Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1843–1846

TETRAHEDRON: *ASYMMETRY*

A practical method for synthesis of terminal 1,2-diols in high enantiomeric excess via oxazaborolidine-catalyzed asymmetric reduction †

Byung Tae Cho * and Yu Sung Chun

Department of Chemistry, Hallym University, Chunchon, Kangwondo 200-702, South Korea

Received 14 April 1999; accepted 6 May 1999

Abstract

Asymmetric borane reduction of α-hydroxy ketones protected with a tetrahydropyranyl (THP) group catalyzed by Corey's CBS reagent using *N*-phenylamine–borane complexes as the hydride source provided the corresponding terminal 1,2-diols with a very high enantiomeric excess.

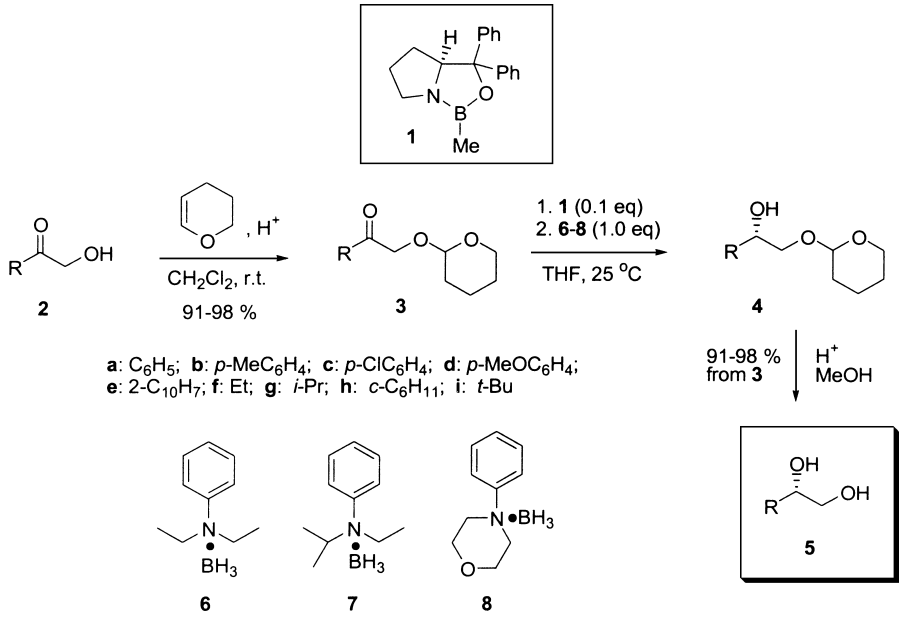
Enantiomerically pure terminal 1,2-diols are important synthetic intermediates.[1] A number of synthetic methods for these compounds have been extensively investigated.[2] Foremost among these methods is the catalytic asymmetric dihydroxylation of olefins.[2a] Another potentially powerful route into optically active 1,2-diols is the asymmetric reduction of α-hydroxy ketones.[3] Very recently we reported oxazaborolidine-catalyzed asymmetric reduction of α-triorganosiloxy ketones using borane–tetrahydrofuran(BH_3–THF) as a reductant to give optically active 1,2-diols.[3a] Although this proves to be a convenient and simple procedure to provide terminal 1,2-diols with enantiomeric excesses (*ee*s) approaching 100%, for most aromatic analogues, this method is not free from certain disadvantages for large scale applications, owing to the low concentration and stability of the BH_3–THF reagent. Also, this method afforded somewhat lower enantioselectivity for unhindered aliphatic analogues compared with those obtained from aromatic analogues. Recently, the wide applicability of amine–borane complexes as reducing agents has been progressively studied, since the amine–borane adducts offer the advantages of being soluble in most common solvents at high concentration and low sensitivity to moisture and air.[4] In fact, highly enantioselective oxazaborolidine-catalyzed borane reduction of prochiral ketones using the *N*,*N*-diethylaniline–borane complex (DEANB) as a reductant has been reported.[4a] In order to develop a practical method useful for the large-scale synthesis of optically active 1,2-diols, we studied the oxazaborolidine-catalyzed asymmetric reduction of protected α-hydroxy ketones **2** using amine–borane complexes as the hydride source.

