Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4307–4311

TETRAHEDRON: *ASYMMETRY*

Catalytic enantioselective borane reduction of aromatic ketones with sulfonyl (*S*)-prolinol

Gao-Shen Yang,[b] Jian-Bing Hu,[a] Gang Zhao,[a,*] Yu Ding [a,*] and Min-Hua Tang [a]

[a]*Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, People's Republic of China*

[b]*Anhui Normal University, Chemistry Department, Anhui, People's Republic of China*

Received 27 August 1999; accepted 27 September 1999

Abstract

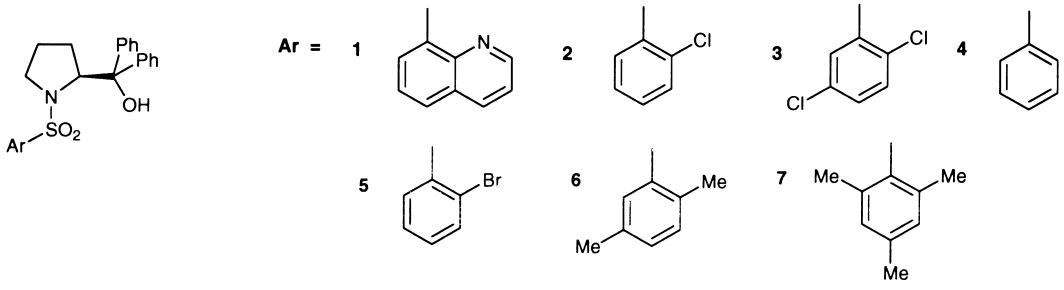
The asymmetric reduction of aromatic ketones was catalyzed by a class of recoverable and highly stable chiral sulfonamides derived from (*S*)-proline to yield optically active secondary alcohols in high yields and with enantiomeric excesses of up to 91%.

1. Introduction

The enantioselective reduction of prochiral ketones to optically active alcohols plays an important role in asymmetric synthesis.[1] Since Itsuno et al. found that chiral alkoxy-amine–borane complexes reduce aromatic ketones enantioselectively,[2] the asymmetric reduction of prochiral ketones to optically active alcohols using chiral catalysts has become one of the most attractive research fields. A variety of chiral catalysts with two heteroatoms to coordinate with borane has been developed and used for asymmetric reduction. Most of them are chiral β-amino alcohols.[3] Among these chiral catalysts, oxazaborolidine–borane complexes prepared from β-amino alcohols are the most effective.[4] Recently, Wills et al. reported that chiral phosphinamides prepared from commercially available L-proline derivatives were efficient catalysts for the highly enantioselective reduction of ketones.[5] In this paper, we would like to report the use of sulfonyl (*S*)-prolinol **1**–**7** (Scheme 1) as chiral catalysts to reduce aromatic ketones to the corresponding alcohols in high yields and with good enantioselectivities.

* Corresponding authors. E-mail: dingyu@pub.sioc.ac.cn

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00437-1



Scheme 1.

2. Results and discussion

2.1. Solvent and temperature

To find optimum reaction conditions, we examined the reduction of bromoacetophenone with chiral catalyst **1** under various experimental conditions. The results are summarized in Table 1. In this study obvious solvent and temperature effects were observed. When the reaction was carried out in THF, it took 6 days to complete the reduction, but in toluene the reaction was completed within 11 h. The results showed the reaction proceeded more smoothly in toluene than in THF at the same reaction temperature (entries 1 and 2). As with previous reports,[6] the higher enantioselectivity was sustained at a higher reaction temperature. When the reaction temperature was raised from room temperature to 110°C, the ee value increased from 0 to 91% (entries 2, 3 and 4). Hence, the best result could be achieved if the reaction mixture was at reflux.

