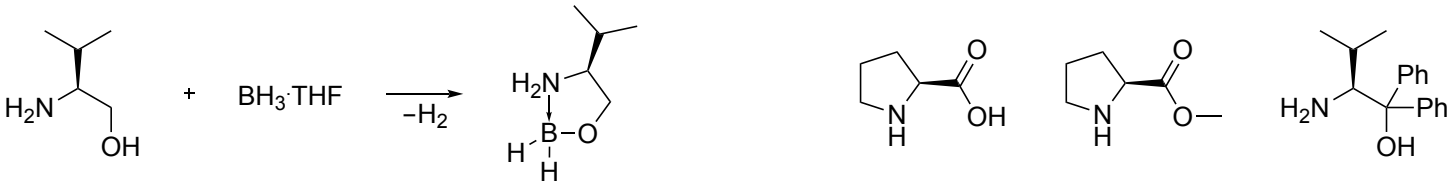
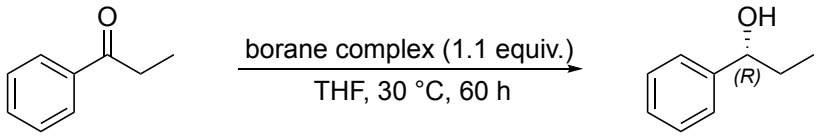
Reinvestigating the Stereoselectivity of CBS Catalysts in Asymmetric Reductions

Seminar talk presented by
Christian Eschmann

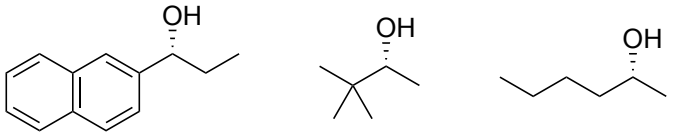
Februar 8th, 2019

Institute of Organic Chemistry
Justus-Liebig University Giessen





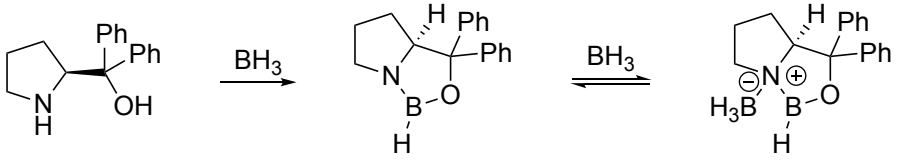
99% yield
46% *ee*

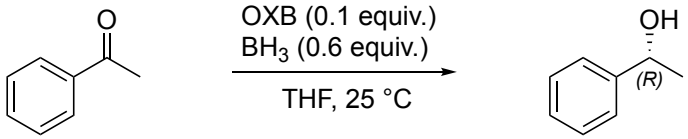


52% *ee* 78% *ee* 55% *ee*

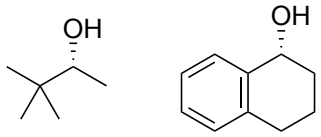
Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc. Chem. Commun.* **1981**, No. 7, 315.
Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Chem. Commun.* **1983**, No. 8, 469–470.

CBS Reduction - Historical Background





99% yield
97% *ee*



92% *ee*

89% *ee*

Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
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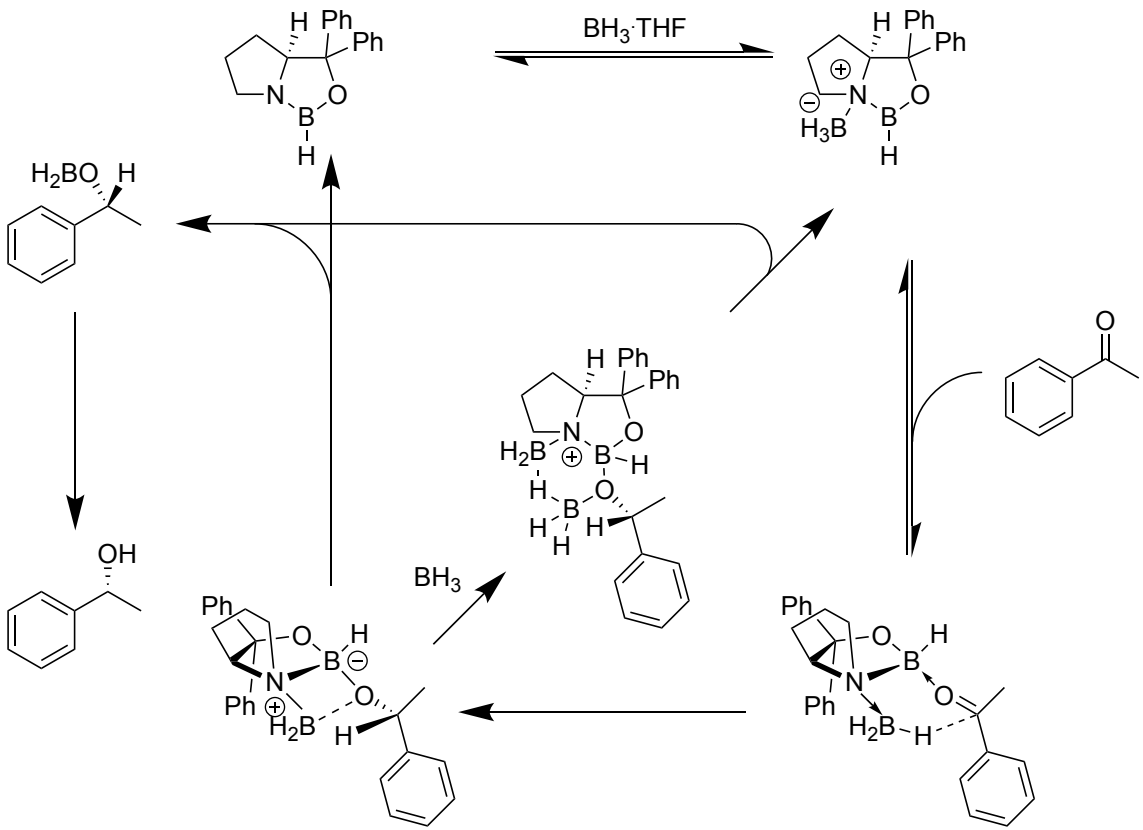
Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.

CBS Reduction - Mechanism



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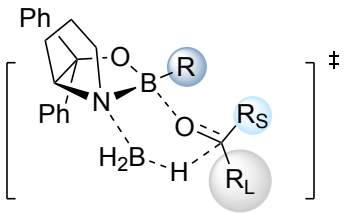
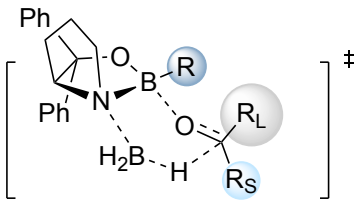
Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.

