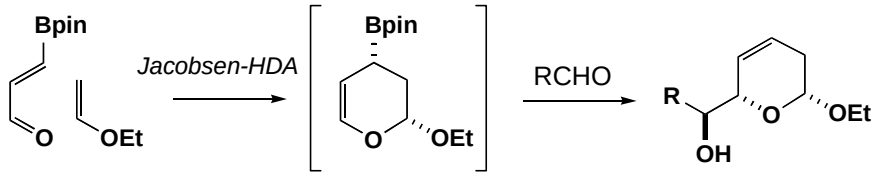


laurencin core ***JACS 1997, 119, 7499***

For an overview, see: Hoffmann et al. ACS Symposium Series 783, Organoboranes for Synthesis, P. V. Ramachandran, H. C. Brown, Ed., Ch 12, pp 160-175, American Chemical Society, Washington, DC, 2000

Substrate-directed allylborations

Hall's sequential HDA-allylation

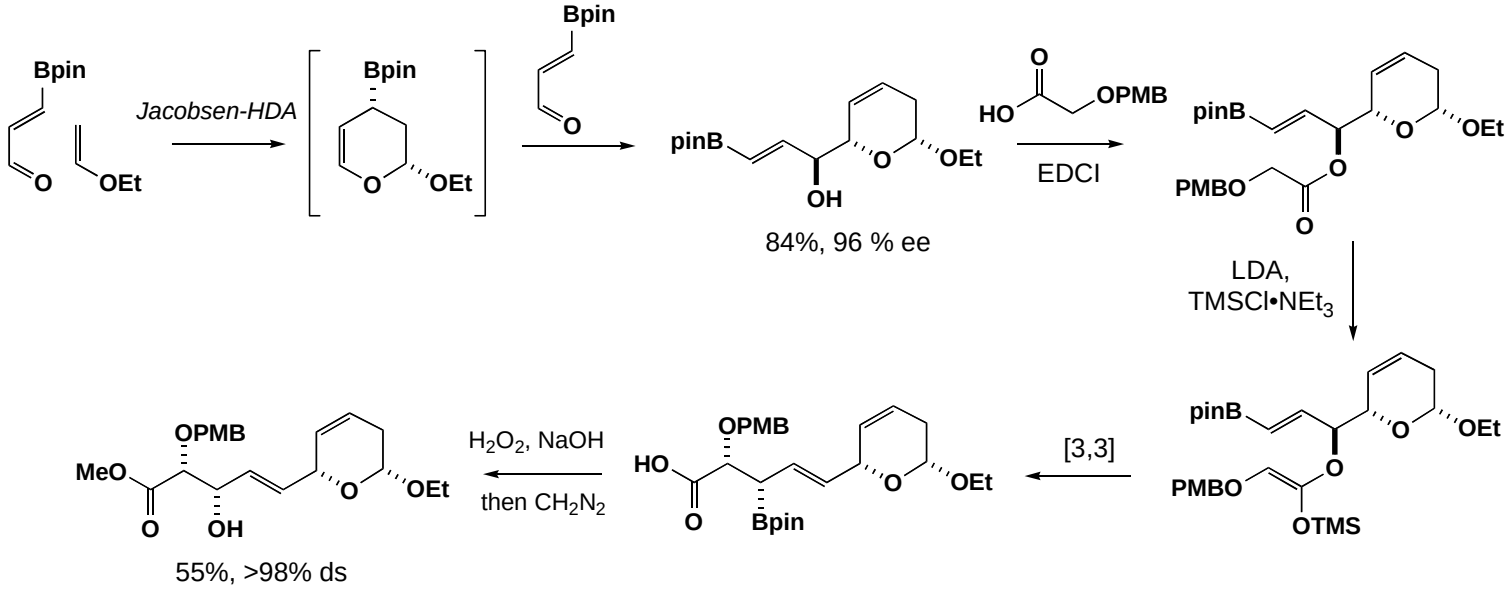


>99% ds, 96%ee
R = aryl, alkyl

QuickTime™ and a decompressor are needed to see this picture.

JACS 2003, 125, 9308
Chem. Eur. J. 2006, 12, 3132
Jacobsen HDA, see: ACIEE 2002, 41, 3059

Application in Synthesis



palmerolide A

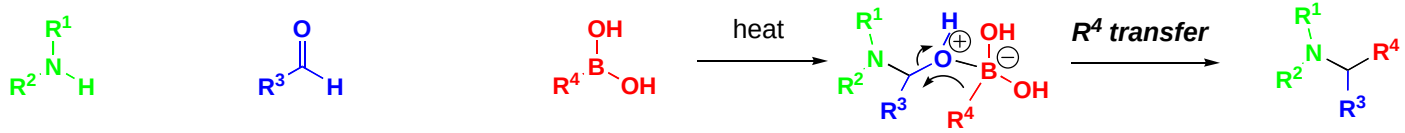
- ***HDA-allylation with aldehyde then sets stage for B-Ireland-Claisen***
- ***Allows hydroxyl differentiation and rapid assembly of carbon framework***

JACS 2009, 131, 14216

Vinylations and Homologations

Petasis Reaction

General Scheme



R^1 = alkyl
R^2 = alkyl, OH, O-alkyl, NHBoc

R^3 = alkyl, COOH, aryl

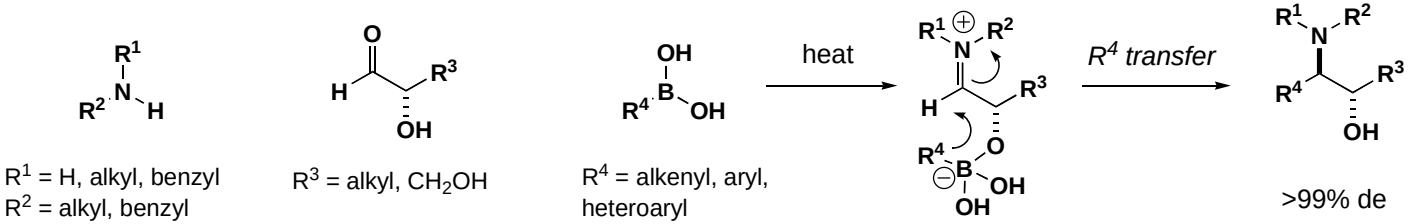
R^4 = alkenyl, aryl, heteroaryl

- Formation of hemiaminal, followed by ate formation
- Transfer of alkenyl or aryl group from intermediate ate complex gives allylic/benzylic amine products
- Mechanism remains a point of discussion

TL, 1993, 34, 583; Tetrahedron 1997, 53, 16463; JACS 1997, 119, 445

Modifications

Hydroxyl-Directed



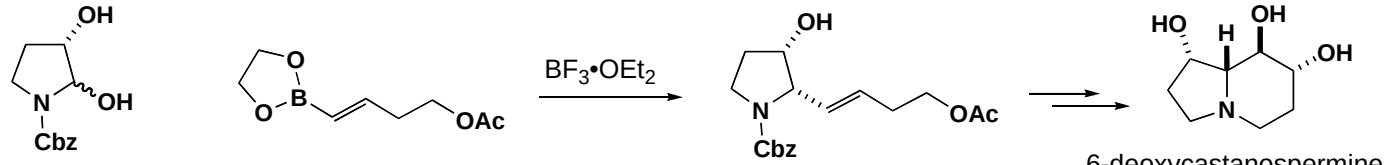
R^1 = H, alkyl, benzyl
R^2 = alkyl, benzyl

