Highly Stereoselective Aldol Reaction of Chiral 3-(*p*-Tolylsulfinyl)furfural with Silyl Ketene Acetal Catalyzed by Lanthanide Triflate

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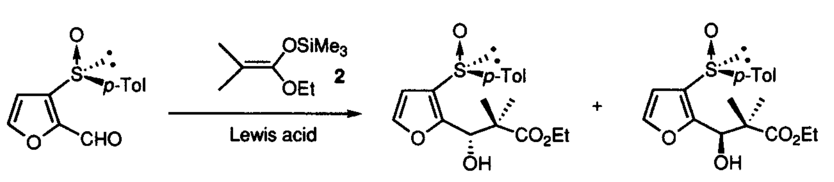
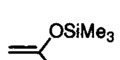
Abstract: The aldol reaction of optically active 3-(*p*-tolylsulfinyl)furfural with silyl ketene acetal catalyzed by a lanthanide triflate proceeded smoothly to give the *syn*- and *anti*-aldol products with high diastereoselectivities in high yield.

Since its pioneering work by Mukaiyama,[1] Lewis acid-promoted crossed aldol reactions between aldehydes and silyl ketene acetals have widely been used to perform a variety of carbon–carbon bond formations. Owing to the importance of this reaction, a large number of attractive methodologies[2] in enantioselective aldol reactions have been developed: 1) enantioselective reaction by the use of a silyl ketene acetal having a chiral auxiliary, 2) the reaction promoted by a chiral Lewis acid, and 3) the reaction of a silyl ketene acetal with a chiral aldehyde. Among these reactions, the use of a lanthanide triflate[3] as a catalyst has recently aroused much attention. In conjunction with a lanthanide-promoted asymmetric aldol reaction,[4] we were interested in the use of the sulfinyl aldehyde **1**.[5] Previously, we have demonstrated that chiral sulfinyl aldehyde **1** undergoes stereoselective allylation[5a] and hetero Diels–Alder reaction[5b] mediated by such a Lewis acid as lanthanide triflates even if the chiral auxiliary may be remote from the reaction site. Despite chiral sulfoxides being useful auxiliaries in asymmetric synthesis,[6] aldol reaction between the aldehyde or ketone with the chiral sulfinyl auxiliary and a silyl ketene acetal has received much less attention.[7] Central to the purpose of this subject was to explore the highly stereoselective aldol reaction with aldehyde **1**. We describe herein the lanthanide triflate-catalyzed aldol reaction of **1** with a silyl ketene acetal.

To obtain chirally functionalized furyl hydroxy propanoates which have been utilized as a chiral building block for natural products synthesis,[8] there have appeared mainly two approaches involving asymmetric aldol reactions[9] of achiral furyl aldehydes with chiral oxazolidine derivatives developed by Evans[10] and resolution of racemic furan derivatives.[11] Our approach relies on the stereoselective reaction of chiral sulfinyl furaldehyde **1** with a silyl ketene acetal followed by desulfinylation. At first we examined the reaction of **1** with silyl enol ether **2**[12] mediated by a Lewis acid under a variety of reaction conditions. Some of the results are summarized in Table 1. When the silyl enol ether **2** was treated with **1** in the presence of 2.0 equiv. of titanium(IV) tetrachloride at −78 °C, the reaction proceeded smoothly to give the aldol products **3** and **4** with 47% de (diastereoisomeric excess). The use of other typical Lewis acids[13] such as tin(IV) tetrachloride and borontrifluoride or the reactions with higher reaction temperature gave no better results. On the other hand, treatment of **1** in the presence of a lanthanide triflate



1 **3** **4**



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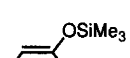

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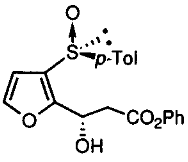
a: R = Me; **b**: R = Et



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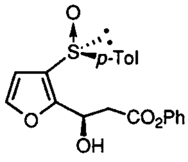

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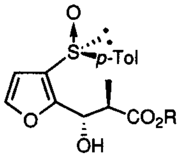

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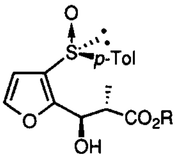

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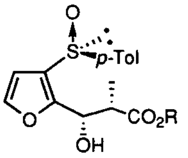
anti major



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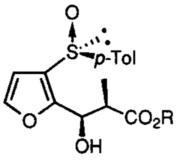