Table 1
Asymmetric reduction of bromoacetophenone using catalyst **1**

$$PhCOCH_2Br + BH_3 \bullet SMe_2 \xrightarrow{\text{Cat.}^a\ \mathbf{1}} PhC^*HOHCH_2Br$$

Entry	Solvent	Temp.(^{0}C)	Time(hr)	Yield (%)[b]	E.e (%)(config.)[c]
1	THF	r.t	204	90	6 (S)
2	toluene	r.t	27	95	0 (S)
3	toluene	100-110	1	88	88 (S)
4	toluene	reflux	1	96	91 (S)
5	THF	reflux	1.5	94	35 (S)

a. 10% mol ratio to ketone.
b. Yield of isolated pure product.
c. Enantiomeric excess was determined by Chiralcel OJ, 10% 2-propanol in hexane as eluent. Configuration of products was established on the basis of specific rotation[7a].

2.2. Chiral catalysts

Based on the above optimum reaction conditions, we chose 2-bromoacteophenone and acetophenone as substrates to examine the effect of various catalysts. The sulfonamide catalysts directly prepared from L-prolinol were stable white crystalline solids and proved to be effective catalysts for ketone reduction by borane. The results are listed in Table 2. All catalysts gave good chemical yields. Among the catalysts examined, catalyst **1** containing a quinoline ring gave the best enantioselectivity for two substrates (entry 1, 85% ee for $PhCHOHCH_3$ and 91% ee for $PhCHOHCH_2Br$). Catalysts **2** and **7** also gave good enantioselectivities (entries **2** and **7**). The results indicated that the nitrogen atom in quinoline is important for improving the enantioselectivity. It was noticed that the catalysts were very stable under our severe reaction conditions and could be recovered in more than 90% yield and reused for the same reaction without any loss in yield or ee. The ^1H NMR spectra and specific rotation of the recovered catalyst proved that it was entirely unchanged after being refluxed for 1 h at 110°C.

Table 2
Reduction of 2-bromoacetophenone and acetophenone using catalysts **1**–**7**

Entry	catalysts[a]	$PhCHOHCH_3$		$PhCHOHCH_2Br$	
		yield(%)[b]	%e.e.(config.)[c]	yield(%)[b]	%e.e.(config.)[c]
1	**1**	95	85 (R)	96	91 (S)
2	**2**	86	61 (R)	99	87 (S)
3	**3**	78	75 (R)	97	81 (S)
4	**4**	92	55 (R)	99	85 (S)
5	**5**	--[d]	--	99	75 (S)
6	**6**	--[d]	--	98	77 (S)
7	**7**	--[d]	--	98	88 (S)

a. 10% mol ratio to ketone.
b. Isolated yield of pure product.
c. Enantiomeric excess was determined by chiralcel OJ ,10% 2-propanol in hexane as eluent.The absolute configuration was determined on base of the sign of the specific rotation.[7a]
d. did not run the reaction.

2.3. Enantioselective reduction of various aromatic ketones using catalyst *1*

We applied the best catalyst **1** to the reduction of various aromatic ketones, and the results are shown in Table 3. For the examined ketones, the catalyst **1** gave moderate to high ees and excellent chemical yields. The results of Tables 2 and 3 show that the reduction of α-haloketones such as α-chloroacetophenone and α-bromoacetophenone could give a higher selectivity (91% for both), which agrees with the results reported by other authors.[5] Moreover, the results also show that α-haloketone **d** was reduced to the corresponding alcohol with (*S*)-configuration, while other ketones (**a**, **b**, **c** and **e**) provided alcohols with (*R*)-configuration. In order to judge if any oxazaborolidines, which were possibly formed by the decomposition of sulfonyl prolinol, catalyzed the reduction, we carried out the following tests: catalysts

Table 3
Asymmetric reduction of aromatic ketones using catalyst **1**[a]