R^3 = alkyl, CH_2OH

R^4 = alkenyl, aryl, heteroaryl

JACS 1998, 120, 11798

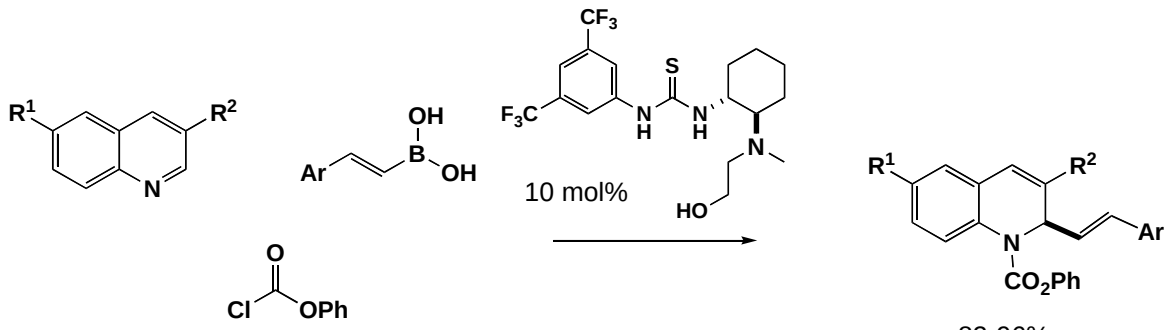
Cyclic N-acyliminium

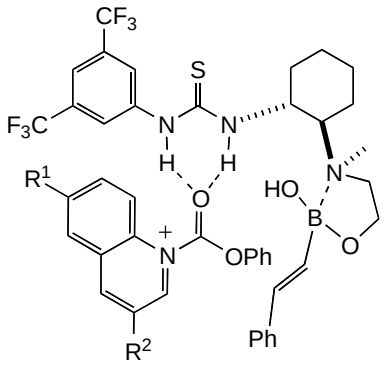


Batey et al. JACS 1999, 121, 5075; TL 2000, 41, 9935

Asymmetric Petasis Reactions

Takemoto - 2007



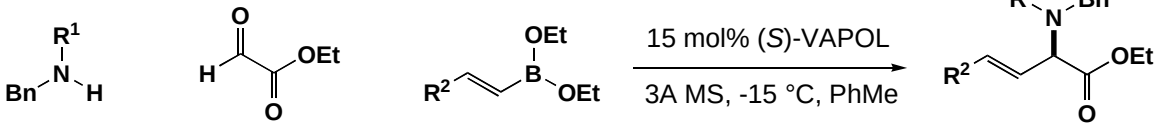


TS-concept

- ***Vinylation of N-acylated quinolines catalysed by isothiourea***

Takemoto et al. JACS 2007, 129, 6687

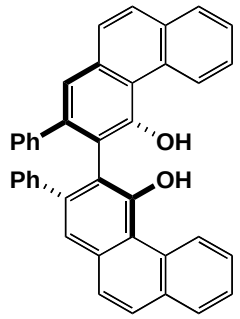
Schaus - 2008



R^1 = alkyl, benzyl

R^2 = aryl, alkyl

78-94% ee



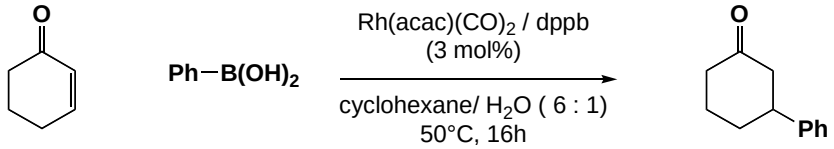
(*S*)-VAPOL

- ***First asymmetric variant of classical Petasis reaction catalysed by chiral biphenol***
- ***Need to use ethyl glyoxalate to achieve high ee's***
- ***Tolerates range of FGs in both amine and vinyl boronate***

Lou & Schaus JACS 2008, 130, 6922

Rh-mediated 1,4-addition of Boronic Acids

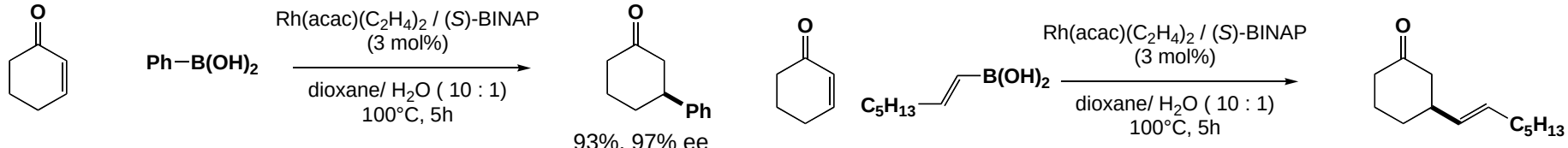
Miyaura-Hayashi 1997



52%

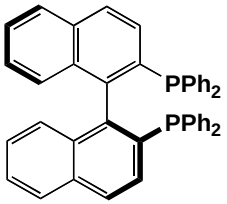
Asymmetric: Miyaura-Hayashi 1998

Miyaura, Hayashi et al. Organometallics 1997, 16, 4229



93%, 97% ee

64%, 96% ee

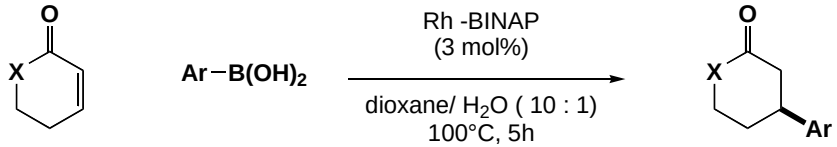


(*S*)-BINAP

- ***Initial report closely followed by asymmetric variant***
- ***Uses Rh-Binap catalyst***
- ***Both aryl and alkenyl boronic acids can be used with generally high ee***
- ***Remains the benchmark for other metal ligand systems***

Miyaura, Hayashi et al. JACS 1998, 120, 5579

Esters and amides



X = O, 97-98% ee
X = NBn, 97-98% ee

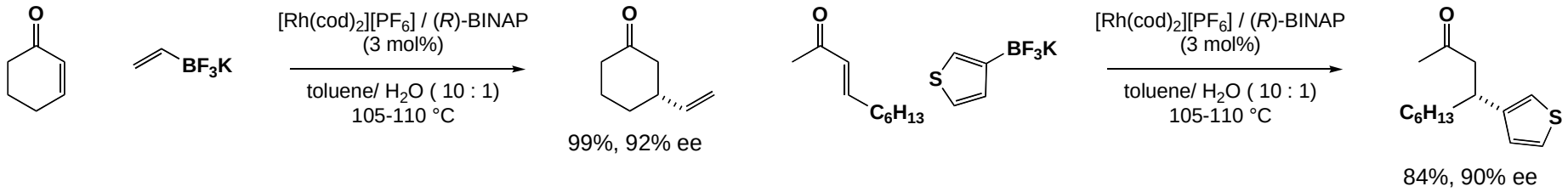
- ***High ee's for cyclic lactone/lactams***
- ***Comparable ee's for acyclic systems under same conditions***

Esters: Hayashi et al. Tetrahedron: Asymmetry 1999, 10, 4047
Amides: Hayashi et al. JOC 2001, 66, 6852

For review, see: Chem. Rev. 2003, 103, 2829

Rh-mediated 1,4-addition of Boronic Acids

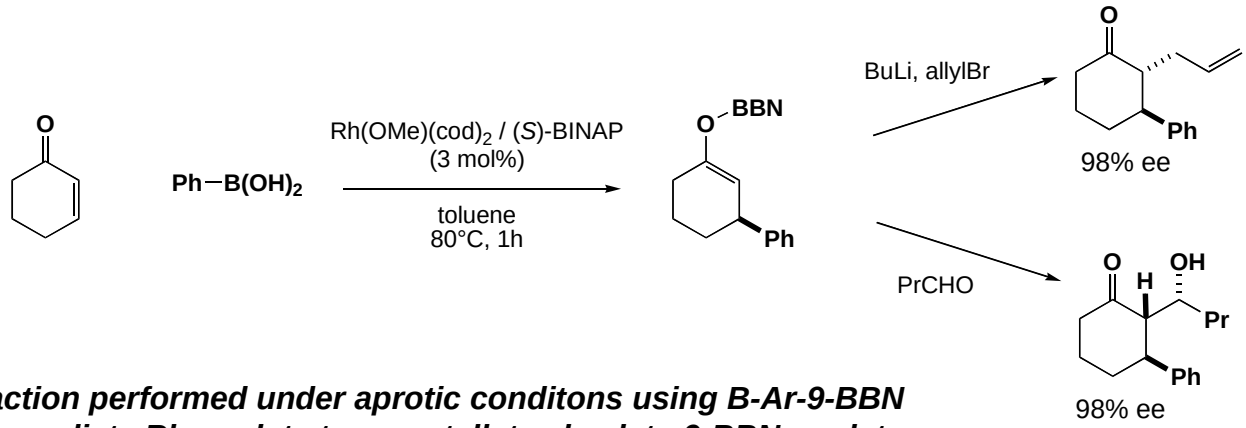
Addition of organotrifluoroborates



- ***Extended to include organotrifluoroborates (easier to handle, greater stability)***
- ***Addition of vinyl group - not possible with vinyl boronic acid***

