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Enantioselective reduction of α-keto esters to 1,2-diols using the $NaBH_4/Me_3SiCl$ system catalyzed by polymer-supported chiral sulfonamide

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Abstract—In the presence of 25 mol% of a polymer-supported chiral sulfonamide, a variety of α-keto esters can be reduced into the corresponding 1,2-diols in good yields and high enantioselectivities using the $NaBH_4/Me_3SiCl$ reducing system.

1. Introduction

Optically active terminal 1,2-diols are versatile and important chiral building blocks in organic synthesis[1] and have found numerous applications as chiral auxiliaries or ligands for asymmetric synthesis.[2] Many methods aimed at the enantioselective synthesis of these compounds have been reported, such as the asymmetric dihydroxylation of olefins,[3] reduction of α-hydroxy ketones protected as their silylethers in a CBS system,[4] and many biological transformations.[5] However some of these cases suffer from inherent drawbacks: For example, dihydroxylation involves the use of toxic OsO_4,[3] while the CBS-oxazaborolidine-catalyzed borane reduction of protected α-hydroxy ketones needs two extra steps of protection and deprotection.[4] Thus, the development of an efficient, economical and environmentally friendly methodology for the synthesis of optically active 1,2-diols is still required. In the past decade, several groups have reported the preparation and application of polymer-supported catalysts derived from chiral amino alcohols for enantioselective reduction.[6] Recently, we have developed a new class of polymer-supported sulfonamides and applied them to the enantioselective reduction of prochiral ketones via $BH_3{\cdot}SMe_2$[7] or $NaBH_4/Me_3SiCl$ (or $BF_3{\cdot}OEt_2$).[8] In these studies we found that the reducing systems of $NaBH_4/Me_3SiCl$ and $NaBH_4/BF_3{\cdot}OEt_2$ could provide an efficient, economical and environmentally friendly methodology for the synthesis of optically active secondary alcohols. Herein, we report the enantioselective synthesis of optically active 1,2-diols by the polymer-supported sulfonamide catalyzed asymmetric reduction of α-keto esters.

2. Results and discussion

As shown in our previous papers, the enantioselective reduction of prochiral ketones and β-keto sulfones with $NaBH_4/Me_3SiCl$ can be achieved with optimal results when the reactions were carried out in refluxing THF with 25 mol% polymer-supported sulfonamide **1** (200–400 mesh, 2% DVB, 2.29 mmol/g N) as the catalyst.[9] Under these same reaction conditions, we first examined the effect of the amount of the reducing system on the reduction of phenyl-glyoxylic acid ethyl ester using 25 mol% of catalyst **1**. In this study, when using an amount of $NaBH_4/Me_3SiCl$ less than 3 equiv to the substrate, the reaction would not go to completion. Surprisingly, under our experimental conditions we obtained the product 1-phenyl-ethane-1,2-diol instead of the desired α-hydroxy ester. The amount of the reducing agent used had no influence on the enantioselectivity (Table 1).

To extend this synthetic procedure to the preparation of 1,2-diols, we investigated further the reaction of a variety of α-keto esters (Table 2). The reductions afforded the corresponding 1,2-diols in good to excellent chemical yields. It is noteworthy that aromatic α-keto esters were reduced with excellent enantioselectivities (94–98%

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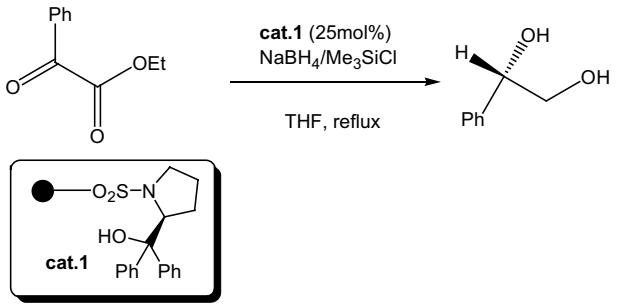
Table 1. The effect of the amount of the reducing agent on the asymmetric reaction[a]



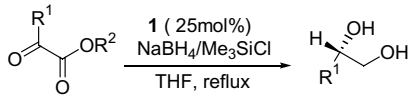
Entry	$NaBH_4/Me_3SiCl$ (mmol)	Yield (%)[b]	Ee (%)[c]
1	1.2/1.2	20	96
2	2.0/2.0	56	96
3	3.0/3.0	83	96
4	3.5/3.5	82	96

[a] The substrate was reduced on the 1 mmol scale; molar ratio: α-keto ester/$NaBH_4/Me_3SiCl$/cat. = 1/1.2–3.5/1.2–3.5/0.25.
[b] Isolated yield after column purification.
[c] Determined by chiral HPLC with a Chiralcel OB column.

