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A highly efficient and stereospecific borane reduction of spiro[4.4]nonane-1,6-dione catalyzed by a chiral oxazaborolidine

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Abstract

A highly stereoselective and enantioselective reduction of racemic spiro[4.4]nonane-1,6-dione catalyzed by an oxazaborolidine reagent is described. The asymmetric reduction of the racemic spirodiketones resulted in enantiomerically pure spirodiols which are useful chiral auxiliaries and also key intermediates for the synthesis of other highly effective chiral ligands. The *trans*,*trans*- and *cis*,*trans*-spirodiols were prepared in high enantiopurity by employing chiral oxazaborolidine as the catalyst. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric reactions; oxazaborolidine; reduction; spiro compounds.

Spiro[4.4]nonane-1,6-diols as precursors of chiral auxiliaries in metal-mediated asymmetric synthesis are of considerable interest.[1] A major obstacle in the development and application of this class of compound and their derivatives is the difficulty in obtaining the pure enantiomers of the chiral diols. The main problems in the current syntheses of spirodiols involving the reduction of diketones are: (1) in the reduction of racemic diketones, the resulting racemic diols are hard to resolve and many byproducts may be produced;[2] and (2) the reduction of enantiomerically pure spirodiketones can solve part of the problem, but unfortunately the preparation of optically pure spirodiketones is difficult. The current method used to resolve the racemic spirodiketones is to repeatedly recrystallize diastereomeric mixtures of derivatives.[3] To improve the overall synthesis of the useful chiral spirodiols, it is highly desirable to develop enantioselective and stereoselective methods for the reduction of the racemic spirodiketones. Amongst the reducing agents[4] used in the asymmetric reduction of carbonyl compounds, chiral oxazaborolidines[5] have been found to be useful in the borane-mediated enantioselective reduction of prochiral ketones giving chiral

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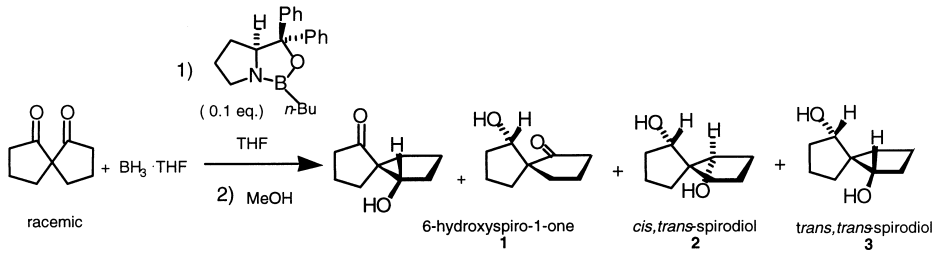
secondary alcohols with predictable configurations. Regardless of the bicyclic chiral center of the spirodiketone, each ketone functionality is prochiral. It is expected from the Corey mechanism[6] that only one stereoisomer may be obtained from each spirodiketone enantiomer via CBS reduction (developed by Corey, Bakshi, and Shibata).[6a] The application of an oxazaborolidine as the catalyst in the reduction of spiro[4.4]nonane-1,6-dione is therefore of interest because it may offer a convenient route to the highly useful, enantiomerically pure chiral spirodiols. Herein, we present the first example of the asymmetric reduction of the racemic spirocyclic dione catalyzed by oxazaborolidine with high enantioselectivity as well as stereoselectivity.

In our initial study, a typical CBS reduction procedure with the chiral *n*-butyl substituted oxazaborolidine[7] as the catalyst was applied to the reduction of the spirodiketone[8] and a remarkable result was observed in the first attempt at the reduction. The *trans*,*trans*-spirodiol **3** was obtained in almost 50% yield (based on the diketone used) and the ee of the *trans*,*trans*-spirodiol was found to be over 99% based on GC analysis.[9] The corresponding *cis*,*cis*-spirodiol was not observed as expected. The presence of 6-hydroxyspiro[4.4]nonan-1-one indicated that the reduction was incomplete. After extending the reaction time to 8 hours, it was found that *cis*,*trans*-spirodiol **2** was the other major product in addition to the *trans*,*trans*-spirodiol **3**. The results from the reduction of spiro[4.4]nonane-1,6-dione catalyzed by the oxazaborolidine are illustrated in Scheme 1.



