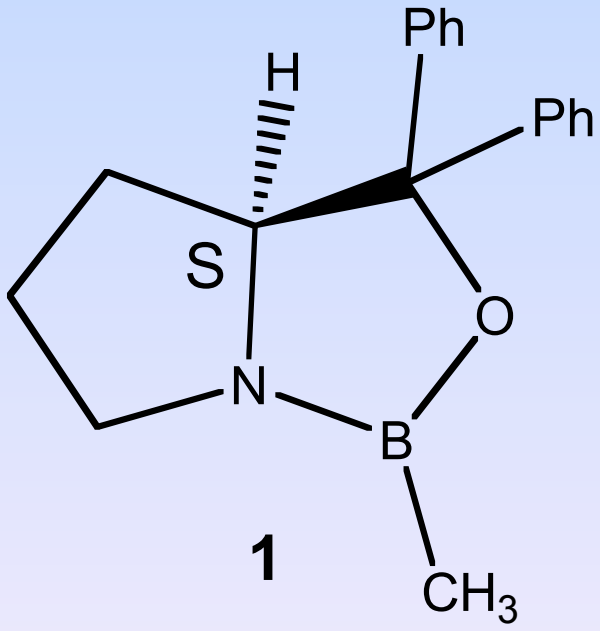
CHIRAL [1,3,2]OXAZABOROLES: PREPARATION AND USE IN ORGANIC SYNTHESIS



1

(S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO[1,2-C][1,3,2]OXAZABOROLE

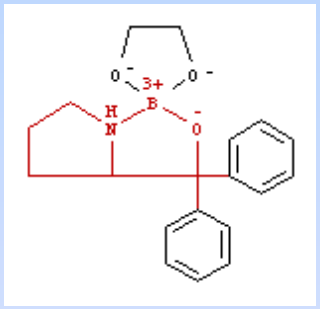
MIKHAIL BARABANOV

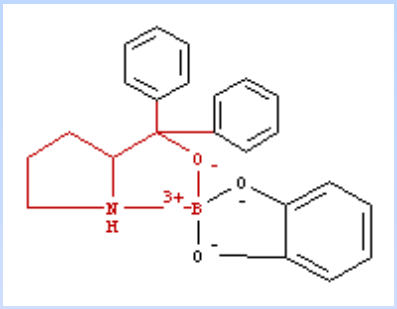
Literature Presentation

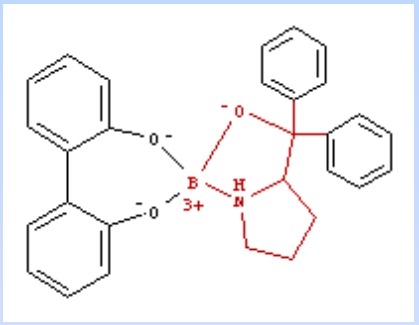
#2

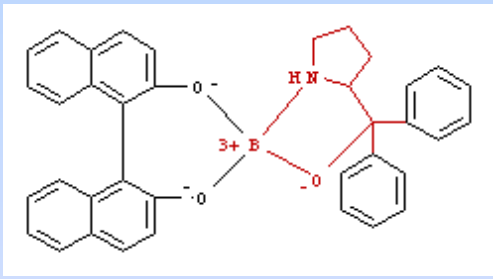
09 JUN 2006

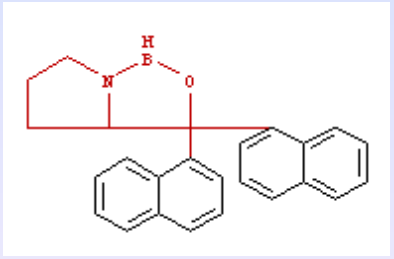
CATALYSTS WITH CHIRAL [1,3,2]OXAZABOROLE FRAMEWORK

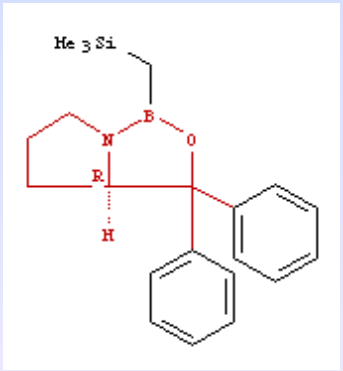


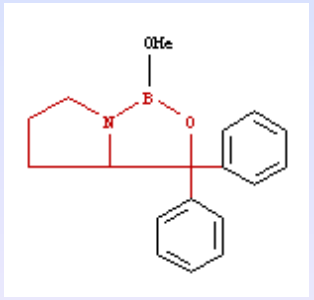


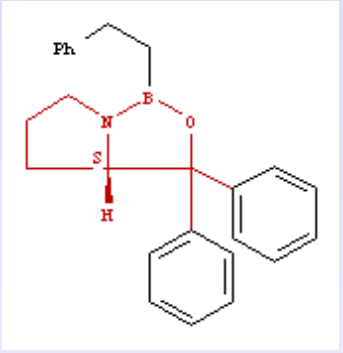


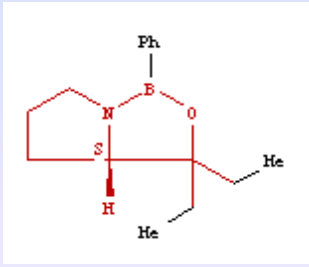










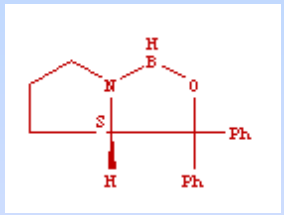


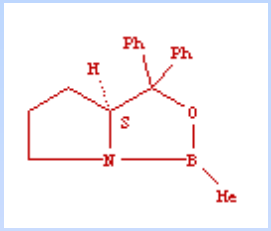
Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317

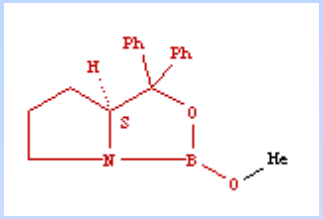
Stepanenko, Viatcheslav; Tetrahedron: Asymmetry 2006, V17(1), P112-115

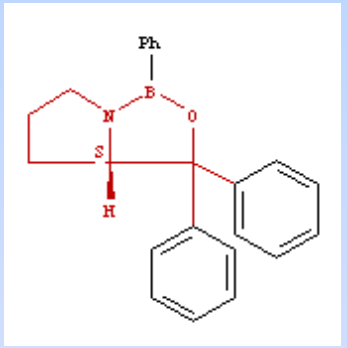
Shan, Zixing; Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 2005, V35(4), P275-279