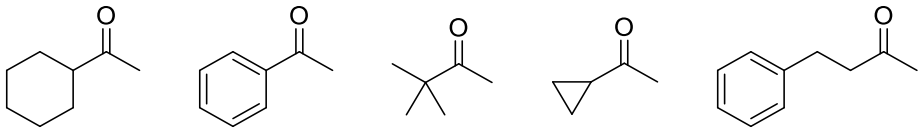
CBS Reduction - Stereochemistry



TS_R



TSs



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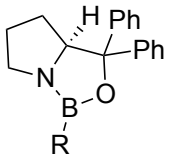
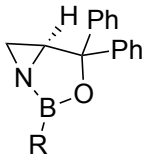
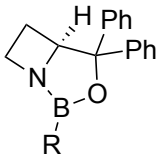
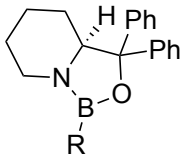
State of the Art - OXB Variation









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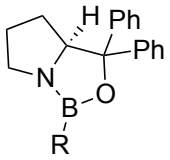
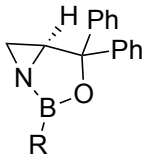
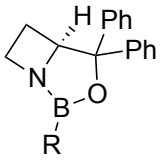
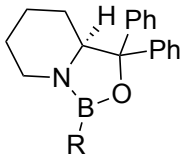
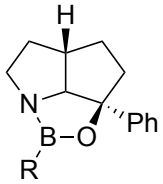
Rao, A. V. R.; Gurjar, M. K.; Sharma, P. .; Kaiwar, V. *Tetrahedron Lett.* **1990**, *31*, 2341–2344.
Masui, M.; Shioiri, T. *Synlett* **1996**, *1996*, 49–50.

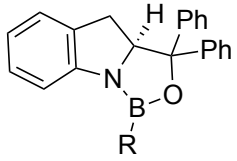


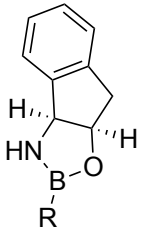


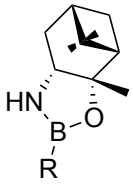












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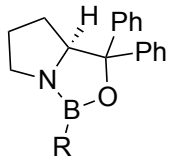
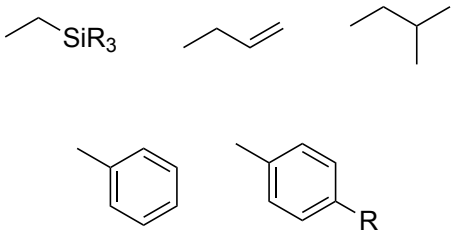
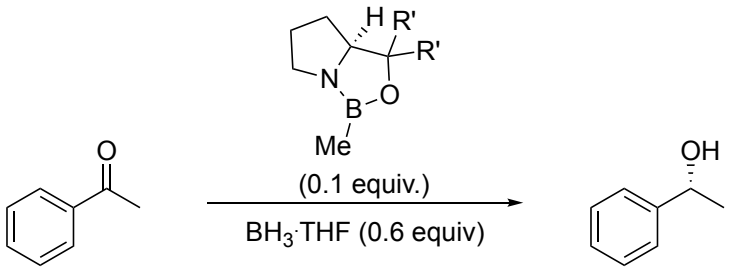
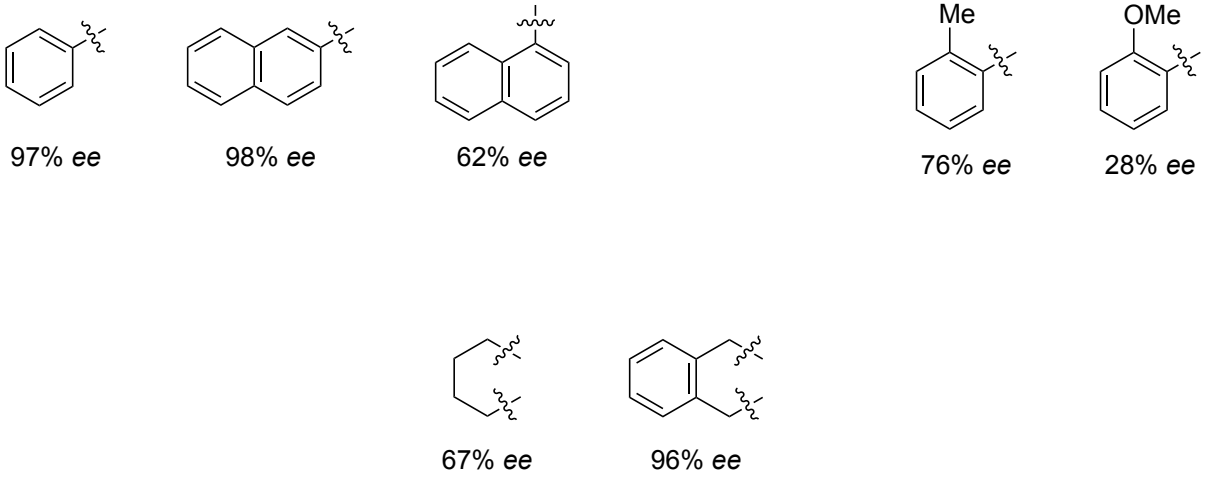


H Me *n*-Bu



Corey, E. J.; Helal, C. J. *Angew. Chem.* **1998**, *37*, 1986–2012.





