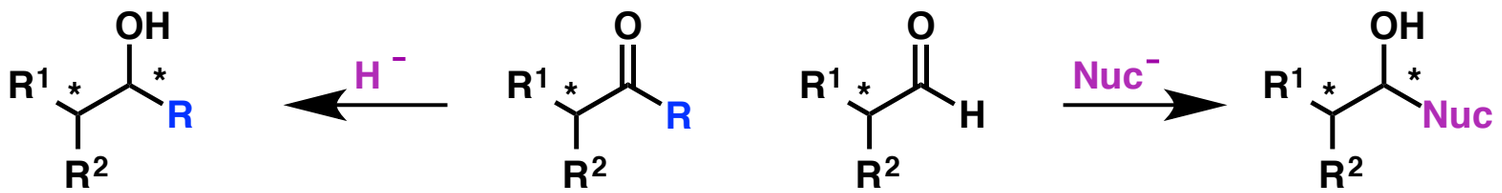
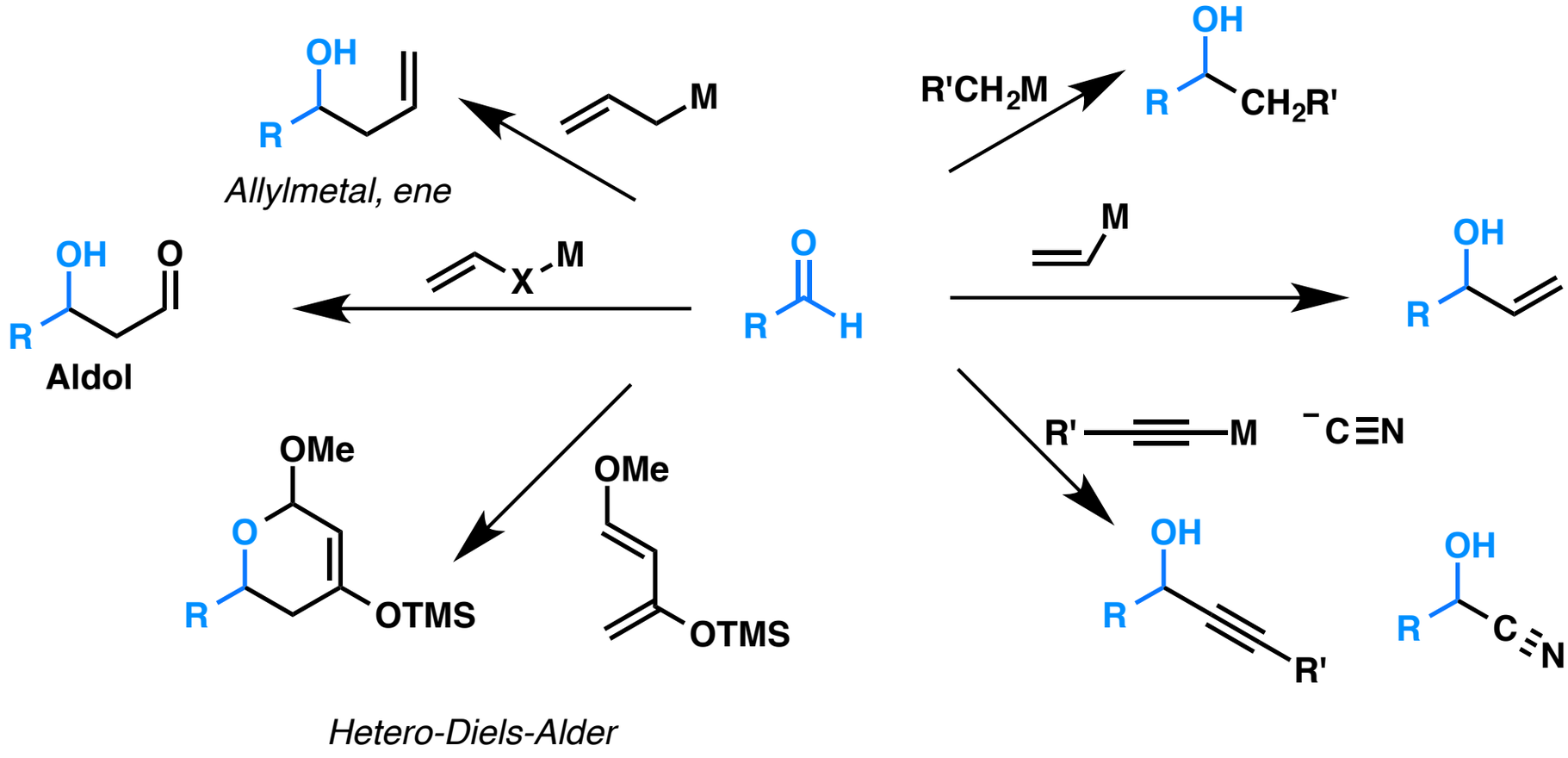
Nucleophilic Addition to C=O



Chiral ketone *Chiral Aldehyde or ketone*

Nuc

Organometallic, enolates (Aldol)
Dienophiles
(Felkin-Anh, Chelation control)

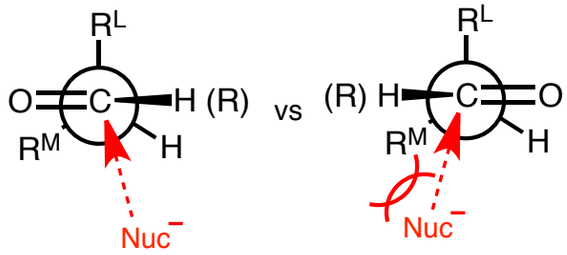


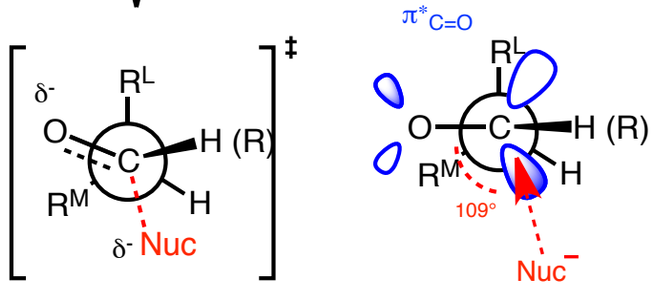
Hetero-Diels-Alder

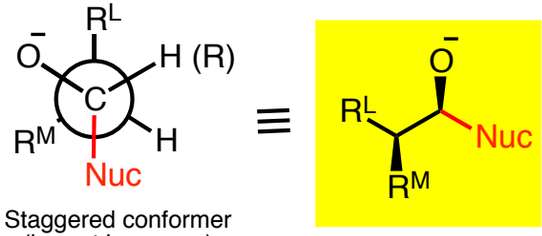
Overview: Carbonyl Addition Reactions

Case 1. R^L and R^M = Carbon

R^L = Largest group (sterically)







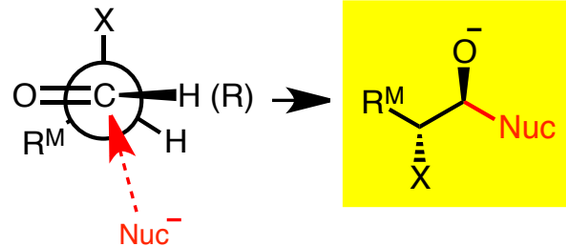
Case 2. R^L = X (O,N,S,halogen, etc.) and R^M = C

Non-accessible lone pairs on X

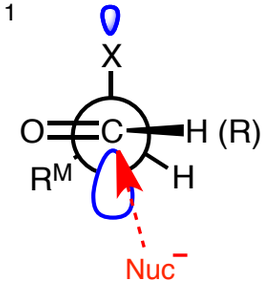
($OSiR_3$, $OCPh_3$)

or accessible lone pairs but metal cannot form a bidentate chelate

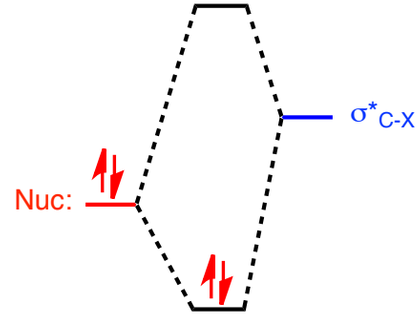
(wrong size - ionic radius or monovalent)



Same reasons as in Case 1



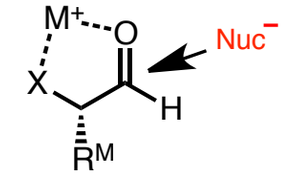
A nucleophile (or lone paire) that intereact with an empty orbital close in energy:

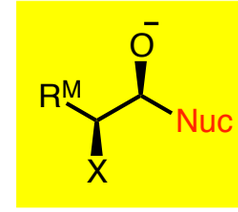


Case 3. Chelate formation

Requirements:

- Metal is Lewis acidic (good ionic radius + multivalent)
- X has an accessible electron pair

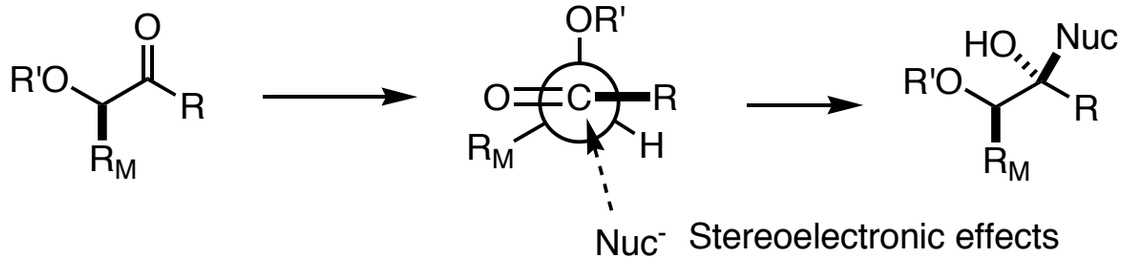




Felkin-Anh vs. Chelation-controlled Addition

Felkin-Anh Stereoelectronic Model can be used to predict the stereochemical outcome of carbonyl addition reaction but sometimes conditions to favor a chelation-controlled product can be used to generate another stereoisomer.

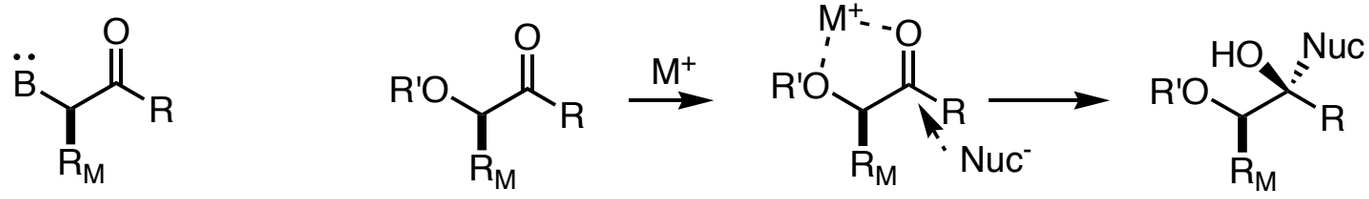
In the absence of chelation: R' = trityl, silyl (Felkin-Anh model)

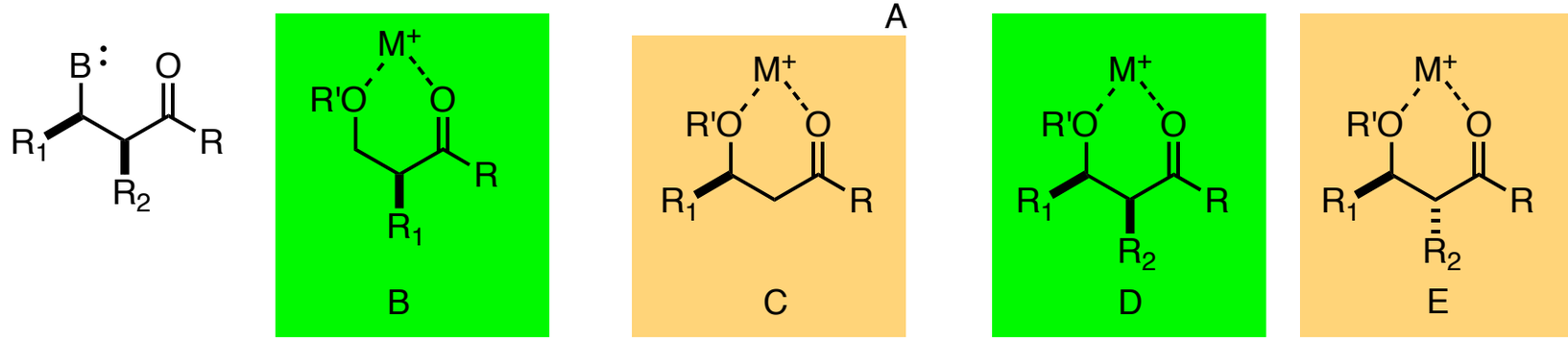


Conditions favor chelation (5, 6 and larger ring between substrate and metal):

- Lewis basic group
- Appropriate Lewis acid (M^+)

Diastereomers

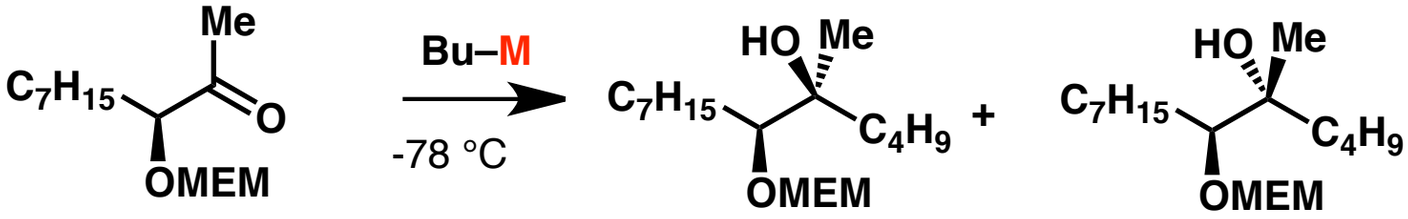




Nucleophilic Additions to C=O: α-Chelates

- effect of the metal and solvent

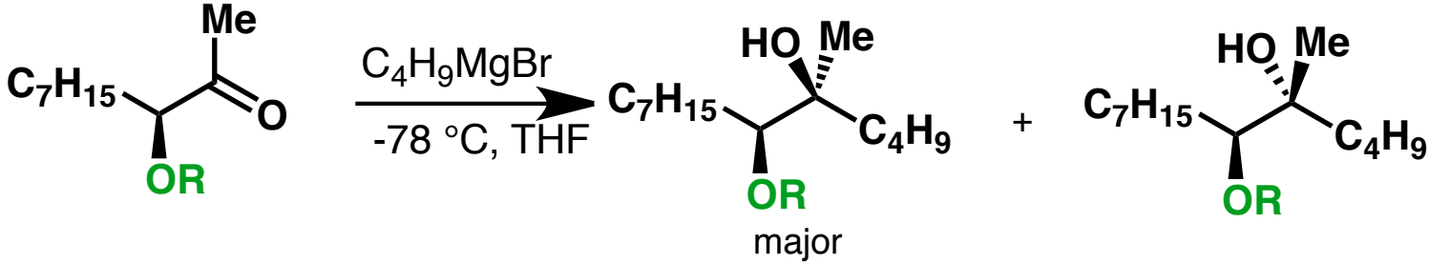
Still, W. C. *Tetrahedron Lett.* **1980**, *21*, 1031.



Solvent	Li	Mg
Pentane	2	9
CH_2Cl_2	3	14
Ether	1	9
THF	0.7	>100

- effect of the protecting group

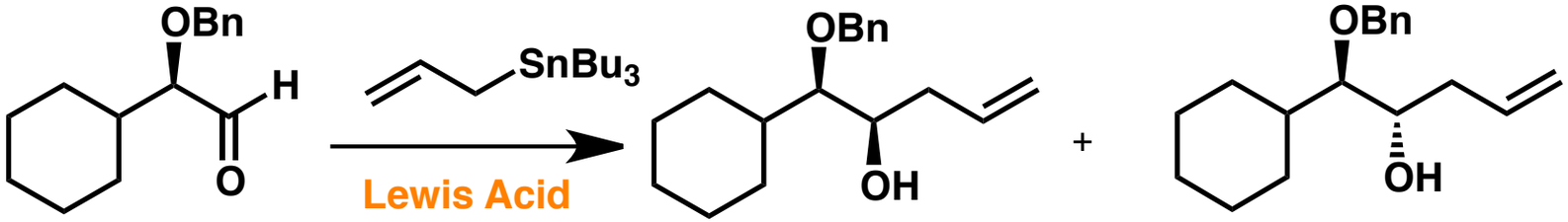
Still, W. C. *Tetrahedron Lett.* **1980**, *21*, 1035.



Protecting group	Mg
–MEM, –OMOM, –MTM	9
$–CH_2Ph$	200
$–CH_2OCH_2Ph$	100

- effect of the metal

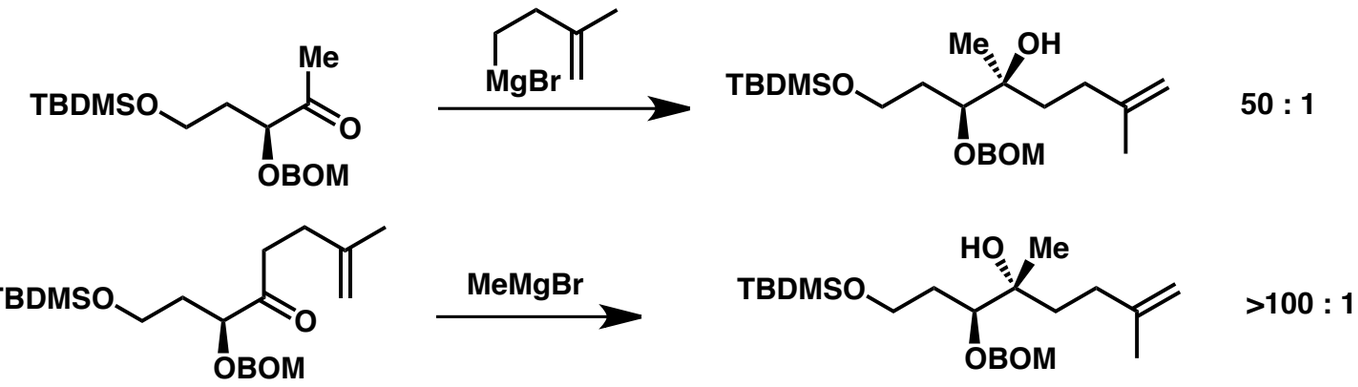
Keck, G. *Tetrahedron Lett.* **1984**, *25*, 265.



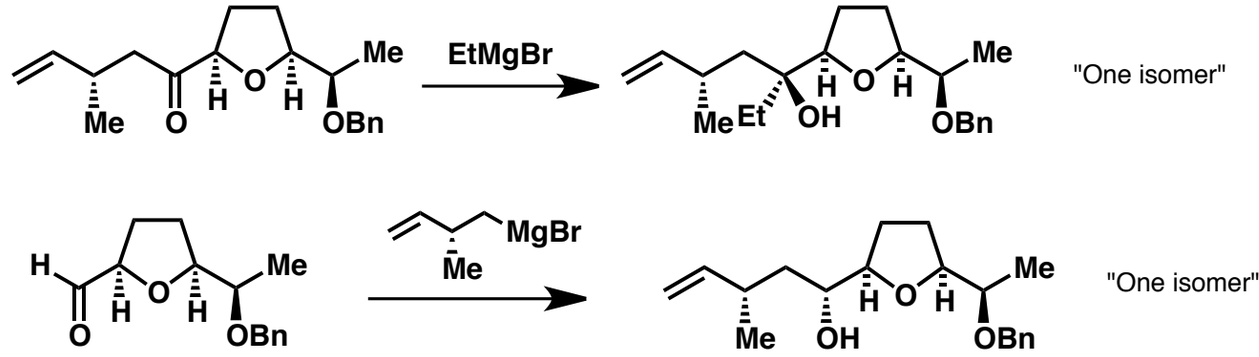
Lewis Acid	Ratio
$BF_3•OEt_2$	39 : 61
$MgBr_2•OEt_2$	>250 : 1
$ZnBr_2$	77 : 23
$TiCl_4$	>250 : 1

Nucleophilic Additions to C=O: α-Chelates - Additional "Classics" Examples

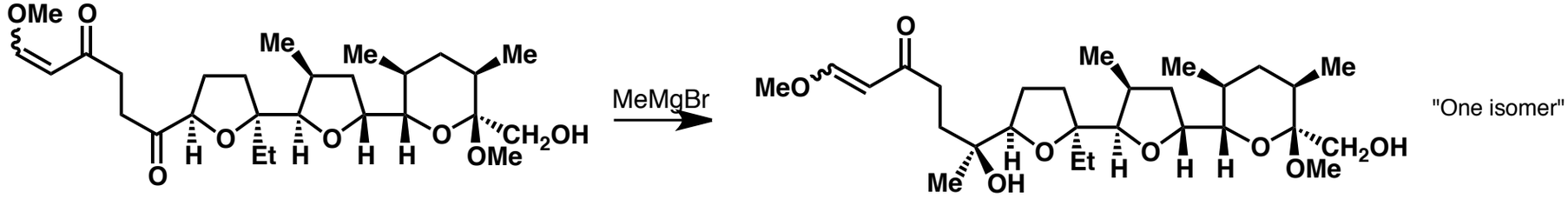
Still, W. C. *Tetrahedron Lett.* **1980**, 1031.



Kishi, Y. *Tetrahedron Lett.* **1978**, 2745.

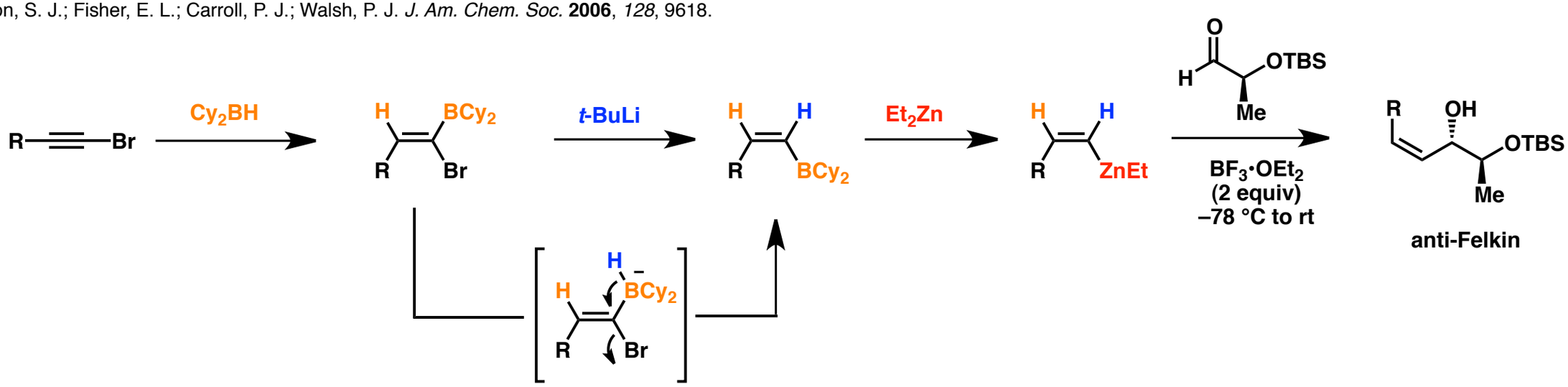


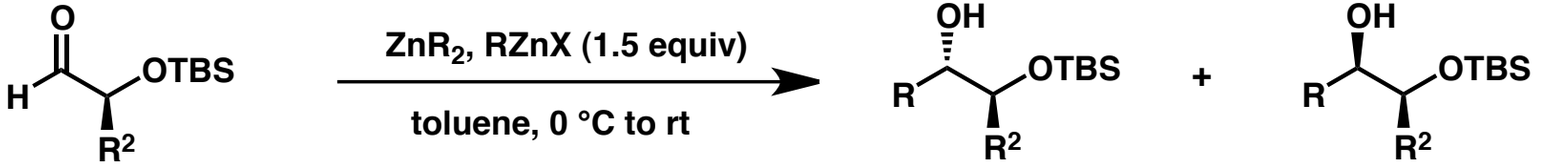
Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260.



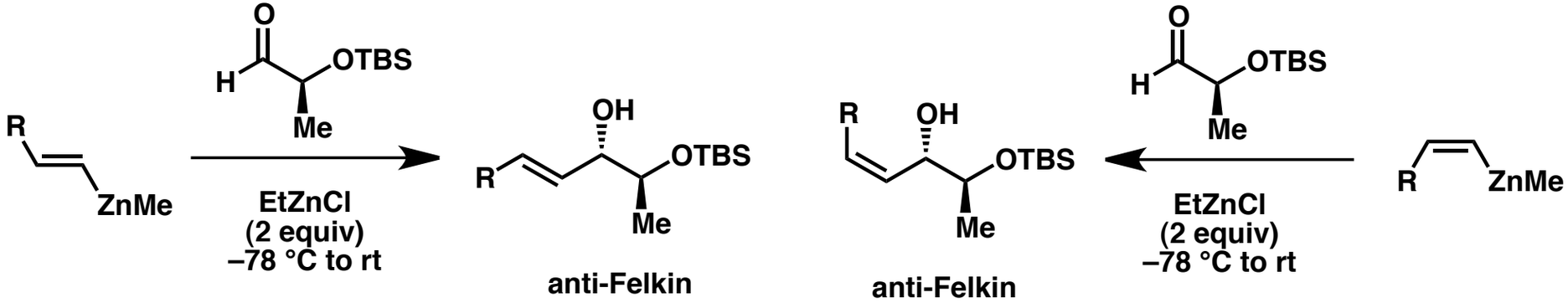
Nucleophilic Additions to C=O: α-Chelates

Jeon, S. J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 9618.



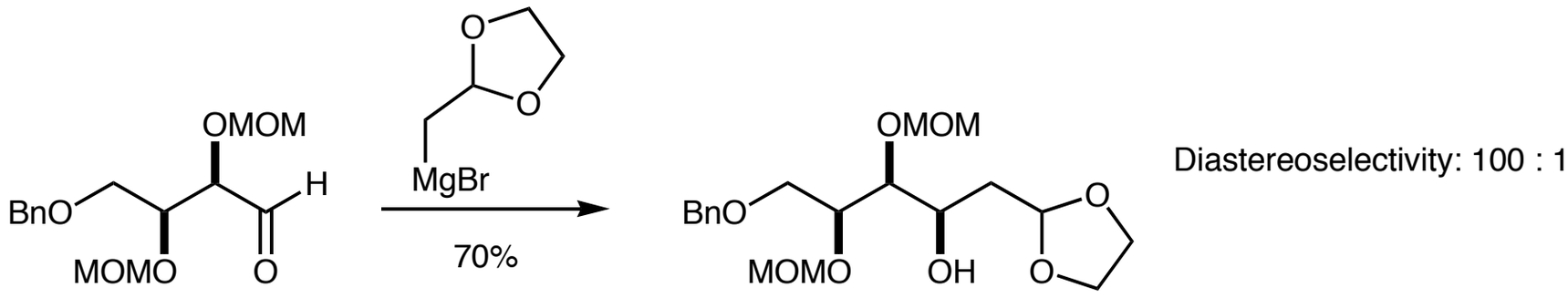


R	Ratio (Yield)
Me	18 : 1 (91%)
Bu	>20 : 1 (87%)
$(CH_2)_4Cl$	16 : 1 (50%)
$(CH_2)_4OTBS$	20 : 1 (47%)



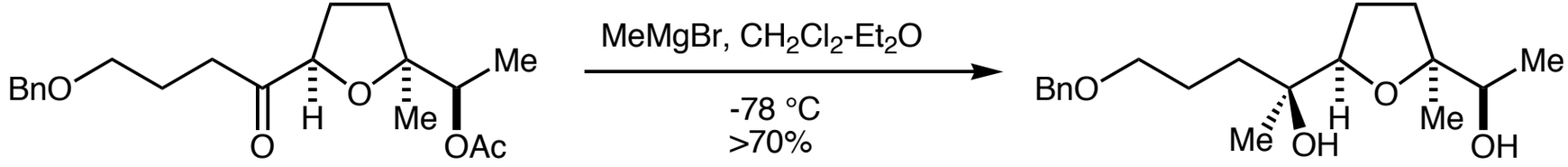
Nucleophilic Addition to α-Alkoxy Carbonyl: Other Examples - 3

Ida, . *J. Org. Chem.* **1986**, *51*, 4246.



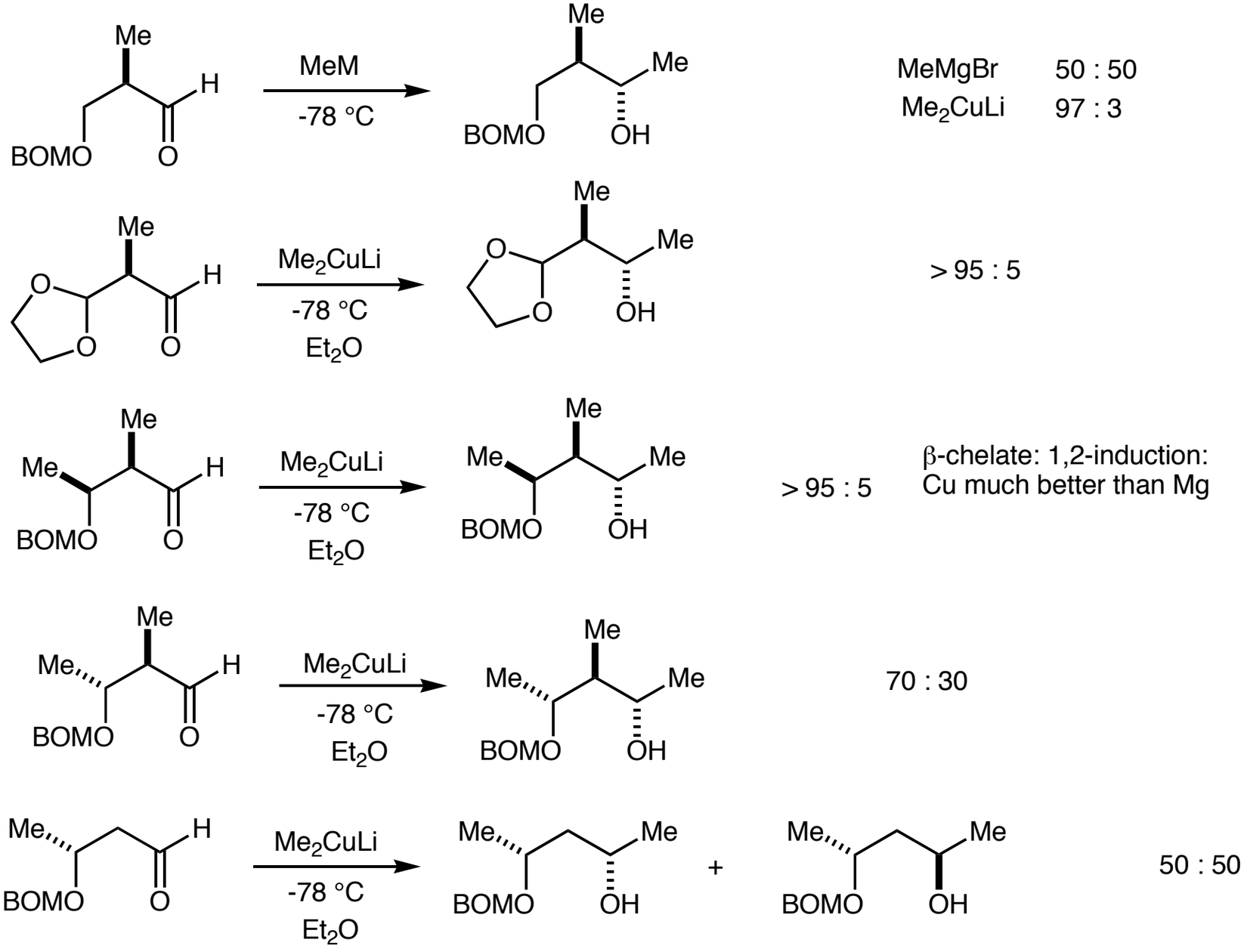
Diastereoselectivity: 100 : 1

Evans, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 5290.



