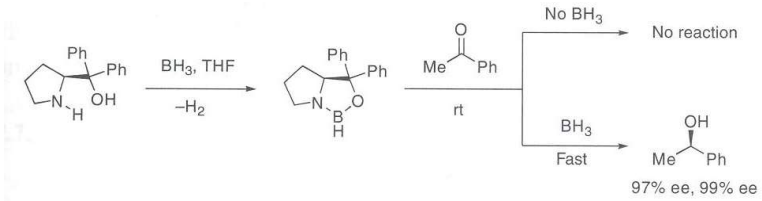
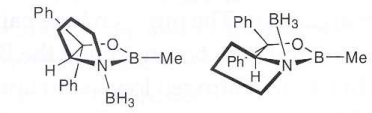
Ossazaborolidine chirali (catalizzatore bifunzionale)

Corey-Bakshi-Shibata (CBS) Reduction



Coordinazione BH_3



Doppia attivazione:

Base di Lewis ($N\cdots BH_3$)

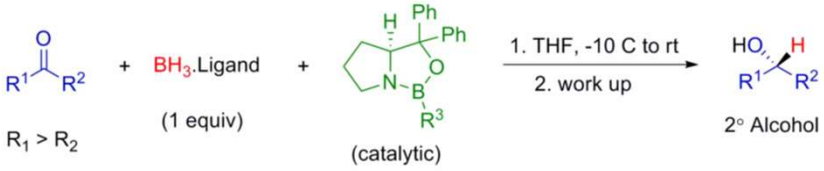
Acido di Lewis ($C{=}O\cdots B$)

favorito **sfavorito**

Angew. Chem. Int. Ed. **1998**, *37*, 1986 – 2012

Ossazaborolidine chirali (catalizzatori bifunzionale)

Corey-Bakshi-Shibata (CBS) Reduction

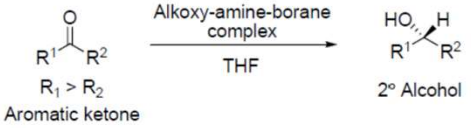


$R^{1\text{-}2}$ = alkyl, aryl; Ligand: THF, Me_2S, 1,4-thioxane, diethylaniline; R^3 = H, alkyl

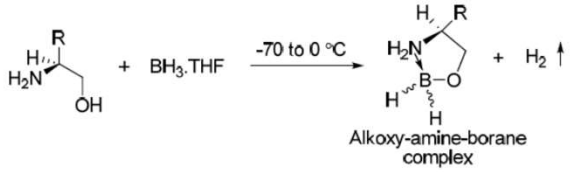
Elias James Corey

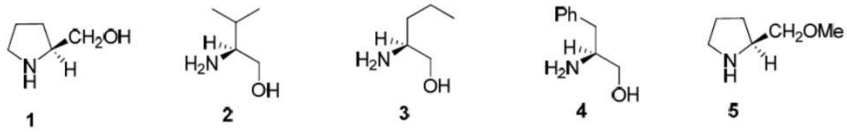
- Born: 12th July, 1928 in Methuen, Massachusetts, USA
- Bachelors Degree in 1948 and Ph. D. in 1951 from MIT
- Faculty in University of Illinois at Urbana-Champaign in 1951
- Faculty in Harvard University in 1959
- Wolf Prize in Chemistry in 1986
- Japan Prize in 1989
- Nobel Prize in Chemistry in 1990 *"for his development of the theory and methodology of Organic Synthesis"*, specifically retrosynthetic analysis
- Priestly Medal in 2004

Previous work by Itsuno and co-workers:



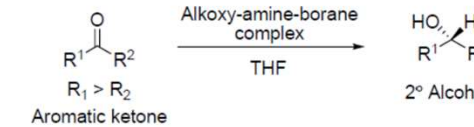
[complex] : [ketone] = 1 : 0.8

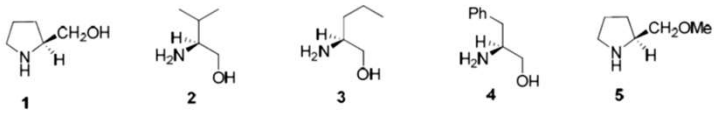




Itsuno, S.; Hirao, A.;Nakahama, S.; Yamazaki, N. *J. Chem Soc., Chem. Commun.* **1981**, 315