1- SUBSTITUTED (S)-TETRAHYDRO-3,3-DIPHENYL-1H,3H-PYRROLO[1,2-C][1,3,2]OXAZABOROLES



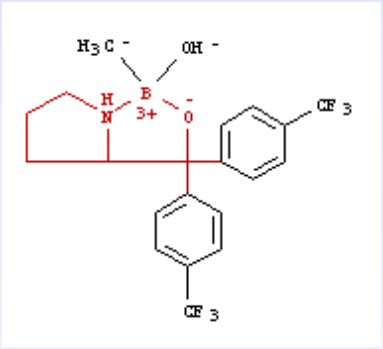


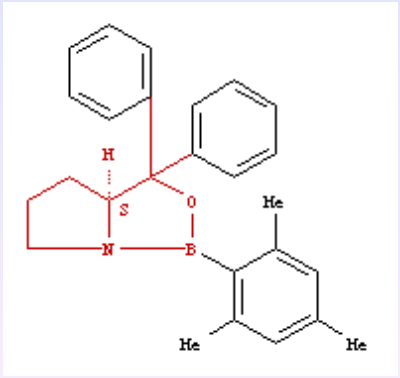




Number of References in CAS Database for Each Catalyst

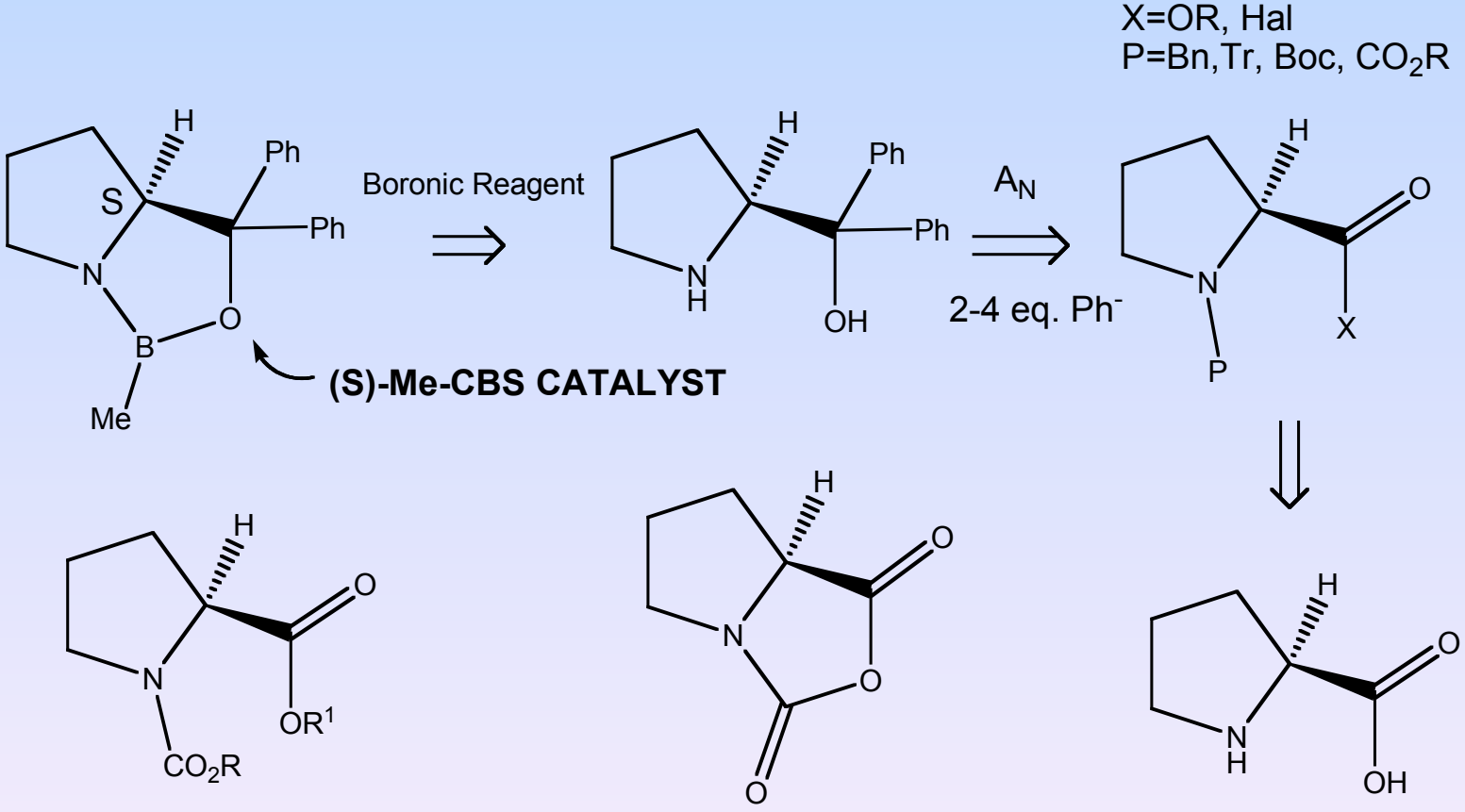
S	**39**	**204**	**6**	**16**
R	**8**	**142**	**4**	**6**



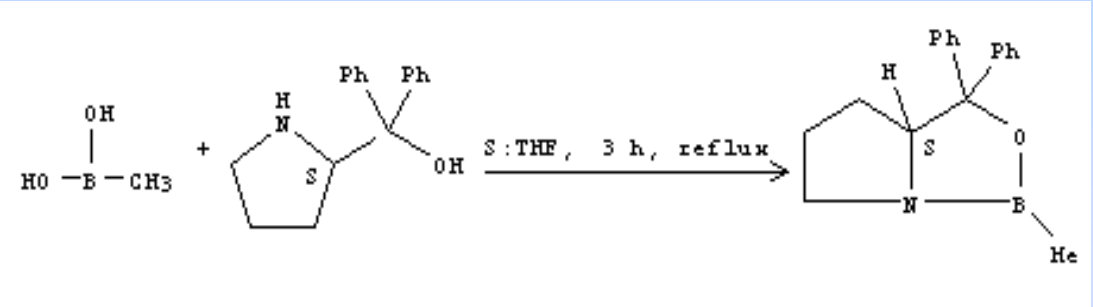


PART I: SYNTHESIS

RETROSYNTHETIC ANALYSIS FOR SUBSTITUTED 1-METHYL[1,3,2]OXAZABOROLE 1



SYNTHESIS OF (S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO-[1,2-C][1,3,2]OXAZABOROLE: BORONIC REAGENTS

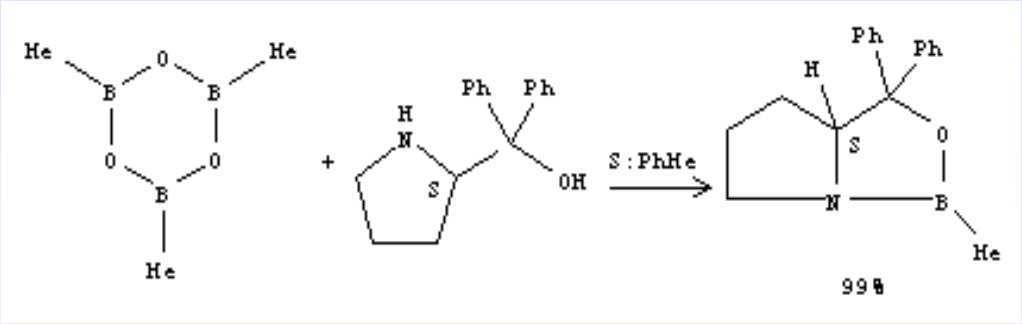


Chirality, 15(8), 674-679; 2003

Organometallics, 23(10), 2362-2369; 2004

94% Journal of Organic Chemistry, 53(12), 2861-3; 1988

86% Journal of the American Chemical Society, 109(25), 7925-6; 1987

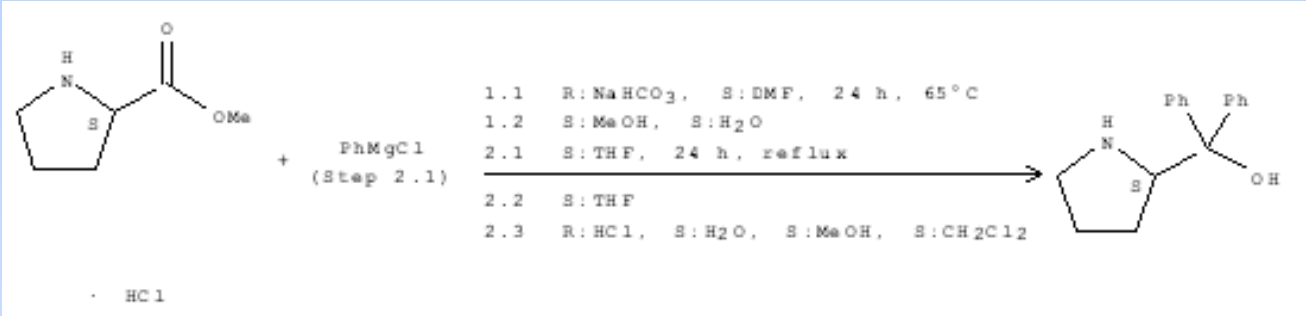


Organic Letters, 5(23), 4249-4251; 2003

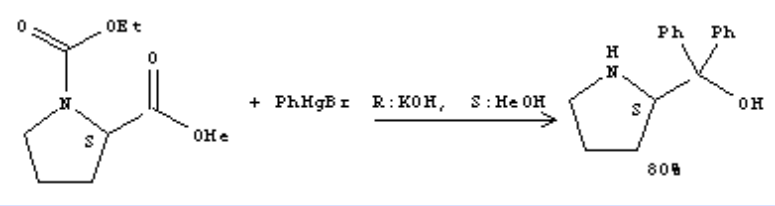
Journal of Organic Chemistry, 58(10), 2880-8; 1993

