Asymmetric Reduction of Oxime Ethers Promoted by Chiral Spiroborate Esters with an O_3BN Framework

Lead Reference:
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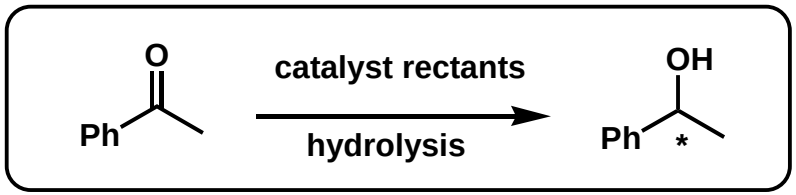
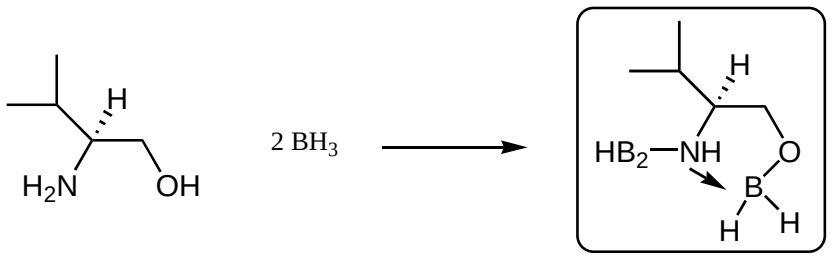
Presented by Zhenyu Zhong

Enantioselective Reduction of Ketones using Oxazaborolidine



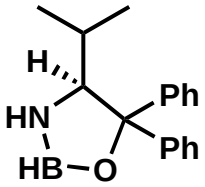
The First Oxazaborolidine catalyst

Itsuno et al . *Perkin Trans* **1985,** 2039.

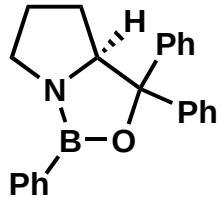


- The yield of reduction using this catalyst depends on the relative amounts of valinol and borane
- The maximum optical yield is reached with a borane-valinol ratio of 2:0

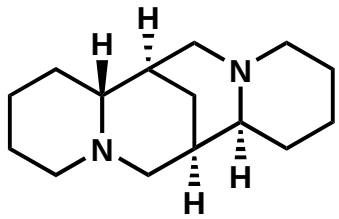
More Examples of Chial Oxazaborolidine Catalysts



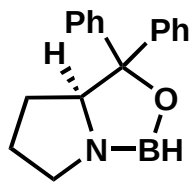
Chem. Comm. **1981,** 315-317



THL. **1989,** *30*, 6275



JACS. **1991,** *113*, 9708



JACS. **1989,** *109*, 5551

Asymmetric Reduction of Ketoximes

- Allows for synthesis of optically active amines, which is important to be used as starting materials for many biologically active compounds
- As well as to serve as auxiliary reagent in asymmetric synthesis and catalysis

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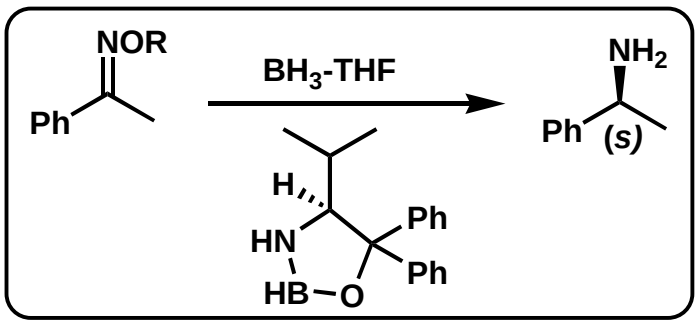
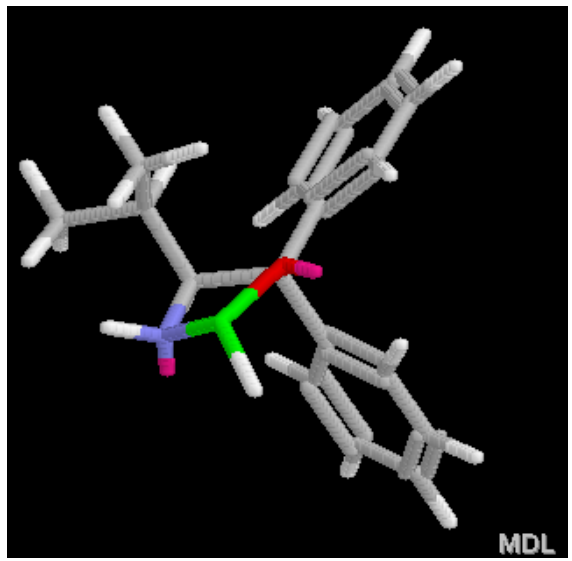
Earlier Work

