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Catalytic Asymmetric Aldol Reaction of Ketene Silyl Acetals with Aldehydes by Use of Chiral Bissulfonamido Zinc(II)

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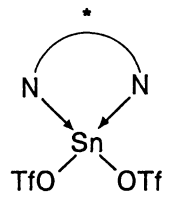
Enantioselective aldol reaction of ketene silyl acetals with aldehydes is effectively performed by use of a catalytic amount of chiral bissulfonamido zinc(II), easily prepared from diethylzinc and chiral sulfonamides.

Asymmetric aldol reaction has been known as an important tool for the preparation of optically active β-hydroxy carbonyl compounds, and recent advancement in perception and methodology realized high syn-anti and diastereofacial selections by using suitable chiral auxiliaries.[1] On the other hand, catalytic asymmetric aldol reaction, which is considered to be the most efficient method for induction of chirality in enantioselective carbon-carbon bond forming reaction, has been known as an extremely difficult problem and satisfactory results were not obtained except for a few cases.[2]

Concerning asymmetric aldol reaction, an effective promoter system, tin(II) triflate ($Sn(OSO_2CF_3)_2$)-chiral diamine-additive complex (**1**), was already reported from our laboratory.[3] This promoter has two characteristic functions; 1) trifluoromethanesulfonyl groups withdraw electrons from the bonded tin(II) atom to enhance its Lewis acidity, and 2) a chiral diamine coordinates to the tin(II) atom to form efficient asymmetric field. Therefore, at that time, it was expected that a design of more effective chiral auxiliary would be possible by just combining a chiral amino group and trifluoromethanesulfonyl group. Based on this consideration, several new chiral auxiliaries; chiral trifluoromethanesulfonamides (**2**) were designed. And we started this



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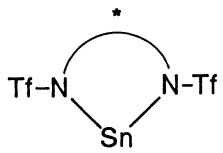


2 Tf = CF_3SO_2-

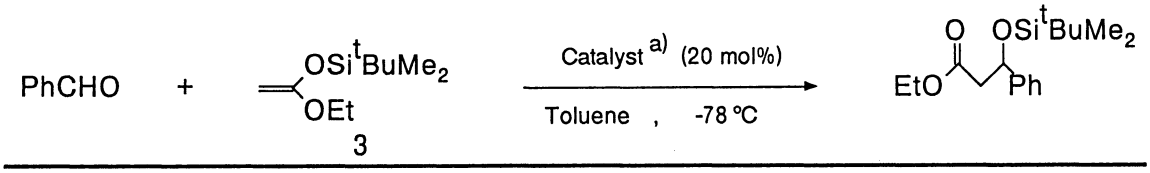
project, however, in the course of our investigation, Ohno and Corey independently reported the highly enantioselective alkylation and Diels-Alder reactions, respectively, by using the chiral ditrifluoromethanesulfonamido boron or titanium.[4]

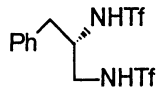
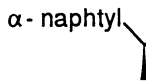
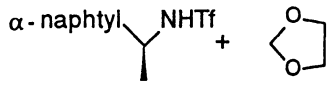
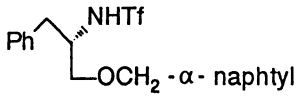
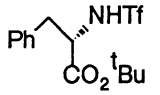
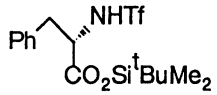
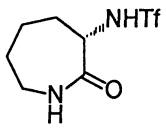
Then we have modulated the topic to employ a novel chiral auxiliary, trifluoromethanesulfonamide derived from monoamine or α-amino acid.[5]

In the first place, the reaction of 1-t-butyldimethylsiloxy-1-ethoxyethylene (3) with benzaldehyde was chosen as a model, and the effect of the chiral sulfonamido tin(II) catalyst was studied. In spite of examining several reaction conditions and chiral auxiliaries, enantiomeric excess did not reach over the middle level (the maximum data was 86% yield with 54% ee).

So we continued to screen other metal salts, and trifluoromethanesulfonamido zinc(II) catalyst, easily prepared from diethylzinc and chiral sulfonamides, was found to be effective for this asymmetric aldol reaction. Then some different types of zinc(II) catalysts, derived from various chiral monotrifluoromethanesulfonamides, were examined by taking the reaction of 3 and benzaldehyde as a model (see Table 1).

Table 1. Effect of Chiral Sulfonamide



Entry	Chiral sulfonamide	Yield / %	ee / %
1		81	6
2		78	46
3 b)		84	61
4		84	54
5		40	5
6		79	60
7		N.R	-

a) Catalyst ; $ZnEt_2$: Chiral sulfonamide = 1 : 2 except for entry 1 (1 : 1).

b) Equivmolar amount of 1,3-dioxolane was added to the zinc(II) catalyst system.

As shown in Entries 1 and 2, bismonosulfonamido zinc (II) is a superior catalyst to disulfonamido zinc (II), giving higher enantioselectivity in the produced aldols. In the above case of disulfonamido zinc(II), it is noted that one side of the zinc(II) catalyst could be completely shielded, however, the other side would be spatially rather open leading to lower selectivity.

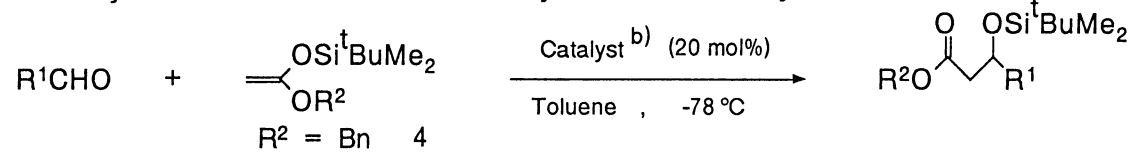
Further, an interesting effect of an additive was observed in the case of naphthylethylsulfonamido zinc(II); when equivmolar amount of 1,3-dioxolane was added to the zinc(II) catalyst system, the enantiomeric excess of the produced aldol was improved from 46% ee to 61% ee (Entry 3). This additive was thought to play a role in

filling the vacant orbital of the zinc(II) atom by coordination leading to the formation of more efficient asymmetric field.

