Communication

Catalytic asymmetric borane reduction of prochiral ketones using chiral camphor-derived mercapto-alcohols

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Abstract Easily available *D*-(+)-camphor-derived chiral mercapto-alcohols **2** and **3** were employed for catalytic asymmetric borane reduction of aromatic ketones. Moderate enantioselectivities with e.e. 20.2—72.1% were obtained with 10 mol% catalyst. Opposite asymmetric induction was achieved when mercapto-alcohols **2** and **3** were used.

Keywords Mercapto-alcohol, ketone, asymmetric borane reduction

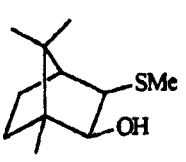
Enantioselective reduction of prochiral ketones leading to chiral secondary alcohols is a topic of current interest.[1] One of the most successful methods is based on the use of chiral 1,3,2-oxazaborolidine as catalysts, a method which was developed by Itsuno *et al.*,[2] and then improved by Corey *et al.* is designated as CBS reduction sometimes.[3] Numerous examples describing the application of this method have been reported by several groups,[4] most of them used various types of chiral 1,2-amino-alcohols as chiral source of the 1,3,2-oxazaborolidine.

During our research on asymmetric epoxidation[5] and aziridination[6] via sulfur ylide route, we found compound **1** was a good chiral source. In conjunction with our interest on metal-catalyzed hydroboration,[7] we tried to explore the enantioselective reduction of prochiral ketones using chiral mercapto-alcohols instead of the chiral amino alcohols which were used in CBS reduction. Owing to strong coordination of boron with nitrogen and sulfur (for example, $BH_3{\cdot}NH_3$ and $BH_3{\cdot}SMe_2$ are stable complexes) and according to oxazaborolidine reduction's mechanism, we envisaged that mercapto-alcohol could also be a source of a corresponding oxathiaborolidine. Recently Jiang[8]

Received March 4, 1998; revised April 14, 1998.

Project supported by the National Natural Science Foundation of China (29790127) and Chinese Academy of Sciences.

and Yang[9] reported that enantioselective reduction of aromatic ketones catalyzed by chiral mercapto-alcohol **2** gave chiral secondary alcohols in moderate to good selectivities, which promoted us to discolse our preliminary results.



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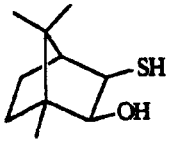

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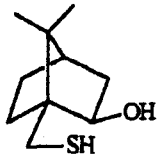

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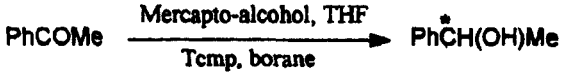
Chiral compounds **1**, **2** and **3** can be prepared conveniently by literature methods[10] from easily available (*D*)-camphor and (*D*)-camphor-β-sulfonic acid in high yields.

We chose acetophenone as a model substrate to perform the reduction. In order to optimize the reaction conditions, the effect of temperature, borane complexes and quantity of mercapto-alcohols used in this reaction were investigated (Table 1).

Table 1 Asymmetric reduction of acetophenone with mercapto-alcohols[a]



Entry	Mercapto alcohol (eq.)	Borane	Temp. (°C)	Yield (%)[b]	e.e. (%)[c]	Config.[d]
1	**2** (0.1)	BH_3·Me_2S	20—25	80	37.1	*S*
2	**2** (0.1)	BH_3·Me_2S	45—50	90	56.0	*S*
3	**2** (0.1)	BH_3·THF	45—50	90	66.9	*S*
4	**3** (0.1)	BH_3·Me_2S	20—25	96	16.8	*R*
5	**3** (0.1)	BH_3·THF	45—50	82	67.8	*R*
6	**1** (0.1)	BH_3·Me_2S	20—25	94	2.0	*R*
7	**3** (1.0)	BH_3·THF	45—50	92	71.5	*R*
8	**3** (0.02)	BH_3·THF	45—50	91	12.0	*R*

a, All reactions were carried out in a ratio of acetophenone:borane=1:1 at a 1.0 mmol scale in THF. *b*, Isolated yields based on acetophenone. *c*, *e.e.* values were determined by HPLC of the isolated alcohol with Chiralcel OD or OJ columns. *d*, Absolute configurations were determined by comparing optical rotations with literature values.