ee). To gain insight into the effect of the electron density of the aromatic ring, a series of α-keto esters bearing a different substituents at the *para* position on the phenyl group was studied. The results show that the electron density of the aromatic rings has little effect on the enantioselectivity (Table 2, entries 6–10). Interestingly, the ester groups R^2 have little effect on the enantioselectivity. Although the yields decreased, different substrate **2a–d** having R^2 ranging from methyl to *tert*-butyl all reacted smoothly to give the same diol with the ee over 95% (Table 2, entries 1–4). The reduction of 4-tolyl-glyoxylic acid ester **2j** and 3-tolyl-glyoxylic acid ester **2k** provided the corresponding diols in 95% and 93% ee, respectively, in contrast to 75% ee for 2-tolyl-glyoxylic acid ester **2l** (Table 2, entries 10–12). These results indicate that the asymmetric induction was sensitive to the steric effects of the substituent proximal to carbonyl group. This is a common phenomenon in oxazaborolidine-catalyzed reductions.[4] In the case of aliphatic analogues, the asymmetric reduction of the α-keto esters **2m–p** afforded somewhat lower enantioselectivities compared with those obtained from aromatic analogues (Table 2, entries 13–16). Notably higher enantioselectivities were obtained when the reaction occurred at the more hindered carbonyl group (Table 2, entry 13). In the same reduction system, α-keto acid **2e** was also reduced to give diol **4** in 78% yield, but the enantioselectivity proved unsatisfactory, being only 15% ee (Table 2, entry 5).

Under the above optimal reaction conditions, homogeneous sulfonamide **15** promoted the reduction of phenyl-glyoxylic acid ethyl ester to give 84.4% ee—less than the polymer-supported sulfonamide **1** (Table 2, entry 1), Scheme 1.

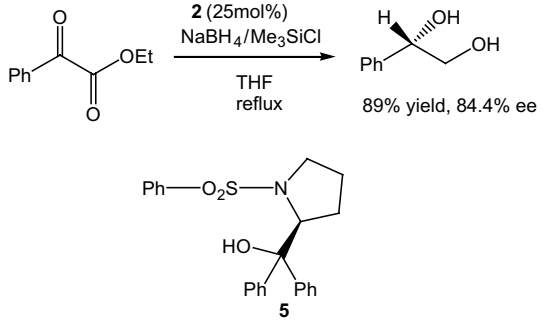
Table 2. Asymmetric reduction of α-keto esters or acid[a]



2a-p **3-14**

Entry	R^1	R^2	α-Keto esters	Diols	Yield (%)[b]	Ee (%)[c]	Config.[f]
1	Ph	Et	**2a**	**3**	83	96	*S*
2	Ph	Me	**2b**	**3**	87	95	*S*
3	Ph	*i*-Pr	**2c**	**3**	74	97	*S*
4	Ph	*t*-Bu	**2d**	**3**	53	95	*S*
5	Ph	OH	**2e**	**3**	78	15	*S*
6	*p*-F–C_6H_4	Et	**2f**	**4**	94	97	*S*
7	*p*-Cl–C_6H_4	Et	**2g**	**5**	67	98	*S*
8	*p*-Br–C_6H_4	Et	**2h**	**6**	62	94	*S*
9	*p*-MeO–C_6H_4	Et	**2i**	**7**	67	95	*S*
10	*p*-Me–C_6H_4	Et	**2j**	**8**	75	95	*S*
11	*m*-Me–C_6H_4	Et	**2k**	**9**	71	93	—[g]
12	*o*-Me–C_6H_4	Et	**2l**	**10**	76	75	*S*
13	*t*-Bu	Et	**2m**	**11**	88	94[d]	*S*
14	$PhCH_2CH_2$	Et	**2n**	**12**	86	62[d]	*S*
15	*n*-Bu	Et	**2o**	**13**	71	45[d]	*S*
16	*n*-Bu	*i*-Pr	**2p**	**13**	46	42	*S*
17	*n*-Bu	*t*-Bu	**2q**	**13**	40	23	*S*
18	*c*-Hex	Et	**2r**	**14**	60	86[e]	*S*

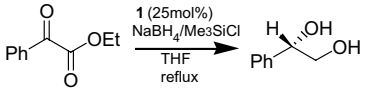
[a] Experiments were performed on a 1 mmol scale; molar ratio: α-keto esters/$NaBH_4/Me_3SiCl$/cat. = 1/3/3/0.25.
[b] Isolated yield after column purification.
[c] Determined by chiral HPLC.
[d] Analytical samples were converted to phenylcarbamates.
[e] Determined by comparison of specific rotations, $[\alpha]_D^{20} = +4.45$ (*c* 1.068, $CHCl_3$)/$[\alpha]_D^{20}$ (lit.[4]) = +4.9 (*c* 1.05, $CHCl_3$, 96% ee).
[f] The absolute configurations were determined by comparison with reported specific rotations.
[g] The absolute configuration was not determined.