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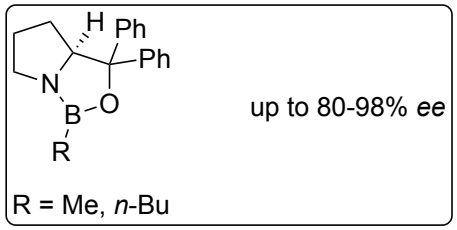
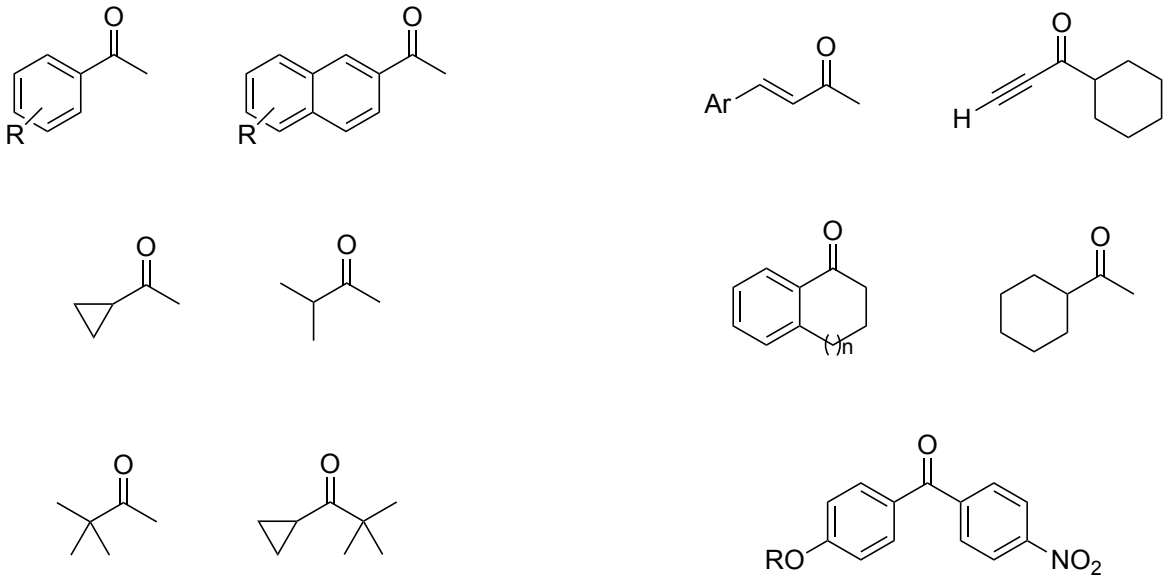
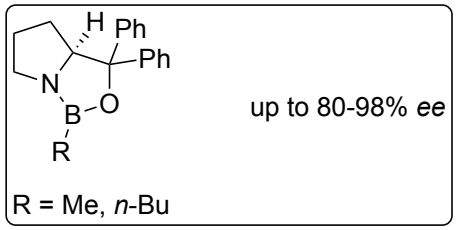
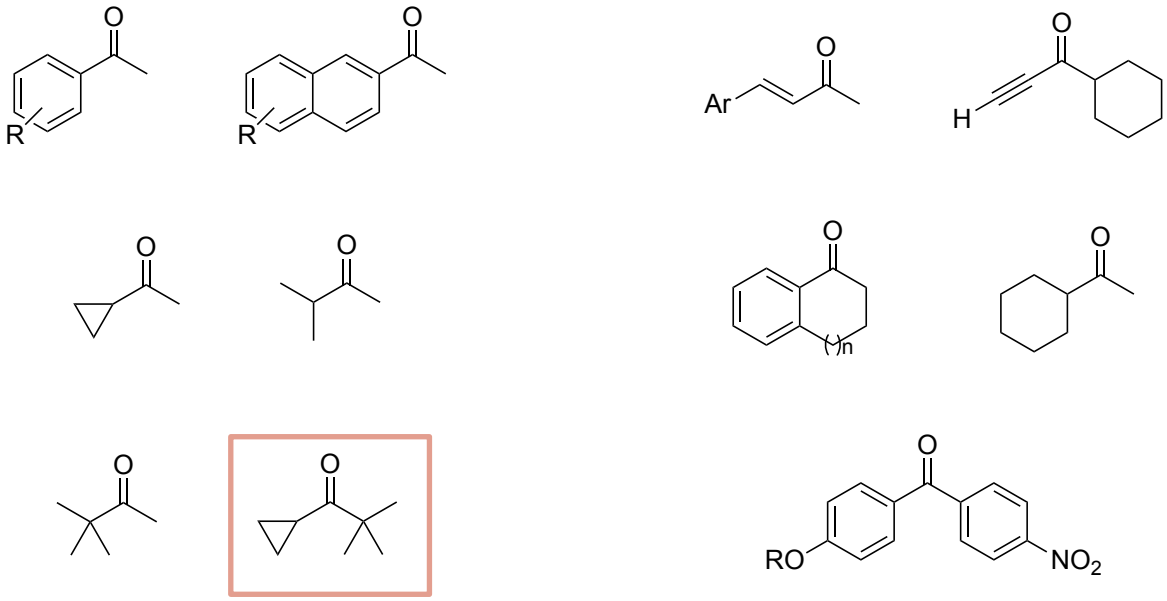
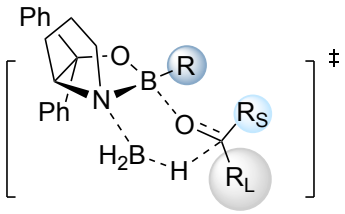

H
Ph
Ph
N
B
O
R
up to 80-98% *ee*
R = Me, *n*-Bu


O
R
O
R
O
Ar
O
H
O
O
O
n
O
O
O
RO
O
NO2

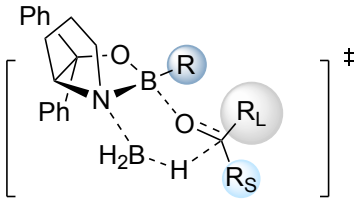
State of the Art - Substrate Scope



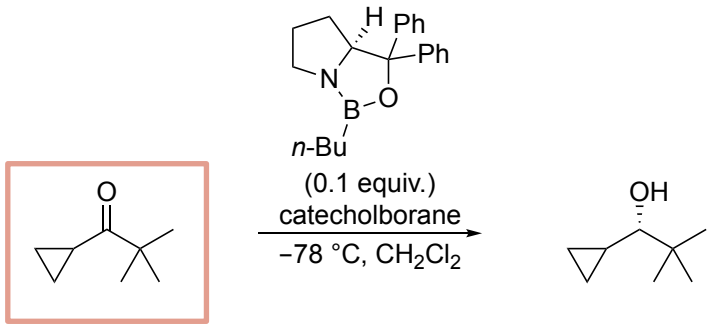




TS_R



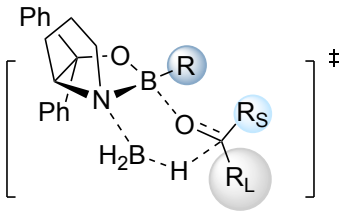
TSs



91% *ee*

Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156.

Role of London Dispersion in the Stereoselectivity of the CBS Reduction



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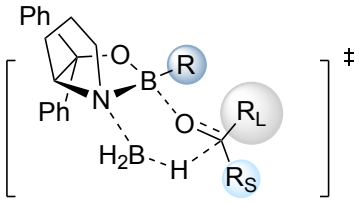
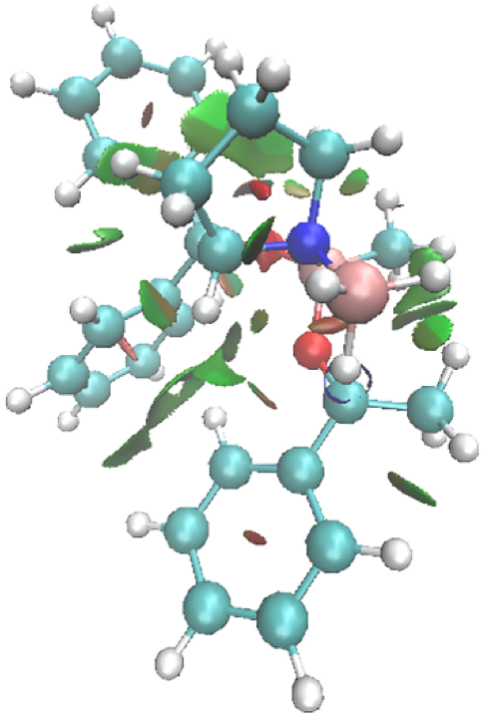
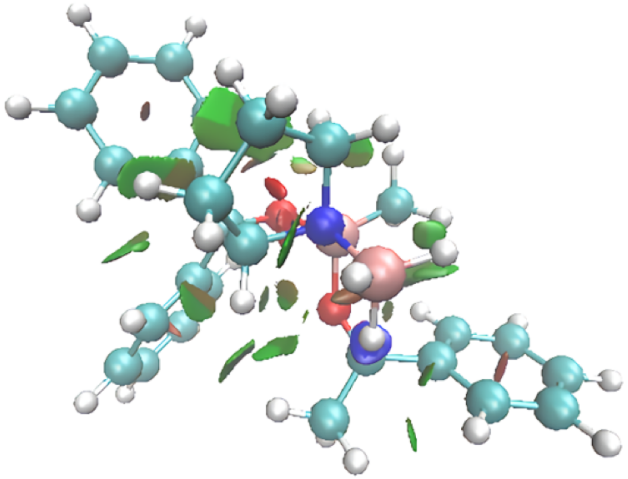