Perkin Trans. **1983,** 1673

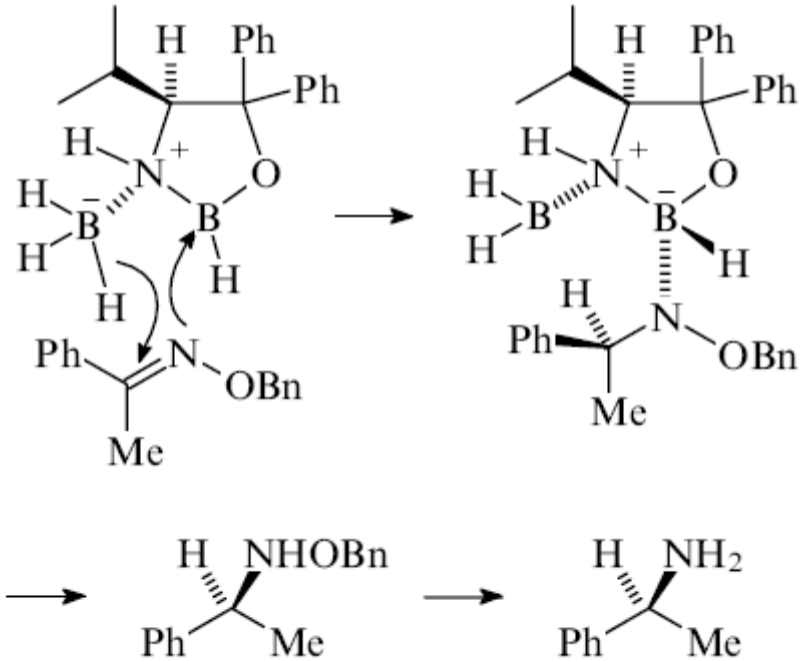


R	BH_3-THF [mol%]	Catalyst [mol%]	*ee* [%]
Me	125	125	**99**
$PhCH_2$	125	125	**91**



Asymmetric Reduction of Ketoximes (Cont'd)

