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Application of MerCO as a chiral catalyst in asymmetric synthesis: asymmetric borane reduction of ketones

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Abstract

The borane reduction of aryl methyl ketones catalyzed by MerCO [(1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol] produced 1-aryl ethyl alcohols in 92% e.e. at 50°C in toluene. Significant temperature and solvent effects were observed in this reaction.

Asymmetric borane reduction has attracted much attention owing to its usefulness in preparing optically active secondary alcohols.[1] Many chiral diols,[2] amino alcohols,[3] and sulfoximines[4] have served as chiral ligands to accelerate the reaction rate and, more importantly, to provide an asymmetric environment for the reacting species. Among these cases, oxygen and nitrogen are used as the coordinating atoms to boron. In general, the oxygen–nitrogen paired ligands give a better enantioselectivity than the corresponding oxygen–oxygen paired bidendate ligands. This phenomenon can be rationalized according to the CBS mechanism proposed by Corey, in which a second molecule of borane coordinates with the more electron rich nitrogen atom. Thus directing the borohydride to specifically approach one of the prochiral faces of the carbonyl group.[5] However, in the diol ligands, the second borane molecular may coordinate to either oxygen atom, and scrambled induction may occur if both oxygen atoms have a similar coordinating capability to the second borane. In principle, the oxygen–sulfur paired bidentate ligands also have a significant affinity difference to coordinate with borane, possibly offering the second borane a clear preference among the two coordinating atoms. Consequently, better stereoselectivity could be expected, but we have found that thiols have rarely been studied for catalytic asymmetric borane reductions.[6,7] Herein, we report the use of MerCO **1** and its derivatives **2**, **3** as chiral oxygen–sulfur paired bidentate ligands accompanied with borane to reduce aryl methyl ketones to the corresponding alcohols.

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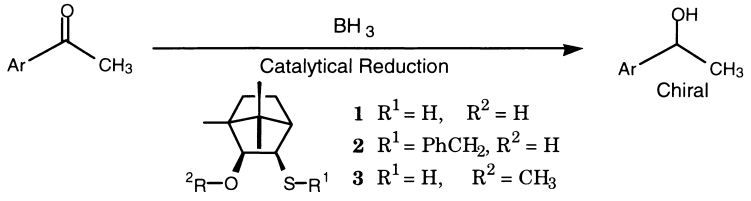
Table 1
Solvent effect on the asymmetric borane reduction of aryl methyl ketones catalyzed by MerCO **1**

Entry	Aryl Methyl Ketones[a]	Temperature (°C)	Solvents	Alcohols Yield[b](%)	% e.e.[c]	Config.
1	Phenyl	25	Toluene	**92**	**73**	***S***
2	Phenyl	25	CH_2Cl_2	**73**	**68**	***S***
3	Phenyl	25	THF	**80**	**42**	***S***
4	2-Naphthyl	25	Toluene	**92**	**75**	***S***
5	2-Naphthyl	25	CH_2Cl_2	**88**	**70**	***S***
6	2-Naphthyl	25	THF	**87**	**52**	***S***
7	Phenyl	50	Toluene	**96**	**87**	***S***
8	Phenyl	50	THF	**99**	**64**	***S***

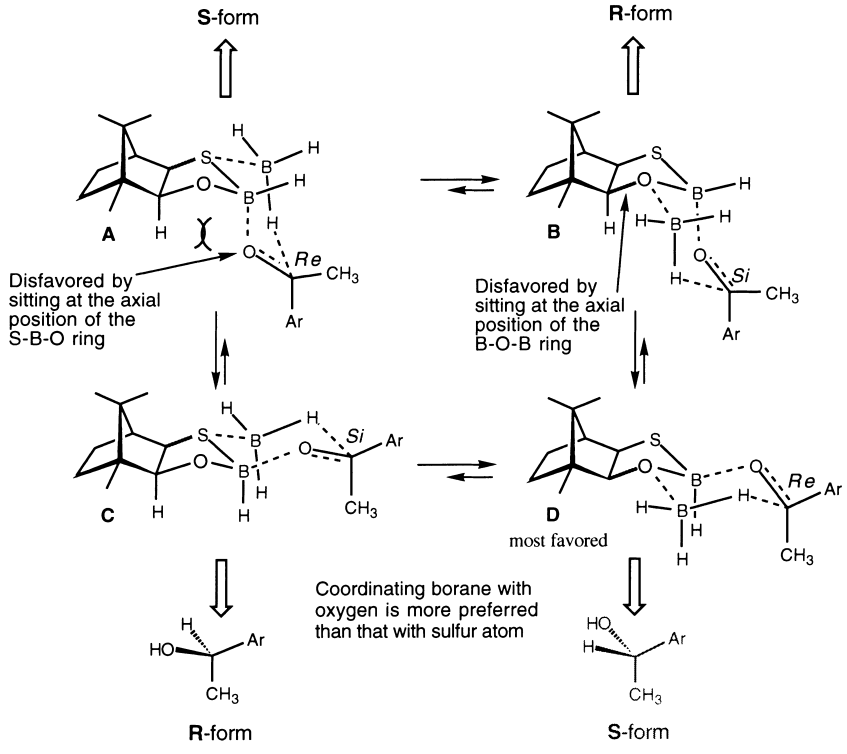
[a] The stoichiometry ratio of ketone : chiral ligand **1** : $BH_3.SMe_2$ was 1.0 : 0.1: 1.1 in the reactions above. [b] The reaction yields were obtained by isolating of the products after purification. [c] The enantiomeric ratios were determined by HPLC analysis with a Chiral-OD column from Daicel.