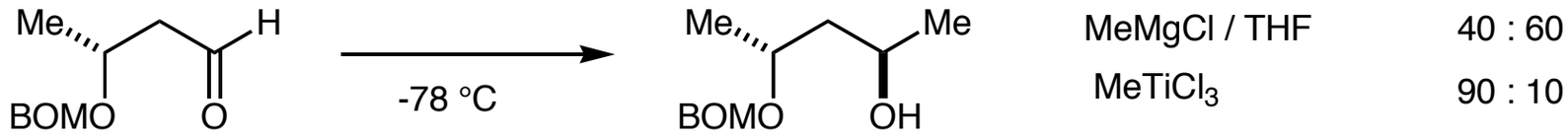
Nucleophilic Addition to β-Alkoxy Carbonyl

Still, W. C. *Tetrahedron Lett.* **1980**, *25*, 1035.



Nucleophilic Addition to β-Alkoxy Carbonyl

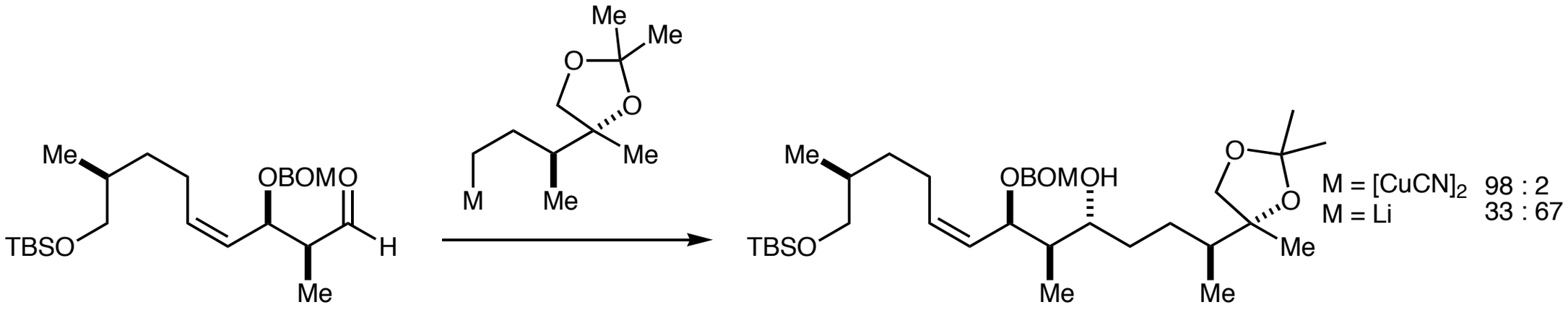
Reetz, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 4833.



β-chelate: 1,3-induction:
Ti much better than Cu

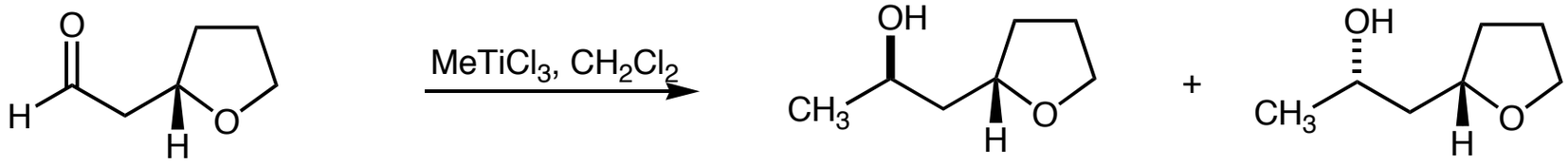
Nucleophilic Addition to β-Alkoxy Carbonyl: Other Examples

Evans, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 4961.



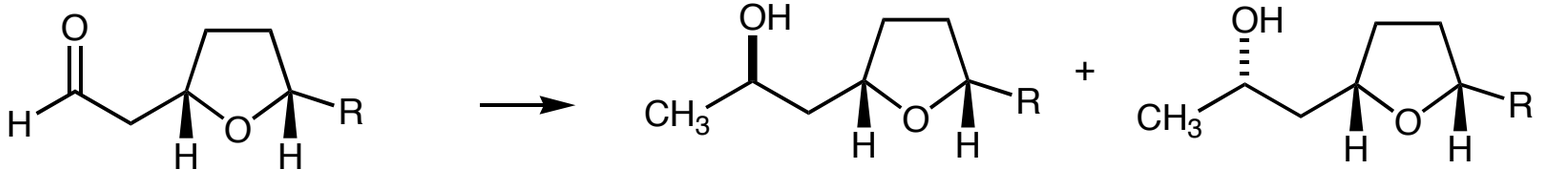
X-206 Intermediate

Baldwin, S. W. *Tetrahedron Lett.* **1991**, *32*, 1937.



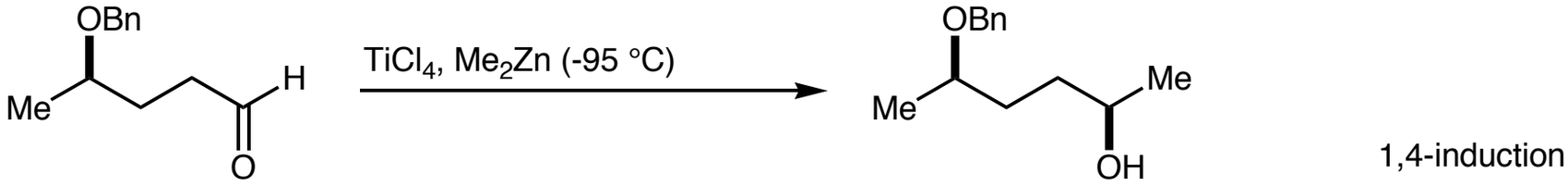
1 : 140 (86%)

Other example: Fujisawa, T. *Chem. Lett.* **1990**, 597.



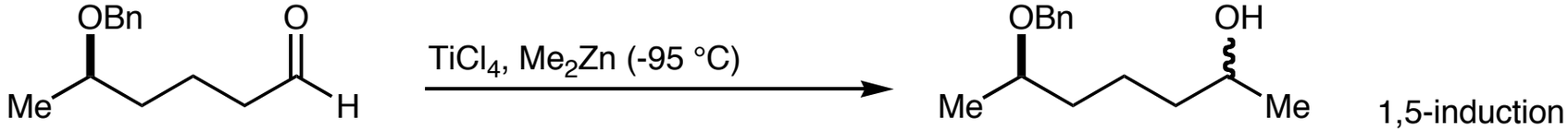
R	$MeTiCl_3$	MeMgBr
t-Bu	80 : 20	45 : 55
$CH_2CH_2OCH_3$	14 : 86	2 : 98

Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 989.



5.7 : 1

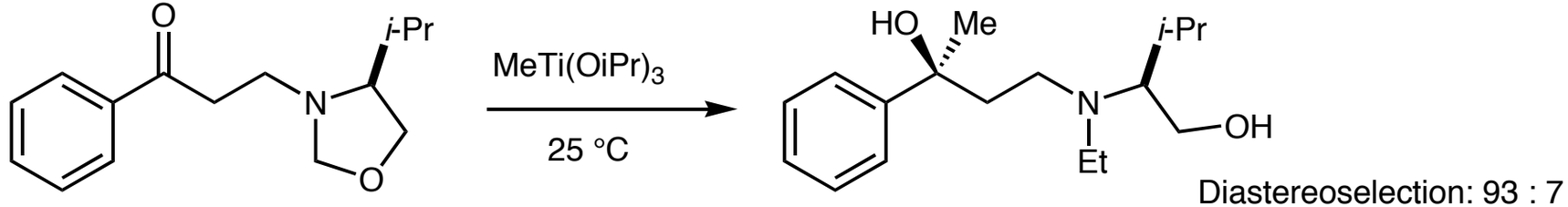
1,4-induction



ca. 1 : 1

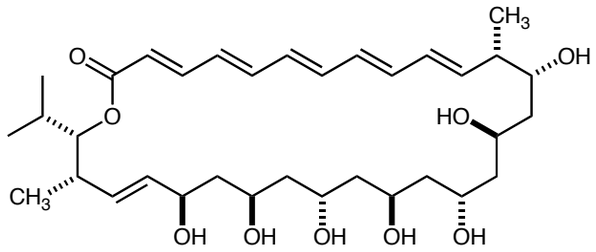
1,5-induction

Takahashi *Chem. Pharm. Bull.* **1986**, *34*, 479.

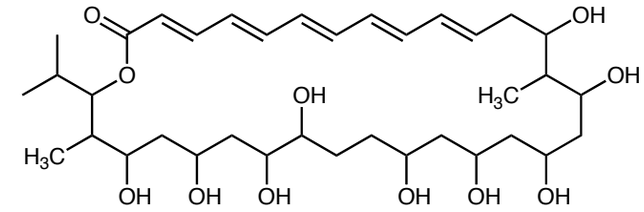


Diastereoselection: 93 : 7

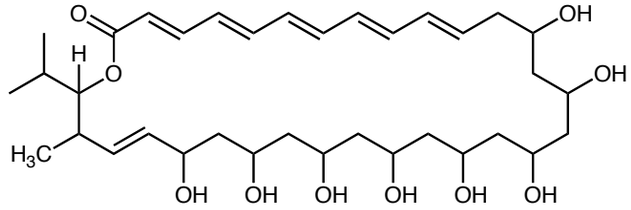
Polyene Macrolide Antibiotics



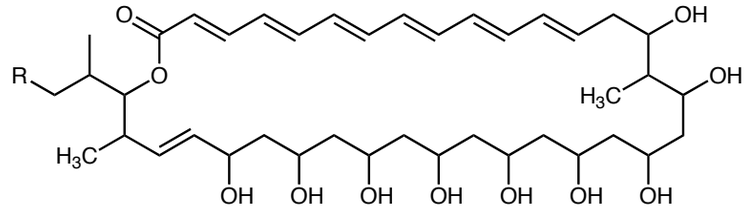
Roxaticin



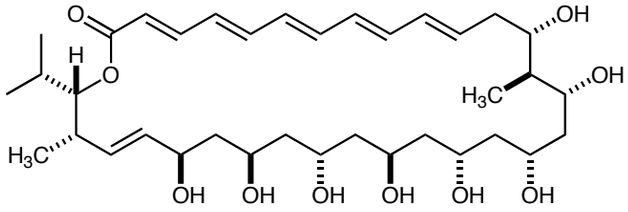
Surgumycin



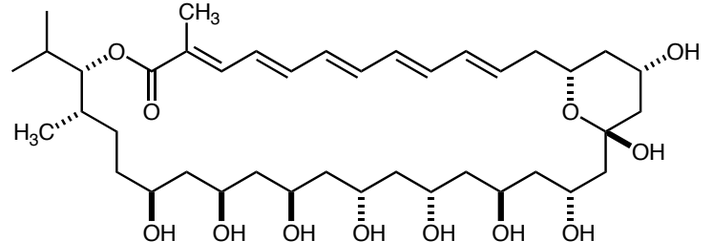
RK-397



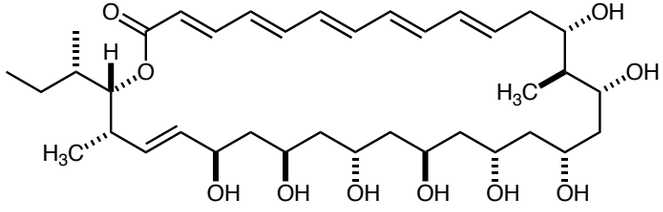
Dermostatin A [R = H]
Dermostatin B [R = CH_3]



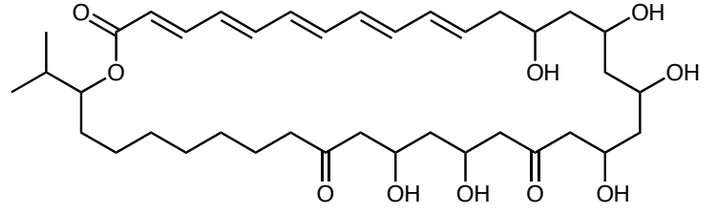
Mycoticin A



Roflamycoin

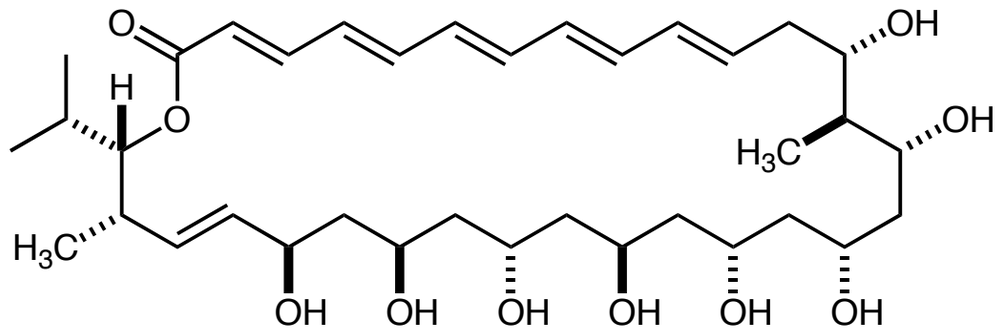


Mycoticin B

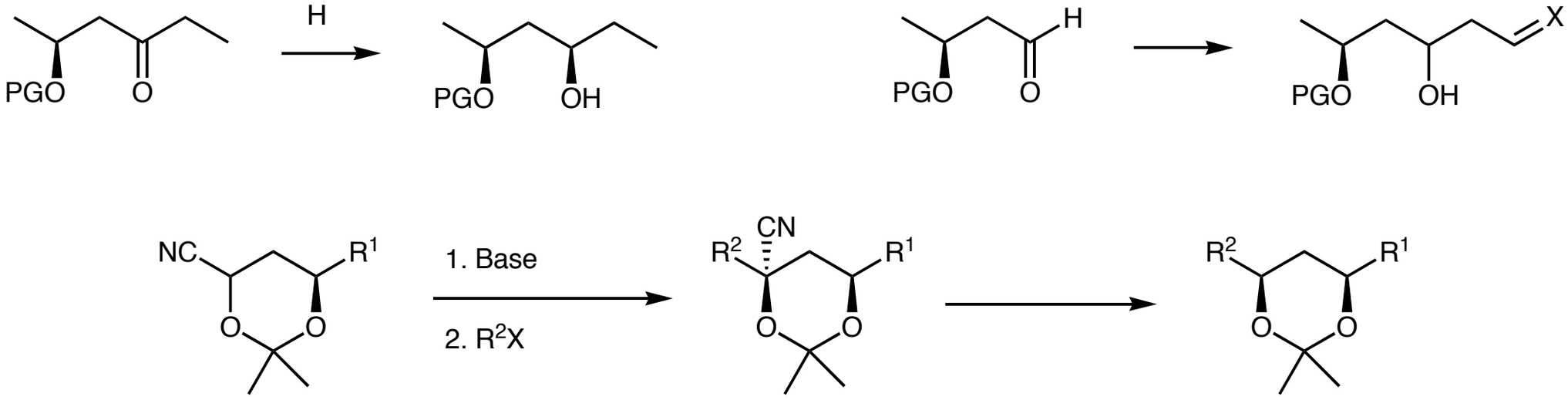


Roseofungin

Retrosynthesis of Mycoticin A

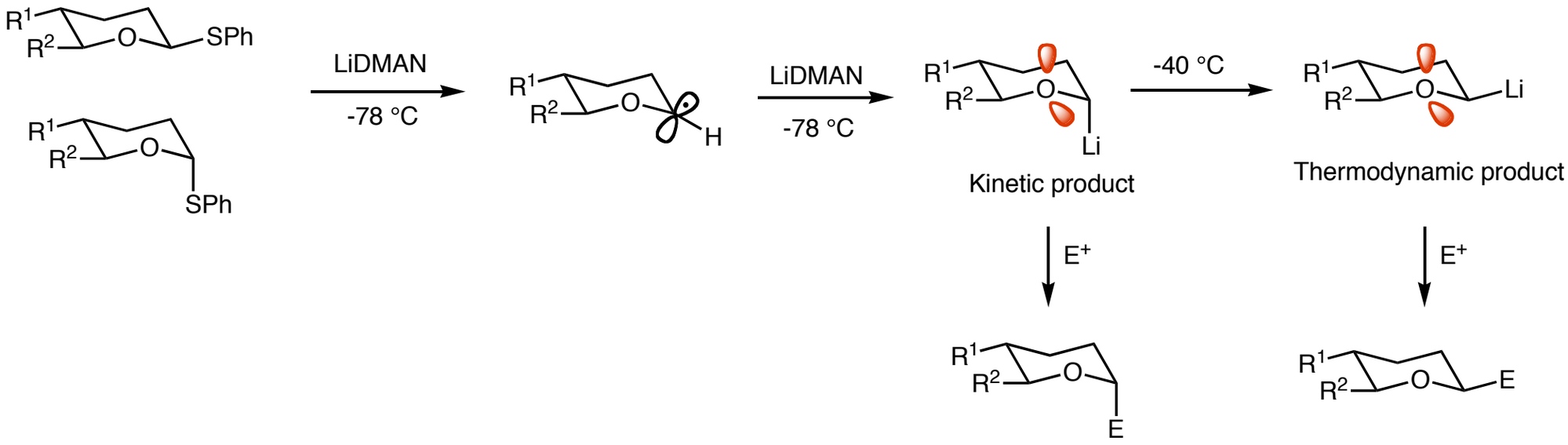


Mycoticin A

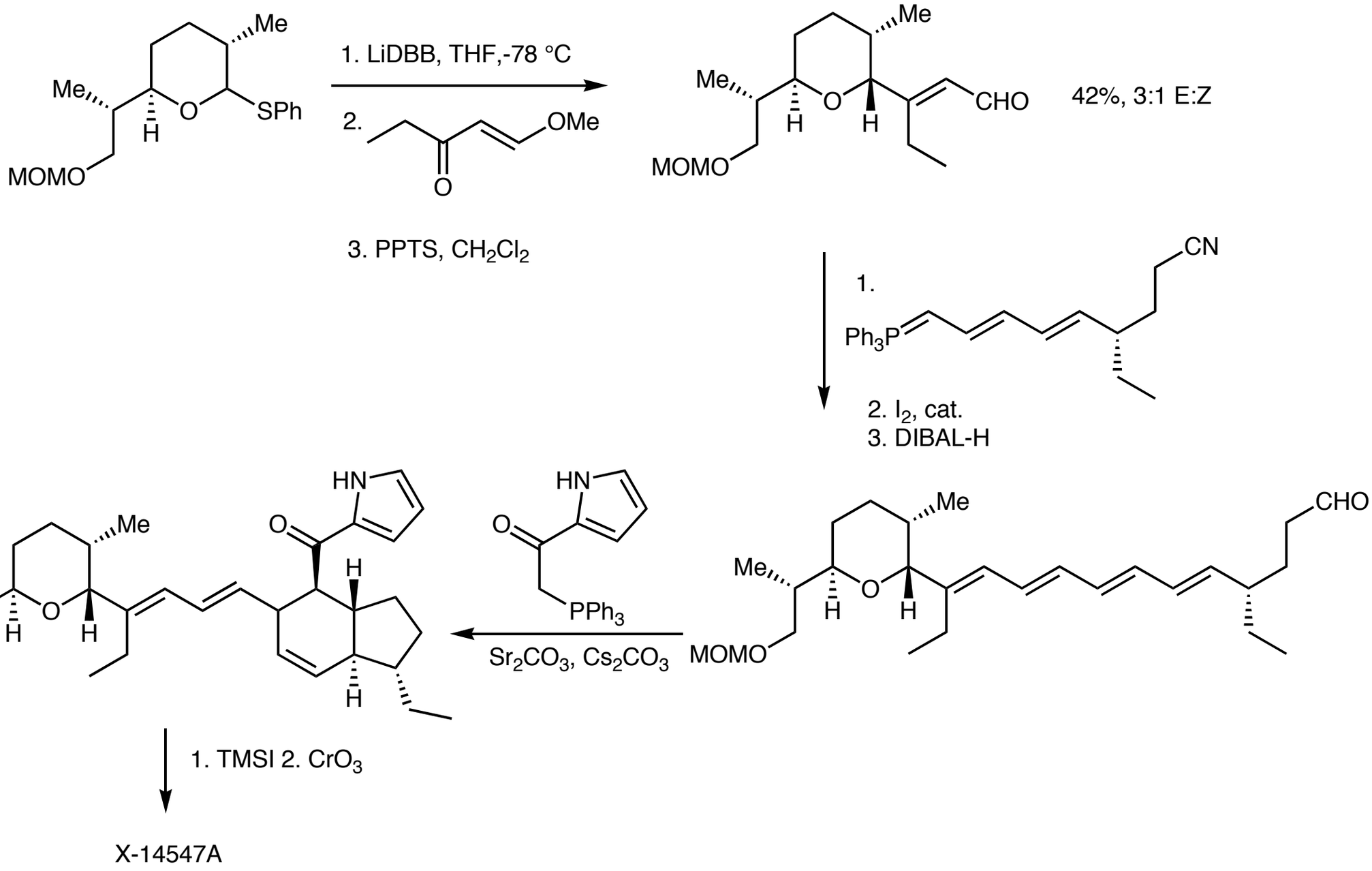


Tetrahydropyranyl α-Lithio Anions

T. Cohen (Pittsburg)

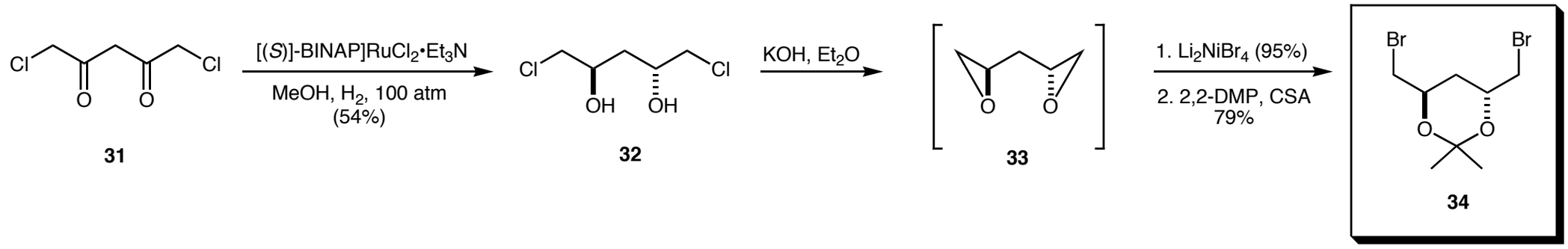


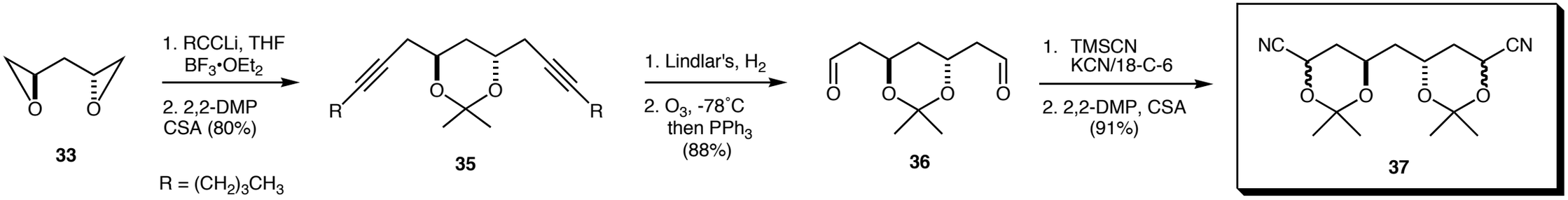
Indanomycin Synthesis



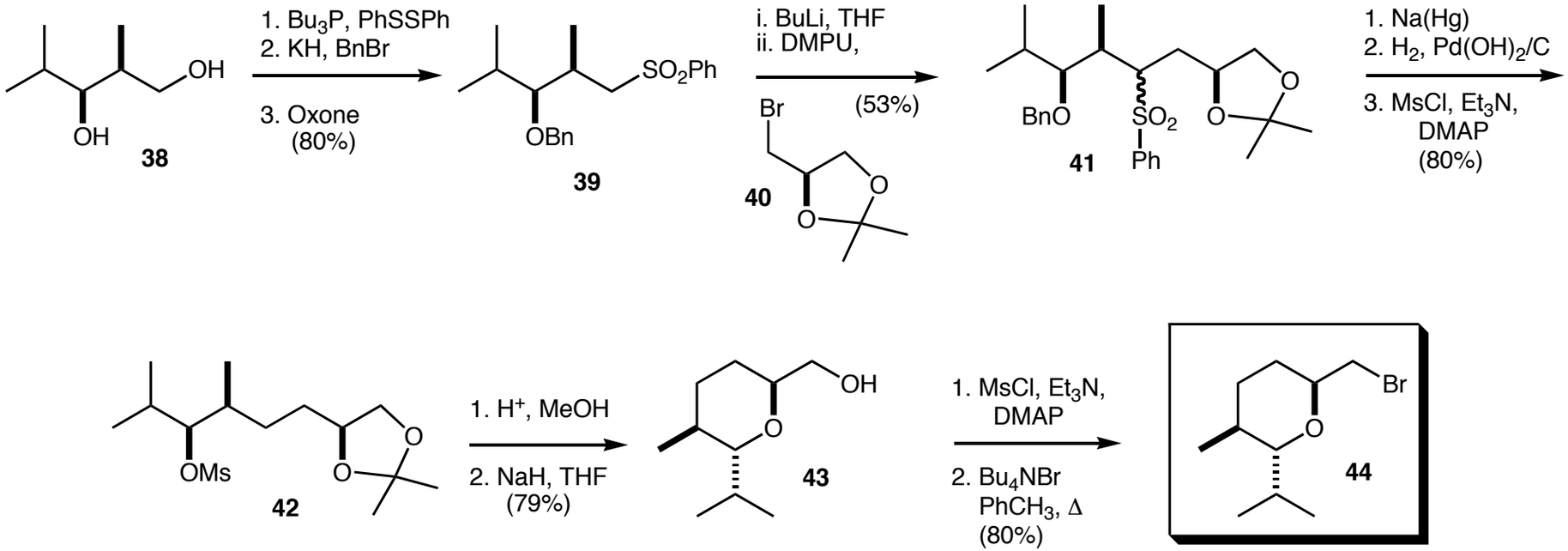
Stereoselective 1,3-Polyol Units

Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

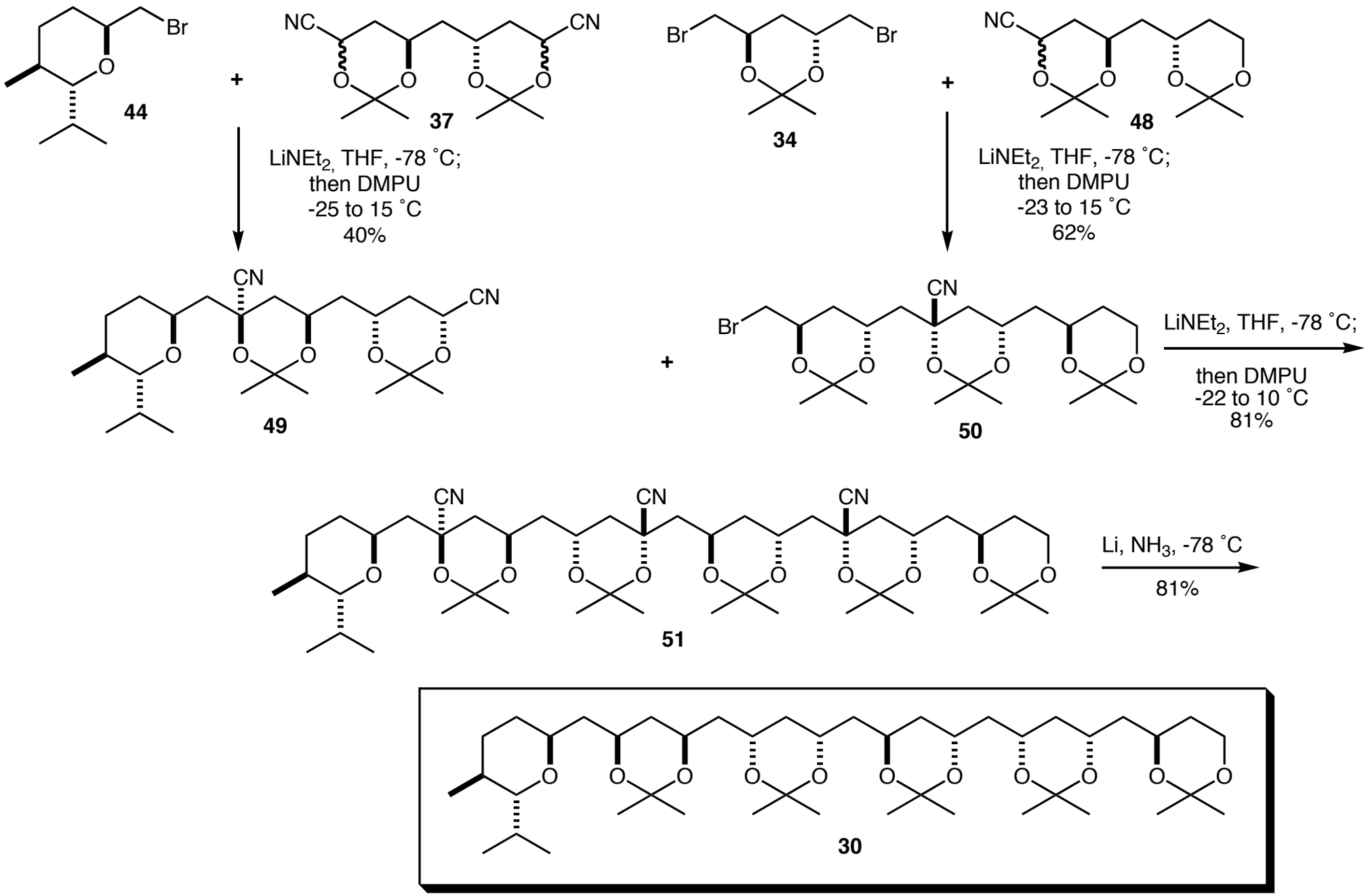




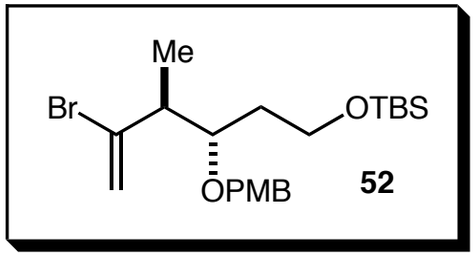
Stereoselective 1,3-Polyol Units



Stereoselective 1,3-Polyol Units



Stereoselective 1,3-Polyol Units



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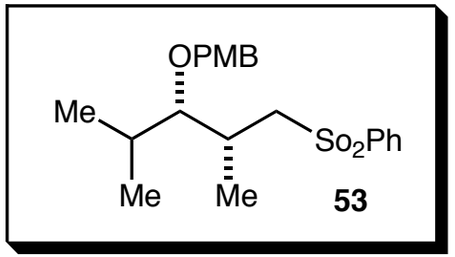
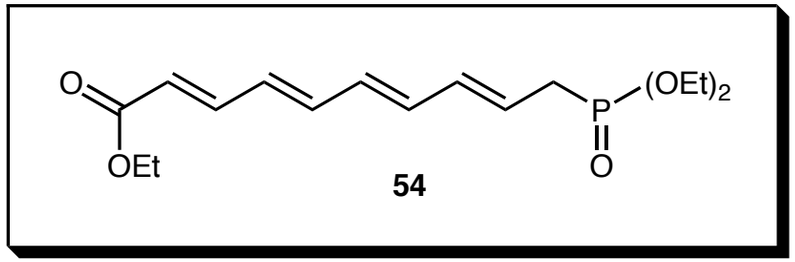
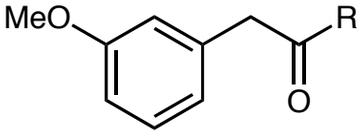


