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STEREO- AND REGIO-CONTROLLED ALDOL SYNTHESIS

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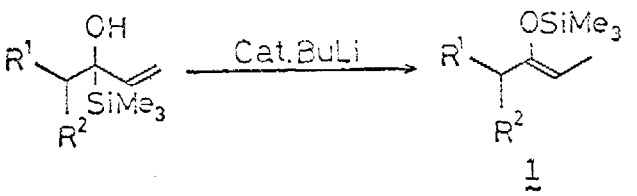
Summary: Treatment of (Z)-trimethylsilyl enol ethers with dibutylboryl trifluoromethanesulfonate followed by removal of trimethylsilyl triflate generated and addition of aldehydes affords the corresponding erythro aldols with almost complete stereo- and regio-selectivities.

Much efforts have been made for the stereo- and regio-controlled aldol synthesis. For effecting such a transformation from enolate equivalents with high efficacy, the following two requirements must usually be satisfied: (1) Stereo- and regio-selective preparation of enolate equivalents, and (2) an effective transfer of their stereochemical features to the resulting aldols. For the latter purpose, dialkylboron enolates have recently been reported to be efficient by several groups[1] because of fairly tight six-membered chair-like transition state. Although several methods have also been developed for satisfying the requirement (1),[1,2] silyl enol ethers appear to be reagents of choice because of relatively easy and general availabilities.

In the previous paper, we reported a stereo- and regio-selective synthesis of (Z)-trimethylsilyl enol ethers 1[3] via rearrangement of the corresponding 1-trimethylsilylallylic alcohols catalyzed by butyllithium.[4]



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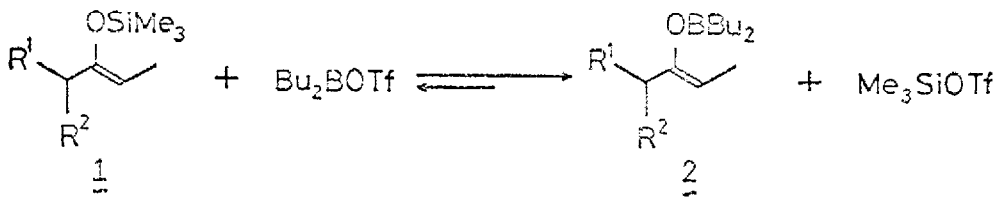
In the present, we describe an efficient transfer of the stereochemical feature of 1 to that of an aldol to give an erythro isomer with high specificity Our examinations are based on the assumption that, on treating with dialkylboryl trifluoromethanesulfonate, an equilibrium may exist between silyl enol ethers 1 and the corresponding boron enolates 2 without any loss of stereo- and regio-

chemical integrities.

NMR studies on a mixture of 1-trimethylsiloxycyclohexene and dibutylboryl trifluoromethanesulfonate have supported a rapid equilibrium usually exists between the silyl enol ether 1 and the corresponding boron enolate 2 in a variety of solvents, e.g. THF, ether, CH_2Cl_2, CCl_4, or hexane: Trimethylsilyl signal attributable to trimethylsilyl triflate appeared at ca.δ 0.53 after short period at low temperature.[5]



1 2

In the next, stereochemical course of the reaction of this system with an aldehyde has been studied by using 3-trimethylsiloxy-2-pentene 1 (Z:E = 96:4).[6] When 1 (R^1 = CH_3, R^2 = H) was treated with equimolar amounts of dibutylboryl trifluoromethanesulfonate and benzaldehyde at -78°C for 30 min in an appropriate solvent, erythro/threo selection (50:50~70:30) was shown to be quite low. Treatment of 1 (R^1 = CH_3, R^2 = H) with the trifluoromethanesulfonate for an appropriate period followed by addition of benzaldehyde improved the erythro/threo selection, but the ratio (erythro:threo = 84:16) was far from satisfactory.

These results have suggested that two types of aldol reactions might take place concomitantly in the present system. The one involves addition of the boron enolate 2 to benzaldehyde (path A) which should give the erythro isomer exclusively if boron-silyl group exchange occurs stereospecifically.[1] As the another one, a trimethylsilyl triflate mediated aldol reaction between the silyl enol ether 1 and an aldehyde (path B) may be conceivable.[7] Indeed, the latter process was found to take place efficiently when treated 1 (R^1 = CH_3, R^2 = H) with benzaldehyde in the presence of the silyl triflate, but no stereo-selection (erythro:threo = 49:51) was observed.