>99% Journal of Organic Chemistry, 56(2), 751-62; 1991

SYNTHESIS OF (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE



-Tetrahedron, 59(10), 1797-1804; 2003

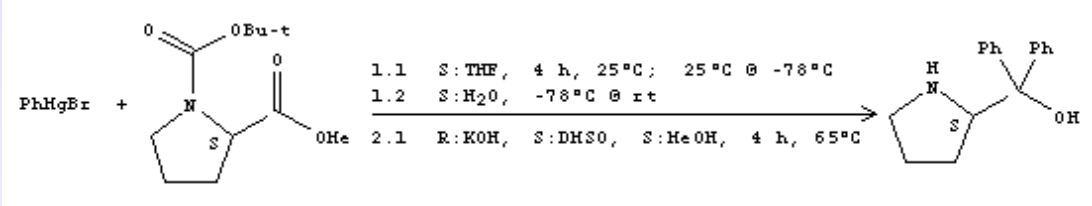


-Organic Letters, 4(17), 2929-2932; 2002

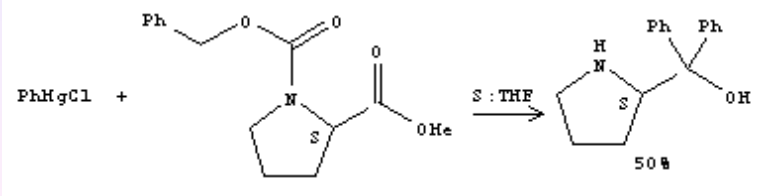
64% Heteroatom Chemistry, 14(1), 42-45; 2003

-Tetrahedron: Asymmetry, 14(1), 95-100; 2003

Tetrahedron, 49(23), 5127-32; 1993

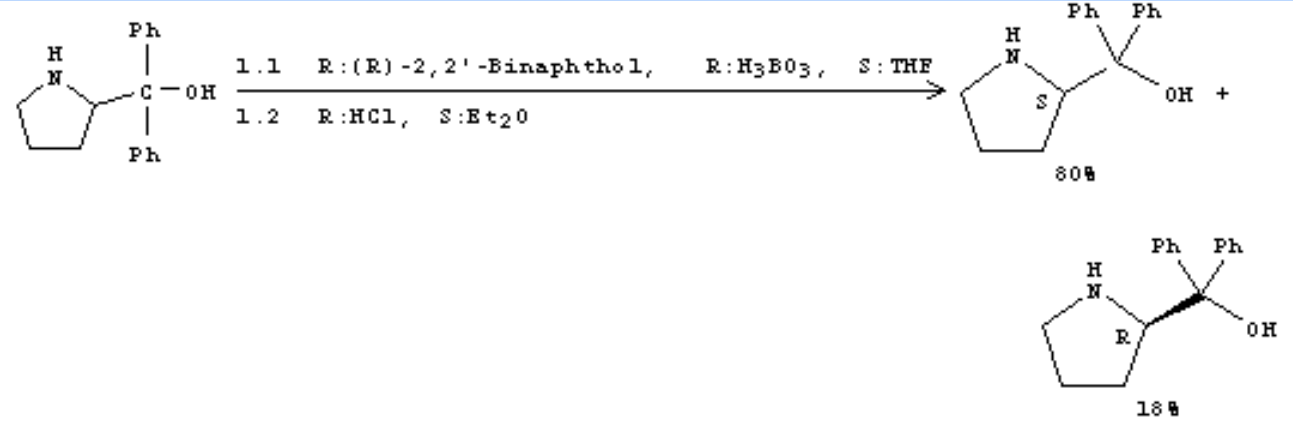


60% Journal of Organic Chemistry, 67(22), 7769-7773; 2002

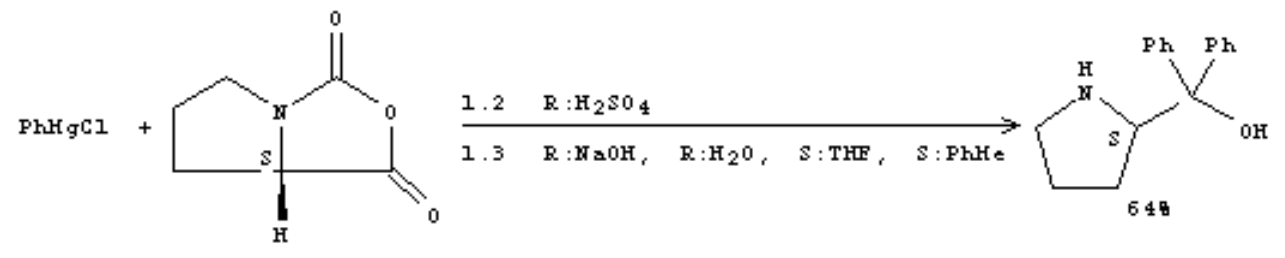


Journal of Organic Chemistry, 53(12), 2861-3; 1988

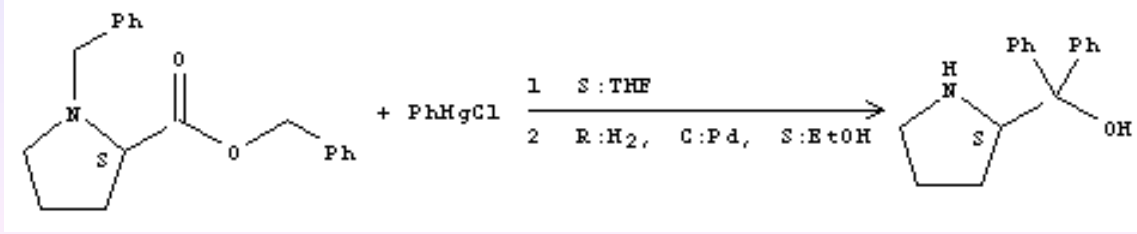
SYNTHESIS OF (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE, CONTINUATION



Journal of Organic Chemistry, 66(11), 3828-3833; 2001

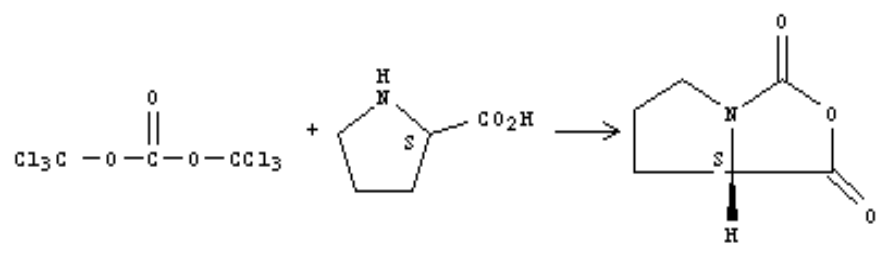


Organic Syntheses, 74, 50-71; 1997

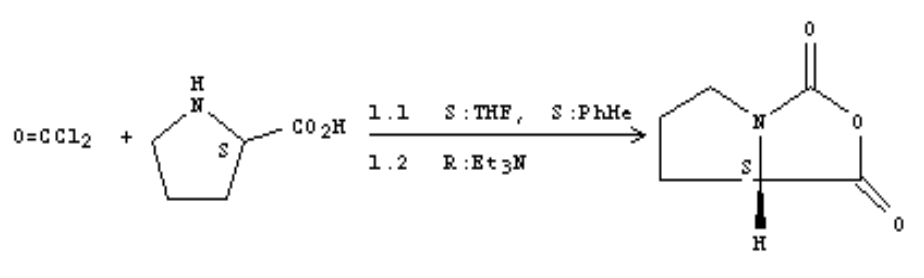


Ger., 4416963, 13 Jul 1995

SYNTHESIS OF (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE PRECURSOR#1: NCA