53

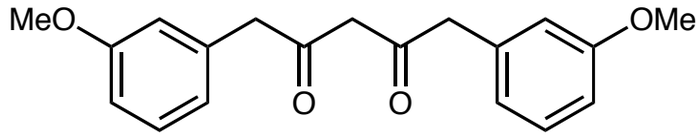


54



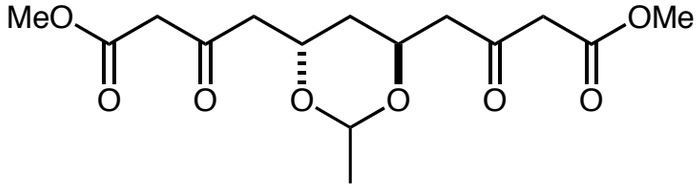
55 R = CH_2SO_2Ph
56 R = OCO'Bu

1. NaH; **56**
2. Zn, HOAc (64%)



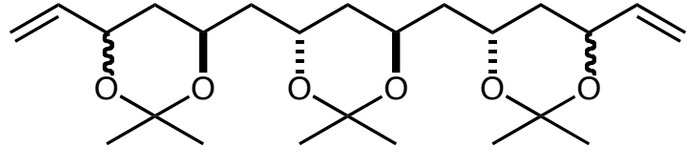
57

1. $RuCl_2[(R)\text{-BINAP})]\cdot Et_3N$, 10%, H_2, 100 atm, (59%)
2. $(EtO)_2CHCH_3$, H^+ (90%)
3. Li, NH_3; then O_3 (60%)



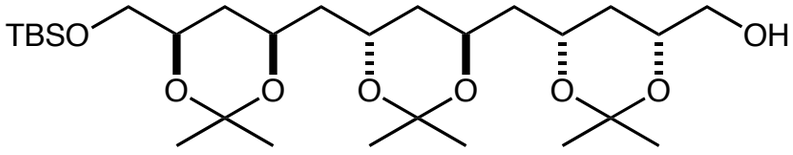
58

1. $RuCl_2[(R)\text{-BINAP})]Et_3N$, 10%, H_2, 100 atm,
2. 2,2-DMP, H^+
3. DIBAL-H; vinylMgBr
4. 2,2-DMP, H^+ (30%)



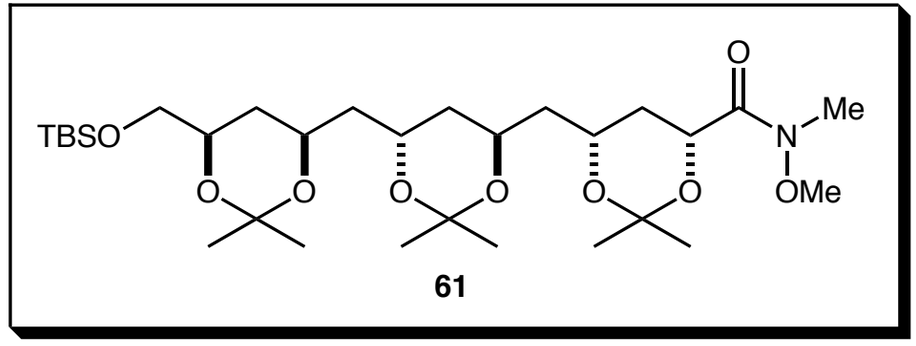
59

1. O_3, DMS
2. K_2CO_3/MeOH
3. $NaBH_4$ (81%)
4. TBSCl (49%)



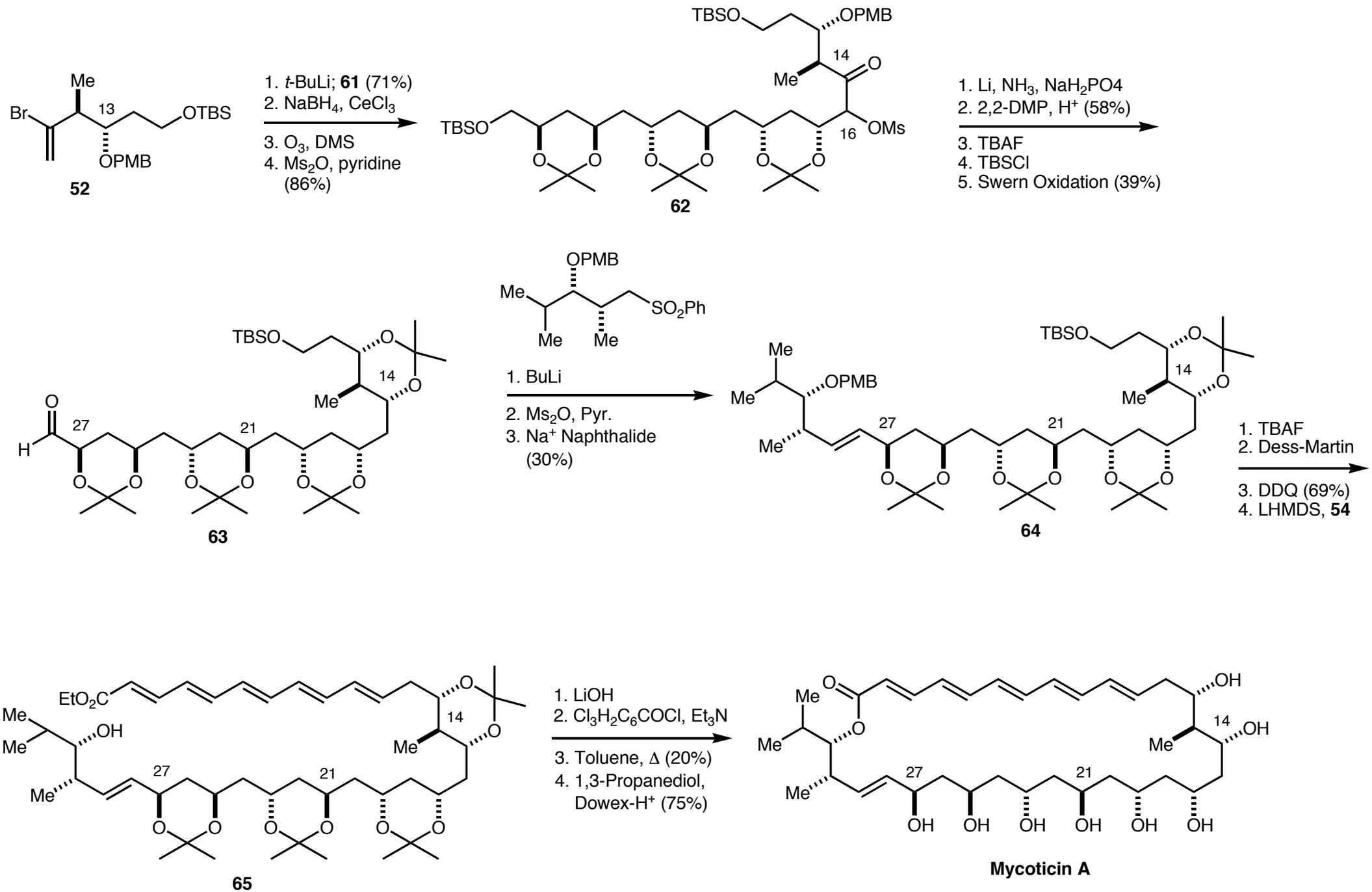
60

1. $RuCl_3$, $NaIO_4$
2. HNMe(OMe) BOP (73%)

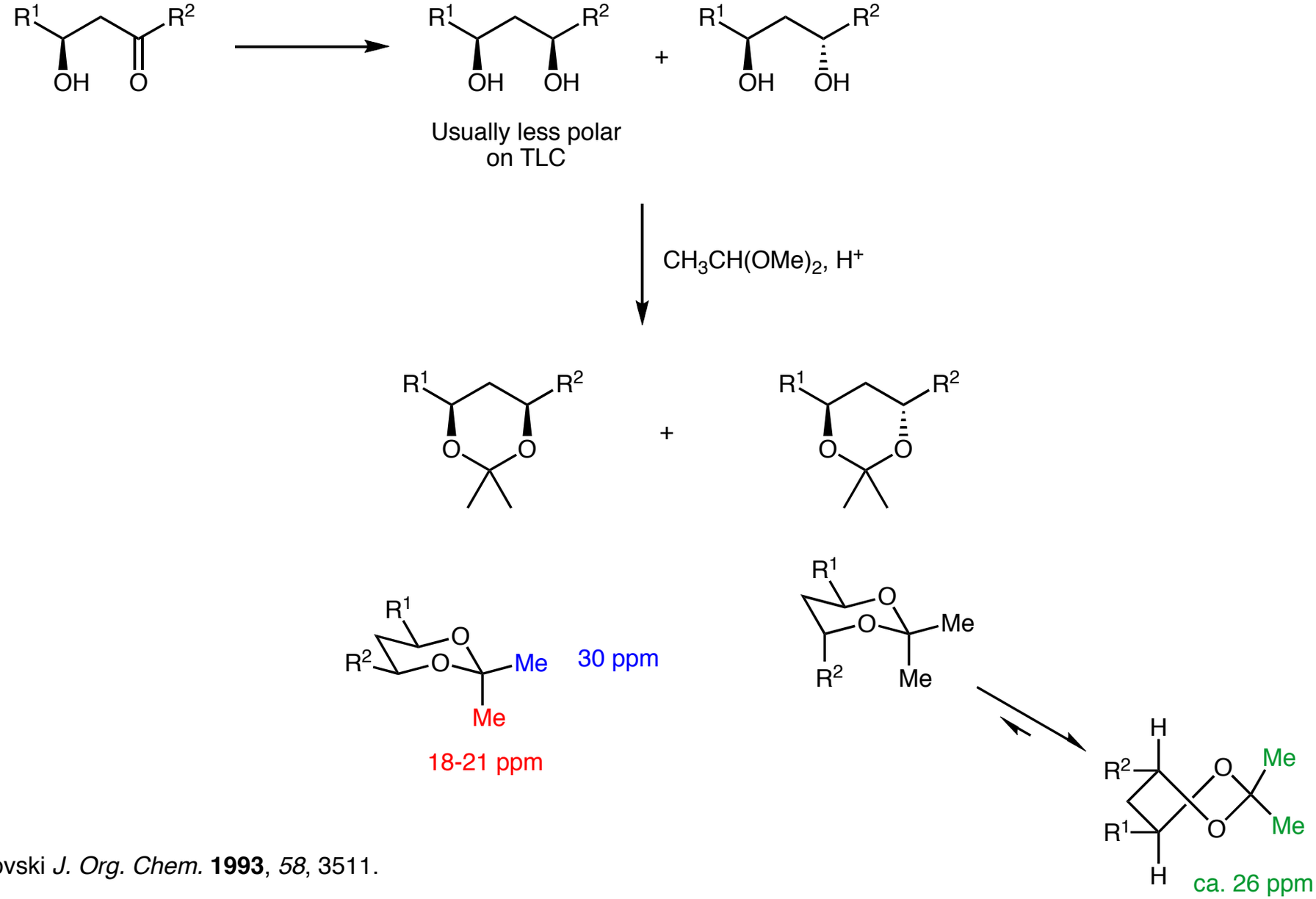


61

Stereoselective 1,3-Polyol Units

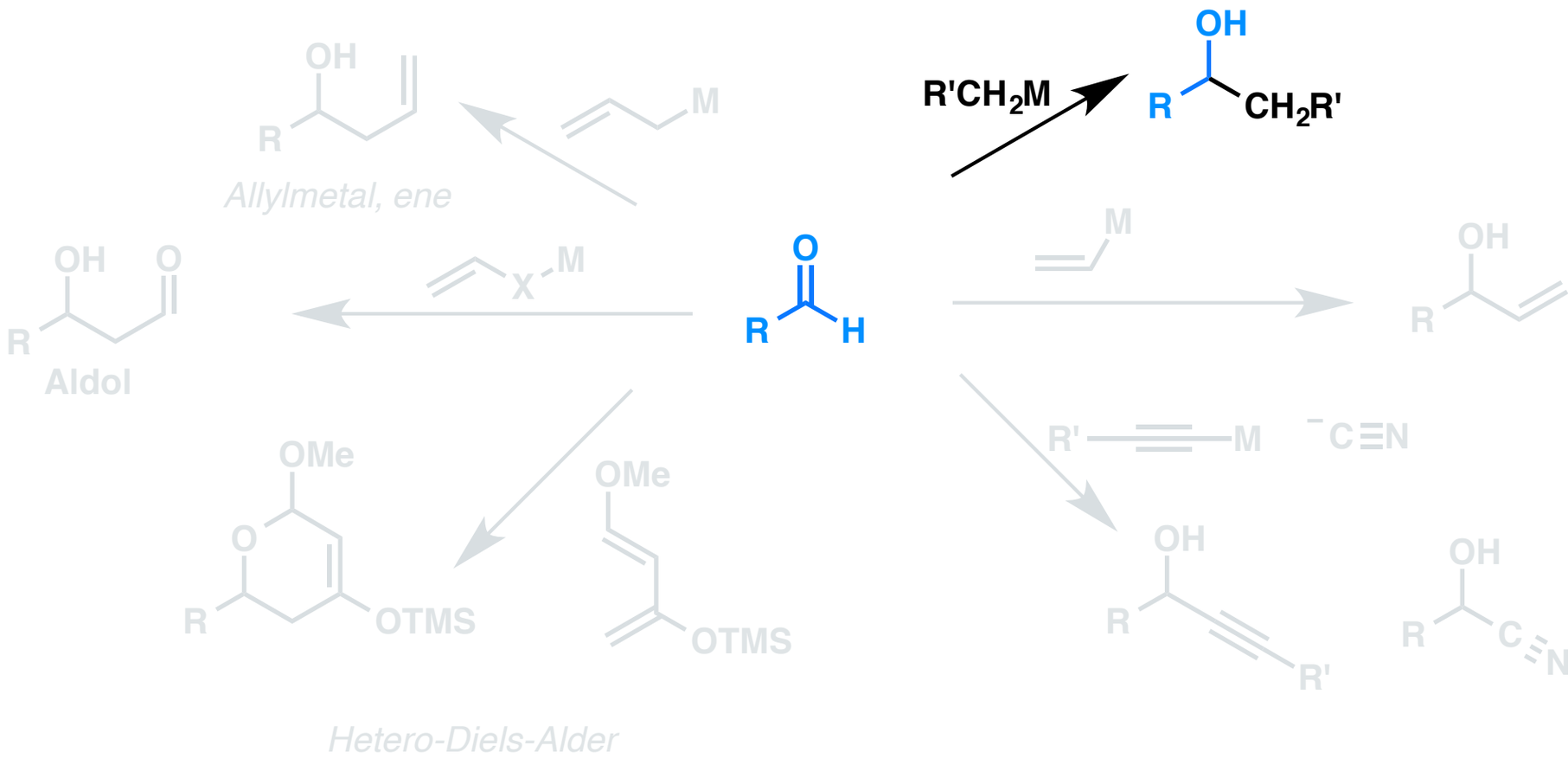


1,3-Polyol Structural Assignment

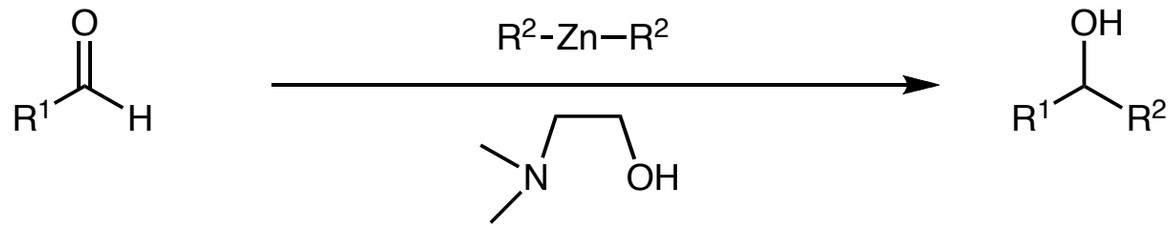


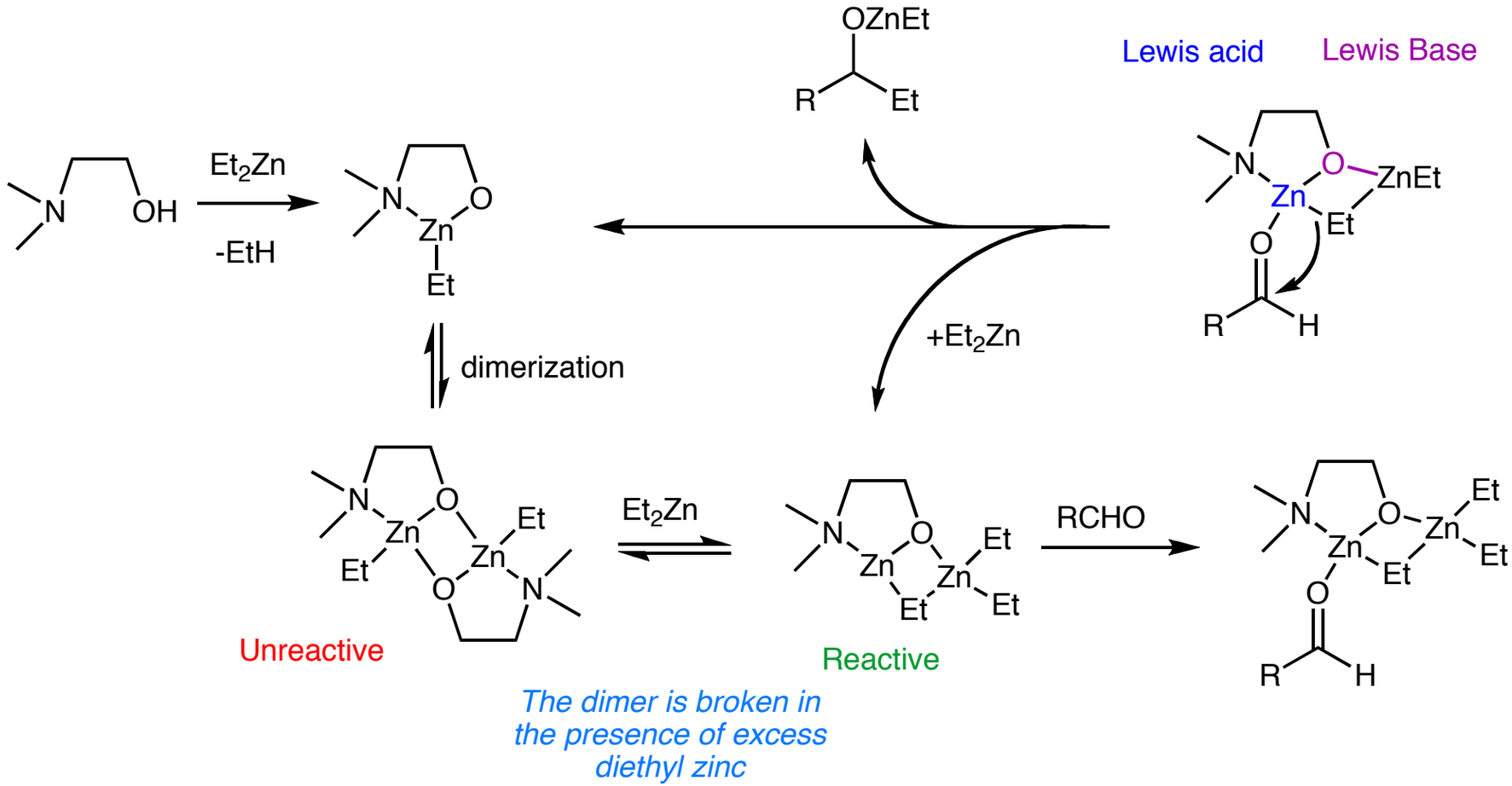
S. Rychnovski *J. Org. Chem.* **1993**, *58*, 3511.

Nucleophilic Addition to C=O

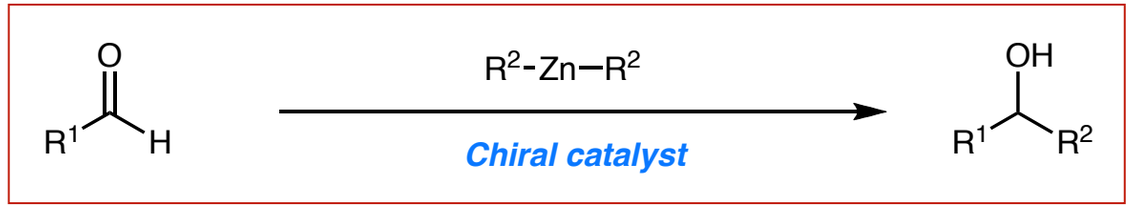


Dual Activation of Amino Alkoxides



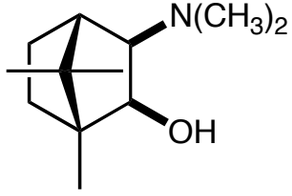


Enantioselective Catalytic Alkylation of Aldehydes

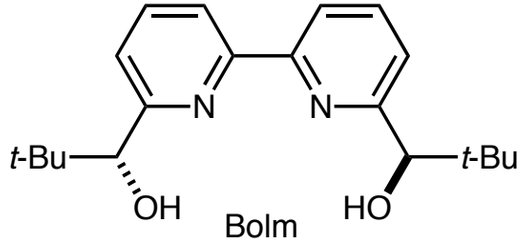


Amino Alcohols/Zinc Alkoxide

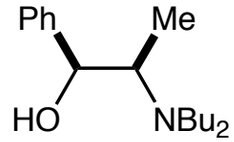
(2-10 mol%)



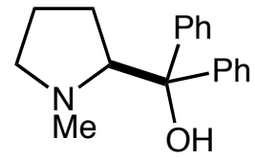
(DAIB)



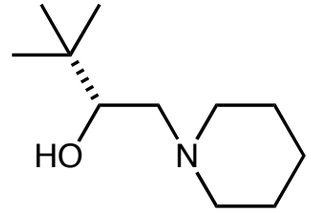
Bolm

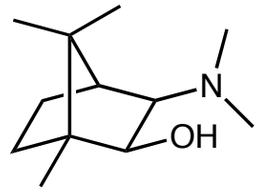


(DBNE)

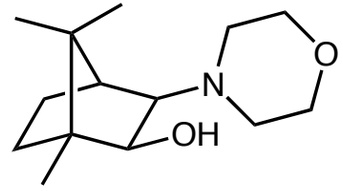


(DPMPM)



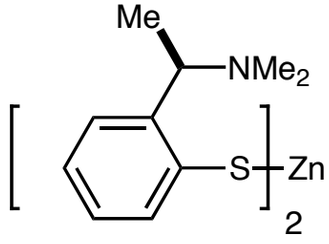


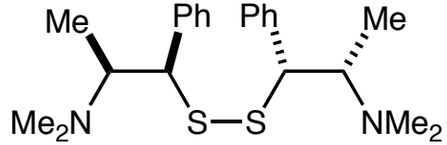
DAIB

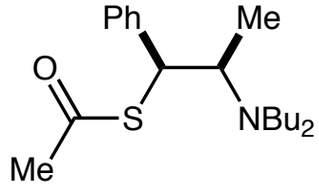


MIB
(2-exo-Morpholinoisoborneol)

Zinc Thiolate

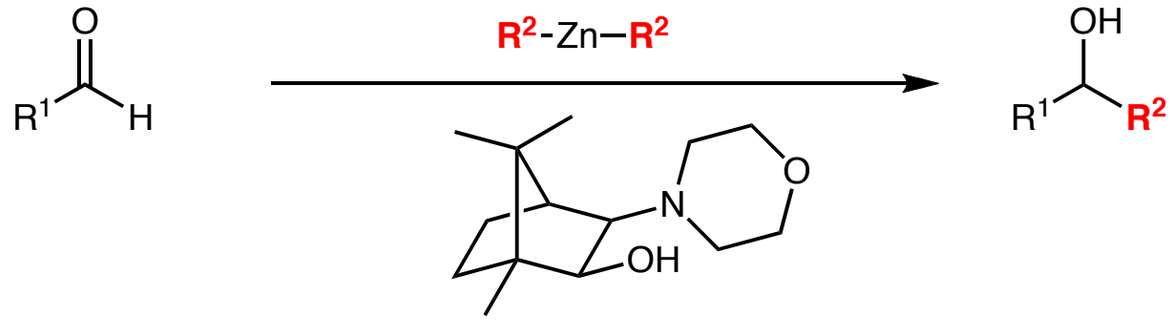




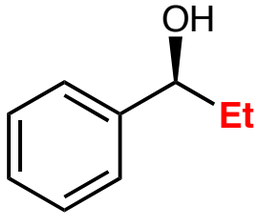


Enantioselective Alkylation of Carbonyl with R_2Zn and MIB

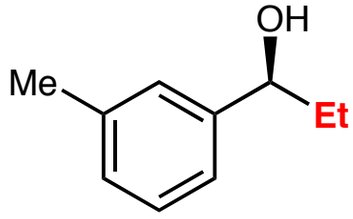
W. A. Nugent



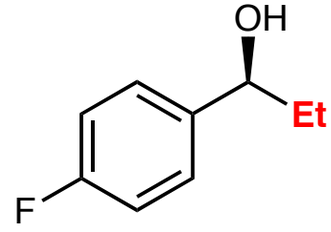
MIB
(2-exo-Morpholinoisoborneol)



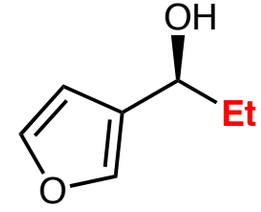
98% (98% ee)



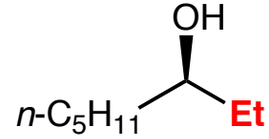
97% (98% ee)



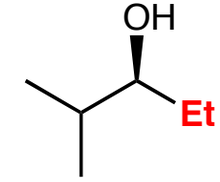
97% (98% ee)



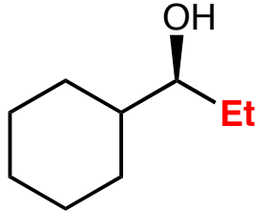
91% (97% ee)



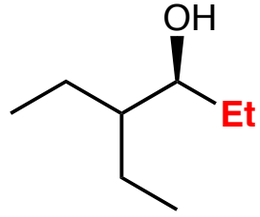
96% (91% ee)



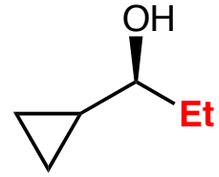
94% (99% ee)



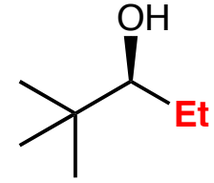
94% (99% ee)



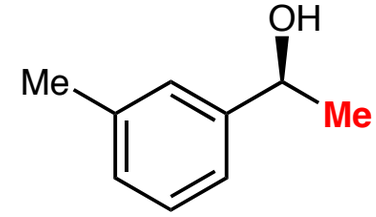
92% (99% ee)



91% (98% ee)

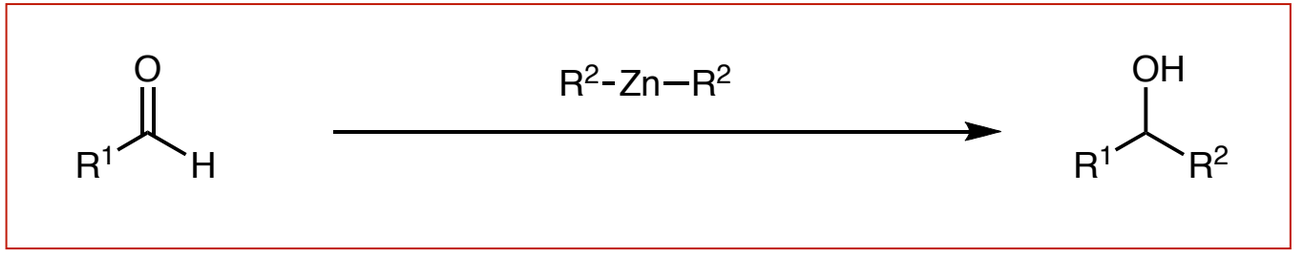


62% (97% ee)



88% (95% ee)

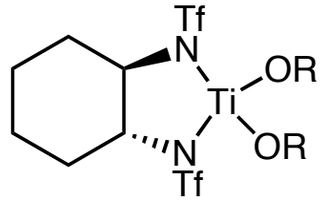
Titanium-based Chiral Lewis Acids



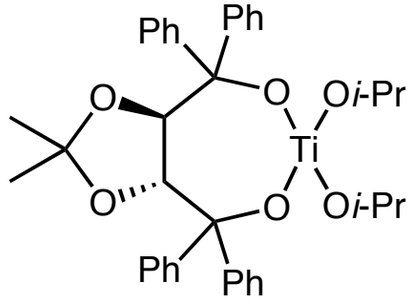
Ohno (0.005-0.04 equiv)

⇨ Knochel

⇨ Walsh

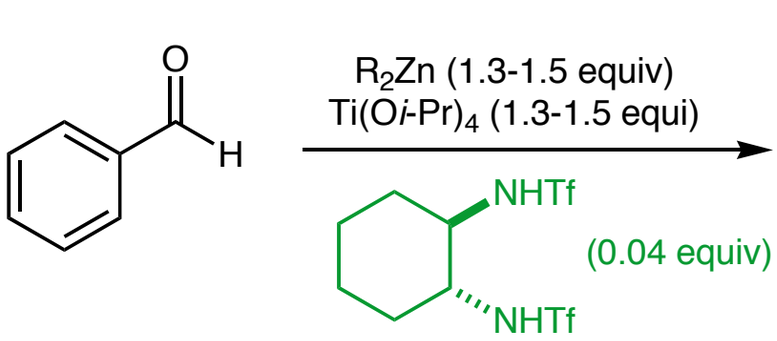


Seebach (0.05-0.20 equiv)

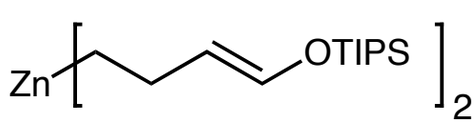


RCHO	R_2Zn
Aliphatic unsaturated Aromatic	Me, Et Functionalized
Aliphatic unsaturated Aromatic	Me, Et Functionalized

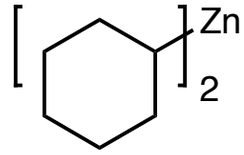
Bis(sulfonamide) complexes: Functionalized Diorganozinc Reagent



