Pergamon

*Tetrahedron: Asymmetry*, Vol. 7, No. 10, pp. 2779-2782, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00360-6

# Enantioselective Reduction of Aromatic Ketones with Borane Catalyzed by (R)-4-Thiazolidinecarboxylic Acids or (R)-4-Thiazolidine Methanol

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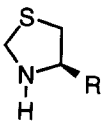
**Abstract**: (R)-4-Thiazolidinecarboxylic acid. (R)-2. 2-dimethyl-4-thiazolidinecarboxylic acid. S-ethyl-(L)-cysteine and L-methionine as chiral auxiliaries in the enantioselective catalytic reduction of aromatic ketones with borane have been investigated. When (R)-cyclic sulfur-containing α-amino acids were used as auxiliaries. the products secondary alcohols possess the (S)-configuration in contrast to Martens' (R)-2-Amino-1. 1-diphenyl-3-(isopropylmercapto)-1-propanol.

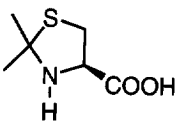

Reduction of prochiral ketones to give optically active secondary alcohols is an important reaction. In recent few years. a lot of papers on the reduction of ketones catalyzed by 1. 3. 2-oxazaborolidines have been reported[1~3]. Brunel and Martens[2] have described the borane reduction of aromatic ketones using simply (S)-proline or (S)-prolinol as chiral auxiliaries respectively. L-cysteine as chiral source is a cheap. commercially available material. and it reacts readily with acetone or formaldehyde to form (R)-2. 2-dimethyl-4-thiazolidinecarboxylic acid or (R)-4-thiazolidinecarboxylic acid respectively[4]. Since their structure is similar to that of proline. it is interest to study the catalytic behaviour of these sulfur-containing cyclic amino acids or alcohols to uncover the catalytic role of sulfur when they are used in the enantioselective reduction of ketones with borane. In this paper. we report the results of our study using these cyclic and noncyclic sulfur-containing amino acids as chiral auxiliaries in the borane reduction of aromatic ketones.

In a typical procedure under argon atmosphere the catalyst (R) or (S) 1~5 (1 mmol) was put in a flask and 8. 5ml (11 mmol) of a solution of $BH_3$ • THF complex was added via syringe at room temperature. The mixture was stirred for at least 12 hours and then heated to 50~60°C. The appropriate aromatic ketone (10 mmol. in 15 ml dry THF) was added dropwise over 90 min. After stirring for another 3 hours at the same temperature. the reaction mixture was cooled to room temperature. Diethyl ether was added and the reaction was quenched with 2N HCl. The organic layer was seperated and the aqueous layer was extracted with diethyl ether (3×15ml). The combined organic layers were washed with

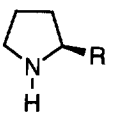
brine. dried ($MgSO_4$) and concentrated under reduced pressure. The crude alcohol was purified by column chromatography on silica gel using petroleum ether (b. p. 60～90℃) : ethyl acetate (4 : 1, v/v) as eluent to afford the corresponding chiral secondary alcohol. The enantiomeric excess was determined by specific rotation analysis. The results of reduction of aromatic ketones in the presence of these chiral catalysts are in Table 1.



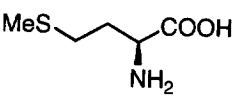
(R)-**1a** (R = COOH)
(R)-**1b** (R = $CH_2OH$)



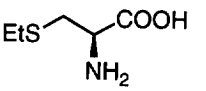
(R)-**2**



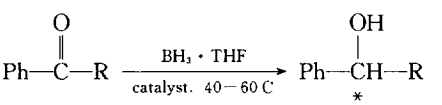
(S)-**3a** (R = COOH)
(S)-**3b** (R = $CH_2OH$)



(S)-**4**



(R)-**5**




As can be seen from Table 1. the enantioselectivity increased as the amount of catalyst increased. The e. e. value of the reduction of α-bromo acetophenone in the presence of sulfur-containing amino acids was higher than that of acetophenone and it was similar with the report of literature[7]. The enantioselectivity was found to increase with temperature. The α-bromo acetophenone was reduced with $BH_3$ • THF and 10 mol% of (R)-1a at 0 C. 20 C. 50 C and 66 C to yield (R)-2-bromo-1-phenyl ethanol in 25. 0%. 38. 1%. 72. 2% and 75. 6% e. e. respectively.