Genet et al. TL 2002, 43, 6155; EJOC 2002, 3552

Tandem 1,4-additon - alkylation/aldol reaction



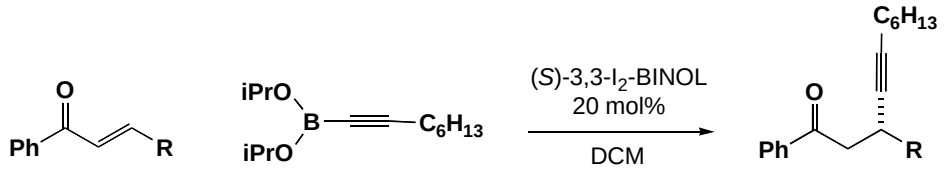
Reaction performed under aprotic conditons using B-Ar-9-BBN
Intermediate Rh-enolate transmetallates back to 9-BBN-enolate
Followed by direct aldol addition
Or further transmetallation with BuLi enables alkylation

Hayashi et al. JOC 2003, 68, 1901

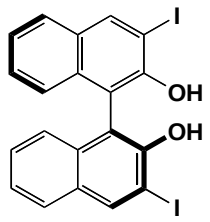
For review, see: Chem. Rev. 2003, 103, 2829

Organocatalytic 1,4-additions of Boronic Esters

Asymmetric Alkynylation: Chong 2005



R = Ph, 94%, 86% ee
R = Me, 89%, 94% ee

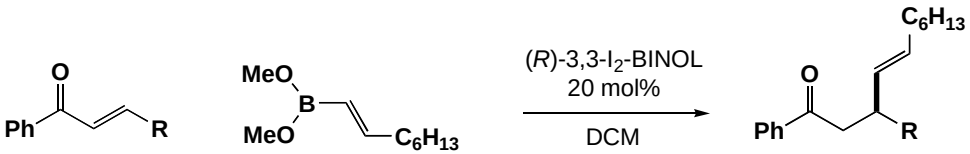


(*S*)-3,3-I_2-BINOL

- ***Asymmetric addition of alkynylboronic ester to enones***
- ***Enone must contain aryl group to achieve high ee***
- ***Chong proposes complete ligand exchange with catalyst- see Schaus allylation for alternative view***

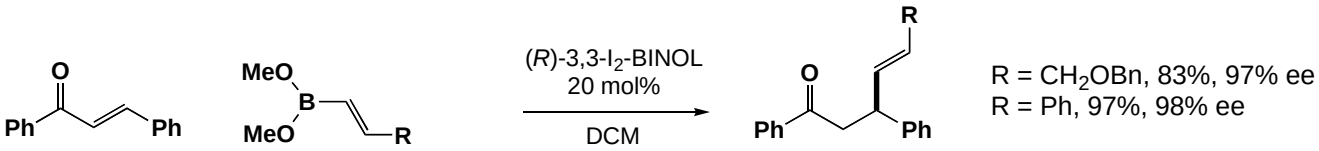
Wu & Chong JACS 2005, 127, 3244

Asymmetric Alkenylation: Chong 2007



R = Ph, 93%, 97% ee
R = Me, 95%, 96% ee
R = CO_2Me, 84%, 97% ee

QuickTime™ and a
decompressor
are needed to see this picture.



R = CH_2OBn, 83%, 97% ee
R = Ph, 97%, 98% ee

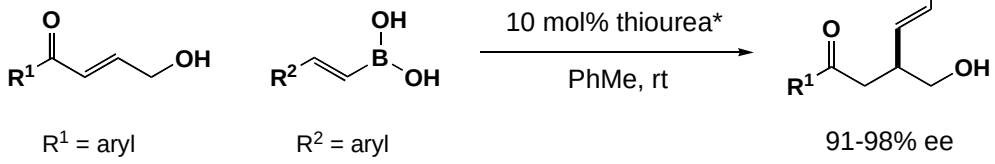
QuickTime™ and a
decompressor
are needed to see this picture.

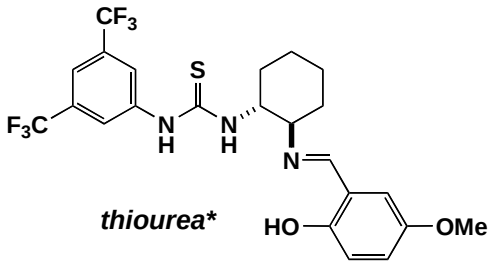
- ***Analogous alkenylation also proceeds with high ee***
- ***Trisubstituted alkenylboronic esters can also be used***
- ***Possible TS's shown for (R)-3,3-I_2-BINOL***

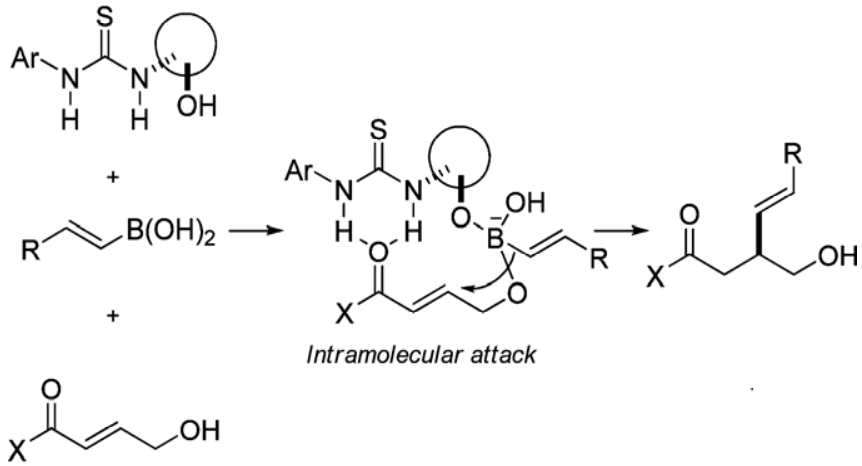
Wu & Chong JACS 2007, 129, 4908

Organocatalytic 1,4-additions of Boronic Acids

Takemoto 2009

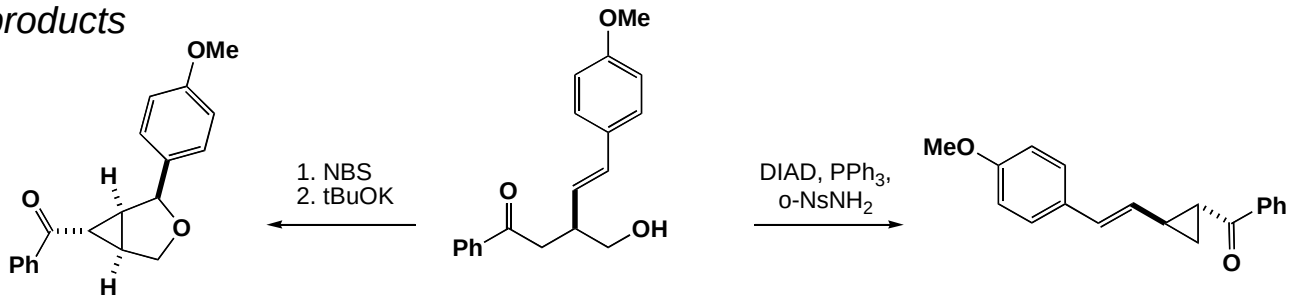






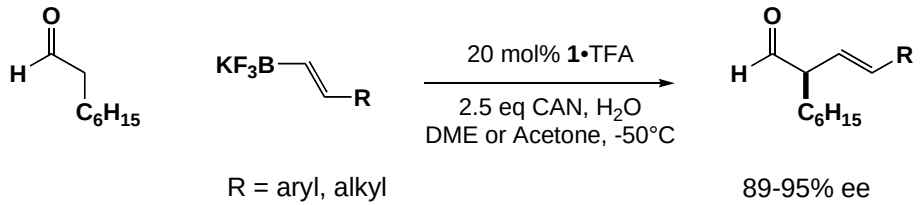
- ***Combination of hydrogen bonding to isothiourea and formation of ate complex between substrate, boronic ester and catalyst prior to intramolecular transfer***

