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Chiral hydroxythiols as catalysts for enantioselective borane ketone reductions

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Abstract

Several chiral 1,2- and 1,3-hydroxythiols derived from (*R*)-camphor, (1*S*)-(+)-10-camphorsulfonyl chloride, cysteine and cystine derivatives were prepared and evaluated as catalysts in borane ketone reductions. Under the best experimental conditions (10 mol% catalyst, THF, 35°C), a 95% yield of (*R*)-1-phenylethanol of 64% *ee* was obtained in the borane reduction of acetophenone.

1. Introduction

The synthesis of enantiomerically enriched alcohols is an interesting challenge since they are often valuable intermediates for the synthesis of natural products. Amongst the variety of asymmetric reactions that may lead to optically active alcohols, enantioselective reduction of prochiral ketones with borane and a chiral ligand, following the pioneering works of Itsuno[1] and Corey,[2] has received considerable attention.[3,4] A variety of chiral controllers with two coordinating heteroatoms taken among O and N have been tested such as N,O (aminoalcohols)[5–7] and N,N (diamines) ligands.[8] We are however aware of only one paper reporting the use of O,S (hydroxythiols) ligands.[9] It should be interesting to investigate further the catalytic ability of these ligands in the enantioselective reduction of prochiral ketones with borane for comparison with aminoalcohols since: (i) nitrogen is replaced by the less electronegative sulfur atom; (ii) two electron pairs are now available on sulfur for coordination (only one for nitrogen); (iii) nitrogen is a hard Lewis base and sulfur a soft one, so the binding of sulfur with the soft Lewis acid BH_3 should be stronger than with a nitrogen atom. In this paper we report our results obtained in borane reduction of various ketones with the use of hydroxythiols **1**–**4** derived from cheap, commercially available (*R*)-(+)-camphor, and of L-cysteine-derived hydroxythiols **5a** and **5b**.

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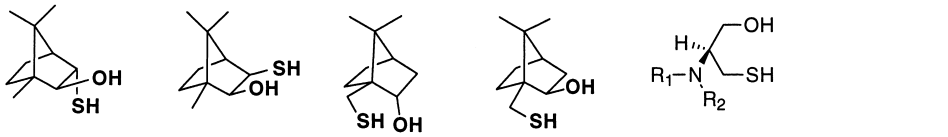


1 2 3 4

5a : $R_1 = H$, $R_2 = CH_2CH_3$

5b : $R_1 = R_2 = CH_3$

2. Results and discussion

2.1. Variation of the reducing agent and the camphor-derived chiral auxiliary

The effect of the nature of the reducing agent ($BH_3 \cdot THF$ or catecholborane) is seen from the results collected in Table 1, concerning the reduction of acetophenone with various catalysts and two borane reagents. Ligand **1** afforded poor results in terms of enantioselectivity, whereas **2**, **3** and **4** were active but moderately selective. Both the activities and selectivities displayed by catecholborane were lower than those obtained with $BH_3 \cdot THF$. Interestingly **3** and **4**, which are epimeric at the carbon bearing the hydroxyl group, produced carbinols of opposite configurations.

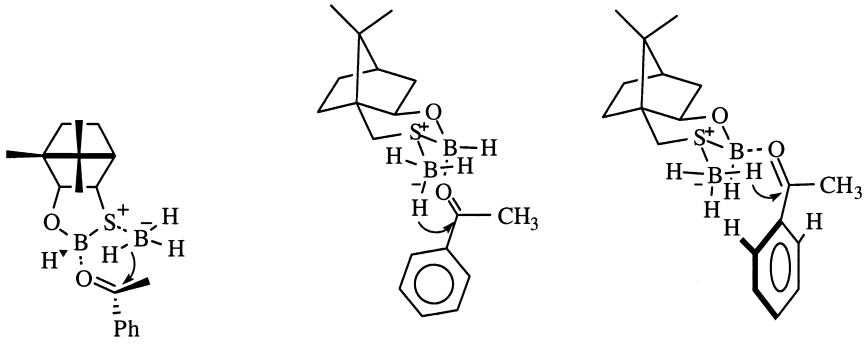
Table 1
Enantioselective reduction of acetophenone in the presence of chiral hydroxythiols and reducing agents[a]