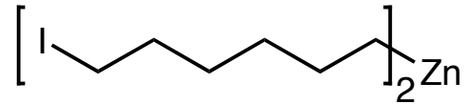
R	ee
Me	73%
Bu	97%
Pentyl	99%
Octyl	92%



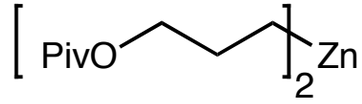
77%, >96% ee



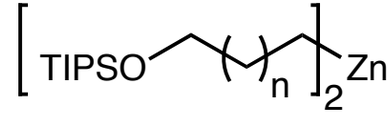
67%, 80% ee



58%, 86% ee

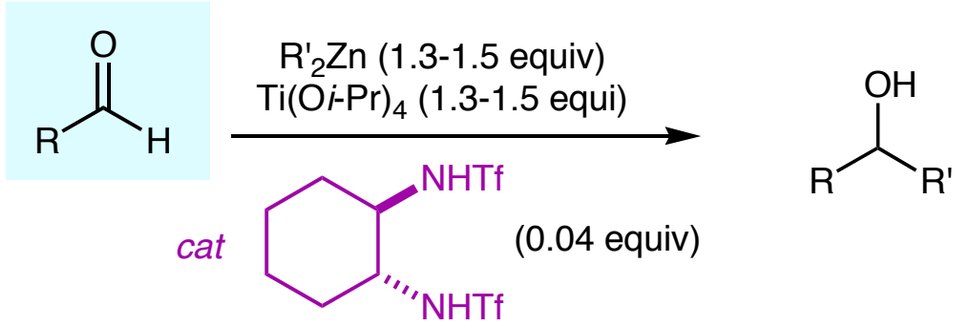


70%, 93% ee

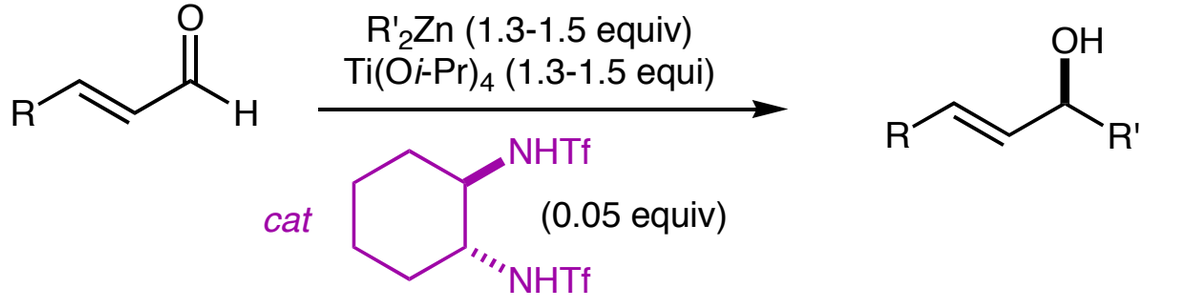


n = 1, 60%, 50% ee
n = 2, 82%, 92% ee
(TBDMS)

Bis(sulfonamide) Complexes: Functionalized Aldehydes

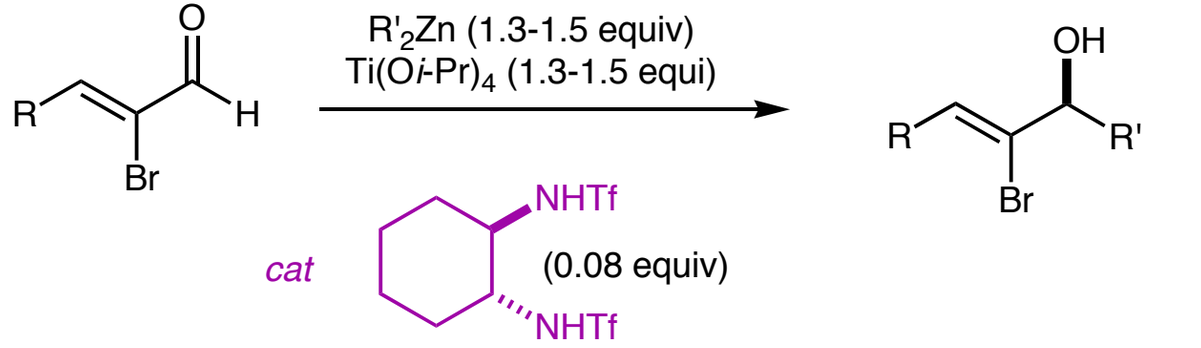


R = Ph
R = Me
R = *n*-Pr
R = *t*-Bu



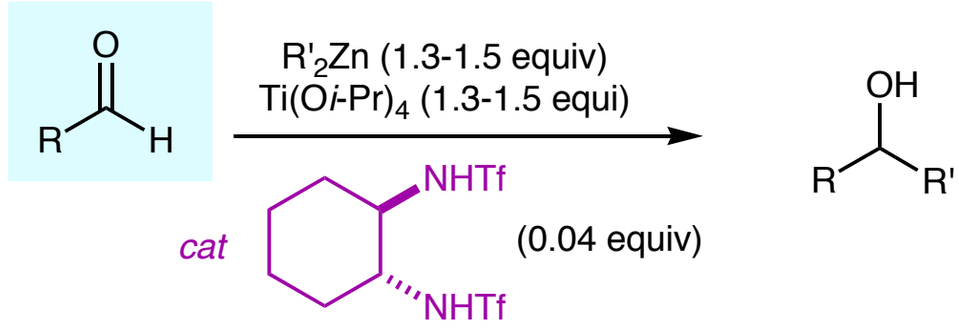
R = Ph, 71-93%, 80-93% ee
R = Me, 69-82%, 70-94% ee
R = *n*-Pr, 68-82%, 89-95% ee
R = *t*-Bu, 54-61%, 97% ee

R = Ph
R = Me
R = *n*-Pr
R = *c*-Hex

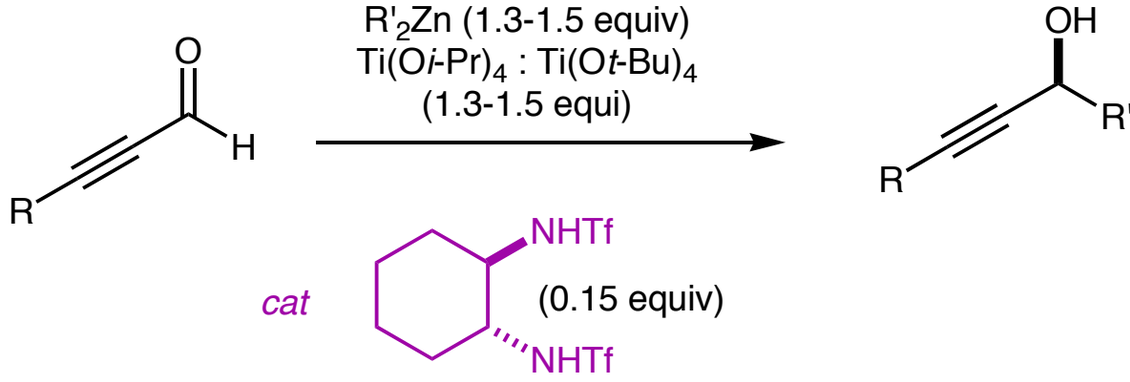


R = Ph, 72-78%, 84-92% ee
R = Me, 63-85%, 84-96% ee
R = *n*-Pr, 69-88%, >96% ee
R = *c*-Hex, 89%, 94% ee

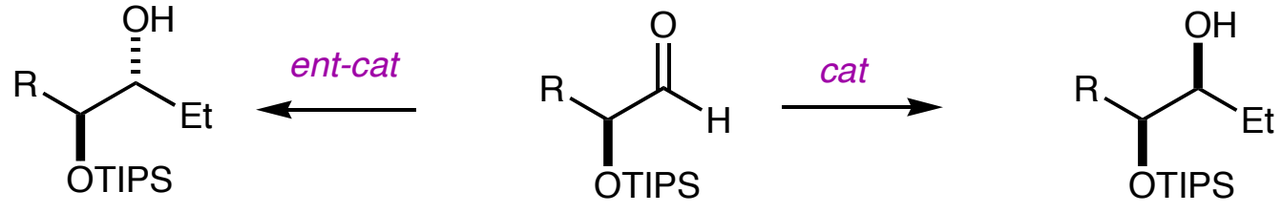
Bis(sulfonamide) Complexes: Functionalized Aldehydes



R = TIPS
R = Bu
R = Ph
R = $TBDPSOCH_2$



R = TIPS, 71-92%, 86-96% ee
R = Bu, 73-83%, 82-91% ee
R = Ph, 85-87%, 88-92% ee
R = $TBDPSOCH_2$, 76%, 94% ee

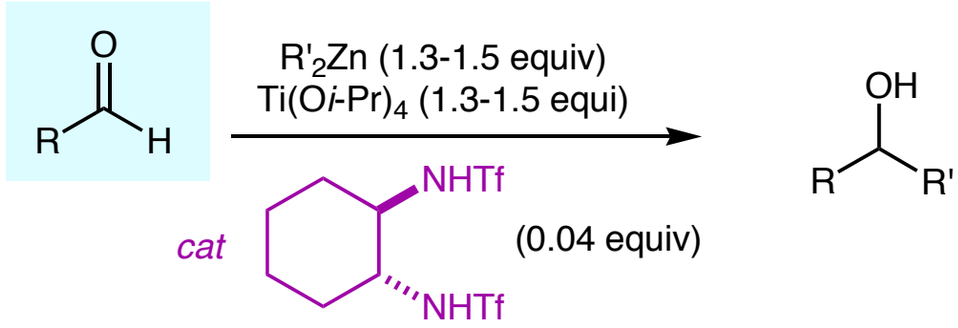


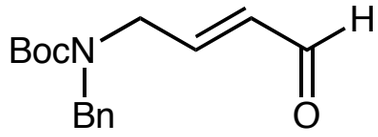
52% yield
dr: 84:16

$R'_2Zn = Et_2Zn$

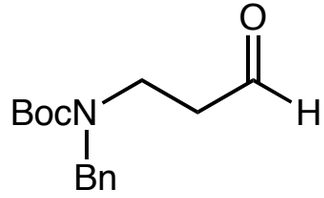
63% yield
dr: 88:12

Bis(sulfonamide) Complexes: Functionalized Aldehydes

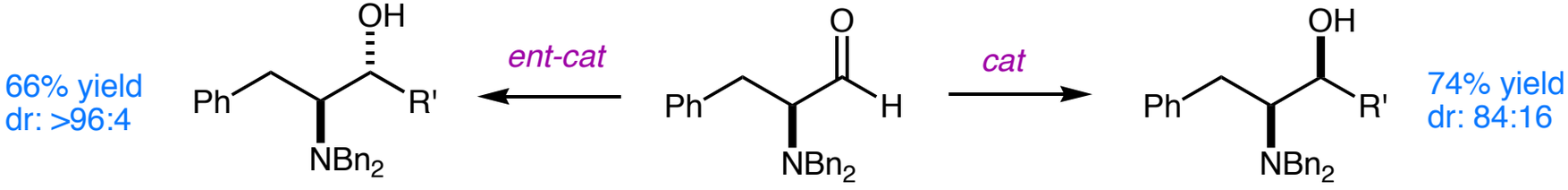




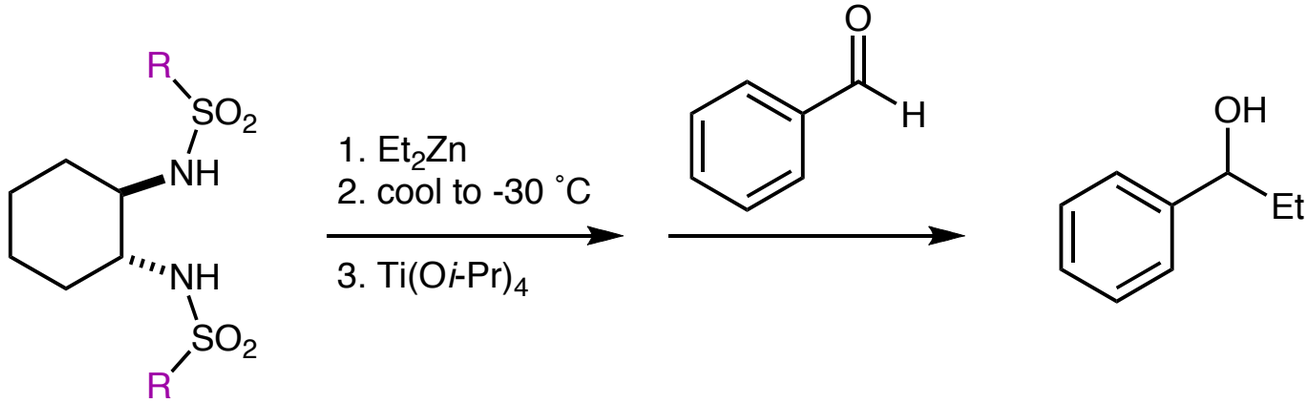
66-86%,
79-95% ee
(90% ee)



79-90%, 95->98% ee

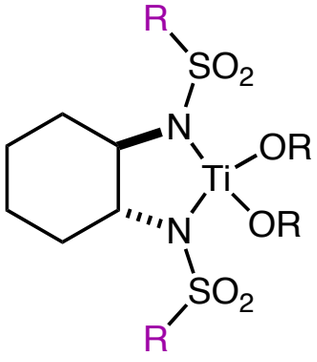


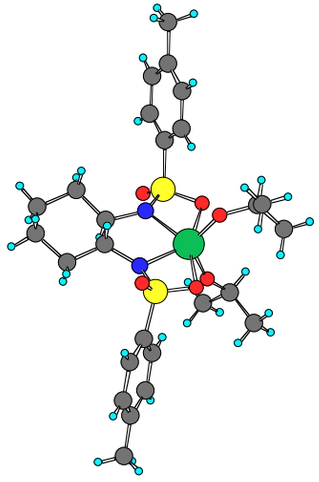
Bis(sulfonamide) complexes: Walsh's Contribution



Original Procedure:

1. Ligand + $Ti(O\textit{i}\text{-}Pr)_4$, 40 ˚C, toluene
2. Et_2Zn then RCHO
3. cool to -30 ˚C





R	ee
4-MeC_6H_4-	98 (97)
2,5-$Me_2C_6H_3$-	84 (84)
1-Naphthyl	93 (92)
CF_3	98 (98)
2,4,5-$Cl_3C_6H_2$-	98 (76-95)
4-$NO_2C_6H_4$	98 (87)

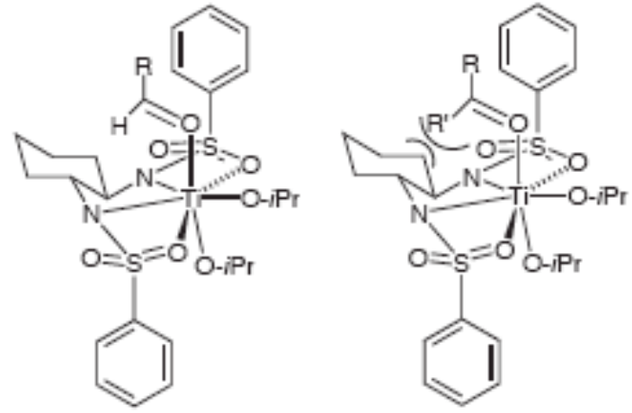


Figure 3 Proposed activation modes for aldehydes and ketones by bis(sulfonamido)Ti(O-*i*Pr)$_2$ complexes.

⇨ Enantioselectivities are essentially very high with several R groups

⇨ Bis(trifluoromethanesulfonamide) is easily prepared from 1,2-diaminocyclohexane

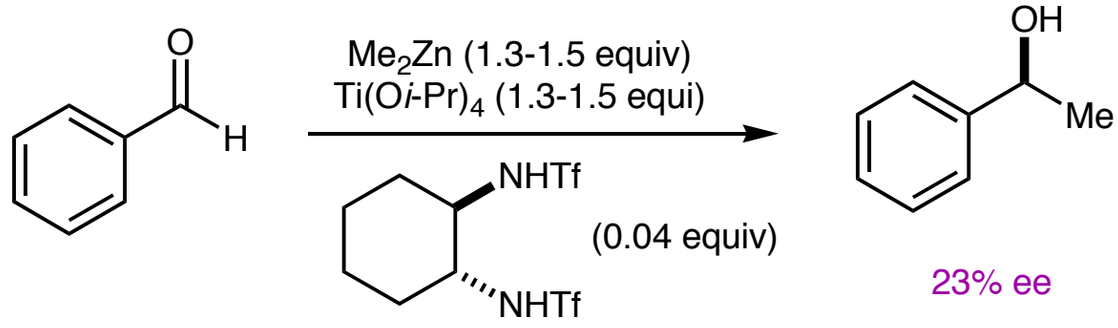
Addition of Diorganozinc to Aldehydes: Mixed Diorganozinc Reagents

⇨ Diorganozinc (R_2Zn): Only one group is transferred.

⇨ Mixed diorganozinc reagents ($RZnR_{NT}$) containing a non-transferable group (R_{NT}) have been used

$R—Zn—CH_2TMS$	$R—Zn—CH_2CMe_3$	$R—Zn—CH_2CMe_2Ph$
76-95% yield 74->95% ee	79-89% yield 89->95% ee	69-71 yield 89-94% ee

Significant improvement for the addition of methyl:



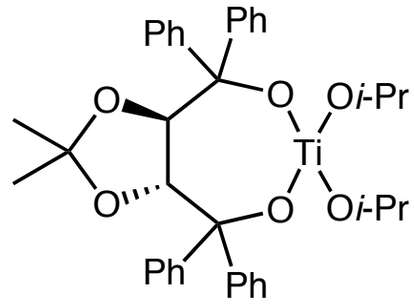
23% ee

$R—Zn—CH_2CMe_3$	92% yield, 93% ee
$R—Zn—CH_2CMe_2Ph$	69% yield, 94% ee

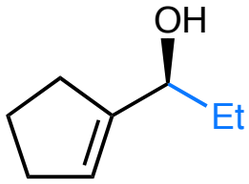
⇨ Has yet been applied in synthesis

Seebach's Titanium-Taddolate

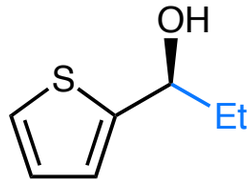
Seebach (0.05-0.20 equiv)



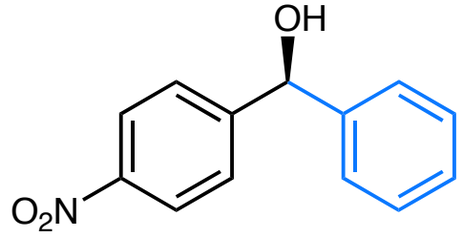
R_2Zn



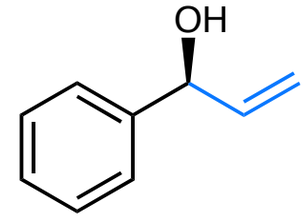
99.5% es



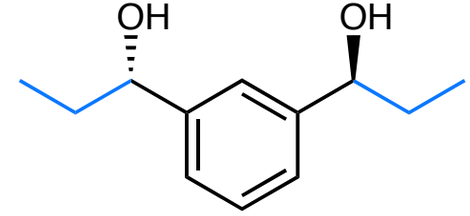
97% es



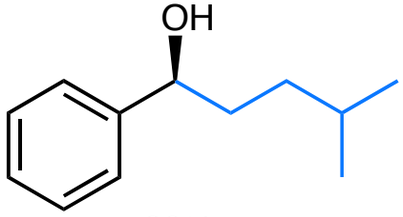
98% es



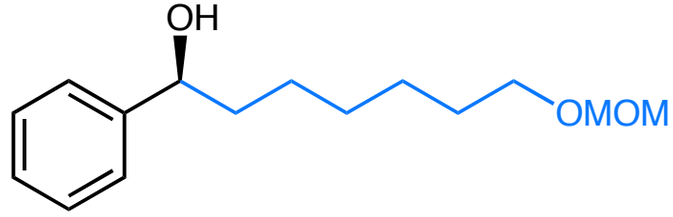
92% es



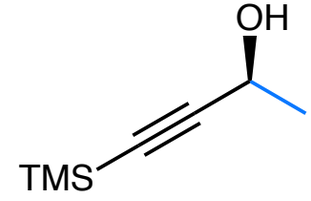
99% es



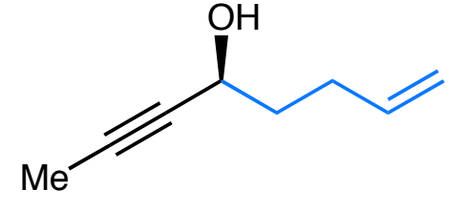
99% es



98% es

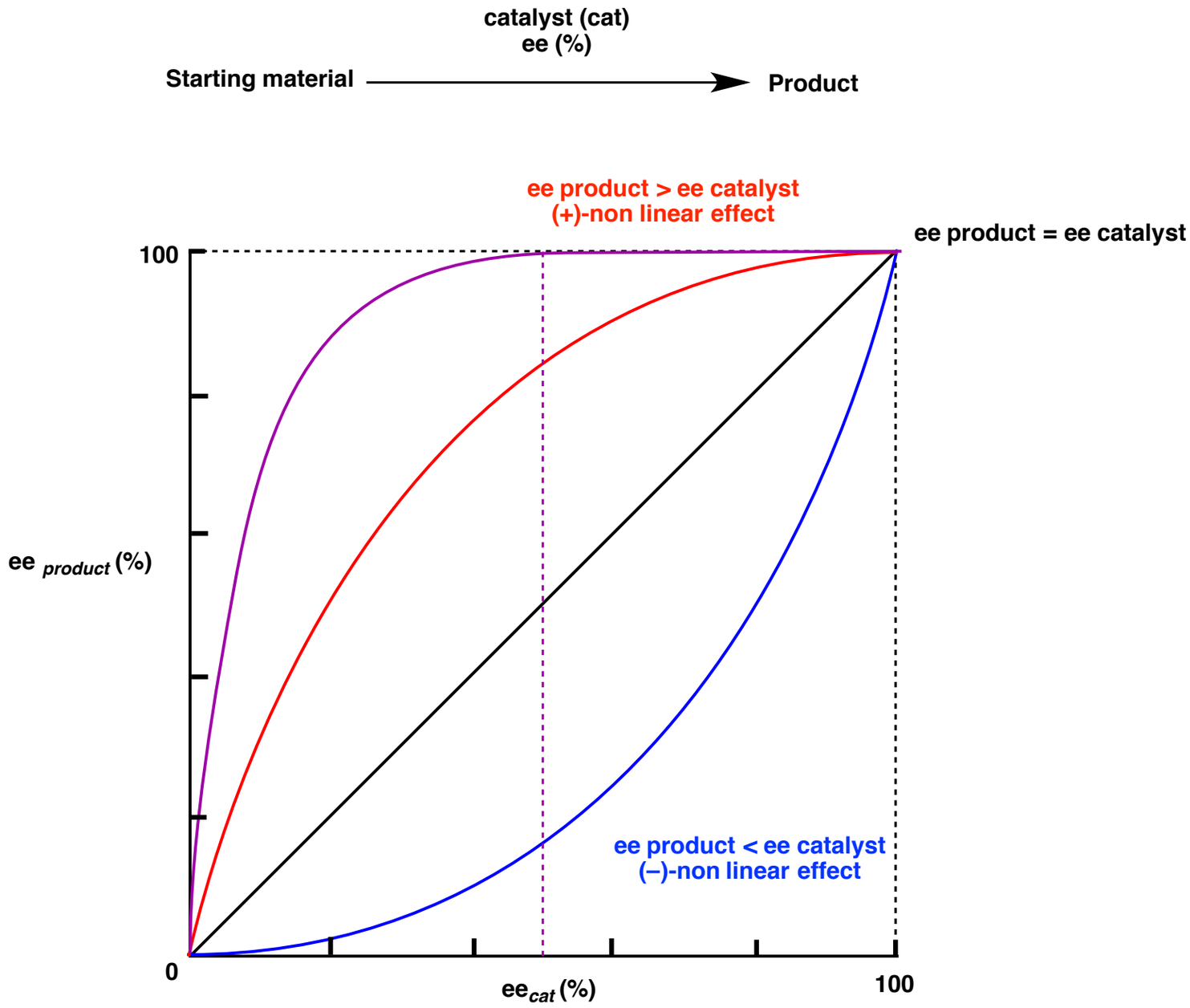


98% es

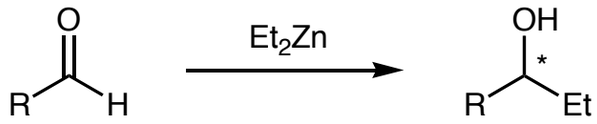


98% es

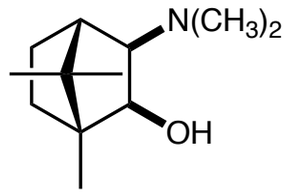
Chiral Amplification Phenomenon: Positive Non Linear Effect



Chiral Amplification Phenomenon: Positive Non Linear Effect



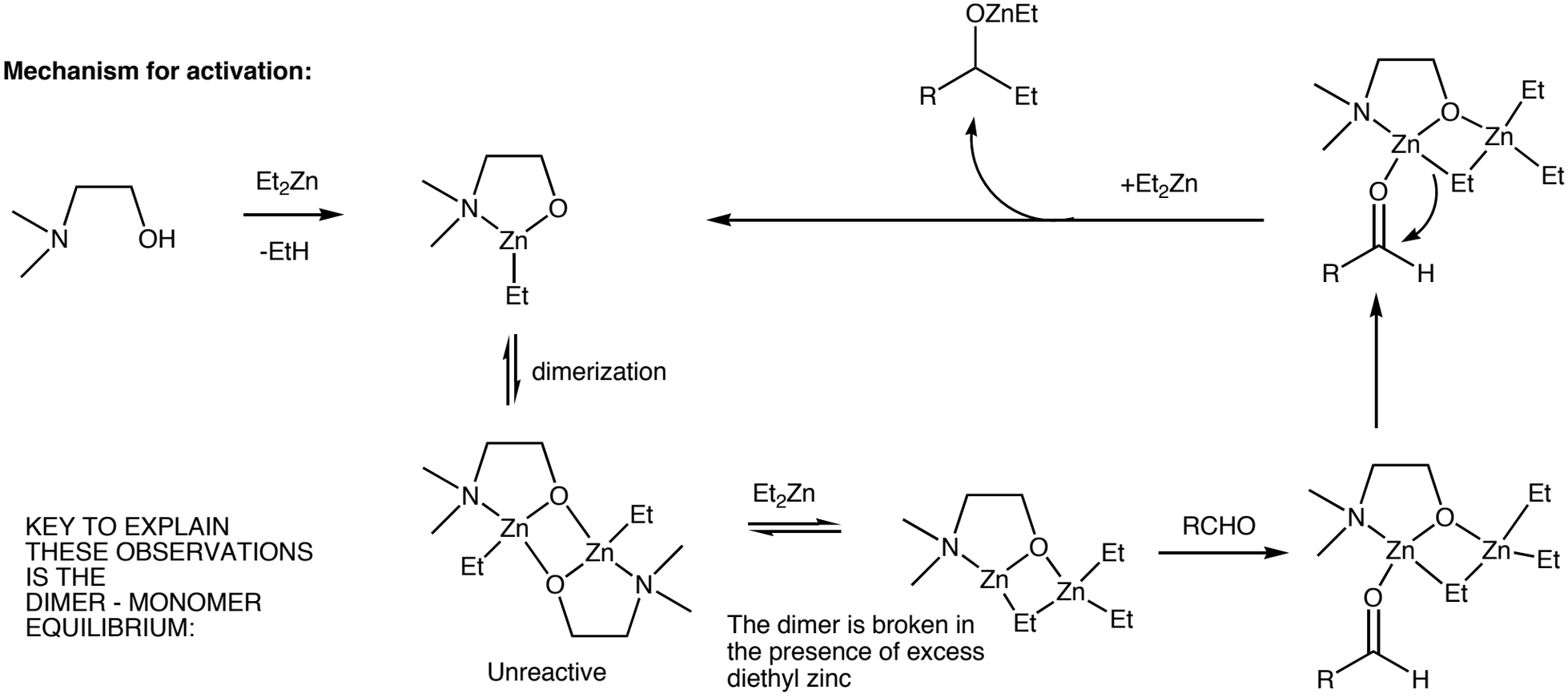
CATALYST:



% ee of catalyst	% ee Product
0%	0%
15%	95%
50%	98%
100%	99%

IMPLICATIONS: A bimetallic complex is involved at some point.

Mechanism for activation:

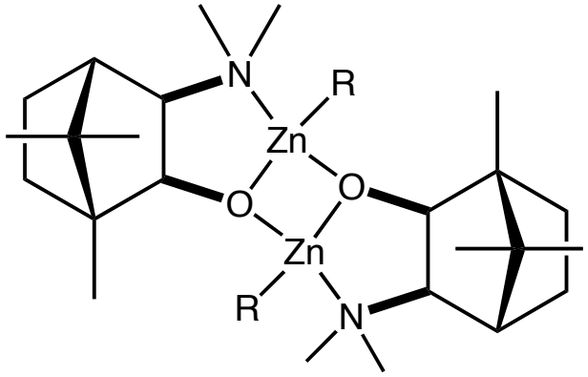


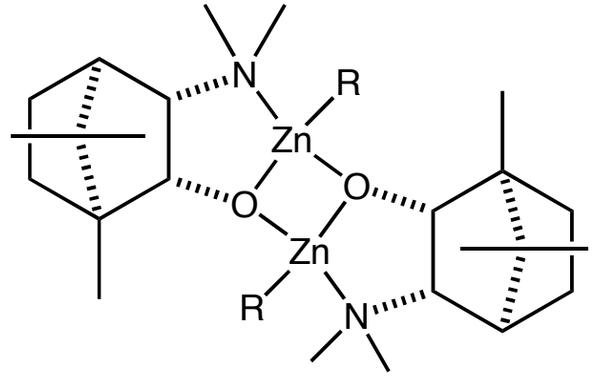
KEY TO EXPLAIN THESE OBSERVATIONS IS THE DIMER - MONOMER EQUILIBRIUM:

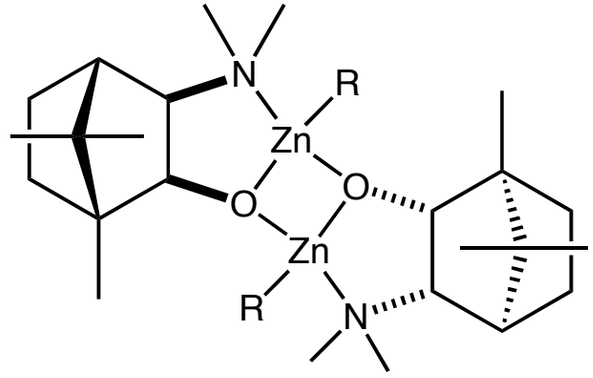
Unreactive

The dimer is broken in the presence of excess diethyl zinc

Non-linear Effects in Asymmetric Catalysis







For ex: 20% ee (60% S, 40%R) catalyst would produce:

(*S*,*S*)-Dimer

10%

(*R*,*R*)-Dimer

0%

(*S*,*R*)-Dimer

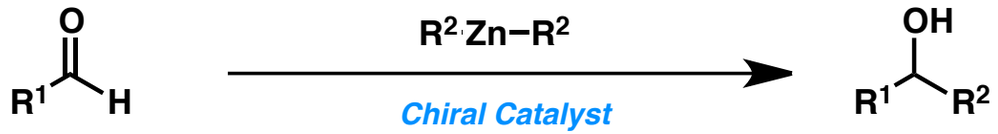
40%

The conversion of (S,R)-dimer (most stable dimer) into the R- and S-monomer is much slower than the conversion of the (S,S)-dimer into 2 S-monomers. Therefore, the minor enantiomer of the catalyst is completely converted into an unreactive (S,R)-dimer. The reaction is therefore mainly catalyzed by the monomeric species resulting from the major enantiomer.