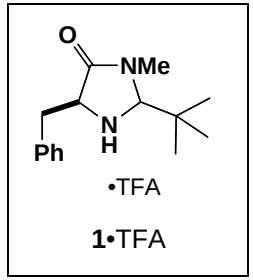
Derivitisation of products



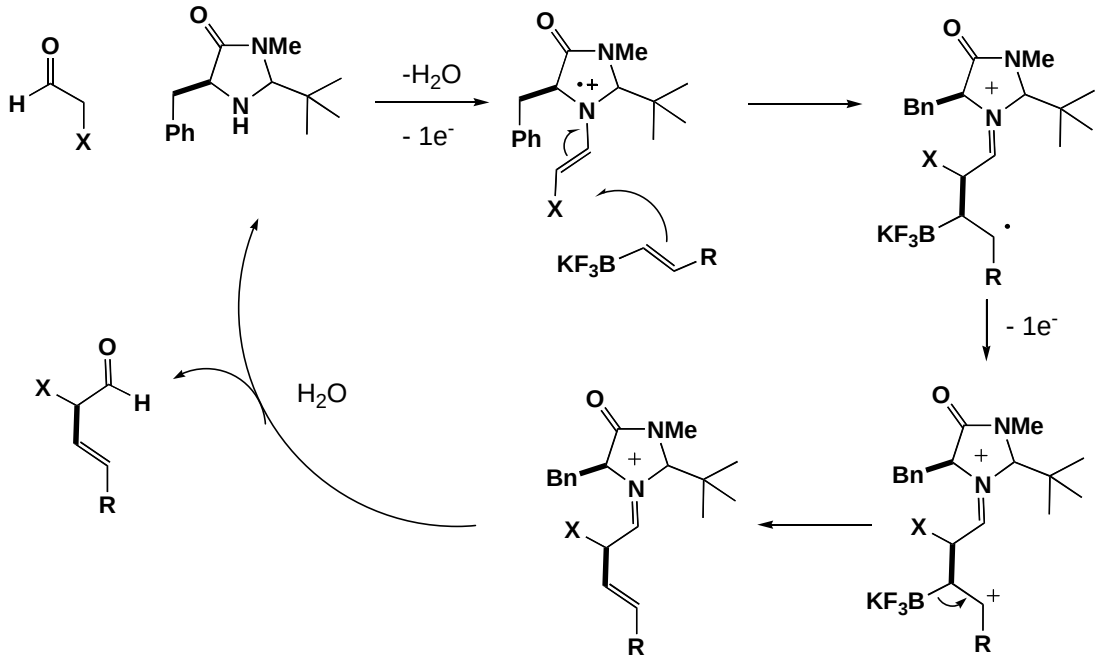
Takemoto et al. OL 2009, 11, 2425

MacMillan's α-vinylation of aldehydes





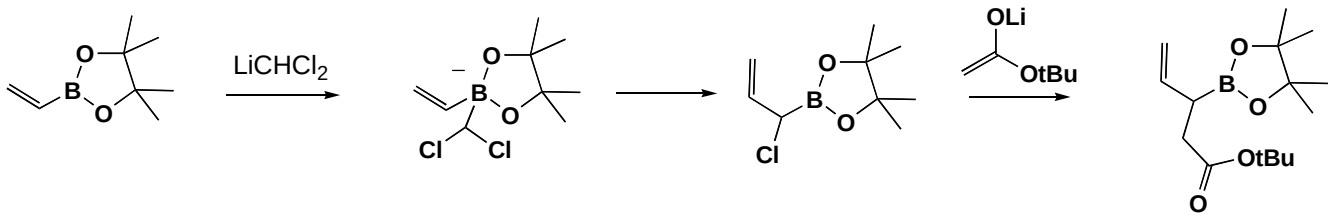
- ***Organo-SOMO catalysis -***
- ***Applicable to range of aliphatic aldehydes with high selectivity***



- ***Single electron oxidation of intermediate enamine***
- ***Radical cation then undergoes reaction with alkene***
- ***Further single electron oxidation of intermediate radical***
- ***Dicationic species then undergoes Peterson-like trans-elimination of boron trifluoride***

Kim & MacMillan JACS, 2008, 130, 398

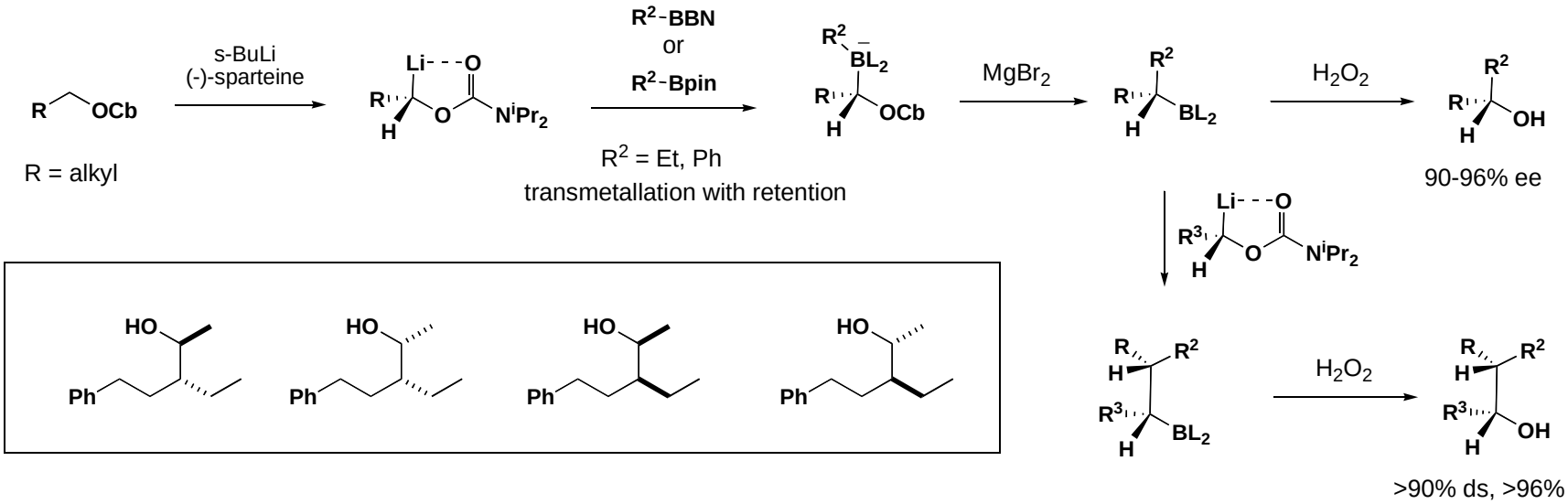
Aggarwal's Homologation of Boranes and Boronic Esters



- ***Matteson reported the homologation of boronic esters in 1980 using $LiCHCl_2$***
- ***Use of chiral pinane diol ester enabled asymmetric version - though applications limited***

Matteson et al. JACS, 1980, 102, 7588 & 7590

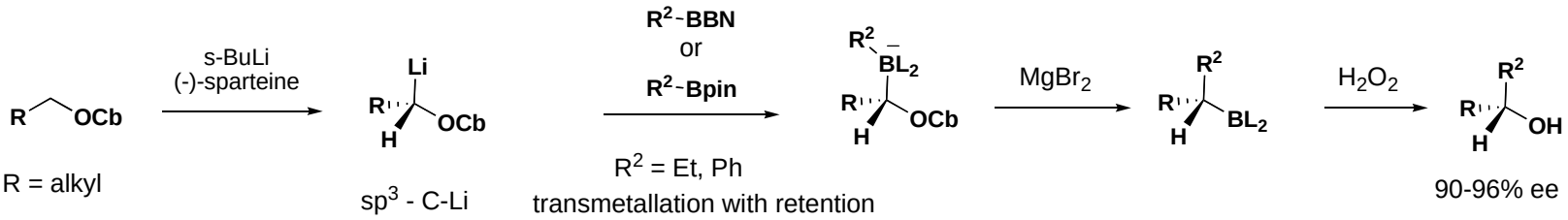
- ***Alternative would be to use chiral deprotonation - Aggarwal 2007***