Entry	Hydroxythiol (10 mol %)	Reducing agent	1-Phenylethanol[b] % e.e. (config.)
1	**1**	BH_3:THF	3 (*R*)
2	**1**	catecholborane	6 (*R*)
3	**2**	BH_3:THF	52 (*S*)
4	**2**	catecholborane	28 (*S*)
5	**3**	BH_3:THF	60 (*S*)
6	**3**	catecholborane	43 (*S*)
7	**4**	BH_3:THF	64 (*R*)
8	**4**	catecholborane	59 (*R*)

[a] Molar ratio of acetophenone : reducing agent : hydroxythiol = 1 : 1.1 : 0.1; temp 35°C. b) Isolated yields are over 90%.

Upon consideration of these results, and owing to the ease of its synthesis, **4** was selected as a ligand for further investigation of a number of parameters (temperature, solvent, catalyst-to-substrate ratio) able to control the reduction.

The absolute configuration of the major enantiomer of the 1-phenylethanol produced with **2** and **4** as auxiliaries can be rationalized according to Corey's asymmetric induction model involving a face-selective hydride transfer via a six-membered transition state. The borane will first coordinate to the most accessible electron lone pair of the sulfur atom, and then the ketonic oxygen will bind to the endocyclic boron atom with the smallest substituent (methyl) *cis* to the vicinal BH bond as depicted in schemes **A** and **B**. For transition state **B**, the two six-membered rings (oxathiaborolidine and hydride transfer) are both in chair-like conformation with a *cis* junction, and an equatorial phenyl substituent. However, a *trans* junction for the two cycles may also account for the *R* configuration in the product provided that the phenyl substituent is axial. Indeed, in such a conformation, the *ortho* hydrogen and carbon atoms of the benzene ring would likely suffer less compression with the axial hydrogens on boron atoms (and no interaction with the adjacent H and O atoms, since these bear no equatorial substituent) than the axial methyl group in the diastereomeric transition state.



2.2. Variation of the temperature

As shown from Table 2, the enantioselectivity was significantly affected by the temperature between 22 and 35°C. A similar trend has been reported by Stone in the borane reduction of acetophenone catalyzed by 10 mol% of the oxazaborolidine derived from (*S*)-diphenylprolinol.[10] Although the optimum temperature appeared to be around 50°C, the following experiments were conducted at 35°C for convenience.

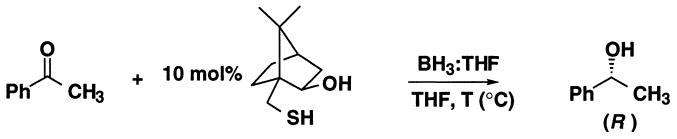
2.3. Variation of the solvent and of the catalyst-to-substrate ratio

From Tables 3 and 4 can be seen the effect on enantioselectivity of the solvent and of the catalyst-to-substrate ratio in the borane reduction of acetophenone. Whereas the nature of the solvent showed no significant effect on enantioselectivity, an increase of the catalyst-to-substrate ratio did improve the enantioselectivity by up to 75% *ee* in the 1-phenylethanol produced.