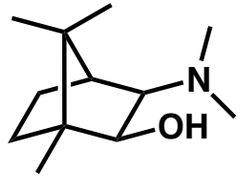
(S,S)-dimer is less stable because of the syn-geometry of the endo fused 5-4-5 ring vs the (S,R)-dimer that has a anti-geometry of the 5-4-5 ring system.

Review: Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2922-2959.

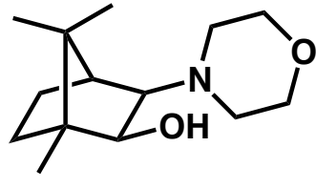
Asymmetric Induction in Dialkylzinc Addition Reactions



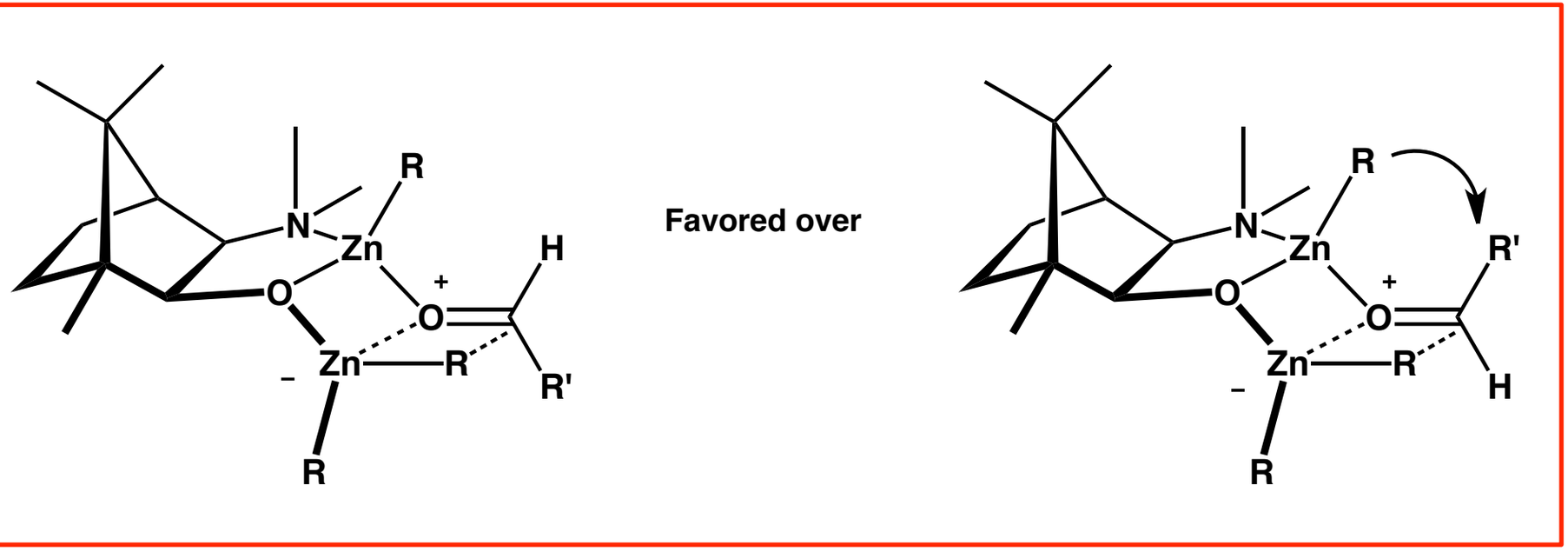
(2-10 mol%)



DAIB

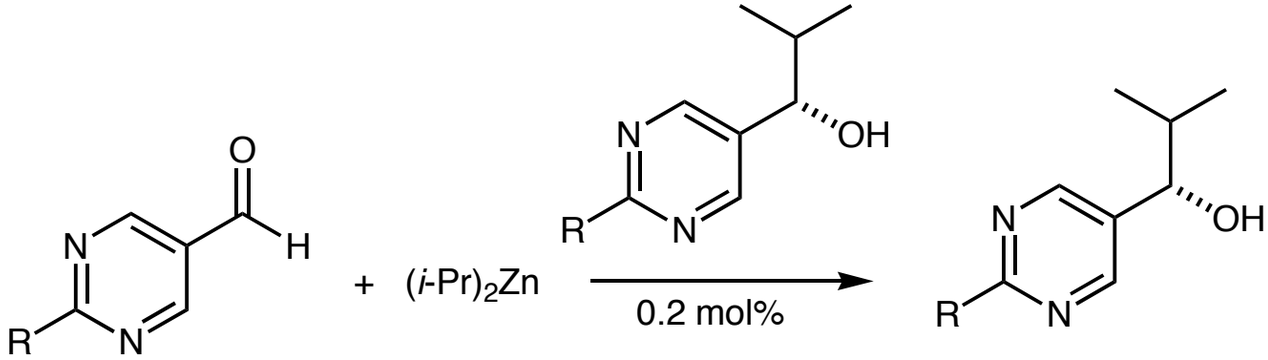


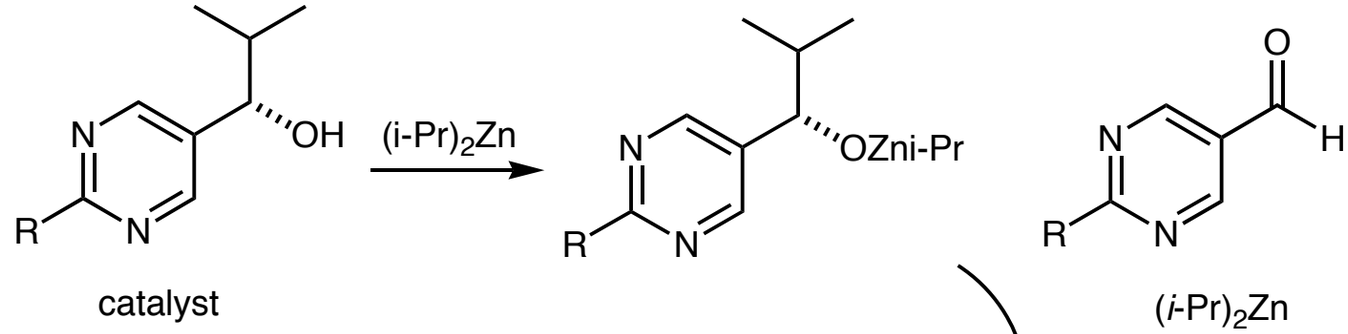
MIB
(2-exo-Morpholinoisoborneol)

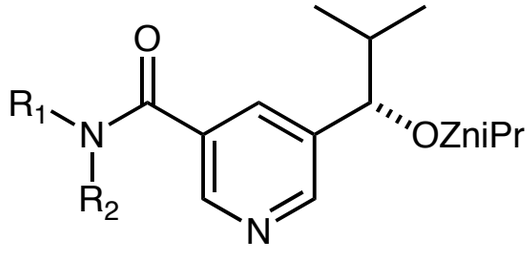


Enantioselective Catalytic Asymmetric Automultiplication

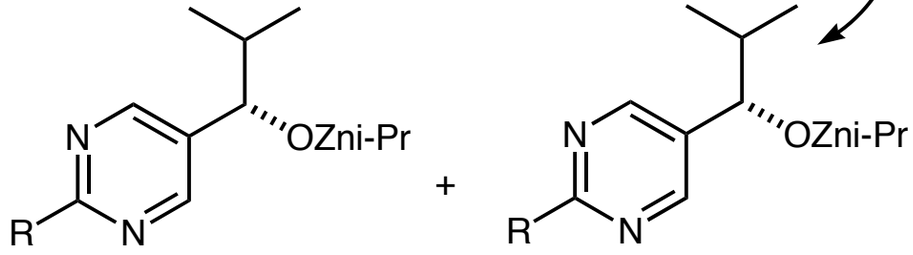
K. Soai *J. Am. Chem. Soc.* **1996**, *118*, 471-472. *Tetrahedron Lett.* **1996**, *37*, 8783. *Tetrahedron* **1996**, *52*, 13355. *Nature* **1995**, *378*, 767.



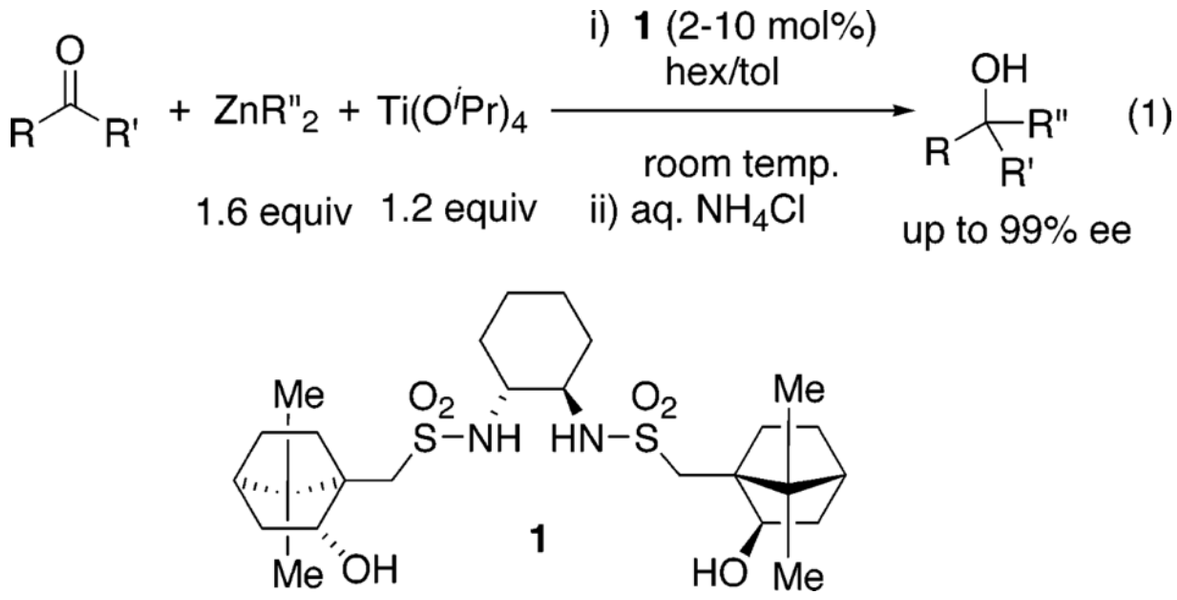




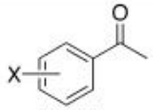
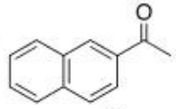
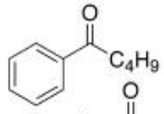
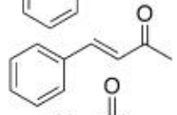
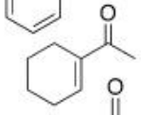
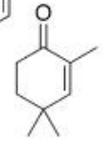
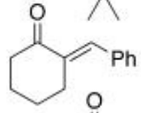
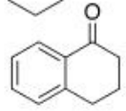
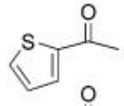
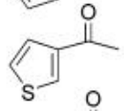
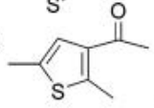
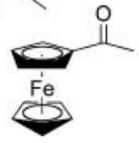
Related systems:



Jeon, S. J.; Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

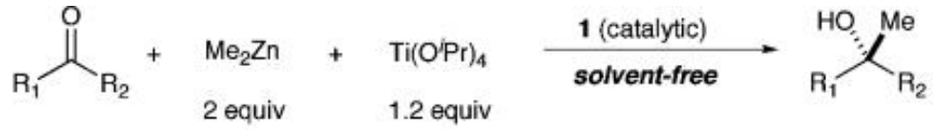


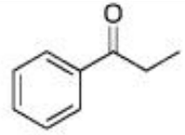
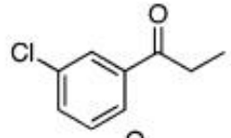
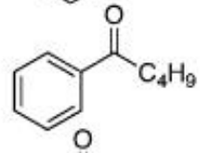
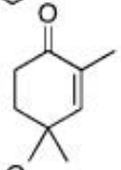
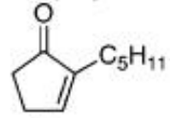
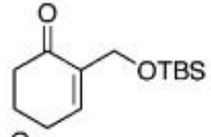
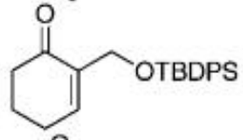
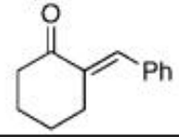
Addition to Ketones

		solvent-free and highly concentrated conditions				standard conditions			
entry	substrates	**1** (mol%)	t (h)	y (%)	ee (%)	**1** (mol%)	t (h)	y (%)	ee (%) (config.)
1	 X = H	1 0.5	4 21	75 78	97[a] 96[a]	2	29	71	96 (*S*)
2	X = 3-CF_3	0.5	17	77	96[a]	2	14	56	98
3	X = 4-OMe	1 1	12 15	50 72	81[a] 89[b]	10	111	85	94
4		0.5 0.5	12 24	74 76	98[a] 98[b]	2	27	90	97
5		1 1	24 24	78 85	80[a] 80[b]	2	102	79	88 (*R*)
6		1	15	71	90[b]	2	26	80	90
7		1	22	53	93[b]	2	46	56	96
8		1	22	36	96[b]	10	40	76	98
9		1	24	30	95[b]	10	38	32	99 (*R*)
10		1	23	35	99[b]	10	22	35	>99
11		1 1	65 72	78 87	80[a] 86[c]	10	40	85	83
12		1 0.5	72 85	85 82	80[a] 80[a]	10	50	85	80
13		1	72	70	96[a]	10	50	75	98
14		1	72	75	89[d]	10	42	86	90

Jeon, S. J.; Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

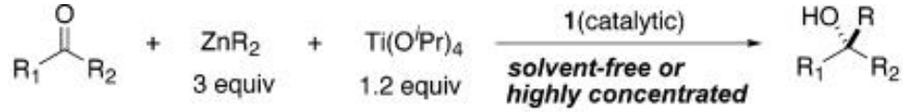
Addition to Ketones

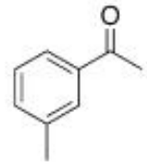
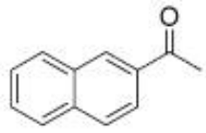
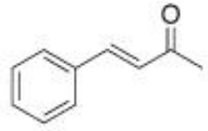


		solvent-free conditions				standard condition				
entry	substrates	**1** (mol %)	t (h)	y (%)	ee (%)	**1** (mol %)	t (h)	y (%)	ee (%)	(config.)
1		1 0.5 0.25 0.25	15 48 60 72	85 83 85 87	92 92 80 92[a]	2	45	83	94	(*R*)
2		1 0.5	45 60	95 95	94 94	2	46	90	96	
3		1 0.5	43 45	95 93	83 77	2	48	81	85	
4		1 0.5	45 44	75 83	96 95	10	40	84	99	
5		1 0.5	22 44	77 78	96 97	10	40	62	99	
6		1 0.5 0.25	24 44 70	90 83 84	97 97 92	10	40	81	99	
7		1	60	90	96	10	60	84	98	
8		1	24	43	99	10	38	20	99	

Jeon, S. J.; Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

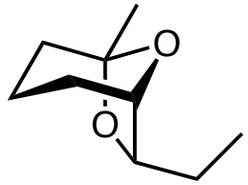
Addition to Ketones



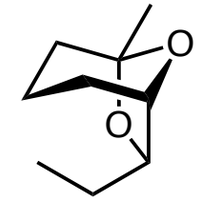
entry	substrates	ZnR_2	solvent-free and highly concentrated conditions				standard conditions			
			1 (mol%)	t (h)	y (%)	ee (%)	**1** (mol%)	t (h)	y (%)	ee (%)
1		$Zn((CH_2)_4OTBS)_2$	1	48	68	79[a]	10	72	89	98
			0.5	70	53	80[a]				
			0.25	82	44	69[a]				
			1	40	68	97[b]				
2		$Zn((CH_2)_5Br)_2$	1	46	66	92[a]	10	72	89	96
			0.5	50	41	92[a]				
			1	46	71	97[b]				
3		$Zn((CH_2)_5Br)_2$	1	40	55	94[a]	10	72	55	94
			0.5	76	47	94[a]				
			0.25	84	30	76[a]				
			0.25	90	30	90[a,c]				
			1	38	72	97[b]				
4		$Zn((CH_2)_3CHMe_2)_2$	1	18	56	94[b]	10	72	75	90
5		$Zn((CH_2)_3CHMe_2)_2$	1	27	63	93[b]	10	72	86	93
6		$Zn((CH_2)_4OTBS)_2$	1	21	76	87[b]	10	120	65	90
7		$Zn((CH_2)_5Br)_2$	1	36	65	89[b]	10	48	48	90

Jeon, S. J.; Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

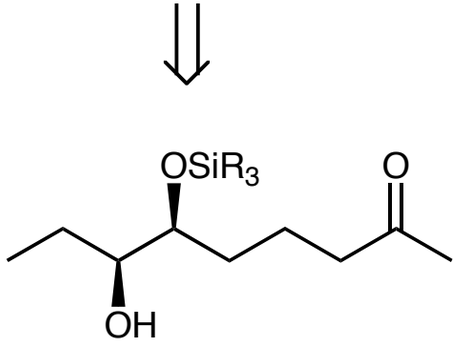
Synthesis of Brevicomin

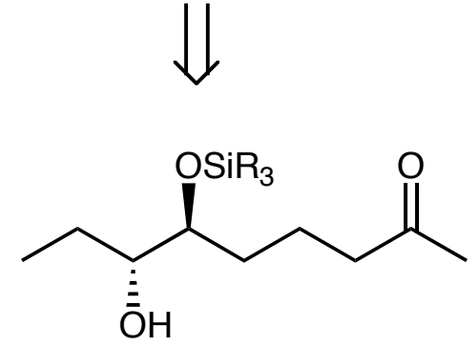


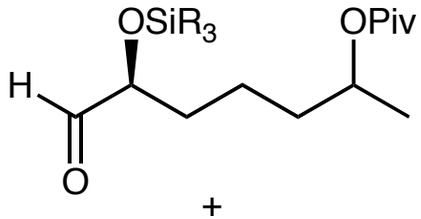
(-)-exo-Brevicomin



(-)-endo-Brevicomin

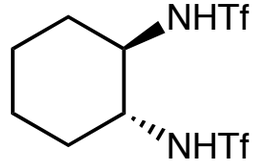


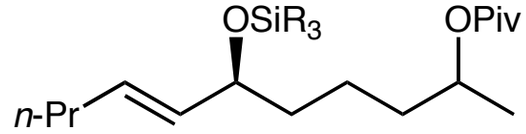


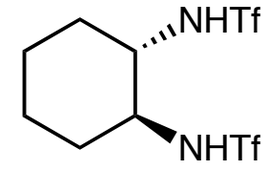


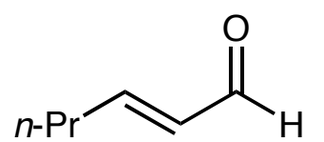
+

Et_2Zn









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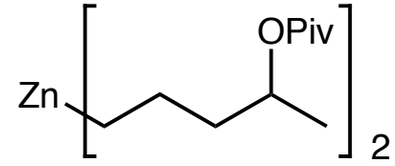
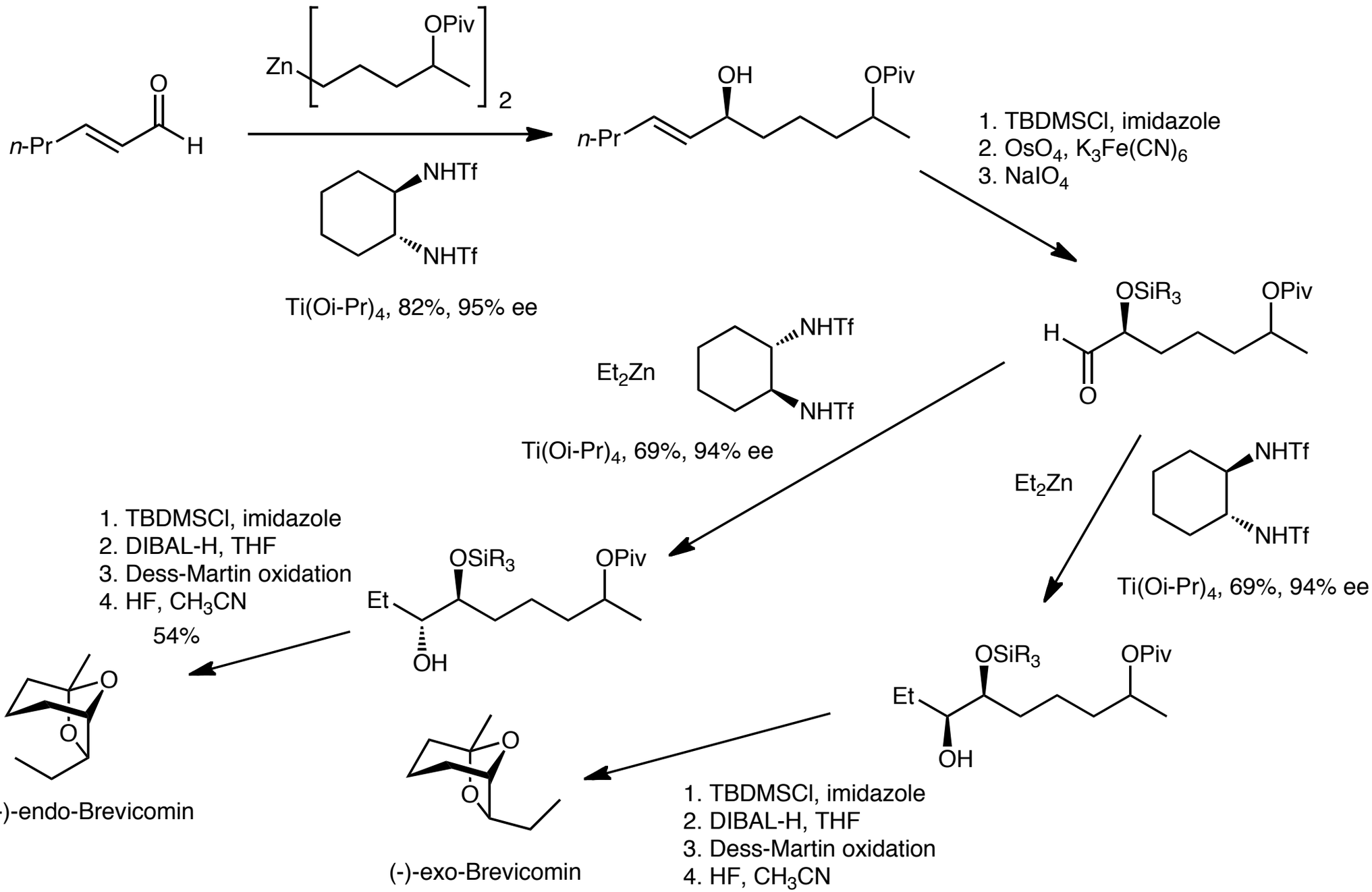
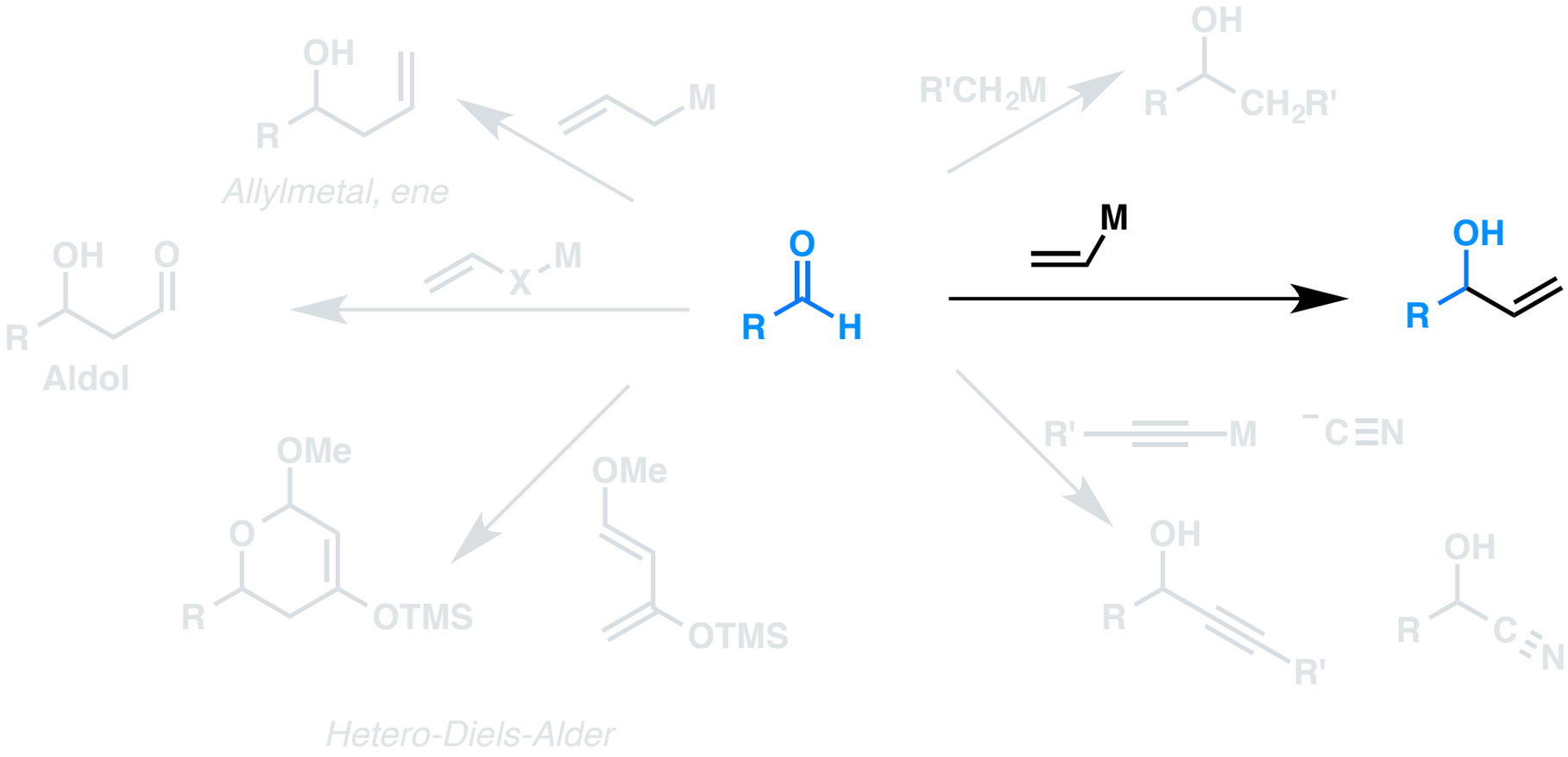


Synthesis of Brevicomin

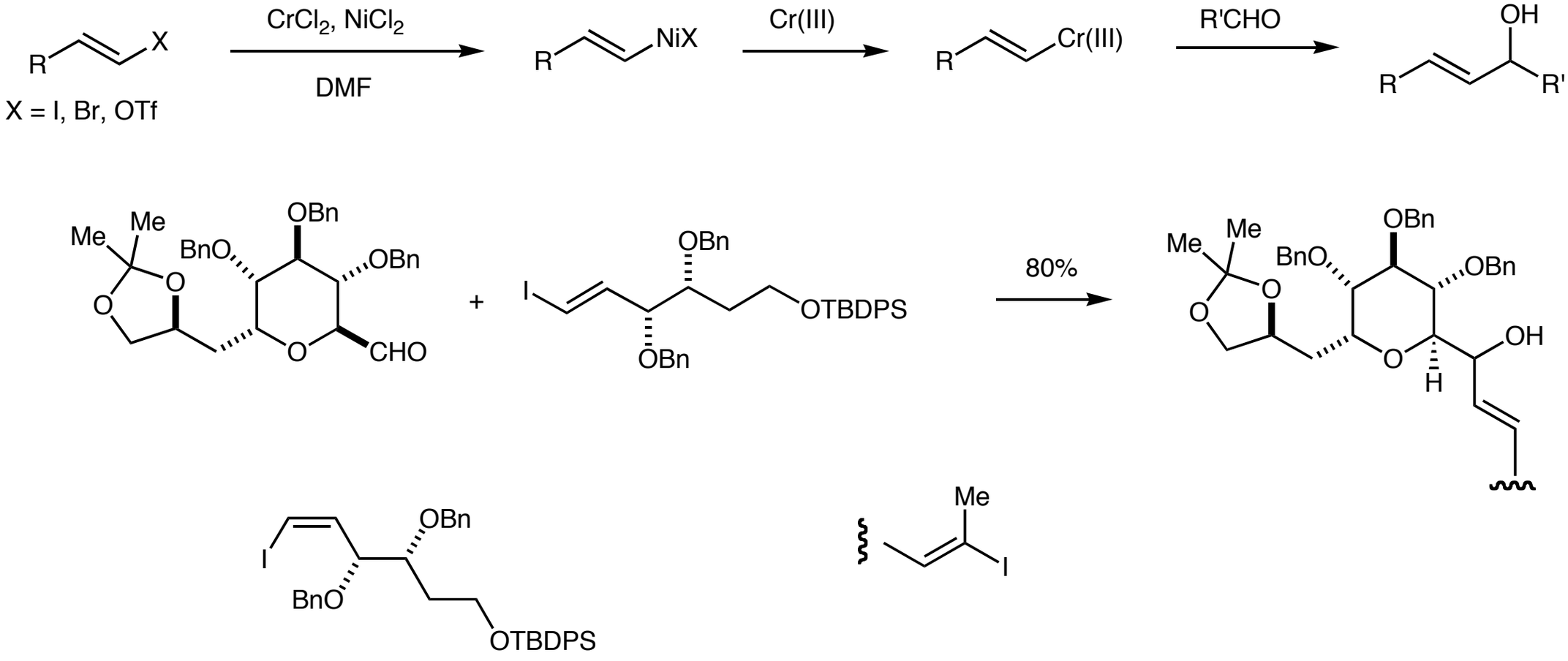


Enantioselective Addition of Non-stabilized Carbon Nucleophiles to C=O



Nozaki-Hiyama-Kishi Reaction

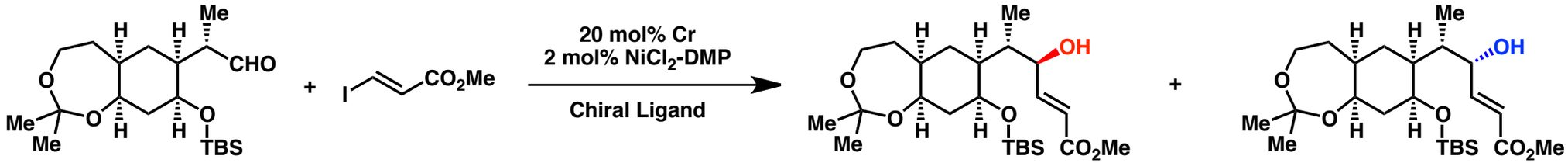
Takai, Nozaki *J. Am. Chem. Soc.* **1986**, 108, 6048 and 7408 (Kishi, *J. Am. Chem. Soc.* **1986**, 108, 5644)

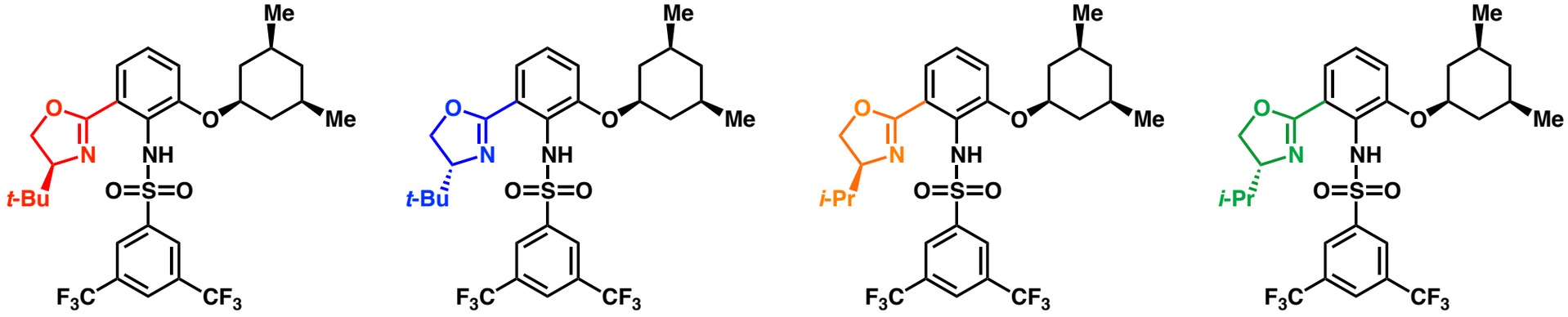


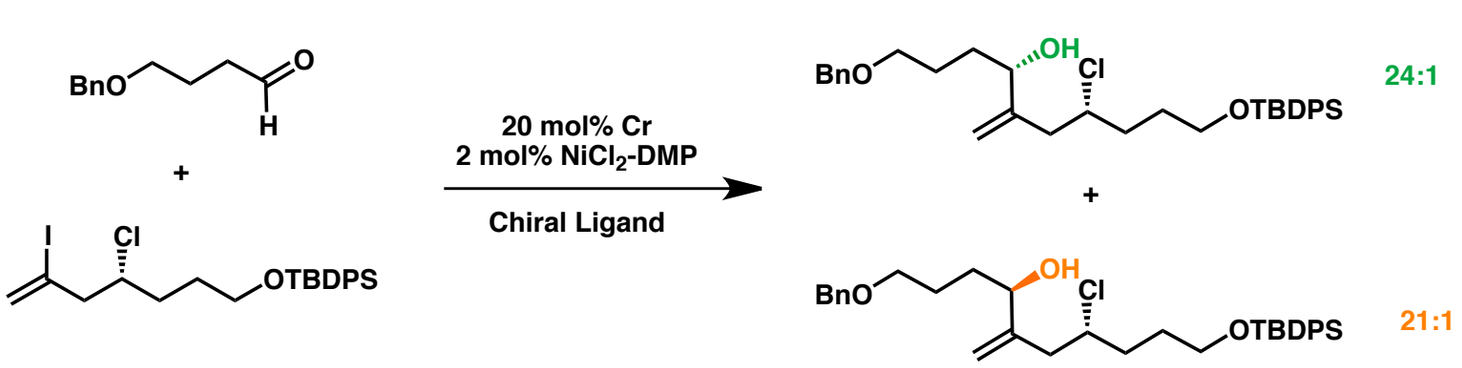
Catalytic version, Fürstner: $CrCl_2$ (catalytic), Mn , TMSCl

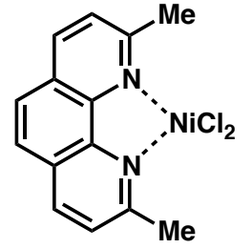
Nozaki-Hiyama-Kishi Reaction

Review: Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.
Guo, H. B.; Dong, C. G.; Kim, D. S.; Urabe, D.; Wang, J. S.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387.









