Bidentate chelation-controlled asymmetric synthesis of α-hydroxy esters based on the glycolate enolate alkylation

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Abstract

(*S*)-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](4-methoxyphenyl)methanol (**4b**) has been synthesized and evaluated as a chiral auxiliary for the asymmetric synthesis of α-hydroxy esters based on bidentate chelation-controlled alkylation of glycolate enolate. © 2000 Elsevier Science Ltd. All rights reserved.

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The widespread use of α-hydroxy esters and their derivatives as chiral synthons in organic synthesis[1,2] has grown collaterally with advances in methodology for their asymmetric synthesis.[3] One of the most important strategies for their synthesis is the ester enolate alkylation of chiral glycolate including both forms of cyclic[4–6] and acyclic structures.[7–10] As far as acyclic chiral glycolate is concerned, the following two features are notable from the previous methods: (1) most of the chiral auxiliaries are attached to the carboxyl group rather than to the hydroxyl group in glycolic acid unit;[7] (2) all of their enolates form cyclic structures by monodentate chelation of the oxygen on α-carbon of glycolate to metal. Herein, we describe the highly stereoselective method for α-hydroxy esters featuring bidentate chelation-controlled asymmetric alkylation of chiral glycolate, in which the chiral auxiliary is attached to the hydroxyl group as ether linkage, as outlined in Scheme 1.
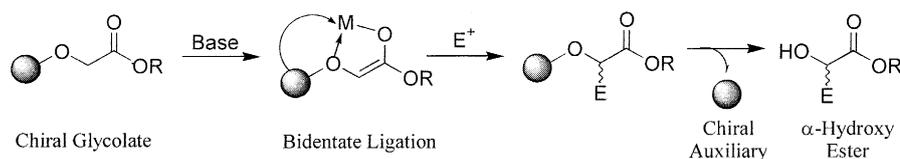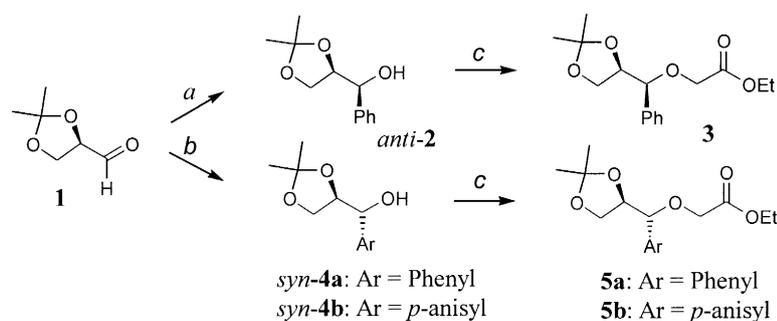

Scheme 1.

However, in consideration of conformational flexibility of ether linkage, acceptable levels of diastereoselection are less likely to be achieved by the previous monodentate chelation-controlled method.

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Thus, it is necessary to construct chiral auxiliary with a molecular architecture that restricts rotation and shields one of the π-faces of enolates. As our initial attempt, the chiral auxiliaries, such as **2** and **4a**, with additional ligation sites were designed for the construction of highly organized polycyclic ring complexes during the glycolate enolate formation. As shown in Scheme 2, the chiral glycolates **3**, **5a** and **5b** were prepared simply, but stereoselectively, by treatment of (R)-2,3-O-isopropylideneglyceraldehyde (**1**)[11] with $Ph_3ZnMgBr_2Mg(Cl)Br)$[12] or organocopper reagent,[13] followed by O-alkylation with ethyl bromoacetate in good yields. Because both (R)- and (S)-form of **1** are readily available,[14] the corresponding enantiomers can be prepared by the same way.

Scheme 2. (a) $Ph_3ZnMgBr_2Mg(Cl)Br$ (b) ArMgBr/THF, CuI, DMS; recrystallization (c) NaH/DME; $BrCH_2CO_2Et$

With both diastereomers **3** and **5a** in hand, our special attention was drawn to the level of stereoselectivity of this glycolate enolate alkylation. Deprotonation of **3** and **5a** was accomplished with LDA in THF at −78°C. Methylation of **3** via its corresponding enolate with CH_3I at −78°C for 2 h furnished a 3:1 mixture of **6** and **7** in 36% yield. However, a dramatic changeover in diastereoselectivity was observed during the alkylation of **5a**. The selectivity ratio up to 45 was accomplished.
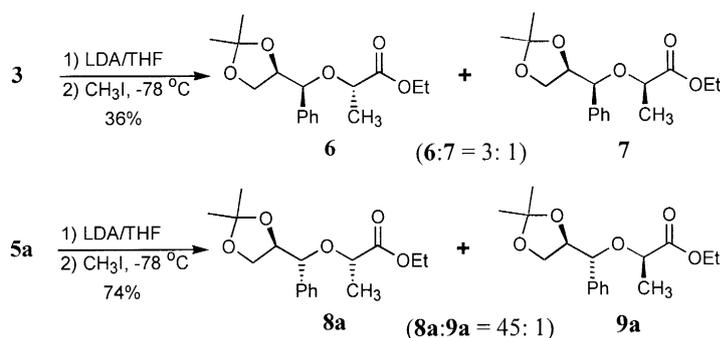

Scheme 3.