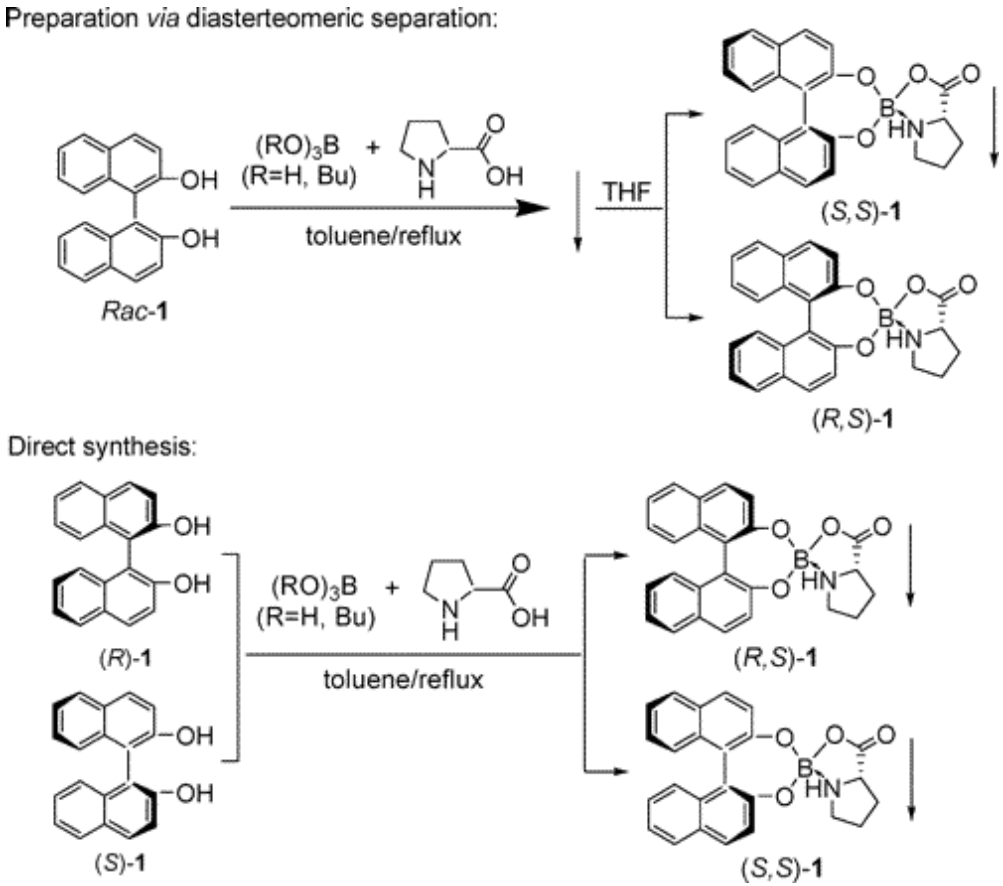
Proposed Mechanism:



Features:

- Addition of borane occurs from opposite side of isopropyl group
- Nitrogen of oxime ether coordinate to boron to form a six-membered TS
- Subsequent stereoselective hydride ion transfer followed by hydrolysis gives the reduced product.

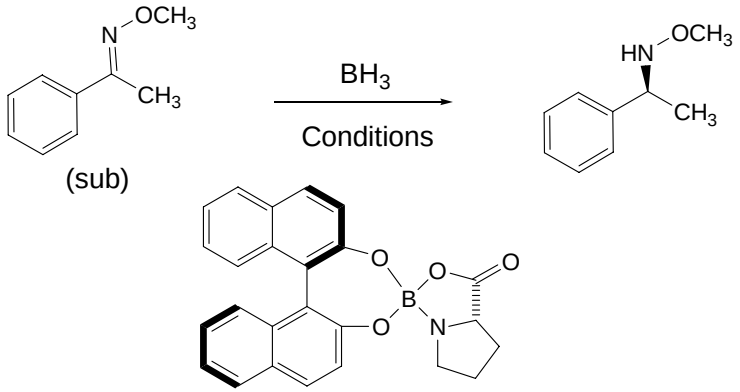
Preparation of Chiral Spiroborate Esters (*R,S)-1* and (*S,R)-1* (Title Paper)



Catalyst:

- Prepared from racemic starting materials via diastereomeic separation
- Highly stable to hydrolysis, thermolysis, oxidation, and recemization.
- Have shown to reduce prochiral ketones, and imines.

Model Reaction Study



(*R,S*)-1

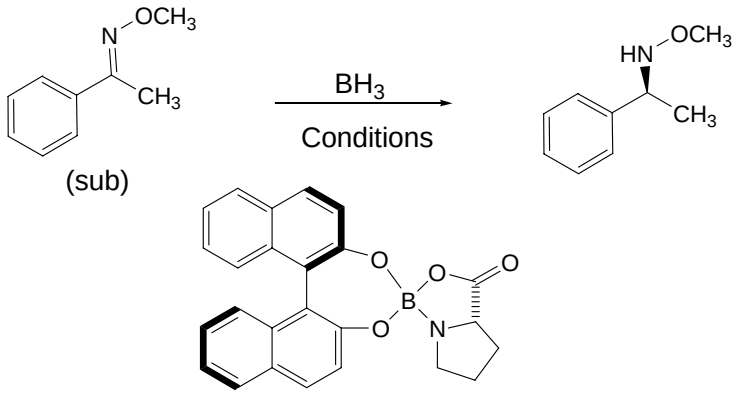
TABLE 1. Effect of the Amount of (*R,S*)-1 on the Reduction of Acetophenone *O*-Methyloxime with Borane[a]

