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HIGHLY STEREOSELECTIVE REDUCTION OF α -KETO ESTERS: UTILITY OF CIS-1-ARYLSULFONAMIDO-2-INDANOLS AS CHIRAL AUXILIARIES

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Summary.

The reduction of α -keto esters bearing cis-1-arylsulfonamido-2-indanol derivatives proceeded with high diastereoselectivities providing the corresponding α -hydroxy esters in excellent yields. The chiral auxiliary group is removed under mild basic conditions and recovered.

The synthesis of optically active (α -hydroxy acids has attracted much attention in recent years because of their importance as chiral building blocks in the synthesis of biologically active natural products.¹ Consequently, a number of useful synthetic methods have been developed over the past several years.² In continuation of our studies directed towards the design and synthesis of molecular probes for biological systems, the synthesis of either enantiomer of the α -hydroxy acid in optically active form became of interest to us. Among various known synthetic methodologies, the diastereoselective reduction of α -keto esters bearing appropriate chiral auxiliaries appears to be straightforward and convenient for our purposes.³ However, the major limitations using this approach have been the low optical yield associated with this reduction process as well as the lack of availability of the effective chiral auxiliaries. Encouraged by our previous applications of cis-1-amino-2-indanol derivatives in the asymmetric aldol reactions,⁴ we have examined the further possibilities of the cis-1-amino-2-indanol derived chiral auxiliaries for asymmetric reduction of α -keto esters. Herein, we report the utility of cis-1-arylsulfonamido-2-indanols⁵ as effective chiral auxiliaries for the asymmetric reduction of α -keto esters with excellent diastereoselectivity and isolated yields. The chiral auxiliaries are easily accessible from commercially available optically active cis-1-amino-2-indanols. The optically active α -hydroxy acids are conveniently obtained after removal of the chiral auxiliary under mild saponification conditions and the chiral auxiliary is recovered quantitatively.

Although, both enantiomers of *cis*-1-amino-2-hydroxyindan are available commercially,⁶ the 1S, 2R-*cis*-aminoindan-2-ol **1** has been utilized as a representative. As shown in Scheme I, reaction of **1** with arylsulfonyl chloride (1 equiv.) and triethylamine (3 equiv.) in CH₂Cl₂ in the presence of a catalytic amount of DMAP at 23°C for 12 h, provided the chiral sulfonamide derivatives **2** (85–92 % yield).⁷ The acylation of hydroxy sulfonamide **2** with the corresponding α -keto acid using 1,3-dicyclohexylcarbodiimide (1.5 equiv.) and DMAP (2 equiv.) in CH₂Cl₂ at 23°C for 12 h, afforded the corresponding α -keto esters **3a-c** in good yield (75–80%) after silica gel chromatography.⁸

Reduction of α -keto esters **3a-c** with a number of metal hydrides was then examined and the results are shown in Table I. As evidenced, reduction of keto ester **3a** with sodium borohydride at 0°C in ethanol proceeded with only moderate diastereoselectivity. However, reduction of **3a-c** with lithium tri-*sec*-butylborohydride (L-Selectride) at -78°C or with bulky lithium tris[(3-ethyl-3-pentyl)oxy]aluminumhydride at 0°C in tetrahydrofuran (THF) resulted in excellent stereoselectivities. The diastereomeric mixture ratio was determined by ¹H NMR (400 MHz) as well as by HPLC analysis of the reduction product prior to chromatography. When the reduction of α -keto esters **3a-b** was carried out with 1 equiv. of L-Selectride and 1 equiv. of ZnCl₂ (Aldrich, 1 M solution in diethyl ether) at -78°C, almost complete diastereofacial selectivity (>99% de by HPLC; 400 MHz ¹H NMR revealed only one diastereomer) was observed. Similarly, reduction of **3c** (entry 12) with L-Selectride in the presence of ZnCl₂ provided high degree of diastereoselectivity (98 : 2). Addition of ZnCl₂ has virtually no effect on the reduction of **3b** with lithium tris[(3-ethyl-3-pentyl)oxy]aluminumhydride at 0°C. Also, L-Selectride reduction in the presence of other Lewis acids such as MgBr₂, Ti(O^{*i*}Pr)₄ or metal salt such as LiBr has no significant effect on the diastereoselectivity. Interestingly, reversal of the stereoselection was observed with L-Selectride reduction in the presence of 1.5 equivalents of HMPA as well as K-Selectride reduction in the presence of 1 equivalent of 18-crown-6.