Scheme 1.

The chemical yield and the enantiomeric excess of the *cis*,*trans*-spirodiol **2** were found to be largely dependent on the reaction conditions such as the borane/spirodiketone ratios and the reaction temperature. The effect of the borane/spirodiketone ratios on the yields and ee values of the products is shown in Table 1.

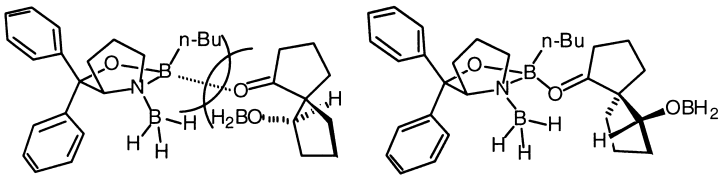
Table 1
The influence of the molar ratio of borane to diketone on the yields and ee values of the products[a]

	relative yields(%)[b]		
borane/diketone ratio (m/m)	**1**	**2** (ee %)[c]	**3** (ee %)[c]
1.2	44	6 (>99)	50 (>99)
1.5	27	28 (89)	45 (>99)
1.8	3	72 (30)	25 (>99)
2.0	0	83 (18)	17 (>99)

(a) Reaction conditions : spirodiketone : oxazaborolidine = 10 : 1 (molar ratio); temperature = 22 °C; reaction time = 8 h. (b) Isolated relative yields after column chromatography with silica gel; the combined yields were over 99% in all cases. (c) The ee values were determined by GC using a 25 m Chrompack Chiralsil-DEX CB capillary column.

From the data in Table 1, it appeared that there was an inverse relationship between the ee values of the *cis*,*trans*-spirodiol and its yields. The ee values of the *cis*,*trans*-spirodiol produced decreased dramatically with the increase of free borane. This might be due to competitive reduction of the second ketone functionality by the enantioselective CBS catalyst and the non-enantioselective free borane. It is worth noting that the ee value of the *trans*,*trans*-spirodiol was independent of the borane/spirodiketone ratio.

The effect of reaction temperature on the product ratios and the corresponding ee values is shown in Table 2. It can be observed from Table 2 that the yields of *cis*,*trans*-spirodiol increased with the reaction temperature for the temperature range tested (–78 to 20°C). No *cis*,*trans*-spirodiol was obtained at –78°C. When the temperature was increased to 20°C, the yield of *trans*,*trans*-spirodiol as well as the ee value of *cis*,*trans*-spirodiol decreased. These data indicate that the reactivity of the *cis*-boronate toward the CBS reduction was much lower than that of the *trans*-boronate. The reduction of the second carbonyl group of the *cis*-boronate was therefore dominated by the free borane instead of the CBS catalyst, especially at higher temperatures. A molecular model of the key intermediate based on Corey's mechanism showed that the alkylborane group of the resulting *cis*-boronate is located near the *syn* face of the other ketone group. The steric hindrance of the *cis* alkylborane group impeded the subsequent coordination of the second ketone to the oxazaborolidine and consequently no *cis*,*cis*-spirodiol was produced. In contrast to the *cis*-boronate intermediate, the coordination of the *trans*-boronate to the oxazaborolidine with the alkylborane on the *anti* face can lead to the *trans*,*trans*-spirodiol enantioselectively.



cis-boronate *trans*-boronate

Table 2
The influence of reaction temperature on the yields and ee values of the products[a]

	relative yields(%)[b]		
Temperature (°C)	**1**	**2** (ee%)[c]	**3** (ee%)[c]
-78	60	0	41 (>99)
-40	43	7 (>99)	50 (>99)
-20	42	9 (96)	49 (>99)
0	42	11 (91)	47 (>99)
20	33	22 (88)	45 (>99)

(a) Borane : spirodiketone : oxazaborolidine = 1.5 : 1 : 0.1 (molar ratio) ; reaction time = 5 h. (b) Isolated relative yields after column chromatography with silica gel; the combined yields were over 99% in all cases. (c) The ee values were determined by GC using a 25 m Chrompack Chiralsil-DEX CB capillary column.

