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Highly Enantioselective Synthesis of Propargylic Alcohols by Way of the Asymmetric Aldol Reaction

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In the presence of a catalytic amount of chiral diamine-coordinated tin(II) triflate, acetylenic aldehydes enantioselectively react with silyl enol ethers of thioesters to afford the corresponding aldol-type adducts, propargylic alcohols, in high yields. The products are easily converted to the corresponding optically active allene derivatives via effective chiral transfer.

Optically active propargylic alcohols are useful intermediates in organic synthesis. The alkynylation of aldehydes using chiral organoalkynyl reagents,[1] the asymmetric reduction of acetylenic ketones using the chiral reducing reagents,[2] the reductive cleavages of acetylenic acetals,[3] etc.[4] have been reported as the conventional methods for the preparation of these compounds, however, they require a stoichiometric amount of chiral source. Recently, the asymmetric alkylation reaction of acetylenic aldehydes with dialkylzinc reagents using a chiral amino alcohol as a catalyst[5] and the elimination reaction of optically pure γ-iodo allylic alcohols prepared by the Sharpless kinetic resolution [6] were reported. Now, we intended to prepare propargylic alcohols by way of the enantioselective aldol reaction of acetylenic aldehydes with silyl enol ethers using a chiral promoter consisting of tin(II) triflate, a chiral diamine derived from (S)-proline and tributyltin fluoride[7] (or dibutyltindiacetate),[8] or a chiral catalyst consisting of tin(II) triflate and a chiral diamine.[9]

Recently we have developed the highly enantioselective aldol reaction of achiral aldehydes with achiral silyl enol ethers by the use of the above mentioned chiral promoter or catalyst. In our continuing study to extend the scope of this asymmetric reaction,[10] the synthesis of optically active propargylic alcohols by the reaction of acetylenic aldehydes with silyl enol ether was examined.

Firstly, the reaction of trimethylsilylpropynal (**1**) with (Z)-1-ethylthio-1-trimethylsiloxypropene served as a model system to test the influence of various parameters on the yield and stereoselectivity of the produced aldol-type adduct **2**. When the reaction was carried out in the presence of tin(II) triflate, (S)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**3**) and tributyltinfluoride or dibutyltindiacetate, the corresponding aldol-type adduct **2** was obtained in a good yield, however, with a low enantiomeric excess. Remarkable improvement on the enantioselectivity was observed when (S)-1-methyl-2-[(N-naphthylamino)methyl]-pyrrolidine (**4**) was employed as a chiral diamine instead of **3**, and the maximum syn/anti ratio and enantiomeric excess (syn/anti=95/5, syn aldol=93%ee) was attained by the combined use of tin(II) triflate, the chiral diamine **4** or (S)-1-methyl-2-[(N-2,3,4,5-tetrahydronaphthylamino)methyl]pyrrolidine (**5**) and dibutyltindiacetate (Table 1). It is noted that the optically active propargylic alcohols having successive two asymmetric carbons can be prepared in high ees by the present reaction.

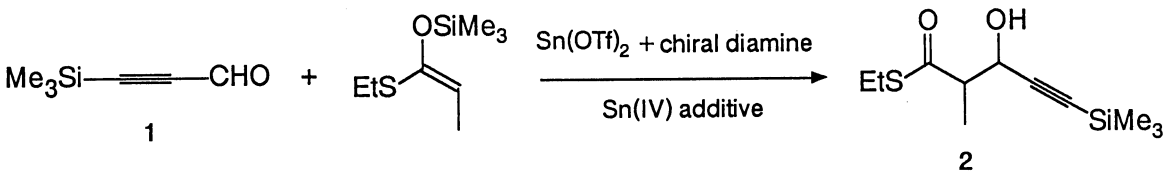
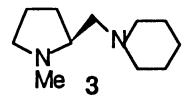
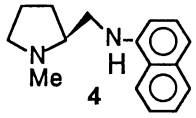
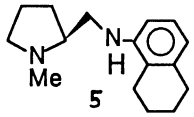


Table 1. Effect of Chiral Diamine and Sn(IV) additive

Chiral diamine	Sn(IV) additive	Yield / %	syn / anti	ee / %
 3	$^{n}Bu_3SnF$	74	66 / 34	5
	$^{n}Bu_2Sn(OAc)_2$	79	70 / 30	10
 4	$^{n}Bu_3SnF$	64	78 / 22	51
	$^{n}Bu_2Sn(OAc)_2$	87	95 / 5	93
 5	$^{n}Bu_2Sn(OAc)_2$	87	96 / 4	93

Next, the catalytic asymmetric aldol reaction was examine in the presence of tin(II) triflate and the chiral diamine **4** (20 mol%) according to the slow addition procedure. The reaction smoothly proceeded at -78 °C to afford the corresponding adduct in 73% yield with a syn/anti ratio of 95/5, and the enantiomeric excess of the syn aldol-type adduct was proved to be 91% after the HPLC analysis.