Chiral compounds **1**–**3** were easily prepared in satisfactory yields from camphor, according to our previous report.[8] In order to find optimal conditions for using these newly developed ligands, we examined the influence of solvent, temperature, and stoichiometry in the borane reduction. Table 1 clearly indicates that a non-polar solvent such as toluene is the best solvent to achieve the highest enantioselectivity for MerCO **1**, which compares with most of the existing ligands (entries 1, 4, and 7). Coordination of THF with boron may compete with the coordination of boron to the chiral ligand, and poor enantioselectivity was observed herein (entries 3, 6, 8). Meanwhile, our results indicate that such a solvent effect is independent of the reaction temperature[9] (entries 7, 8).

The transition states proposed in Scheme 1 reveal that the *S* configuration of the alcohol should be obtained from MerCO **1** catalyzed borane reduction. The fact that boron is a hard acid, which would prefer to coordinate with oxygen as a relatively harder base than sulfur atom, accounts for why transition states **B** and **D** are more favorable than **A** and **C**. On the other hand, the bulky camphor backbone is oriented at the axial position of the six-membered ring ligand–borane–ketone complex in transition state **B** whereas the 2-hydroxyl group of the camphor skeleton is set at the equatorial position in the ligand–borane–ketone complex shown in **D**. The preference of the aryl group to remain in the equatorial position would cause the borohydride to approach the *Re*-face of the ketone, thereby leading to the *S*-alcohol according to the spatial arrangement of transition state **D**. Furthermore, the bulkier 2-naphthylketone ensures that the aryl group is set at the equatorial position, accounting for the observation of a higher enantioselectivity (entry 4 vs 10). Closely examining the electronic effect of the substituents on the aryl group of the ketones did not reveal an obvious trend (entries 20–25; Table 2).

Comparing the e.e. values of the 1-phenylethanol listed in Table 1 reveals that higher enantioselectivities are achieved at higher reaction temperatures when other factors are kept the same.[9,10] More detailed temperature studies in Table 2 suggest that the maximum e.e. values of the alcohols are always obtained when reaction temperature is kept at around 50°C (entries 4 and 10). The above results imply that a chiral ligand–borane–ketone complex is formed at around 50°C, thereby making it the effective chiral



Scheme 1.

reducing agent. At a lower reaction temperature the chiral borane complex is not formed completely.[11] Therefore, a portion of the ketone is reduced by free borane, without the chiral ligands to yield the racemic alcohols. When the reaction temperature markedly exceeds 50°C, the reaction between the ketone and free borane becomes fast enough to compete with the chiral ligand associated borane. Therefore, the enantioselectivity falls to 6% e.e. when the reaction temperature is maintained at 110°C (entry 8). This hypothesis is further supported by a two stage temperature study, in which the chiral ligand and borane are initially mixed at a higher temperature to accelerate the formation of the chiral ligand–borane complex; ketone is then added at a lower temperature. Our results show a better enantioselectivity when the ketone is added at lower temperature than that of the constant high temperature process (entry 7 vs 15 and 8 vs 16). On the other hand, alkylation of either 2-hydroxyl or 3-mercapto group of MerCO **1** significantly weakens their coordination with boron, possibly destroying the chiral ligand–borane–ketone complex and diminishing the enantioselectivities. Nevertheless, the low e.e. of the alcohols produced using catalysts **2** and **3** indirectly confirms the chelation of borane to both 2-hydroxyl and 3-mercapto groups as well as their importance in the enantioselectivity of the reduction process.

In summary, this study has successfully demonstrated a novel thiol type chiral catalyst, MerCO **1**, for the asymmetric borane reduction. The optimum conditions to use this catalyst in borane reduction is 50°C in toluene, which also implies that the formation of chiral ligand–borane–ketone complex is essential for stereoselective reduction. Currently, we are investigating the novel thiol catalyst with even stronger chelating capability and its application to aliphatic ketone systems.