3





Entry	Amino-alcohol	Ketone	Solvent	Yield (%)	$[\alpha]_D^{20}$/°	Optical yield (%)	Absolute configuration
1	(**1**)	EtCOPh	THF	99	+20.74	44	(*R*)
2	(**1**)	EtCOPh	THF	93	+21.49	46	(*R*)
3	(**1**)	EtCOPh	C_6H_6	100	+3.41	7.3	(*R*)
4	(**1**)	EtCOPh	MeOH-H_2O (2:1)	100	+7.80	17	(*R*)
5	(**1**)	EtCOPh	$CHCl_3$	88	–8.29	18	(*S*)
6	(**1**)	MeCOPh	THF	98	+23.30	44	(*R*)
7	(**2**)	MeCOPh	THF	99	+25.60	49	(*R*)
8	(**2**)	EtCOPh	THF	99	+27.93	60	(*R*)
9	(**2**)	β-Naphthyl methyl ketone	THF	93	+21.49	52	(*R*)
10	(**3**)	EtCOPh	THF	100	+19.08	41	(*R*)
11	(**4**)	EtCOPh	THF	100	+17.59	37	(*R*)
12	(**5**)	EtCOPh	THF	99	+7.43	16	(*R*)

OH group plays an important role

Itsuno, S.; Hirao, A.;Nakahama, S.; Yamazaki, N. *J. Chem Soc., Chem. Commun.* **1981**, 315

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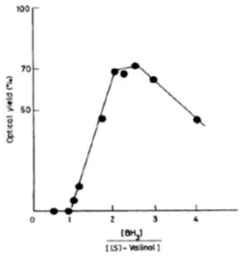

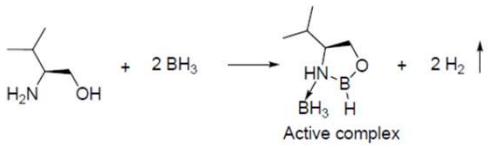

- **(*S*)-Valinol gives the best selectivity**
- **Optimum [BH_3] : [(*S*)-Valinol] is 2:1 to 3:1**
- **Structure of active complex responsible for asymmetric reduction**
- **Amino alcohol can be recovered after reaction and recycled**
- **(*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol showed better selectivity**

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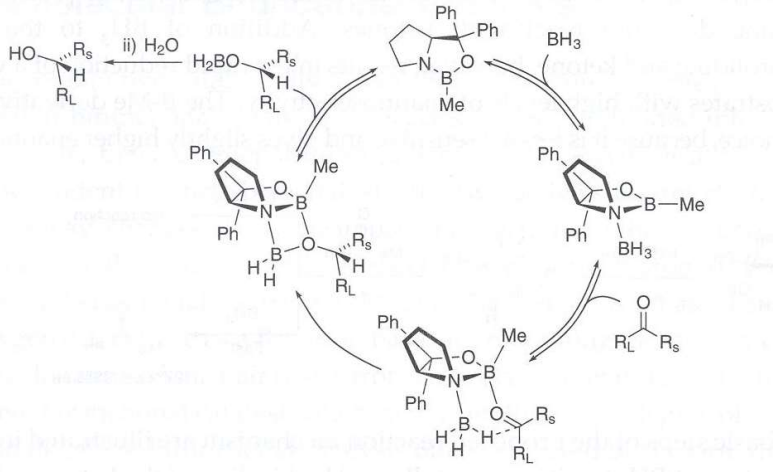
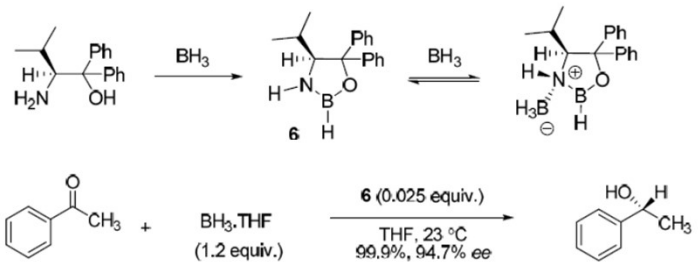
Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1673