The absolute configurations of the new asymmetric centers of **4** and **5** were assigned after removal of the chiral sulfonamides and comparison of the optical rotations of the resulting α -hydroxy acids with literature values.⁹ For example, treatment of α -hydroxyester obtained in entry 4 with aqueous lithium hydroxide in THF at 23°C for 2h afforded the optically pure R-mandelic acid ($\alpha_D^{23^\circ}$ -156°, c, 0.23, H₂O). The enantiomeric excess of this asymmetric reduction was determined (>99 % by ¹⁹F NMR) by formation of the Mosher ester¹⁰ of the corresponding methyl ester.¹¹

The high degree of stereoselection associated with this asymmetric reduction may be attributed to the chelation of carbonyl oxygens with a metal ion. In the α -keto esters **3a**, reduction by L-Selectride most likely proceeds through the *s*-cis conformation **A** because of the metal chelation as shown (Fig. I). The presence of the vicinal toluenesulfonamide blocks the approach of the hydride from the *Re*-face and therefore, *Si*-face hydride attack leads to the preferential formation of **4**. Consistent with this rationale, a more sterically demanding 1-naphthalenesulfonamide bearing chiral auxiliary **3b**, has exhibited a even higher degree of stereoselection. Similarly, the presence of ZnCl₂ is likely to promote strong metal chelation between the carbonyl oxygens, resulting in the formation of nearly single isomer **4**. On the other hand, when the reduction was carried out with L-Selectride in the presence of HMPA or with K-Selectride in the presence of 18-crown-6, the corresponding metal ions are sequestered. As a consequence, the reduction proceeded through the preferred *s*-trans conformation **B**, resulting in the reversal of stereoselection. Such reversal of stereochemistry has been previously observed.¹²

In summary, 1*S*, 2*R* and 1*R*, 2*S*-cis-1-arylsulfonamido-2-indanols readily prepared from commercially available optically active cis-1-amino-2-indanols, have been found to be highly effective chiral auxiliaries for the asymmetric reduction of α -keto esters with excellent stereoselectivity. The chiral auxiliaries were removed under mild conditions and recovered

fully. Thus, depending upon the choice of chiral auxiliary, the reducing agent and additives, either enantiomer of the α -hydroxy acids can be obtained in high enantiomeric excess and excellent isolated yield. Further applications of these new chiral auxiliaries in asymmetric synthesis are in progress.

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Figure I.
Stereo chemical model

Scheme I.
Synthesis of hydroxy acid

Table I. Reduction of α -keto esters

Entry	Esters	Reductant	Temp (time)	Yields ^a	Ratio(4/5) ^b
1.	3a	NaBH ₄ (EtOH)	0°C (15 min)	90%	62:38
2.	3a	L-Selectride	−78°C (15 min)	96%	85:15
3.	3a	LiAl(OCEt ₃) ₃ H	0°C (1 h)	94%	95:5
4.	3a	L-Selectride/ZnCl ₂	−78°C (15 min)	96%	>99:1
5.	3a	L-Selectride/LiBr	−78°C (15 min)	95%	88:12
6.	3a	K-Selectride/18-crown-6	−78°C (15 min)	96%	5:95
7.	3b	L-Selectride	−78°C (15 min)	94%	94:6
8.	3b	LiAl(OCEt ₃) ₃ H	0°C (1 h)	95%	97:3
9.	3b	L-Selectride/ZnCl ₂	−78°C (15 min)	96%	>99:1
10.	3b	L-Selectride/HMPA	−78°C (15 min)	96%	20:80
11.	3c	L-Selectride	−78°C (15 min)	93%	94:6
12.	3c	L-Selectride/ZnCl ₂	−78°C (15 min)	90%	98:2

^aYield of pure products after silica gel chromatography^bDetermined by HPLC and 400 MHz ¹H NMR spectroscopy