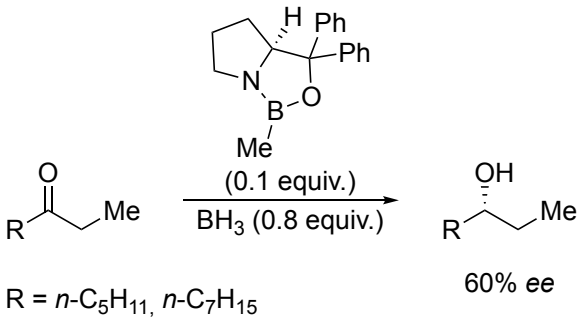
TSs





Calculations done by Lijuan Song

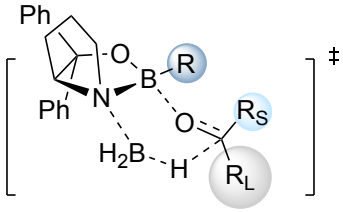
- can we increase **attractive** substrate-catalyst **interaction** to increase stereoselectivity?
- Just few publications about reduction of linear aliphatic ketones
- increase substrate pool



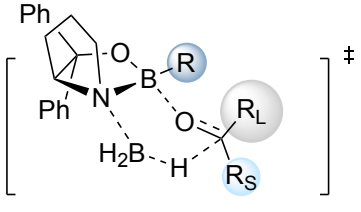
R = *n*-C_5H_{11}, *n*-C_7H_{15}

60% *ee*

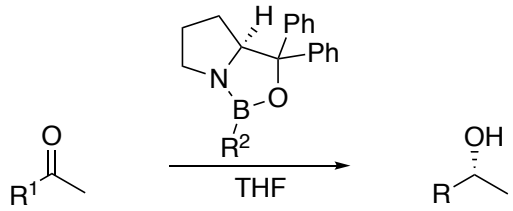
Cho, B. T.; Kim, D. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 1385–1391.



TS_R



TSs



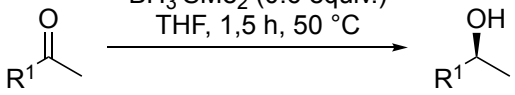
R^1	R^2	ee / %	$\Delta\Delta G_{sol}$ / kcal·mol^{-1} (without D3)	$\Delta\Delta G_{sol}$ / kcal·mol^{-1} (with D3)
Ph	Me	97	1.8	3.3
Cy	Me	85	0.9	1.0
Cy	Cy	-	-0.4	2.3
Cy	CH_2Cy	-	1.0	3.5

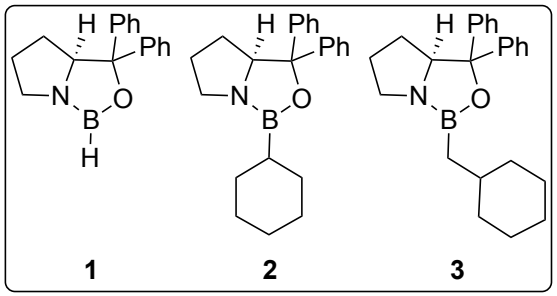
$\Delta\Delta G_{sol} = \Delta G_{sol}(TS_S) - \Delta G_{sol}(TS_R)$

$T = 298\ K$

B3LYP/6-311G(d,p) (SMD), B3LYP-D3(BJ)/6-311G(d,p) (SMD) - Calculations done by Lijuan Song

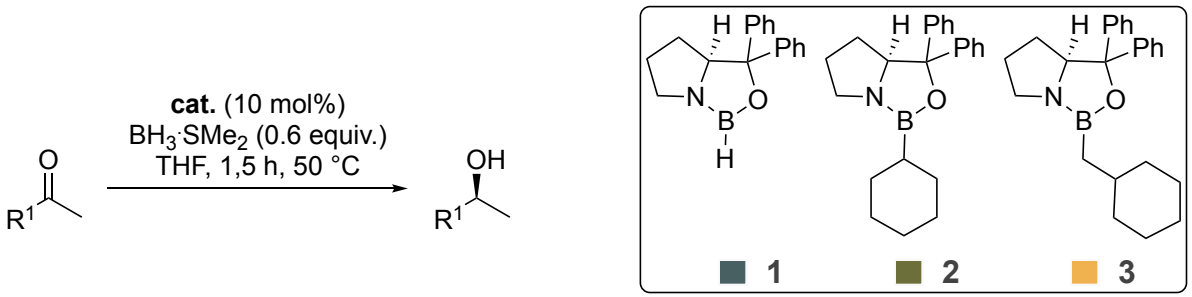
Results - Variation of Boron Substituent

