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NEW CROSS-ALDOL REACTION *via* VINYLOXYBORANES

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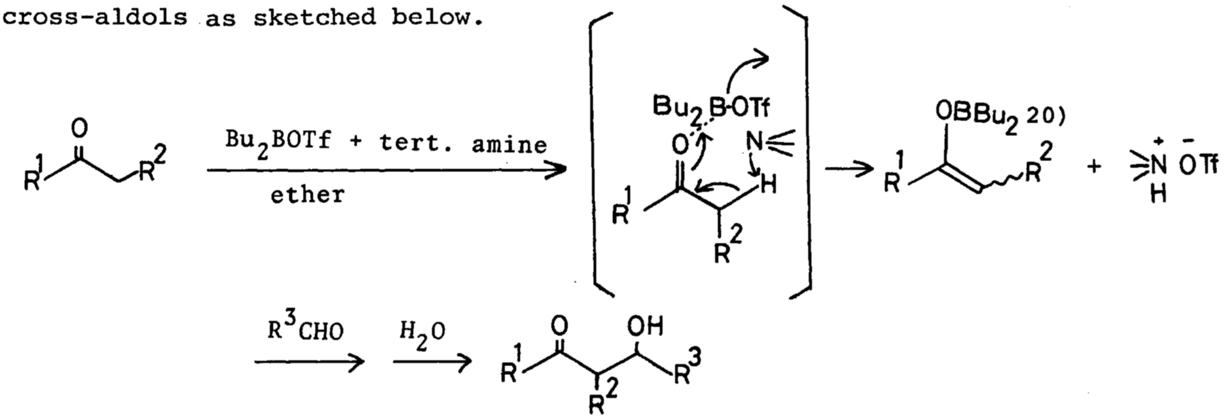
A new synthesis of cross-aldols from two different carbonyl compounds by using di-n-butylboryl trifluoromethanesulfonate and tertiary amine is described. In the case of methyl ketones, the reaction takes place in regiospecific manner to afford the corresponding aldols in good yields.

The aldol reaction1) is one of the most important methods for the formation of carbon-carbon bonds. However, the intermolecular aldol reaction between two different carbonyl compounds has not been practically employed, because of the complex mixture formation based on the rapid equilibrium of the enolate anions originated from two different carbonyl compounds. During these eight years, several methods2)-9) have been devised to avoid these problems. In most cases, the masked carbonyl compounds have been employed for the generation of specific enolates or their equivalents.

It was reported from our laboratory that vinyloxyboranes reacted with various carbonyl compounds to give the corresponding β-hydroxyketones or β-hydroxyesters in excellent yields under mild reaction conditions.5) Despite the utility of vinyloxyboranes,5),10),11) the methods for the preparation of those directly derived from ketones have not been generally feasible ones.12)-15) Recently Köster16) et al. demonstrated a general method for the synthesis of vinyloxyboranes directly from ketones and triethylborane by use of diethylboryl pivalate as a catalyst17) at high temperature. Now we wish to report a new and useful method for the synthesis of cross-aldols by the reaction of vinyloxyboranes formed from a wide variety of ketones and di-n-butylboryl trifluoromethanesulfonate (triflate) with aldehydes.

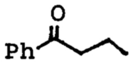
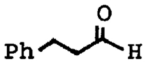
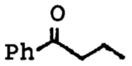
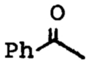
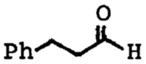
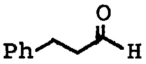
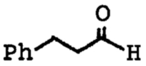
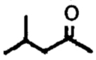
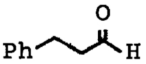
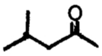
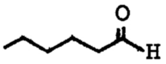
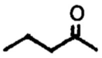
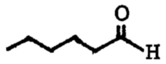
In the course of our studies, it was found that tri-n-butylborane reacts with trifluoromethanesulfonic acid at room temperature to give di-n-butylboryl triflate in 84% yield.18) This triflate reacts with ketones in the presence of tertiary amines such as diisopropylethylamine or 2,6-lutidine to produce ammonium triflates19) n re vinyloxyboranes which in turn react with aldehydes to give cross-aldols as sketched below.



