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Study on Bicoordination Chiral Inducement Catalysis of (R)-4-Thiazolidinecarboxylic Acid

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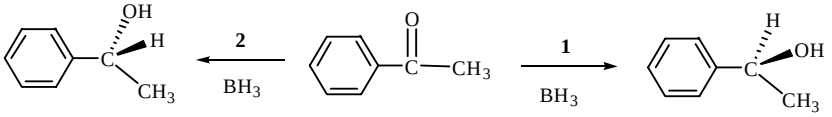
Abstract: The bicoordination chiral inducement catalysis of (R)-4-thiazolidinecarboxylic acid in the enantioselective borane reduction of prochiral ketones has been studied. The fact that the absolute configuration of the main product can be changed by simply using different operation methods was firstly verified. And the reason of bicoordination chiral inducement was discussed.

Keywords: Bicoordination chiral inducement, (R)-4-thiazolidinecarboxylic acid.

The asymmetric borane reduction of the prochiral ketones has been well studied in organic synthesis and many excellent chiral catalysts were synthesized [1–7]. The reaction mechanism has been verified by Corey and further developed by others [8–10]. The fact reported in literature that the configuration of (R)-4-thiazolidinecarboxylic acid **1** and L-proline **2** is same but their chiral inducement is contrary [10, 11] that was noted by us.



(R)-1-phenylethanol (S)-1-phenylethanol

However, a different phenomenon was discovered when we studied enantioselective borane reduction of acetophenone catalysted by **1**. (S)-1-Phenylethanol with 50% e.e. was obtained by operation method II (II stands for literature method.)[11], but (R)-1-phenylethanol with 74% e.e. was obtained by operation method I (I stands for our method.) [10, 12]. It is seldom reported before that the configuration of the main product can be adjusted by simply changing operation method in same reaction with same chiral catalyst. The main differences between method I and method II are operation procedure, reaction temperature and solvent. In operation method II, after all BH_3-THF has been added quickly, ketone is added dropwise *via* syringe slowly and the reaction is carried out in THF at 66 ℃. While in operation method I, ketone and BH_3-THF are added dropwise *via* syringe, respectively, at the same time over 1 h and the reaction is carried

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out in toluene at 110 ℃. To research the causes of this phenomenon, three sets of the experimental condition using acetophenone as a model ketone were designed. The results were summarized in **Table1**.

The data in **Table 1** demonstrate: (1) **1** has bicoordination chiral inducement in asymmetric borane reduction of acetophenone. The configuration of the main product is only subject to operation method. (2) The e.e. values of the products obtained in toluene are always higher than those obtained in THF (Entry 1-5). (3) The reaction temperature has little influence on e.e. values when over 66 ℃ (Entry 6-12). (4) The effect of addition time on e.e. values is more significant than that of stirring time. Suitable addition time is 60-70 minutes in operation method I, and 100-110 minutes in operation method II (Entry 13-21).

Table 1 Effects of operation method, reaction temperature and solvent on the asymmetric borane reduction of acetophenone catalyzed by 10mol% **1**

Entry	Operation	T (°C)	Solvent	t_1 (h)[a]	t_2 (min) [b]	Yield (%)	Config.[c]	%e.e.[d]
1	I	66	Tol	0.25	65	72	R	73
2	I	66	Tol+THF	0.25	62	83	R	64
3	I	66	THF	0.25	65	83	R	22
4	II	66	Tol	10	105	85	S	50
5	II	66	THF	12	95	82	S	39
6	I	110	Tol	0.25	65	84	R	71
7	I	90	Tol	0.25	65	77	R	74
8	I	66	Tol	0.25	65	72	R	73
9	I	28	Tol	0.25	65	80	R	9
10	I	0	Tol	0.25	65	72	/	0
11	II	110	Tol	10	105	79	S	50
12	II	66	Tol	10	105	85	S	50
13	I	66	Tol	0.25	45	83	R	50
14	I	66	Tol	0.25	65	72	R	73
15	II	66	Tol	0	108	86	S	34
16	II	66	Tol	1	108	77	S	39
17	II	66	Tol	3	28	78	S	30
18	II	66	Tol	3	45	81	S	31
19	II	66	Tol	3	108	74	S	45
20	II	66	Tol	3	204	80	S	50
21	II	66	Tol	10	105	85	S	50

[a] t_1 is stirring time. [b] t_2 is addition time. [c] Absolute configuration was assigned by comparison of the optical rotation with that reported in literature. [d] The e.e. values of chiral alcohols were obtained by HPLC on chiralcel OJ column.

Acetophenone was replaced by other ketones under the optimal conditions in the following experiments. The results summarized in **Table 2** indicated that the bicoordination chiral inducement of **1** has a certain degree of generality.