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syn major

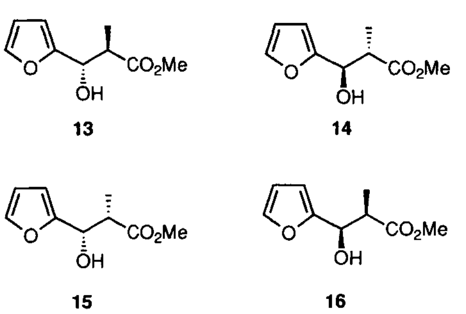
Table 1

entry	silyl enol ether	reaction conditions		solvent	additive /	equiv.	product[c]	*anti* : *syn*	de / %	isolated yield / %
		time / h	temp. / °C							
1	**2**	1	−78	CH_2Cl_2	$TiCl_4$	2.0	**3** and **4**	–	47	89
2	**2**	1.5	0	CH_2Cl_2	$Yb(OTf)_3$	1.0	**3** and **4**	–	96	89
3	**2**	5	0	CH_2Cl_2	$Yb(OTf)_3$	0.2	**3** and **4**	–	94	86
4	**2**	1	0	THF	$Yb(OTf)_3$	0.05	**3** and **4**	–	92	94
5	**2**	1	0	THF	$Nd(OTf)_3$	0.05	**3** and **4**	–	95	92
6	**2**	1	0	THF	$Sm(OTf)_3$	0.05	**3** and **4**	–	96	99
7	**5**	5	0	THF	$Nd(OTf)_3$	0.05	**6** and **7**	–	90	96
8	**8a**[a]	1	0	THF	$Yb(OTf)_3$	0.05	**9a**, **10a**, **11a** and **12a**	79 : 21	90[d] / 93[e]	97
9	**8b**[b]	1	0	THF	$Yb(OTf)_3$	0.05	**9b**, **10b**, **11b** and **12b**	75 : 25	≥99[d] / ≥99[e]	95

[a] Contaminated by *Z*-isomer of **8a** (*E* : *Z* = 5.3 : 1). [b] Contaminated by *Z*-isomer of **8b** (*E* : *Z* = 7.3 : 1). [c] Product ratios were determined by ^1H NMR analysis. [d] De value of *anti*-products indicates that **9** in excess is diastereoisomeric to **10**. [e] De value of *syn*-products indicates that **11** in excess is diastereoisomeric to **12**

afforded **3** with high diastereoselectivity (92-96% de). Since lanthanide triflate was found to be an effective catalyst (5% mole used), other silyl enol ethers **5** and **8a-b**[12] were examined to evaluate the selectivity of the reaction. For the reaction of **1** with **5**, the phenylester **6** was obtained as the major product with 90% de. In the case of **8**, the reactions gave the *anti*-product **9** and *syn*-product **11** as the major isomers with high diastereoface selectivity (≥90% de) and with moderate stereoselectivity (*anti vs syn*).

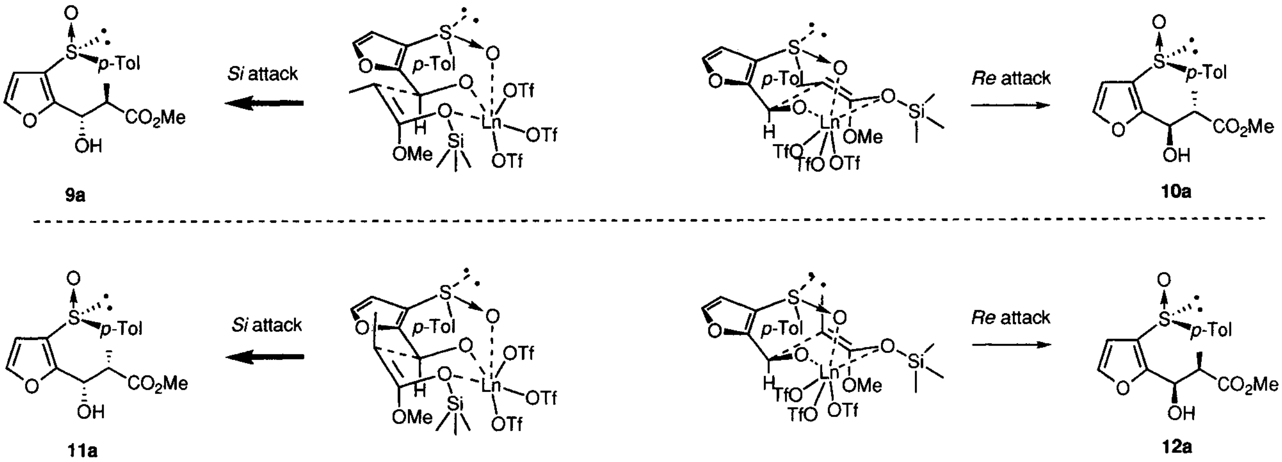
The major products **3** and **6** were readily separated by recrystallization of the original mixture from **4** and **7**, respectively. The ratios of these products were determined by ^{1}H NMR analysis since unsatisfactory separation was observed by HPLC analysis in some cases. The diastereoisomeric relationship (*anti*- and *syn*-isomers) of the products **9-12** was suggested on the basis of the *vicinal* coupling constants (*anti*-isomers have larger coupling constants than those of the corresponding *syn*-isomers in β-hydroxy esters).[14] All possible isomers for determining the product ratio in the reaction by ^{1}H NMR analysis could be prepared as follows: in the case of **9a-12a**, deoxygenation of the sulfinyl group in **9a** and **11a** (**9a** : **11a** = *ca.* 7:1 mixture) with SmI_2 afforded the corresponding sulfides which were further reoxidized with 3-chloroperoxybenzoic acid to give rise to a mixture of **9a**, *ent*-**10a** (= the enantiomer of **10a**), **11a**, and *ent*-**12a**, in a rough ratio of 3.5:3.5:0.5:0.5. The absolute stereochemistry of four diastereoisomers **9a**, **10a**, **11a**, and **12a** was confirmed by comparison with known compounds **13-16**,[11a] obtained in 62% yield by desulfinylation of a mixture of **9a-12a** with Raney Ni (Scheme 1). The stereochemistry of **6** was finally established by single-crystal X-ray analysis[15] of (±)-**6** although optically active **6** was not obtained as suitable crystalline material. The stereostructure of other isomers were tentatively assigned.