Ossazaborolidine chirali (meccanismo proposto)



6

Ligand/Catalyst optimization (Corey)



From possible mechanistic pathway :
Competition between α-BH_3 adduct and β-BH_3 adduct decreases selectivity

Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551

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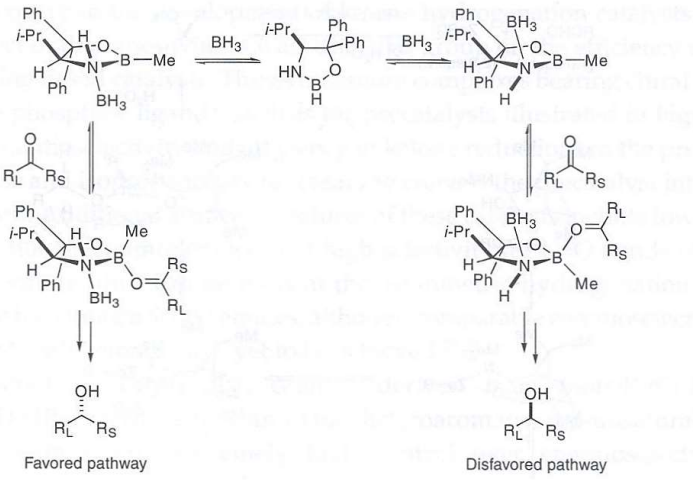
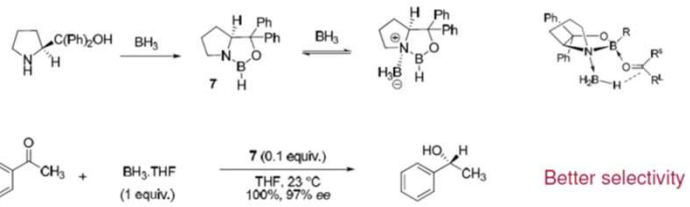
Ossazaborolidine/BH_3

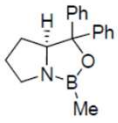
i due diastereoisomeri portano ai due alcoli enantiomerici



8

Ligand/Catalyst optimization (Corey)





Further improvement in catalyst:

1. B-H catalyst is extremely air and moisture sensitive
2. B-Me catalyst is less sensitive
3. Preparation is easier
4. Same or higher enantioselectivity

Corey, E. J.; Helal, C. J. *Angew. Chem.,Int. Ed. Engl.* **1998**, *37*, 1986

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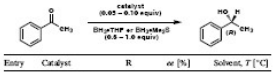
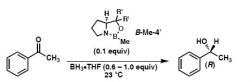
Ossazaborolidine: Ottimizzazione del catalizzatore

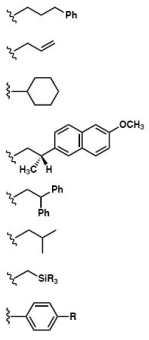


Entry	Catalyst	R	*ee* [%]	Solvent, *T* [°C]
1		H	94	THF, 23
2		H	94	$PhCH_3$, 23
3		H Me	97 75	THF, 23 $PhCH_3$, 23
4		H Me	97 97	THF, 23 THF, 23
5		Me	98	THF, 0
6		H	87	THF, 0
7		H Me	96 92	THF, 23 $PhCH_3$, 27
8		Me	86	THF, 0
9		H Me	94 93	THF, 25–30 THF, 0–5



Entry	R'	*ee* [%]
1		97
2		98
3		62
4		76
5		28
6		82
7	$CH_2CH_2CH_2CH_2$	55
8[a]		67
9[a]		71
10[b]		96
11[b]	CF_3	60

[a] The oxazaborolidine (0.15 equiv) was formed from the corresponding precursor by reaction with BH_3·THF and contains a hydrogen atom on boron instead of the methyl group. The reduction was carried out at 0 °C. [b] The group on the oxazaborolidine boron atom was *n*-pentyl.