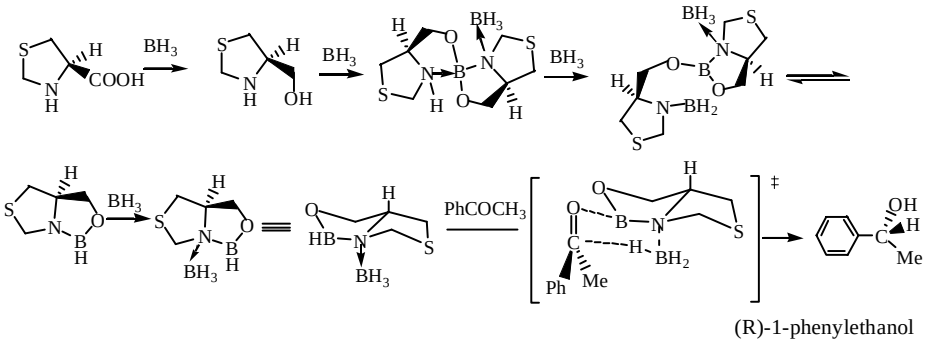
The bicoordination chiral inducement catalysis of **1** arises from its structure and the asymmetric reduction mechanism of oxazaborolidine. After analyzing the experiment results above and the structure of the catalyst, we come to the conclusion that (R)-1-phenylethanol is obtained when the reaction follows the pathway shown in **Scheme 1.**

Table 2 Effects of operation method on asymmetric borane reduction of three other prochiral ketones catalyzed by 10mol% **1** in Toluene at 66°C

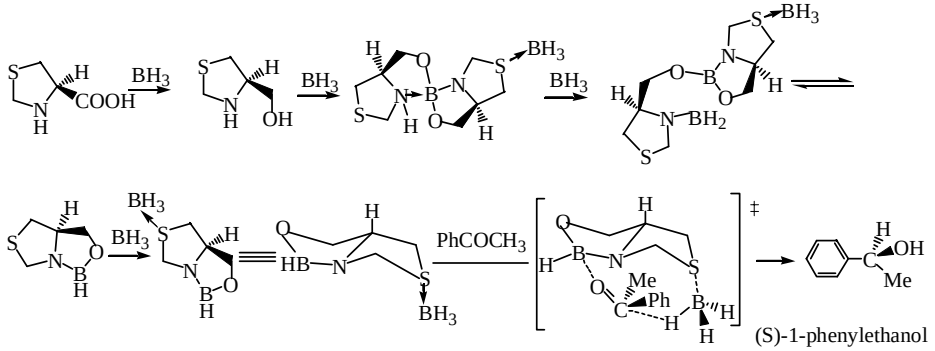
Prochiral ketones	Operation	t_1 (h)[a]	t_2 (min)[b]	Yield(%)	Config.[c]	%e.e.[d]
α-chloroacetophenone	I	0.25	70	90[e]	S	57
	II	4	120	93	R	52
α-bromoacetophenone	I	0.25	70	64[f]	S	40
	II	4	120	74	R	34
p-methylacetophenone	I	0.25	70	73	R	20
	II	4	120	74	S	35

[a, b, c, d] The same with those in **Table 1**. [e] Yield by column separation (eluent: ethyl acetate: petroleum = 1: 5, V/V). [f] Yield by vacuum distillation.

Scheme 1



Scheme 2



However, there is one sulfur atom in **1**. Like nitrogen, sulfur can also coordinate with borane. Herein, we believe (S)-1-phenylethanol is obtained when the reaction follows the pathway in **Scheme 2**.

Comparison of the two reaction pathways leads to a conclusion that the configuration of the main products is R or S depends on the competition between the two pathways. The competition was affected by the following 3 elements: 1) the respective rates of the coordination of the sulfur and nitrogen with borane; 2) the relative stability

between the sulfur-borane complex and the nitrogen-borane complex; 3) the relative level of the energy between the two transition states in the reduction step. On one hand, according to the soft-hard acid base theories and the analysis on the sites of the nitrogen and sulfur atoms in the molecule, the coordination of borane to the sulfur is easier than that with the nitrogen. Consequently, when borane was added quickly at one time (method II), the concentration of the sulfur-borane complex was much higher than that of the nitrogen-borane complex, which made the reaction mainly follow pathway in **Scheme 2**, affording (S)-1-phenylethanol. On the other hand, the energy of transition state of six-membered rings is lower than that of eight-membered ones (supported by MM2 computation). Accordingly, when borane and ketone were added dropwise simultaneously (method I), the reaction mainly followed pathway in **Scheme 1**, affording (R)-1-phenylethanol.

In summary, the bicoordination chiral inducement of (R)-4-thiazolidinecarboxylic acid in the enantioselective borane reduction of prochiral ketones was verified by sets of experimental condition. Because of the bicoordination chiral inducement, the configuration of the main product can be adjusted simply by changing operation method. It is very different from the traditional methods which control the configuration of products through converting the configuration of the chiral ligands. It is very significant in organic synthesis. Work is now in progress to synthesize more chiral ligands with similar structure and to select preferable ones among them.

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