Several examples of this asymmetric aldol reaction was summarized in Table 2, and in every case the aldol-type adducts, optically active propargylic alcohols, are obtained in good yields with high enantiomeric excesses. Relative and absolute configuration assignments were made, after hydrogenation of the acetylenic parts, by comparison with the authentic samples.[7,8] It is noteworthy that a higher ee was attained by the catalytic asymmetric aldol reaction in the case of using the acetic acid thioester derivatives. On the other hand, when the propionic acid thioester derivatives were employed, higher diastereo- and enantioselectivities were observed in the stoichiometric reaction. These observations support our accumulated experimental data that a little different asymmetric envioronments are created between the three components promoter (tin(II) triflate, a chiral diamine, tributyltin fluoride or dibutyltindiacetate) and two components catalyst (tin(II) triflate, a chiral diamine).[11]

A typical experimental procedure is described for the catalytic asymmetric aldol reaction of trimethylsilylpropynal (**1**) with (Z)-1-ethylthio-1-trimethylsiloxypropene; to a solution of tin(II) triflate (0.08 mmol, 20 mol%) in propionitrile (1 ml) was added (S)-1-methyl-2-[(N-naphthylamino)methyl]pyrrolidine (**4**, 0.088 mmol) in propionitrile (1 ml). The mixture was cooled to -78 °C, then a mixture of **1** (0.4 mmol) and the silyl enol ether (0.4 mmol) was slowly added to this solution over 4.5 h. The mixture was further stirred for 3 h, then quenched with saturated aqueous sodium hydrogen carbonate. After usual work-up, the aldol-type adduct was isolated as the corresponding trimethylsilyl ether.

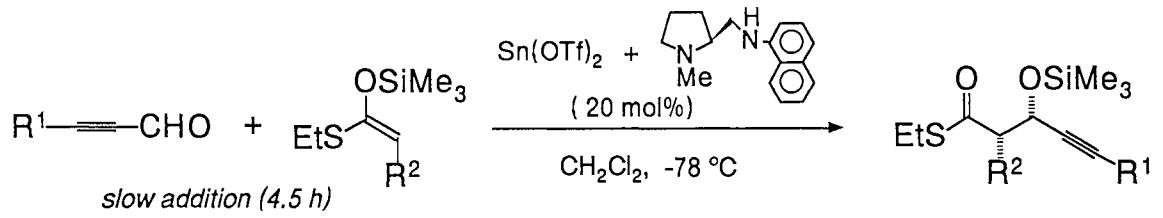
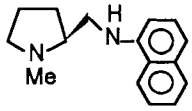


Table 2. The Asymmetric Aldol Reaction of Acetylenic Aldehydes

R^1	R^2	Yield/%	syn/anti [a]	ee/% [b]
$SiMe_3$	Me	73 (84)	95/ 5 (93/ 7)	91 (92)
Ph	Me	82 (92)	90/10 (93/ 7)	86 (93)
^nBu	Me	67 (84)	93/ 7 (97/ 3)	91 (96)
Me	Me	77 [c] (71)	86/14 (96/ 4)	88 (97)
^nBu	H	63 (38)	———	88 (80) [d]

( ): $Sn(OTf)_2$ +  + $^nBu_2Sn(OAc)_2$ (100 mol%)

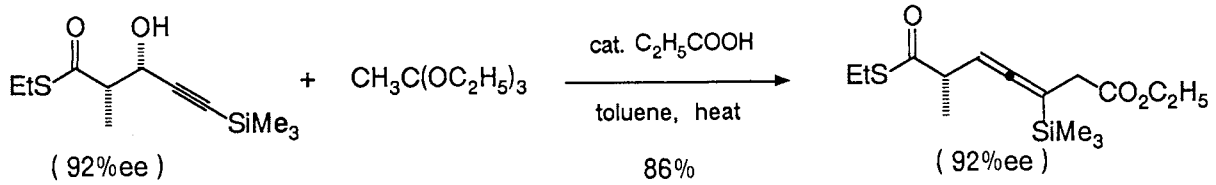
a) Determined by ^1H NMR and HPLC analysis.

b) Determined by HPLC analylsis (Daicel Chiralcel).

c) C_2H_5CN was used as a solvent.

d) $^nBu_3SnF$ was employed instead of $^nBu_2Sn(OAc)_2$.

Thus obtained propargylic alcohol was easily converted to the corresponding optically active allene derivative under the influence of triethylorthoformate and propionic acid via effective chiral transfer.[12]



Further investigations to utilize the optically active propargylic alcohols as chiral synthons are now in progress.

References

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