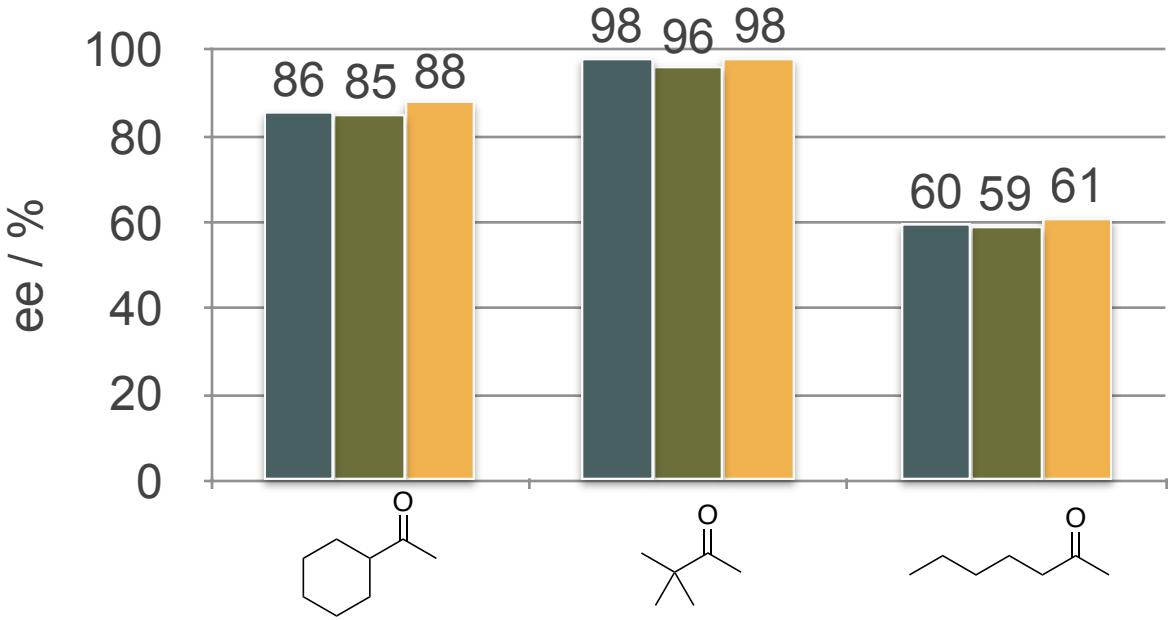




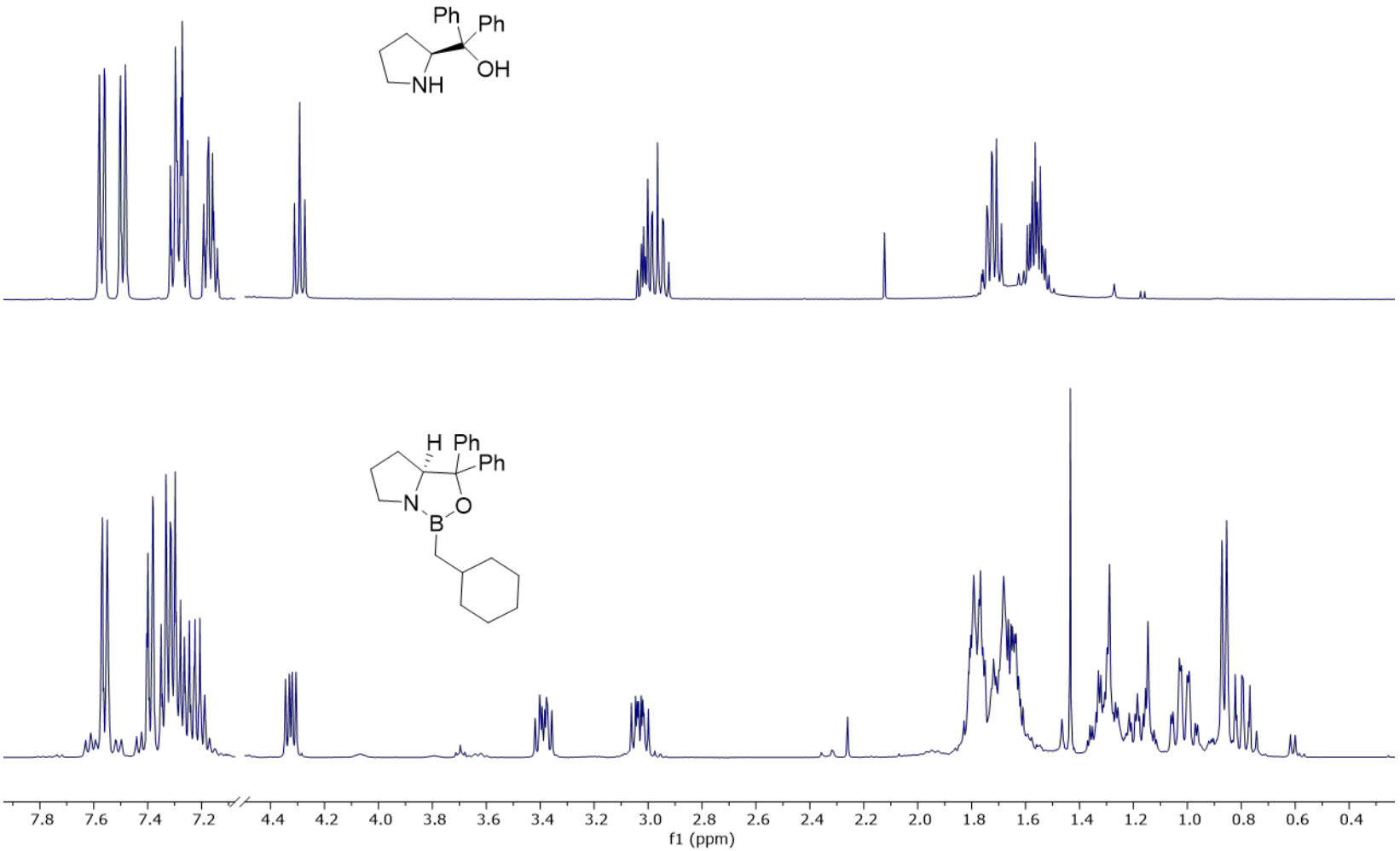
cat.	R^1	Conversion[b] [%]	ee[b] [%]
1	Cy	99	86
2	Cy	99	85
2	Cy[a]	63	52
3	Cy	99	88
1	^{t}Bu	99	98
2	^{t}Bu	99	96
3	^{t}Bu	99	98
1	*n*-hept	?	60[c]
2	*n*-hept	?	59[c]
3	*n*-hept	?	61[c]

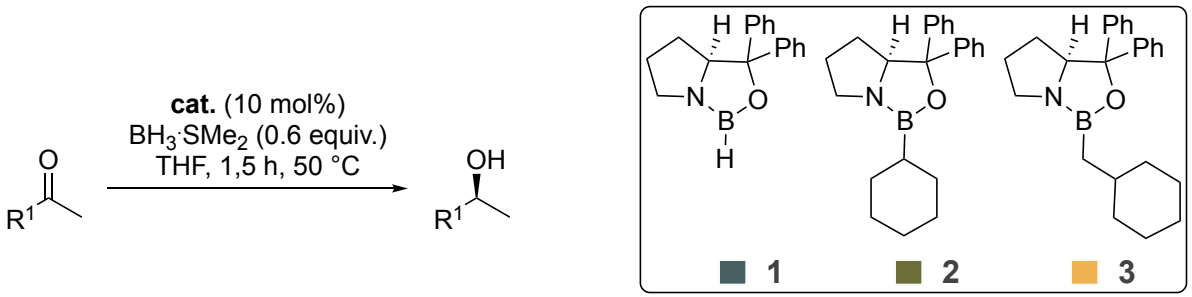
a: Reduction done at -10 °C; b: determined by chiral GC; c: determined by chiral GC of acylated products