Entry	substrate	yield (%)[b]	e.e (%)	Config.[f]
1	propiophenone **a**	95	65[c]	R[7a]
2	p-bromoacetophenone **b**	98	83[d]	R[7b]
3	2-acetonaphthone **c**	99	85[d]	R[7c]
4	α-chloroacetophenone **d**	98	91[d]	S[7a]
5	methyl 3-benzoylpropionate **e**	89	78[e]	R[7d]

a. 10% mol ratio to ketone. b. Isolated yield of pure product. c. Determined by chiralcel OJ, 5% 2-propanol in hexane as eluent. d. Determined by chiralcel OJ, 10% 2-propanol in hexane as eluent. e. Determined by chiralcel OD, 2% 2-propanol in hexane as eluent. f. The absolute configuration was determined on basis of the sign of the specific rotation .[7a]

1 and **2** were refluxed with $BH_3 \cdot SMe_2$ for 1 h in toluene and then cooled down to room temperature. Acetophenone was added into each catalyst at rt and the reaction mixtures were stirred for 27 h. After work-up reduction products were separated in 88 and 87% yield. Their specific rotations were $[\alpha]_D^{24}$=5.3 (*c* 2.73, $CHCl_3$), ee 4.3% for catalyst **1** and $[\alpha]_D^{24}$=0 (*c* 3.01, $CHCl_3$) for catalyst **2**. Therefore, we do not think there is any oxazaborolidine in this catalytic reduction. It is interesting that the chiral sulfonamide catalysts are active only at high temperatures. A tentative mechanism proposed by Wills et al. for chiral phosphinamide catalysts[5] could be a clue to explaining the stereochemical course, but the details of this catalytic reduction of aromatic ketones need to be explored further.

In conclusion, we have developed a new enantioselective reduction of ketones by borane using a readily available, recoverable sulfonamide. This work has been extended to polymer bound catalysts and will be reported very soon.

3. Experimental

3.1. General procedure for the reduction of aromatic ketones

All reactions were carried out under Ar and anhydrous conditions. Toluene was distilled from calcium hydride. THF was dried over sodium benzophenone ketyl and freshly distilled just before use.

A 10 ml toluene solution of catalyst (0.2 mmol) and $BH_3 \cdot SMe_2$ (2.2 ml, 2.2 mmol) was refluxed for 1 h. Then the aromatic ketone (2 mmol) in toluene (10 ml) was added by syringe pump over a period of 1 h, and the reaction mixture stirred for an additional 5–20 min. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×10 ml). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using light petroleum–EtOAc as the eluent to give the pure alcohol product and the recovered catalyst as a white crystalline solid.

References

1. Singh, V. K. *Synthesis* **1992**, 605.
2. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun*. **1981**, 315–317.

3. (a) Hulst, R.; Heres, H.; Peper, N.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1373–1384. (b) Sibi, M. P.; Cook, G. R. *Tetrahedron Lett*. **1999**, *40*, 2477–2480. (c) Martens, J.; Dauelberg, C.; Behnen, W.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 347–350. (d) Cho, B. T.; Chun, Y. S. *J. Org. Chem*. **1998**, *63*, 5280–5282. (e) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1539–1542.
4. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1987–2012, and references cited therein.
5. (a) Gamble, M. P.; Studley, J. R.; Wills, M. *Tetrahedron Lett*. **1996**, *37*, 2853–2856. (b) Gamble, M. P.; Smith, A. R.; Wills, M. *J. Org. Chem*. **1998**, *63*, 6063–6071, and references cited therein.
6. (a) Brunel, J. M.; Pardigon, O.; Faure, B.; Buono, G. *J. Chem. Soc., Chem. Commun*. **1992**, 287. (b) Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255–2260.
7. (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Chem. Commun*. **1985**, 2039–2044. (b) Mathie, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem*. **1993**, *58*, 2880–2888. (c) Chen, C. P.; Prasad, K.; Repic, O. *Tetrahedron Lett*. **1991**, *32*, 7175–7178. (d) Mukaiyama, T.; Tomimoki, K.; Oriyama, T. *Chem. Lett*. **1985**, 813–816.