CHEMISTRY LETTERS, pp. 2069-2072, 1989.

A Highly Enantioselective Synthesis of 2-Substituted Malates by Asymmetric Aldol Reaction

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In the presence of a chiral promoter consisted of chiral diamine coordinated tin(II) triflate and tributyltin fluoride, silyl enol ether of S-ethyl ethanethioate reacts with α-ketoesters to afford the corresponding aldol-type adducts, 2-substituted malates, in good yields with excellent enantiomeric excesses.

2-Substituted malic acids are widely distributed in nature as a variety of natural sources produced by plants or microorganisms.[1] Of more interest is their common inclusion as carboxylic acid component in biologically active pyrrolizidine alkaloids, and intense efforts have been made to prepare these carboxylic acid residues as optically active forms.[2,3] Concerning asymmetric synthesis of 2-substituted malates, asymmetric aldol reaction of acetic acid derivatives with α-ketoesters is one of the most prospective methods, however, only poor asymmetric induction has been realized in the literatures.[3] Recently, it was reported from our laboratory that tin(II) enolate of 3-acetyl-thiazolidine-2-thione reacts with α-ketoesters in the presence of a chiral diamine to afford the corresponding aldol-type products in high enantiomeric excesses.[4]

In the previous papers, we have reported on the quite efficient aldol reactions of silyl enol ethers of thioester[5] or esters (ketene silyl acetals)[6] with aldehydes by the use of a new chiral promoter system, a combined use of chiral diamine coordinated tin(II) triflate and tributyltin fluoride. These reactions realized excellent diastereo- and enantioselectivities starting from both achiral silyl enol ethers and aldehydes by using the chiral promoter. In this communication, we would like to describe on the application of these aldol reactions to the enantioselective synthesis of 2-substituted malates.

In the first place, the reaction of silyl enol ether of S-ethyl ethanethioate with methyl pyruvate was carried out in the coexistence of tin(II) triflate, (S)-1-methyl-2-[(piperidin-1-yl)methyl]-pyrrolidine and tributyltin fluoride. The reaction smoothly proceeded to afford the corresponding aldol-type adduct in 73% yield with 83% ee. Next, in order to improve the enantioselectivity, several reaction conditions were examined. It was found then that the structure of chiral diamines strongly influenced on the selectivity and that the best enantiomeric excess (92% ee) was obtained when (S)-1-n-pentyl-2-[(piperidin-1-yl)methyl]-pyrrolidine was employed as a chiral diamine (Table 1).

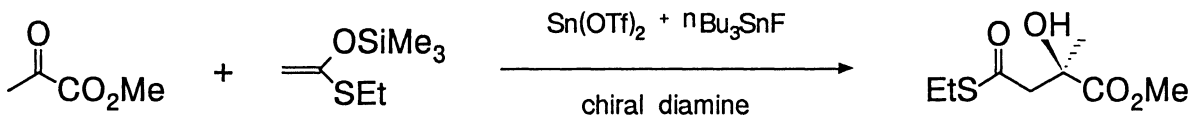
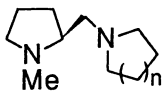
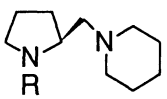
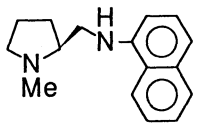


Table 1. Effect of chiral diamine

Chiral diamine		Yield/%	ee/%
	n=1	67	67
	n=2	73	83
	n=3	63	56
	R=Me	73	83
	R=Et	80	81
	R=n-Pr	52	78
	R=n-Bu	74	87
	R=n-Pent	78	92
	R=n-Hex	68	82
		70	4

Other examples are demonstrated in Table 2. Methyl isopropylglyoxylate and methyl phenylglyoxylate also react with silyl enol ether of S-ethyl ethanethioate to give the corresponding 2-substituted malates in good yields with almost perfect enantiomeric excesses (>98% ee).

A typical experimental procedure is described for the reaction of silyl enol ether of S-ethyl ethanethioate(1) with methyl pyruvate; to a solution of tin(II) triflate (0.4 mmol) and (S)-1-n-pentyl-2-[(piperidin-1-yl)methyl]pyrrolidine (0.48

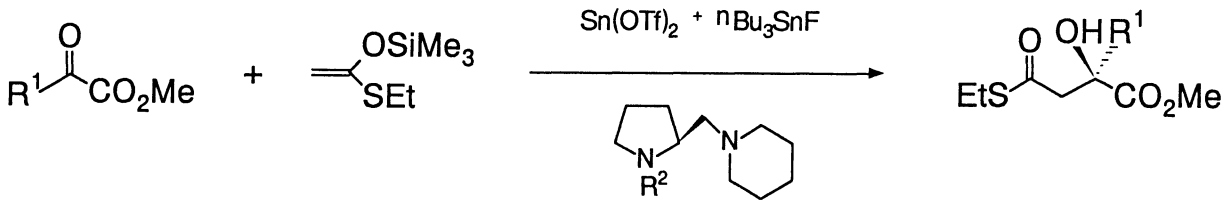


Table 2. Asymmetric aldol reaction of silyl enol ether of S-ethyl ethanethioate with α-ketoesters

R^1	R^2	Yield/%	ee/%(config.[a])
Me	n-Pent	78	92 (R)
i-Pr	Me	76	>98 (S)
i-Pr	n-Pent	81	>98 (S)
Ph	Me	74	>98
Ph	n-Pent	74	>98

a) Determined by comparing with the authentic samples of the corresponding dimethyl esters.[4)]

mmol) in dichloromethane (1 ml) was added tributyltin fluoride (0.44 mmol) at room temperature. The mixture was stirred for 30 min, then cooled to -78 °C and 1 (0.4 mmol) in dichloromethane (1 ml) was added. After the mixture was further stirred for 30 min, methyl pyruvate (0.36 mmol) in dichloromethane (1 ml) was added, and the reaction mixture was stirred for 24 h, then quenched with aqueous sodium hydrogen carbonate. After usual work-up, the desired aldol-type adduct, methyl 2-hydroxy-2-methyl-4-ethylthio-4-oxo-butanate, was obtained in 78% yield. The enantiomeric excess was determined to be 92% by measurement of the ^{1}H-NMR spectrum using $Eu(hfc)_3$ as a chiral shift reagent.

Thus, highly enantioselective synthesis of 2-substituted malates was performed by the asymmetric aldol reaction using the chiral promoter system. It would be noted that the present reaction is applicable not only to an aldehyde function but also to a ketone function of α-ketoester. The precise reaction mechanism is not yet clear, however, the formation of three component complex consisted of tin(II) triflate, chiral diamine and tributyltin fluoride, was supported by its ^{119}Sn-NMR spectrum. Since it was confirmed by measurement of ^{1}H-

NMR spectrum that no metal exchange reaction of silicon and tin occurred, the above promoter works as a Lewis acid, efficiently activates an α-ketoester, and a silyl enol ether directly attacks from one enantioface of the α-ketoester predominantly.

Detailed experimental conditions and transition state of this reaction will be reported in the near future.

References

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(Received August 30, 1989)