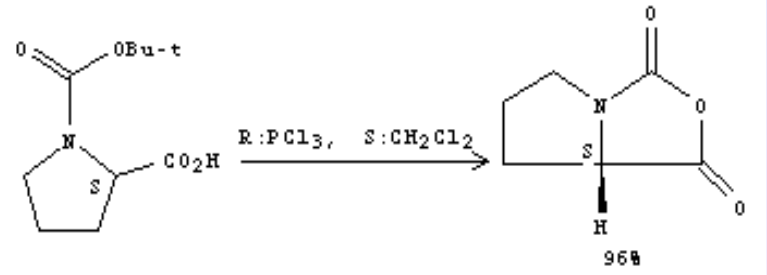


Organic & Biomolecular Chemistry, 1(18), 3238-3243; 2003



Organic Syntheses, 74, 50-71; 1997

95% Journal of Organic Chemistry, 56(2), 751-62; 1991



Tetrahedron, 50(30), 9051-60; 1994

NUCLEOPHILIC ADDITION TO NCA: BY-PRODUCTS EXPLANATION

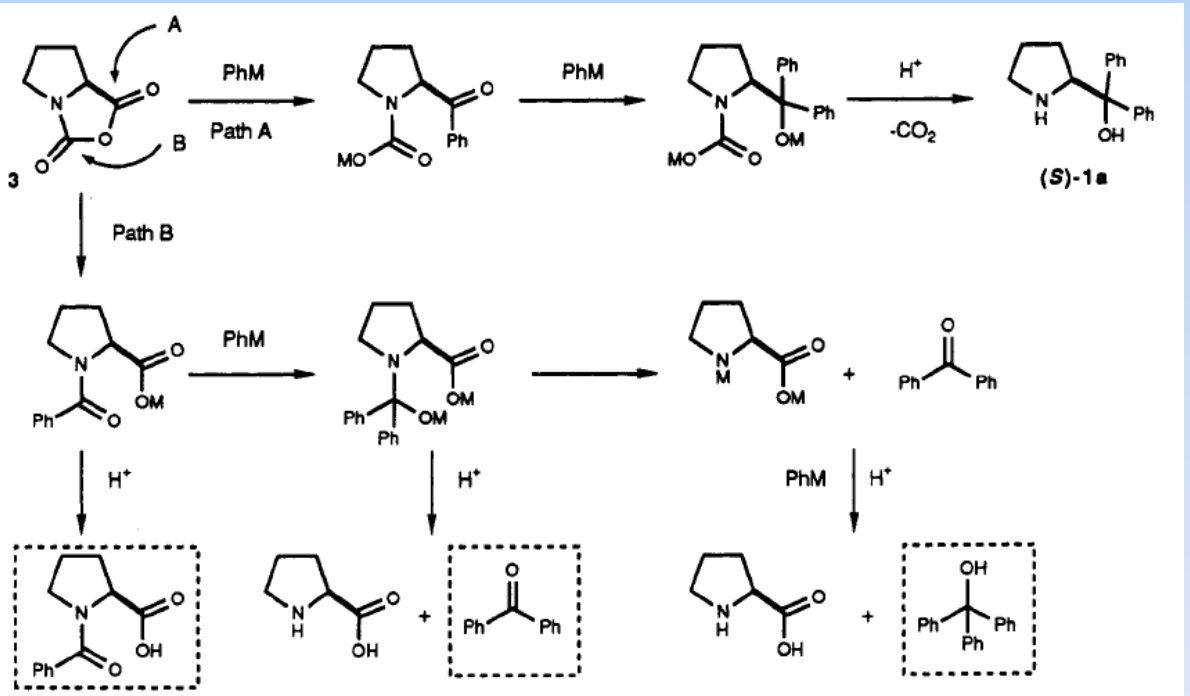


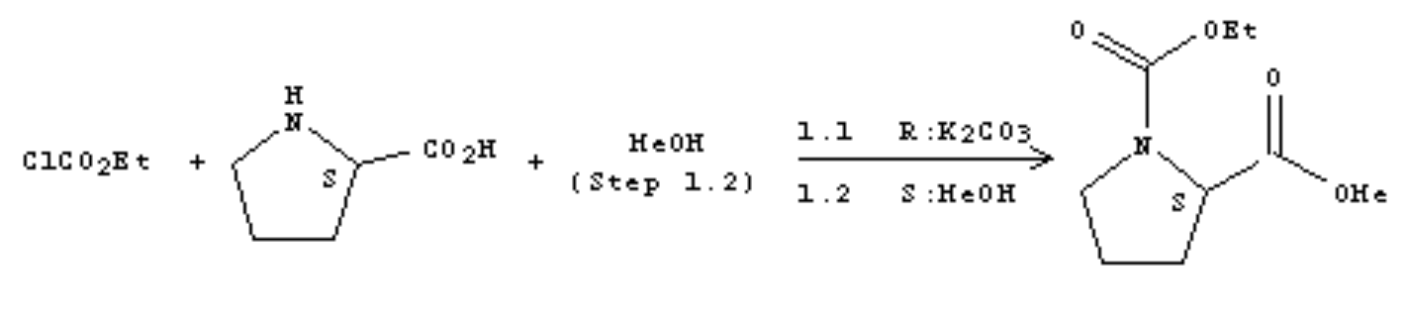
Table I. Pro-NCA Addition to Grignard

entry	grignard	substrate, M	solvent	temp, °C	time, h	yield, %	ee,[a] %
1	PhMgCl	0.1	THF	−78	4	12	99.4%
2	PhMgCl	0.4	THF	−20	3	78	99.4
3	PhMgCl	0.4	THF	0	3	73	99.2
4	PhMgCl	0.4	THF	25	3	64	99.2
5	PhMgCl	0.4	THF	45	2	43	98.2
6	PhMgCl[b]	0.2	THF	−20	3	56	99.0
7	PhMgCl	0.2	THF/tol	−15	3	69	99.2
8	PhMgCl	0.2	THF/CH_2Cl_2	−15	3	61	99.2
9	PhMgBr	0.2	THF/Et_2O	−15	3	62	99.2
10	PhMgCl	0.4	THF	−15	3	78	99.4
11	PhMgCl	0.2	THF	−15	3	76	99.4
12	PhMgCl	0.1	THF	−15	3	72	99.2
13	PhMgCl	0.05	THF	−15	3	73	99.2

[a] Enantiomeric excess (ee) determined by capillary GC analysis of the (*R*)-MPTA amide derivative. [b] Inverse addition.

Journal of Organic Chemistry, 56(2), 751-62; 1991

SYNTHESIS OF A CARBOXYETHYL-PROTECTED L-PROLINE DERIVATIVE



84% Journal of Organic Chemistry, 70(3), 898-906; 2005

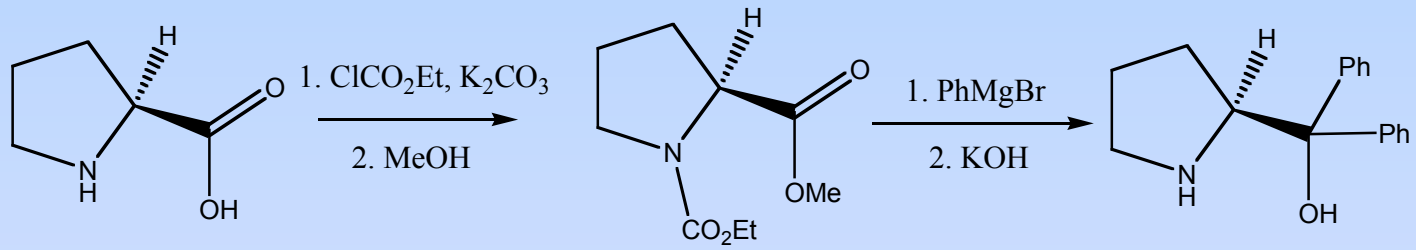
97% Tetrahedron: Asymmetry, 16(5), 1055-1060; 2005
Helvetica Chimica Acta, 86(1), 91-105; 2003

100% Heteroatom Chemistry, 14(1), 42-45; 2003, original reference: Kanth, J. V. B.; Periasamy, M. *Tetrahedron* 1993, **49**, 5127.

95% Tetrahedron: Asymmetry, 14(1), 95-100; 2003

95% Synthetic Communications, 25(10), 1523-30; 1995

COMPARISON OF TWO ATTRACTIVE WAYS TO (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE: WHICH ONE IS THE BEST?