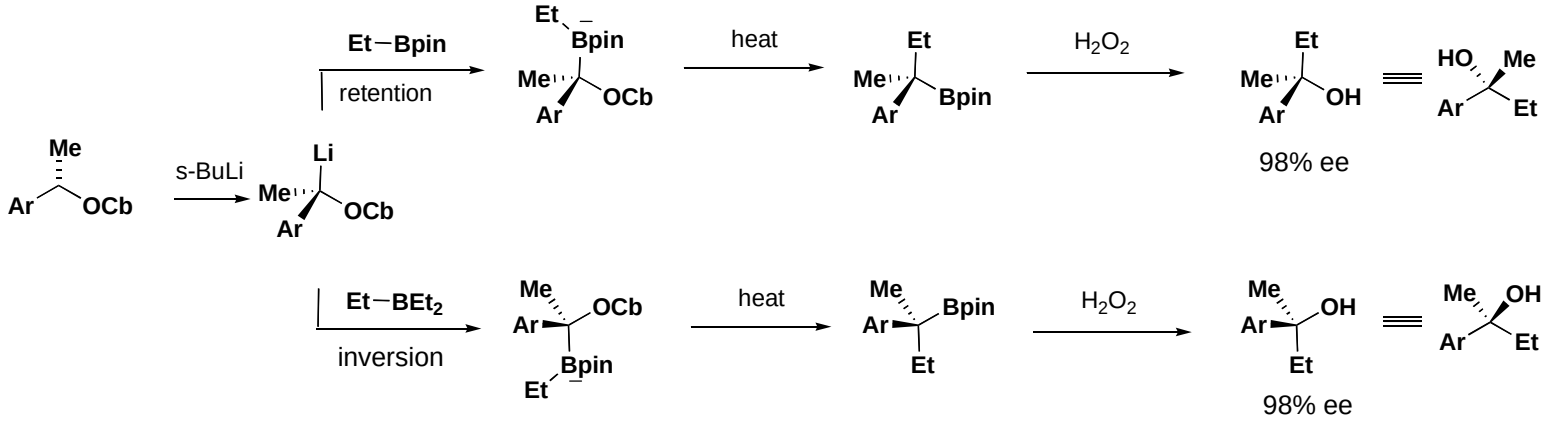
- ***Utilises Hoppe's chiral deprotonation to give stabilized lithiated carbamates***
- ***Reaction with alkyl/aryl boranes or boronates proceeds with retention***
- ***Migration of alkyl/aryl group from B to C -***
- ***Further iterations possible by sequential addition of lithiated carbamates/migration process***
- ***Either enantiomer of lithiated carbamate available by use of appropriate sparteine/ sparteine surrogate***

Aggarwal et al. ACIEE 2007, 46, 7491

Aggarwal's Homologation of Boranes and Boronic Esters



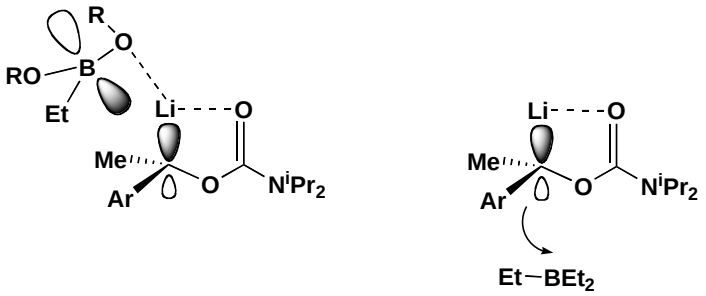
• ***For R = alkyl: transmetallation occurs with retention- C-Li sp³ hybridised***



• ***With substituted benzylic-type carbamates - lithiated carbamate has more sp2 character, resulting in flatter anion - interaction with Ar group***

• ***For boronic ester- interaction with Li and OR group of boronic ester delivers on same face as metal -retention***

• ***For borane- no complexation and significant electron denisty on opposite face - inversion***