2.4. Variations of the substrate

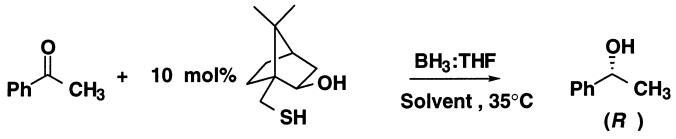
Various types of ketones were reduced under the optimized conditions determined above: temperature (35°C), THF as the solvent and 10 mol% catalyst were chosen as standard conditions. Hydride delivery

Table 2
Effect of temperature on the enantioselectivity of the reduction of acetophenone



Entry	Temperature (°C)	1-Phenylethanol % e.e.
1	22	40
2	35	64
3	50	68
4	66	60

Table 3
Effect of the solvent on the enantioselectivity of the reduction of acetophenone with $BH_3 \cdot THF$/**4**



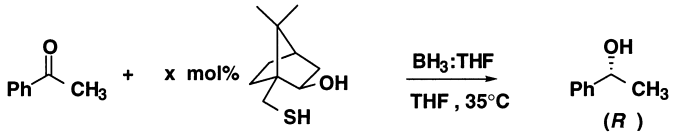
Entry	Solvent	(*R*)-1-Phenylethanol % e.e.
1	THF	64
2	CH_2Cl_2	66
3	1,4-Dioxane	61
4	Toluene	57

took place on the same enantioface of acetophenone, 2-chloroacetophenone and 4-bromoacetophenone (Table 5).

2.5. *Variation of the chiral auxiliary: derivatives of* N*-substituted cysteine and cystine*

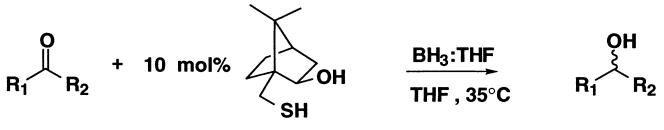
To date, L-cysteine-derived auxiliaries used in borane reduction of ketones were mainly *S*-alkylated compounds.[11,12] We wanted to investigate the influence of the nitrogen substitution on the selectivity. Compounds **5b**, **6** and **7** were evaluated as catalysts in the borane reduction of acetophenone. 3 mol equivalent of $BH_3 \cdot THF$ to **6** were necessary to ensure a rapid reduction of acetophenone, suggesting that an actual catalyst is formed after reduction of the acid and the amide functions. As can be seen from

Table 4
Effect of % catalyst on the enantioselectivity of the reduction of acetophenone with $BH_3 \cdot THF$/**4**



Entry	Catalyst **4** (x mol %)	1-Phenylethanol % e.e.
1	5	36
2	10	64
3	20	73
4	100	75

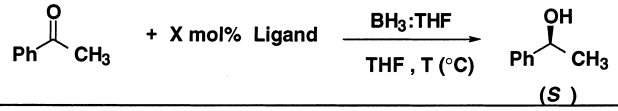
Table 5
Enantioselective reduction of ketones with $BH_3 \cdot THF$



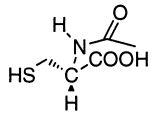
Entry	R^1	R^2	Carbinol Yield (%)	% e.e. (config.)
1	C_6H_5	CH_3	95	64 (*R*)
2	C_6H_5	CH_2Cl	91	45 (*S*)
3	C_6H_5-CH_2CH_2-	CH_3	>99	32 (*S*)
4	4-Br C_6H_4	CH_3	>99	56 (*R*)
5	(4-CH_3O) C_6H_4	CH_3	84	5 (*R*)
6	(*E*)-C_6H_5CH=CH	CH_3	25	15 (*R*)

Table 6, the enantioselectivity increased as the amount of catalyst and the temperature increased to 40°C. Acetophenone was reduced with $BH_3 \cdot THF$ and one equivalent of **6** at 40°C to give a quantitative yield of (*S*)-phenylethanol in 65% *ee* (entry 3). The influence of a substituent on the nitrogen atom was further shown to be crucial since the *N*,*N*-dimethylcysteinol **5b** displayed no enantioselectivity (entry 10).