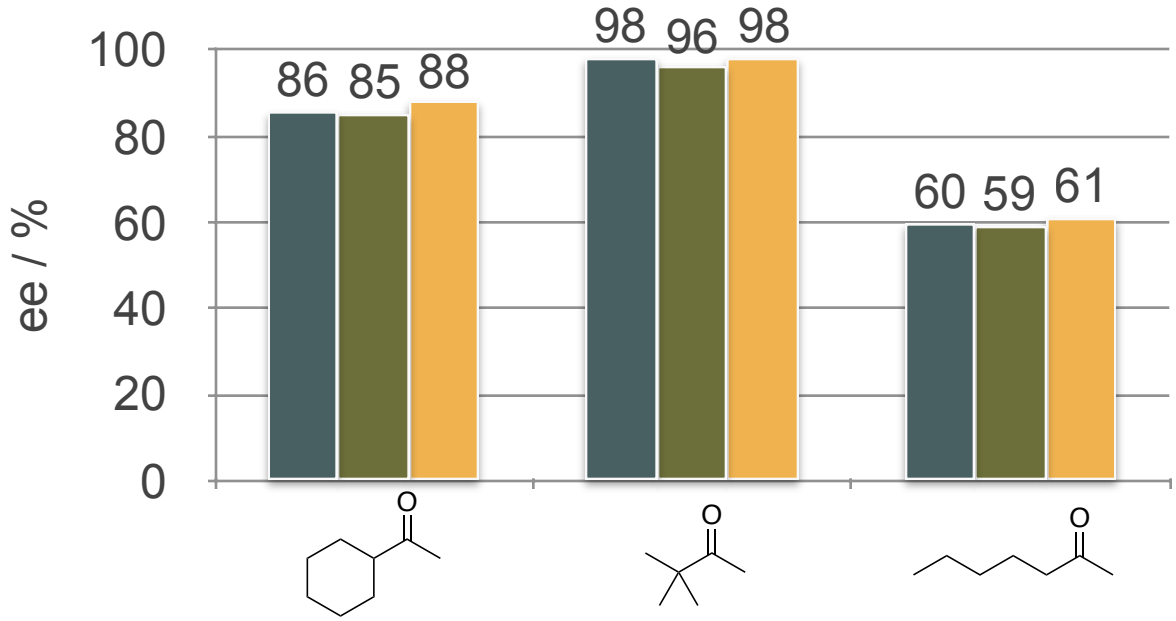

cat. (10 mol%)
BH3·SMe2 (0.6 equiv.)
THF, 1,5 h, 50 °C
R1
OH
H Ph
Ph
N
B
O
H
1
2
3

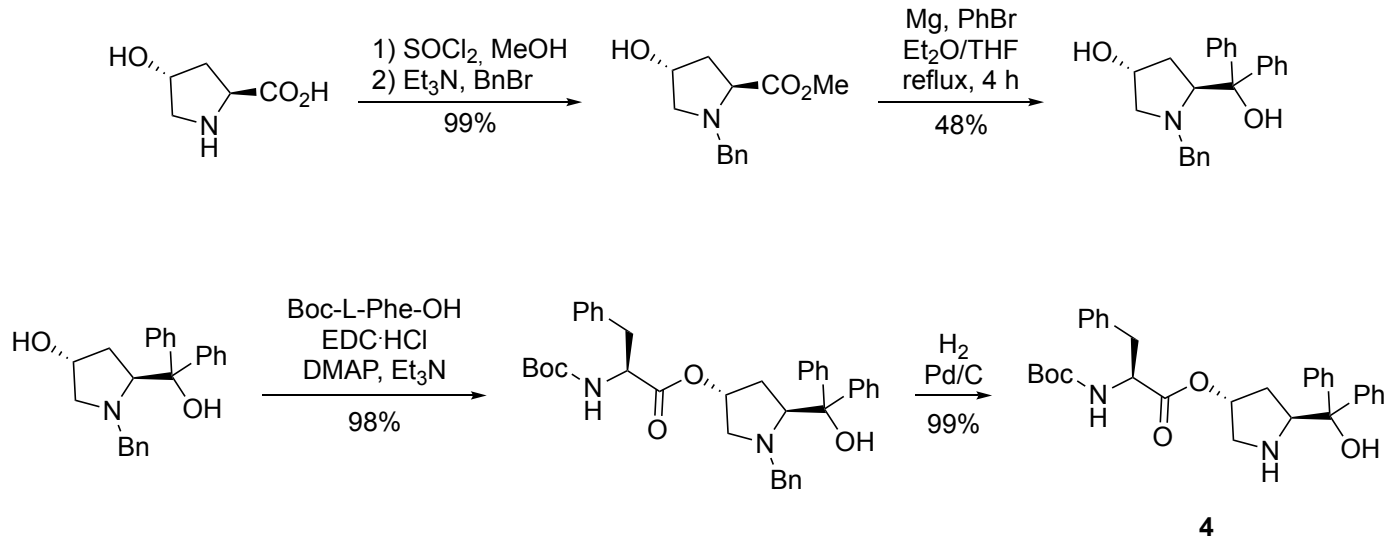

ee / %
100
80
60
40
20
0
86 85 88
98 96 98
60 59 61
O

NMR Charakterisierung




cat. (10 mol%)
BH3·SMe2 (0.6 equiv.)
THF, 1,5 h, 50 °C
O
R1
OH
R1
H Ph
Ph
N
B
O
H
1
2
3


ee / %
100
80
60
40
20
0
86 85 88
98 96 98
60 59 61
O
O
O



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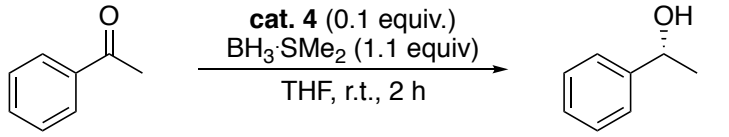
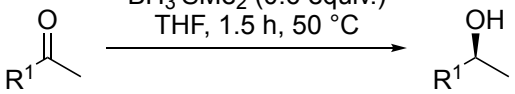
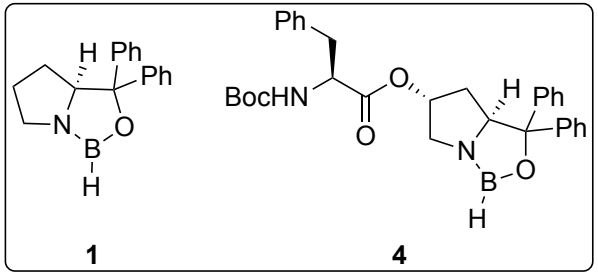


