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ERYTHRO-SELECTIVE ALDOL REACTION USING PHENYLDICHLOROBORANE

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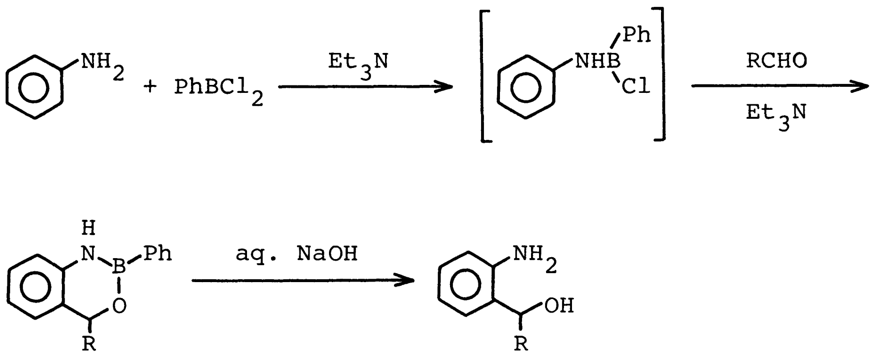
High erythro-selectivity could be attained in the aldol reaction of ethyl ketones with aldehydes using phenyldichloroborane in the presence of ethyldiisopropylamine.

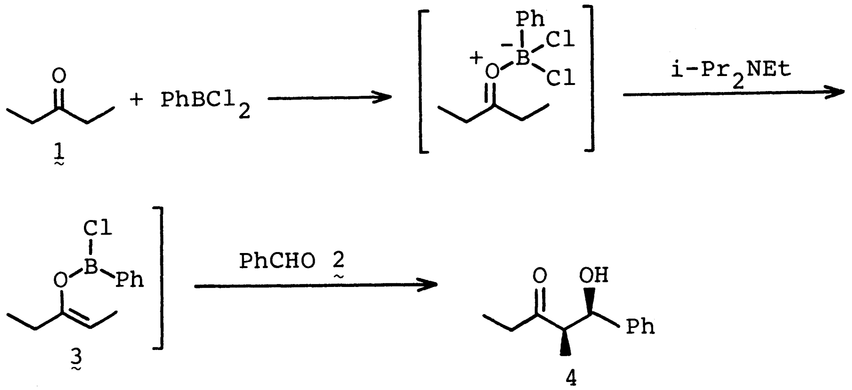
Recently, we found that the ortho-selective Friedel-Crafts-type substitution reaction of aniline with aldehydes smoothly proceeds in the presence of phenyldichloroborane and tertiary amine (Eq. 1).[1] When dialkylboryl triflate, which is an effective enolating reagent for the acyclic stereoselective aldol reaction,[2] was used instead of phenyldichloroborane, the reaction did not proceed and the starting material was recovered. These findings prompted us to investigate the aldol reaction using phenyldichloroborane. Here we wish to report a convenient and exclusive erythro-selective aldol reaction using phenyldichloroborane - it is one of the most erythro-selective aldol reactions. Phenyldichloroborane is readily prepared[3] and can be stored more than a year in a sealed tube. It is also less expensive and easier to handle than dialkylboryl triflate. The reactions of various ethyl ketones with aldehydes are shown in Table 1.



(1)

In the typical procedure for the reaction of 3-pentanone $\underset{\sim}{1}$ with benzaldehyde

2, phenyldichloroborane (1.2 mmol) and a solution of 2 (1.2 mmol) in dichloromethane (3.0 ml) containing ethyldiisopropylamine (2.4 mmol) were added sequentially to a stirred solution of 1 (1.0 mmol) in dichloromethane (3.0 ml) at -78 °C under argon. After the mixture had been stirred at -78 °C for 5 h, 1 M sodium hydroxide solution (6.0 ml) was added, and the mixture was warmed to 0 °C



(2)

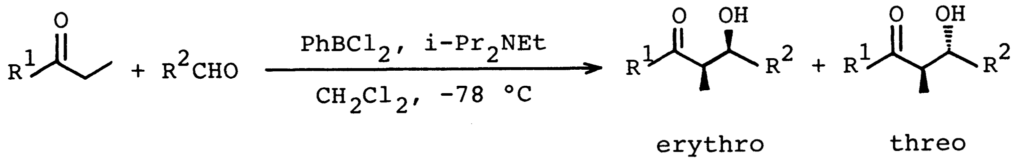
only erythro isomer
quant.

under stirring. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane extract was washed with water, dried ($MgSO_4$), and concentrated. When the residue was purified by chromatography (SiO_2, 2 g; benzene:ethyl acetate, 10:1), it gave only the erythro isomer 4 in almost quantitative yield (Eq. 2).

High erythro-selectivity was obtained in all the reactions. In the case of 2-methyl-3-pentanone with benzaldehyde, erythro-selectivity was drastically improved, compared with the reaction using dibutylboryl triflate (erythro/threo = 44/56$^{4)}$) (Run 9). Unfortunately, regioselectivity could not be obtained (Run 13).

In these reactions, if aldehyde was added after ethyldiisopropylamine to a mixture of ketone and phenyldichloroborane, a moderate amount of self-condensed product of ketone was obtained. Consequently, aldehyde and ethyldiisopropylamine must be added together to complete the reaction. This suggests that under kinetic control, the generated boron enolate in Z-form 3 is extremely reactive due to the high Lewis acidity of the boron moiety by the electron-withdrawing effect of the chlorine and the phenyl group, and thus reacts with unenolized

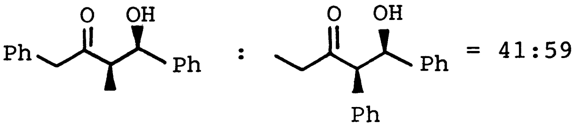
Table 1. Aldol Reaction of Ethyl Ketones with Aldehydes Using $PhBCl_2$



Run	R^1	R^2	Time/h	Yield/%	erythro/threo a)
1	C_6H_5	C_6H_5	22	74	<95:5
2	"	n-C_3H_7	"	52	<99:1
3	"	$C_6H_5CH_2$	"	54	<99:1
4	"	i-C_3H_7	"	55	<99:1
5	C_2H_5	C_6H_5	5	quant.	<99:1
6	"	n-C_3H_7	3	84	<99:1
7	"	$C_6H_5CH_2$	"	80	<99:1
8	"	i-C_3H_7	"	96	<99:1
9	i-C_3H_7	C_6H_5	"	98	<94:6
10	"	n-C_3H_7	"	77	<99:1
11	"	$C_6H_5CH_2$	"	67	<99:1
12	"	i-C_3H_7	"	80	<99:1
13	$C_6H_5CH_2$	C_6H_5	"	98	<99:1 b)

a) All ratio was determined from ^{1}H-NMR.4)

b) A mixture of two regioisomers was obtained.



ketone existing in the reaction medium even at -78 °C. This high erythro-selectivity may be due to the speculations as follows. The boron enolate is formed in completely Z-form kinetically. And also, the high Lewis acidity of the boron enolate **3** makes six-membered ring in the transition state more fixed than that of the reaction of dialkylboryl triflate. Consequently, the 1,3-diaxial interaction of the chlorine or the phenyl group and the alkyl group of ketone seems to be more effective. But unfortunately, the identification of the Z-form **3** was unsuccessful due to the instability of this compound.

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References

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