R
H
CH_3
CH_2CH_3
$CH_2CH_2CH_2CH_3$
$CH_2CH_2CH_2CH_2CH_3$


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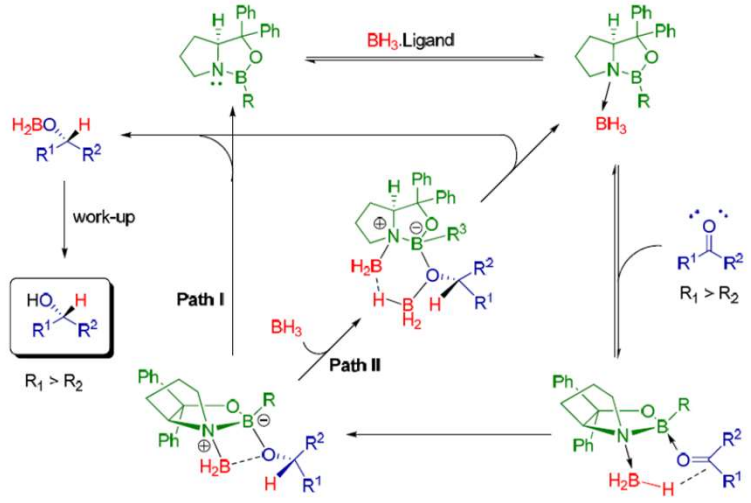
Ossazaborolidine chirali (meccanismo proposto)



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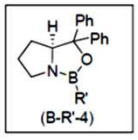
Ossazaborolidine: scopo della reazione

Ketone	ee [%]	Catalyst	L_2BH	T [°C]
Aryl-alkyl ketone	99	*B*-Me-**4**	BDEA	30
	99.7	*B*-*n*Bu-**4**	CB	-78
	99	*B*-Me-**4**.BH_3	BMS	30
Diaryl ketone	95	*B*-*n*Bu-**4**	CB	-78
	93	*B*-*n*Bu-**4**	CB	-78



Abbreviations

BDEA = BH_3.diethylaniline
CB = Catechol borane
BMS = $BH_3.Me_2S$

Electronic Effect

Corey, E. J.; Helal, C. J. *Angew. Chem.,Int. Ed. Engl.* **1998**, *37*, 1986

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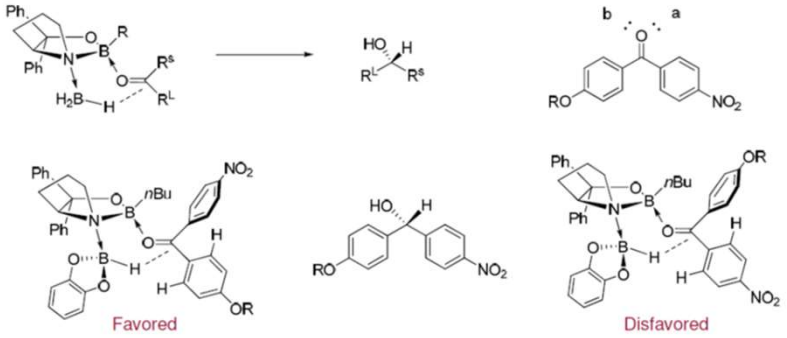
Ossazaborolidine: scopo della reazione



Reasons for the favored intermediate:

- +R effect makes ketone-boron coordination stronger
- -I effect makes carbonyl carbon more nucleophilic

E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1995**, *36*, 9153

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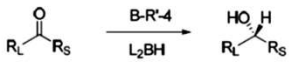
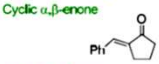
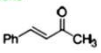
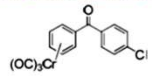
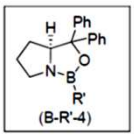
Ossazaborolidine: scopo della reazione



Ketone	*ee* [%]	Catalyst	L_2BH	*T* [°C]
R_L R_S				
Cyclic α,β-enone 	96	*B*-Me-4.BH_3	BMS	-20
Acyclic α,β-enone 	97	*B*-*n*Bu-4	CB	-78
Dialkyl ketone 	97.4	*B*-Me-4	BDEA	20
	≥99	*B*-Me-4	BDEA	20
Ketones in ligands of metal complexes 	98	*B*-*n*Bu-4	CB	-40



