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Diastereofacial selectivity in aldol-type condensation induced by optically pure α-sulfinyl acetate with α-substituted aldehydes

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This Letter is dedicated with respect to the late Dr. Charles Mioskowski

Abstract

Highly diastereoselective aldol-type condensations induced by the chiral magnesium enolate of *tert*-butyl *p*-tolyl sulfinyl acetate were performed with optically pure alkyl or hydroxy α-substituted aldehydes. The addition of chiral α-sulfinyl acetate to various aldehydes, α-substituted or not, results mainly with a *syn* stereochemistry of the two newly created stereocenters. Applications were investigated for the synthesis of *syn* and *trans* 1,2-diol models and polysubstituted precursor for natural products.

Keywords: Asymmetric aldolization; Chiral sulfinyl acetate; 1,2-Diol; β-Hydroxyester analogs

The control of the stereochemistry in the synthesis of complex natural products and their analogs requires various methodologies. In particular, much efforts have been devoted to the prevalent chiral enolate chemistry for the stereoselective construction of asymmetric centers in aldol condensation.[1] To this end, the use of chiral auxiliaries in asymmetric acetate aldol addition remains one of the most common and convenient strategy in organic synthesis. This procedure is widely developed in the literature to obtain with high diastereoselectivity, β-hydroxy acid derivatives which are chiral building blocks for the elaboration of bioactive compounds.[2]

For our part, we have been using for the last few years the chiral α-sulfinyl acetate in asymmetric aldol-type condensations[3] as shown in Figure 1.

The well known optically active sulfoxide derivatives[4] were first studied by Gilman, and then successively developed by Andersen and Solladié. They are prepared from diastereomerically pure (−)-(*S*) or (+)-(*R*) menthyl *p*-tolyl sulfinate **1** by treatment with a Grignard or other organometallic reagents.[5] In this way, the two enantiomers of *t*-butyl *p*-tolyl sulfinyl acetate **2** (Scheme 1) were obtained

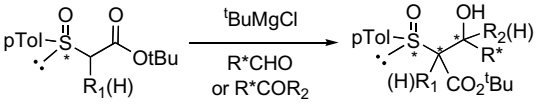
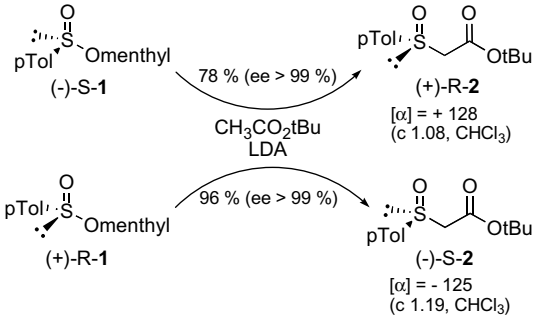


Fig. 1. General diastereoselective aldol-type reaction directed by optically pure α-sulfinyl ester.



Scheme 1. Synthesis of the enantiomers of *tert*-butyl *p*-tolyl sulfinyl acetate **2**.

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in high yield from the appropriate menthyl sulfinate ester (−)-*S* **1** or (+)-*R* **1** and the lithium anion of *tert*-butyl acetate.

Subsequently, as shown in Figure 1, an aldehyde can be added now to the magnesium enolate of the α-sulfinyl acetate **2**, generating two new centers at C1 and C2 whose stereochemistry is governed by the chirality of the α-sulfinyl ester **2**. Such concept of asymmetric aldolization induced by optically pure sulfinyl ester was pioneered 30 years ago by Solladié and Mioskowski[5f,6] and then has been used successfully in many applications in which an enantiomerically pure β-hydroxyester was needed.[7] Since then, a number of examples have been reported involving the use of chiral α-sulfinyl acetamides,[8] dihydrooxazoles,[9] hydrazones[10] or cyclic sulfinamides.[11] But in all these cases, the sulfoxide products were directly subjected to desulfurization resulting in β-hydroxycarbonyl derivatives (or β-aminoacid, when the sulfinyl ester **2** was added to an imine function[12]) with no consideration for the absolute configuration assignment at C1.