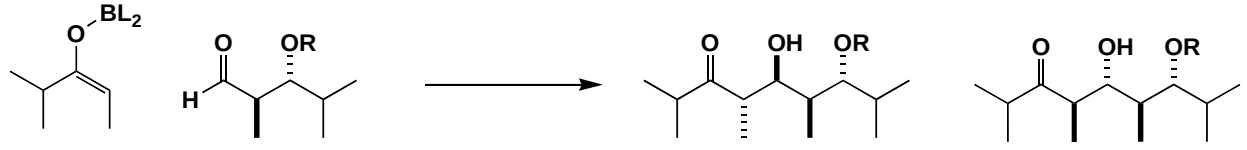


Aggarwal et al. Nature 2008, 456, 778

Extras

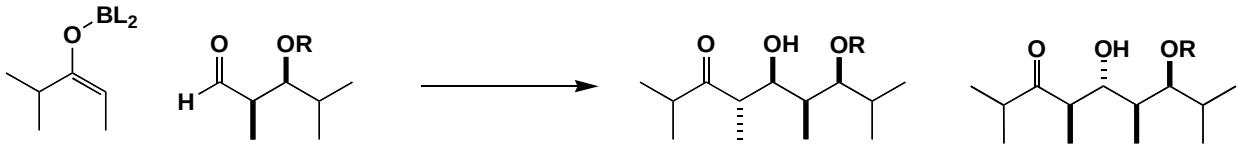
β-alkoxy aldehydes

For E-enolates - effect of β-oxygen is moderate, Felkin adduct predominates



L = cHex

	R	*major*	*minor*
centres reinforcing	TBS	99	1
	PMB	93	7

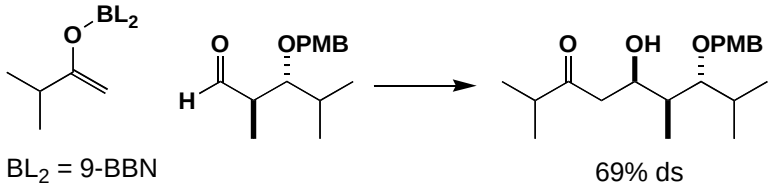


L = cHex

	R	*major*	*minor*
centres non-reinforcing	TBS	94	6
	PMB	74	26

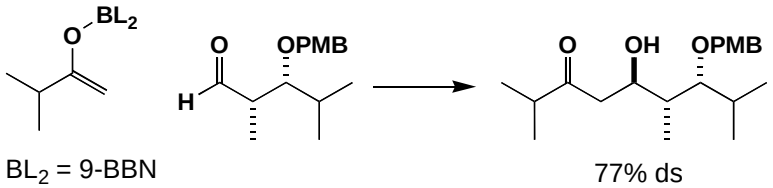
Evans JACS 1995, 117, 9073

For methyl ketones - effect of β-oxygen is not so predictable



BL_2 = 9-BBN

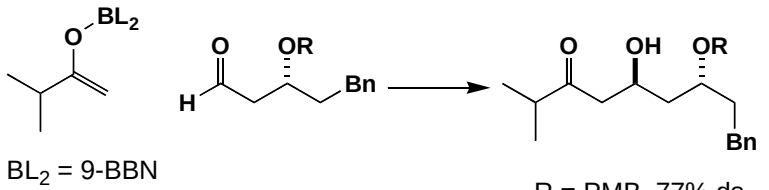
69% ds



BL_2 = 9-BBN

77% ds

β-OPMB dominates - 1,3-anti addition



BL_2 = 9-BBN

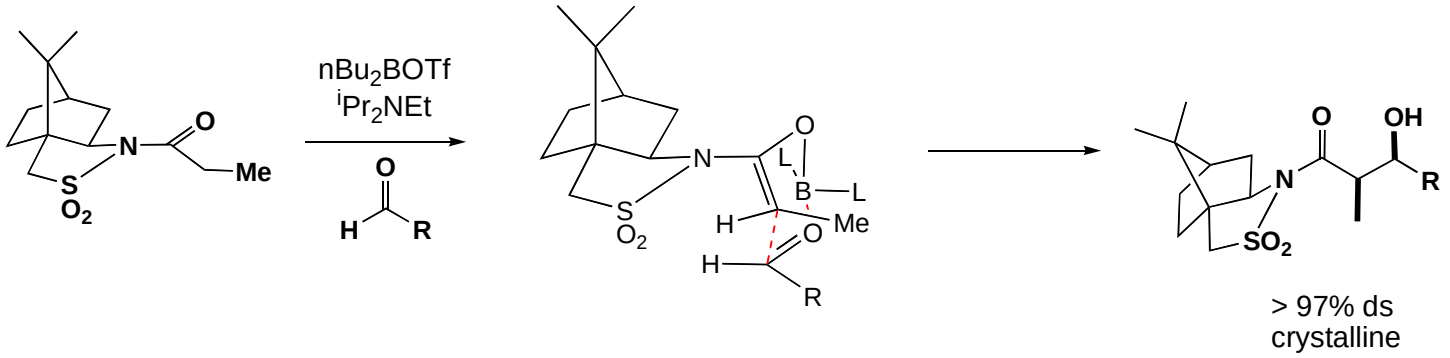
R = PMB, 77% ds

R = TBS, 48% ds

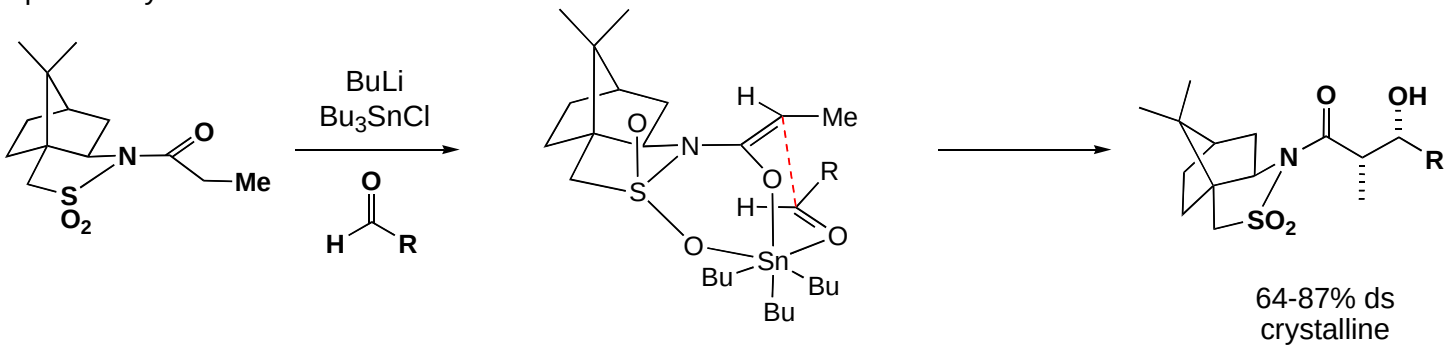
L = cHex

89% ds

Chiral Auxiliaries: Oppolzer's Sultam



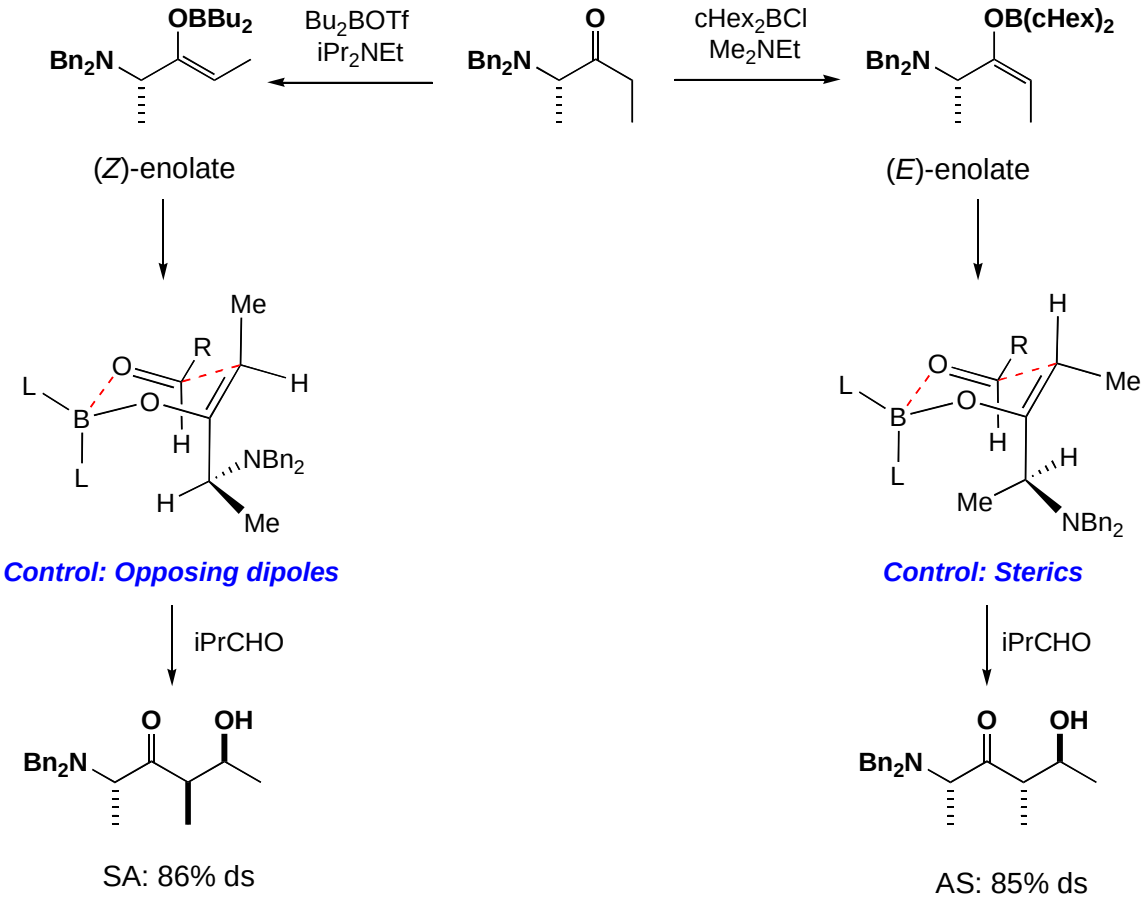
Complimentary Sn-aldol



Oppolzer et al. JACS 1990,112, 2767

Substrate Control: α-amino ethyl ketones

α-amino ethyl ketones

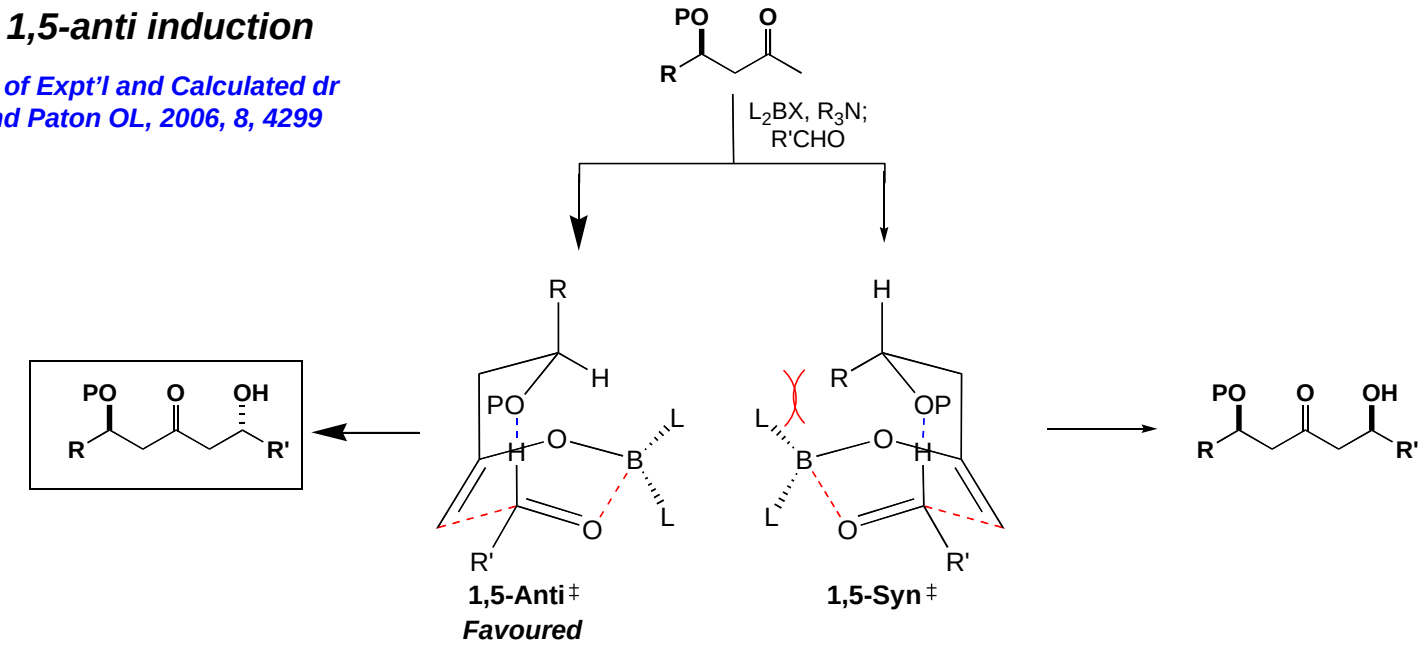


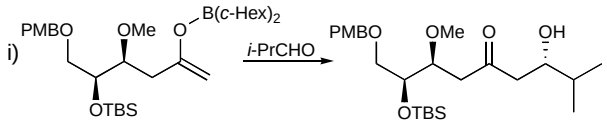