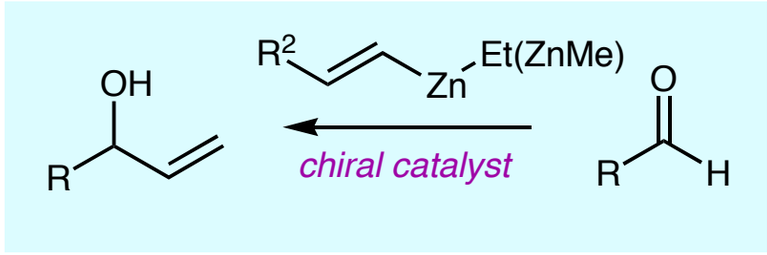
Addition of Vinylic Reagents to Aldehydes

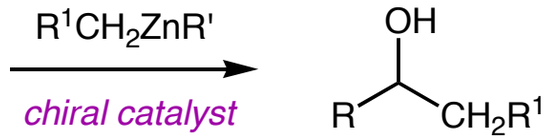
Oppolzer

DAIB or DPMPM

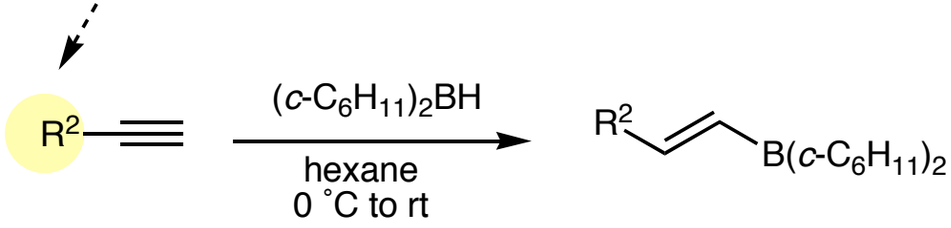
R^2 = Bu, *t*-Bu, cyclohexyl

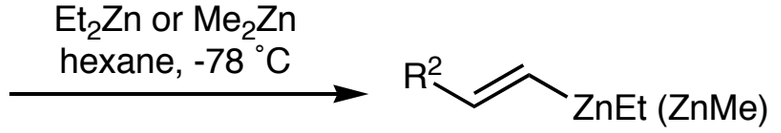
80-98% ee

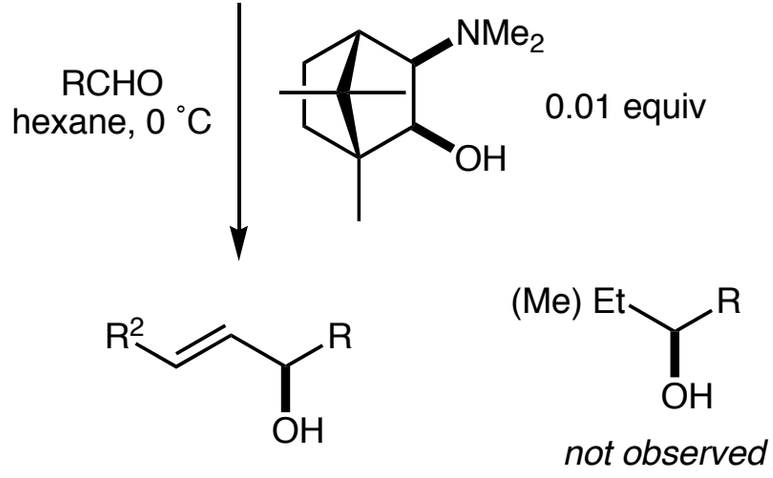




not much impact on the ee





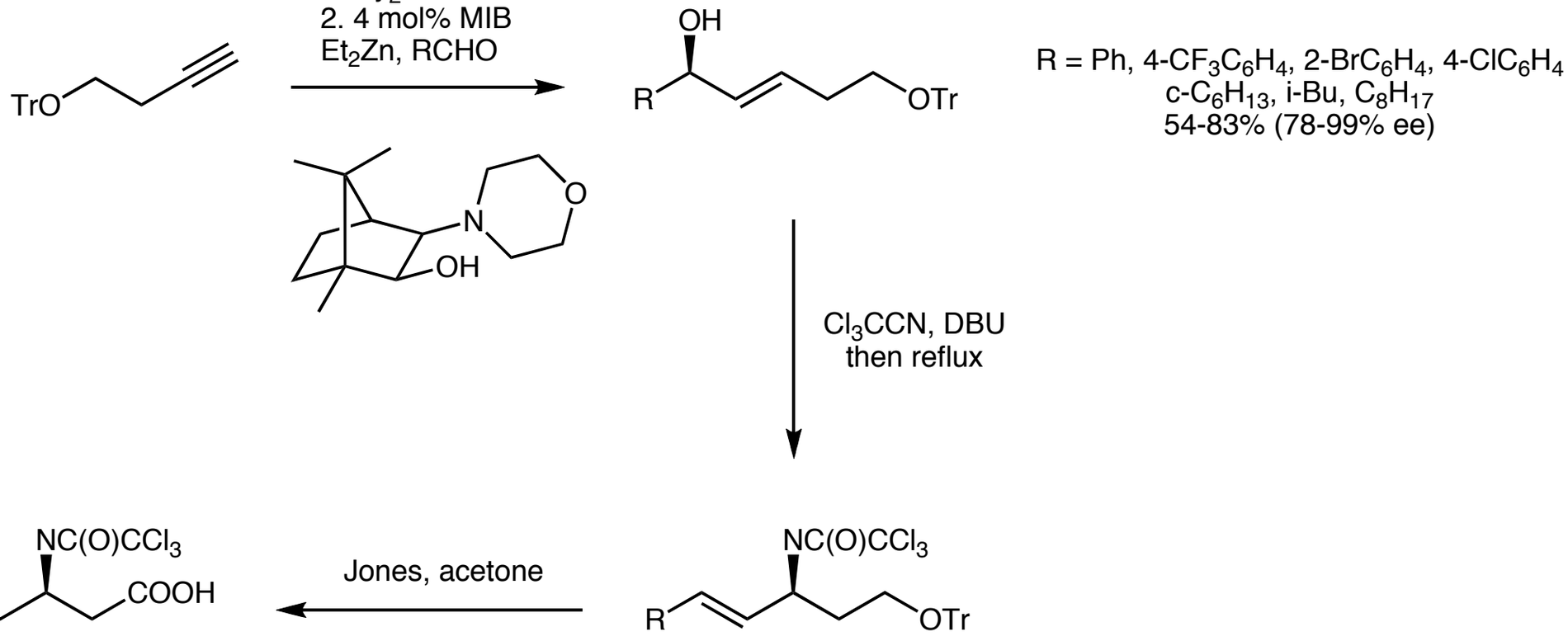


R	R^2	R'_2Zn	Yield	ee
Ph	Bu	Me_2Zn	87	96
Ph	C_6H_{13}	Et_2Zn	77	92
Ph	C_6H_{13}	Me_2Zn	85	94
Et	C_6H_{13}	Et_2Zn	91	84
Bu	C_6H_{13}	Et_2Zn	86	85
i-Bu	C_6H_{13}	Et_2Zn	78	85
c-C_6H_{13}	C_6H_{13}	Et_2Zn	70	91
t-Bu	C_6H_{13}	Et_2Zn	28	73

Addition of Vinylic Reagents to Aldehydes

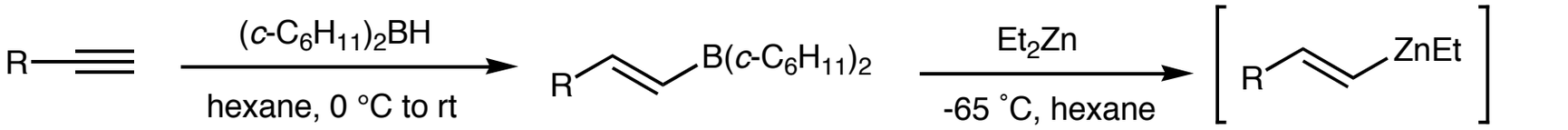
Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677-10683. Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225-12231.

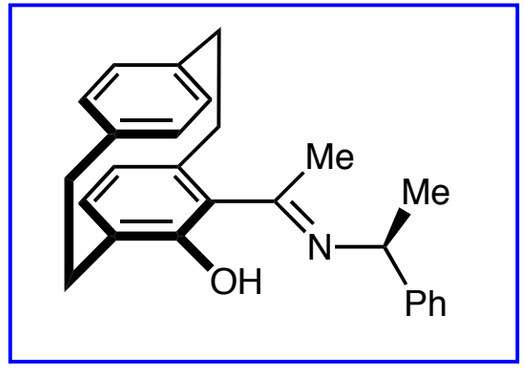
P. Walsh



[2,2]Paracyclophane-based Ligand

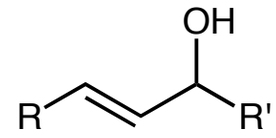
Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *25*, 4119-4122.





R'CHO
-30 ˚C

Chiral Ligand
(2 mol%)



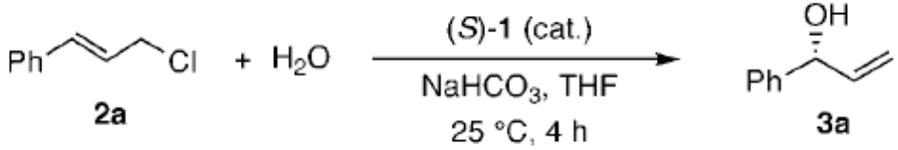
R	R'	Yield (%)	ee (%)
Hex	Ph	71	86
Hex	4-ClPh	88	97
Hex	4-MeOPh	62	91
Hex	cyclohexyl	80	>98
Hex	*t*-Butyl	89	>98
t-Bu	4-ClPh	88	89

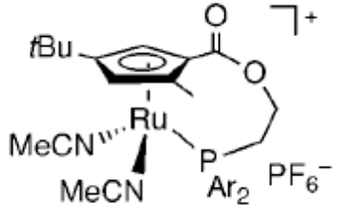
⇨ 1,2-disubstituted alkenylzinc were not as effective (ee: 75-88%)

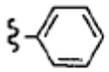
Synthesis of ligand by resolution: Rozenberg *Eur. J. Chem.* **2000**, 3295.

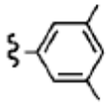
Alternative Approach to the Chiral Allylic Alcohols

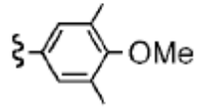
Table 1: Reaction of cinnamyl chloride (**2a**) with water.[a]

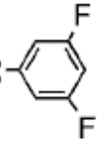


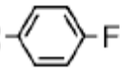


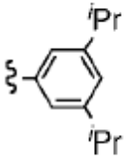
(*S*)-**1a**: Ar = 

(*S*)-**1b**: Ar = 

(*S*)-**1c**: Ar = 

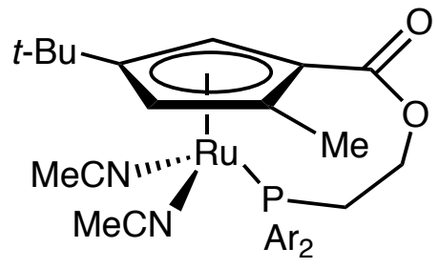
(*S*)-**1d**: Ar = 

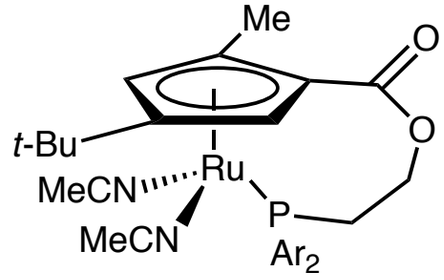
(*S*)-**1e**: Ar = 

(*S*)-**1f**: Ar = 

Entry	Cat.	Yield [%][b]	*ee* [%][c,d]
1	(*S*)-**1a**	99	81 (*R*)
2	(*S*)-**1b**	99	88 (*R*)
3	(*S*)-**1c**	99	90 (*R*)
4	(*S*)-**1d**	99	88 (*R*)
5	(*S*)-**1e**	99	87 (*R*)
6	(*S*)-**1f**	97	81 (*R*)

[a] Reaction conditions: **2a** (1.0 mmol), cat. (10 µmol), $NaHCO_3$ (1.2 mmol), THF (4 mL), and H_2O (0.5 mL), 25 °C, 4 h. [b] Yields of the isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Configuration is given in parentheses. THF = tetrahydrofuran.

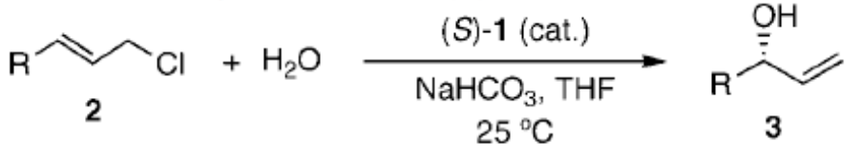




Kanbayashi, N.; Onitsuka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5197.

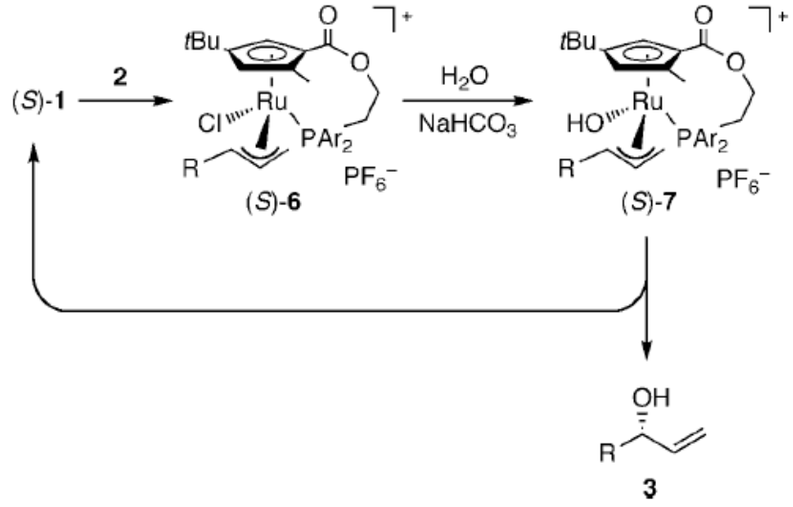
Alternative Approach to the Chiral Allylic Alcohols

Table 2: Reaction of allylic chlorides (**2**) with water.[a]



Entry	Substrate	Cat.	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**2b** (R = 4-MeC_6H_4)	(*S*)-**1d**	4	99	90 (*R*)
2	**2c** (R = 4-$MeOC_6H_4$)	(*S*)-**1b**	4	99	76 (*R*)
3	**2d** (R = 4-$CF_3C_6H_4$)	(*S*)-**1c**	12	99	94 (*R*)
4	**2e** (R = 4-$MeO_2CC_6H_4$)	(*S*)-**1c**	12	99	93 (*R*)
5	**2f** (R = 4-$OHCC_6H_4$)	(*S*)-**1c**	12	93	93 (*R*)
6	**2g** (R = 1-naphthyl)	(*S*)-**1c**	4	99	90 (*R*)
7	**2h** (R = 2-naphthyl)	(*S*)-**1c**	7	95	89 (*R*)
8	**2i** (R = (*E*)-PhCH=CH)	(*S*)-**1b**	4	96	96 (*R*)
9	**2j** (R = $PhCH_2CH_2$)	(*S*)-**1d**	12	99	85 (*S*)
10	**2k** (R = *n*-C_5H_{11})	(*S*)-**1d**	18	78	83 (*S*)
11	**2l** (R = *c*-C_6H_{11})	(*S*)-**1b**	18	87	97 (*R*)
12	**2m** (R = *t*BuPh_2SiOCH_2)	(*S*)-**1c**	12	99	90 (*R*)

[a] Reaction conditions: **2** (1.0 mmol), cat. (10 μmol), $NaHCO_3$ (1.2 mmol), THF (4 mL), and H_2O (0.5 mL), 25 °C, 4 h. [b] Yields of the isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Configuration is given in parentheses.



Scheme 2. Proposed reaction pathway for asymmetric allylic hydroxylation.

Kanbayashi, N.; Onitsuka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5197.

Vinylation of Ketones

Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538-6539.

Scheme 3. Asymmetric Vinylation of Ketones

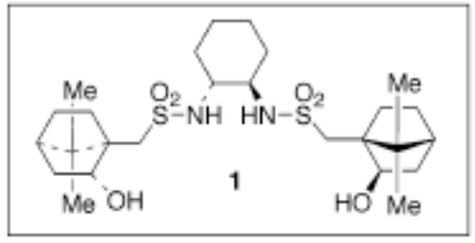
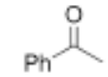
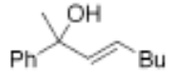
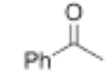
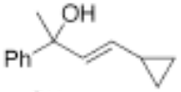
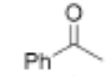
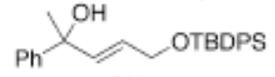
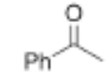
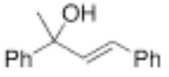
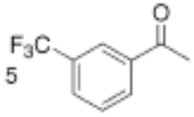
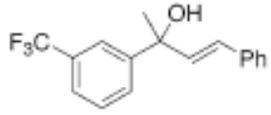
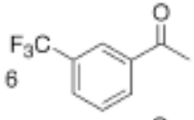
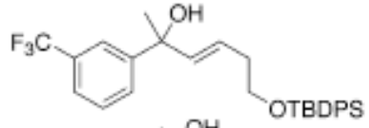
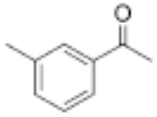
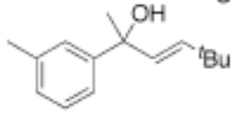
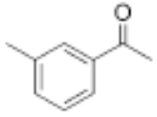
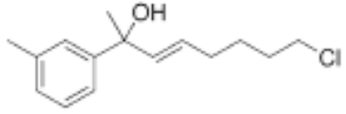
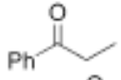
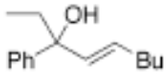
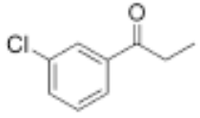
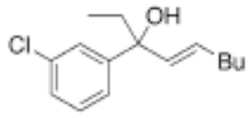
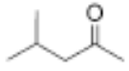
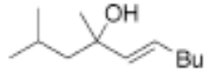
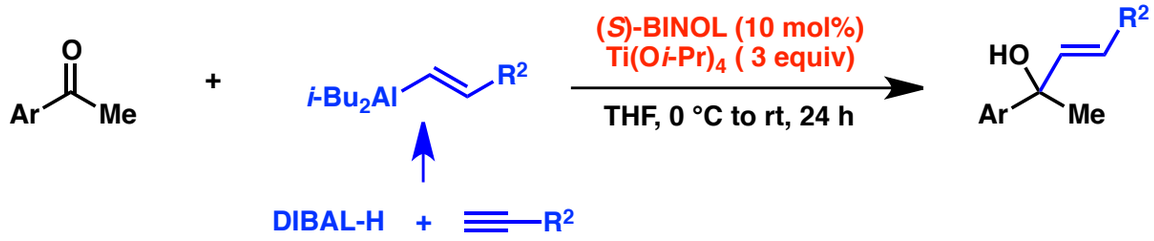


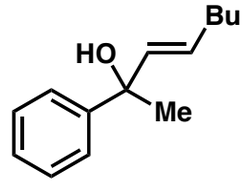
Table 1. Asymmetric Vinylation of Acyclic Ketones

entry	substrate	product	ee (yield)
1			93 (85)
2			95 (90)
3			89 (92)
4			87 (92)
5			88 (84)
6			90 (94)
7			92 (93)
8			90 (98)
9			94 (90)
10			93 (93)
11			79 (85)

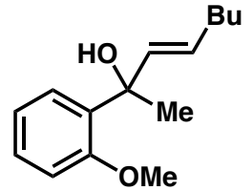
Vinylation of Ketones

Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499.

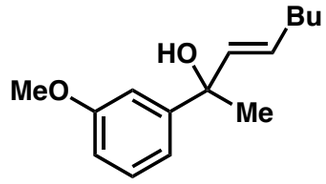




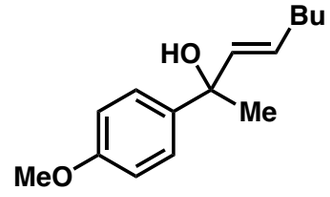
91%, 92% ee



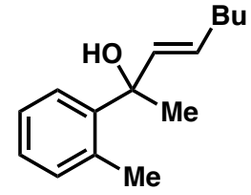
87%, 86% ee



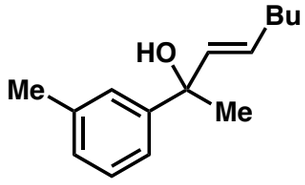
80%, 81% ee



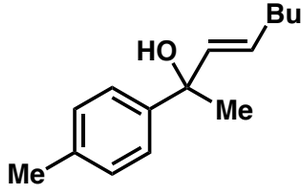
93%, 87% ee



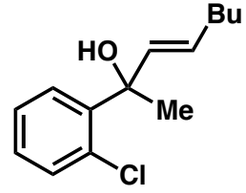
87%, 98% ee



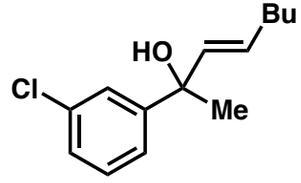
87%, 93% ee



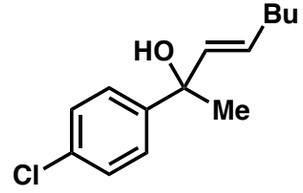
92%, 92% ee



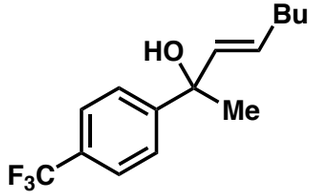
85%, 90% ee



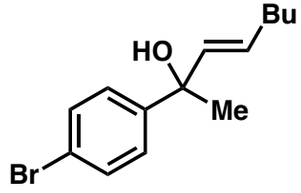
88%, 91% ee



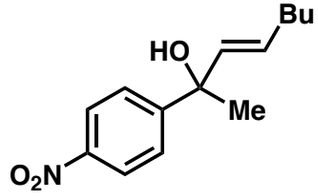
90%, 97% ee



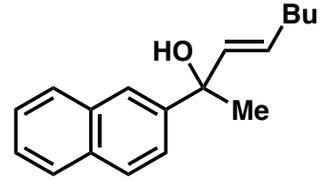
94%, 96% ee



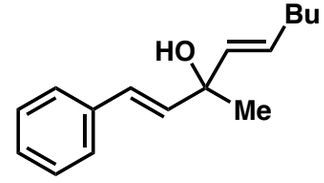
89%, 91% ee



92%, 95% ee

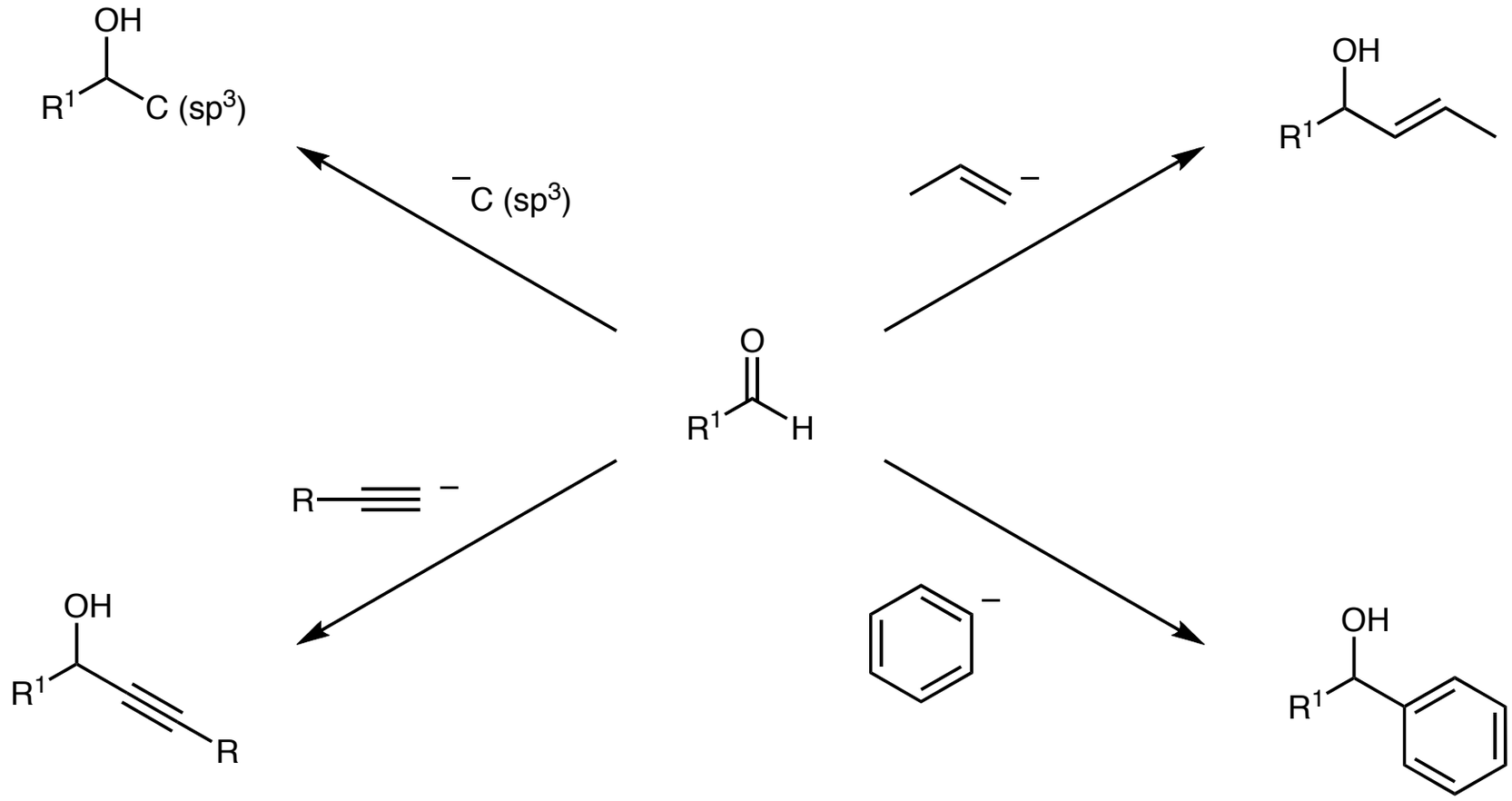


92%, 92% ee

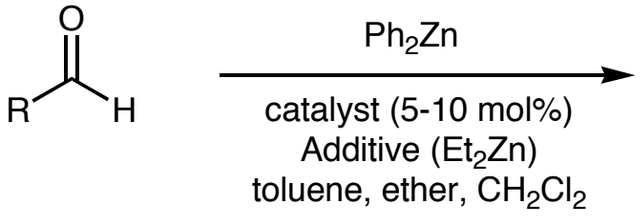


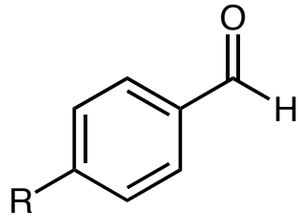
92%, 82% ee

Enantioselective Addition of Non-stabilized Carbon Nucleophiles to C=O



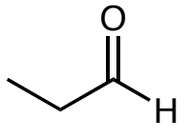
Addition of Diphenylzinc to Aldehydes



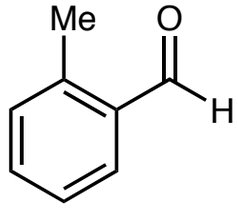


R = OMe, 90%, 87% ee
R = Cl, 86%, 94% ee

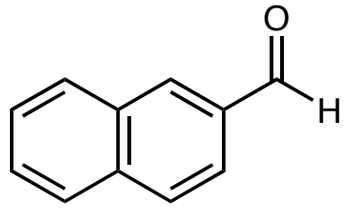
R = Cl, 92%, 95% ee



90%, 87% ee

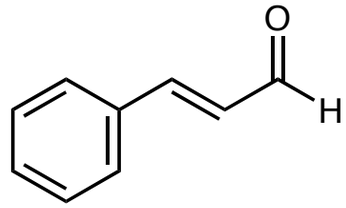


87%, 91% ee



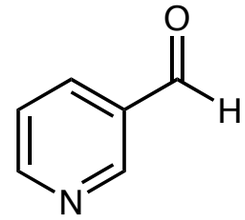
66%, 87% ee

90%, 88% ee

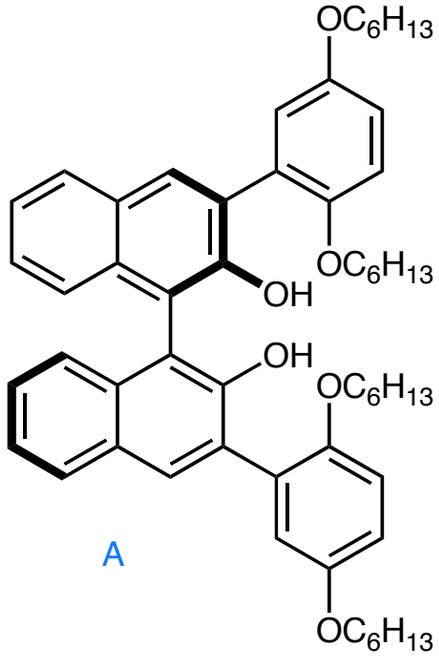


94%, 83% ee

92%, 87% ee



89%, 86% ee



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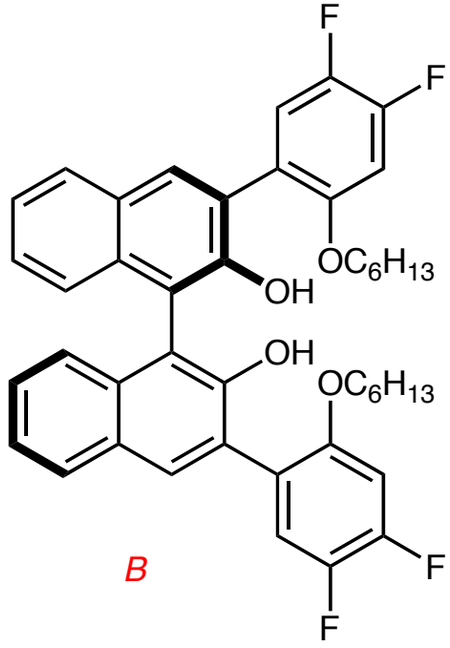