entry	(*R,S*)-**1**/sub/BH_3	*T*/°C	time/h	yield/%	ee/%	config
1	0.1:1:2	rt	48	58	42	*S*
2	0.2:1:2	rt	48	60	48	*S*
3	0.5:1:2	rt	48	69	81	*S*
4	0.8:1:2	rt	48	80	84	*S*
5	1.0:1:2	rt	48	84	84	*S*

[a] Sub represents acetophenone *O*-methyloxime. The yields were obtained after distillation under reduced pressure.

In this model reaction, the enantiomeric excess of the reduction product was increased with the increase of the amount of the spiroborate.

Model Reaction Study (Cont'd)



(*R,S*)-1

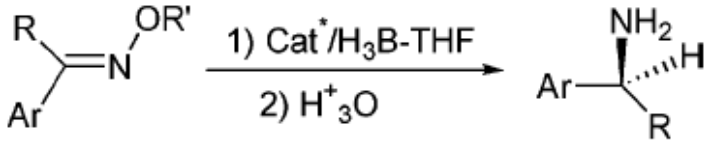
TABLE 2. Effect of the Reaction Condition on the Reduction of Acetophenone *O*-Methyloxime[a]

entry	borates	BH_3/sub/ borates	*T*/°C	time/h	yield/%	ee/%	config
1	(*R,S*)-**1**	1.5:1:1	0−5	48	76	98	*S*
2	(*R,S*)-**1**	1.5:1:1	rt	48	78	91	*S*
3	(*R,S*)-**1**	1.5:1:1	reflux	48	82	59	*S*
4	(*R,S*)-**1**	2.0:1:1	rt	48	84	84	*S*
5	(*S,S*)-**1**	2.0:1:1	rt	48	95	71	*S*
6	(*R,S*)-**1**	2.4:1:1	rt	48	97	79	*S*
7	(*S,S*)-**1**	2.4:1:1	rt	48	97	61	*S*

[a] Sub represents acetophenone *O*-methyloxime. The yields were obtained after distillation under reduced pressure.

In this model reaction, The optimum condition for the enantiomeric excess of the reduction is achieved with 1.5 eq excess of BH_3 at low temperature.