Abbreviations

BDEA = BH_3.diethylaniline
CB = Catechol borane
BMS = $BH_3.Me_2S$

Corey, E. J.; Helal, C. J. *Angew. Chem.,Int. Ed. Engl.* **1998**, *37*, 1986

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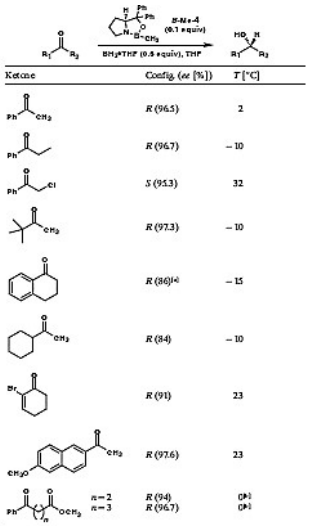
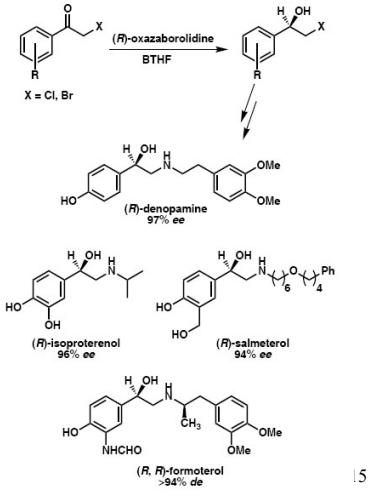
Ossazaborolidine: scopo della reazione



Ketone	Config. (*ee* [%])	*T* [°C]
Ph, CH_3	*R* (96.5)	2
Ph, CH_2CH_3	*R* (96.7)	−10
Ph, Cl	*S* (95.3)	32
CH_3	*R* (97.3)	−10
	R (86)[a]	−15
CH_3	*R* (84)	−10
Br	*R* (91)	23
CH_3O, CH_3	*R* (97.6)	23
Ph, $(CH_2)_n$, OCH_3	*n* = 2 *R* (94) *n* = 3 *R* (96.7)	[b] [b]

[a] 0.25 equiv of *B*-Me-4. [b] The reaction time was 25 min.

β-agonisti



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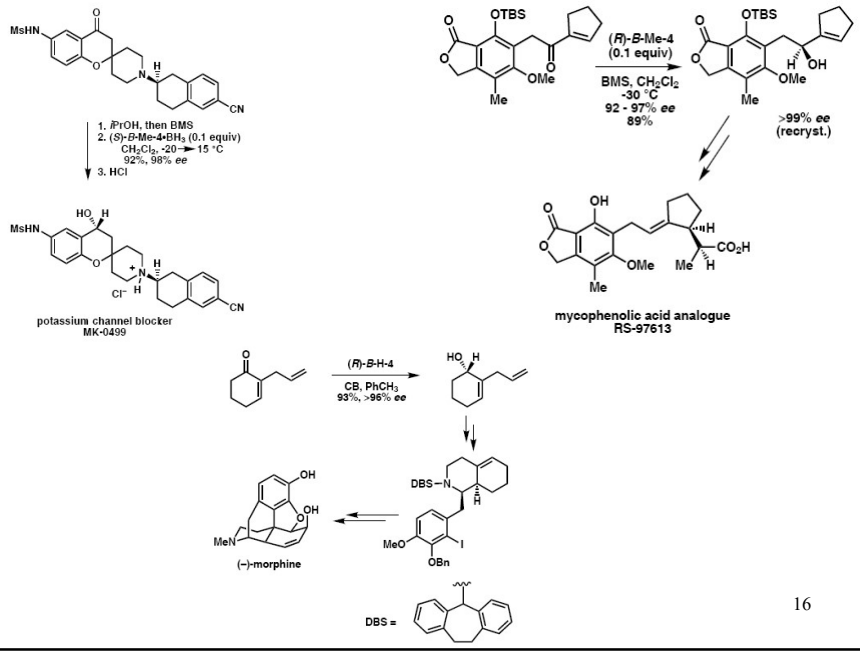
Ossazaborolidine: scopo della reazione