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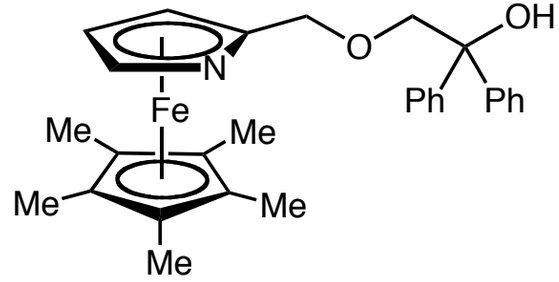
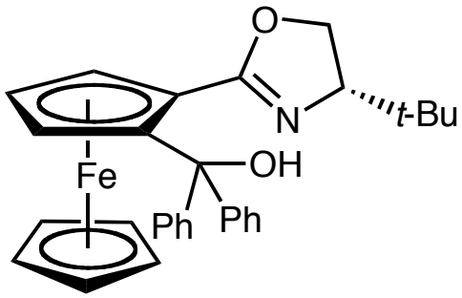


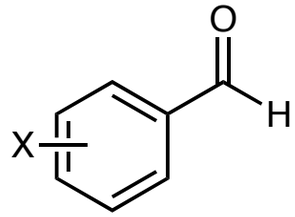
Fu
88-94% yield
86-90% ee
(Substituted benzaldehydes only)
Me_2Zn (83% ee to PhCHO)
Ph_2Zn (57% ee to 4-ClC_6H_4CHO)

Polymeric versions have also been used

Phenyl Transfer of Mixed Diorganozinc: Bolm's Improvement



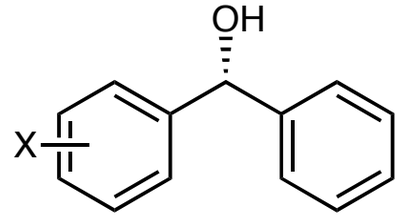
catalyst



Ph_2Zn (0.65 equiv)
Et_2Zn (1.3 equiv)

catalyst (0.1 equiv)

toluene,
10 °C, 16 h



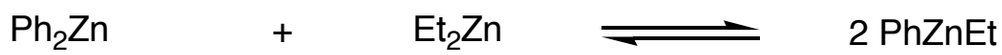
$Ph_2Zn + Et_2Zn$

PhZnEt

R in RCHO	Yield	ee	conf.
4-ClC_6H_4	86	97	*R*
4-$MeOC_6H_4$	82	98	*R*
3-$MeOC_6H_4$	99	96	*R*
4-MeC_6H_4	86	98	*R*
4-PhC_6H_4	98	97	*R*
2-Np	70	96	*R*
2-BrC_6H_4	64	91	*R*
2-Furyl	99	95	*R*
E-PhCH=CH	97	90	*R*
t-Bu	68	94	*S*
Bn	82	83	*S*
$CHMe_2$	75	91	*S*

Addition of Ph_2Zn to Aldehydes

⇨ Unlike with Et_2Zn, the addition to aldehydes proceeds smoothly even in the absence of a catalyst

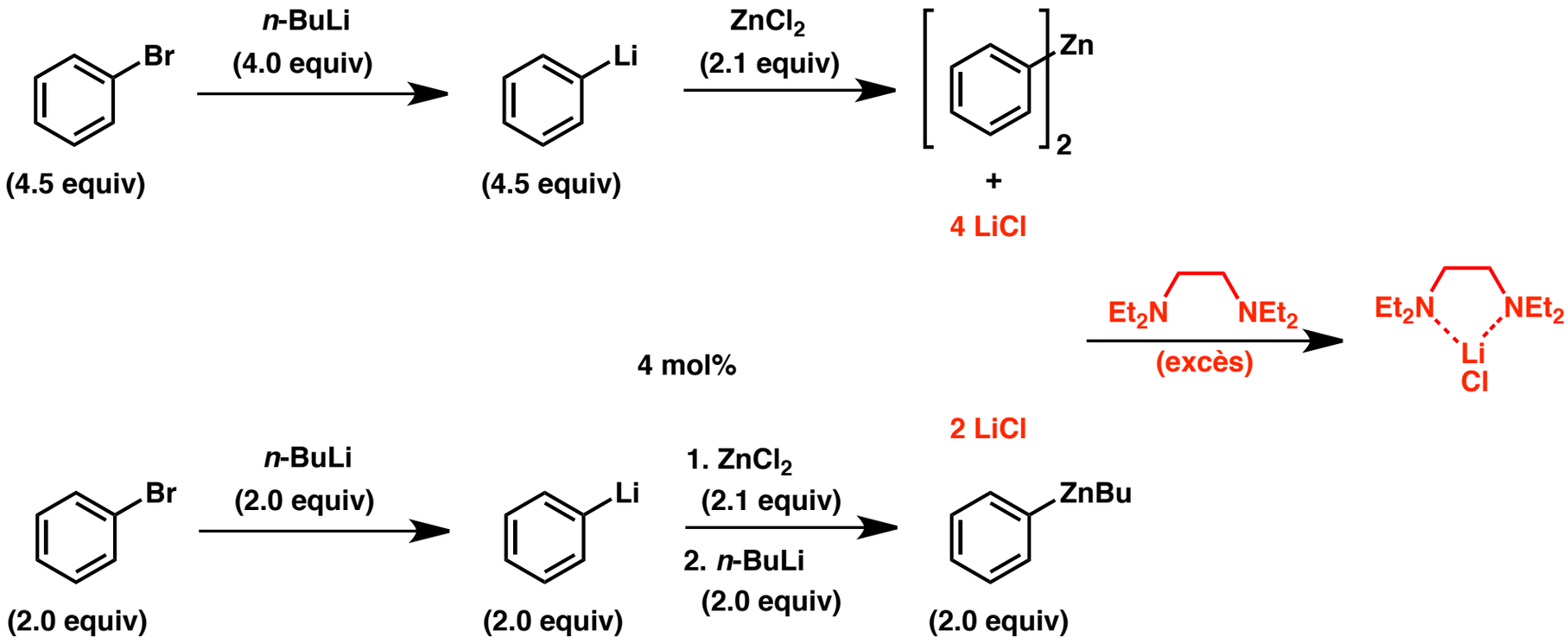


more reactive *less reactive*

⇨ Use of a large excess of Et_2Zn presumably displaces the equilibrium toward the formation of PhZnEt

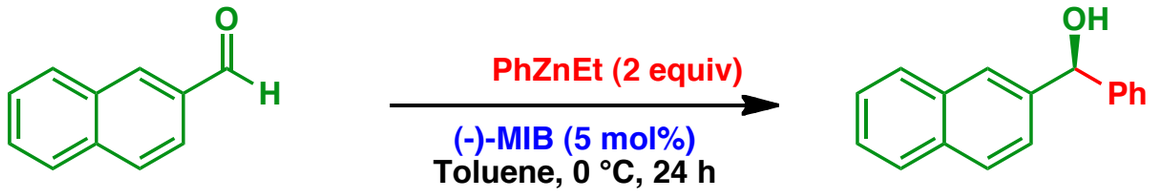
⇨ No other arylzinc reagent has been tested

Arylation of Aldehydes: Walsh's Solution

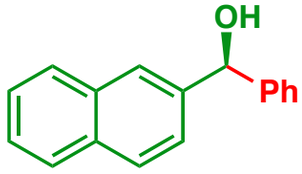


Arylation of Aldehydes

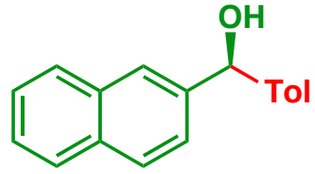
Kim, J. G.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4175-4178.



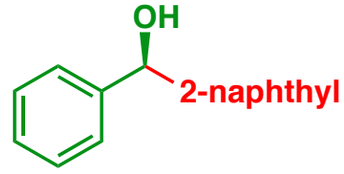
MIB
(2-exo-Morpholinoisoborneol)



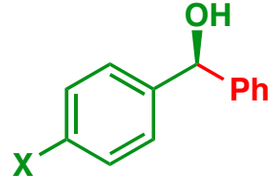
99%, 92% ee



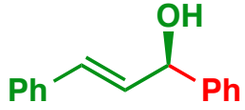
90%, 92% ee



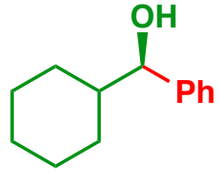
96%, 89% ee



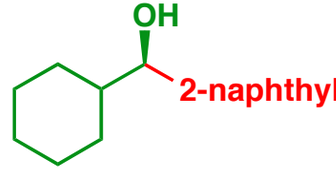
X = F: 89%, 84% ee
X = Cl: 85%, 90% ee
X = OMe: 90%, 90% ee



91%, 84% ee

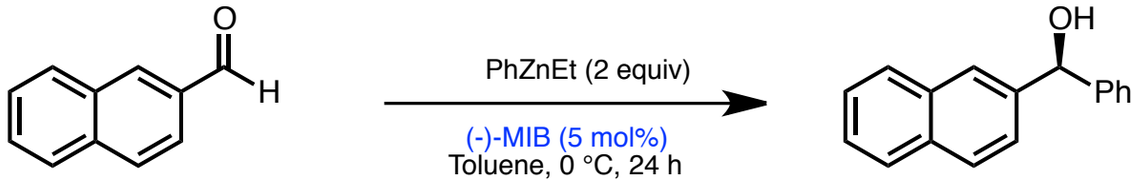


92%, 85% ee



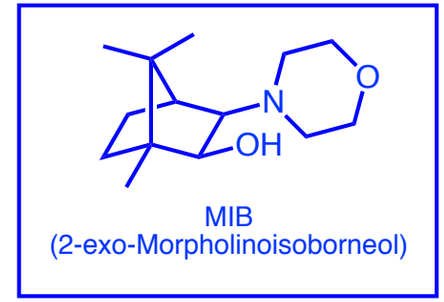
92%, 82% ee

Preparation of Salt-Free Mixed Diorganozinc Reagents



Ph_2Zn (1 equiv) + Et_2Zn (1 equiv) — 98%, 98% ee

Ph_2Zn (1 equiv) + Et_2Zn (1 equiv), ether — 98%, 95% ee

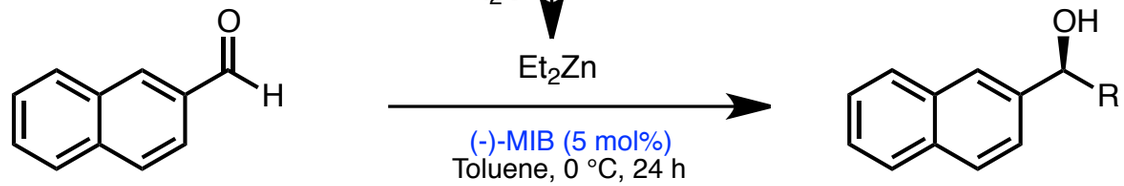


MIB
(2-exo-Morpholinoisoborneol)

$ZnCl_2$ (2 equiv) + EtMgBr (3.9 equiv) + NaOMe (4.8 equiv)

Et_2O ↓ *Centrifugation*

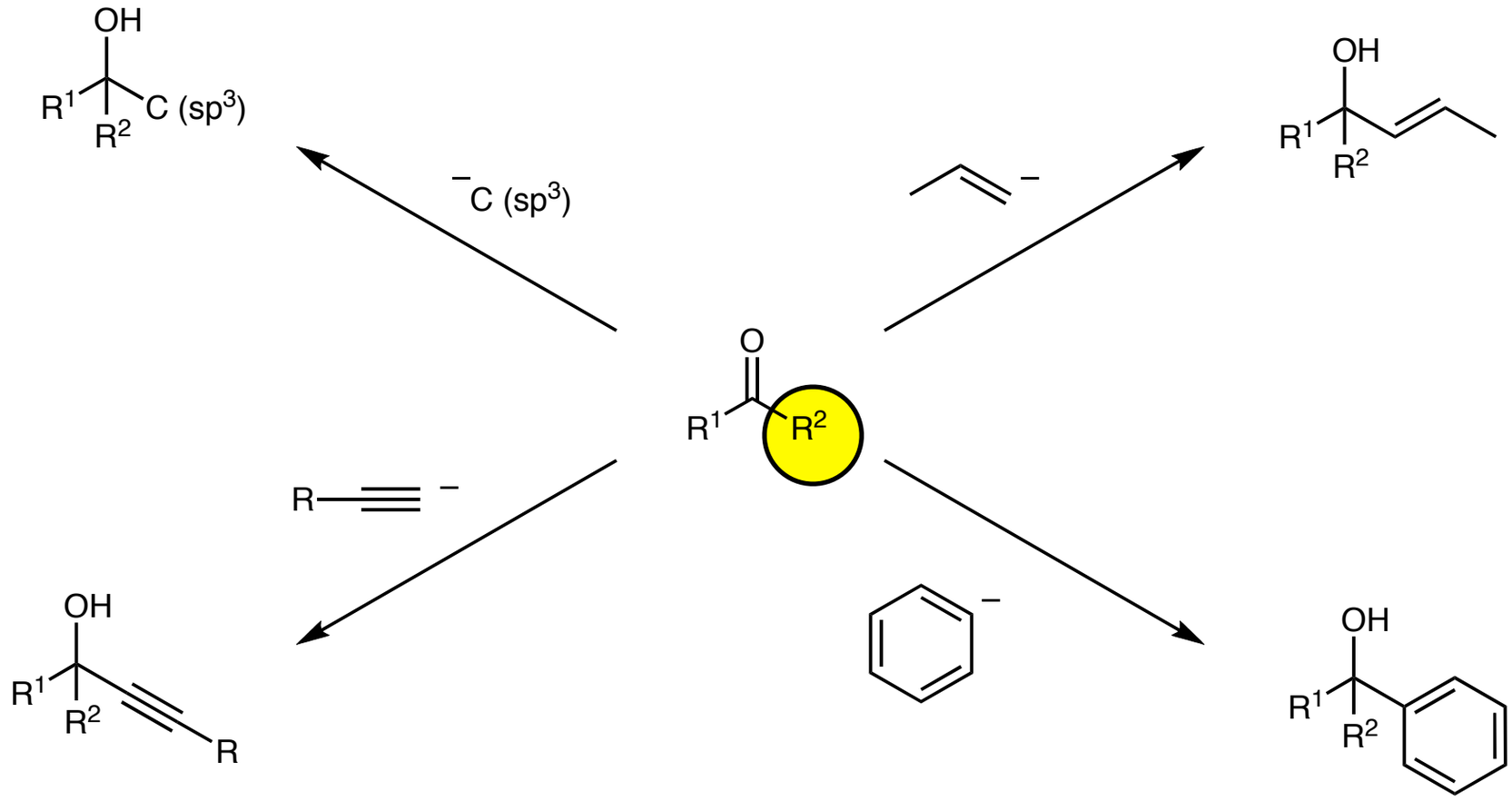
Et_2Zn



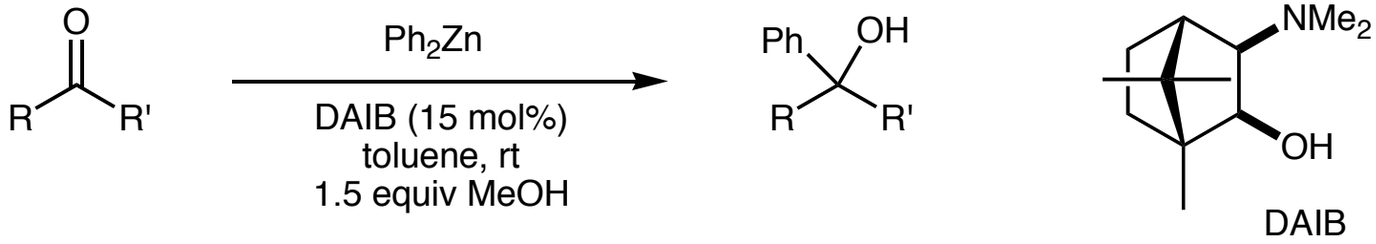
Et_2Zn: 96%, 98% ee (R = Et)

$ZnCl_2$ (2 equiv) + EtMgBr (2.0 equiv) + PhMgBr (1.9 equiv) + NaOMe (4.8 equiv) → EtZnPh: 98%, 98% ee (R = Ph)

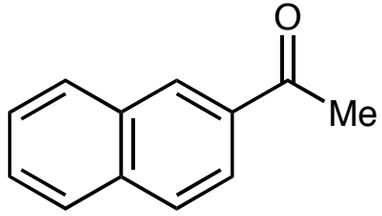
Enantioselective Addition of Non-stabilized Carbon Nucleophiles to C=O



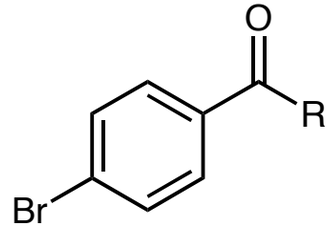
Enantioselective Addition of Ph_2Zn to Ketones



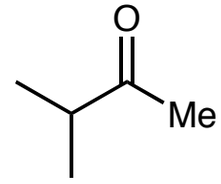
DAIB



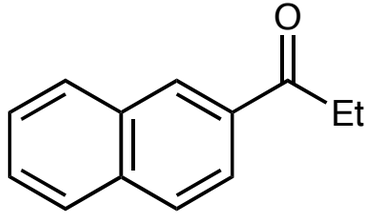
58%, 72% ee



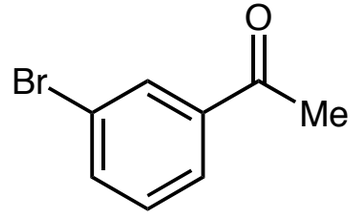
R = Me, 53%, 80% ee
R = Et, 83%, 90% ee



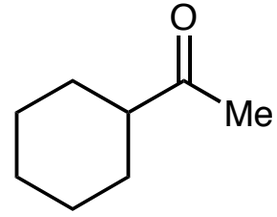
63%, 60% ee



79%, 86% ee

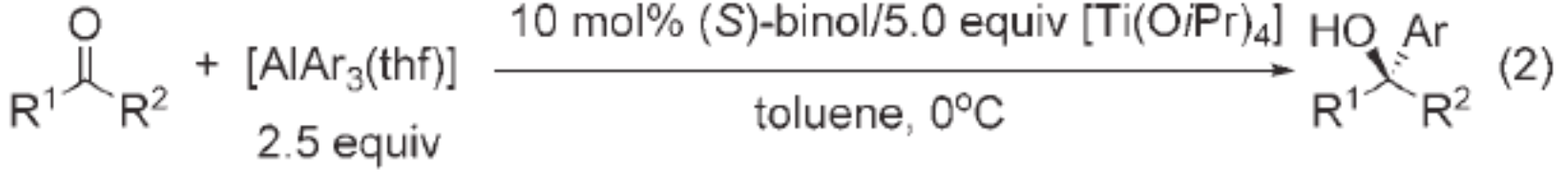


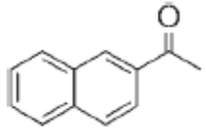
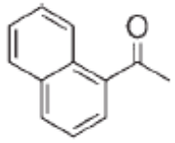
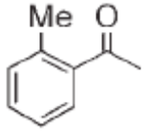
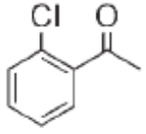
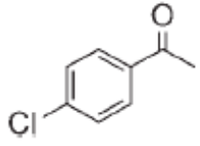
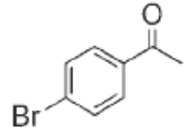
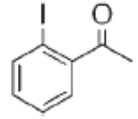
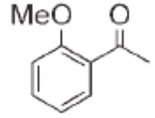
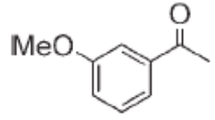
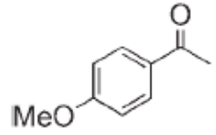
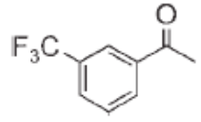
91%, 91% ee



76%, 75% ee

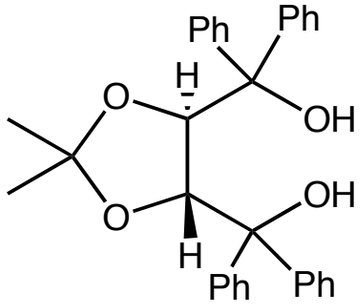
Arylation of Ketones



Entry	Substrate	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1		Ph	12	85	93
2		Ph	36	38	90
3		Ph	12	35	90
4		Ph	12	73	97
5		Ph	12	92	93
7		Ph	12	90	93
8		Ph	168	50	96 (*R*)
9		Ph	12	98	30
10		Ph	36	74	77
11		Ph	36	97	93
12		Ph	12	91	85

Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 5373.

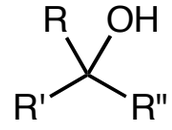
Grignard Addition to Ketones: Stoichiometric Process

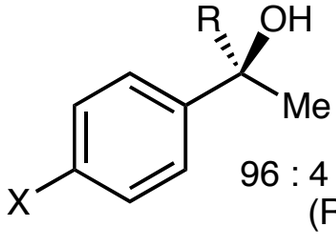


DIOL A

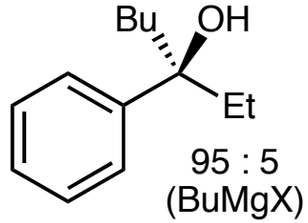
3 RMgBr

1. 1 eq of diol A
2. ketone (-100 °C)
3. NH_4Cl

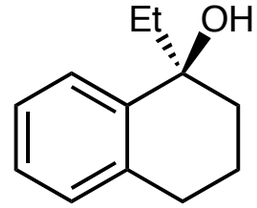




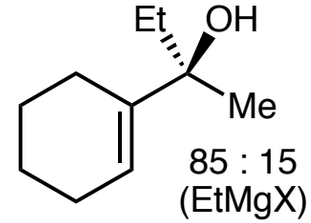
96 : 4 to > 99 : 1
(RMgX)



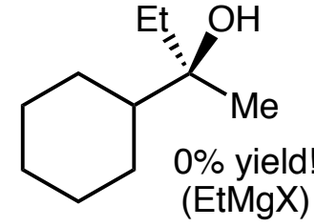
95 : 5
(BuMgX)



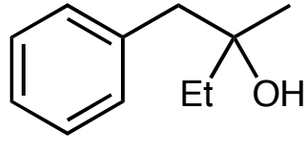
95 : 5 (97:3 Np)
(EtMgX)



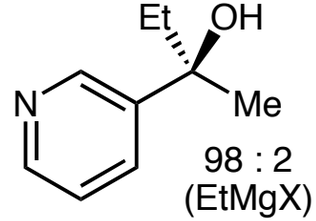
85 : 15
(EtMgX)



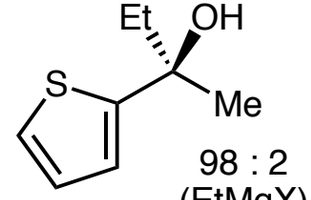
0% yield!
(EtMgX)



75 : 25
(EtMgX)



98 : 2
(EtMgX)

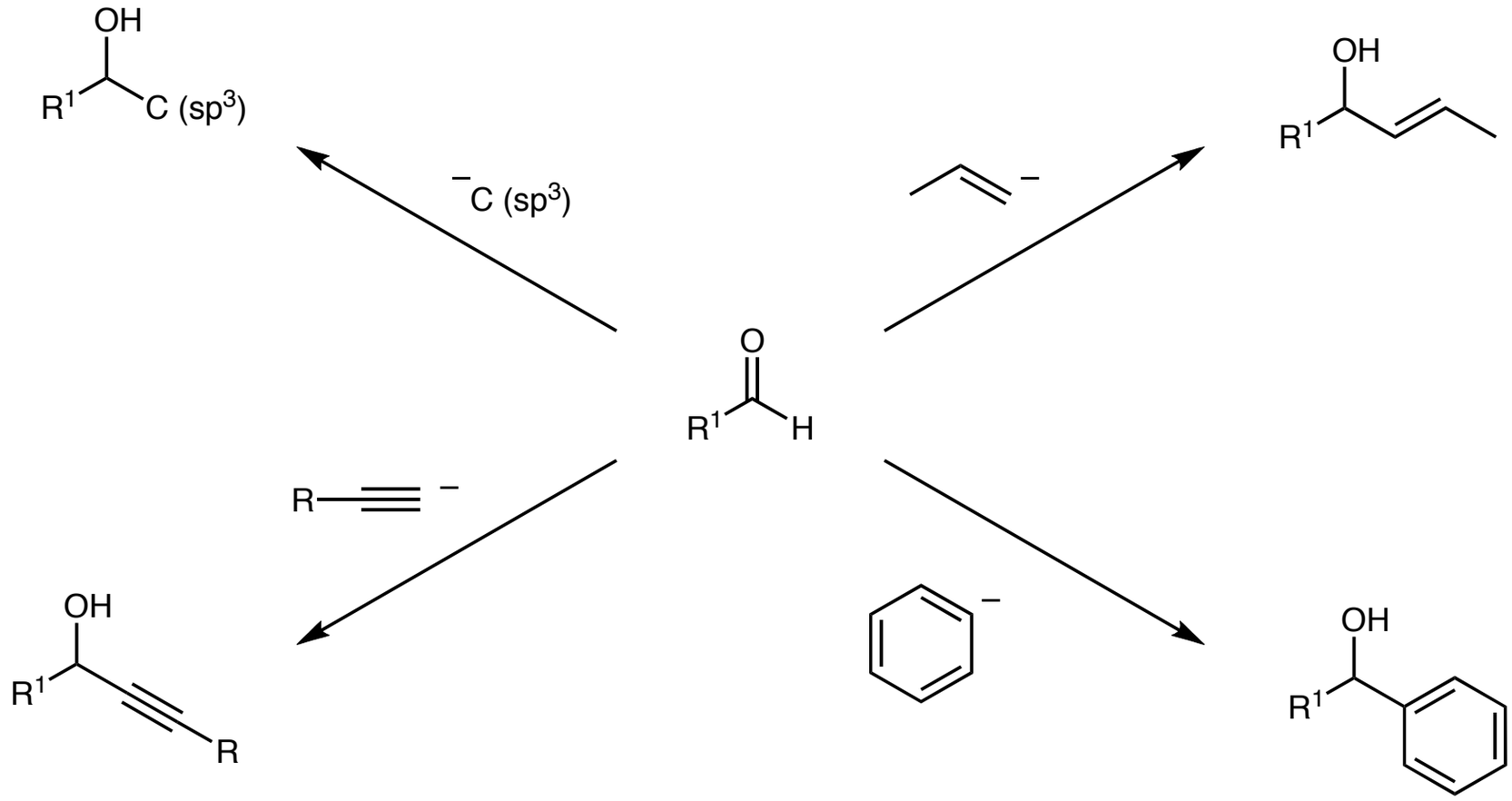


98 : 2
(EtMgX)

Enantioselective addition of Grignard reagents to ketones (stoichiometric amounts of chiral ligand)

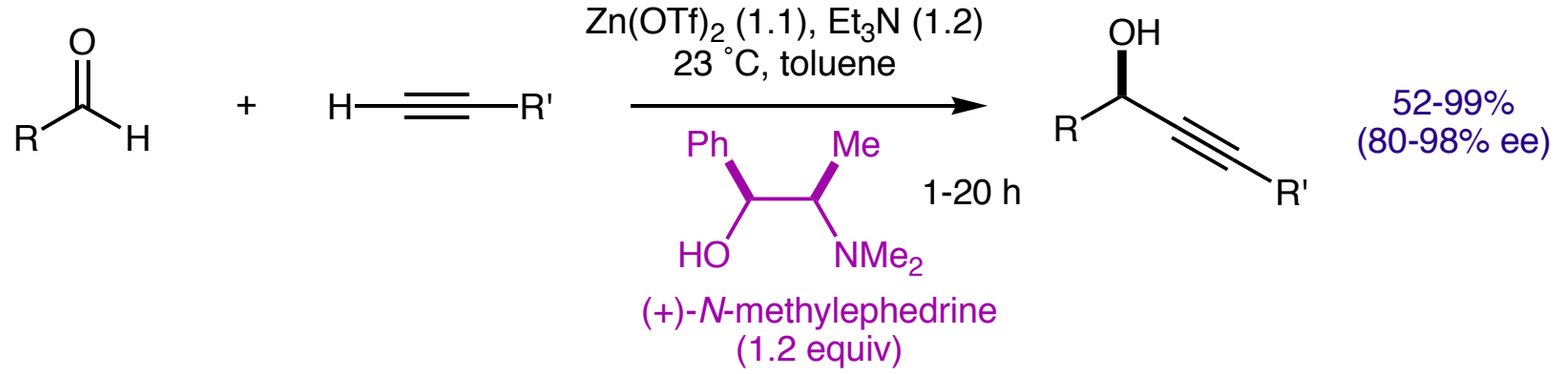
Weber, B.; Seebach, D. *Angew. Chem. Int. Ed.* **1992**, *31*, 84-86.

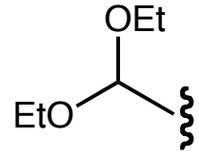
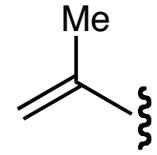
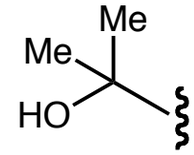
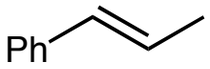
Enantioselective Addition of Non-stabilized Carbon Nucleophiles to C=O



Trost, B. M.; Weiss, A. H. *Advanced Synthesis & Catalysis* **2009**, *351*, 963.