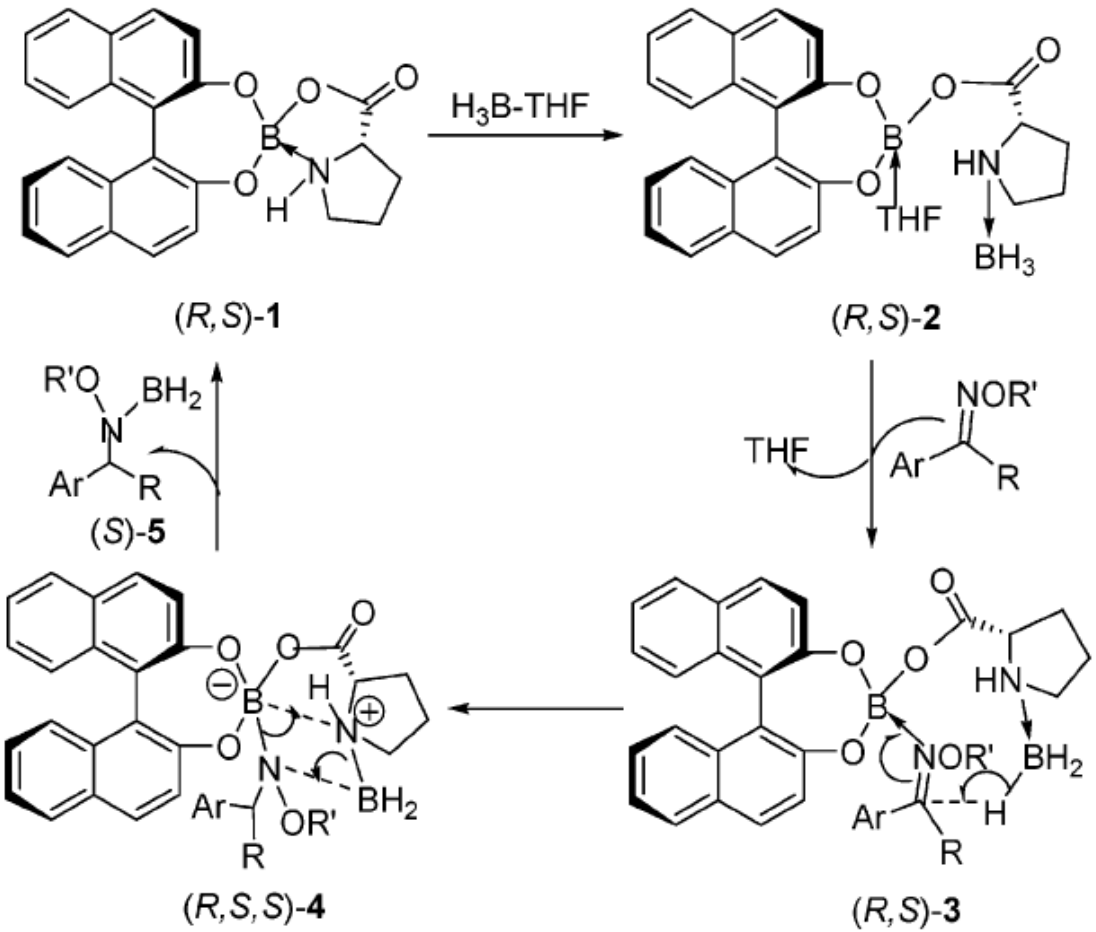
TABLE 3. (*R*,*S*)-1-Promoted Asymmetric Reduction of Aralkyl Ketoxime Ethers[a]



	Ar(R)C=NOR′					
entry	Ar	R	R′	isolated yield/%	ee[b]/%	config[c]
1	Ph	Me		76	98	*S*
2	Ph	Me	Bn	74	89	*S*
3	Ph	Et	Me	78	92	*S*
4	Ph	Et	*n*-Bu	76	80	*S*
5	Ph	Et	Bn	80	81	*S*
6	4-NO_2-C_6H_4	Me	Me	86	96	*S*
7	4-NO_2-C_6H_4	Me	*n*-Bu	78	75	*S*
8	4-NO_2-C_6H_4	Me	Bn	84	90	*S*
9	4-MeO-C_6H_4	Me	Me	83	90	*S*
10	4-MeO-C_6H_4	Et	Me	87	89	*S*
11	4-MeO-C_6H_4	Pr	Me	85	88	*S*

- The electronic property of the substituent in aromatic ring of the aralkyl ketone slightly affects the sterioselectivity (Entry 6-9)
- The enantioselectivity of the reduction appears to decrease with the increase of alkyl chain in OR
- The reduction is insensitive to the size of R group in terms of stereoselectivity and yield. (9-11)

SCHEME 3. Possible Mechanism for the Asymmetric Borane Reduction of Prochiral Oxime Ethers Promoted by a Chiral Spiroborate Ester



Features:

- Oxime ether replace THF to form (*R*,*S*)-3
- Upon H transfer and rearrangement, spirobrate was reformed.
- The reduced product was then obtained after aqueous workup.

Conclusions

- A new class of chiral promoter for borane reduction of prochiral aralkylketoxime ethers has been discovered.
- The influence of reaction condition on the enantioselectivity of reduction was investigated.
- A possible mechanism of the catalytic reduction was suggested.