(S)-L-Proline

100%

64%

Heteroatom Chemistry, 14(1), 42-45; 2003, original reference: Kanth, J. V. B.; Periasamy, M. *Tetrahedron* 1993, **49**, 5127.

cheap, nontoxic, high yield

(S)-L-Proline

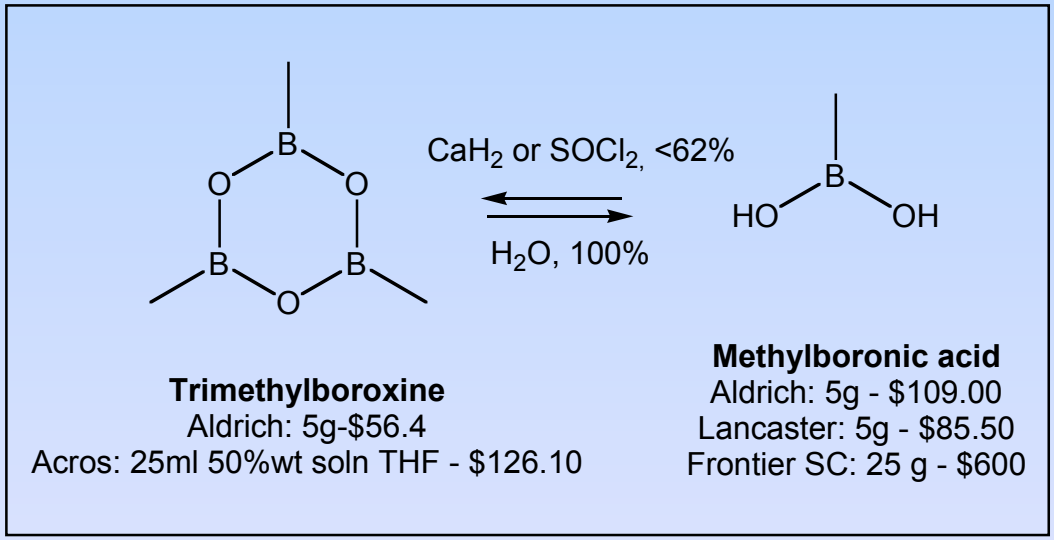
(NCA) N-CarboxyAnhydride

44% [1]
50-56% [2]
73% [3]

1. Organic & Biomolecular Chemistry, 1(18), 3238-3243; 2003
2. Organic Syntheses, 74, 50-71; 1997
3. Journal of Organic Chemistry, 56(2), 751-62; 1991

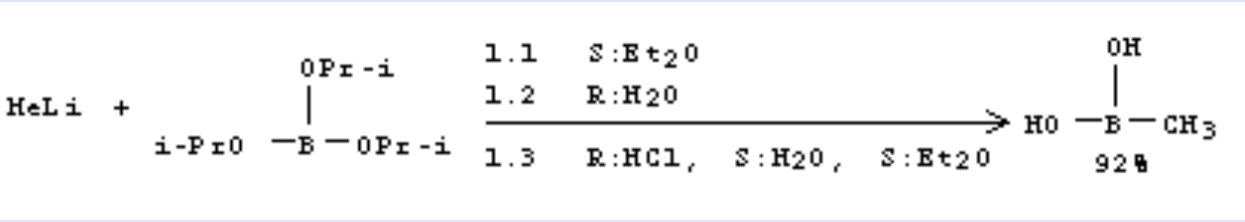
hard-to-buy reagents, poisonous

TRIMETHYLBOROXINE OR METHYLBORONIC ACID?



Trimethylboroxine
Aldrich: 5g-$56.4
Acros: 25ml 50%wt soln THF - $126.10

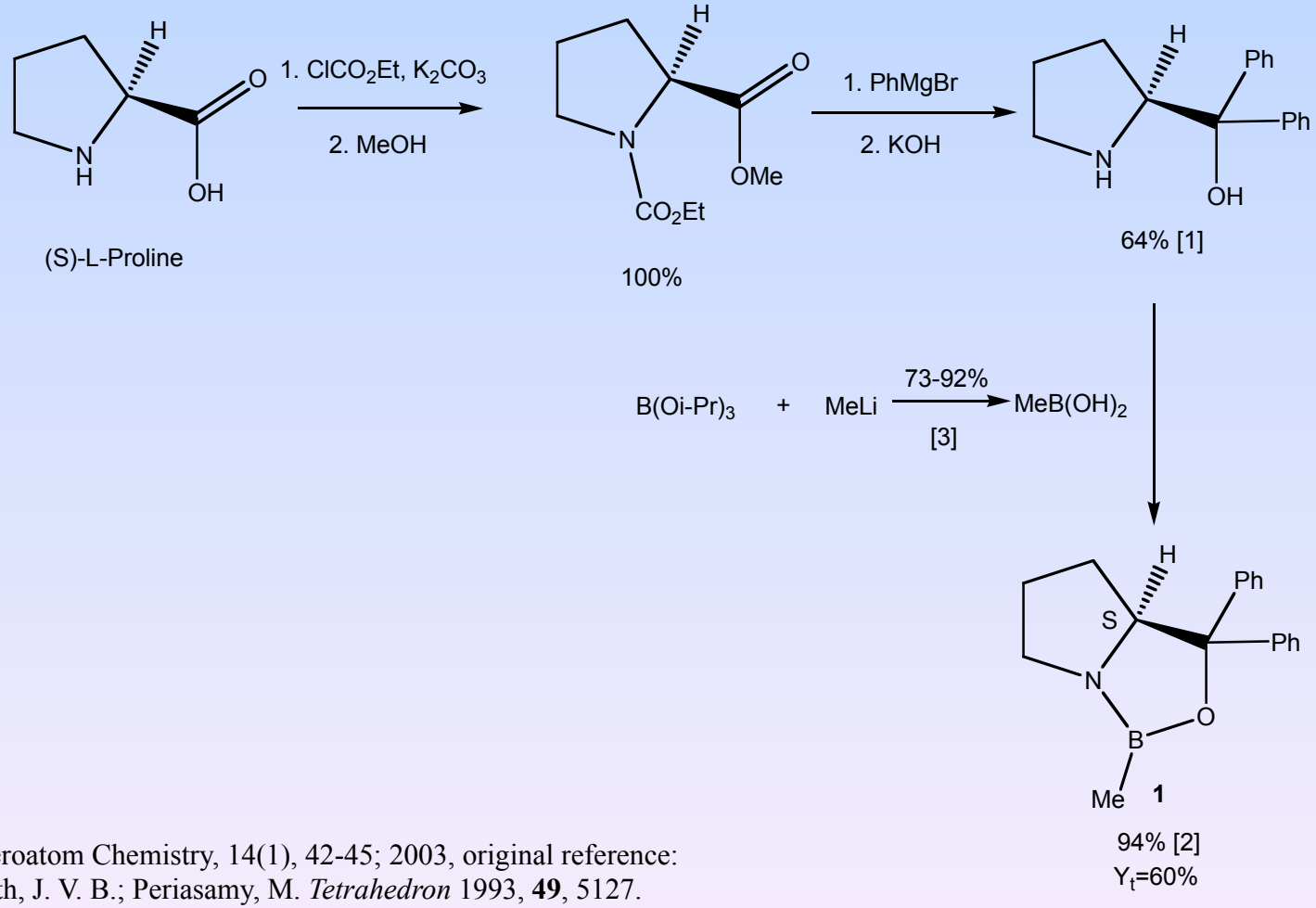
Methylboronic acid
Aldrich: 5g - $109.00
Lancaster: 5g - $85.50
Frontier SC: 25 g - $600



92% U.S., 5039795, 13 Aug 1991
73% Organometallics, 4(5), 816; 1985

If synthesized via methyllithium, the price of 40 g of methylboronic acid would be ca $200