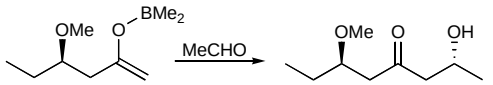
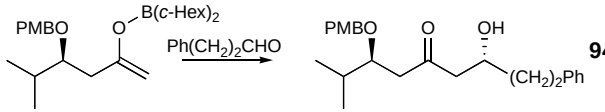
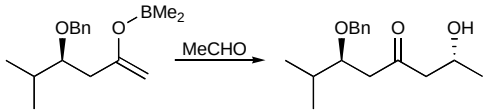
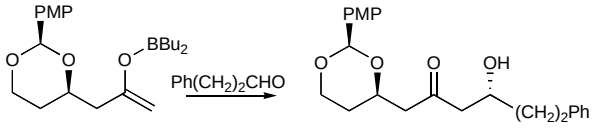
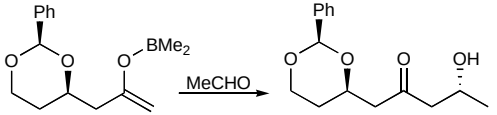
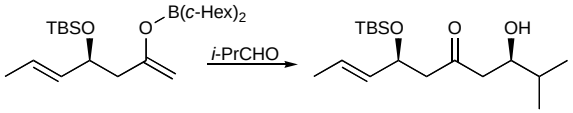
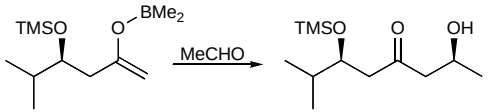
Paterson and Mackay: TL 2001, 42, 9269

Substrate Control - β-oxygenated methyl ketones

Origin of 1,5-anti induction

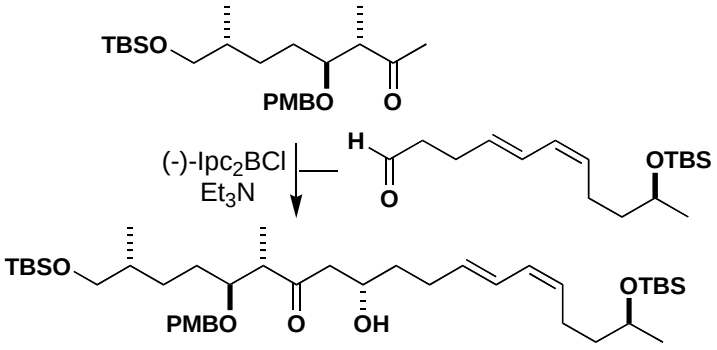
Comparison of Expt'l and Calculated dr
Goodman and Paton OL, 2006, 8, 4299



methyl ketone	major adduct	exp. dr	model system	major adduct	pred. dr
i) 		**75:25**[8]			**80:20**
ii) 		**94:06**[5]			**97:03**
iii) 		**93:07**[5]			**100:00**
iv) 		**58:42**[3]			**66:34**

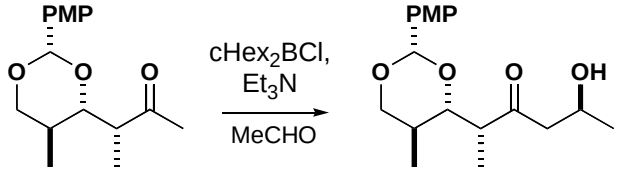
Substrate Control: Merging 1,4- and 1,5-induction

combine effects to increase selectivity



83%, 95% ds

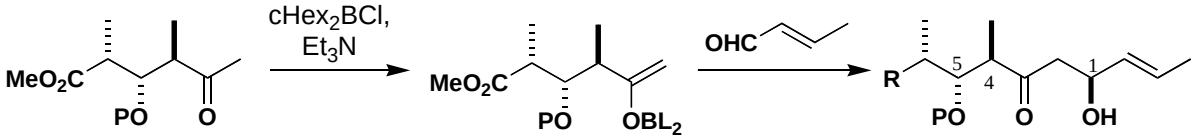
Mulzer & Burger *TL* 1998, *39*, 803



>95% ds

Dias et al. OL 2002, 4, 4325

Paterson discodermolide synthesis



P = TBS, PMB

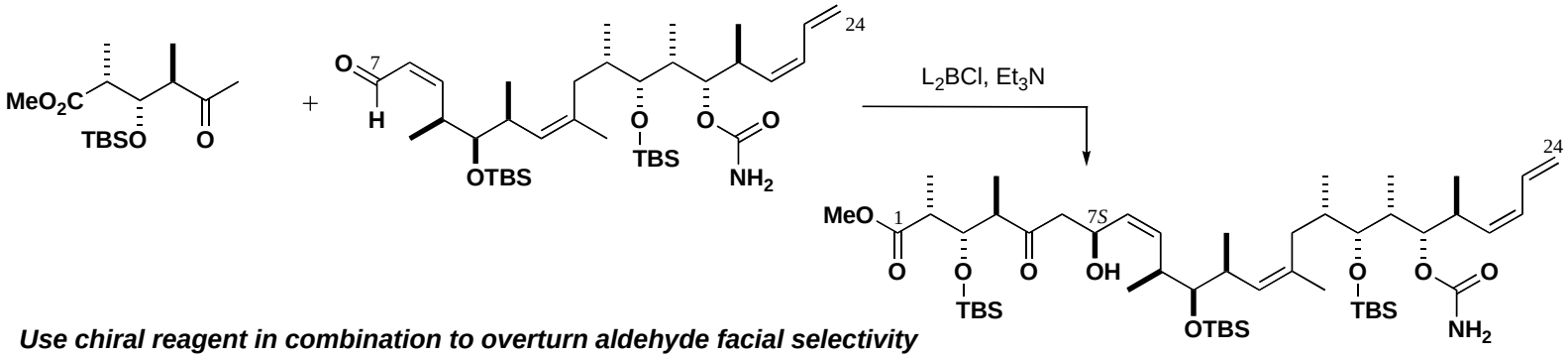
1,4-*syn* 1,5-*anti* (major)

P = TBS (62%, 54% ds)

P = PMB (73%, 95% ds)