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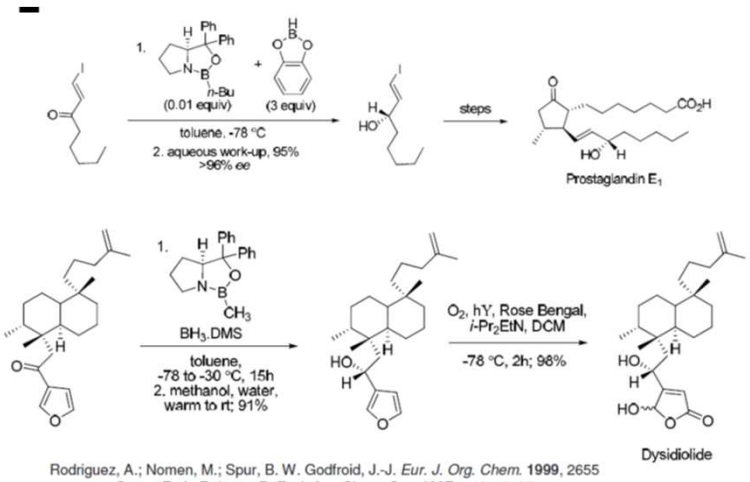
Ossazaborolidine: scopo della reazione



Rodriguez, A.; Nomen, M.; Spur, B. W. Godfroid, J.-J. *Eur. J. Org. Chem.* **1999**, 2655
Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425

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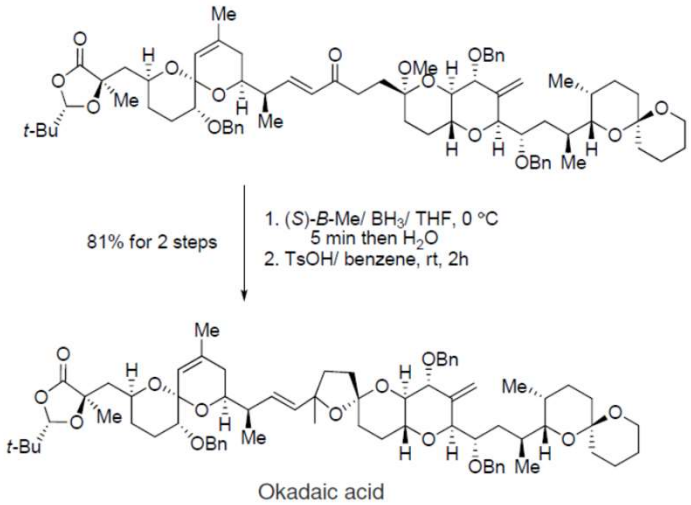
Ossazaborolidine: scopo della reazione



Okadaic acid

Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534

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Product #	Image	Description	Molecular Formula
649317		(*R*)-(+)-2-Methyl-CBS-oxazaborolidine ≥95%	$C_{18}H_{20}BNO$
457698		(*R*)-(+)-2-Methyl-CBS-oxazaborolidine solution 1 M in toluene	$C_{18}H_{20}BNO$
674656		(*R*)-(+)-2-Methyl-CBS-oxazaborolidine solution 1 M in THF	$C_{18}H_{20}BNO$
649309		(*S*)-(−)-2-Methyl-CBS-oxazaborolidine ≥95.0%	$C_{18}H_{20}BNO$
674648		(*S*)-(−)-2-Methyl-CBS-oxazaborolidine solution 1 M in THF	$C_{18}H_{20}BNO$
457701		(*S*)-(−)-2-Methyl-CBS-oxazaborolidine solution 1 M in toluene	$C_{18}H_{20}BNO$
654299		(*R*)-(+)-o-Tolyl-CBS-oxazaborolidine solution 0.5 M in toluene	$C_{24}H_{24}BNO$
654302		(*S*)-(−)-o-Tolyl-CBS-oxazaborolidine solution 0.5 M in toluene	$C_{24}H_{24}BNO$

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