OPTIMIZED SYNTHESIS OF (S)-Me-CBS 1

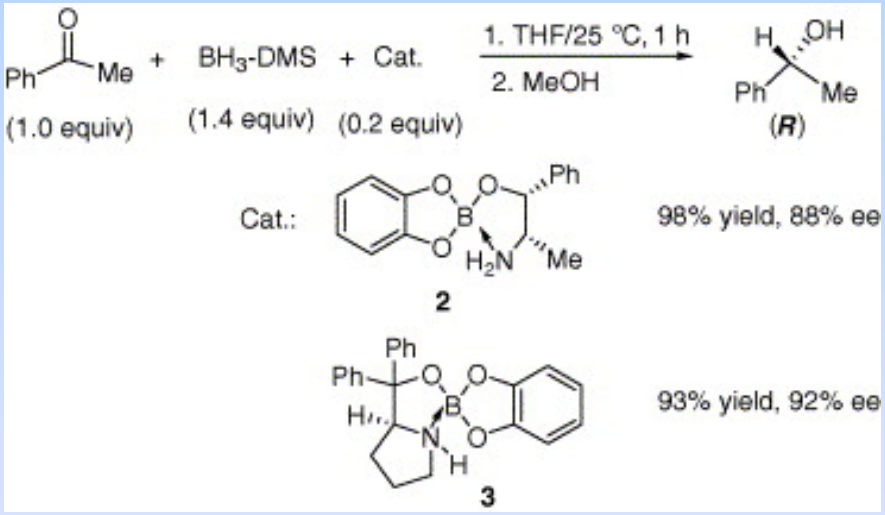


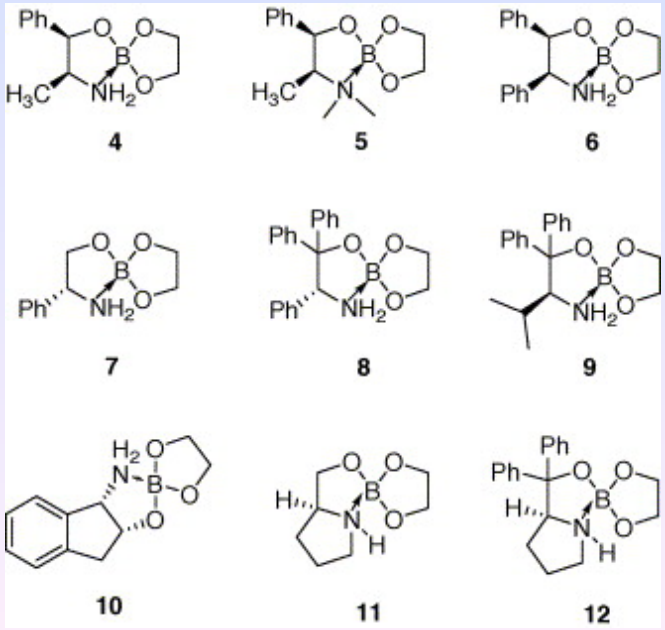
1. Heteroatom Chemistry, 14(1), 42-45; 2003, original reference: Kanth, J. V. B.; Periasamy, M. *Tetrahedron* 1993, **49**, 5127.

2. Journal of Organic Chemistry, 56(2), 751-62; 1991

3. Organometallics, 4(5), 816; 1985

PART II: USE OF CHIRAL CATALYSTS
RECENT DATA, EXAMPLE # 1





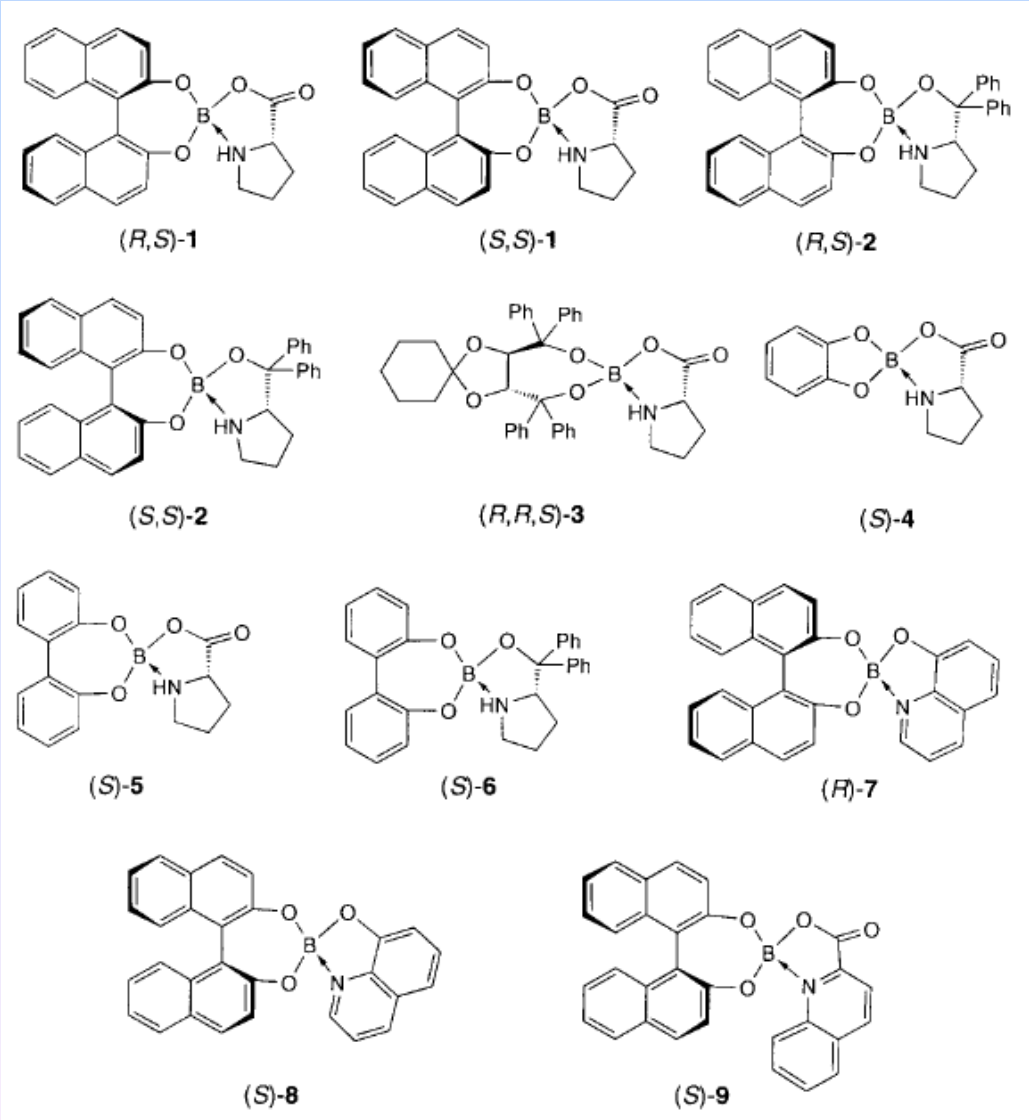
Enantioselective borane reduction of acetophenone with spiroborate esters **4–12** as catalysts[a]

Entry	Cat.	mol %	Yield[b] (%)	ee%[c]	Conf.
1	**4**	20	92	92	*R*
2	**4**	10	75[d]	90	*R*
3	**4**	5	84	88	*R*
4	**4**	2.5	85	75	*R*
5	**5**	10	85[d,e]	0	—
6	**6**	10	87	90	*R*
7	**7**	10	94	82	*S*
8	**8**	20	75	98	*R*
9	**8**	10	99	96	*R*
10	**9**	10	89	98	*S*
11	**9**	5	97	98	*S*
12	**10**	10	75	95	*S*
13	**10**	5	96	94	*S*
14	**11**	10	93	83	*R*
15	**12**	10	98	99	*R*
16	**12**	5	95	98	*R*

[a] 1 equiv of ketone:1 equiv of borane at rt, 1 h.
[b] Purified by Kugelrohr distillation.
[c] Determined by GC on a chiral column (CP-Chiralsil-DexCB).
[d] Crude product.
[e] Traces of ketone was left after 3 h.

Stepanenko, Viatcheslaff; Tetrahedron: Asymmetry 2006, V17(1), P112-115

EXAMPLE # 2



Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317

CARBONYL GROUP REDUCTIONS: YIELDS AND ee.

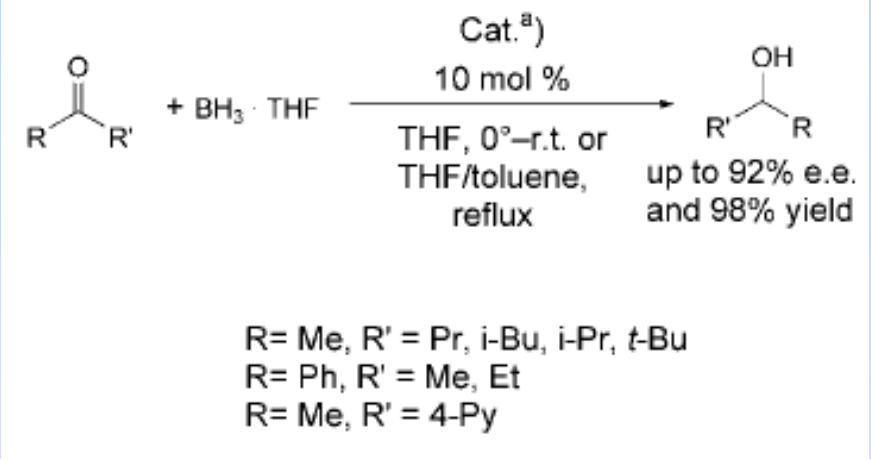
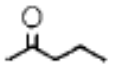
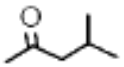
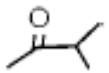
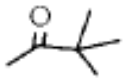
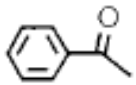
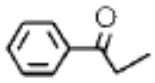
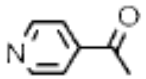