Scheme 1.

It is noteworthy that after the reduction was complete, the polymer-supported sulfonamide **1** could be recovered by simple filtration followed by washings with water and ethyl acetate. Recycling of the chiral polymer catalyst was tested by the reduction of phenyl-glyoxylic acid ethyl ester (Table 3). The results showed that the chiral polymeric catalyst could be reused at least five times with little or no loss of performance.

Table 3. The recycling of polymeric catalyst



Run	Yield (%)[a]	Ee (%)[b]
1	77	95.1
2	77	94.4
3	74	95.2
4	76	94.6
5	73	95.2

[a] Isolated yield after column purification.
[b] Determined by chiral HPLC.

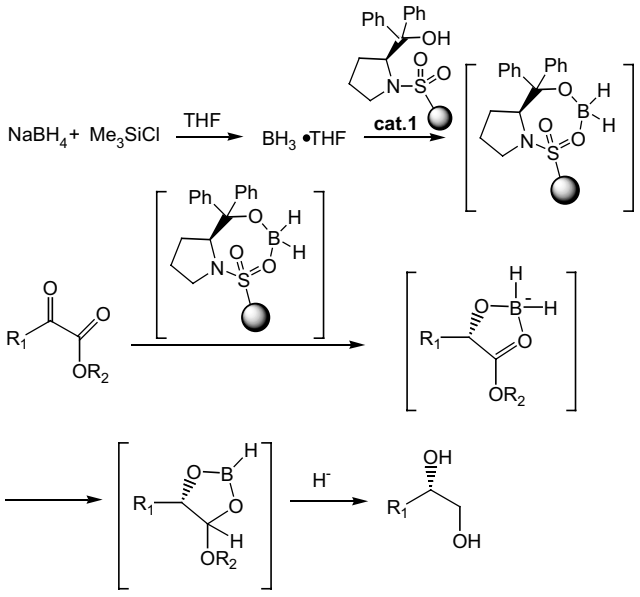
Although the reaction mechanism is not exactly clear, a possible mechanism for the reduction of α-keto esters was proposed according to the reduction of α-hydroxy esters with borane-dimethyl sulfide and catalytic sodium tetrahydroborate (Scheme 2).[10]

3. Conclusion

In conclusion, the results reported here offer a practical and highly enantioselective methodology for the synthesis of optically active 1,2-diols. Due to the efficiency, low cost and high enantioselectivity observed, this method represents a very useful alternative to previously reported procedures.

4. Experimental

All reactions were carried out under a dry Ar atmosphere. THF was freshly distilled over sodium/benzophenone ketyl before use. α-Keto esters were prepared according to the reported procedure.



Scheme 2.

4.1. Typical procedure for the asymmetric reduction of α-keto esters

Me_3SiCl (0.42 mL, 3.2 mmol) was added to a suspension of $NaBH_4$ (121 mg, 3.2 mmol) in THF (10 mL). The suspension was heated under reflux and stirred for 1 h. The polymeric catalyst **1** (106 mg, 0.25 mmol) was then added and the reaction mixture heated under reflux for another 0.5 h. Then a THF (10 mL) solution of phenyl-glyoxylic acid ethyl ester (158 mg, 1 mmol) was added at a rate of 3 mL/h by syringe pump. After the addition was complete, the mixture was treated with water (10 mL) and filtered. The polymeric catalyst was washed several times with EtOAc and water. The resulting aqueous solution was extracted with EtOAc (3 × 15 mL) and dried over Na_2SO_4. The solution was evaporated and purified by silica gel chromatography (eluent: $V_{Hexane}/V_{EtOAc} = 1/1$) to give a white solid (128 mg, 83% yield): ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (1H, s), 2.93 (1H, s), 3.64–3.75 (2H, m), 4.81 (1H, dd, $J = 2.8$ and 7.8 Hz), 7.26–7.36 (5H, m); IR: 3235 cm^{-1} (br, 2OH). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.53; H, 7.34. $[\alpha]_D^{20} = +69.5$ (c 1.025, $CHCl_3$) {lit.[9] $[\alpha]_D^{20} = +71.9$ (c 1.04, $CHCl_3$)}. The enantiomeric excess was determined to be 96% by Chiralcel OB column chromatography (eluent: $V_{Hexane}/V_{i\text{-}PrOH} = 9/1$).

Acknowledgements

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