Encouraged with this result, we then set about optimizing the efficiency of this alkylation process. A minor structural tuning for syn-**4a** was made at first, then syn-**4b** with $[\alpha]_D^{22}$ −37.2 (c 0.4, $CHCl_3$) was finally selected as a chiral auxiliary due to its enhanced crystallizability (mp 46–47°C, recrystallized from hexane–EtOAc) and the fact that it could be more easily removed from the chiral glycolate after reaction. To examine the efficiency of syn-**4b** as a chiral auxiliary in this reaction, the chiral glycolate **5b** was prepared and subjected to alkylation. The following procedure is representative. Compound **5b** (324 mg, 1 mmol) in THF (3 ml) was added in a dropwise manner to a solution of LiHMDS (1.8 mmol) in THF (7 ml) at −78°C. After 10 min, benzyl bromide (10 mmol) was added, and the solution was stirred for an additional 20 min. The reaction was quenched by addition of water, then warmed to room temperature. Conventional work-up followed by column chromatography (SiO_2, 8% ethyl acetate in hexane) afforded

281 mg (77%) of a diastereomeric mixture of **8b** and **9b** with $[\alpha]_D^{26}$ −79.1 (*c* 0.23, EtOH) as an oil. In comparison with authentic samples, the diastereomeric ratio of **8b** to **9b** in the crude product was found to be exceeding 300 by capillary GLC analysis (OV-1). As shown in Table 1, the preferential formation of **8b** over **9b** was observed in all cases, and the ratio is seen to be highly dependent on solvent as well as R groups. THF is the optimal solvent for this reaction. Low chemical yields and diastereoselectivities in toluene or ether seemed to be associated with the aggregation of lithium enolate. The bulkier and the more reactive R group becomes, the higher is the selectivity attained in the alkylation (entries 6 and 10). This result is correlated with the observation that prolonged reaction time and use of stronger base (entries 3 and 6) resulted in lowering the selectivity, presumably due to racemization.

Table 1
Diastereoselective alkylation of **5b** and deprotection to **10**
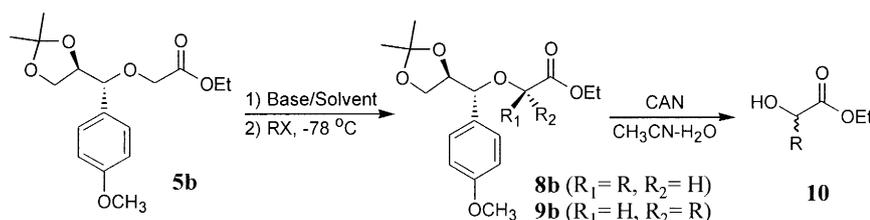
| Entry	Solvent	Base	Additive	RX	Alkylated Product[a]		10	
					% yield	8b : 9b	% yield	R/S
1	Ether	LDA	None	MeI	38	2 : 1	-	-
2	Toluene	LDA	None	MeI	15	2 : 1	-	-
3	THF	LDA	None	MeI	74	53 : 1	-	-
4	DME	LDA	None	MeI	64	26 : 1	-	-
5	THF	LDA	HMPA	MeI	68	8 : 1	-	-
6	THF	LiHMDS	None	MeI	86	100 : 1	71	S
7	THF	LiHMDS	None	EtI	25(83)[b]	130 : 1	73	S
8	THF	LiHMDS	None	EtOTf	85	16 : 1	-	-
9	THF	LiHMDS	None	Allyl Br	36	180 : 1	77	S
10	THF	LiHMDS	None	BnBr	77	>300 : 1	85	S

[a] The diastereomeric ratios of the products were determined by capillary GC analysis.

[b] An yield in parenthesis is a conversion yield.

The preferential formation of **8b** over **9b** and the unprecedented high level of stereoselection associated with this asymmetric alkylation may be rationalized by considering the following plausible transition state model of highly organized enolate complex, resulted from bidentate chelation of the internal two oxygens with lithium ion. In this model, the cyclic ring containing enolate is puckered to upside minimizing the steric interaction with aromatic ring nearby. This transition state model also explains why the relative configuration of chiral auxiliary is critical to stereoselection and chiral glycolate **3** derived from *anti*-**2** does not work well, as evidenced in Scheme 3. As shown in Table 1, any external polar ligands such as HMPA and EtOTf (entries 5 and 8) could destroy the chelation complex, resulting in lowering the stereoselectivies.

The absolute configurations of newly created chiral center on **8b** were assigned after removal of the chiral auxiliary with CAN and comparison of the optical rotations of the resulting α-hydroxy esters with literature values.[5,15] For example, treatment of the benzylated products (0.11 mmol) in entry 10, with ceric ammonium nitrate (0.18 mmol) in 10% aqueous CH_3CN (1 ml) at room temperature for 30 min afforded (*S*)-(−)-ethyl 2-hydroxy-4-phenylpropionate with $[\alpha]_D^{21}$ −25.1(*c* 1.0, benzene) in 85%

yield. This hydroxy ester was subjected to HPLC analysis using chiral column (Chiracel OD, hexane/2-propanol), and found to be enantiomerically pure.
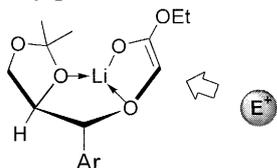
In conclusion, the asymmetric synthesis of α-hydroxy esters using **4b** has been successfully carried out, and the following features are notable: (1) we have developed a new chiral auxiliary entirely different from the previously reported; (2) the unprecedented high stereoselectivity over 300 is obtained; (3) from a mechanistic point of view, this is a first example of the bidentate chelation-controlled alkylation of chiral glycolate, in which the chiral auxiliary played the dual role as a chiral inducer as well as a protecting group; (4) during the removal of the chiral auxiliary with CAN, **4b** was oxidized to the corresponding ketone, however, which upon treatment with L-selectride,[16] can be readily recovered for reuse. In addition, the convenience for its preparation and mild condition for its removal from the glycolate without racemization make this method an attractive route to optically active α-hydroxy esters. Further applications using this chiral auxiliary are currently underway.

Acknowledgements

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