Recently, we have clearly assigned by X-ray analysis the absolute stereochemistry of the β-hydroxyester **3** (Fig. 2) which was obtained by direct aldol condensation from the magnesium enolate of the sulfinylester (−)-*S* **2** and achiral 3-benzyloxypropanal.[3]

Thus, these earlier results revealed a *syn* aldol relationship between the two newly created centers C1 and C2 as shown in molecule **3** (mp = 108 °C; $[\alpha]_D$ −199 (*c* 0.85, $CHCl_3$)) with a coupling constant of 5.5 Hz between H-1 and H-2.[13] We have also noticed an unexpected substituent effect when α,β-unsaturated aldehyde was used which necessarily involves a different transition state as previously postulated[5e] (Fig. 3). On this basis we needed to explore the effect of α-substituted chiral aldehyde in the view to observe if in this case, the aldolization is matching either with achiral or α,β-unsaturated aldehyde situation.

In this Letter, we will examine a new series of condensations using various α-substituted (alkyl or hydroxyl) aldehydes. To our knowledge, no examples of α-substituted aldehydes in aldol condensation with optically pure sulfinyl ester were described so far. We first achieved in good yield (65%) the condensation of (−)-*R* **2** and 3-benzyloxypropanal to isolate by simple crystallization product **4** (mp = 108 °C; $[\alpha]_D$ +195 (*c* 1, $CHCl_3$)), which is the enantiomer of **3**. The structure as well as the *syn* stereochemistry of **4** were assigned by ^{1}H NMR analysis (J = 5.48 Hz between H-1 and H-2). That means a real transfer of chirality from the optically pure sulfinyl acetate to the prochiral α-unsubstituted aldehyde with high π-diastereofacial selectivity as shown in Figure 3.

Interested in the synthesis of natural products, we have selected compound **10** as a suitable fragment (Scheme 2). We envisaged our application in aldol condensation of the chiral sulfinylester (−)-*S* **2** with the readily available aldehyde **9** having an α-methyl group.

Aldehyde **9** was obtained by baker's yeast microbial reduction of ethyl acetylacetate to produce the (*S*)-ethyl β-hydroxy butanoate **5** in high enantiomerical purity.[14] Then α-alkylation with LDA/MeI, according to the Frater–Seebach protocol[15] led to the *anti* compound **6** in 63% yield. A sequential silylation–reduction of the ethyl (+)-(2*S*,3*S*) 3-hydroxy-2-methylbutyrate **6** followed by a Swern oxidation[16] furnished the desired aldehyde **9** (69% yield for three steps). Subjection to an aldol condensation with the chiral sulfinylester (−)-*S* **2** provided the expected sulfoxide **10** as the sole isomer according to the ^{1}H NMR analysis of the crude material. Sulfoxide **10** was isolated by column chromatography from the unreacted sulfinyl ester, as an oily compound (68% yield, $[\alpha]_D$ −130 (*c* 0.82, $CHCl_3$)). Its absolute stereochemistry was elucidated by NMR analysis. A coupling constant of 3 Hz is consistent with a *syn* stereochemistry between H-1 and H-2 in comparison with the value of 5.48 Hz for the known *syn* correlation in **3** and **4**. Moreover, an *anti* stereochemistry was clearly established (NOESY) between H-2 and H-3. Consequently, on the basis of ^{1}H NMR spectral data we assigned the configuration (S_S,1*R*,2*S*,3*R*,4*S*) to sulfoxide **10**.

Then, we extended this aldol-type condensation to α-hydroxy substituted aldehydes leading to the synthesis

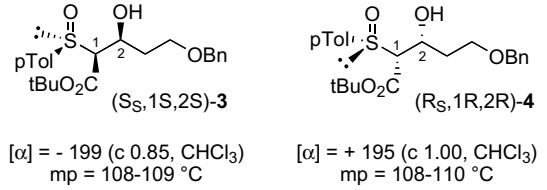


Fig. 2. Configuration of **3** and **4** obtained by aldolization reaction.