During the above mentioned transformation, di-n-butylboryl triflate, a strong Lewis acid, plays an important role in each step, namely it can readily form the complex with ketone and eliminate the stable triflate anion from the complex by the action of tertiary amine.

A typical reaction procedure is described for the reaction of 2-methyl-4-pentanone and 3-phenylpropanal; to a solution of di-n-butylboryl triflate (0.301 g, 1.1 mmol) and diisopropylethylamine (0.142 g, 1.1 mmol) in 1.5 ml of ether was added dropwise 2-methyl-4-pentanone (0.100 g, 1.0 mmol) in 1.5 ml of ether at -78° under argon with stirring. After the mixture was stirred for 30 min, 3-phenylpropanal (0.134 g, 1.0 mmol) in 1.5 ml of ether was added at that temperature. The reaction mixture was allowed to stand for 1 hr, then added to pH 7 phosphate buffer at room temperature and extracted with ether. After removal of ether, the mixture was treated with 30% H_2O_2 (1 ml) in MeOH (3 ml) for 2 hr and water was added.
The mixture was concentrated in vacuo to remove most of the methanol and extracted with ether. The ethereal layer was washed with 5% solution of $NaHCO_3$ and saturated solution of NaCl, dried over Na_2SO_4 and the solvent was removed. The crude oil was purified by preparative tlc to give 3-hydroxy-7-methyl-1-phenyl-5-octanone(0.192 g, 82%). The absorption in the nmr at ca. δ2.1 which is characteristic of the acetyl group was very small, suggesting the reaction proceeds regiospecifically.
The results are summarized in Table.

Table Yields of cross-aldols

Ketone	Aldehyde	Yield of aldol, %[a]
		83 [b]
	PhCHO	80 [b]
		75
		80 [c]
		72 [c]
		82
		70 [d]
		65 [d]

a) All of the products gave satisfactory nmr, ir data for assigned structures of the authentic samples. Yields are based upon the aldehydes. b) The reaction was carried out using 2,6-lutidine as trifluoromethanesulfonic acid captor in n-hexane at room temperature. c) Reactant ratio, triflate : amine : ketone : aldehyde = 1.2 : 1.2 : 1.1 : 1.0. d) The reaction proceeded only at the methyl site of the ketone. Absence of the regioisomers was confirmed by comparison with authentic samples (separable on 10% QF$_1$ at 130°).

It should be noted that the present cross-aldol reaction between ketones and aldehydes would provide a practically useful tool in organic synthesis, because of its mild reaction conditions, the simplicity of the procedure and high regiospecificity.

The authors are grateful to Drs. Isao Kuwajima and Toshio Sato for their gifts of 3-hydroxy-7-methyl-1-phenyl-5-octanone, 6-hydroxy-2-methyl-4-undecanone and 6-hydroxy-4-undecanone.

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17) In the cases of methyl ketones, cyclopentanone and cyclohexanone, the corresponding vinyloxyboranes are reported too reactive to result in the predominant formation of self-aldols.

18) The equimolar amounts of tri-n-butylborane and trifluoromethanesulfonic acid are mixed at room temperature under argon. Distillation gave very hygroscopic oil (b.p. 37°/0.12 mmHg). ir (CCl_4): 1405, 1380, 1200, 1150, 1050, 1015, 640, 620 cm^{-1}.

19) A white precipitate probably of the ammonium triflate appeared soon.

20) The nmr signal (δ5.4) corresponding to the vinyl proton of dibutyl (1-phenylbutenyloxy)borane (reference 16) was observed in the case of 1-phenyl-1-butanone which was treated with dibutylboryl triflate and 2,6-lutidine in the absence of the solvent.

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