From Table 1 we know that temperature is important, the higher the temperature, the higher *e.e.* values were obtained (from 37.1% to 56.0%, Entries 1, 2), which is consistent with the results of Martens, Jiang, Corey, *etc.*[11] In addition, different types of borane complexes also influence the enantioselectivity of products (compare Entry 2 *vs.* 3 and Entry 4 *vs.* 5). BH_3·THF is the better choice of borane complexes. This may be explained that sulfur atom of Me_2S could compete with the sulfur of chiral mercapto-alcohols. For the effect of quantity of mercapto-alcohols on enantioselectivity,

Table 2 Asymmetric borane reduction of prochiral ketones with mercapto-alcohols **2** and **3**[a]

Entry	Substrates	Mercapto-alcohol	Yield (%)[b]	e.e. (%)[c]	Config.[d]
1	PhCOMe	**2**	90	66.9	*S*
2	PhCOMe	**3**	82	67.9	*R*
3	PhCOEt	**2**	97	32.1	*S*
4	PhCOEt	**3**	91	26.1	*R*
5	$PhCOCH_2Br$	**2**	86	46.7	*R*
6	$PhCOCH_2Br$	**3**	90	57.3	*S*
7	*p*-ClC_6H_4COMe	**2**	87	72.1	*S*
8	*p*-ClC_6H_4COMe	**3**	89	64.4	*R*
9	*p*-$MeOC_6H_4COMe$	**2**	90	64.8	*S*
10	*p*-$MeOC_6H_4COMe$	**3**	93	63.8	*R*
11	α-tetralone	**2**	97	20.2	*S*
12	α-tetralone	**3**	98	37.0	*R*

a, All reactions were carried out in a ratio of ketone:borane:mercapto-alcohol=1:1:0.1 at a 1.0 mmol scale in THF at temperature 45—50°C. *b*, Isolated yields based on ketones. c, e.e. values were determined by HPLC analysis of the isolated alcohol with Chiralcel OD or OJ columns. *d*, Absolute configurations were determined by comparing optical rotations with literature values.

we found that 10% is the best choice. We also found that slow addition of ketones was beneficial for enhancing enantioselectivity. The best result was obtained at 45—50°C with BH_3·THF as reductant at $<3.5\times10^{-2}$ mmol/min addition rate of the aromatic ketones.

It is noteworthy that the free SH plays an important role in the asymmetric borane reduction of ketones. When the SH was converted to SMe, the *e.e.* value of the product (Entry 6 in Table 1) was greatly lowered (from 37.1% *e.e.* to 2.0% *e.e.*), and the absolute configuration of the major isomer is opposite.

We found that the absolute configuration of the secondary alcohol was *S* on using chiral mercapto-alcohol **2**. It is interesting to note that when mercapto-alcohol **3** was used, the configuration of the alcohol is reversed to *R*. In general it is difficult to synthesize both enantiomers of products in asymmetric synthesis because both antipodes of ligands are not always readily available, especially for ligands from natural sources. Ligands **2** and **3** are easily prepared, and they are not mirror image to each other, only the SH and OH groups are differently disposed, from SH to OH, it is clockwise in **2** and counterclockwise in **3**. From a synthetic viewpoint our method would be attractive and desirable. The results of several substrates are summarized in Table 2.

From Table 2 we found that all kinds of aromatic ketones reacted with borane in the presence of chiral mercapto-alcohols **2** or **3**. Moderate to good asymmetric inductions were obtained (from 20.2% to 72.1%), and the highest *e.e.* was obtained in the reduction

of *p*-chloroacetophenone. Both enantiomers of all products were obtained.

In 1991, Tanaka[4d] and his co-workers reported asymmetric borane reduction of aromatic ketones using camphor-derived chiral amino-alcohol similar to **2**, and 13—79% *e.e.* values were obtained, which were slightly higher than those using the mercapto-alcohols in our case. From a reaction viewpoint of asymmetric borane reduction mercapto-alcohol is an analogue of amino-alcohol.

The enantiocontrolled reduction observed here can be visualized by the mechanism shown in Fig 1. Similar to that for oxazaborolidines advanced by Corey and others,[12] the complex formed by borane and oxathiaborolidine coordinates with the acetophenone to make a six-membered cyclic transition state. The chair-like transition state shown in Fig. 1 is thought to be preferential.[12] The *Re* face hydride attack leading to *S*-alcohol is with chiral mercapto-alcohol **2** as catalyst, while *Si* face hydride attack is favourable with ligand **3** as catalyst.

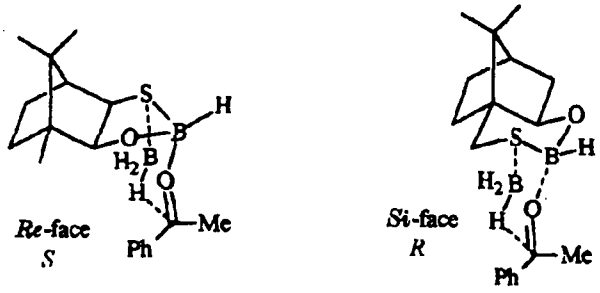


Fig. 1 Reaction transition state of asymmetric borane reduction.

In summary, in addition to the currently used chiral amino-alcohols in CBS reduction, mercapto-alcohol is also an efficient catalyst for enantioselective borane reduction to provide moderate to good enantioselectivities for ketones. Both enantiomers of chiral secondary alcohols can be obtained using two different ligands **2** and **3**. Further investigation of this reaction using sulfur containing ligand is undergoing.

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