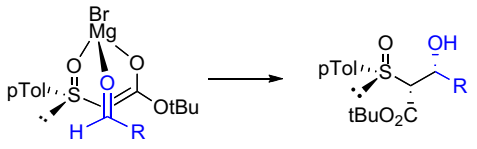
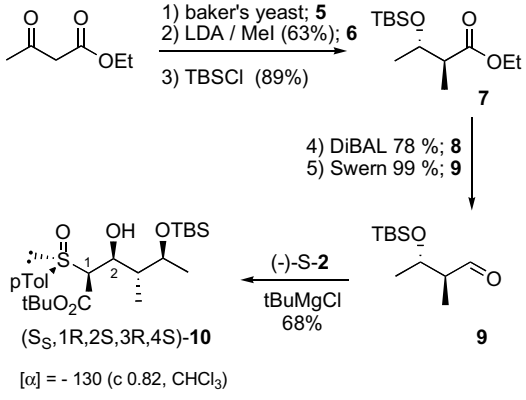
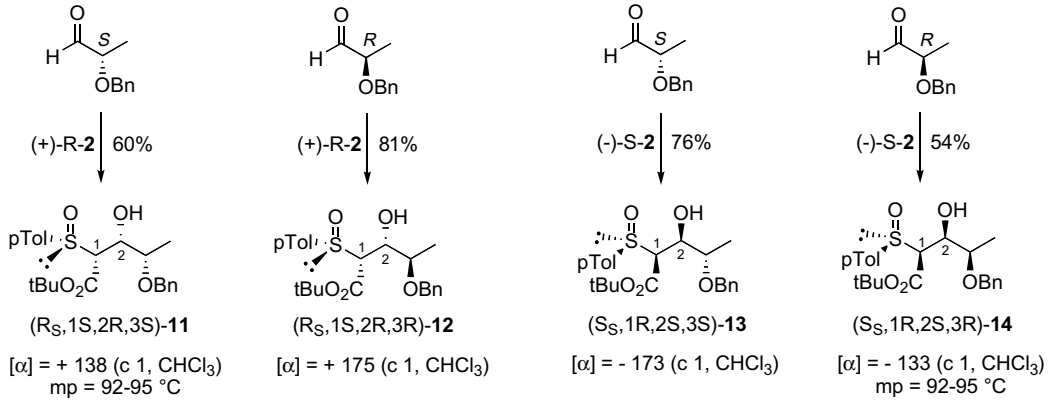


Fig. 3. Illustration of a plausible chelated intermediate.



Scheme 2. Synthesis of sulfoxide **10**.



Scheme 3. Aldol-condensation of sulfinyl ester (+)-*R*-**2** and (−)-*S*-**2** with (*R*) and (*S*) 2-benzyloxypropionaldehyde.

of highly functionalized *syn* and *anti* 1,2-diol models (Scheme 3).

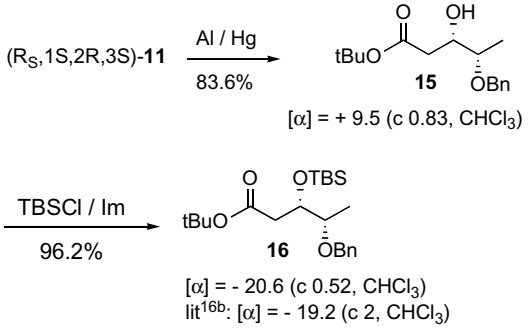
Thus, the treatment of magnesium enolate of sulfinyl ester (+)-*R* **2** with (*S*) and (*R*) 2-benzyloxy propionaldehyde gave, respectively, the aldol products **11** and **12** in good yields. On the other hand, we have obtained the aldol products **13** and **14** using the sulfinyl ester (−)-*S* **2**. Enantiomers **11** and **14** were isolated by simple crystallization, whereas the oily enantiomers **12** and **13** had to be purified by column chromatography. In the case of **11**, the absolute configuration was determined through derivative **16** (Scheme 4). Indeed, after desulfurization of **11**, the resulting β-hydroxyester **15** (84% yield; $[\alpha]_D$ +9.5 (*c* 0.83, $CHCl_3$))[17] was silylated with *tert*-butyldimethylsilyl chloride to afford the known[17b] silylether **16** (96% yield) as it can be seen from the ^1H and ^{13}C NMR data.

