CHEMISTRY LETTERS, pp. 217-220, 1994.

A Novel Chiral Catalyst System, Tin(II) Triflate, a Chiral Diamine, and Tin(II) Oxide, in Asymmetric Aldol Reactions

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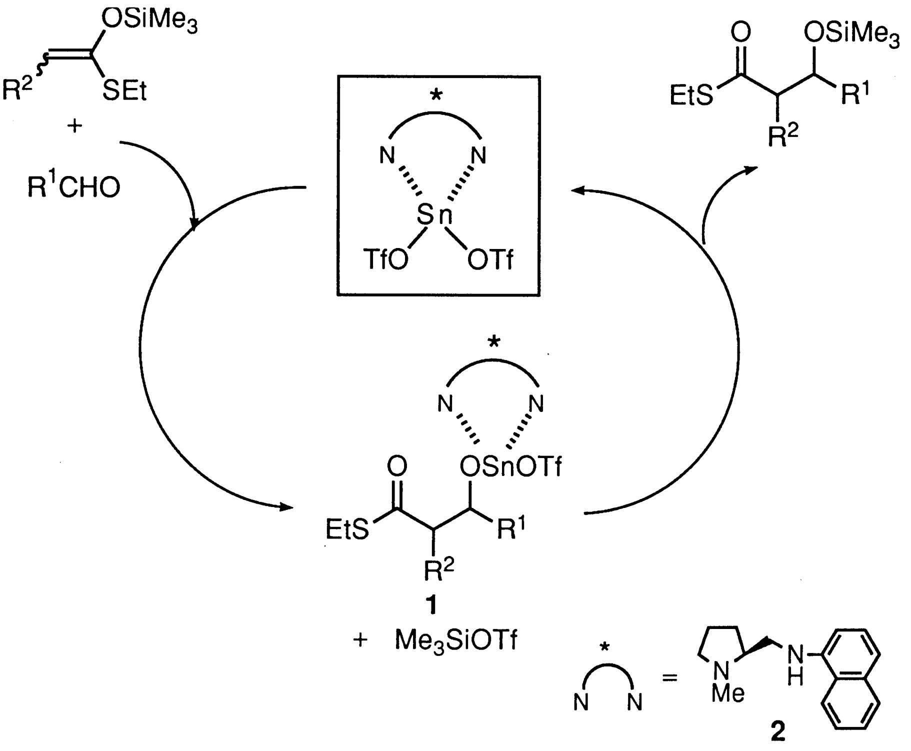
In the presence of a novel chiral catalyst system consisting of tin(II) triflate, a chiral diamine, and tin(II) oxide, highly enantioselective aldol reactions of the silyl enol ether of S-ethyl ethanethioate or S-ethyl propanethioate with aldehydes proceeded smoothly to afford the aldol adducts in high yields.

Asymmetric aldol reactions are one of the most powerful methods to create new chiral centers with the formation of a carbon-carbon bond, and have been actively investigated in this decade.1) In particular, a catalytic asymmetric aldol reaction that produces a large amount of optically active aldol adduct from a catalytic amount of chiral source is of great synthetic value, and much effort has been made in order to achieve higher yields and selectivities.2)

We have already reported the catalytic asymmetric aldol reaction of the silyl enol ether of S-ethyl ethanethioate or S-ethyl propanethioate with aldehydes using a chiral tin(II) Lewis acid consisting of tin(II) triflate and a chiral diamine.3) This was the first example of a highly stereoselective and catalytic asymmetric aldol reaction of enolate components with aldehydes, in which new techniques using propionitrile as a solvent and slow addition in order to facilitate the catalytic cycle were first introduced. In the course of our investigation to develop a more efficient chiral catalyst system, we found that tin(II) oxide worked as an effective additive in our original system to improve the yields, diastereo- and enantioselectivities. We now report a novel catalyst system consisting of tin(II) triflate, a chiral diamine, and tin(II) oxide, which effectively catalyzes the asymmetric aldol reaction of silyl enol ethers with aldehydes.