Table 2
Temperature effect on asymmetric borane reduction of aryl methyl ketones catalyzed by MerCO **1**

Entry[a]	Aryl Methyl Ketones[b]	Ligand (eq.)	Temperature (°C)	Alcohols Yield,[c]%	% e.e.[d]	Config.
1	Phenyl	**1** (0.1)	25	92	73	***S***
2	Phenyl	**1** (0.1)	40	98	79	***S***
3	Phenyl	**1** (0.1)	45	90	83	***S***
4	Phenyl	**1** (0.1)	50	96	87	***S***
5	Phenyl	**1** (0.1)	55	92	81	***S***
6	Phenyl	**1** (0.1)	60	96	80	***S***
7	Phenyl	**1** (0.1)	80	94	79	***S***
8	Phenyl	**1** (0.1)	110	93	6	***S***
9	2-Naphthyl	**1** (0.1)	45	98	85	***S***
10	2-Naphthyl	**1** (0.1)	50	96	91	***S***
11	2-Naphthyl	**1** (0.1)	55	99	80	***S***
12	Phenyl	**1** (0.1)	50 -> 25	96	78	***S***
13	Phenyl	**1** (0.1)	80 -> 25	88	76	***S***
14	Phenyl	**1** (0.1)	110 -> 25	90	76	***S***
15	Phenyl	**1** (0.1)	80 -> 50	91	87	***S***
16	Phenyl	**1** (0.1)	110 -> 50	88	85	***S***
17	Phenyl	**2** (0.1)	25	87	4	***S***
18	Phenyl	**3** (0.1)	25	84	22	***R***
19	2-Naphthyl	**2** (0.1)	50	96	7	***S***
20	2-Naphthyl	**3** (0.1)	50	98	16	***R***
21	*p*-methoxyphenyl	**1** (0.1)	50	88	70	***S***
22	*p*-Chlorophenyl	**1** (0.1)	50	90	80	***S***
23	*p*-Nitrophenyl	**1** (0.1)	50	94	92	***S***
24	1-Naphthyl	**1** (0.1)	50	98	86	***S***
25	6-Methoxy-2-naphthyl	**1** (0.1)	50	98	64	***S***

[a] In the reactions above, toluene was used as a solvent and ketones were consumed completely. [b] The stoichiometry ratio of ketone : chiral ligand : $BH_3.SMe_2$ was 1.0 : 0.1: 1.1 in all of the reaction above. [c] The reaction yields were achieved by isolating the products after purification. [d] The enantiomeric ratios were determined by HPLC analysis with a Chiral-OD column from Daicel.

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References

1. Deloux, L.; Srebnik, M. *Chem. Rev*. **1993**, *93*, 763.
2. Midland, M. M. *Asymmetric Synthesis*, *Vol 2*, Academic Press: New York, 1983, pp. 45–70, and references cited therein.
3. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1987, and references cited therein.
4. Bolm, C.; Felder, M. *Tetrahedron Lett*. **1993**, *34*, 6041 and 8079.
5. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551.

6. For sulfur containing chiral catalysts in borane reduction see: (a) Li, X.; Xie, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2779. (b) Trentmann, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2033. (c) Calmes, M.; Escale, F.; Paolini, F. *Tetrahedron: Asymmetry* **1997**, *8*, 3691.
7. (a) A preliminary presentation was given by us in the *1st National Symposium for Organic Chemistry*, Chengdu, China, 1997, IL 18. (b) Zhou, Y. G.; Hou, X. L.; Dai, L. X. *Chin. J. Chem*. **1998**, *16*, 284.
8. (a) Lee, D.-S.; Hung, S.-M.; Lai, M.-C.; Chu, H.-Y.; Yang, T.-K. *Org. Prep. Proc. Int*. **1993**, *25*, 673. (b) Yang, T.-K.; et al. *J. Org. Chem*. **1994**, *59*, 914.
9. Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897, and references cited therein.
10. (a) Brunel, J.-M.; Pardigon, O.; Faure, B.; Buono, G. *J. Chem. Soc., Chem. Commun*. **1992**, 287. (b) Private communication with Prof. Dai Li-Xin at Shanghai Institute of Organic Chemistry in China.
11. General procedure: to a solution of chiral ligand in toluene was added $BH_3 \cdot SMe_2$ at specified temperature and stirred for 60 min. The ketone was added slowly over a period of 60 min then stirred at specified temperature for another 30 min. The reaction mixture was quenched with 3N NaOH (aq.) and extracted with ethyl acetate. The organic layer was concentrated in vacuum and passed through a short silica column, then subjected to HPLC analysis.