The optical rotation of **16** $[\alpha]_D$ −20.6 (*c* 0.52, $CHCl_3$) is identical to that reported in the literature[17b] ($[\alpha]_D$ −19.2 (*c* 2, $CHCl_3$)). Consequently, we can assign the (*R*) absolute configuration at C-2 of the aldol product **11**. Besides, the coupling constant between H-1 and H-2 in the compound **11** has a value of 5.6 Hz, which indicates a *syn* stereochemistry—that is the (R_S,1*S*,2*R*,3*S*) configuration for this sulfoxide **11** (mp = 92–95 °C; $[\alpha]_D$ +138 (*c* 1, $CHCl_3$)).

In the same manner, its expected enantiomer **14** (mp = 90–93 °C; $[\alpha]_D$ −133 (*c* 1, $CHCl_3$)) obtained from (−)-*S* **2** and (*R*) 2-benzyloxy propionaldehyde shows a coupling constant of 5.9 Hz between H-1 and H-2, which is consistent with a *syn* stereochemistry. Finally, in the aldol condensation of the appropriated sulfinate **2** with the (*R*) or (*S*) 2-benzyloxy propionaldehyde leading to the pure enantiomers **12** ($[\alpha]_D$ +175 (*c* 1, $CHCl_3$)) and **13** ($[\alpha]_D$ −173 (*c* 1, $CHCl_3$)), we observed obviously in both cases a *syn* stereochemistry in agreement with their coupling constant of 2.9 Hz between H-1 and H-2. That implies the (R_S,1*S*,2*R*,3*R*) and (S_S,1*R*,2*S*,3*S*) configurations for sulfoxides **12** and **13**, respectively. The specific rotation $[\alpha]_D$ and ^1H coupling constant values of the different adducts[18] are summarized in Table 1.

In this Letter, we have shown a straightforward use of the readily available chiral α-sulfinyl acetate (*R*) and (*S*)-**2** in controlled asymmetric aldol reactions with α-substituted aldehydes. We have observed a high *syn* diastereoselective induction, independently of the chirality of the aldehydes. The desired products can be obtained in good yield and in multigramme amounts either by simple crystallization or by column chromatography of the main isomer. The absolute configuration at C1 of the sulfoxide aldol product was also determined to generate further controlled reactions like an asymmetric epoxidation or anything else.

In conclusion, this method constitutes a powerful route to optically pure α-alkylated β-hydroxyesters analogs as well as highly functionalized *syn* and *trans* α-diols which are potent intermediates for the synthesis of a variety of natural products and bioactive macromolecules.



Scheme 4. Conversion of sulfoxide **11** to the known protected α-diol **16**.

Table 1
Characteristic details for the different cited sulfoxides

Sulfoxides (configuration)	Yield (%)	[α]	Mp (°C)	$\delta H_1/J_{1-2}$ (ppm)/(Hz)
3 (S_S,1*S*,2*S*)	60	−199	108–109	3.49/5.5
4 (R_S,1*R*,2*R*)	65	+195	108–110	3.49/5.5
10 (S_S,1*S*,2*S*,3*R*,4*S*)	68	−130	Oil	3.63/2.9
11 (R_S,1*S*,2*R*,3*S*)	60	+138	92–95	3.58/5.6
12 (R_S,1*S*,2*R*,3*R*)	81	+175	Oil	3.87/2.9
13 (S_S,1*R*,2*S*,3*S*)	76	−173	Oil	3.87/2.9
14 (S_S,1*R*,2*S*,3*S*)	54	−133	90–93	3.58/5.9

Supplementary data

Experimental procedures and spectroscopic data for the compounds and copies of ^{1}H NMR and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.033.

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