Scheme 1

In these aldol reactions, it is probable that the sulfinyl group plays an important role not only as a chiral auxiliary but also as a chelating agent with the aldehyde carbonyl, resulting in fairly rigid transition state for effecting asymmetric induction. The results can reasonably be accomodated by the cyclic transition state model[16] for this type of aldol condensation, which involves the least sterically hindered approach of the silyl ketene acetal. That is, the chelating model of **1** with a lanthanide metal (= Ln) might be preferable (Scheme 2). The organolanthanide metal, which has a long ion radii, could coordinate with the aldehyde carbonyl and the sulfinyl oxygen, resulting in favored 7-membered cyclic transition state. For the reaction of **8a**, either (*E*)- or (*Z*)-silyl ketene acetal should thus attack from the *Si* face of the aldehyde carbonyl due to the steric repulsion with the *p*-tolyl group, giving the aldol products **9a** and **11a** respectively as the major products. Chan *et al.*[12a] reported that the reactions of aldehydes with **8b** produced *anti*-isomers with preference to *syn*-isomers. The observed *anti/syn* stereoselectivity might be compatible with their results. Application to natural product synthesis and further investigation to improve stereoselectivity by the use of other silyl enol ethers such as *O*-silyl ketene *O,S*-acetals are in progress.

Typical Procedure for Aldol Condensation: to a solution of $Yb(OTf)_3$ (40 mg, 0.06 mmol) in dry tetrahydrofuran (THF) (10 mL) at 0 °C was added the aldehyde **1** (300 mg, 1.3 mmol) in dry THF (2.5 mL). After being stirred for 10 min, it was treated with a solution of the silyl ketene acetal **2** (304 mg, 1.9 mmol) in dry THF (2.5 mL), and the mixture was stirred for 1 h. The reaction mixture was quenched by adding 3% hydrochloric acid (8 mL) and the mixture was stirred for 15 min. The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with saturated brine (15 mL), dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The product ratio of **3** and **4** (**3** : **4** = 96:4) was determined by ^{1}H NMR analysis of the crude material. Isomerically pure **3** was separated from **4** by column chromatography on silica gel with hexane-ethyl acetate (3:2→1:1) followed by recrystallization of the resulting mixture (422 mg, 94%) from ethyl acetate-hexane. **3**: mp 70-72 °C (hexane-ethyl acetate); $[\alpha]_D^{22}$ −43.7° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ_H 1.28 (3 H, s, Me), 1.29 (3 H, t, *J* = 7.1 Hz, Me), 1.33 (3 H, s, Me), 2.39 (3 H, s, Me), 4.22 (2 H, dq, *J* = 7.1, 0.7 Hz, CH_2), 4.72 (1 H, d, *J* = 8.1 Hz, OH), 5.13 (1 H, d, *J* = 8.1 Hz, CH), 6.24 (1 H, d, *J* = 2.0 Hz, furan), 7.28 (1 H, d, *J* = 2.0 Hz, furan), 7.29 (2 H, d, *J* = 8.3 Hz, ArH), 7.56 (2 H, d, *J* = 8.3 Hz, ArH); IR ($CHCl_3$) ν_{max} 3400, 3000, 1720, 1460, 1135, 1090, 1035 cm^{-1}.



Scheme 2

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