To exclude this non-stereospecific process (path B) from the present system, it has been examined to remove the silyl triflate initially from the equilibrium mixture. Thus, 1 (R^1 = CH_3, R^2 = H) and dibutylboryl trifluoromethanesulfonate was stirred at 0°C for 30 min in ether, and then the low-boiling silyl triflate was removed together with the solvent in vacuo (0°C, 5.0 Torr., 10 min). To the resulting solution was added an ethereal solution of an equimolar amount of benzaldehyde at -78°C and it was stirred for 2 hr at that temperature. Almost complete stereo-selection (erythro:threo = 95:5)

could be achieved by this procedure and the corresponding aldol 4 (R^1 = CH_3, R^2 = H, R = C_6H_5) was obtained in 63% yield.

Considering the stereochemical results of addition reaction of boron enolates to aldehydes,[1] stereochemical feature of the double bond of the enolate appears to remain completely unchanged during the exchange of the silyl group with dibutylboryl moiety.

In addition to the high stereoselectivity mentioned above, regiochemical outcome of the double bond is also rigorously maintained during conversion of 1 to 2. Thus, as shown in the Table, various kind of aldols can be prepared in highly stereo- and regio-controlled manner, starting from the corresponding silyl enol ethers 1.

It has never been reported so far on a stereo- and regio-selective aldol synthesis, starting from ketones having two types of different methylene groups neighboring to their carbonyl groups. The present method appears to offer one of most efficient solutions for this kind of synthetic problems.

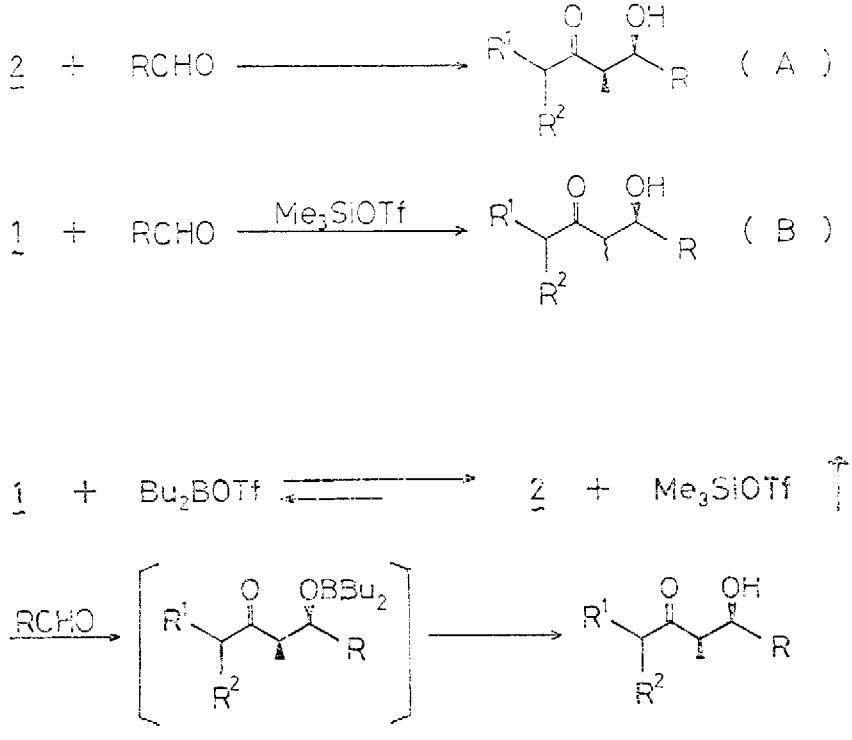


Table. Preparation of Aldol 4.

R^1	R^2	E:Z ratio of 1	R	Yield of 4,%	Erythro:Threo ratio of 4
CH_3	H	96:4	C_6H_5	63	95:5
C_4H_9	H	95:5	C_6H_5	74	94:6
C_8H_{17}	H	91:9	C_6H_5	80	91:9
$C_6H_5CH_2$	H	95:5	C_6H_5	82	95:5
C_2H_5	C_2H_5	99:1	C_6H_5	73	exclusively erythro 4[a]
$-(CH_2)_5-$		98:2	C_6H_5	76	exclusively erythro 4[a]
$-(CH_2)_5-$		98:2	$C_6H_5CH_2CH_2$	64	>98:2

a) The corresponding threo isomer could not be detected by NMR analysis.

References

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