Table 6
Enantioselective reduction of acetophenone in the presence of chiral auxiliaries and reducing agents



Entry	Catalyst (mol%)	Temperature (°C)	1-Phenylethanol % e.e.
1	**6** (100)	0	7
2	**6** (100)	25	58
3	**6** (100)	40	65
4	**6** (100)	66	57
5	**6** (10)	25	33
6	**6** (10)	40	47
7	**6** (10)	66	47
8	**7** (10)	25	12
9	**7** (10)	40	32
10	**5b** (10)	25	0



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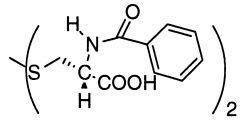

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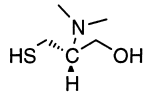

5b

3. Conclusion

This exploratory work has shown that hydroxythiols and hydroxyaminothiols can serve as active and enantioselective chiral auxiliaries in catalytic borane reduction of ketones. Hydroxythiol **4** proved to be the best ligand among the thiols assayed for acetophenone reduction, giving for an amount of 10 mol% catalyst at 35°C in THF a >95% yield of 1-phenylethanol of 64% *ee*. A comparable (65%) enantioselectivity could be recorded but with a stoichiometric amount of *N*-acetylcysteine as chiral auxiliary. The substitution on the nitrogen atom of the cysteine or cysteinol used as ligands for borane reduction of acetophenone was shown to noticeably influence the enantioselectivity. Compounds **5** (R_1=H) being readily available from *N*-acylated cysteine or cystine should constitute a promising new class of sulfur-containing auxiliaries for borane-mediated enantioselective reduction of ketones.

4. Experimental

4.1. General

Melting points were measured on a Reichert apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 200 or a Bruker AC 250 spectrometer and signals are expressed downfield from tetramethylsilane used as an internal standard. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ and coupling constants (J) in hertz. ^{13}C NMR spectra were interpreted with the aid of DEPT (135) experiments. Optical rotations were taken on a Perkin–Elmer 341 polarimeter. GC–MS analyses were performed with a Varian 3400 spectrometer. High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer. Enantiomeric excesses were determined by chiral phase HPLC analysis using Thermo Separation Products P100 and Varian equipped with a Chiralcel OD-H column (25 cm×4.6 mm i.d.) *i*-PrOH:hexane=10:90, 0.5 ml min^{-1} except for 4-bromo-α-methylbenzyl alcohol (*i*-PrOH:hexane=1:99, 1 ml min^{-1}). Enantiomeric excess of 4-methoxy-α-methylbenzyl alcohol was evaluated by chiral HPLC on Pirkle (*S,S*)-Whelk 01 (25 cm×4.6 mm), *i*-PrOH:hexane=1:99, 1 ml min^{-1}. Enantiomeric excesses were the means of two experiments and fell in ±2% error limits. Absolute configurations were assigned either from comparison with the elution order (chiral chromatography) with the data reported in the literature[13] or from comparison with optical rotations taken from the literature for 4-phenylbutan-2-ol[14] and 4-methoxy-α-methylbenzyl alcohol.[15]

4.2. Materials

The solvents were distilled under argon before use. (1*S*)-(+)-10-Camphorsulfonyl chloride ([α] +30, *c* 1; $CHCl_3$, lit. [α] +33) was purchased from Aldrich. (*R*)-(+)-Camphor ([α] +43 (*c* 0.1; C_2H_5OH), lit. [α] +44) was purchased from Janssen.

4.3. (1R,2S,3S)-endo-3-(Mercapto)-1,7,7-trimethylbicyclo[2,2,1]heptan-2-ol **1**

The title compound was prepared starting from (*R*)-(+)-camphor and benzyl thiotosylate in four steps in an overall yield of 13% following the literature method.[16,17]

4.4. (1R,2S,3R)-exo-3-(Mercapto)-1,7,7-trimethylbicyclo[2,2,1]heptan-2-ol **2**

Same as for **1** (20% yield).[16,18,19]

4.5. exo-10-Mercaptoisoborneol **3** and its endo-isomer **4**[20]

The title compounds were prepared from (1*S*)-(+)-10-camphorsulfonyl chloride in 49% and 8% yield respectively, as white solids following literature method. **3**: chiral GC: *ee*=97.4%. **4**: chiral GC: *ee*=98.3%.