In the asymmetric aldol reaction using the chiral tin(II) Lewis acid, the catalytic cycle shown in Scheme 1 was postulated. The key step was believed to be the metal exchange process from tin(II) to silicon on the initially produced aldol adduct **1**. If this step is slow, the trimethylsilyl triflate (TMSOTf)-promoted aldol reaction4) of the aldehyde with the silyl enol ether proceeds to result in lower selectivities. In order to suppress the undesirable reaction (to keep TMSOTf at as low a concentration as possible during the reaction), slow addition of the substrates to the catalyst in propionitrile was successfully performed. We also thought that higher stereoselectivities might be obtained when the Lewis acidity of TMSOTf was reduced by using an additive. This idea was obtained from our recent report on the catalytic asymmetric aldol reaction using TMSOTf, a chiral diamine, and tin(II) oxide.5) In this reaction, TMSOTf interacted with the lone pair electron of tin(II) oxide, and consequent weakening of the Lewis acidity of TMSOTf resulted in high selectivities. We thought that it might be possible to reduce the Lewis acidity of various triflates by using this interaction.



Scheme 1. The Catalytic Cycle of the Asymmetric Aldol Reaction.

As a preliminary experiment, the model reaction of the silyl enol ether of S-ethyl propanethioate with benzaldehyde was attempted using 1 mol% of TMSOTf and 100 mol% of tin(II) oxide. After mixing the substrates in propionitrile at -78 °C for 10 min, only a trace amount of aldol adduct was observed. On the other hand, the aldol adduct was obtained in a 75% yield under the same conditions in the presence of 1 mol% of TMSOTf *without tin(II) oxide*. From these experiments, it was clear that tin(II) oxide was able to reduce the catalytic activity of TMSOTf in the aldol reaction.

We then evaluated a novel catalyst system consisting of tin(II) triflate (20 mol%), chiral diamine **2** (20 mol%), and tin(II) oxide (40 mol%) in the reaction of the silyl enol ether of S-ethyl ethanethioate with 2-hexenal. The reaction proceeded smoothly to give the adduct in a 61% yield with 62% ee. The important role of tin(II) oxide in the present reaction was obvious from the fact that a lower yield (50%) and a lower selectivity (22% ee) were observed when the same reaction was carried out *without tin(II) oxide* (tin(II) triflate (20 mol%) and chiral diamine **2** (20 mol%)). The effect of other metal oxides in the aldol reaction is shown in Table 1. When germanium(II) oxide (GeO), germanium(IV) oxide (GeO_2), tin(IV) oxide (SnO_2), or titanium(IV) oxide (TiO_2, Rutile) was employed, some improvement of the yield and selectivity was observed, however, the best result was obtained when tin(II) oxide was used.

The new chiral catalyst system[6)] was applied to the asymmetric aldol reaction of silyl enol ethers with aldehydes (Table 2). In every case, the yields and the selectivities were rather improved, compared with those of the previous work.[3)]

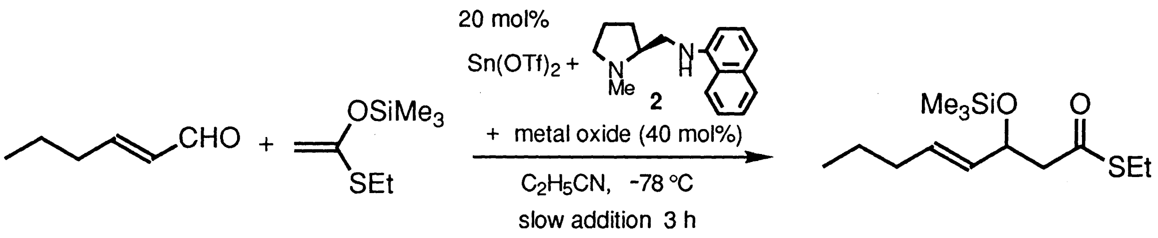


Table 1. The Effect of Metal Oxides

Entry	Metal oxide	Yield / %	ee / %
1	—	50	22
2	SiO	40	15
3	TiO	43	15
4	TiO_2 (Rutile)	47	30
5	GeO	46	33
6	GeO_2	42	32
7 [a]	SnO	61	62
8	SnO_2	54	44
9	PbO_2	39	14

a) 83% yield, 84% ee (slow addition 4 h, see Table 2, Entry 8)