* Corresponding author. E-mail: btcho@sun.hallym.ac.kr

† Catalytic enantioselective reactions. Part 17.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00184-6

Initially, we selected the tetrahydropyranyl (THP) group as a protecting group for the hydroxy group because of its ease of introduction, the low cost of dihydropyran, its general stability to most nonacidic reagents, and its ease of removal. The tetrahydropyranylation of **2** was carried out by treating **2** with excess 3,4-dihydro-2*H*-pyran (DHP) in the presence of a catalytic amount of *p*-toluenesulfonic acid in dichloromethane at room temperature. We started our study by comparing the asymmetric reduction of 2-(tetrahydro-2*H*-pyran-2-yloxy)-1-phenylethanone **3a** catalyzed by Corey's CBS reagent **1**[5] using commercially available *N*-phenylamine–borane reagents, namely, *N*,*N*-diethylaniline–borane **6**, *N*-ethyl-*N*-isopropyl-aniline–borane **7** and *N*-phenylmorpholine–borane **8**. The reduction was carried out by adding **3a** over 1 h to a solution of 1.0 equiv. of each amine–borane adduct in the presence of 10 mol% of **1** in THF at 25°C (Scheme 1).[6] As shown in Table 1, all the reactions were complete within 10 min to provide 2-(tetrahydro-2*H*-pyran-2-yloxy)-1-phenylethanol **4a** in 91–95% yields, which was easily converted to 1-phenyl-1,2-ethanediol **5a** by the usual work-up procedure in almost quantitative yields. The enantiomeric excess of **5a** determined by HPLC analysis using a chiral column revealed 100% *ee* in all the cases using the amine–borane adducts **6**–**8** (entries 1–3). Encouraged by these results, the same procedure was applied to other aromatic analogues such as **3b**–**e** having *p*-tolyl, *p*-chlorophenyl, *p*-methoxyphenyl and 2-naphthyl groups, respectively. Again, we obtained the corresponding product 1,2-diols with very high enantiomeric excesses (entries 4–12). For aliphatic analogues **3f**–**i** bearing ethyl, isopropyl, cyclohexyl, and *tert*-butyl groups, respectively, we also obtained the product diols with high enantioselectivities, such as 85–88% *ee* for **3f**, 90–91% *ee* for **3g**, 97% *ee* for **3h** and 97% *ee* for **3i** (entries 13–21). Such high enantioselectivities for both aromatic and aliphatic analogues revealed that the present procedure was superior to our previous report[3a] for synthesis of optically active 1,2-diols via oxazaborolidine-catalyzed asymmetric reduction. Among the amine–borane complexes **6**–**8** used, structural effects of the amine on their asymmetric inductions were not observed. We assume that the reduction would be initiated by **1**–BH_3 formed by coordination of oxazaborolidine **1** with free BH_3 liberated from dissociation of the amine–borane reagents,[11] resulting in a catalytic process by **1**,[5] based on a very slow reduction with the borane adducts themselves under the same reaction conditions.



Scheme 1.

Table 1
Asymmetric reduction of **3** with amine–borane complexes **6**–**8**in the presence of 10 mol% of **1**in THF at 25°C[a]