The shielding of the second ketone by the *cis* alkylborane group, which prevented further reduction of the spirodiketone by the oxazaborolidine, did not prevent the reduction of the *cis*-spiro-β-hydroxyketone by the free borane from the other less sterically demanding face of the second carbonyl group. The experimental data were consistent with the competitive reduction of the

spirodiketone by free borane and the CBS catalyst. The reduction of the first ketone functionality was strongly driven by the CBS catalyst, but the reduction of the second ketone group was less straightforward. While the *cis*-boronate reacted with free borane to give **2**, the reaction of the *trans*-boronate with free borane also gave **2** and consequently the yield of **3** decreased in the presence of an excess of free borane.

In conclusion, we have developed a convenient method for the production of enantiopure *trans*,*trans*-1,6-spiro[4.4]nonane-diol and *cis*,*trans*-spiro[4.4]nonane-diol via the asymmetric reduction of spirodiketone catalyzed by oxazaborolidine. This study also reveals the potential of the CBS catalysts in the reductions of other di- or multi-ketone containing compounds.

Acknowledgements

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8. The *B*-*n*-butyl oxazaborolidine was prepared in the same manner as reported in the literature.[7] The *B*-*n*-butyl oxazaborolidine (0.1 mmol) was dissolved in dry THF (2 mL) and transferred into a three-necked flask under nitrogen. A borane–THF complex was then added slowly to the flask and stirred at room temperature for 15 min. The resulting mixture was cooled, and was added dropwise to a solution of spirodiketone (152 mg, 1.0 mmol) in dry THF (8 mL) over 10 min. The reaction mixture was stirred for 5–8 h, and decomposed by addition of methanol (1 mL) at 0°C. After evaporating the solvents, the residue was diluted with diethyl ether (10 mL) and purged with dry HCl gas to precipitate the amino alcohol (the CBS catalyst precursor). The amino alcohol hydrochloride salt was removed by filtration, and the filtrate was extracted with ethylacetate (5 mL×3), washed with brine, dried over $MgSO_4$ to give the crude product. The product was then purified by chromatography through silica gel with the eluent of ethylacetate:hexane = 2:3 to separate the reductive stereoisomers. The R_f

values are given as follows: 0.57 (**1**), 0.33 (**2**), 0.2 (**3**). For information on characterization of compound **1**, please refer to: *J. Am. Chem. Soc.* **1959**, 81, 2729. As for compounds **2** and **3**, see Ref. 2b.

9. Compound **2** was first treated with trifluoroacetic anhydride (0.2 mL) in the presence of Et_3N (0.5 mL) in refluxing THF (2.5 mL) for 2 h to obtain the corresponding triflate derivative. After the usual extraction workup, the triflate product was then analyzed by GC with a Chrompack Chirasil-DEX CB capillary column (25 m) for the determination of enantiomeric excesses. The ee values of compound **3** can be determined directly under similar GC conditions without any further transformations. The analytical conditions and the retention times are listed in the following: Oven temperature: 110°C, carrier pressure (nitrogen): 15 psi. (*1S*,*5S*,*6R*)-triflate isomer of **2**: 10.5 min; (*1S*,*5R*,*6R*)-triflate isomer of **2**: 10.9 min. Oven temperature: 180°C; carrier pressure (nitrogen): 15 psi. (*1R*,*2S*,*6R*)-isomer of **3**: 6.7 min; (*1S*,*5R*,*6S*)-isomer of **3**: 7 min.