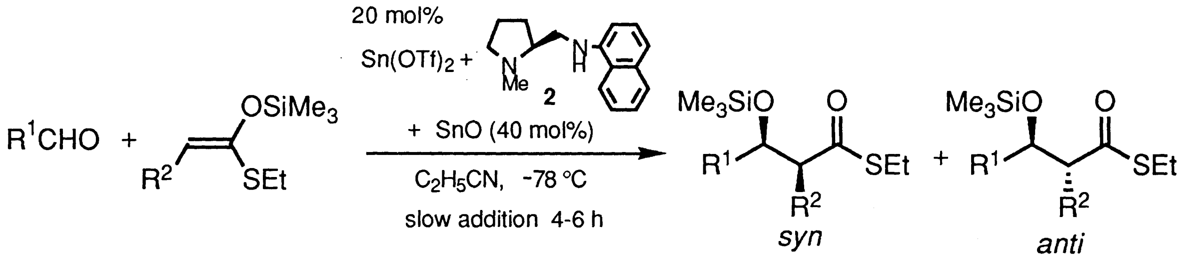


Table 2. Catalytic Asymmetric Aldol Reactions Using a Novel Catalyst System

Entry	R^1	R^2	This work			Previous best results[3]		
			Yield / %	syn/anti	ee / %	Yield / %	syn/anti	ee / %
1	Ph	Me	78	95/ 5	93	77	93/ 7	90
2	$CH_3(CH_2)_6$	Me	81	100/ 0	>98	80	100/ 0	>98
3	$CH_3CH{=}CH$	Me	85	99/ 1	95 [a]	76	96/ 4	93
4	$CH_3(CH_2)_2CH{=}CH$	Me	81	100/ 0	94	73	97/ 3	93
5	$CH_3(CH_2)_3$	H	71	—	92	79	—	91
6	i-Pr	H	50	—	92 [a]	48	—	90
7	c-C_6H_{11}	H	78	—	94	81	—	92
8	$CH_3(CH_2)_2CH{=}CH$	H	83	—	84 [a]	65	—	72

a) 20 mol% of SnO was used.

A typical experimental procedure is described for the reaction of the silyl enol ether of S-ethyl ethanethioate with 2-hexenal: to a stirred suspension of tin(II) triflate (0.08 mmol, 20 mol%) and tin(II) oxide (0.16 mmol, 40 mol%) in propionitrile (1 ml) was added chiral diamine **2** (0.088 mmol) in propionitrile (1 ml). The mixture was cooled to -78 °C, and a mixture of the silyl enol ether of S-ethyl ethanethioate (0.4 mmol) and 2-hexenal (0.4 mmol) in propionitrile (1 ml) was slowly added to this suspension over 4 h. This mixture was further stirred for 1 h, then quenched with saturated aqueous sodium hydrogen carbonate. After a usual work up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether. The enantiomeric excess was determined by HPLC using Daicel CHIRALCEL OD, after derivation to the alcohol.

Thus, a novel chiral catalyst system consisting of tin(II)triflate, a chiral diamine, and tin(II) oxide was developed to generate a highly efficient asymmetric aldol reaction of the silyl enol ether of S-ethyl ethanethioate or S-ethyl propanethioate with several aldehydes. High yields and selectivities brought about by the interesting use of a metal oxide are noteworthy features of this reaction.

This work was partially supported by a Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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6) An active species of the new chiral catalyst system is different from that of the TMSOTf-a chiral diamine-SnO system.5) The active species of the latter system was formed by mixing TMSOTf, SnO, and then a chiral diamine at room temperature, and mixing the reagents at -78 °C gave no active species. Furthermore, high selectivities were obtained when more than 50 mol% of the catalyst was used.

(Received October 4, 1993)