Except in a very few case[2a]. the borane reduction of acetophenone in the presence of (S)-2-(diphenylhydroxymethyl) pyrolidine and other (S)-chiral amino alcohols usually gave (R)-1-phenyl ethanol. Corey have suggested a reasonable reaction mechanism[8]. According to the mechanism. acetophenone was reduced with $BH_3$ • THF and (R)-4-thiazolidinecarboxylic acid or (R)-2. 2-dimethyl-4-thiazolidinecarboxylic acid should give (R)-1-phenyl ethanol. but the result of our experiment is (S)-1-phenyl ethanol. Our proposed rationale is that $BH_3$ molecule can coordinate with either the nitrogen or the sulfur atom of (R)-4-thiazolidinecarboxylic acid. Because nitrogen is a hard Lewis base and sulfur is a soft Lewis base. according to the rule of hard and soft acids and bases. proposed by Pearson[9]. soft acid $BH_3$ will mainly coordinate with sulfur atom of (R)-1a. The boron of the oxazaborolidine moiety coodinates with the prochiral ketone cis to the $BH_3$ molecular[8]. An intramolecular hydride transfer from $BH_3$ moiety to the carbonyl substrate to yield the (S)-1-phenyl ethanol then takes place.

**Table 1. Enantioselective reduction of ketones in the presence of chiral catalyst and borane**

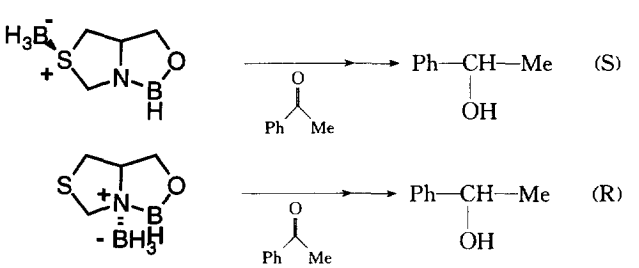
| entry | catalyst (mol%) | ketone | chiral secondary alcohol[a] | |
|---|---|---|---|---|
| | | | configuration | e. e. %[b] |
| 1 | (R)-1a (10) | PhCOMe | S | 25. 4 |
| 2 | (R)-1a (20) | PhCOMe | S | 39. 3 |
| 3 | (R)-1b[c] (10) | PhCOMe | S | 31. 2 |
| 4 | (R)-1b (20) | PhCOMe | S | 45. 3 |
| 5 | (R)-1a (10) | $PhCOCH_2Br$ | R | 72. 2 |
| 6 | (R)-1a (20) | $PhCOCH_2Br$ | R | 75. 4 |
| 7 | (R)-2 (10) | PhCOMe | S | 18. 7 |
| 8 | (R)-2 (20) | PhCOMe | S | 26. 1 |
| 9 | (R)-2 (10) | $PhCOCH_2Br$ | R | 47. 6 |
| 10 | (S)-3a (10) | PhCOMe | R | 21. 3 |
| 11 | (S)-3a (10) | $PhCOCH_2Br$ | S | 58. 0 |
| 12 | (S)-3a (20) | $PhCOCH_2Br$ | S | 68. 5 |
| 13 | (S)-3b (10) | PhCOMe | R | 37. 3 |
| 14 | (S)-3b (10) | $PhCOCH_2Br$ | S | 75. 0 |
| 15 | (S)-4 (10) | PhCOMe | R | 35. 4 |
| 16 | (S)-4 (20) | PhCOMe | R | 40. 6 |
| 17 | (R)-5 (10) | PhCOMe | R | 22. 1 |

a. The isolated yields of the chiral secondary alcohols were 70～80%.

b. The e. e. -values of chiral secondary alcohols abtained were calculated from specific rotations based on the following maximum rotations $[\alpha]_D^{22}=-52.5$ (2. 27. $CH_2Cl_2$. S) for (S)-1-phenylethanol[5] and $[\alpha]_D^{25}=-39$ (8. 00. $CHCl_3$. R) for (R)-2-bromo-1-phenylethanol. 93% e. e.[6].

c. (R)-4-Thiazolidine carboxylic acid was reduced with $BH_3$ • THF and hydrolyzed for use without purifying further.

In the other hand. $BH_3$ can also coordinate with nitrogen moiety of the catalyst which leads to (R)-1-phenyl ethanol. Maybe this is why the e. e. value of the product of reduction of acetophenone and α-bromo acetophenone reduced with $BH_3$ • THF and (R)-cyclic sulfur-containing amino acids is not very high compared with Corey's catalysts[8].



The enantioselective reduction of acetophenone with borane catalyzed by L-methionine and S-ethyl-L-Cysteine provide (R)-1-phenyl ethanol. As their structure is not as rigid as that of cyclic sulfur-containing amino acids and amino alcohols. $BH_3$ mainly coordinates with nitrogen to lead to the products with the usually configuration.

**Acknowledgements**: We are thankful for the financial support from Union Laboratory of Asymmetric Synthesis. Chengdu Institute of Organic Chemistry. Chinese Academy of Sciences and the National Science Foundation of China.

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(*Received in Japan* 18 *July* 1996; *accepted* 20 *August* 1996)