Next, new chiral zinc(II) catalyst consisted of sulfonamide containing one more functional group as ester was designed based on the consideration that carbonyl oxygen of the ester could coordinate to the zinc(II) atom to form C_2 symmetric structure leading to an efficient chiral atmosphere. Several such auxiliaries were examined by taking the above mentioned model reaction (Entries 4-7), and good enantiomeric excess was obtained when the chiral bissulfonamido zinc(II) catalyst derived from sulfonamide containing silyl ester group was employed.

Several aldehydes were successfully applied to this asymmetric aldol reaction (Table 2). The best result (93% ee) was obtained when bromal was employed. Since Br3C-group is a synthetic equivalent of carboxylic acid, the product of the present reaction would be employed as an interesting chiral building block. On the other hand, when cyclohexanecarboxaldehyde was used, the enantioselectivity was rather low.

Table 2. Asymmetric Aldol Reaction of Ketene Silyl Acetals with Aldehydes [a]



Entry	Chiral sulfonamide [c]	R^1CHO	R^2	Yield / %	ee / % [e]
1	A	PhCHO	Et	79	60
2	A	c-C_6H_{11}CHO	Bn	76	23
3	A	2-FurylCHO	Bn	95	47
4 [f]	A	BnOCOCHO	Et	84	49
5	A	CCl_3CHO	Bn	70 [d]	72
6	A	CBr_3CHO	Bn	63 [d]	80
7	B	CCl_3CHO	Bn	61 [d]	88
8	B	CBr_3CHO	Bn	66 [d]	93

a) All reagents should be freshly distilled.

b) Catalyst ; $ZnEt_2$: Chiral sulfonamide = 1 : 2

c) Chiral sulfonamide ;

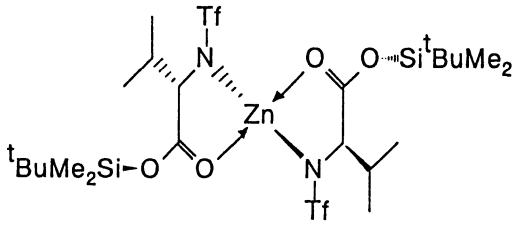
d) The aldol adduct was isolated as the alcohol form.

e) Determined by HPLC analysis of the corresponding alcohol derivatives (in the case of Entry 3 determined of siloxy ester.).

f) The aldol reaction of these substrates proceeded by using the sulfonamide containing amide group (Table 1 , Entry 7) , and the corresponding adduct was obtained in 19% yield with 92%ee. This low reactivity is thought to be due to weak Lewis acidity of zinc(II) by strong coordination of amide to zinc(II).

A typical experimental procedure is described for the reaction of 1-t-butyldimethylsiloxy-1-benzyloxyethylene(4) with bromal; to a suspension of (S)-N-[(trifluoromethyl)sulfonyl]-valine (0.1 mmol) in toluene (2 ml) was added the ketene silyl acetal 4 (0.11 mmol) in toluene (1 ml) at room temperature to prepare the silyl ester B. This mixture was stirred for 30 min, and then 0.055 ml of diethylzinc in hexane (1 M) was

added. This mixture was further stirred for 30 min at the same temperature, then cooled to -78 °C. The ketene silyl acetal **4** (0.29 mmol) in toluene (1 ml) and bromal (0.25 mmol) in toluene (1 ml) were added successively (in the case of benzaldehyde and cyclohexanecarboxaldehyde, the mixture of the aldehyde and the ketene silyl acetal in toluene was added to the catalyst.). The reaction mixture was further stirred for 22 h at -78 °C, then quenched with phosphate buffer (pH=7). After usual work up, the desired aldol, 3-hydroxy-4,4,4-tribromobutylic acid benzylester, was obtained in 66% yield. The enantiomeric excess was determined to be 93% ee by HPLC analysis (Daicel CHIRALCEL OD).



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The precise structure of bissulfonamido zinc(II) is not yet clear, however, it is assumed that the active species (5) was composed of one zinc(II) atom and two chiral sulfonamides. It should be noted that the combination of zinc(II) and the chiral trifluoromethanesulfonamide containing silyl ester group enhanced the enantiomeric excess probably due to formation of a rigid C_2 symmetric structure by the coordination of the silyl ester to zinc(II) atom. While alkyl ester group, rather weakly coordinated to zinc(II) atom, led to lower selectivity of the aldol product (Table 1, Entry 5).

Thus, this new catalyst, chiral bissulfonamido zinc(II), easily prepared from diethylzinc and chiral sulfonamides, realizes the highly enantioselective aldol reaction between both achiral ketene silyl acetals and aldehydes. Further investigations to develop other asymmetric reactions by using this chiral catalyst are now in progress.

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3) S. Kobayashi and T. Mukaiyama, *Chem. Lett.*, **1989**, 297.

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5) Quite recently Yamamoto and Helmchen reported the asymmetric Diels-Alder reaction using the catalyst derived from metal sources (BH_3,Et_2AlCl, and $TiCl_4$) and chiral sulfonamides derived from α-amino acid. M. Takasu and H. Yamamoto, *Synlett*, **1990**, 194 ; D. Sartor, J. Saffrich, and G. Helmchen, *ibid.*, **1990**, 197.

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