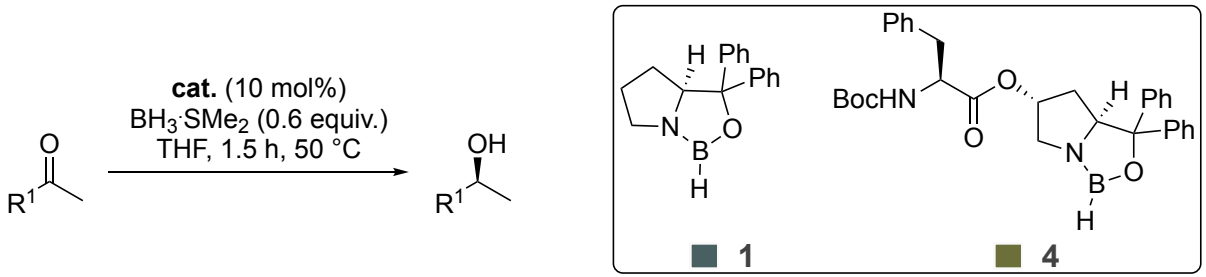
99% conversion
78% *ee*

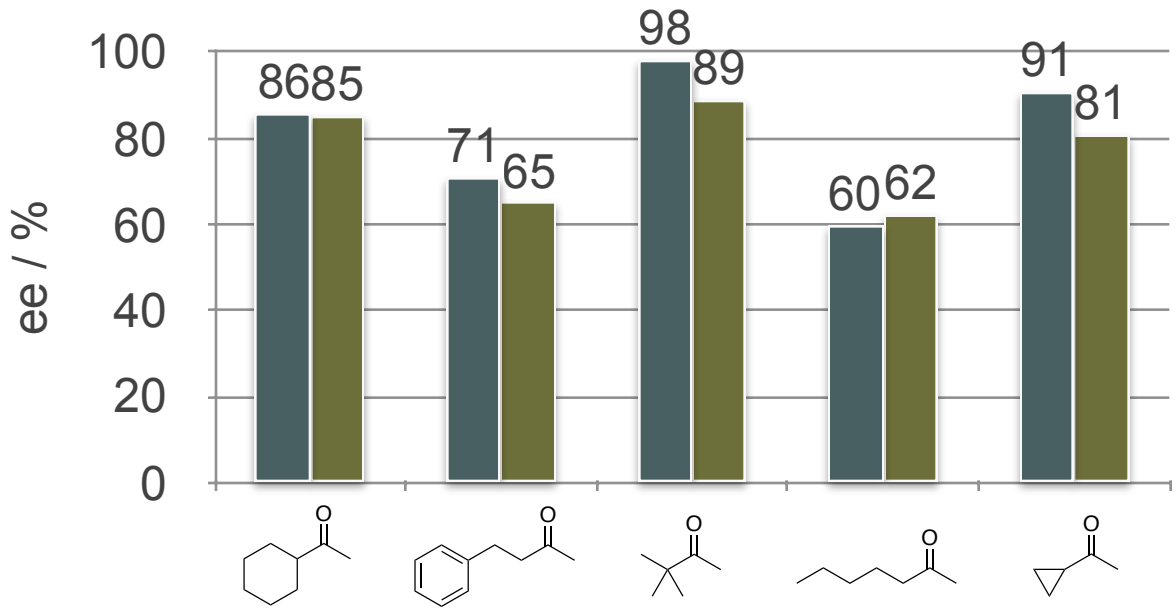


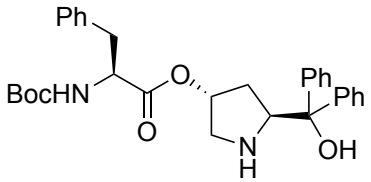


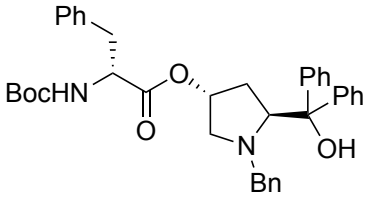
cat.	R^1	Conversion[c] [%]	ee[c] [%]
1	Cy	99	86
4	Cy	99	85
4	Cy[b]	84	68
1	CH_2CH_2Ph	99	71
4	CH_2CH_2Ph	99	65
1	^{t}Bu	99	98
4	^{t}Bu	99	89
1	*n*-hept	?	60[d]
4	*n*-hept	?	62[d]
1	Cyclopropyl	99	91
4	Cyclopropyl	99	81

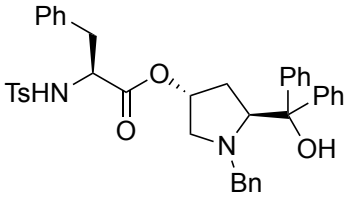
b: -10 °C; c: determined by chiral GC; d: determined by chiral GC of acylated products

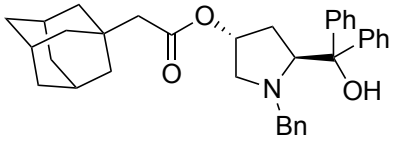

cat. (10 mol%)
BH3·SMe2 (0.6 equiv.)
THF, 1.5 h, 50 °C
R1
OH
BocHN
Ph
1
4

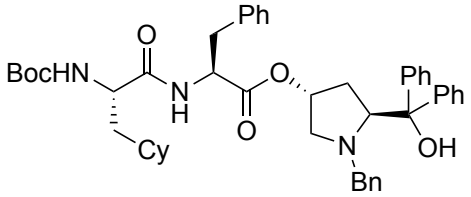

ee / %
100
80
60
40
20
0
86
85
71
65
98
89
60
62
91
81

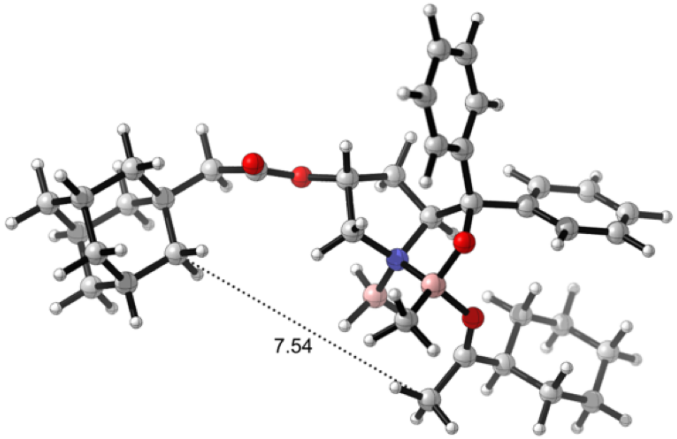

Ph
BocHN
O
O
Ph
Ph
N
H
OH

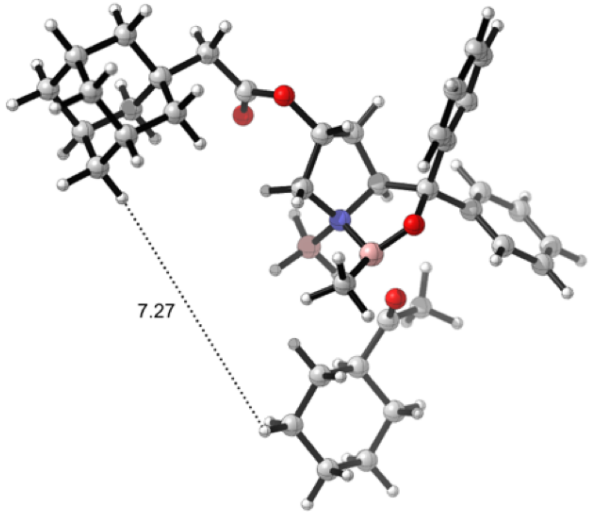

Ph
BocHN
O
O
Ph
Ph
N
Bn
OH


Ph
TsHN
O
O
Ph
Ph
N
Bn
OH


O
O
Ph
Ph
N
Bn
OH


Ph
O
BocHN
N
H
O
O
Ph
Ph
Cy
N
Bn
OH

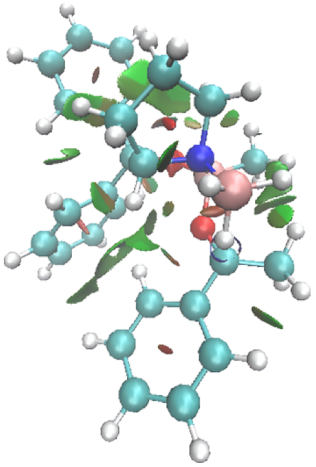


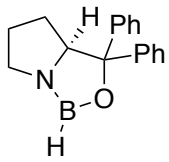


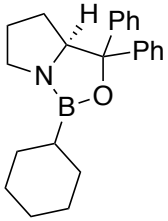
Calculations done by Lijuan Song

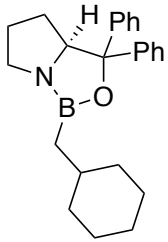
Summary

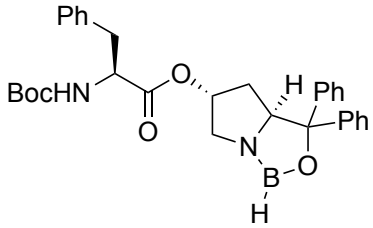
- CBS Reduction powerful reaction with high stereoselectivity for many substrates
- originally selectivity just attributed to sterics
- London Dispersion is a decisive interaction for high selectivity
- modify CBS catalyst zu maximize substrate-catalyst interaction