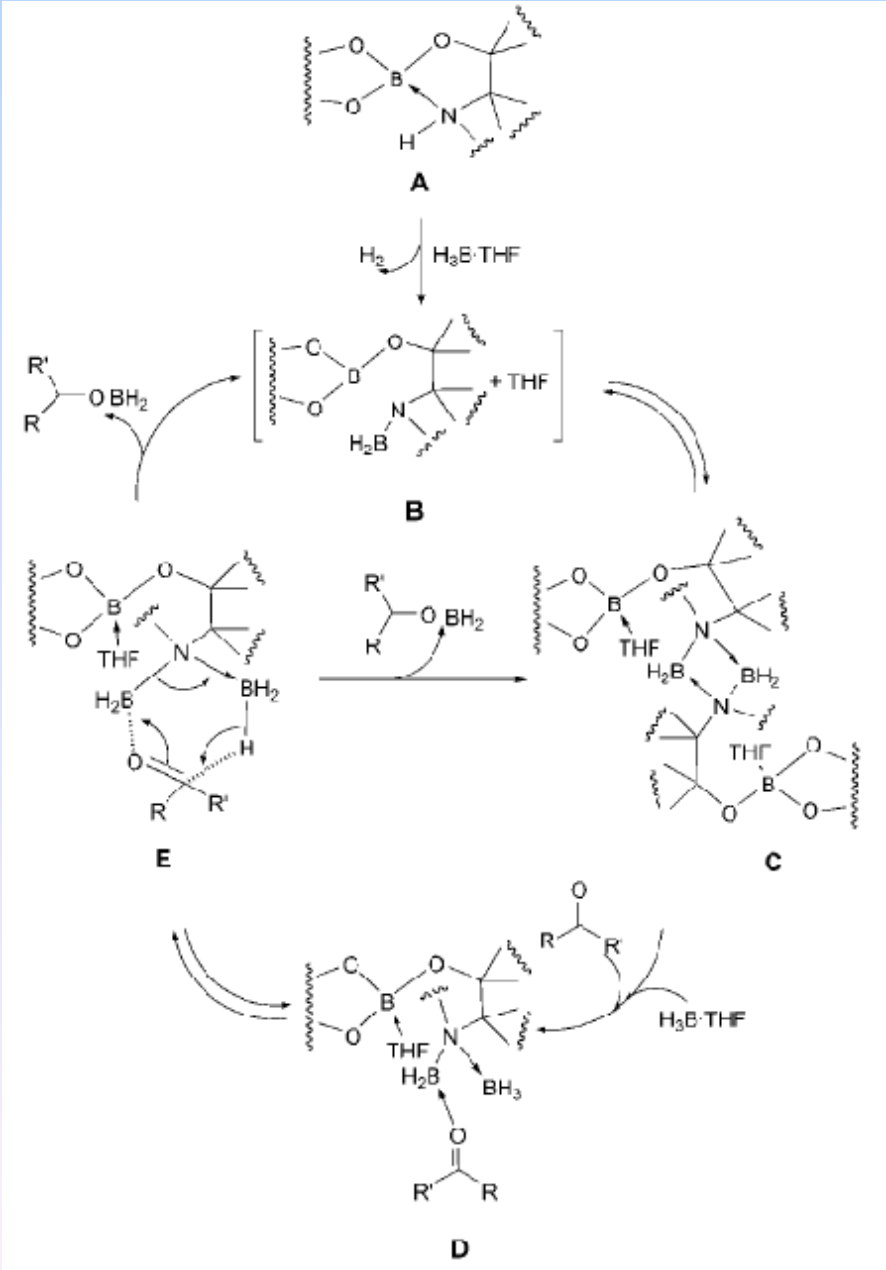
Table 1. *Enantiomer Excess* (% ee) *of* (R)*-Secondary Alcohols Obtained from Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by* (R,S)-**1**, (S,S)-**1**, (R,S)-**2**, *and* (S,S)-**2**[a])

							
(*R*,*S*)-**2**	47	50	66	68	92	81	59
(*S*,*S*)-**2**	6	14	32	....	68	31	3
(*R*,*S*)-**1**	53	....	64	....	76	53	3
(*S*,*S*)-**1**	23	42	64	....	60	49	11

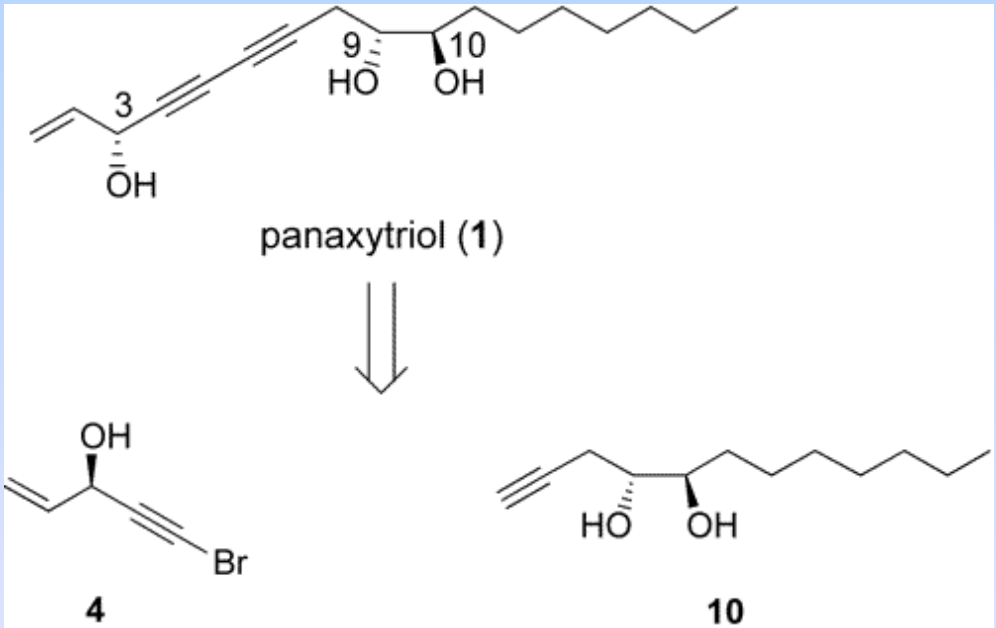
[a]) All reductions were performed in a ketone/borane/catalyst molar ratio of 1 : 0.6 : 0.1 in THF at 0–5° for 2 h; exception: 20 h for 1-(pyridin-4-yl)ethanone and gave (*R*)-secondary alcohols in high yield. The ee of (*R*)-secondary alcohols were obtained by comparison with the maximum of specific rotations (see [6–12], resp.) and analysis of the ^{1}H-NMR spectra of diastereoisomeric phosphite esters formed with the phosphorochloridite of (4*R*,5*R*)-*trans*-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol as a chiral derivatizing agent [3][13].

Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317

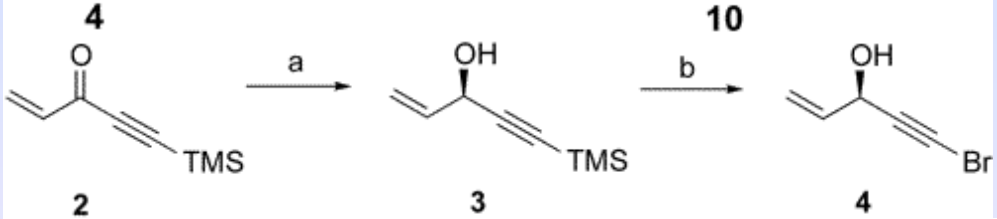
MECHANISM OF CHIRAL CATALYST ACTION PROPOSED



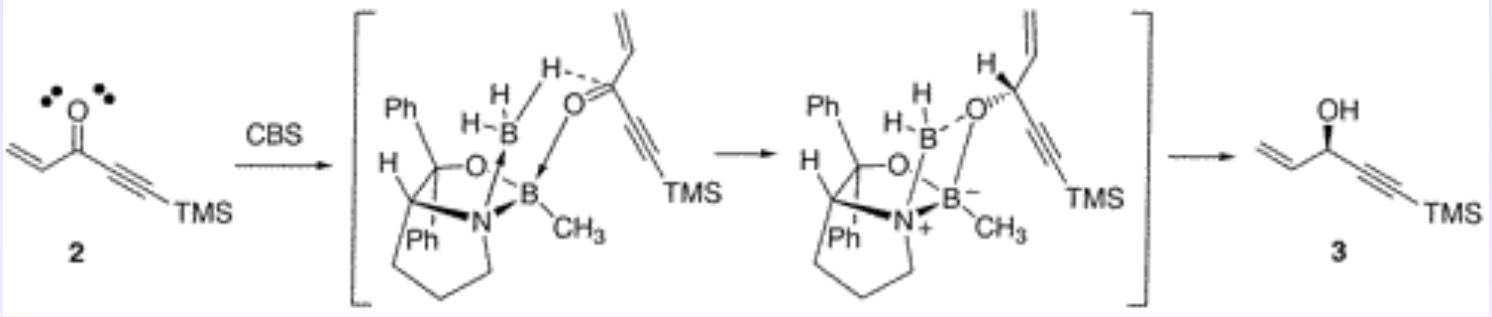
EXAMPLE#3:
THE USE OF (*R*)-Me-CBS CATALYST IN PANAXYTRIOL SYNTHESIS



Scheme 1. Antitumor components of *Panax ginseng*, panaxytriol (**1**)