4.6. N,N-Dimethylamino-S-benzyl-L-cysteinol

To *S*-benzyl-L-cysteinol (5 g, 25.3 mmol) was added 8 ml of HCHO at 37% and 7.6 ml of HCOOH. After stirring for a few minutes at room temperature, the mixture was refluxed for 12 h. The solution was cooled to room temperature, HCl 1 N was added, then extracted with Et_2O, washed with $NaHCO_3$

and re-extracted with Et_2O. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude was distilled at 225°C under 8×10^{-2} mm Hg. A colorless oil was obtained with 83% yield. ^{1}H NMR: δ 7.28–7.18 (m, 5H, aromatics); 3.67 (s, 2H, CHS); 3.66 (dd, *J*=9, 4, 1H, CH_2); 3.23 (dd, J_{gem}=*J*=9, 1H, CH_2); 2.9 (1H, OH); 2.68 (m, *J*=9, 1H, CH); 2.58 (dd, *J*=4, 13, 1H, CH_2); 2.18 (s, 6H, CH_3); 2.13 (dd, *J*=9, 13, 1H, CH_2). ^{13}C NMR: δ 137 to 128 (aromatics); 63 (CH); 60 (CH_2O); 39 ($2CH_3$); 36 (CH_2SH); 26 (CH_2). $[\alpha]_D^{20}$ +57.8 (*c* 10.1; $CHCl_3$). HRMS for $C_{12}H_{19}NOS$ calcd 225.1187. Found: 225.1188.

4.7. N,N-*Dimethylamino*-L-*cysteinol* ***5b***

To *N*,*N*-dimethylamino-*S*-benzyl-L-cysteinol (1 g, 4.4 mmol) in 3 ml of Et_2O were added a cold solution (−78°C) of liquid ammoniac and 1.1 g (47.8 mmol) of sodium in small pieces to obtain a blue color. After stirring for 4 h at −78°C, the mixture was allowed to return to room temperature. Water (10 ml) and 1 M HCl (45 ml) were added. After concentrating the aqueous layer under reduced pressure, the residue was taken up in absolute ethanol, filtered and treated with Et_2O to precipitate the crystalline hydrochloric acid salts. These salts were dissolved in water and 12 M HCl was added. The aqueous layer was extracted with $CHCl_3$, dried over $MgSO_4$, concentrated under reduced pressure and white crystals were obtained with 40% yield, mp 67–70°C. ^{1}H NMR: δ 3.71 (dd, *J*=4.4, 10.5, 1H); 3.34 (t, *J*=10.1, 1H); 2.9 (m, 2H); 2.7 (OH); 2.38 (dd, *J*=10.1, 10.1, 1H); 2.29 (m, 7H, $2CH_3$, 1H). ^{13}C NMR: δ 64.08; 60.24 (CH_2); 40.22 (CH_3); 33.81 (CH_2). $[\alpha]_D^{20}$ +120 (*c* 1; $CHCl_3$). (Disulfur $C_{10}H_{24}N_2O_2S_2$: calcd C 44.74, H 9.02. Found: C 44.94, H 9.06, mp 67–69°C.)

4.8. Enantioselective borane reduction of ketones

To the catalyst **1**–**4**, **5b**, **6** or **7** (0.2 mmol) in 1 ml dry THF under argon was added a solution of $BH_3\cdot$THF (2.2 ml, 2.2 mmol) via syringe at room temperature and stirred for 1 h at the required temperature. The ketone (2 mmol in 750 ml of dry THF) was added dropwise over 1 h. The reaction mixture was stirred for 1 h at the same temperature, cooled to room temperature, then quenched with 1 M HCl. The aqueous layer was extracted with diethyl ether. The organic layers were dried and concentrated under reduced pressure. Boron salts were precipitated in hexane and filtered before HPLC analyses.

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