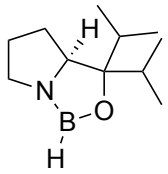


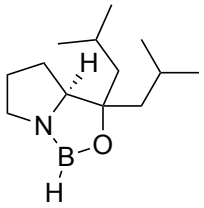


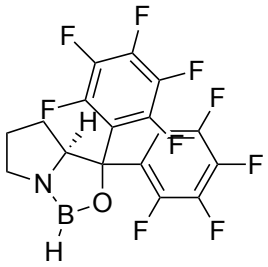


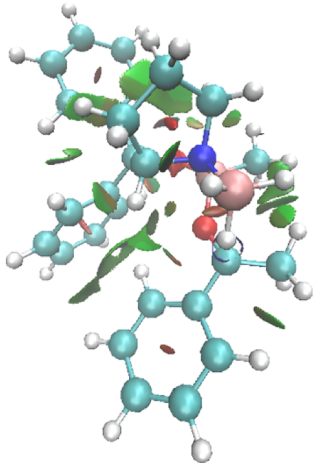


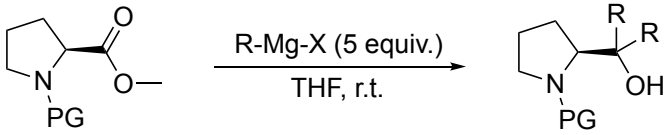
- substituent at boron no significant effect
- *trans*-hydroxyproline moiety to far away from catalytic center


H
N
B
O
H


H
N
B
O
H


F
F
F
F
F
H
F
F
N
B
O
H
F
F



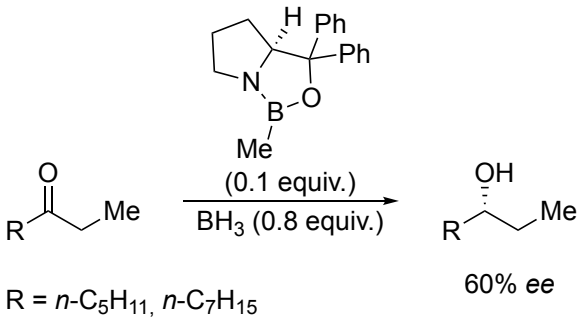

O
N
O
PG
R-Mg-X (5 equiv.)
THF, r.t.
R
R
N
OH
PG

PG = Bn, Boc

Acknowledgement

Prof. Dr. Peter R. Schreiner
Lijuan Song
Lab B204 and B205
PRS group

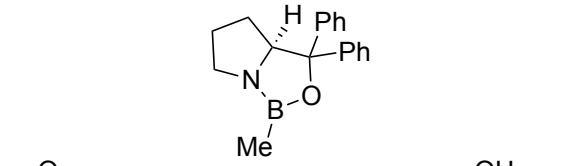
CBS Reduction - Substrate Scope



R = *n*-C_5H_{11}, *n*-C_7H_{15}

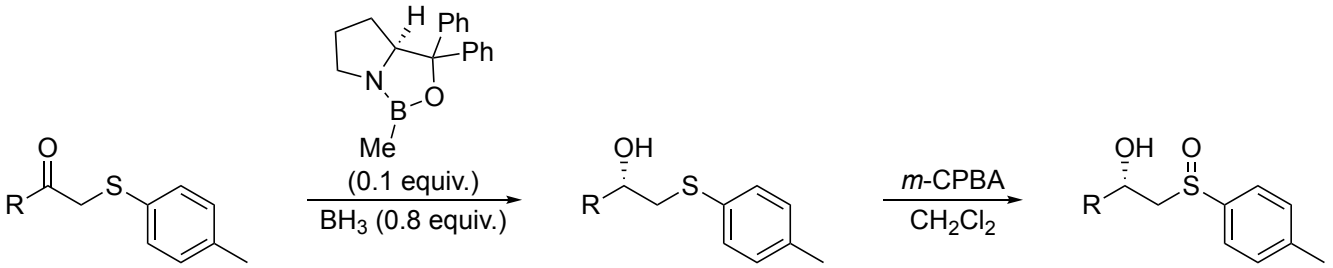
60% *ee*

Cho, B. T.; Kim, D. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 1385–1391.



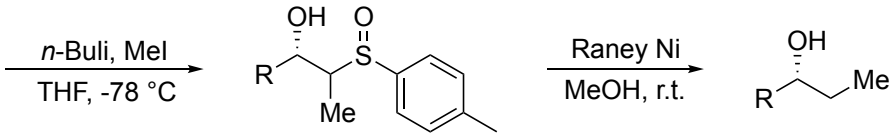
R = *n*-C_5H_{11}, *n*-C_7H_{15}

60% *ee*

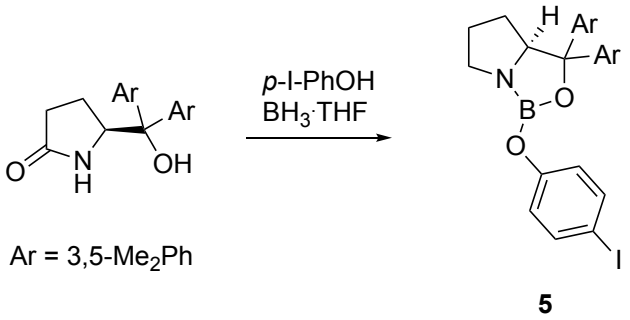


R = *n*-C_5H_{11}, *n*-C_7H_{15}

80% *ee*

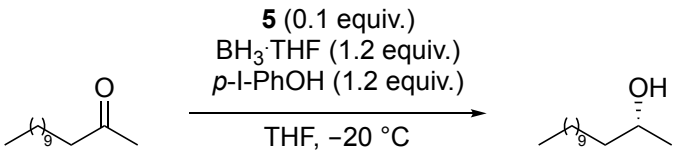


Cho, B. T.; Kim, D. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 1385–1391.



Ar = 3,5-Me_2Ph

5



85% yield
75% *ee*

Kawanami, Y.; Mikami, Y.; Hoshino, K.; Suzue, M.; Kajihara, I. *Chem. Lett.* **2009**, *38*, 722–723.
Kawanami, Y.; Yanagita, R. *Molecules* **2018**, *23*, 2408–2422.