P = TBS: ***ACIEE, 2000, 39, 377; TL 2000, 41, 6935; JACS 2001, 123, 9535***

P = PMB: ***Florence & Paterson, unpublished***

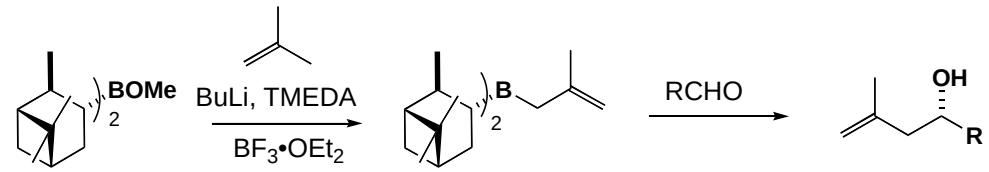


L	Yield	ds
cHex	67	16
(+)-Ipc	87	84

Use chiral reagent in combination to overturn aldehyde facial selectivity

Asymmetric Allylboration: Brown's Ipc-Reagent Diversity

Methallylation



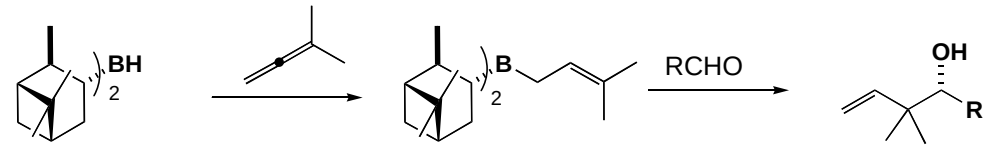
(-)-Ipc$_2$BOMe

90-96% ee

• ***acetone aldol equivalent***

TL 1984, 25, 5111; JOC 1986, 51, 432

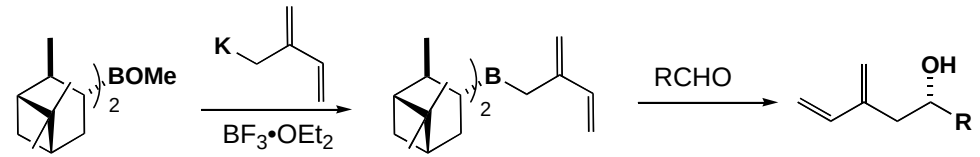
Isoprenylation



(-)-Ipc$_2$BH

89-96% ee

TL 1984, 25, 1215; JOC 1986, 51, 432

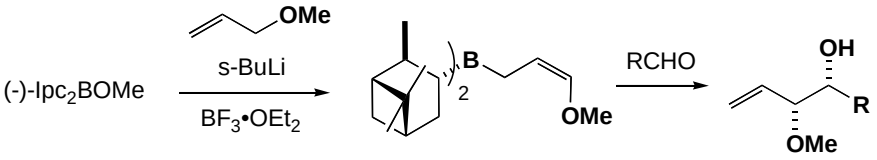


(-)-Ipc$_2$BOMe

90-96% ee

TL 1990, 31, 455

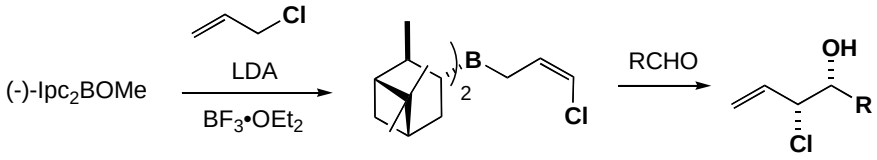
methoxyallylation



95-96% ee

JACS 1988, 110, 1535

chloroallylation

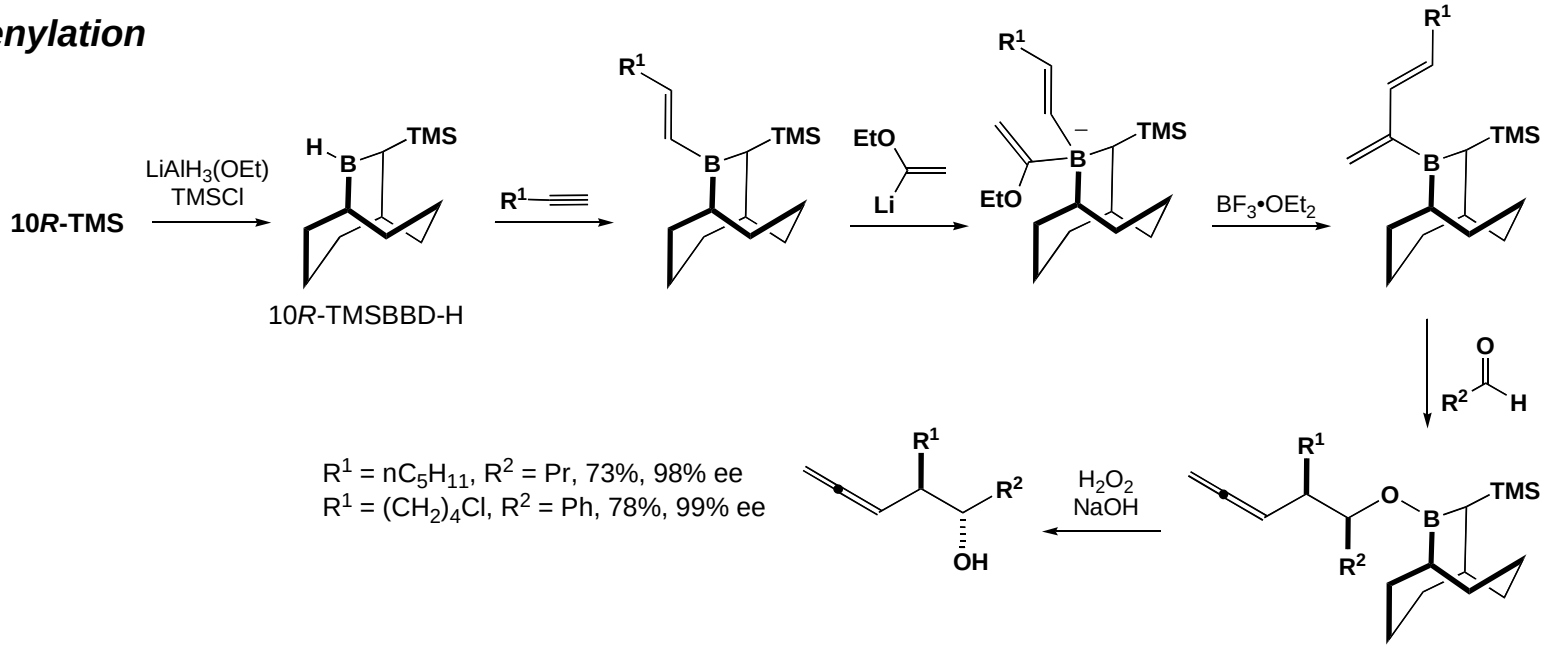


90-99% ee

Hu, Jayaraman & Oehlschlager JOC 1996, 61, 7513

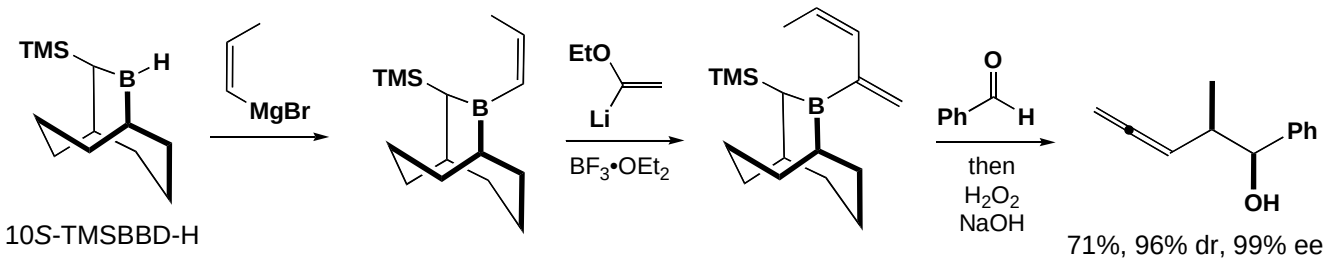
Asymmetric Allylboration: Soderquist's 10-TMS-9-BBD Reagents

Anti-allenylation



- ***Sequential alkyne hydroboration-insertion-allylation to give 1,2-anti-3-allenes***
- ***Tolerates wide-range of terminal alkynes***
- ***High levels of selectivity***
- ***Syn variant is also comparable***

syn-allenylation



Soderquist et al. JACS 2009, 131, 9924