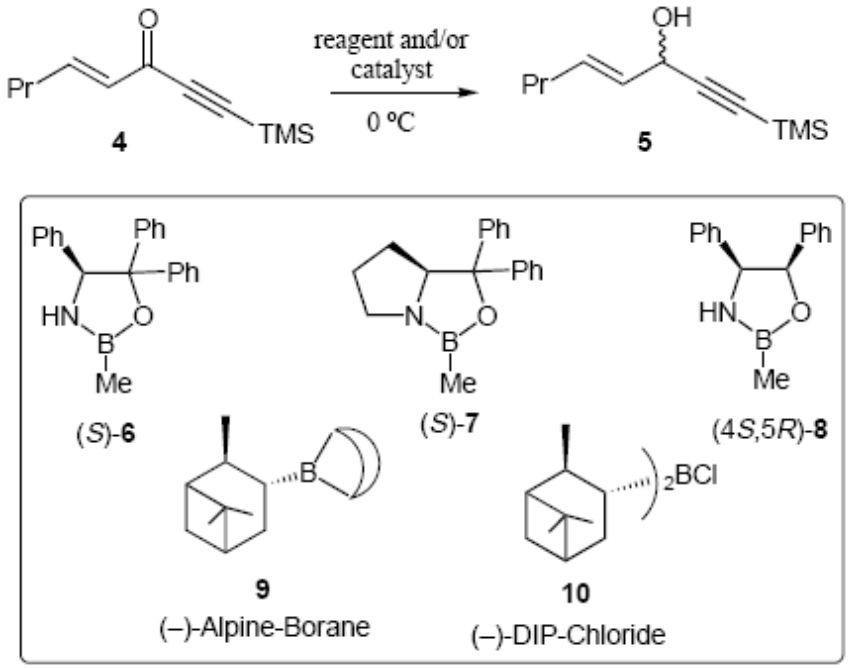
Scheme 2. Enantioselective Synthesis of Left-Hand Piece Using CBS Reduction Reaction conditions: (a) (*R*)-Me-CBS, BMS, -30 C, 10 min, 75%, >99% ee; (b) NBS, cat. $AgNO_3$, acetone, rt, 1 h, 100%.



Scheme 3. A proposed model for the CBS reduction of **2**.

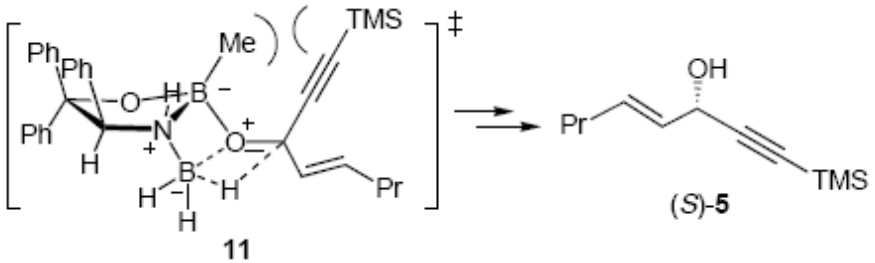
Straightforward Synthesis of Panaxytriol: An Active Component of Red Ginseng
Yun, H.; Danishefsky, S. J. Org. Chem.; (Note); 2003; 68(11); 4519-4522.

EXAMPLE#4:
COMPARISON OF MISC CHIRAL CATALYSTS



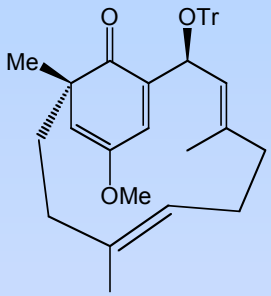
entry	reagent and/or catalyst	alcohol	t	yield[d]	ee[e]
1[a]	BH_3:SMe_2 / (*S*)-**6**	(*S*)-**5**	<15 min	90%	95%
2[a]	BH_3:SMe_2 / (*S*)-**7**	(*S*)-**5**	<15 min	85%	95%
3[a]	BH_3:SMe_2 / (4*S*,5*R*)-**8**	(*S*)-**5**	<15 min	80%	70%
4[b]	(–)-**9**	(*R*)-**5**	overnight	93%	92%
5[c]	(–)-**10**	(*R*)-**5**	overnight	47%	39%

[a]Reactions were carried out by addition of **4** (1 mmol) to a mixture of BH_3:SMe_2 (1.2 mmol) and catalyst (1 mmol) in THF. [b]Reduction was performed with 2.5 mmol of **4** in neat **9** (10 mmol) according to ref. 10. [c]Reduction was performed with 1.3 mmol of **4** in neat **10** (1.5 mmol) according to ref. 11. [d]Isolated yield after chromatography. [e]Determined by ^{19}F NMR analysis of the corresponding Mosher esters.



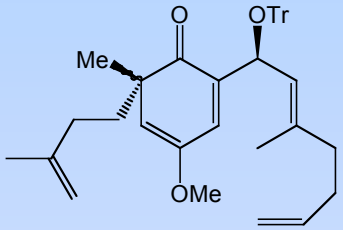
Garcia, J.; López, M.; Romeu, J.: Synlett 1999, 4, 429-431.

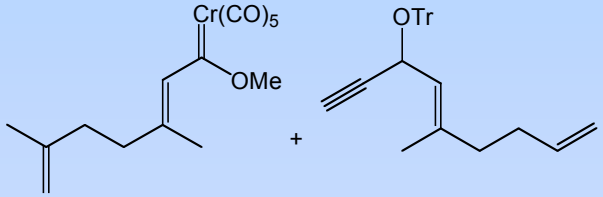
(S)-Me-CBS CATALYST IN THE SYNTHESIS OF PHOMACTINS



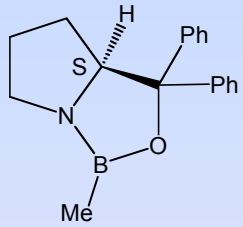
Grubbs II Catalyst

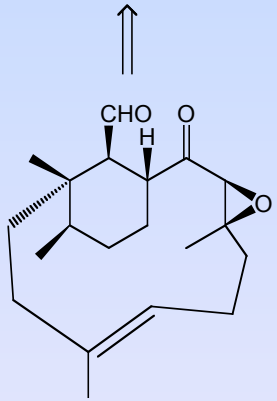
90%



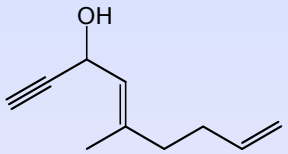


Selectivity: 98:2 = Sin:Anti, 75% Yield



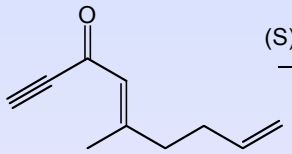


Phomactin D

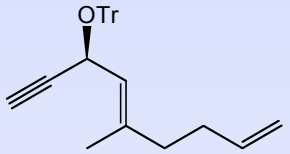


88%

MnO2

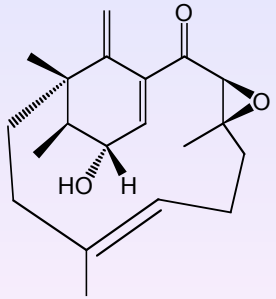


(S)-Me-CBS

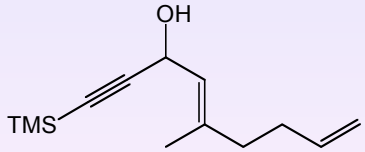


S-DIENYNOL

TBAF



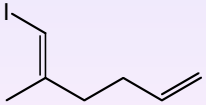
Phomactin B_2



54%

1. BuLi

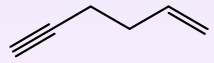
OHC—≡—TMS



50%

1. $AlMe_3/ZrCp_2Cl_2$

2. I_2



50%