Entry	Compd	Amine-borane	Diol (**5**)			
			Yield (%)[b]	$[\alpha]^{22}_D$	% Ee	Config
1	**3a**	**6**	91	+38.89 (*c* 3.60, EtOH)	99[c] (100)[d]	S[d]
2	**3a**	**7**	95	+38.93 (*c* 3.63, EtOH)	99[c] (100)[d]	S[d]
3	**3a**	**8**	92	+38.88 (*c* 3.58, EtOH)	99[c] (100)[d]	*S*[d]
4	**3b**	**6**	96	+69.14 (*c* 1.14, $CHCl_3$)	99[e] (100)[f]	*S*[f]
5	**3b**	**7**	96	+69.16 (*c* 1.10, $CHCl_3$)	99[e] (100)[f]	*S*[f]
6	**3c**	**6**	94	+58.12 (*c* 1.74, $CHCl_3$)	95[g]	*S*[h]
7	**3c**	**8**	92	+58.06 (*c* 1.73, $CHCl_3$)	94[g]	*S*[h]
8	**3d**	**6**	95	+74.11 (*c* 0.52, $CHCl_3$)	95[c]	*S*[i]
9	**3d**	**8**	96	+74.10 (*c* 0.50, $CHCl_3$)	95[c]	*S*[i]
10	**3e**	**6**	98	+32.62 (*c* 1.32, EtOH)	99[j] (100)[k]	*S*[k]
11	**3e**	**7**	96	+32.63 (*c* 1.31, EtOH)	99[j] (100)[k]	*S*[k]
12	**3e**	**8**	97	+32.61 (*c* 1.35, EtOH)	99[j] (100)[k]	*S*[k]
13	**3f**	**6**	92	-11.20 (*c* 2.45, EtOH)	86[g]	*S*[l]
14	**3f**	**7**	94	-11.15 (*c* 2.15, EtOH)	85[g]	*S*[l]
15	**3f**	**8**	92	-11.35 (*c* 2.25, EtOH)	88[g]	*S*[l]
16	**3g**	**6**	92	+9.43 (*c* 1.11, $CHCl_3$)	91[g]	*S*[m]
17	**3g**	**7**	91	+9.41 (*c* 1.02, $CHCl_3$)	90[g]	*S*[m]
18	**3h**	**6**	93	+4.95 (*c* 1.21, $CHCl_3$)	97[g]	*S*[n]
19	**3h**	**8**	92	+4.97 (*c* 1.16, $CHCl_3$)	97[g]	*S*[n]
20	**3i**	**6**	92	+21.51 (*c* 1.01, $CHCl_3$)	97[g]	*S*[o]
21	**3i**	**7**	95	+21.48 (*c* 0.93, $CHCl_3$)	97[g]	*S*[o]

[a] [**3**] : [amine-borane] = 1 : 1. [**3**] = 0.6 M. The reaction was complete within 10 min to give the monotetrahydropyranylated alcohols **4**. [b] Isolated and purified yield of the product diols **5** obtained by deprotection of **4** with acid-catalyzed hydrolysis. [c] Determined by HPLC analysis using a Daicel Chiralcel OB chiral column; hexane/*i*-PrOH = 9/1. [d] Based on $[\alpha]_D^{23}$ –38.4 (*c* 1.12, EtOH), 99 % ee, *R*: ref. 7. [e] Determined by HPLC analysis using a Daicel Chiralcel OB chiral column; hexane/*i*-PrOH = 9/4. [f] Based on $[\alpha]_D^{23}$ –67.0 (*c* 0.9, $CHCl_3$), >97 % ee, *R*: ref. 8. [g] Determined by GC analysis of its bis-trifluoromethyl acetate using a Chiraldex G-TA column (Astec Inc). [h] Based on $[\alpha]_D^{23}$ –60 (*c* 1.0, $CHCl_3$), 98 % ee, *R*: ref. 8. [i] The absolute configuration is not known, but probably *S*, based on the elution order and the sign of rotation value of the product diol **5d**. [j] Determined by HPLC analysis using a Daicel Chiralcel OD chiral column; hexane/*i*-PrOH = 9/1. [k] Based on $[\alpha]_D^{23}$ –31.2 (*c* 0.997, EtOH), 99.5 % ee, *R*: ref. 7. [l] Based on $[\alpha]_D^{25}$ –12.87 (*c* 2.5, EtOH), *S*: ref. 9. [m] Based on $[\alpha]_D^{20}$ +10.3 (*c* 1.15, $CHCl_3$), *S*: ref. 10. [n] Based on $[\alpha]_D^{23}$ –4.8 (*c* 0.922, $CHCl_3$), 91 % ee, *R*: ref. 7. [o] Based on $[\alpha]_D^{20}$ +14.7 (*c* 0.135, $CHCl_3$), 67 %ee, *R*: ref. 7.

In conclusion, we have developed a practically useful and efficient synthesis of both aliphatic and aromatic terminal 1,2-diols with very high *ee* by the asymmetric reduction of α-hydroxy ketones protected with a THP group catalyzed by Corey's CBS reagent using *N*-phenylamine–borane complexes **6**–**8** as the hydride source. This procedure can be used as an excellent alternative to a facile synthesis of optically active terminal 1,2-diols.

Acknowledgements

This study was financially supported by the Hallym Academy of Sciences, Hallym University (1999) and OCRC/KOSEF.

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