Addition of Alkynes to Aldehydes: Carreira's Approach

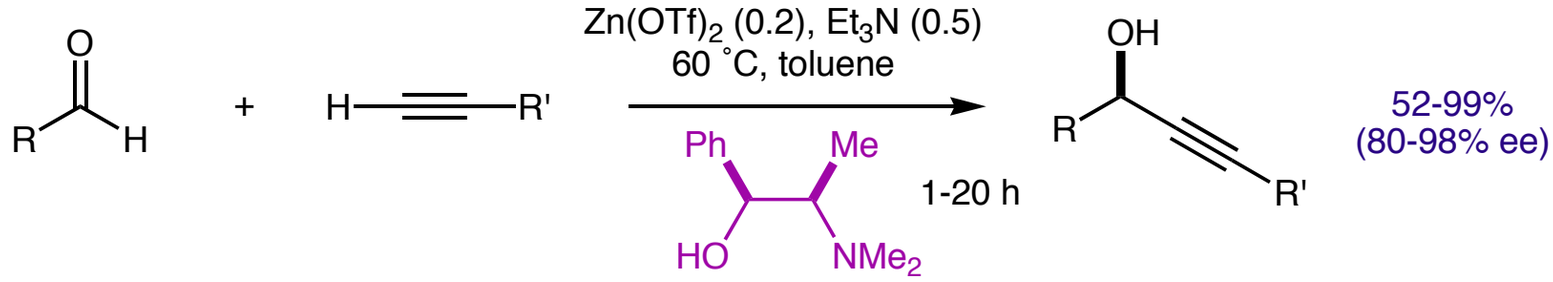


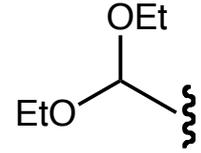
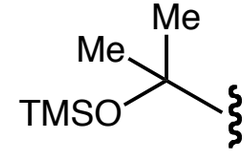
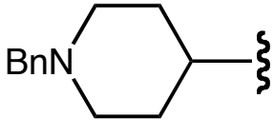
R \ R'	Ph	$Ph(CH_2)_2$	TMS	$TMSCH_2$	$TBDMSOCH_2$			
$c\text{-}C_6H_{11}$	99% (96% ee)	98% (99% ee)	93% (98% ee)	84% (98% ee)	83% (98% ee)	90% (98% ee)	94% (98% ee)	97% (98% ee)
i-Pr	95% (90%)	90% (99% ee)						97% (98% ee)
		39% (80% ee)						
t-Bu	99% (94% ee)	84% (99% ee)						
Ph	53% (94% ee)	52% (96% ee)						
$t\text{-}BuCH_2$	90% (97%)	72% (99% ee)						

Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.

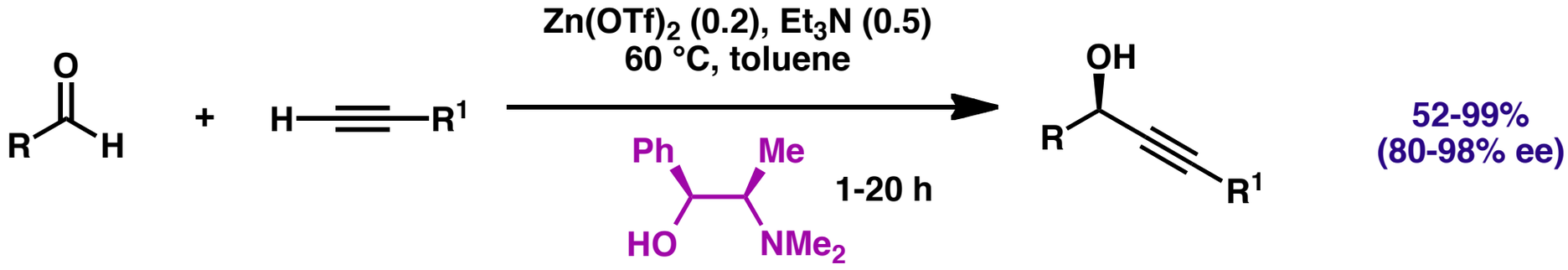
Catalytic Version

Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

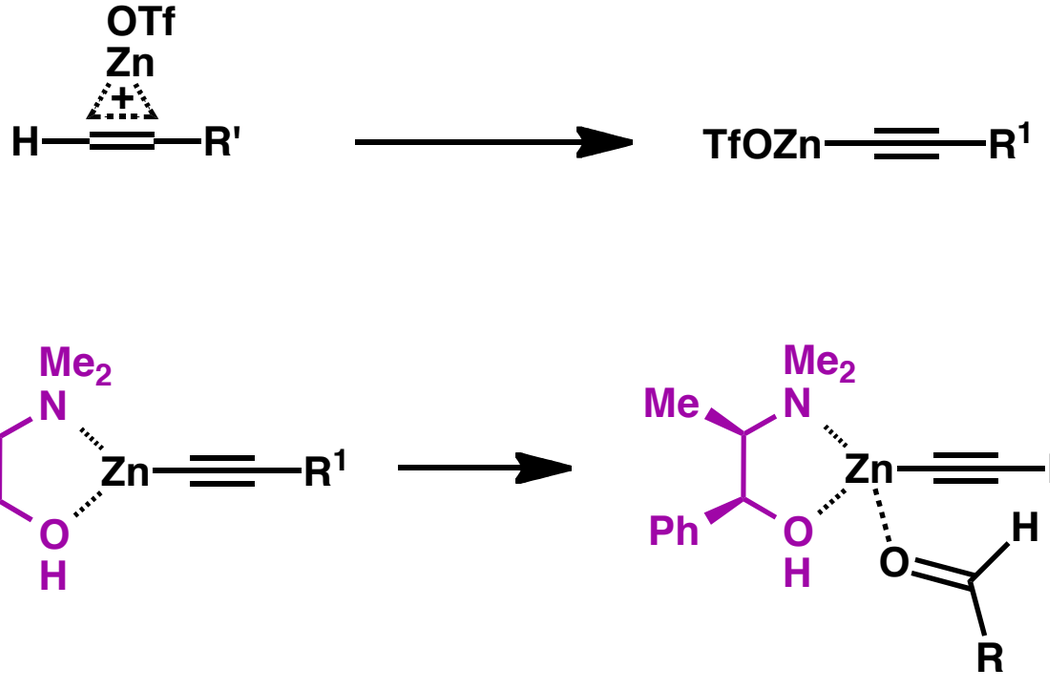


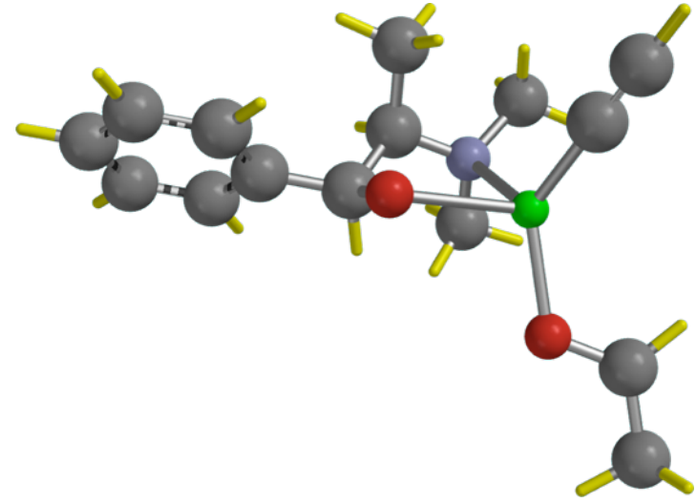
R \ R'	Ph	$Ph(CH_2)_2$	TES	Bu	$TBDMSOCH_2$		Bn_2NCH_2	
c-C_6H_{11}	94% (86% ee)	89% (94% ee)	85% (96% ee)	81% (93% ee)		88% (94% ee)	91% (97% ee)	80% (99% ee)
i-Pr								77% (98% ee)
							81% (94% ee)	
t-Bu		45% (92% ee)			81% (93% ee)			

Carreira's Alkynylation

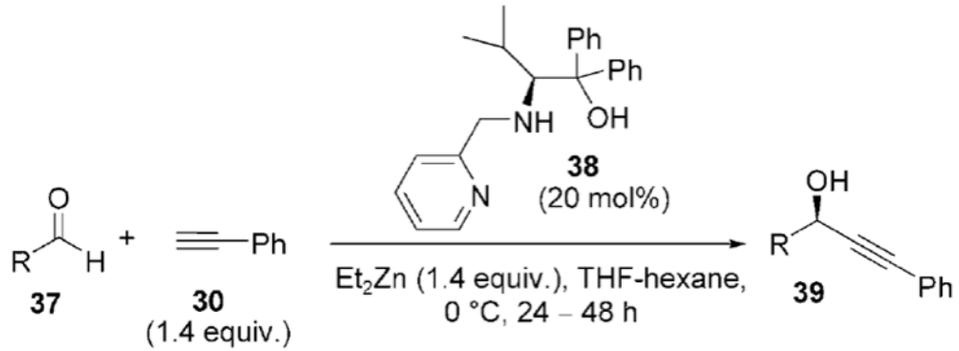


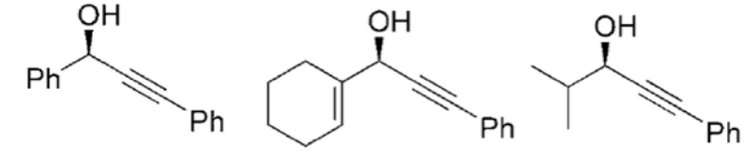
(+)-*N*-methylephedrine
(0.22 equiv)





Alkynylation of Aldehydes

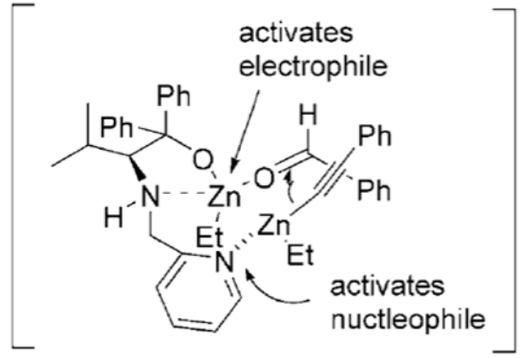




95%, (94% *ee*) **39a**

88%, (90% *ee*) **39b**

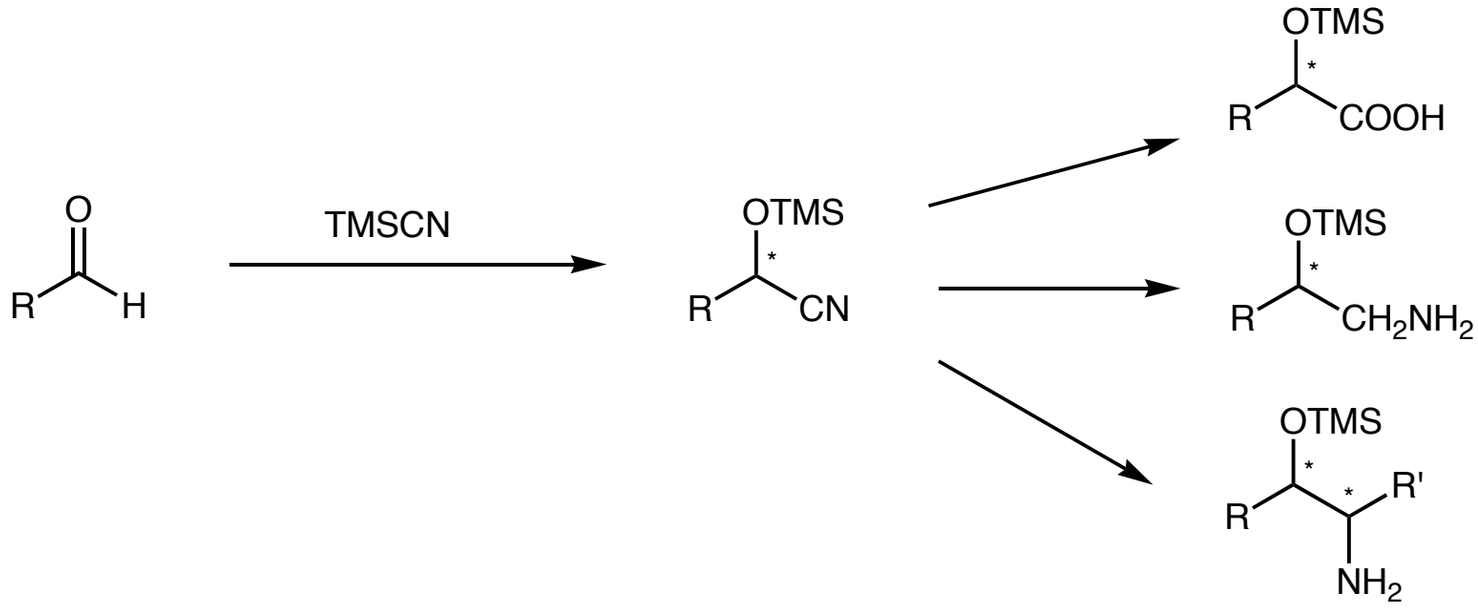
91%, (91% *ee*) **39c**



40

Kang, Y. F.; Liu, L.; Wang, R.; Yan, W. J.; Zhou, Y. F. *Tetrahedron-Asymmetry* **2004**, *15*, 3155.

Cyanohydrin Formation: sp Carbon Nucleophiles



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Wilkinson, H. S.; Grover, P. T.; Vandenbossche, C. P.; Bakale, R. P.; Bhongle, N. N. et al. *Org. Lett.* **2001**, *3*, 553-556.
Ward, D. E.; Hrapchak, M. J.; Sales, M. *Org. Lett.* **2000**, *2*, 57-60.
Nicolaou, K. C.; Vassilikogiannakis, G.; Kranich, R.; Baran, P. S.; Zhong, Y. L. et al. *Org. Lett.* **2000**, *2*, 1895-1898.
Myers, A. G.; Zhong, B. Y.; Kung, D. W.; Movassaghi, M.; Lanman, B. A. et al. *Org. Lett.* **2000**, *2*, 3337-3340.

Chiral Catalysts:

Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537-540.
Hwang, C.-D.; Hwang, D.-R.; Uang, B.-J. *J. Org. Chem.* **1998**, *63*, 6762-6763.
Bolm, C.; Muüller, P.; Harms, K. *Acta Chem. Scand.* **1996**, *50*, 305-315.
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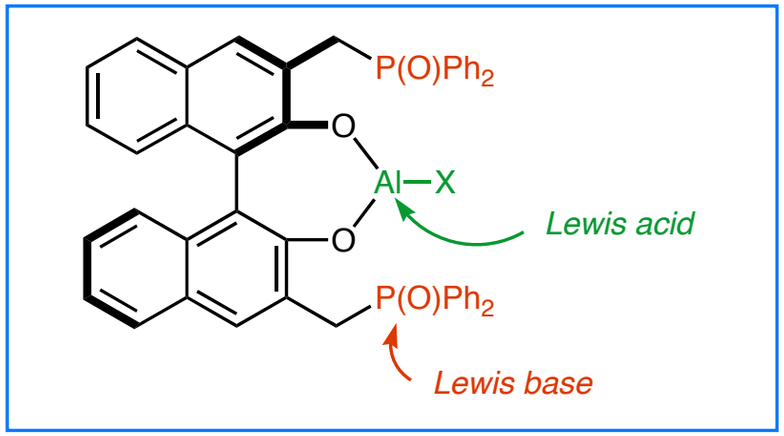
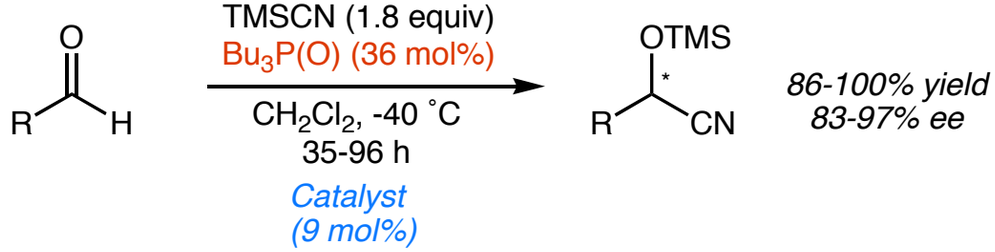
Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000**, *2*, 1617-1619.

Recent review:

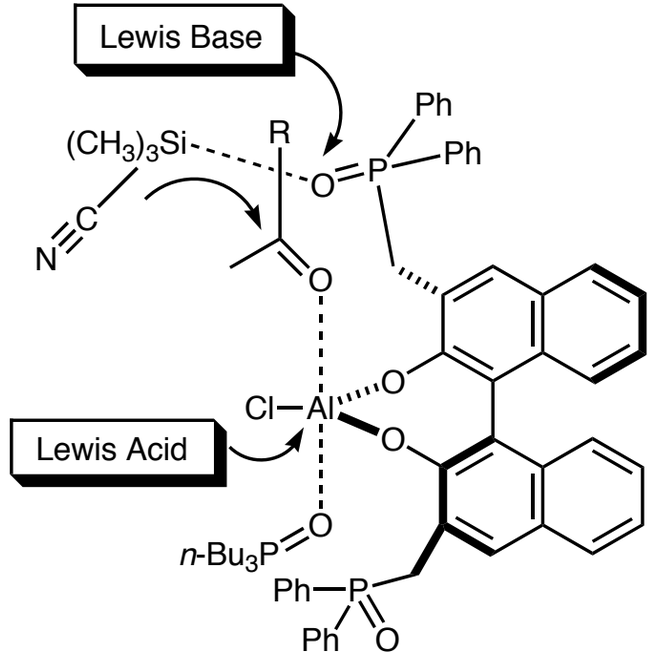
Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.

Enantioselective Cyanohydrin Formation: Shibasaki's Aluminum Catalyst





⇨ TMSCN added over 10 h with syringe pump.



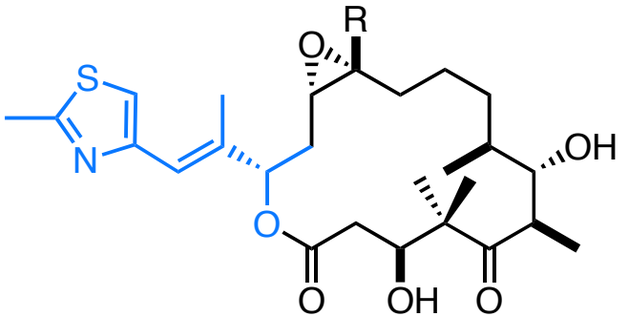
R	yield	ee
Ph	97	97
Hex	100	98
i-Pr	96	90
Et_2CH	98	83
t-BuCH=CH_2	94	97
Ph	98	96
p-MeC_6H_4	87	90
2-Furyl	86	95

$Me_3P(O)$ is used as additive for aromatic aldehydes

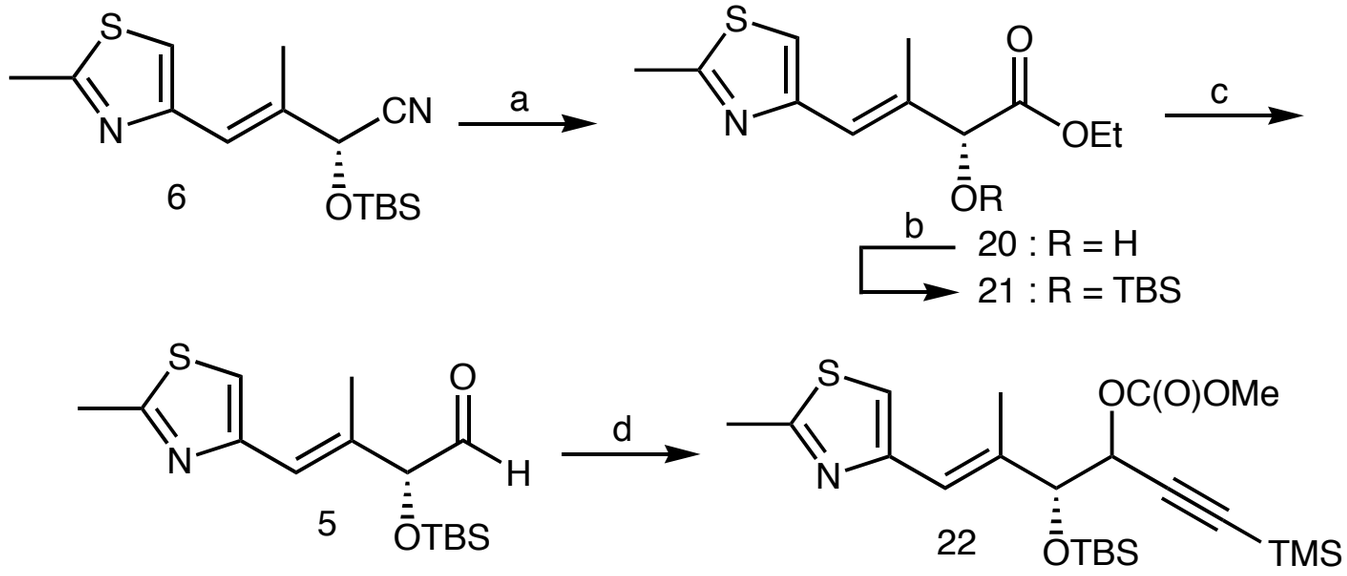
Review (concept): Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 1236-1256.

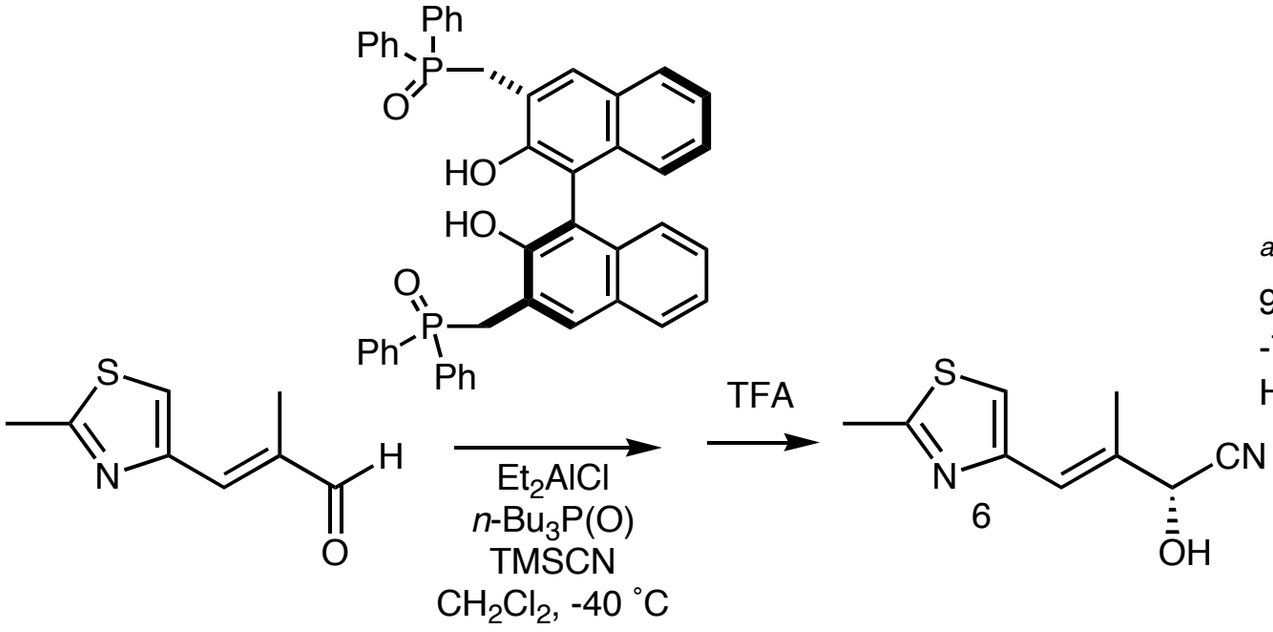
Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641-2642.

Application to Epothilone



Epothilone A: R = H
Epothilone B: R = Me

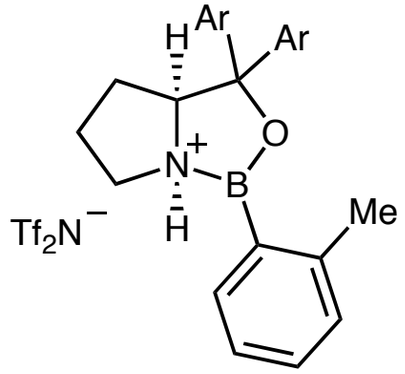




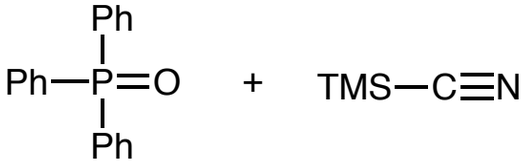
[a] (a) HCl, EtOH, H_2O, 90 ˚C, 83%; (b) TBSCl, imidazole, DMF, 99%; (c) DIBAL, toluene, -78 ˚C, 94%; (d) TMSC=CLi, THF, -78 ˚C; then $ClCO_2Me$, 79%; (e) $Pd(OAc)_2$, *n*-Bu_3P, HCO_2NH_4, benzene, 50 ˚C 51%

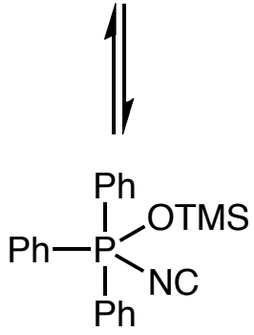
D. Sawada, M. Shibasaki, *Angew Chem Int Ed* **2000**, *39*, 209. Sawada, D.; Kanai, M.; Shibasaki, M. *J Am Chem Soc* **2000**, *122*, 10521-10532.

Enantioselective Cyanosilylation



catalyst





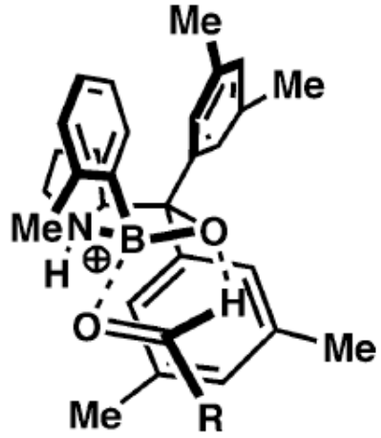
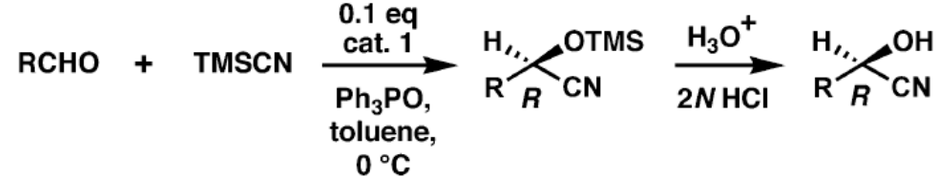


Table 1. Oxazaborolidinium-Catalyzed Cyanosilylation of Aldehydes

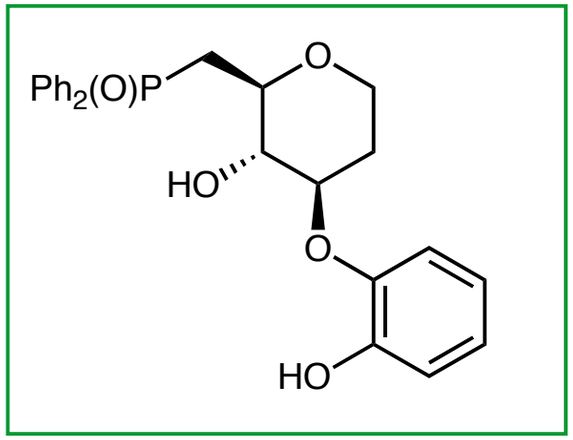


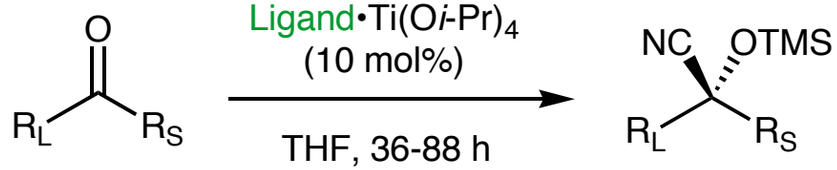
R	time, h	% isolated yield	% ee[a,b]
phenyl	40	94	95
2-tolyl	72	95	91
4-anisyl	40	91	90
4-cyanophenyl	144	98	97
cyclohexyl	40	97	90
tert-butyl	40	96	91
n-hexyl	48[c]	96	91

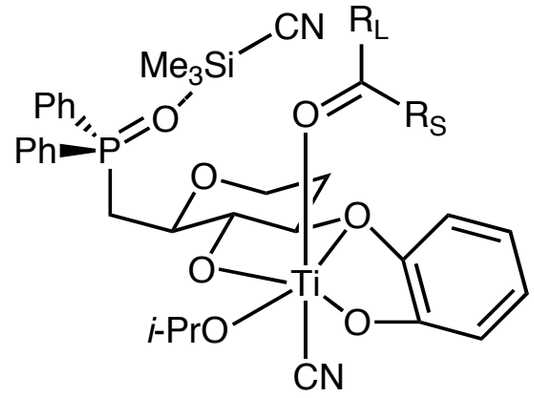
[a] Enantioselectivities determined by GC or ^{1}H NMR analysis of cyanohydrins. [b] Performed using 0.2 equiv of Ph_3PO. [c] Reaction temp = −20 °C.

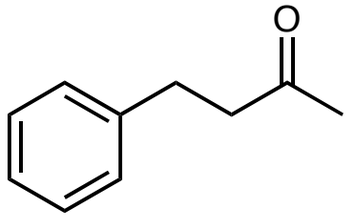
Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106-8107.

Cyanohydrin From Ketones

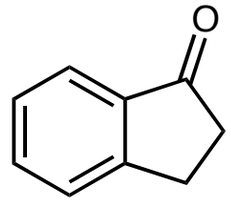




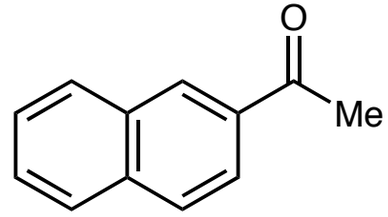




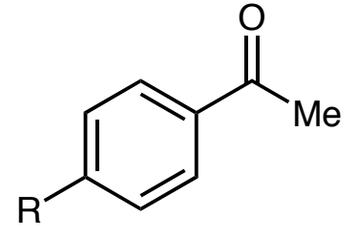
92% (85% ee)



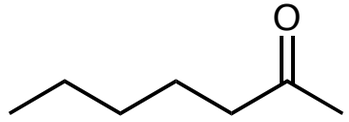
72% (69% ee)



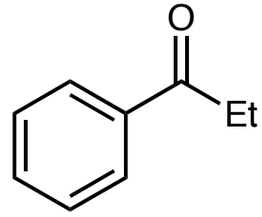
82% (95% ee)



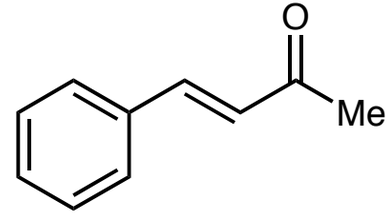
R = H, 85% (92% ee)
R = Me, 80% (90% ee)
R = Cl, 82% (92% ee)



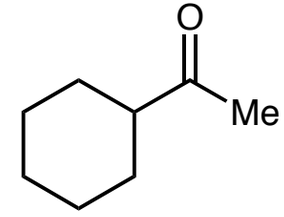
88% (76% ee)



89% (91% ee)



72% (91% ee)



86% (90% ee)

Shibasaki *J. Am. Chem. Soc.* **2000**, *122*, 7412